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Commentary

Long-term follow-up studies in pelvic floor dysfunction: the Holy Grail or a realistic aim?

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Introduction––trends in surgery for pelvic floor dysfunction in UK

Pelvic floor dysfunction (PFD) affects over 50% of women of middle age[1] and presents a huge clinical and economic burden to health services. Over 53 000 women were admitted to hospital with a diagnosis of either urinary or faecal incontinence or pelvic organ prolapse (POP) within the NHS in England in 2005–06, and over 41 500 operations were performed for the treatment of these various domains of PFD.[2]

There have been dramatic trends in the surgical procedures undertaken in recent years; between 1997–98 and 2005–06, the annual number of operations undertaken for stress urinary incontinence (SUI) increased by 28%, despite over 90% reduction in the numbers of colposuspension and needle suspension procedures and 50% reduction in bladder neck buttress, sling and urethral bulking procedures.

The increase was entirely due to the rapid introduction of the tension-free vaginal tape (TVT) (Gynecare®; Ethicon, Somerville, NJ, USA) in 1998 and similar minimally invasive synthetic suburethral sling procedures subsequently (Figure 1).[2]

Similar trends are now emerging in prolapse surgery, perhaps as a result of the widespread marketing and uptake of mesh to augment pelvic floor support.

Although current Office of Population Censuses and Surveys (OPCS) coding does not allow accurate identification of procedures where mesh has been used, there has been a 19% increase in all prolapse surgery in the past 3 years (excluding vaginal hysterectomy, which obviously may be undertaken for a variety of indications) (Figure 1).[2]

It seems unlikely that these trends in our surgical activity represent actual changes in the patterns of PFD in the UK. They may reflect an increasing unwillingness on the part of women to accept symptoms previously looked on as part of their lot, or their increasing willingness to accept the newer less invasive procedures than previous surgical options; they may signal an increased preparedness on the part of surgeons to intervene at an earlier stage in the natural history of the disease; or they may provide yet a further example 'disease mongering' or the over-medicalisation of personal or social problems by industry.[3] If these trends are commercially driven, we should be more circumspect before accepting them; if they are genuinely patient or professionally driven, we need to ensure that both surgeons and patients are sufficiently aware of the outcomes of our surgery to allow them to make informed decisions; the longevity of treatment effects and the possibility of late adverse effects are clearly important elements of that evidence base.

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How should we define 'long term'?

The International Consultations on Incontinence (ICI) have been co-sponsored by the World Health Organization, the International Union Against Cancer, the International Continence Society (ICS), the International Committee on Urological Diseases, and la Société Internalionale d'Urologie. In its first iteration, published in 1999, the ICI suggested definitions for durations of surgical follow up: short term being up to 3 months, medium term from 3 to 12 months, and long term over 12 months.[4]

There are occasions when case reports or short-term trial follow up and the early presentation of outcomes may be not only appropriate but also indeed mandatory. If serious unexpected adverse events come to light during early experience with procedures, colleagues and patients must be made aware. Where significant differences in efficacy or safety outcomes become apparent before the end of a study, it may be ethically unacceptable to continue randomisation. There are, however, other less worthy drivers to the early presentation and publication of research. The pressures from academic institutes to encourage research productivity in their employees may be considerable. Where there is commercial involvement in the research, there may be even more profound influences over publication strategy.[5] The most recent development in stress incontinence surgery, the so-called 'single incision tape' or 'short tape' is perhaps a case in point. Although other groups may have been working on the concept at around the same time, it seems that the first iterations of such devices were implanted in human subjects in 2003 (J. Browning *et al.*, unpubl obs.). Despite very limited data being available, several similar devices have already been introduced to the market, and a number of presentations have recently been made. Eight abstracts presented to the 2007 International Urogynecological Association and ICS meetings, describing case series where one particular device had been implanted and had median follow-up periods between 4 and 18 weeks (mean 7.6 weeks).[6] One can learn little from such short-term reports other than confirmation of the feasibility of the procedure and immediate operative complications.

In an electronic literature search for studies on urinary incontinence or POP published in the past 25 years, 127 papers were identified, which included the phrase 'long term' in their title or abstract. Although the follow-up periods in these studies ranged from 1 to 14 years, the mean duration of follow up in those investigating surgical treatments was 59.5 months (SD 30.5; 95% CI 53.4–65.6), whereas the mean in drug trials was 13.1 months (SD 4.4; 95% CI 10.4–15.8) ($P < 0.0001$) (Figure 2). The small number of

epidemiological studies identified in the same search had a mean follow-up period of 136 months.

