Institution: University of Nottingham (UoN)		
Unit of Assessment: 9		
Title of case study: QuantMRI: Quantitative MRI for healthcare, pharmaceuticals and nutrition		
Period when the underpinning research was undertaken: 1st Jan 2000 – 31st Dec 2020		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by the submitting HEI:**
Susan Francis	Professor	2001 – present
Penny Gowland	Professor	1990 – present
Period when the impact occurred: 1st August 2013 – 31st December 2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

We have developed a range of quantitative Magnetic Resonance Imaging (MRI) methods that allow a comprehensive, non-invasive assessment of human physiology *in vivo*. These methods have been applied to a range of dynamic processes including studies of the gastrointestinal (GI) tract, respiratory tract, kidneys and heart. Our MRI innovations in this area have: (1) been exploited by the medical technology and pharmaceutical sectors to provide information to regulators and licensing agencies which has influenced European Consensus and NICE guidelines and led to commercial impact (*Baxter Healthcare and BBraun, Fresenius Kabi and Fresenius Medical Care, Procter & Gamble, Simulations Plus*); (2) provided insights for industry and regulators in the assessment of the health benefits of food products (*Unilever, Zespri International Limited*); (3) provided new quantitative imaging biomarkers of disease progression and treatment response (*JEB technologies, Motilent*).

2. Underpinning research

The Sir Peter Mansfield Imaging Group (SPMIG) in the School of Physics and Astronomy (SoPA) are pioneers in the development of novel quantitative MRI (qMRI) techniques to enable the non-invasive measurement of key biophysical parameters *in vivo*. This approach transcends standard imaging performed in routine clinical radiology, by providing unique spatio-temporal information on the dynamic phenomena that underlie complex physiological processes. The SPMIG has harnessed its considerable expertise in the physics of MRI and its long experience in fast imaging, to develop novel, integrated MR acquisition and analysis protocols for dynamic mapping of NMR relaxation times (T_1 and T_2), viscosity, flow, organ motility and other key measures. Importantly, these unique tools allow a comprehensive assessment of the function of individual organs, and of interactions between organs, all in a single examination, enabling innovative studies of disease processes and responses to therapies. Here we present the underpinning research on the gastrointestinal (GI) tract, upper respiratory tract, kidney and heart which led to this case study.

Since 2000, through longstanding collaborations with Professors Robin Spiller and Luca Marciani (National Institute of Health Research (NIHR) Nottingham Biomedical Research Centre), the SPMIG has developed and optimised qMRI for the measurement of key biophysical parameters to study GI function **[i-v, I-III]**, including: gut motility; the breakdown of model particles to study intraluminal forces; intraluminal emulsification of fat; gastric emptying and intraluminal viscosity of model meals **[1-3];** small bowel water content and colonic volumes **[4];** and water pocket volumes in the bowel and colonic motility **[5]**. Examples of applications include *in vivo* studies of intragastric gelation **[1]**, the fate of aerated drinks in the gastric lumen **[3]**, and gastric emptying of preoperative metabolic preconditioning drinks in healthy volunteers **[6]**. Since 2013 **[7]**, the group have developed novel MR marker capsules, combined with bespoke MRI sequences for detecting them with high sensitivity, to measure whole-gut transit time without ionizing radiation; these markers have recently been used in a first-in-child study **[8]**. These methods have also been re-purposed to study the upper respiratory tract **[9, IV].**

The application of qMRI to understand kidney function forms part of a collaboration with Professor Dileep Lobo (NIHR Nottingham Biomedical Research Centre), and Professors Nicholas Selby and Maarten Taal (Centre for Kidney Research and Innovation, University of Nottingham). The SPMIG has a long history of developing Arterial Spin Labelling (ASL)

methods to measure tissue perfusion (blood flow) using intrinsic magnetic labelling of blood. This has been adapted to measure renal and cardiac perfusion, crucially overcoming the need to administer contrast agents contraindicated in kidney disease. We have combined ASL with other qMRI methods **[vi, vii]** for the assessment of hemodynamics (blood flow and perfusion **[10]**), oxygenation, and microstructure (inflammation and fibrosis), providing new insights into physiology in health **[11, V-VI]** and renal disease **[12]**, most recently in an international study of COVID-19-associated renal injury **[viii]**. We performed the world's first intradialytic qMRI studies, overcoming technical hurdles to allow patients to undergo dialysis within the challenging MRI environment, providing new information on the cardiac **[11, VII]** and multiorgan (cardiac/renal/brain) blood flow "stress" that occurs during dialysis **[VIII]**.
Since 2000 our work on qMRI has been supported by the Research Councils (GBP33.8M), Trusts and Charities (GBP5.5M), Industry (GBP3.9M), and Government (GBP1.8M).

