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FEATURE

VAGINAL MESH IMPLANTS

How mesh became a four letter word

Jonathan Gornall charts the rapid rise and precipitous fall of vaginal mesh—a story that offers lessons for the entire medical community, and for manufacturers and regulators

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A simple pyramid shaped graph derived from Hospital Episode Statistics for England over the past two decades tells the story—or at least part of the story—of how mesh became a four letter word.

When it was introduced in 1998 as a novel surgical treatment for stress urinary incontinence, the polypropylene mesh sling was hailed as a quick and easy remedy for women and eagerly adopted by surgeons. Twenty years later, amid claims that it has left many thousands of women around the world irreversibly harmed, mesh is at the centre of a storm of protest that has launched tens of thousands of compensation claims, divided the medical profession, exposed major flaws in regulatory procedures, and raised serious questions about the financial relations between clinicians and researchers and the manufacturers of devices that outraged campaigners say are not fit for purpose.

The story is hair raising, offering lessons for the entire medical community, manufacturers, and regulators.

In 1998-99 just 214 women in England had treatment for stress urinary incontinence, a common condition typically triggered by childbirth or the menopause, with an innovative and minimally invasive technique known as the tension-free vaginal tape (TVT) procedure. But the following year there was an explosion in the use of the procedure and a closely related variant using transobturator tape (TOT).[1]

By 2001 the TVT procedure had already become "the most performed operation for stress incontinence in the UK,"[2] and by 2009 the annual number of operations using polypropylene mesh tape had climbed to an all time high of 11 365 in England.[3] Over the same period, use of the previous standard treatment for the condition, colposuspension, a major abdominal procedure, all but ceased, falling from 3719 procedures in 2000-01 to just 276 by 2008-09. In 2016-17, only 205 were carried out.

Meanwhile, the overall number of surgical procedures for stress incontinence more than doubled, from 6687 in 2000-01 to 13 201 in 2008-09.[3] As a health technology assessment in 2003 predicted, this trend meant that every year thousands of women who previously would not have had surgery were being offered the new, easier, and apparently less disruptive treatments by surgeons new to the techniques.[4] By 2014, 29 different products had appeared on the market, and between 2005 and 2013 over 170 000 devices were sold in the UK, and more than 3.6 million worldwide.[5]

Mesh's subsequent fall from grace was almost as precipitous as its rise. From the peak of 11 365 operations in 2008-09, by 2016-17 the number of TVT and TOT procedures had fallen to just 6227.

Shortly after mesh tape was introduced for stress urinary incontinence, mesh sheets were also adopted to treat pelvic organ prolapse in women, though these procedures were never carried out on the same scale. In 2007-08 there were 1481 mesh procedures in England for pelvic prolapse; by 2016-2017 there were just 546. However, as would become clear, the complication rates for the prolapse procedures were much higher.[6]

Unmet need

Stress urinary incontinence is caused by a weakening of the ligaments (hypermobility) or muscles (sphincter deficiency) of the urethra and affects up to a third of women over the age of 40.[7] Until 1998 the standard surgical treatment was colposuspension, a major abdominal procedure in which vaginal tissue around the urethra is raised and held in an elevated position by sutures attached to ligaments at the back of the pubic bone. At that time colposuspension involved an average of seven days in hospital and a long recovery period—a daunting prospect for patients and a costly one for NHS trusts. It was a prime target for replacement.

"Not only is colposuspension major surgery, it also requires more resources," says Cathryn Glazener of the University of Aberdeen's Health Services Research Unit, who has published extensively on both pelvic prolapse and stress incontinence. "So only women who had really bad incontinence were deemed suitable for colposuspension. For anyone who just leaked a little bit they thought, well, you just have to put up with it, you're not bad enough to take the risk of having more major surgery."

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By contrast, the arrival of mesh procedures, apparently just as successful as colposuspension but done under local anaesthetic in under 30 minutes, seemed like a cost effective godsend to patients, surgeons, and their hospitals.

A narrow strip of mesh tape is inserted through the vagina and positioned as a sling under the urethra, with the two ends of the tape passed upwards and threaded through two incisions in the abdomen. In the variant TOT, the ends of the tape pass through small incisions in each groin.[8] As TVT's name suggests, the tape is designed to remain tension-free, allowing normal functioning of the bladder, until it is tightened by sudden muscle contraction and brings pressure to bear on the urethra, preventing stress leakage.

Even though, in 2003, each TVT kit cost £425 (€500; $590) plus VAT,[9] the economic advantages seemed obvious. In 2000-01, just before use of TVT exploded, the 3719 colposuspensions carried out in England and Wales cost the NHS a total of 26 174 bed days.[3] By 2008-09, when the number of day case mesh procedures was at its height, the 276 colposuspensions carried out accounted for only 1200 bed days.[3]

Then, as reports of serious complications began to emerge and medical negligence lawyers started to circle, the mesh bubble burst.

What went wrong?

Exactly what happened depends on who you ask. Anti-mesh campaigners insist that all mesh devices, whether for incontinence or prolapse, are not fit for purpose. They want them scrapped and compare the mesh "scandal" to the thalidomide disaster. Regulators and many surgeons and their professional bodies continue to insist that mid-urethral slings remain the best treatment available for most women with stress urinary incontinence and that mesh still has an invaluable role in carefully selected women with prolapse.

Either way, nobody involved with the mesh revolution emerges covered in glory—not the companies who aggressively hustled the products into widespread use, not the regulators who aided and abetted them on the flimsiest of evidence, and not the medical profession, which failed to ensure surgeons were properly trained or that patients were carefully selected and properly informed of the risks and, perhaps most importantly, failed to set up comprehensive registries for the new procedures that might have identified unforeseen complications far sooner.

The story also exposes the extent to which individual surgeons, researchers, and professional bodies are reliant on device manufacturers for financial support, creating a potential for bias and even a public perception of corruption that undermines the medical profession's ability to argue the evidential case for mesh convincingly. In the process, it exposes the weakness of the most recent attempt by the NHS to exorcise the longstanding spectre of conflicts of interest that haunts the health service and medical research.[10-12]

As it is not feasible to study absolute long term safety and performance of any implant in patient groups of sufficient size and diversity before market launch, post-marketing surveillance is vital. For this surveillance to be effective in picking up problems in a timely fashion, manufacturers, notified bodies, clinicians, patients, and regulatory authorities all have an important role,[5] but in the case of mesh this role was largely neglected.

