Institution: University of Liverpool

Unit of Assessment: 10 – Mathematical Sciences

Title of case study: Mathematical modelling of an aneurysm sealing system triggers patient safety policy that withdraws surgical practice from the NHS

Period when the underpinning research was undertaken: June 2015 – January 2018

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:
Prof Alexander Movchan	Professor of Applied Mathematics	January 1999 – Present
Prof Natalia Movchan	Professor of Applied Mathematics	January 1999 – Present
Dr Giorgio Carta	Postdoctoral Research Associate	June 2015 – May 2016
Dr Luca Argani	Postdoctoral Research Associate	April 2016 - June 2018

Period when the claimed impact occurred: April 2017 – December 2020

Is this case study continued from a case study submitted in 2014? N

1. Summary of the impact

Researchers at the University of Liverpool developed a mathematical model of an aneurysm sealing system that led to new national patient safety regulations, mandating a lifesaving change in surgical practice. Approximately 837 patients across the UK have benefitted from safer alternative treatment and lifelong monitoring. From 2013 the Nellix® EndoVascular Aneurysm Sealing (EVAS) system was one of two keyhole surgical procedures used in the NHS for abdominal aortic aneurysms. In 2016 surgeons reported unexplained movement of the device causing life-threatening complications. Our bespoke model explained this movement by modelling everyday forces on the sealed aneurysms. Results from the model were combined with clinical data to underpin the regulatory policy that completely withdrew the procedure from NHS practice in January 2019.

2. Underpinning research

The research underpinning this impact was carried out by the research group of Prof A. Movchan, Professor of Applied Mathematics at the University of Liverpool, in collaboration with consultant vascular surgeons Prof F. Torella, Prof R. Fisher and Mr M. Wall and interventional radiologist Prof R. McWilliams, all honorary professors in the University's Department of Mathematical Sciences since May 2016. Initial meetings of the group in 2015 originated from links established during setup of the EPSRC Liverpool Centre for Mathematics in Healthcare (EP/N014499/1, GBP2,004,298), for which Prof A. Movchan and Prof N. Movchan were both Co-Investigators.

2.1. Clinical context - treating abdominal aortic aneurysms

An aneurysm is a stretched blood vessel caused by weakness of the arterial wall. The most common artery affected is the aorta (main artery) in the abdomen. Timely detection and treatment of abdominal aortic aneurysms is essential as the swelling can get bigger and rupture. The majority of unruptured aneurysms are suitable for endovascular (keyhole, minimally-invasive) treatment rather than open surgery, reducing hospital stay and overall recovery time.

From February 2013 to January 2019 the two endovascular options for treating unruptured abdominal aortic aneurysms in the NHS were i) conventional endovascular aneurysm repair

(EVAR) and ii) the novel Nellix® EndoVascular Aneurysm Sealing (EVAS) system (©Endologix Inc. Irvine, Ca, USA). The former involves inserting a stent to support the weakened blood vessel from within. The latter involves the use of polymer filled endobags, completely sealing the aneurysm and holding the stent graft in place. Any movement (migration) of stent-grafts can compromise the seal, allowing blood to re-enter the aneurysm ('endoleak') and can require further surgical intervention. If left untreated, endoleaks can cause the aneurysm to rupture, leading to a fatal bleed.

During early adoption the Nellix EVAS system was thought to improve the durability of a repair by reducing leaks and therefore the need for further intervention.

2.2. Modelling the Nellix EVAS aneurysm sealing system

Clinical members of the collaboration detailed above were treating patients at the Royal Liverpool University Hospital with the Nellix EVAS system from 2013. By 2016 they were observing movement of the stent-grafts in some patients, despite adherence to the instructions for use. It was unclear however, why or how this migration was occurring. Profs Torella and McWilliams as part of the specialist Liverpool endovascular surgical team approached mathematician Prof A. Movchan with their observation and the group set out to understand this observed but unexplained movement of the stent-grafts. The problem was unsolvable with clinical data alone and no modelling had previously been attempted. The collaboration and resulting solution drew on the existing expertise of Prof A. Movchan's group (as listed above, along with PhD student Sara Frecentese) in the simulation of fluid–structure interaction and wave propagation problems in stented arteries **[3.1]**.

Bespoke mathematical modelling of the Nellix EVAS system was completed by Prof A. Movchan and Dr Argani in 2017, with clinical input and data provided by Profs Torella, McWilliams, Fisher and Wall **[3.2]**. The research produced a three-dimensional model that explained the effect of both static forces (e.g. gravity) and dynamic forces (e.g. vibrations) from everyday activities on the sealed aneurysms, using both idealised and real patient geometries. This was the first ever model to consider the effects of these forces on the durability of Nellix EVAS devices. The model took into account the pressure of the blood and the subsequent stresses and deformations in the aortic wall. It also factored in the effects of friction on the interaction between the polymer of the Nellix EVAS system and the aorta. CT imaging data from patients fitted with the Nellix EVAS system was linked to the three-dimensional code.

