Institution: Queen Mary University of London

Unit of Assessment: A1 (Clinical Medicine)

Title of case study: Development and validation of innovative colorectal surgery procedures

1. Summary of the impact

Professor Norman Williams and colleagues, based at Queen Mary, developed innovative surgical procedures for patients with anorectal diseases to preserve function, reduce morbidity, eliminate the need for a permanent stoma and reduce its complications. They tested these in clinical trials and showed them to be effective and improve quality of life. The APPEAR procedure (designed to preserve continence in patients who would otherwise require a permanent stoma) is now used internationally and electrically stimulated gracilis muscle (ESGN) is well established as a treatment for end-stage faecal incontinence (FI). The team has harnessed the science of neuromodulation to provide minimally invasive methods of treating FI and developed robust processes for technological development, training and dissemination. Two patents have been filed for innovative surgical instruments and these have been developed commercially.

2. Underpinning research

The research described below took place at Queen Mary between 1993 and 2013, led by Professor Norman Williams who is currently President of the Royal College of Surgeons.

Anorectal disease is common, burdensome, and may produce complications that are costly to manage. Traditional treatments included mutilating surgery with significant physical and psychological side effects. Incorporation of new technologies and rigorous research methods have recently produced a range of promising new treatments:

2a: Sphincter Reconstruction and Neuromodulation. Before ESGN was shown to be viable clinically, it was necessary to demonstrate that the fast twitch gracilis muscle could be converted to slow twitch muscle capable of functioning as a sphincter. Studies in animals and man showed that physiological and biochemical properties of striated muscle could be modified by specific stimulation parameters [1]. Having shown in man that ESGN was a viable anal sphincter replacement, its use was extended for Total Anorectal Reconstruction in patients with anorectal agenesis or previous complete anorectal excision [Williams 1993-; 3 MD Research Fellows (RFs) 1995-1998]. Despite the evolution of sacral nerve stimulation (SNS) over a 10-year period, there had been almost no robust controlled evaluations of this therapy alone or against newer, less invasive neuromodulatory therapies, and its mechanism of action was yet to be established. Studies of the effects of SNS on rectal sensory function [2] and cortical processing thereof provided a rationale for use in patients with abnormal rectal sensation with a GB / Ireland multicentre trial to optimise electrode insertion technique based on cortical responses. Four further national multicentre trials (three NIHR / HTA) are in progress to assess the impact of less invasive techniques e.g. Percutaneous Tibial Nerve Stimulation (PTNS) in patients with FI or RED [Knowles 2009-; Carrington (RF) 2009-12; Thin (RF) 2010-13; Horrocks (RF) 2011-13].

2b: Anal Fistula Eradication. The development of the 'snug seton' method which allows a slow (over months) controlled division of enclosed sphincter muscle to effect fistulotomy has resulted in published acceptable continence preservation. The use of biomaterials in anal fistula management has evolved by exploration of host-xenograft interactions between man and acellular porcine dermal cross-linked collagen. Pilot studies of the use of collagen, either as a solid implant or as a suspension held within fibrin glue, as a definitive treatment yielded good success rates with no functional compromise as assessed clinically and manometrically, and at long follow-up [Lunniss PJ (SenLect) 1997-. Hammond TM MD Res 2000-2002].

2c: Rectal Augmentation. The use of small intestine to increase rectal capacity (Rectal Augmentation) [3] resulted from studies demonstrating that patients with rectal hypersensitivity and FI exhibited reduced rectal compliance, low rectal volumes and high pressure propagating rectal contractions on ambulatory motility studies (Williams, Scott SM Physiologist 1990- , Lunniss PJ Senior Lecturer 1995-2011, Chan CLH RF 2003-6). Collaboration with the Peripheral Nerve Unit at Imperial (Prof P Anand) showed that rectal hypersensitivity was related to neuronal sprouting and an increase in TRPV1 receptors [4].