The rapid adoption of the technology is alarming. TVT was invented by Ulf Ulmsten, a Swedish obstetrician and gynaecologist. He sold the rights to global healthcare giant Johnson and Johnson in 1997, on the back of just two studies that he and his colleagues had carried out, and the procedure was in use in the US by 1998.[13 14]

TVT gained rapid approval in the US thanks to the principle of "substantial equivalence,"[15] under which a device can be fast tracked if its makers can show it works in a similar way to a product that has already been approved. The first modern mesh product was Boston Scientific's ProteGen sling, approved for use by the FDA in 1996. Made from woven polyester treated with bovine collagen, it was recalled in January 1999 after it was found to cause high rates of erosion, infection, and pain.[16] But Johnson and Johnson's Ethicon subsidiary was still able to piggyback Ulmsten's TVT to market on the strength of ProteGen's original approval.[17]

The story of how TVT then came to be approved in England—even as a large scale Ethicon funded study comparing the new procedure with colposuspension was still enrolling patients—is disturbing.

A 2002 paper in *The BMJ* reported the results of the first randomised controlled trial of the new procedure, sponsored and funded by the mesh manufacturer Ethicon. It concluded that, "in the short term," TVT was as effective as colposuspension at curing stress incontinence. Perioperative complications were more common, but "colposuspension was associated with more postoperative complications and longer recovery."[18]

But in an extraordinarily candid exchange between the trial's investigators, published in a book the same year by the Royal College of Obstetricians and Gynaecologists (RCOG),[19] concern was expressed that approval for TVT had already been granted in the UK in the absence of any evidence of its safety and efficacy.

The discussion, at an RCOG study group convened in 2001, focused on the decision made by the Safety and Efficacy Register of New Interventional Procedures (SERNIP), a forerunner of the National Institute for Health and Care Excellence, to give TVT an A rating. David Richmond, then a consultant gynaecologist at Liverpool Women's Hospital and later president of RCOG from 2013 to 2016, is recorded in the verbatim minutes as saying these ratings "should be based on randomised control trials, and I find that quite astonishing."

Paul Hilton, consultant gynaecologist and urologist at the Royal Victoria Infirmary, Newcastle upon Tyne, and lead investigator of the UK and Ireland TVT Trial Group, whose investigation was still ongoing, agreed. It was "highly regrettable," he said, that TVT had been A rated "on the basis of no evidence at all," other than "documentation submitted by the manufacturers of the device."[20]

Another trial investigator, Paul Abrams from Bristol's Southmead Hospital, said he too had been "upset and worried" by TVT "leaping" from SERNIP category C ("Safety and efficacy not proven: should be used only as part of a primary research programme, using appropriate methodology and registered with SERNIP") to A ("Safety and efficacy established: procedure may be used"). He had written to the Department of Health to express concern that SERNIP was "an ineffective body because … it has no government backing." He had also written twice to SERNIP asking on what basis they had altered TVT's category "and they did not reply."

Hilton, now retired, told *The BMJ* that Ethicon had begun marketing TVT in the UK early in 1998, even before the trial it was sponsoring had started recruiting patients. As a result, Hilton asked the company to fund "a register of TVT procedures, so that outcomes, and especially adverse outcomes, could be

identified and quantified" but "they declined to support such a development."

A spokesperson for Johnson and Johnson said it was "not familiar" with the request to establish a registry in 1998, but insisted Ethicon had "a long history of supporting pelvic mesh tape registries and the data provided by these registries is an important part of our post-market surveillance programme."

Even as other surgeons around the country were eagerly adopting the new, untested procedure, says Hilton, "I did not carry out TVT in my own unit, other than in the trial context, until randomisation was completed and outcomes reported."

Introduction of TVT in the UK had two immediate consequences, both with long term implications. Many more women than previously had surgical treatment for stress incontinence every year, and the standard surgical treatment, colposuspension, was dropped almost overnight.

Wael Agur, a urogynaecologist who was part of the NHS England working group on transvaginal mesh and a member of the Scottish independent mesh review panel, believes the aggressive fast tracking of TVT shunted a promising evolution of colposuspension into a siding, where it has languished ever since. "Surgery for stress incontinence was at a crossroads," he says. "Colposuspension was a procedure that had evolved over decades and the next natural progression was to perform the surgery by keyhole. Several researchers were working on this and making fantastic progress, when Johnson and Johnson went in and flooded the market with TVT."

That view is reflected in the published results of the MRC funded COLPO (Colposuspension; is Laparoscopic Preferable to Open?) trial, in which 291 women with stress incontinence from six UK centres were randomised between March 1999 and February 2002 and assessed at six, 12, and 24 months. But by the time the trial was published in 2006, the number of colposuspensions had already fallen steeply and there was an air of weary recognition in the paper that laparoscopic colposuspension had been supplanted by TVT. The keyhole procedure was "not inferior to open colposuspension in terms of curing stress urinary incontinence," the authors concluded. But "since 1999, when the COLPO trial began, widespread adoption of the TVT suburethral procedure has occurred, particularly in Europe." Because of the perceived benefits, including "no significant difference in cure rate between open colposuspension and TVT," the novel procedure had "largely replaced colposuspension as the treatment of choice in the UK over the past two or three years."

A final observation by the COLPO team now seems heavy with prescience: "Initial fears about mesh erosion have not been confirmed, although longer term data on larger numbers of women will be needed to provide greater reassurance about this."[21]

Unheeded recommendations

NICE, which picked up the ball that had been dropped by SERNIP, thought so too. Like its short lived predecessor, in 2003 NICE approved TVT for the treatment of stress urinary incontinence, but did so with a raft of caveats. If all of them had been heeded, today's mesh crisis might have been largely averted.

When NICE issued its final appraisal of Ethicon's Gynecare TVT device in January 2003 it stated clearly that it was recommending the procedure as only "one of a range of surgical options for women with uncomplicated urodynamic stress incontinence in whom conservative management has failed."

Furthermore, properly selected patients should be "fully informed of the advantages and drawbacks" and the procedure should be done "only by surgeons who have received appropriate training in the technique, and who regularly carry out surgery for stress incontinence in women."

This advice reads like a checklist of the complaints made by women who have subsequently come forward to say they were harmed by mesh—that they weren't offered alternative surgical or non-invasive interventions, that they weren't warned of the dangers of TVT, and that their surgery was carried out by an inexperienced surgeon.