Clearly, then, there is wide variation in the understanding of individual researchers and clinicians as to the definition of 'long term'. In general, however, there seems to be consensus that the efficacy and safety of surgical interventions requires to be judged over a longer timescale than that of nonsurgical treatments. Although there are potential issues of cumulative adverse effects, drug interactions, and perhaps most importantly patient compliance that may need longer follow up, most of the important outcomes of pharmacotherapies are considered evaluable over 12 months. The general view would seem to be that in order to be considered safe and efficacious in the long-term surgical procedures require evaluation over at least 5 years.

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Why are long-term studies required?

Many surgical reviews have emphasised the paucity of information on long-term outcomes of surgery for PFD.[7–11] Guidance from the Interventional Procedures Programme of the National Institute for Health and Clinical Excellence (NICE) has commonly highlighted the lack of long-term efficacy data or poor long-term outcomes from procedures used for PFD,[12–17] and the recently published *Interventional Procedures Programme Methods Guide* gives urinary and faecal incontinence as exemplars where durable results from interventions are essential to their being considered efficacious.[18] The guide also indicates that, while for some procedures adverse events are likely to occur within a short time of the operation, for those involving the implantation of prosthetic material, as in many of the more recently introduced developments in urogynaecology, the possibility of adverse events in the long term is always relevant.[18] The NICE clinical guideline on urinary incontinence emphasises in several of its clinical and research recommendations the need to inform women of the lack of long-term outcomes data and the importance of directing future research to secure such information,[19] and every one of the currently available Cochrane systematic reviews on surgery for SUI or POP emphasises the need for longer term follow up among their research implications.[20–26]

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Definitions of cure and patient expectations from treatment

The definition of cure and surgical outcome remains problematic, and women's expectations from their surgery are even more difficult.[27] National Institutes of Health define cure of SUI as the resolution of the symptom of incontinence, the resolution of the clinical sign of stress incontinence, and the absence of new symptoms or adverse effects.[28] Recommendations regarding standards of outcome have been defined by the ICS,[29,30] the Society for Urodynamics and Female Urology,[31] the American Urological Association,[32] and the ICI.[33] All emphasise that as incontinence is a multidimensional phenomenon, the outcome of treatment should be seen within various domains. These might include: patient's observations (i.e. symptoms), quantification of symptoms (e.g. frequency/volume charting or urine loss by pad testing), the physician's observations and objective measurements (e.g. urodynamic investigations), quality-of-life measurements (e.g. using generic, condition-specific or dimension-specific questionnaires), and socio-economic evaluations (e.g. cost-effectiveness analysis). In emphasising the need for a multidimensional approach to the evaluation of continence, each of these consensus reports indicates that no single outcome measure is adequate to summarise the effects of treatment; as a result, none gives a clear statement as to the most relevant single variable or combination of variables to act as a primary outcome measure in trials of therapeutic intervention.

Clearly, such a variety of possible definitions for cure will inevitably give a range of 'cure rates' even for a single procedure in a single study; comparison between procedures and across studies becomes extremely problematic. For example, it has been shown that, using a range of subjective, objective, and combined definitions for cure as recommended by the above organisations, the cure rate in the 'UK TVT:colposuspension RCT' might lie between 6 and 81% at 6 months, even though there were no significant differences between the procedures compared for any individual definition.[27]

Patient-centred goals

A woman's perception of their urinary incontinence, their expectations for benefit, and their ultimate satisfaction with treatment have complex relationships.[34] Satisfaction with surgical treatment and improvement in symptoms and quality of life are strongly associated with a woman's expectations and preparedness for surgery; they do not necessarily correlate with objective cure of incontinence.[35,36] Clearly, expectations of women need to be realistic and preferably agreed with the surgeon preoperatively. The majority of women will in fact describe several goals from surgery for PFD: urinary or

bowel symptom relief, improvements in activity, lifestyle, or general health, enhanced self-image or relationships, and restoration of physical appearance are among the more commonly recorded.[37] Some of these patient-centred goals may take longer to achieve than others,[38] and hence, long-term follow up is crucial to ensure that goals are met and maintained.