2d: Vertical Reduction Rectoplasty and Colonic Conduit: Physiological investigations showed that patients with megarectum and rectal hyposensitivity may have both afferent neuropathy and increased compliance (laxity of the rectal wall). Vertical Reduction Rectoplasty was devised to correct the specific physiological abnormalities in the second group [Gladman MA PhD thesis 2002-5]. Colonic conduit was developed as an antegrade enema solution in adults with severe RED without their native appendix [5].

2e: The APPEAR Procedure: This technique, designed to excise the distal part of the anorectum and preserve continence, was developed following study of the physiology of the anorectal reflexes responsible for continence and appreciation that receptors responsible were sited in the pelvic floor musculature [6]. Physiological and imaging studies before and after APPEAR demonstrate that this is an effective technique that should reduce the present permanent stoma rate significantly [Murphy J & El-Gendy K (RFs) 2008-10, Bryant CH (RF) 2010].

2f: Prevention of Parastomal Herniation. A collagen implant was investigated to examine its interaction with human tissue and determine if reinforcement of the stoma trephine could reduce incidence of parastomal hernia. Results showed the approach to be feasible The pilot study provided vital information on host/implant interaction that assisted in modifying the material for other clinical uses. Further studies investigated whether a stapling technique (SMART) could be combined with the collagen implantation to simultaneously create the trephine and reinforcement. These studies have now led to a multicentre international trial [Hotouras A (RF) 2010- , Thaha M (Clinical Fellow) 2009-11].

3. References to the research

1. George BD, Patel J, Watkins ES, **Williams NS**, Swash M. Physiological and histochemical adaptation of the electrically stimulated gracilis muscle to neoanal sphincter function. *British Journal of Surgery* 1993; 80:1342-46 (Winner, Moynihan Prize Association of Surgeons 1993)
2. **Knowles CH**, Thin N, Gill K, Bhan C, Grimmer K, Lunniss PJ, **Williams NS**, Scott M. Prospective randomized double-blind study of sacral nerve stimulation in patients with rectal evacuatory dysfunction and rectal hyposensitivity. *Annals of Surgery* 2012; 255: 643-9.
3. Murphy J, Chan CLH, Vasudevan SP, Scott SM, Lunniss PJ, **Williams NS**. Rectal Augmentation: Short and mid term evaluation of a novel procedure for severe faecal urgency and incontinence. *Annals of Surgery* 2008; 247: 421-427.
4. Chan CLH, **Facer P**, **Davis JB**, **Smith GD**, **Egerton J**, **Bountra C**, **Williams NS**, Anand P. Sensory fibres expressing capsaicin receptor TRPV1 in patients with rectal hypersensitivity and faecal urgency. *Lancet* 2003; 361: 385-391.
5. **Williams NS**, Hughes SF, Stuchfield B. Continent colonic conduit for rectal evacuation in severe constipation. *Lancet* 1994; 343: 1321-1324.
6. **Williams NS**, Murphy J, **Knowles CH**. Anterior perineal plane for ultra-low anterior resection of the rectum (the APPEAR technique): a prospective clinical trial of a new procedure. *Annals of Surgery* 2008; 24:750-758.

4. Details of the impact

4a: Sphincter reconstruction and neuromodulation: ESGN, SNS and PTNS. The development of an ESGN to replace an absent or severely damaged anal sphincter has allowed many patients who were destined to life with a permanent stoma to avoid this fate. The innovator of ESGN (Prof Williams from Queen Mary) won the Nessim Habif Prize from University of Geneva in 1995 and the Galen Medal of the Worshipful Company of Apothecaries in 2003. National Specialist Commissioning Advisory Group (NSCAG) funding in 1997 enabled the establishment of the Colorectal Development Unit (CDU) for trialling new procedures. ESGN was approved by NICE in 2003 [7] and reviewed by Health Technology Assessment NHS R&D HTA programme in 2005 [8]. Clinical Commissioning Groups receive funding if patients are referred for ESGN. Over 100 procedures had been performed in UK in 2005 [8] with many more since and the procedure is conducted in other European centres and Southeast Asia [9;10].