There were, NICE noted, few data on longer term complications, though problems that had been seen already included "erosion of the tape material into the bladder, urethra, or vagina." The available data "suggest that this occurs at a rate of about 1%," but further long term data were required.

Crucially, NICE also recommended that observational data on effectiveness and safety of the procedure should be collected over at least 10 years. Preferably, "this should be nationally co-ordinated in the form of a registry of audit data to include both the numbers of procedures carried out and measures of outcome and adverse events."[9]

Again, had that advice been adopted, either by the NHS or the various professional groups whose members were rushing to embrace mesh procedures, by 2013 a decade of data would have been available, offering crucial insights into long term complications that might have spared many more women from experiencing problems.

Later in 2003 more warning shots were fired, in a 210 page systematic review of the effectiveness of TVT carried out by researchers at the University of Aberdeen's Health Services Research Unit as part of the NHS health technology assessment programme.

"At face value," the review concluded in September 2003, TVT was almost as effective as colposuspension, no riskier in the short term, and likely to be cost effective. But these conclusions, the authors stressed, should be treated with caution, because there was "very limited information currently available about the long-term performance of TVT … in terms of both continence and unanticipated adverse effects." It was, they added, "striking" that although 230 000 women worldwide had already had the TVT procedure, only five randomised controlled trials, in just 470 patients, had been carried out.

Crucially, there should be "a surveillance system to detect longer term complications, if any, associated with the use of tape; and rigorous evaluation before extending the use of TVT to women who are currently managed non-surgically."[4]

There was, in other words, no shortage of prophetic warnings in 2003, but the mesh genie was already out of the bottle and being promoted by manufacturers. By 2002-03 over 4000 TVT and TOT operations a year were being carried out in England and no registry of procedures was in sight.

Tim Hillard, a consultant obstetrician and gynaecologist at Poole Hospital NHS Foundation Trust and clinical lead for patient safety for the RCOG, says things were moving fast. "The British Society of Urogynaecology [BSUG], which was very much in its infancy, was saying, 'Let's keep a register of these things,' but meanwhile the tape explosion had been followed by a prolapse mesh explosion."

Registry delays

At BSUG, work on setting up a registry "started in the mid-2000s but really got going in about 2007," he says. But this was nine years after the first TVT procedure had been carried out in England and four years after NICE's call for an audit. If a registry had been set up at the outset, by 2007 the best part of a decade of data on tens of thousands of procedures would have been available.

Even after the BSUG registry was set up, getting surgeons to use it was another matter. "It was voluntary," says Hillard. "Over the past 10 years the number of people using the database has increased dramatically, but if you go back to 2010 probably only about 30% were using it."

Things began to improve, he says, after NICE issued guidance on the clinical management of urinary incontinence in women in 2013 and once again emphasised that surgeons "should maintain careful audit data and submit their outcomes to national registries."[20] But this was merely an echo of the call for action NICE had made a decade earlier, when it had first granted TVT its cautious approval, and had repeated it in 2006.

In a summary of the evidence on the benefits and risks of vaginal mesh implants in 2014, the Medicines and Healthcare Products Regulatory Agency (MHRA) noted that it had attended the British Association of Urological Surgeons and RCOG conferences in 2013 and, while there had been "much discussion about the use of vaginal mesh implants, and knowledge of patient concerns … there were no indications of vaginal mesh implants being unsafe." Perhaps, the MHRA report suggested, echoing the point that NICE had been attempting to drum home since 2003, this was because there was "currently no national registry in the UK where clinicians have to input data relating to surgical procedures involving vaginal mesh implants." The BSUG database, "currently being used by 20-30% of urogynaecologists," could be adapted, but discussions on a national registry involving BSUG, BAUS, RCOG, and MHRA were still ongoing.[5]

Yet progress towards a national database for mesh procedures can be described only as glacial. In its interim report in December 2015, the NHS England mesh working group noted that "it is very difficult to ascertain the true rate of adverse incidents for [mesh] procedures [and] ideally the group would like to see the establishment of a registry to provide this as well as data on the longer term outcomes." But its only recommendation—17 years after TVT had first been approved for use in the UK—was for yet more delay. "A cost-benefit analysis should be undertaken," it suggested, "to inform discussions on whether such a registry would be viable and the scope for using and building on existing data sources."[22]

When the final report of the mesh group was delivered 19 months later, it reported only that a registries subgroup would "continue to meet to consider the best way to capture accurate data on the use of mesh and mesh complications" and would make recommendations by November 2017.[23] But it didn't. According to the NHS England website "discussions are continuing with the registry sub-group and a recommendation will now be made early in 2018."[24] It wasn't until 21 February 2018 that Jeremy Hunt, the former health secretary, announced in the House of Commons that his department would be investing £1.1m "to develop a comprehensive database for vaginal mesh to improve clinical practice and identify issues."[25]

At the same time the government announced it had accepted calls from campaigners and the All Party Parliamentary Group on Surgical Mesh Implants for a retrospective audit of vaginal mesh implants. The RCOG said that, while it supported the audit, which would amount to nothing more than an analysis of Hospital Episode Statistics, it would be of "limited value in understanding the nature of the problems women experienced." What was really needed, it said—with no apparent sense of irony, given the profession's 20 year failure to pick up and run with this particular ball—was "a mandatory prospective registry of all of these procedures."

It fell to Kath Sansom, a Cambridgeshire journalist who founded the campaign group Sling the Mesh after treatment for stress incontinence in 2015 left her in agony, to point out that "a prospective register is 20 years too late." Campaigners, she said, "would like every single woman who has ever received a mesh implant to be contacted individually so that she may give a clear idea of her outcome on a national recall basis."[26]

As predicted, when the promised audit was delivered, it proved to be nothing more than a summary of what was already publicly known through Hospital Episode Statistics and shed no light on claims that mesh was a public health disaster. Equally predictably, it was dismissed by disappointed campaigners as a "whitewash."[27]

In July 2018 the use of mesh implants to treat stress urinary incontinence was suspended in the NHS in line with an interim recommendation of the Independent Medicines and Medical Devices Safety Review[28] being led by Julia Cumberlege.[29] The BSUG condemned the temporary ban as "unnecessary" and "not based on any scientific logic or thinking."[30]

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FEATURE

VAGINAL MESH IMPLANTS

The trial that launched millions of mesh implant procedures: did money compromise the outcome?