3. References to the research

Publications: ***Academic staff*** and **PDRAs** working within the SPMIG of the SoPA.

[1] **Hoad, C.L.**, Rayment, P., **Spiller, R.C.**, Marciani, L., **de Celis Alonso, B.**, Traynor, C., Mela, D.J., Peters, H.P.F., ***Gowland, P.A.***, *In Vivo* Imaging of Intragastric Gelation and Its Effect on Satiety in Humans, *J Nutrition* **134**, 2293-2300, 2004. DOI: 10.1093/jn/134.9.2293.
[2] Mudie, D.M., **Murray, K.**, ***Hoad, C.L.***, **Pritchard, S.E.,** Garnett, M.C., Amidon, G.L., ***Gowland, P.A***., Spiller, R.C., Amidon, G.E., Marciani, L., Quantification of gastrointestinal liquid volumes and distribution following a 240 mL dose of water in the fasted state, *Mol Pharm* **11**, 3039-47, 2014. DOI:10.1021/mp500210c.
[3] **Murray, K.**, **Placidi, E.**, Schuring, E.A., **Hoad, C.L.**, [..], **Pritchard, S.E.**, Stoyanov, S.D., ***Gowland, P.A.***, Spiller, R.C., Peters, H.P., Marciani, L., Aerated drinks increase gastric volume and reduce appetite as assessed by MRI: a randomized, balanced, crossover trial, *Am J Clin Nutr* **101**, 270-8, 2015. DOI: 10.3945/ajcn.114.096974.
[4] Wilkinson-Smith, V., **Dellschaft, N.**, Ansell, J., **Hoad, C.**, Marciani, L., **Gowland, P.**, Spiller, R., Mechanisms underlying effects of kiwifruit on intestinal function shown by MRI in healthy volunteers, *Aliment Pharmacol Ther* **49**, 759-768, 2019. DOI:10.1111/apt.15127.
[5] **Hoad, C.L.**, Menys, A., [..]., **Murray, K.**, [..], Spiller, R.C., Taylor, S.A., ***Gowland, P.A.***, Colon wall motility: comparison of novel quantitative semi-automatic measurements using cine MRI. *Neurogastroenterol Motil* **28**, 327-35, 2016. DOI: 10.1111/nmo.12727.
[6] Lobo, D.N., Hendry, P.O., [..], Marciani, L., **Totman, J.J.**, Wright, J.W., Preston, T., ***Gowland, P.***, Spiller, R.C., Fearon, K.C., Gastric emptying of three liquid oral preoperative metabolic preconditioning regimens measured by magnetic resonance imaging in healthy adult volunteers, *Clin Nutr* **28**, 636-41, 2009. DOI: 10.1016/j.clnu.2009.05.002.
[7] **Chaddock, G.**, Lam, C., **Hoad, C.L.**, **Costigan, C.**, **Cox, E.F.**, **Placidi, E.**, [..], Marciani, L., ***Gowland, P.A.***, Spiller, R.C., Novel MRI tests of orocecal transit time and whole gut transit time, *Neurogastroenterol Motil* **26**, 205-14, 2014. DOI:10.1111/nmo.12249.
[8] Sharif, H., Abrehart, N., **Hoad, C.L.**, **Murray, K.**, [..], ***Gowland, P.A.,*** Spiller, R.C., [..], Marciani, L., YPAG, Feasibility Study of a New Magnetic Resonance Imaging Mini-capsule Device to Measure Whole Gut Transit Time in Paediatric Constipation, *J Pediatr Gastroenterol Nutr* **71**, 604-611, 2020. DOI: 10.1097/MPG.0000000000002910.
[9] **Pritchard, S.**, Glover, M., [..], ***Gowland, P***., Effectiveness of 0.05% oxymetazoline (Vicks Sinex Micromist (R)) nasal spray in the treatment of objective nasal congestion demonstrated to 12 h post-administration by magnetic resonance imaging. *Pulmonary Pharmacology & Therapeutics* **27**, 121-6, 2014. DOI: 10.1016/j.pupt.2013.08.002.
[10] Gardener, A., ***Francis, S.,*** Multislice perfusion of the kidneys using parallel imaging. *Magn Reson Med* **63***,* 1627-1636, 2010. DOI: 10.1002/mrm.22387.
[11] Chowdhury, A.H., **Cox, E.F.**, ***Francis, S.T.***, Lobo, D.N., A randomized, controlled, double-blind crossover study on the effects of 2-L infusions of 0.9% saline and plasma-lyte® 148 on renal blood flow velocity and renal cortical tissue perfusion in healthy volunteers, *Ann Surg* **256**, 18-24, 2012. DOI:10.1097/SLA.0b013e318256be72.
[12] **Buchanan, C.**, Mahmoud, H., **Cox, E.**, [..], ***Francis S.*** Quantitative assessment of renal structural and functional changes in CKD using multi-parametric MRI. Nephrology Dialysis Transplantation **35**, 955-964, 2020. DOI: 10.1093/ndt/gfz129.