This advanced and complex procedure was never intended as first-line therapy for uncomplicated FI but has transformed the lives of the most severely affected individuals (e.g. when the sphincter

is entirely absent or has been severely traumatised) for whom no effective treatment was previously available. The lessons learnt in the development of ESGN paved the way (conceptually and technically) for the development of sacral nerve stimulation (SNS), which is now the mainstay of neuromodulatory therapy for bowel disease internationally (Medtronics sales of $1 billion to 2012 for SNS [11]: NICE guidelines 2007 and 2011 [12]). The trial of SNS in patients with RED (see above) is changing the paradigm of patient selection for this procedure [1]. The uptake of PTNS by NHS pelvic floor services has spread nationally (UK) as a result with a recent NICE guideline [13] and 7 recently reported case series.

4b: Anal fistula procedures. The snug seton method is now a standard technique for certain fistulas, adopted worldwide, and described in the most popular UK postgraduate textbook of coloproctology [14] and is part of the Great Britain and Ireland guidelines [15]. A multicentre European trial (the first of its type in fistula surgery) assessing the efficacy of collagen paste is testament to the enthusiasm with which it is being greeted by the surgical community [16].

4c: Rectal augmentation to improve FI in patients with rectal hypersensitivity. This procedure is used in extreme cases and has provided important data that has helped elucidate the cause of rectal hypersensitivity in faecal urgency and visceral pain. Drug development has followed this observation and allied observations in other viscera particularly in respect to TRPV1 antagonists by GSK [17].

4d Vertical reduction rectoplasty (VRR) and colonic conduit for rectal evacuation disorders (RED). Patients with RED represent the majority of those investigated for chronic constipation. Our research, utilising new investigative tools such as ambulatory manometry, rectal barostat compliance measurements and rectal sensitivity tests has shown that we can identify a certain subgroup who can benefit from VRR an innovative procedure we have designed. These procedures are now included in textbooks [18] with recent resurgence especially toward the use of anterograde continence procedures.

4e: The APPEAR (Anterior Perineal PlanE for ultra-low Anterior Resection). APPEAR retains gastrointestinal continuity and preserves acceptable continence in patients who would otherwise require a permanent stoma. In Europe the total number of stomas constructed each year is 160,000 with an annual cost to the NHS (appliances etc) of £250 million. The first paper in 2008 having demonstrated feasibility, a multicentre trial commenced in 2009 with uptake to date in UK, Germany, China, Iran, Indonesia and South America [19]. This new procedure has reduced the need for permanent stoma in two thirds of patients. Results have been replicated in the other centres cited. Externally quantified economic benefits of stoma prevention can be calculated as £50,000 based on 2 QALYs and £12,000 p.a. in avoided stoma management costs [20]. The innovative stapler design and grasper designed and patented for the APPEAR was awarded the Worshipful Company of Cutlers' Surgical Prize 2011 [21]. The IPR (held by the inventor NS Williams and Queen Mary) has been commercialised internationally (patents WO2012032302 and WO2012032303) [22].

4f: Procedures designed to prevent parastomal hernias. Parastomal hernias are a major problem for patients who undergo stoma formation and affect some 50% of all ostomates over 10 years, of whom 1/3 require further, often unsuccessful surgery. The new technique SMART (Stapled Mesh Stoma Reinforcement Technique) is now the subject of a randomised, multicentre, international trial (commenced 2011). The stapling equipment that enables SMART also won the Cutlers' Surgical Prize for 2011 [21] and is part of a collaborative commercial venture with Frankenman International (Queen Mary receives royalties on the product) [23].

4g: Process development. After a national competition, Williams' group were designated as one of only two pilot NIHR Healthcare Technology Cooperatives (HTCs) in 2007. The remit was to facilitate interactions between healthcare and industry to develop technology for patient benefit in the field of bowel disorders. The initial funding was renewed for a further 3 years in 2009 (circa £900,000) by a programme board (of TSB and NIHR). The HTC was favourably reviewed by RAND [20] and had leveraged £1.6 million in further funding. The team was invited to bid for more funding as part of a policy to extend the HTC concept and was successful in being awarded a grant of £800K (2012-14) after open competition.