Vaginal mesh implants are currently suspended in the NHS pending the findings of a major government review. **Jonathan Gornall** goes in search of the obstetrician who invented mesh and uncovers how the original evidence was mired in a multimillion pound deal, industry funded research, and undisclosed conflicts of interest

Jonathan Gornall *investigative journalist, Suffolk, UK*

In March 1997, Swedish obstetrician and gynaecologist Ulf Ulmsten received an offer he couldn't refuse. A year earlier Ulmsten, the head of obstetrics and gynaecology at Uppsala University Hospital, had published a paper reporting the results of a revolutionary surgical procedure to treat stress urinary incontinence in women.

The standard surgical treatment at the time was colposuspension, a procedure little changed since it was first developed in 1959, in which the neck of the bladder is lifted, compressing the urethra, and sutured to the pelvic bone. It required open abdominal surgery and involved several days in hospital and lengthy recovery. By contrast, Ulmsten's mid-urethral sling procedure, in which a narrow length of plastic mesh tape is inserted through the vagina to act as a sling, or hammock, to raise and support the urethra, could be done under local anaesthetic as an outpatient procedure.

A study of 75 women treated in Ulmsten's department at Uppsala University Hospital with what became known as the tension-free vaginal tape (TVT) procedure gave impressive results—84% (63) of the women with stress incontinence were completely cured throughout a two year follow-up period, and another 8% (5) were "significantly improved."[1] The results suggested TVT was at least as successful as colposuspension in treating stress urinary incontinence,[2] with the added benefits that patients could get back to their lives more quickly and surgeons could perform more and easier procedures at less cost to their hospitals.

Ulmsten, aware that his results might be considered, in his words, "too positive" because all 75 operations had been carried out by experienced urogynaecologists in his department, organised a larger, multicentre study to find out how easy, effective, and safe the procedure could be in "ordinary" gynaecological units.

But what few if any others knew at the time, including Ulmsten's research collaborators, was that even before this second study got under way Ulmsten had signed an agreement with Ethicon, a subsidiary of global medical giant Johnson and Johnson, that would make him a very rich man—provided the results of the second trial echoed those of the first.

Details of this shocking conflict of interest emerged in 2014, during a US product liability case brought against Ethicon and Johnson and Johnson by Linda Batiste, who claimed she had been left in severe pain by the insertion of mesh tape derived from the original TVT device, and that this transobturator tape (TOT) had been designed defectively. Batiste was awarded $1.2m in damages by a Texas jury. This was overturned on appeal in 2015 but the case led to an undisclosed settlement by Johnson and Johnson in 2016.[3]

Commercial stakes

During the trial in 2014 the jury was shown a licensing agreement signed in March 1997 between Johnson and Johnson and Medscand, the company Ulmsten had set up to exploit his invention. Ulmsten had filed a patent application in the US listing himself and colleague Jan Clarén as inventors on 25 February 1997 and assigned the patent to Medscand.[4] The following month Johnson and Johnson agreed to pay Medscand a series of payments that amounted to $1m (£770 000; €870 000) provided that the proposed second trial upheld the findings of the first. It is not clear what if anything Jan Clarén knew of the deal. Attempts were made to contact him through Invent Medic, a Swedish company with which he is involved, but he did not respond to questions or requests for an interview.

Giving evidence during the Batiste trial, Michael Margolis, an assistant clinical professor in the department of obstetrics and gynaecology at University of California, Los Angeles, said that the message to Ulmsten implicit in the deal with Johnson and Johnson was "Prove … that this procedure works and it is safe, and we'll pay you money … If you don't prove it, you don't get paid." What happened next, Margolis told the court, was "human

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nature. What do you think he is going to do?" This, he said, had been "wallet driven research."

The paper reporting the results of the follow-up study, in which 131 women in six hospitals in Sweden and Finland were fitted with the device, appeared in the *International Urogynecology Journal* in 1998.[5] The results were even better than before: 119 patients (91%) were declared cured of stress incontinence, which meant "they did not leak urine postoperatively, either objectively or subjectively," and a further nine (7%) were "significantly improved."

"Most encouraging," reported Ulmsten and his coauthors, was "the low complication rate in 'less experienced' hands." There was one bladder perforation, which was fixed during the operation, and a single case of a wound becoming infected, but both patients were among those cured of their incontinence. Ulmsten and his coauthors concluded that "TVT can be considered a safe and effective procedure."[5]

A spokesperson for Johnson and Johnson confirmed to *The BMJ* that it had paid Ulmsten $1m. She did not confirm that the payment was agreed to be conditional on the follow-up study proving successful. She also said that in 1999 the company had "paid Medscand a total of $24 525 000 to purchase all assets associated with the TVT business."

Medscand and its US arm, Medscand (USA), was sold in 2001 to another US company, Cooper Surgical, for $12m.[6] Johnson and Johnson said it accepted that its lucrative financial offer to Ulmsten had been on the table before the second trial was carried out but rejected any suggestion that this had compromised the results of that trial.

"As part of our due diligence in licensing the TVT product from Medscand, Johnson & Johnson was interested in evaluating evidence that the TVT device would be safe and effective and that Dr Ulmsten's results … could be replicated in the hands of other surgeons in other institutions," its spokesperson said. She added that none of the trial centres had received any financial support from Ethicon for conducting this study, but did not comment on the claim that Ulmsten, the lead investigator, had been promised considerable sums of money if the second trial replicated the results of the first.

Johnson and Johnson said it had been satisfied that the second trial showed that "the TVT device and the procedure to implant it held immense value to the broader medical community separate and apart from the surgical skills of its inventor." Both studies, it added, had been published in the *International Urogynecology Journal*, "one of the pre-eminent journals in this field."

The journal included an editorial comment with Ulmsten's second paper in 1998 noting that "many questions remain regarding the diagnostic criteria they used in selecting their patients, as well as the degree of testing performed postoperatively." Furthermore, additional studies were needed to confirm the results.

But Ulmsten's twin papers alone would serve as the launch pad for a procedure that, despite no knowledge of long term outcomes and the compromised nature of the evidence supporting its efficacy, was quickly nodded into play by regulatory bodies and rapidly adopted by surgeons around the world.