2.3. Key findings from the mathematical model

Results from the model showed that elastic deformation of the aorta and endoprosthesis induced by static forces and vibrations during daily activities can cause movement of the stent-grafts and disruption of the seal. A key finding was that the additional mass of the polymer in the Nellix EVAS system made it respond differently to forces such as gravity when compared to conventional stents **[3.2]**. These findings enabled the clinicians to make new recommendations about use of the Nellix EVAS system that underpinned withdrawal of the procedure from the NHS as described in section 4.

3. References to the research

3.1. Frecentese S, Argani LP, Movchan AB, Movchan NV, Carta G, and Wall ML. (2018). Waves and fluid–solid interaction in stented blood vessels. Proc. R. Soc. 474:2209. doi:10.1098/rspa.2017.0670

3.2. Argani L, Torella PF, Fisher RK, McWilliams, RG, Wall ML, and Movchan AB. (2017). Deformation and dynamic response of abdominal aortic aneurysm sealing. Scientific reports, 7: 17712. doi:10.1038/s41598-017-17759-3

4. Details of the impact

Abdominal aortic aneurysms can be life-threatening and all men aged 65 in the UK are invited for screening. The majority of people requiring treatment each year undergo endovascular (keyhole) procedures, rather than open surgery. From February 2013 to January 2019, the Nellix® EndoVascular Aneurysm Sealing (EVAS) system was one of two endovascular treatments used in the NHS **[5.1a]**. During 2017, applied mathematics research at the University of Liverpool explained critical patient safety issues with the Nellix EVAS system, by modelling its physical properties for the first time **[3.2]**. Impacts on health, policy and practice arising from this research include:

- **4.1.** Reducing the risk of life-threatening complications for approximately 837 patients **[5.1b]** who have received safer alternative treatment and additional check-ups.
- **4.2.** Regulatory policy that withdrew the Nellix EVAS procedure from NHS practice and required enhanced monitoring of existing patients **[5.2]**.

4.1. Improved patient safety

Two groups of patients are benefitting from improved health and wellbeing as a result of this body of research and in particular **[3.2]**. Firstly, patients who would have been fitted with the Nellix EVAS system had it not been recalled, who are now receiving alternative safer treatment **[5.1b]**. Secondly, all patients fitted with the Nellix EVAS system who are now receiving enhanced lifelong surveillance **[5.1b]**.

Each of these patients is benefitting from a reduced risk of life-threatening complications associated with the Nellix EVAS device. Complications averted include endoleaks that can cause the aneurysm to rupture, with a mortality rate of 80%. Clinical findings indicate a failure rate of approximately 50% for Nellix EVAS devices **[5.3]**, more than twice that of conventional endovascular aneurysm repairs (EVAR). The rupture rate for Nellix EVAS is 2.44 per 100 patient-years, compared to 0.6 per 100 patient-years for EVAR **[5.4]**.

Between 2013 and 2018, 23 hospitals in England carried out Nellix EVAS procedures for abdominal aortic aneurysms **[5.5]**. At the peak of use, one specialist centre was using it for more than half of all endovascular repairs **[5.6]**. Using available data, approximately 611 patients across the UK were fitted with the Nellix EVAS system between August 2013 and December 2018 **[5.1b]**. These patients are all benefitting from lifelong additional monitoring as a result of mathematical model **[3.2]** explaining safety issues, leading to the policy change **[5.2]** explained in section **4.2** below.

One consultant surgeon from a Greater Manchester hospital explains: "*The team's* [Prof Movchan et al] *research work has had a significant impact on clinical practices in my hospital indicated by tangible clinical benefits with the intensified clinical and imaging monitoring and surveillance of more than 25* [Nellix] *EVAS cases treated in my hospital*" **[5.7]**.

At December 2020, approximately 226 patients in the UK have received safer alternative treatment (such as conventional EVAR) rather than Nellix EVAS since national withdrawal of the procedure in January 2019 **[5.1b]**. This has reduced their risk of life-threatening complications and need for further surgical intervention.

Even before the national withdrawal, surgeons were beginning to change their practice in response to emerging research. In Liverpool, there was an 83% reduction from 69 Nellix EVAS procedures in 2015 to just 12 in 2017 **[5.6]**, as key research results were becoming available **[3.2]**. One Liverpool-based consultant surgeon and research collaborator explains how the modelling results *"…played a significant role in the results generated by our* [clinical] *research and subsequent clinical practice*" **[5.8]**.