[13] **Buchanan, C.**, Mohammed, A., **Cox, E.**, Köhler, K., Canaud, B., Taal, M.W., Selby, N.M., ***Francis, S.***, McIntyre, C.W., Intradialytic Cardiac Magnetic Resonance Imaging to Assess Cardiovascular Responses in a Short-Term Trial of Hemodiafiltration and Hemodialysis, *J Am Soc Nephrol* **28**, 1269-1277, 2017. DOI:10.1681/ASN.2016060686.

Patents:

European patent, Magnetic Resonance Imaging Methods for the Study of Gastrointenstinal Transit, EP 3166488 A1, WO 2016005731 A1.

Key Research Council and charity grants:

[i] 'Assessment of gut transit in paediatric constipation without ionizing radiation: Magnetic Resonance Imaging transit mini-capsules and methods', PI: Marciani, NIHR i4i II-LB-0814-20002 (Oct 2015 – July 2019), GBP603,109.
[ii] 'Assessment of gut transit in paediatric constipation without ionizing radiation: Magnetic Resonance Imaging transit mini-capsules and methods 2 (MAGIC2)', PI: Marciani, NIHR i4i NIHR200014, (July 2019- July 2022) GBP1,224,841.
[iii] 'The causes of constipation. Reclassifying constipation using MRI and high resolution manometry to define mechanism of disease and target treatment', PI: Spiller, MRC MR/N026810/1, (Jul 2016- Sept 2020), GBP1,544,488.
[iv] 'Evaluation of Crohn's disease activity with MRI-adding value though quantitative assessment of intestinal motility', PI: Menys, NIHR i4i II-LA-0716-20005, (Sept 2017- Sept 2019), GBP725,776.
[v] 'Understanding mechanisms for variation in beneficial effects of dietary fibre in Irritable Bowel Syndrome', PI: Whelan, MRC MR/N029097/1, (Aug 2016-Jan 2019), GBP778,061.
[vi] 'Imaging of intrarenal haemodynamics, oxygen metabolism, fibrosis in Chronic Kidney Disease', PI: Francis, Animal Free Research, (March 2014-March 2017), GBP107,623.
[vii] 'UK Renal Imaging Network (UKRIN): Enabling clinical translation of functional MRI for kidney disease', PI: Francis, MRC MR/R02264X/1, (Sept 2018 – Sept 2021), GBP795,786.
[viii] 'Acute kIDnEy injury in coviD-19 (AIDED)', PI: Francis, MRC MR/V037005/1 (Nov 2020-Dec 2021), GBP100269.

Medical Technology Industrial funding:

[I] Mitochondrial function. PI: Lobo, *Fresenius Kabi*, (May 2008 – June 2009), GBP64,000
[II] MRI Study of Stomach Volumes and Satiety, PI: Marciani and Gowland, *Unilever Research Laboratorium Vlaardigen*, (Jan 2011 – Dec 2014), GBP75,063.
[III] The effect of kiwifruit on gastrointestinal fluid distribution and transit in healthy volunteers, PI: Spiller, *Zespri International Limited*, (Mar 2017- Apr 2019), GBP249,566.
[IV] Evaluation of MRI to detect changes in nasal patency following a single dose of Vicks Sinex Micromist®. PI: Gowland, *Procter & Gamble*, (Mar 2010 – Aug 2011), GBP20,000.
[V] The effects of crystalloid and colloid infusions on renal and superior mesenteric blood flow. PI: Lobo, *Baxter Healthcare*, (Sep 2010- Sep 2012), GBP48,000.
[VI] The physiological effects of isovolemic coloids versus crystalloids on cardiac output & renal blood flow, PI: Lobo, *BBraun*, (Jan 2014 – Jan 2018), GBP97,003.
[VII] Dynamic effects of online haemodiafiltration on cardiac function and myocardial perfusion utilising cardiac MRI, PI: Taal & Francis, *Fresenius Medical Care*, (Apr 2014 – July 2016), GBP250,858.
[VIII] HD-REMODEL: Haemodialysis Interventions, PI: Taal & Francis, *Fresenius Medical Care*, (Apr 2017 - May 2020), GBP250,858.