Unknown influence

Twenty years on from Ulmsten's controversial multicentre study, it is difficult to determine whether the outcome of the trial, which since 2000 has led to an estimated 200 000 procedures in England and Wales alone and three million around the world, was influenced by the vast amount of money that was apparently at stake for its inventor. Ulmsten, who died in 2004, can't answer that question, though his obituary in the journal that had carried the crucial 1998 paper recalled his "great personal qualities of modesty and integrity."[7]

Ulmsten's financial relations with Johnson and Johnson were not acknowledged in the paper, though declarations of conflicts of interest were not common at that time. Johnson and Johnson insists subsequent research has confirmed the authenticity of Ulmsten's trials. "In the 20 years that have passed since the study was published in 1998, hundreds of clinical studies with no connection to Dr Ulmsten or Ethicon, including over 100 randomised, controlled trials, have evaluated the clinical performance of TVT, further validating its safety and effectiveness," it said. "Scientists from around the world who have conducted and reviewed independent research on pelvic mesh agree it is an important treatment option for women [and] several medical societies comprised of physicians practising in the field of female pelvic medicine have published position statements recognising mid-urethral slings (such as TVT) as the gold standard for the treatment of stress urinary incontinence."[9 10]

It is not clear how many of Ulmsten's coauthors on the 1998 paper knew of his deal with Johnson and Johnson. Attempts to contact all but one of them were unsuccessful. But Christian Falconer, one of the coauthors, says that he had known nothing about the transfer of TVT rights from Medscand to Johnson and Johnson—"this was the domain of Ulf Ulmsten"—nor about any payments to Medscand, in which he had not been a shareholder. "To the best of my knowledge," he adds, "I have never been involved in any 'wallet driven' research."

Whatever the effect of Ulmsten's deal with Johnson and Johnson, it is now accepted that no matter how "hands off" industry backing seems to be, nor how independently investigators believe they are acting, it affects the outcome of research. A systematic review by Cochrane in 2017 analysed 75 papers and concluded that drug and device studies sponsored by industry were "more often favourable to the sponsor's products than non-industry sponsored drug and device studies, due to biases that cannot be explained by standard 'risk of bias' assessment tools."[11]

The cloud of suspicion hanging over the events of 1997 is not dissipated by the fact, revealed in evidence in various court hearings, that some of the documentation relating to the early days of Medscand and TVT, including what one lawyer described as "the core Ulmsten data," was destroyed in a fire in an independent storage facility in Lausanne, Switzerland, in September 2009.[12 13] According to testimony in 2014, only a single binder of patient data from Ulmsten's Scandinavian multicentre study survived.[14]

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FEATURE

VAGINAL MESH IMPLANTS

Vaginal mesh implants: putting the relations between UK doctors and industry in plain sight

Despite government guidance, it remains difficult to unpick industry funding of clinicians in the UK—and specialists in vaginal mesh treatment are no exception. **Jonathan Gornall** reports on the NHS surgeons, professional bodies, royal colleges, and medical conferences that benefit from corporate funding and how this financial involvement is hidden from patients

Jonathan Gornall *investigative journalist, Suffolk*

The associations of individual surgeons and professional bodies with device manufacturers have done little to assuage the concerns of anti-mesh campaigners that sections of the medical profession are biased towards the technology. They argue that conflict of interest played a part in the rapid adoption of mesh for the treatment of stress urinary incontinence and pelvic organ prolapse.

Research funding by industry is a fact of modern medical life and, despite evidence that it can create unconscious bias affecting results, not in itself evidence of any kind of corruption. But, in the absence of any UK or European equivalent to the US Physician Payments Sunshine Act,[1] which puts all relations between doctors and industry in plain sight, these (often hidden) competing interests undermine public confidence in the healthcare system.

Kath Sansom, founder of the patient group Sling the Mesh, has diligently unearthed connections between UK doctors and companies through a series of freedom of information requests and has a list of surgeons and units that have accepted industry funding in one form or another. "A lot of these individuals were on the original [guidelines] panels looking into mesh implants," she says. "A lot were flown out to America to fancy hotels to have their training in mesh implants and given research grants and sponsorship. This creates the disturbing impression that a surgeon's judgment might be clouded and that the treatment patients are getting might not be based 100% on a conviction that this is the best treatment in terms of safety and efficacy."

Most journals require that authors' conflicts of interest are clearly stated, but campaigners for more transparency say this information is a closed book to the average patient, who has no way of knowing whether their surgeon is involved with a company whose product they are proposing to implant.

On the other hand, as one clinician said on condition of anonymity, if doctors can be accused of conflicts of interest for accepting industry funding, could the same not be said of campaigners who are suing the NHS and manufacturers and hoping to be awarded large sums in compensation?

Industry funded research

The tension-free vaginal tape (TVT) procedure seems to have got off on the wrong foot because of a deal between its inventor, Ulf Ulmsten, and device manufacturer Ethicon.[2] And its reputation was not enhanced by the fact that Ethicon funded the first trial of the procedure in the UK.

The UK and Ireland TVT Trial Group's first paper, published in *The BMJ* in July 2002, found that "surgery with tension-free vaginal tape is associated with more operative complications than colposuspension, but colposuspension is associated with more postoperative complications and longer recovery." Vaginal tape, the authors concluded, "shows promise for the treatment of urodynamic stress incontinence because of minimal access and rapid recovery times." Cure rates at six months "were comparable with colposuspension."[3]

A two year follow-up paper was published in 2004 (concluding that TVT "appears to be as effective as colposuspension" for urodynamic stress incontinence), and a third paper, based on five years of follow-up of 98 patients who had had TVT and 79 who had had colposuspension, followed in 2008. It too reported no significant difference between TVT and colposuspension for the cure of incontinence and noted that "the effect of both procedures on cure of incontinence and improvement in quality of life is maintained in the long term."[4]

Industry funded doctors

Details of competing interests were recorded on all three papers. Karen Ward of Liverpool Women's Hospital's gynaecology department, who coordinated the trial, "was supported by a grant from Ethicon Ltd who also provided materials and additional support to collaborating centres" and both Ward and Paul Hilton had been "reimbursed by Ethicon Ltd for conference expenses

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where this, and related work has been presented." The 2004 paper noted that "funding for the trial was provided by Ethicon Ltd" and the acknowledgments on the papers thanked Ethicon's "monitoring staff."