Patient expectations for the longevity of treatment

While we are perhaps becoming more alert to our women's goals with respect to their surgical treatment, we know little or nothing about their expectations of the longevity or durability of that effect. It is clear that many women with symptoms of PFD will not look on them as being particularly bothersome or socially disabling and will not wish treatment for them;[39] many others, however, will delay seeking assessment or treatment for their symptoms, for many years.[40,41] The reasons for delay include the thought that symptoms were normal or would simply go away and shame or embarrassment; fear of needing an operation was the primary reason for delay in 15–20% of women.[40,41] It might be assumed that if women do present with symptoms of PFD, they have come to accept that these are not normal or acceptable, are bothersome or disabling, and are unlikely to resolve without treatment. While they often hope that simpler treatments will be appropriate for them, they have usually, but certainly not always, also come to accept that if this is not the case, they can accept surgery. Given the psychosocial impact that this decision will have had on them and their families, whatever their perceived goals for treatment, it is likely that they will expect any positive outcomes achieved to be long lasting.

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Difficulties of interpreting long-term studies

Given the repeated calls for long-term follow up in studies for the treatment of PFD, one might reasonably ask: 'why are there so few long-term studies of high scientific quality in this area?' There are, however, considerable logistic problems associated with undertaking such research, and given that those difficulties are often inadequately addressed, there is a common corollary of difficult interpretation of the results.

Trends in symptoms of PFD with age

Several studies have shown that the prevalence of any urinary incontinence tends to increase up to middle age, then plateaus or falls between 50 and 70 years, with a steady increase with more advanced age (Figure 3).[42] These trends appear to reflect a reduction

in complaints of SUI in those aged 50 years and older, with an increase in urge incontinence (UUI) and mixed incontinence (MUI) in women aged 60 years and older.[42] Data from the UK have shown similar results,[39] and pooled analysis also confirms the trends to be apparent globally.[43]

Most reports on the prevalence of POP have examined specific patient groups rather than the general population, and the majority are based on examination findings rather than symptoms. Few studies have adequately reported the prevalence of symptomatic POP, although those using validated questionnaires report figures between 7 and 28%.[1,44–46] A recent UK study found that 13.5% of parous women reported symptoms of prolapse 20 years after their first delivery (mean age 46 years).[1] Trends in the prevalence of prolapse with increasing age have not been reported, although a study which included repeat pelvic examination in a group of women aged 40–80 years showed that, while both progression and regression in findings was seen, the prevalence of stage 2 prolapse increased from 19% at baseline to 29% after 5 years.[47] It was also apparent in this study that most women were unaware of their prolapse and few were bothered by it, making the evaluation of symptoms more relevant than examination findings.

It is apparent that these temporal trends in the prevalence and types of PFD affecting women are important in the interpretation of long-term outcomes from treatment. While the recurrence of symptoms of SUI over time may reflect a genuine decline in effectiveness of previously applied treatment, it could arise as a result of a real deterioration in the woman's urethral function with increasing age (at least in women up to the sixth decade of life, on the basis of the trends demonstrated above). Similarly, the onset or deterioration of urge symptoms may be due to the so-called *de novo* bladder overactivity, as an adverse effect of surgery; again, however, it may be no more than the general incidence of these symptoms arising in a woman who just happens to have previously undergone stress incontinence surgery.

Perhaps, the most important issue here is that researchers and their readers bear this confounder in mind; how one deals with it in analysis or interpretation is more difficult. In very large long-term studies, one might make allowance for the age-related prevalence of SUI or UUI; in smaller studies, this is probably not feasible. For example, UUI and MUI together increase in prevalence by approximately 0.25% per year between 20 and 60 years and 0.5% per year between 60 and 80 years. Hence, in a study of women of median age of 50 years at recruitment, one might anticipate an additional 1.25 and 5.0% to report new UUI symptoms over the course of 5 and 15 years of follow up, respectively, regardless of any effect from the intervention. The 1% incidence of *de*

novo UUI in women undergoing TVT and 4% in those undergoing colposuspension at 5 years of follow up in the 'UK TVT:colposuspension RCT' may therefore be more easily assessed.[48]