Prizes and Recognition:

Professor Susan Francis, International Society of Magnetic Resonance in Medicine (ISMRM) Fellow of the Society (2020) "*in recognition of sustained contributions to MRI*."
Professor Penny Gowland, Institute of Physics (IoP) Peter Mansfield Medal and Prize (2020) for "*being an outstanding world-class scientist who has made major contributions in developing novel techniques for quantitative Magnetic Resonance Imaging (MRI) to enable innovative, non-invasive investigations into human anatomy, physiology and biology*."

4. Details of the impact

Our work on developing qMRI methods has had significant impact through three principal routes, by providing (1) information to medical technology and pharmaceutical industries,

regulators and licencing agencies; (2) critical assessment of health benefits of food products for industry and regulators; (3) new quantitative imaging biomarkers of disease and treatment response. The value of these studies to the commercial sector can be gauged by grants to the SPMIG totalling GBP1.6M in the REF2021 assessment period; exemplar projects are listed below.

1) Testing pharmaceuticals to inform industry, regulators and licencing agencies

Our use of qMRI to directly monitor physiology in human subjects has attracted the interest of companies who are seeking to optimise drug and therapy formulations.

a) With *Baxter Healthcare* (a multinational health care company) and *BBraun* (a German medical and pharmaceutical device company) **[V, VI]**, we performed studies using our qMRI methods to assess changes in renal haemodynamics during infusions of fluids after surgery (Postoperative Fluid Therapy). We confirmed that hyperchloraemia acidosis caused by saline overload can lead to a decrease in renal blood flow and perfusion, a phenomenon we demonstrated in humans for the first time **[11]**. Our results influenced international guidance on improved fluid therapy for optimal patient care (*NICE Guidelines: Intravenous fluid therapy in adults in Hospital*, 10 December 2013 **[a, page 153]**, in addition to five European guidelines **[a]**). Due to increased awareness of saline-induced hyperchloraemic acidosis, as demonstrated by our research and incorporated into guidelines, balanced fluids rather than saline are now the choice of fluid therapy in hospitals in the UK and Europe.

b) We used our qMRI methods to study gastric emptying of liquid oral preoperative metabolic preconditioning regimens measured in healthy adults with the global healthcare company *Fresenius Kabi* **[6, I; 2009]**. Results of this study were used as evidence in the ESPEN preoperative fasting guidelines **[b, page 629; 2017].**

c) In 2015 with *Fresenius Medical Care*, we performed ground-breaking first-in-human intradialytic MRI **[c]** to examine the acute effects of haemodialysis treaments on cardiac blood flow (Cardiac MRI in Dialysis (CAMRID), Clinical Trial NCT02494843) **[13, VII]**. In 2018 this was followed by a study of haemodialysis on multiorgan blood flow (HD-REMODEL: HaemoDialysis interventions to REduce Multi-Organ Dysfunction and Effect on quality of Life Assessed by MRI Scanning, Clinical Trial NCT03280901) **[VIII]**. *Fresenius Medical Care* state '*quantitative MRI techniques developed at Nottingham have provided us with unprecedented understanding on how dialysis acutely affects organ function, influencing our dialysis treatments'* **[c]**.

d) For the last 40 years, the pharmaceutical industry has inferred critical information on the behaviour of drug preparations in the gut from bench measurements that have little relevance *in vivo* (e.g. dissolution in 900 mL of water under a vortex). The rate of dissolution is highly dependent on the volume and distribution of water in the gut, and so in 2014, we measured the water pocket volumes within the gut following ingestion of a 240 mL water drink (standard recommended by the US Food and Drug Administration (FDA) for testing solid oral dosage forms) **[2]**. This generated the "*Mudie model*" that is now a component of *Simulations Plus* software *GastroPlus* **[d]**. This has provided the pharmaceutical industry with the first pharmacokinetic simulation software based on actual *in vivo* measurements.

e) With *Procter & Gamble (P&G)* **[9, IV; 2014]** we used qMRI methods to show that a standard 100 µg dose of oxymetazoline Sinex spray maintained the volume of open airway in the nasal sinuses for 12 hours. *P&G* went on to use our MRI data to inform computational fluid dynamics simulations of airflow through the sinuses aimed at understanding the impact of the changes in sinus volume on airway resistance. On the basis of this work *P&G* were able to generate new licences and modify existing licences across the world, demonstrating 12 hours of duration of action, compared to previous claims of only 8 hours **[e]**. *P&G* state *'this was successful in convincing the regulatory authorities across Europe to make a change to the licensed duration of action for Vicks Sinex Soother/Aloe nasal spray. This result has had a big impact to our Vicks Sinex business in Europe*' **[e]**.