Hilton, who retired as a consultant urogynaecologist three years ago, told *The BMJ* that the trial "was planned in 1997-98 and was undertaken to the highest standards of research governance at the time." In the '90s, he said, "funding for surgical research from medical research councils was virtually non-existent. Had we not had commercial funding the trial almost certainly would not have been undertaken at all.

"Readers of our papers, and the subsequent reviews that have included its outcomes, must of course be aware of the trial funding and declared interests; the credibility of the work, however, lies in the quality and transparency of the protocol and trial reports. But, would I seek commercial funding for medical research myself, two decades on? Never."

But the medical profession's financial involvement with mesh manufacturers cannot be dismissed as historical. Harder to explain to aggrieved patients is why some researchers and professional bodies accept financial support from industry while others do not.

In September 2017 a joint meeting of the European Urology Association and the European Urogynaecological Association published a consensus statement on the use of implanted materials to treat pelvic organ prolapse and stress urinary incontinence. Of the 24 coauthors of the paper, 17 declared financial relations of some sort—as consultants, speakers, researchers, etc—with a total of 34 companies. All three UK coauthors declared links with industry: two with five companies and the other with six.

Discovering the precise nature of these involvements, and their financial value, is no easy task for members of the public, despite NHS guidelines on the management of conflicts of interest that came into force in June 2017. Designed to increase transparency and bolster public confidence that health service money is being well spent, the guidelines require all NHS trusts to publish a public annual register of interests on their websites. The guidance applies to all "decision making staff," clinical or administrative, and a spokesperson for NHS England told *The BMJ* that this specifically included clinical staff who had the power to enter into contracts on behalf of their organisation or who are involved in making decisions about the commissioning of medicines and medical devices.[5]

Some trusts, however, seem to be interpreting this definition narrowly to include only non-clinical, board level executives, while others have so far failed to make registers publicly available online.

Linda Cardozo is a professor of urogynaecology and a consultant gynaecologist at King's College Hospital, London, who in addition to being a coauthor of the 2017 consensus paper is a former president of the European Urogynaecological Association. In June 2014 Cardozo was a cosignatory of a letter sent to members of the Royal College of Obstetricians and Gynaecologists after the "unexpected" decision by the Scottish government to suspend the use of all mesh for treatment of stress incontinence and pelvic organ prolapse, which, said the letter, would "cause alarm to women not only in Scotland but in the rest of the UK."[6]

According to her declaration on the 2017 consensus paper, Cardozo has received money from six drug manufacturers: "Allergan, Astellas, BMR, Pfizer, Pierre-Fabre, and Syner-Med." *The BMJ* has been able independently to establish the value of only three of those associations—from Allergan (a speaker honorarium and consultancy), Astellas (speaker honorarium, consultancy, fellowship, and travel grant), and Syner-Med (consultancy) in 2016, for a total of £20 762 (€23 000; $29 000)—but only after drilling into the transparency declarations of those companies lodged with the Association of the British Pharmaceutical Industry.[7] Even under ABPI's voluntary declaration scheme, which applies only to drug companies and not to device manufacturers, disclosure is hit and miss.

There is no indication that Cardozo has ever received support from a manufacturer of mesh products, but there is no public record of any of her financial relations on the King's College Hospital website. Indeed, contrary to NHS guidance that trusts must maintain public registers of interests on their websites, members of the public must contact the foundation trust office to view the register. If they do, they will find that it is a register of the interests only of "directors and governors."

In April a spokesperson said the trust "has a standards of business policy in place that governs staff conduct in this area," but was "in the process of updating its conflict of interest policy and the register of interests that sits alongside it." A draft policy was in circulation and a full register would be in place within weeks. It was not. On 5 October a spokesperson told *the BMJ* that the policy had not been ratified by the board until July. Guidance and information about it would "shortly be circulated to staff … and a register of interests subsequently published on the trust's website."

Cardozo declined to disclose how much money she had received from industry over the past 10 years, from which companies, and for what purposes. However, she told *The BMJ* that it was "standard practice" for companies developing new drugs or devices "to approach the leaders in the field for their advice and guidance" and, for doctors, "engaging in such a process is part of one's duty." It was not, she said, "in itself a conflict of interest but a reflection of that person's standing within the scientific and medical community." It was "only right that doctors are compensated for the time they spend advising companies and that their travel and accommodation costs are covered as well as any out-of-pocket expenses."

It was, she added, "important that any relations with industry are clearly disclosed where facilities exist to do so—eg, when speaking at conferences or sitting on official committees such as the RCOG." By ensuring that any potential conflicts of interest were disclosed and known to others, "decisions are less likely to be impaired or influenced by a secondary interest. In clinical practice it is important the doctors decide what treatment is appropriate for each patient based on the most up-to-date guidelines and evidence published in peer reviewed literature, and not on any relationship they may have developed with a pharmaceutical company or device manufacturer."

She had, she said, "often gone to companies to ask for support for trainees to present their research at local, national, and international meetings" and "requested sponsorship to put on educational meetings and run courses and to sponsor such activities at the RCOG and the Royal Society of Medicine. Thus the majority of the money that I obtain from industry is not for personal gain but for the greater good of others."

The failure of some trusts to comply with NHS guidelines on the management of conflicts of interest contributes to a lack of clarity that benefits neither patients nor doctors. The UK organiser of the 2017 consensus paper was Chris Chapple, a consultant urological surgeon at Sheffield Teaching Hospitals NHS Foundation Trust. Chapple has published and lectured extensively on the problems caused by the use of mesh and is

working with materials scientists at Sheffield University to develop a polyurethane based alternative.

On the consensus paper he declared five industry associations: "consultant, speaker, and researcher for Allergan, Astellas, Boston Scientific, Medtronic, and Recordati." The value of only one of these associations—the £10 162 he received as a speaker, consultant, and researcher from Astellas in 2016—is publicly available, again through ABPI transparency data. Medtronic and Boston Scientific are both manufacturers of mesh products, but Chapple says his involvement with Medtronic was as a member of its advisory board on sacral neuromodulation and he was "not aware they marketed a vaginal mesh product." He had "never spoken on mesh on their behalf", nor on behalf of Boston Scientific, which had given an unrestricted educational grant to support the consensus meeting between the European Urogynaecology Association and the European Association of Urology, of which Chapple is secretary general. The meeting "was not attended by the company [which] did not see the programme and only saw the report when it was published in *European Urology*."