The optimum time for trials of new procedures

It is self-evident that a new health technology should be safe, clinically effective, cost-effective, and socially, legally, and ethically acceptable. Several factors may influence whether, when and how evaluation of these characteristics is undertaken for new and fast-changing technologies; these have been enumerated in a Health Technology Assessment (HTA) report.[49]

- *Product champions and opinion leaders* may pioneer the introduction of new technologies on the basis of observational reports, leading to widespread diffusion before adequate evaluation; this may then place constraints on the methods of evaluation that can be subsequently effected.
- Favourable *media coverage* may lead to patient or physician demands for new, unevaluated health technologies. This may exert pressure on purchasers to adopt the technology and dissuade women from participating in comparative trials in case they are randomised to the standard treatment.
- The period during which a clinician has genuine *clinical uncertainty or equipoise* between new and existing treatments may be quite short, and this has implications for the timing of assessment, particularly in the form of randomised controlled trials (RCTs). Once clinicians come to prefer either the standard or the alternative treatment, they may consider that they have a duty to provide only that treatment which they believe to be in the best interests of their patients.
- The existence of a *learning curve* also influences the timing of assessments of new technologies. It has been suggested that assessments undertaken before clinicians have acquired sufficient skill in a new procedure will result in misleading findings on benefits and costs. The optimum time to undertake a study, however, can often only be recognised in retrospect, and when the stability of a new technology becomes obvious, clinicians may no longer be prepared to randomise.

Losses to follow up and the handling of missing data

The loss of women during follow up is perhaps the greatest practical difficulty in undertaking prospective long-term follow-up studies. Even where women have given informed and written consent to a protocol including repeated review, examination,

investigation, or questionnaire follow up, maintaining their enthusiasm over time may be problematic. This is perhaps particularly the case if they are happy with the outcome of their treatment, although where they are less satisfied women may lose confidence in those undertaking initial trial treatments and may seek further opinions at alternative clinics or hospitals. Similarly, maintaining the enthusiasm of research staff over time may present its own problems, especially if those initially involved have moved on to new posts. Adequately powered surgical trials almost inevitably require to be undertaken on a multicentre basis, and such difficulties will be greater where those involved feel less personal responsibility for the outcome. As a result patient withdrawal or losses to follow up become an increasing problem with increasing trial duration. In the recently published 5-year results of the 'UK TVT:colposuspension RCT', of 344 women initially randomised, 316 (92%) received the treatment allocated, 304 (88%) were followed up at 6 months, 245 (71%) followed up at 2 years, and 177 (51%) provided data at 5 years, with full subjective and objective outcomes available for only 121 (35%).[48] This study is of course not unique in its high attrition rate. The long-term cohort studies examined within in the recent NICE guideline on urinary incontinence found dropout rates between 2 and 76% (median 40%) in studies extending up to 17 years.[19]

The high dropout rates associated with long-term follow-up studies have an inevitable impact on the statistical power of their results and on the confidence that can be attributed to any conclusions drawn. What is perhaps more important than the ultimate sample size and statistical power is the transparency with which the missing data are managed within a study. Are attempts made to compare the women withdrawn from the study with those remaining to estimate the potential for bias? What assumptions are made about missing data? Are data assumed to be missing at random or are withdrawals assumed to be failures or cures? Is a 'last observed result carried forward' approach taken? Each of these approaches will have a different impact on calculated cure rates.[48]

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What does long-term follow up tell us that short-term studies do not?

Trends in efficacy over time

There have been many examples where initial promising results published by the inventor or early proponents of a device or procedure have not been replicated by others, or where the efficacy falls off with increased duration of follow up. This was seen

for bladder neck needle suspension procedures of the Stamey-Pereyra type, where Stamey's own publications indicated a cure in 91% of women,[50,51] and other early reports suggested cure on average in 78% of women.[52] Longer term results (albeit in case series rather than RCTs) showed cure rates of 43–68% at 4–5 years[53,54] and 20–33% at 10 years.[55,56] Unpublished results from the Leeds group showed 80% cures at 1 year (n = 186), declining to 45% at 2 years, 18% at 4 years and to only 6% at 10 years (n = 17).[57]

A cross-sectional follow-up study of colposuspension included 109 women out of 366 (30%) actually operated on in the study period;[58] it was not stated, but assumed that those followed up were an unbiased sample of those operated on. On this assumption, the subjective cure rate was reported as 94% at 3 months, but fell to 80% at 5 years and 72% at 10–20 years (mean 13.8 years); objective cure rates were comparable at the same time points.[58] The Cochrane review of colposuspension also indicates a cure rate of 70% after 5 years.[25]