2) Scientific assessment of health benefits for the food industry and regulators

As part of a Framework Agreement with *Unilever* to develop functional foods, we used our GI methods to perform studies of the fate of fat, and the production of foam within the stomach to explore the control of satiety with Slim-Fast **[3]**. Unilever states that '*the novel insights on the gastrointestinal behaviour of aerated drinks provided by MRI by measuring*

separate volumes of foam, liquid, and air layers in the stomach has greatly improved our understanding of foam stability' **[f, II]**. In 2018, we conducted a study with *Zespri International Limited* **[4, III]**, the world's largest marketer of kiwifrui, using our qMRI methods to show that kiwifruit increases water retention in the small bowel and ascending colon, and total colonic volume. These results have '*boosted Zespri's global health marketing and supported gut health marketing in their current online campaign*' https://www.zespri.com/en-NZ/digestive-health. Our work was also '*one of the key studies that was used as evidence for Zespri's bid for a European Food Safety Authority (EFSA) health claim on laxation'* and led to an '*overall increase in brand value'* **[g]**.

3) Development of imaging biomarkers for clinical impact in healthcare

a) Building on Chaddock *et al.* 2014 **[7],** we developed a new medical device, MR transit markers TransiCap™, on which we hold patents (EP 3166488 A1, WO 2016005731 A1) **[h]**. TransiCap™ provides a new method to assess GI transit in the paediatric and adult population, providing an alternative to ionising radiation X-ray and radiopaque devices currently in use worldwide. We have worked with *JEB Technologies Ltd*, a UK-based precision engineering company expert in the design, development, assembly and manufacture of medical products, to develop TransiCap™ under GBP1.8M NIHR i4i grants **[i-ii]**. *JEB Technologies* state **[j]:** '*Since 2016, we have worked with your group on the manufacturing, CE marking and commercialisation of TransiCap™'. JEB has invested over and above £350,000 of our own money into the development. Working closely with the clinical teams, and utilising their core skills, we have been able to further enhance the product which has enabled us to shorten the development time. [..] it has enabled our project dedicated engineering and regulatory teams to fully understand clinical unmet needs, and patient benefits this device provides.'* We performed the first-in-child study **[9]** and a multicentre paediatric clinical trial MAGIC2 (Clinical Trial ISRCTN42273449) **[iii]** is underway to assess the efficacy of TransiCap™ in determining whole gut transit time, and to inform treatment selection in paediatric constipation.

b) Our work has strongly influenced *Motilent*, a technology company focused on delivering innovative analysis services for quantitative investigation of the gut **[k]**. *Motilent* has CE Marked its core technology GIQuant® which provides a clinically validated, objective disease-activity score for Crohn's disease of the small bowel based on intestinal motility. The SPMIG's impact on the company is outlined by their founder, *Motilent* CEO who writes **[k]**: '*The UoN GI imaging team and Motilent jointly pioneered a method to quantify colonic motility…. We now offer these measures in our STMM* (*Spatio-Temporal Motility MR) package, used in conjunction with the outputs from GIQuant*. *Our collaboration with the UoN GI imaging team, has brought greater attention to our respiratory motion (RespCorrect) technology.'* The benefit of such technology is seen in diseases like Crohn's where intestinal motility (previously assesed invasively) is an early biomarker of treatment response to drugs. We are currently working on NIHR, MRC **[iii-v]** and Innovate UK grants (GBP3M) with *Motilent* as commercial lead.

5. Sources to corroborate the impact that has occurred / is occurring to date

[a] NICE guidelines on 'Intravenous fluid therapy: Intravenous fluid therapy in adults in hospital', published 10 December 2013, and European guidelines on perioperative care.
[b] ESPEN guideline: Clinical nutrition in surgery, Clinical Nutrition 36 (2017). DOI: 10.1016/j.clnu.2017.02.013.
[c] Letter of support from Vice President Operations & Strategy, Fresenius Medical Care.
[d] Details on use of the "Mudie Model" in GastroPlus software, FDA workshop May 2016 https://www.fda.gov/downloads/drugs/newsevents/ucm503765.pdf.
[e] Letter of support Global Medical & Technical Affairs Cough & Cold Leader, Proctor & Gamble Personal Healthcare International.
[f] Letter of support from Technology Director, Unilever.
[g] Letter of support from Leader, Zespri International Ltd.
[h] MR transit markers TransiCap™ patents (EP 3166488 A1, WO 2016005731 A1).
[j] Letter of support from Head of Medical Devices, JEB Technologies.
[k] Letter of support from Chief Executive Officer, Motilent.