But none of this is apparent on Sheffield Teaching Hospitals NHS Foundation Trust's website. Back in April a spokesperson said the trust was "in the process of updating its conflict of interest policy and the register of interests that sits alongside it" and a full register would be in place within weeks, but it was not. The policy was not ratified by the board until July, and this week a spokesperson said the trust was "just waiting for the electronic recording system which supports this to be finalised ... We are hoping this will be up and running very soon."

The third UK coauthor of the consensus statement was Mohamed Abdel-Fattah, a consultant urogynaecologist at Aberdeen Maternity Hospital, who declared five industry associations: "past speaker for Bard, Coloplast, AMS, Pfizer, and Astellas; research grant from Coloplast; previous chairman of the Scottish Pelvic [Floor] Network, sponsored by various industrial companies."

Royal colleges and professional groups

As Abdel-Fattah's declaration reminds us, it isn't only individual clinicians who have financial links with industry but professional groups. Although these links are often declared on their websites, they represent a source of influence that patients are unlikely to be aware of. For example, the Ethicon Foundation Fund offers travel grants to fellows and members of the Royal College of Surgeons, the Royal College of Physicians and Surgeons of Glasgow,[9] the Royal College of Surgeons of Edinburgh[10] and the Royal College of Surgeons in Ireland.[11] In its annual report for 2016-17, the Royal College of Surgeons acknowledges "funding partnerships" with 68 companies, including Ethicon, Cook Medical, and Medtronic. In that year donations and grants from all sources, including companies, foundations, individuals, charitable trusts, and endowments, amounted to £5.3m.

The Royal College of Obstetricians and Gynaecologists also offers Ethicon awards to its members. In 2016 three members received "student elective awards" and one senior consultant was given a travel award. Accounts for the year to December 2015 (the most recent that are publicly available) show a contribution of £133 402 from Ethicon.[12] On a section of its website promoting advertising, sponsorship, and exhibition opportunities to companies, the college says there are "a wide variety of ways in which the RCOG can help you connect with our global network of 16,000 Fellows and Members and the wider O&G community." Companies are invited to "portray key messages to a focused, influential audience, leaving a strong and lasting impression of your brand and organisation."[13]

Much of the concern over mesh has centred on the failure of the medical profession to set up an effective register of procedures when mesh was introduced; this could have highlighted long term adverse outcomes before they became widespread. Although the British Society of Urogynaecology (BSUG) did set up a register in the mid-2000s, the fact that this was done with industry support has raised suspicions among anti-mesh campaigners.

The issue was raised by a patient member of the NHS England mesh working group, which included a response from BSUG in its 2015 interim report. "Setting up and running a database of this sort entails significant time and costs which we as a society do not have," said BSUG. The initial costs had been met "by the acceptance of several unrestricted educational grants from a number of companies [including] a number of the companies that manufacture tapes for stress urinary incontinence and mesh for prolapse surgery." The companies "had no say in the way the database was designed or run."[14]

Industry funded conferences

There are three main annual global conferences for urologists and urogynaecologists, and each one is heavily dependent on financial support from industry.

ICS 2018, organised by UK registered charity the International Continence Society, was held in Philadelphia over three days at the end of August. On its website ICS invited industry to "be part of the largest global meeting on continence." Companies were offered the opportunity to "reach key thought leaders … researchers, and clinicians" by exhibiting, organising symposia or otherwise promoting themselves. Among the 23 companies signed up for the exhibition at the Pennsylvania Convention Centre were Medtronic, Boston Scientific, and Coloplast. Of the 3258 worldwide members of ICS, 43% are from Europe and some 112 clinicians from the UK signed up to attend ICS 2018.

The ICS is unusual among professional bodies in that the biographical details of members posted on its site include disclosures. For example,

Paul Abrams, professor of urology at the Bristol Urological Institute, is a former general secretary of the ICS. He declared on 17 February 2018 that he had the following "existing or known future financial relationships or affiliations": speaker honorariums from Pierre Fabre, Coloplast, Sun Pharma, Ferring, Astellas, and Pfizer; consultant work for Ferring, Ipsen, Pfizer, and Astellas; and trial participation with Astellas. Amounts are not given, but the ABPI website shows that in 2016 Astellas and Pfizer paid Abrams a total of £39 946 in fees for "service and consultancy."

Marcus John Drake, a urologist at the Bristol Urological Institute and a trustee of ICS, declared the following financial relations on 19 January 2018: speaker honorariums from Pfizer, Allergan, Ferring, and Astellas; consultancy work and research grants from Ferring and Astellas; and trial participation with Allergan and Astellas. ABPI data reveals Astellas paid him £47 000 in 2016 (less than the £68 897 he received from two companies the previous year) in fees for "service and consultancy."

The International Urogynecological Association, whose annual meeting took place over four days at the end of June, also relies on industry support. Industry sponsors of the meeting in Vienna included Neomedic International, which produces mesh products, and Promedon, which produces mesh products and bulking agents to treat stress incontinence, and mesh devices for pelvic organ prolapse. The two dozen or so exhibitors included Coloplast.

A spokesperson for the association declined to say how much money industry had contributed to its 2018 conference but said that typically about 20-25% of the revenue generated by such meetings came from industry, with the balance coming from "registrations, educational grants, local support, etc." Speakers are required to display slides disclosing industry links at the beginning of presentations, and IUGA publishes an online disclosure report.

The 2018 annual meeting of the European Association of Urology, billed as "Europe's largest urological event," took place in Copenhagen on 16-20 March and was attended by 10 000 urologists from over 100 countries, including the UK. The association offered "numerous benefits" for companies exhibiting at the meeting, including "targeted promotion opportunity, excellent exposure and an outstanding occasion to explore the market." It featured an exhibition with stands from more than 120 companies, including AMI and Coloplast, which make mesh products.

More than observers

The UK Pelvic Floor Society, whose members use synthetic meshes for prolapse and incontinence surgery, is supported by

Shire, Cook Medical, Medtronic, THD, and BK Medical. On its website the society "gratefully acknowledges the indispensable role that healthcare companies play in helping the society to maintain its focus on our ambitious and progressive programmes … as well as unconditional financial support through educational grants to allow for the development and maintenance of our web based database."