A recent summary of 79 case cohort studies published on the TVT procedure indicates that efficacy is maintained at 80–90% up to 8 years, regardless of whether subjective, objective, combined, or patient-centred outcome measures were used.[19] The data from the 'UK TVT:colposuspension RCT' also point to maintained cure, with objective cure (on the basis of a negative ICS 1-hour pad test) in 85% at 6 months,[59] 80% at 2 years,[60] and 81% of women at 5 years.[48]

These are just three procedures from the many available that indicate cure rates in the 80–90% range from early or short-term studies; *the long-term outcomes were of the order of 20, 70 and 80%, respectively.* Clearly, if women have expectations of long-term improvement in their symptoms, we can only adequately inform their decisions over whether they should undergo surgery, and what procedure they wish to undergo if we have long-term comparative data available.

Late adverse effects

Although there is no generally accepted categorisation, two reviews have described complications following incontinence surgery as immediate (within 24 hours), early (24 hours to 6 weeks), and late (6 weeks onwards).[61,62] Such a categorisation would imply that all important surgical complications would be captured in 'short term' follow-up studies, although this is clearly not the case, and there are late adverse effects that can only be adequately evaluated in the long term.

Prolapse following incontinence surgery

It has long been recognised that some operations for SUI are associated with the subsequent development of POP, particularly of the uterus or vaginal vault and posterior wall.[63] Colposuspension was originally described for the treatment of prolapse with incontinence;[64] while several studies have shown it to be an effective treatment for cystocele, other series have reported that up to one-third of women require subsequent surgery for POP.[61,63,65] In a 10- to 15-year follow-up study of 127 women undergoing Burch colposuspension, 19% were found to have anatomical defects (although it not clear how many were symptomatic); of these, only 17% were apparent within the first 2 years, and over half arose over 5 years after surgery.[66]

It has not previously been possible to say whether the POP seen after colposuspension was a result of the procedure itself or simply another manifestation of the PFD that these women already had, that is women with SUI are likely to be at increased risk of developing POP, and an increased need for prolapse surgery would not be unexpected in women undergoing incontinence surgery. The report of 5-year outcomes from the 'UK TVT:colposuspension RCT' gives some further insights; there was a significant increase in women showing clinical findings or undergoing surgery for POP after colposuspension, which was not seen in those undergoing TVT.[48] Hence, it is likely that colposuspension is indeed contributory to the development of vaginal vault and posterior wall prolapse, albeit in a group of women with known PFD. The true significance of such effects of surgery is only likely to be resolved by long-term comparative trials.

Incontinence following prolapse surgery

The onset of apparent *de novo* stress incontinence following surgery for POP is well recognised and has been shown in case series in up to 30% of women.[67] While many women with POP describe some urinary symptoms, most do not report stress incontinence; despite this, between 20 and 100% (mean 55%) of women with POP have evidence of so-called 'occult stress urinary incontinence' when investigated urodynamically with their prolapse reduced. It is assumed that this group may be at particular risk of developing new symptoms of stress incontinence following repair of their prolapse. Meta-analysis on the impact of POP surgery on continence carried out within a Cochrane systematic review was limited and inconclusive, although there was evidence that the addition of TVT to endopelvic fascia plication and colposuspension to abdominal sacrocolpopexy were followed by a lower risk of women developing new postoperative SUI.[26] In a recent trial of sacrocolpopexy for the treatment of vault prolapse, in which women without symptoms of stress incontinence were randomised to

undergo or not undergo concurrent colposuspension, significantly more women in the control group experienced bothersome symptoms of stress incontinence (25 versus 6%).[68] These results were evident from an interim analysis undertaken when 50% of women had completed 3 months of follow up and, in fact, lead to the premature curtailment of recruitment. This study, while perhaps indicating a potential benefit from interim analysis and early presentation of outcomes, does belie the fact that benefits shown in this study were achieved at the expense of increased blood loss and operation time, and economic evaluation was not included in the study; it also precludes conclusion on the durability of the observed benefits.