Among the achievements of the HTC (now called Enteric) has been the development of a de novo specialty specific network of over 20 colorectal surgical centres through which national multicentre trials are already underway e.g. HTA-funded CONFIDeNT study of PTNS [24]. Furthermore the group has raised charitable income (circa £3million) including a Wolfson Foundation Grant to develop a National Centre for Bowel Research and Surgical Innovation that opened in March 2012.

5. Sources to corroborate the impact

7. NICE Guideline. Stimulated Graciloplasty for Faecal Incontinence (IPG 159) www.nice.org.uk/nicemedia/live/11024/30589/30589.pdf 2003 (still current).
8. Tillin T, Chambers M, Feldman R. Outcomes of electrically stimulated gracilis neosphincter surgery. *Health Technology Assessment* 2005; Vol 9 No 28.
9. Contact to endorse SNS: a professor who pioneered SNS for faecal incontinence and can ratify the importance of this expansion of the technique.
10. Rosetrees Prize for Surgical Research awarded to Emma Carrington 2011 www.rcseng.ac.uk.
11. *Transforming for Growth: Innovating for Life*. Medtronics Annual Report 2012. http://www.medtronic.com/wcm/groups/mdtcom_sg/@mdt/@corp/documents/documents/ar12_annual_report_final.pdf
12. NICE Guideline. Sacral Nerve Stimulation for Faecal Incontinence (IPG99) www.nice.org.uk/nicemedia/live/11079/30919/30919.pdf November 2004 (still current).
13. NICE Guideline. Percutaneous Tibial Nerve Stimulation for Faecal Incontinence. (IPG 395). www.nice.org.uk/nicemedia/live/13159/54562/54562.doc May 2011.
14. Textbook & Guidelines: A Companion to Specialist Surgical Practice. Colorectal Surgery. 4th. Edn 2009. WB Saunders, London, Chapter 14, p 223 – 242.
15. The treatment of anal fistula: ACPGBI Position Statement. Colorectal Disease 2007; 9 (Supplement 4): 18 – 50.
16. Study protocol. A Prospective, Multi-center, Observational Study of the Use of Permacol™ Collagen Paste to Treat Anorectal Fistulas. NCT01624350. http://clinicaltrials.gov/show/NCT01624350
17. Holzer P. Transient receptor potential (TRP) channels as drug targets for diseases of the digestive system. *Pharmacological Therapeutics* 2011; 131: 142-70.
18. O'ConnellPR, Madoff RD, Solomon M. *Rob & Smith's Operative Surgery of the Colon, Rectum and Anus*. Hodder Arnold; 6th Revised edition: 2012.
19. Williams NS, Murphy J, Knowles CH. Anterior perineal plane for ultra-low anterior resection of the rectum (the APPEAR technique): a prospective clinical trial of a new procedure. *Annals of Surgery* 2008; 24: 750-758.
20. Kryl D, Marjanovic S, Chonaill SN, Ridsdale H, Yaqub O. *Healthcare Technology Co-operatives: Filling a niche in the English R&D landscape*. Prepared for the Department of Health (England). RAND Corporation 2011. www.rand.org/pubs/technical_reports/TR932.html
21. Worshipful Company of Cutlers' Surgical Prize 2011 www.cutlerslondon.co.uk
22. Published patents:

    a) Williams, N.S and Weng, Z. 'Method and Apparatus for Forming Stoma Trephines and Anastomoses' WO2012032302, Filed by Queen Mary and Frankenman International Ltd, 15.03.2012.

    b) Williams, N.S and Weng, Z. 'Forceps Comprising a Trocar Tip' WO2012032303, Filed by Queen Mary and Frankenman International Ltd, 15.03.2012
23. Contact to endorse collaboration with Frankenman International: Director of R&D at Frankenman International Limited.
24. Enteric: The Bowel Function Healthcare Technology Co-operative. www.bowelfunctionhtc.org.uk