The minutes published on the society's website, which was paid for by industry, show that it has a close link with one mesh company. On 20 January 2015, the society's executive meeting in Bristol was attended by two Medtronic representatives—Ruth Hodgkinson, a product manager, and Nick Inman, a market development manager. According to the minutes, Hodgkinson "had worked on an industry sponsorship document for financing" the society. "The emphasis was on industry presence at our three meetings—ACP, two-day annual meeting, and scientific meeting," read the minutes. "Ruth said the real attraction for a company was sponsorship of a symposium at a meeting. Prices from 15k—etc."

The notes suggest that the industry representatives were more than mere observers of the society's business: Hodgkinson "stated that industry wishes [the society] to be a separate entity from other societies … for example, her company (Medtronic & Covidien) would wish to use different sources to fund different activities—eg annual conference funding, immersion courses, small chapter meetings etc." Two consultant colorectal surgeons—Mark Mercer-Jones, current honorary secretary of the society's executive committee, and Andrew Williams, the current chair of the society—were assigned to work on this with Hodgkinson, whose name crops up again in the minutes in a discussion about training. Again, it is Mercer-Jones and Williams who are "to discuss with Ruth formation of immersion courses in LVMR [laparoscopic ventral rectopexy]."[15]

Hodgkinson features in the minutes of a subsequent meeting in London in 2015, when it was recorded that the prospectus for attracting industry sponsorship for a forthcoming meeting in Manchester "would be worked on between Mark Mercer-Jones, Andy Williams and Ruth Hodgkinson." It was also recorded that the two surgeons had met Hodgkinson "to debrief" after running an LVMR training course at Gateshead.[16]

Not all members are comfortable with such close involvement. In an email chain sent to me, apparently in error, in April this year, one member of the Pelvic Floor Society wrote: "I have completely dissociated myself from any personal industry sponsorship now, going to the lengths of turning down a fee from [company name redacted by *The BMJ*] for talking last year. It is just not worth it." The writer added: "We have to be really careful about what is written in minutes that are publicly available."

In 2017 Mercer-Jones and Williams were two of four coauthors of a position statement by the Pelvic Floor Society issued on behalf of the Association of Coloproctology of Great Britain and Ireland on the use of mesh in ventral mesh rectopexy (VMR). The statement, issued "in light of ongoing concerns by the media and public groups surrounding the use of mesh in patients with pelvic organ prolapse (POP) and female stress urinary incontinence (SUI)," advised patients that "VMR … is the best available treatment in the UK to restore normal rectal function."

Of the four authors, three declared conflicts of interest. Charles Knowles, professor of surgery at the National Bowel Research Centre, Queen Mary University London, was "a paid consultant and speaker for Medtronic in relation to sacral neuromodulation," Williams was a "non paid consultant for Cook Medical and Medtronic in relation to pelvic floor surgery and anal fistula surgery," and Mercer-Jones was "a preceptor [instructor] for Medtronic in relation to LVMR."[17]

The subject of the consensus statement had been raised at a meeting of the society at Bristol in January 2013, along with a suggestion that device company Cook Medical was involved . "Global consensus statement on LVMR—[Mercer-Jones] will discuss with Cook in Oxford," the minutes read.[18]

Williams told *The BMJ* there was "no doubt that [the society] is reliant on industry funding. In fact, without it, it would not exist … to encourage full membership there are no fees and so we are reliant on generating our own funding [and] unfortunately this means industry involvement."

The society was, he said, "aware of the potential criticisms levelled at us for engaging with industry" but "the focus for industry financial support has changed over the past five years with companies under much stricter regulation for compliance and a real drive to support education rather than just product placement."

The recent position statement had been "very clear not to bias for any specific type of mesh" and was "a completely non-biased paper with no direction towards the companies that support us the most." The society, he added, had "striven to maintain integrity and independence, despite our reliance on industry funding. I have total confidence in saying that with regard to training, information, and the database we are completely impartial and industry has had, and will never have, any bias on our activity. We are, however, extremely grateful to our industry supporters, without whom none of the achievements of the PFS to date would have been possible."

UK trails in transparency stakes

Regardless of the perceived or actual effect of such extensive industry influence within specialist branches of the medical profession, none of this information is freely or easily available to the public in the UK. The UK trails far behind the US, where since 2013 pharmaceutical and medical device companies have had to publicly record all financial relations with physicians, which can be viewed online through the easily searchable Open Payments portal managed by the Centers for Medicare and Medicaid Services.[1]

The reporting system, legislated in the Sunshine Act, was set up after a series of reports identified extensive conflicts of interest,[19] with one study finding that over 80% of doctors in the US received gifts and 28% accepted payments from industry.[20] A linked analysis of Sunshine Act and Medicare prescribing data published in 2016 found that across the 12 specialties examined "the receipt of payments was associated with greater prescribing costs per patient, and greater proportion of branded medication prescribing," suggesting that financial links between doctors and industry influenced clinical decisions.[21]

In the UK, the recent NHS guidance on conflicts of interest notwithstanding, it is industry that is leading the way on transparency. The ABPI's voluntary Disclosure UK site went live in June 2016, but as yet there is no equivalent window on the activities of the medical device manufacturing community.

Device manufacturers are represented in the UK by the Association of British Healthcare Industries. A spokesperson told *The BMJ* that "the relationship between industry and healthcare professionals has long been an important factor in developing and delivering advancements to patient care" and that "the provision of continuing medical education, attendance

at clinical events and advisory work are all examples of where a payment to an individual or an institution may be appropriate."

But, while it was "imperative that robust mechanisms are in place to ensure transparency and scrutiny around any such payments," and the association's mandatory code of practice required that "all transactions between a company and a healthcare professional are reported to the NHS employer,"[22] it had no plans to follow the voluntary transparency lead of the ABPI. "All payments are known within the NHS and are open to managerial oversight within the organisation," said the spokesperson. In addition, NHS England's conflicts of interest guidance "also requires healthcare professionals to report such transactions, and the system does not allow for opting out." But any such declarations aren't yet generally open to public scrutiny.

Searching the US Open Payments database for details of payments by some of the leading mesh device companies shows what legislation can achieve in terms of transparency as well as the scale of corporate financial outreach to medical professionals in the US. In 2016 Ethicon made 459 "general" payments (anything not related to research) worth a total of £5.08m. Ethicon Endo-Surgery paid out $29.4m in general payments and $1.5m in research. Medtronic paid out $94.2m in 110 000 transactions and invested £5.9m in over 1000 research initiatives. Boston Scientific paid $33.5m in general payments and $15.5m in research. Individual doctors in receipt of these funds are easily identifiable.

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