Erosion of tapes and meshes

Undoubtedly, the greatest concern about synthetic materials implanted during surgery for SUI or POP is their potential to erode into the urinary tract and vagina. While the subjective handling of a material and its intended application may influence the surgeon's choice, more basic properties such as its chemical composition, coating, elasticity, flexural rigidity, edge bonding, and most importantly the nature of the weave and pore size influence the risk of erosion and infection. The materials used in hernia repair were classified by Amid,[69] and his classification has been adopted to describe materials used in surgery for PFD. Type I meshes are macroporous, having pore size >75 μm, and thus allow macrophages, fibroblasts, and collagen fibres to penetrate interstices; these are currently preferred for surgery for SUI[19] and for POP.[70]

The early appearance of mesh in the vagina has been attributed to failure of vaginal skin healing as distinct from true erosion *(why?),* which is usually a later phenomenon. It has also been argued that both processes may represent a spectrum of adverse host reaction of varying severity, defective wound healing starting the process, with secondary infection, and ultimately sinus-tract formation or abscess and tape rejection.[70] The report of two women with mesh erosion identified 5 years following TVT (a type I mesh) who had normal findings on examination at 4 years tends to gainsay this proposal.[48] Most series of suburethral tapes report erosion rates of less than 3%, although up to 20% has been found with one type III material.[71] Vaginal mesh erosions after abdominal sacrocolpopexies have been found in 0.5% with Prolene® (Ethicon, Somerville, NJ, USA), 3.1% with Mersilene® (Ethicon), 3.4% with GoreTex® (WL Gore & Associates, Newark, DE, USA), and 5.5% with Teflon® (E.I. du Ponte de Nemours and Company, Willmington, DE, USA).[72] Siliconised materials have also been associated with particularly high rates of erosion in both sacrocolpopexy[73] and suburethral sling procedures.[74] In addition to the above mentioned mesh properties, it is intuitive that the erosion rate associated with a surgical mesh will relate to the overall surface area and/or mass of material implanted. One might therefore anticipate even greater problems

associated with the newer more complex procedures incorporating mesh interposition with 'neoligament' extensions or 'total vaginal mesh' reconstructions. Up to 13%, erosion has been reported from a multicentre study of a 'total vaginal mesh' procedure with only 3 months of follow up.[75]

It is now clear that while many of these adverse events occur within the first year of implantation, late erosion can occur. With the apparent increased use of implanted materials in surgery for PFD, it is vital to have robust information not only of the benefit that accrues in terms of reduced recurrences but also of the rate of complications and the need for mesh trimming or removal. In the evaluation of such late complications in particular large national surgical registries such as those established in Austria[76] and Finland[77] or patient safety databases held by government bodies[78,79] may provide particularly useful information.[80]

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Conclusion

Surgical practices in urogynaecology are changing rapidly, with the increasing application of synthetic tapes to support the urethra in SUI, and meshes to replace, reinforce, induce, or consolidate endopelvic fascia in POP. ***These developments often appear to be driven by commercial interest rather than by clinical need.*** In the context of surgical treatment for PFD, existing literature suggests that 'long term' is generally considered to imply outcomes at 5 years or more. Although the RCT is looked on as the 'gold standard' of clinical research, case series or large-scale registries can provide vital information on the incidence of late and uncommon postoperative complications. Many of the recent developments have been supported at best by short-term case series, and long-term follow-up trials of high quality are few in number. *Pharmageddon?* (*sic.*) is an hypothesis,[81] recently defined by Social Audit as describing 'the prospect of a world in which medicines and medicine produce more ill-health than health, and when medical progress does more harm than good'.[82] **This is not a concept unique to pharmaceutical treatments, and we should safeguard our women against the prospect of *Impharmageddon!* by ensuring adequate evaluation of long-term outcomes of all pelvic floor surgery, most particularly those involving implanted materials.**

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Disclosure of interests

I have no current personal or nonpersonal, specific or nonspecific interests to declare. I was previously the principle investigator for a multicentre randomised comparative trial of surgery for SUI funded by *Gynecare*;[48] I have also been involved in development work on devices for use in surgery for SUI and POP funded by *GyneIdeas*.

I am currently a member of the NICE Interventional Procedures Advisory Committee and the HTA Therapeutic Procedures Panel; I previously chaired the Guideline Development Group responsible for the NICE clinical guideline on urinary incontinence.

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Contribution to authorship

This manuscript is wholly the work of the named author; no individuals fulfilling the criteria for authorship are unnamed.

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