4.2. New regulatory policy and national change in clinical practice

The Nellix EVAS system attained its CE mark, a legal requirement to place a device on the market in the UK, in February 2013. Research from Liverpool **[3.2]** resulted in the device being fully withdrawn from NHS practice on the 25th January 2019 via publication of a Medical Device Alert from the UK's Medicines and Healthcare Regulatory Agency (MHRA) **[5.2, 5.9]**. The alert required UK centres to "*Immediately stop further implants of the device*" due to a "*high risk of graft failure*" **[5.2]**.

MHRA Medical Devices Alerts are the primary means of communicating safety information to healthcare organisations for immediate action. In addition to stopping all procedures and recalling unused stock, the policy mandated enhanced surveillance for all patients already fitted with the Nellix EVAS system **[5.2]**.

The key finding from Liverpool's mathematical model was how aneurysms treated with Nellix EVAS evolve over time in a different way to those treated with conventional EVAR, due to the additional mass of the polymer **[3.2]**. This result was instrumental in the collaborating clinicians being able to make transformative clinical recommendations about use of the device **[5.8, 5.9]**. Their medical paper on the incidence and extent of movement of Nellix EVAS systems set out how the definition of stent movement being used in the NHS at the time was inappropriate for the Nellix EVAS system **[5.9]**. They recommended that a different, new definition and movement measurement technique was needed for the Nellix EVAS and that use of the system should continue under close surveillance only **[5.9]**.

One of the Liverpool-based consultant surgeons and research collaborator explains *"… the mathematical modelling work done in collaboration with Prof Movchan underpinned and led to the development of that paper*" **[5.8]**. **Findings from our model [3.2] and resulting clinical recommendations [5.9] were central to the complete recall of Nellix EVAS from the NHS, being one of only three evidence sources on the Medical Device Alert [5.2].** This was the only one of the three underpinning sources to use mathematical modelling.

5. Sources to corroborate the impact

5.1. Data on the number of Nellix EVAS and conventional EVAR procedures carried out in the UK for treating abdomonial aortic aneurysms.

- **a)** Email from the National Vascular Registry detailing the number of Nellix EVAS and EVAR procedures carried out in the UK in 2016, 2017 and 2018.
- **b)** Estimates using data in [5.1a] for the number of patients who have averted the EVAS procedure since 2019 and the number of patients fitted with Nellix EVAS between August 2013 and December 2018.

5.2. Medicines and Healthcare products Regulatory Agency (MHRA) Medical Device Alert. (January 2019). Nellix Endovascular Aneurysm Sealing (EVAS) System - Device recall and enhanced patient surveillance (MDA/2019/002). See reference 2 of 3 - the recommendations of the collaborating clinicians [5.9], underpinned by Liverpool's mathematical model [3.2].

5.3. Clinical study indicating approximate 50% failure rate of Nellix EVAS after three years (see p.6/347): Harrison S.C., et al. Editor's Choice – Mid-term Migration and Device Failure Following Endovascular Aneurysm Sealing with the Nellix Stent Graft System – a Single Centre Experience. Eur J Vasc Endovasc Surg. (2018) 56(3):342-348. doi:10.1016/j.ejvs.2018.06.031

5.4. Clinical study detailing rupture rates for Nellix EVAS compared to EVAR (see p.9/465): Stenson KM, et al. Migration and sac expansion as modes of midterm therapeutic failure after endovascular aneurysm sealing. J Vasc Surg (2020) 71(2):457-469.e1. doi:10.1016/j.jvs.2019.04.482

5.5. Email from NHS England confirming that 23 hospitals carried out Nellix EVAS procedures for treating abdominal aortic aneurysms between August 2013 and December 2018.

5.6. Email and data from Liverpool University Hospitals NHS Trust on the number of Nellix EVAS and EVAR procedures carried out for treating abdominal aortic aneurysms from 2013 to 2018.

5.7. Letter from Consultant Vascular & Endovascular Surgeon at Pennine Acute Hospitals NHS Trust, Greater Manchester explaining the impact of the research on clinical practice.

5.8. Letter from Consultant Vascular and Endovascular Surgeon and research collaborator at the Royal Liverpool University Hospital explaining the importance of the mathematical model in subsequent clinical research and practice.

5.9. Clinical recommendations underpinned by the mathematical model [3.2] cited in the policy alert [5.2]: Yafawi, A., McWilliams, R.G., Fisher, R.K., England, A., Karouki, M. and Torella, F., 2019. Stent frame movement following endovascular aneurysm sealing in the abdominal aorta. Journal of Endovascular Therapy, 26(1), pp.54-61. doi:10.1177/1526602818814548