TOPAS™ Treatment for Fecal Incontinence

PMA P140006

Sponsor Executive Summary

For the Gastroenterology-Urology Devices Panel of the Medical Devices Advisory Committee

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ASTORA Women's Health, LLC

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LIST OF ABBREVIATIONS

ADE	Adverse Device Effect
AE	Adverse Event
AEAC	Adverse Event Adjudication Committee
CI	Confidence Interval
CRADI	Colo-Rectal-Anal Subscale of the PFDI-20
CRAIQ	Colo-Rectal-Anal Subscale of the PFIQ-7
DMC	Data Monitoring Committee
FI	Fecal Incontinence
FIQoL	Fecal Incontinence Quality of Life Questionnaire
HUD	Humanitarian Use Device
ISO	International Organization for Standardization
LOCF	Last Observation Carried Forward
MCID	Minimal Clinically Important Difference
MRSA	Methicillin-resistant *Staphylococcus aureus*
NPPS	Numeric Pelvic Pain Scale
PFDI-20	Pelvic Floor Distress Inventory (Short Form)
PFIQ-7	Pelvic Floor Impact Questionnaire (Short Form)
PFR	Pelvic Floor Repair
PISQ-12	Pelvic Organ Prolapse/Urinary Incontinence Sexual Function Questionnaire (Short Form)
PMA	Pre-Market Approval
POP	Pelvic Organ Prolapse
PRO	Patient Reported Outcome
QoL	Quality of Life
SAE	Serious Adverse Event
SD	Standard Deviation
SNS	Sacral Nerve Stimulation
SSQ-8	Surgical Satisfaction Questionnaire
SUI	Stress Urinary Incontinence
UADE	Unanticipated Adverse Device Effect
US	United States

1 EXECUTIVE SUMMARY

ASTORA Women's Health, LLC (hereafter "ASTORA"; formerly American Medical Systems, Inc.) designed the TOPAS™ Treatment for Fecal Incontinence (hereafter "TOPAS system"), a mesh implant with minimally invasive delivery, to provide support to the anorectum and reduce the incidence of fecal incontinence (FI) episodes in women.

The TOPAS system is comprised of a knitted, Type 1 polypropylene monofilament mesh, which is covered by removable insertion sheaths, and two insertion needles. Implantation is through a transobturator approach via two small incisions in both the thighs and buttocks, requiring about 30 minutes for implantation and a short period for recovery. The implanted mesh is self-fixating and permanent with tissue in-growth providing additional anatomical support to the anorectum.

In a pre-market approval (PMA) study, the TOPAS system substantially reduced FI episodes 3 months after implantation with the benefit being durable through 36 months of follow-up. Patients with reduced FI episodes had sustained improvement in FI symptom severity, quality of life (QoL), and pelvic floor distress and impact. There were no cases of device migration, revision, erosion, or unanticipated adverse device effects (UADEs). The treatment efficacy and safety experience during implantation and in follow-up supports approval of the device in the United States (US).

The TOPAS PMA study affirms that the TOPAS system provides a safe and effective treatment option with a positive benefit-risk profile for patients with FI. FDA approval of the TOPAS system to treat FI would provide a needed therapeutic option that currently does not exist for women who have failed more conservative therapies such as dietary modification, pelvic floor muscle training and pharmacotherapy. The proposed indication for use is:

> *The TOPAS™ Treatment for Fecal Incontinence is intended to treat women with fecal incontinence (also referred to as accidental bowel leakage) who have failed more conservative therapies.*

1.1 UNMET MEDICAL NEED IN TREATMENT OF FECAL INCONTINENCE

Fecal incontinence (also called "accidental bowel leakage") is the involuntary loss of solid or liquid stool that causes social or hygiene problems (Bliss et al., 2013) and is a complex disease resulting from abnormality in the coordination between the anal sphincter, pelvic floor function, stool consistency, rectal compliance, and neurologic function (Paquette et al., 2015). In the general population, the prevalence is estimated to range from 0.4 to 18% (Macmillian et al., 2004). In women in the US, about 5-10% report one FI episode each month (Markland et al., 2010; Whitehead et al., 2009; Wu et al., 2014).

FI is caused by a combination of congenital, anatomic, neurologic, and functional abnormalities (Varma and Madoff, 2001). Some factors that contribute to FI include diabetes mellitus, multiple sclerosis,

inflammatory bowel disease, pregnancy and obstetric injuries, and aging. In women, FI is typically due to a weakened anal sphincter, reduced pelvic floor muscle function, disturbed rectal sensation, or decreased capacity (Bharucha et al., 2005) and is most commonly caused by birth trauma (Wang et al., 2006).

Because of profound social fear of FI, women with FI often alter their lifestyle to prevent FI accidents from occurring in public. Extensive social avoidance can lead to isolation that may have debilitating impact on self-image and QoL (Norton, 2004). Reduced work productivity, reduced days at work, increased risk for depression, and other psychiatric co-morbidities are common in patients with FI (Landefeld et al., 2008; Minor, 2004; Norton, 2004; Xu et al., 2012). Because of the significant morbidity that occurs in patients with FI, there is substantial economic impact on patients (Dunivan et al., 2010; Xu et al., 2012) and the healthcare system (Sung et al., 2007). The average annual total cost for FI was $4,110 per patient in 2010 (Xu et al., 2012). The total cost for inpatient surgical procedures to treat FI in females was an estimated $24.5 million in the US in 2003 (Sung et al., 2007).

Traditionally, the first line of treatment for FI is conservative therapy which includes changes in diet, treatment with medications, and pelvic floor muscle training. In FI patients who have failed conservative therapy, current surgical options include sphincteroplasty, sacral nerve stimulation (SNS), injection of bulking agents, radiofrequency energy delivery, and placement of an artificial bowel sphincter. When all other options have failed, fecal diversion, such as with colostomy, is generally regarded as a surgical option of last resort (Rogers et al., 2006).

InterStim® SNS and the Solesta® injectable bulking agent were both approved by the FDA in 2011 for the treatment of FI. These devices demonstrated effectiveness in studies supporting device approval, however 27% (Interstim SSED, 2011) and 43% (Solesta SSED, 2011) of patients treated in the InterStim and Solesta PMA studies, respectively, were non-responders at 12 months. Overall, about 30-50% of patients fail treatment with injectable bulking agents and SNS (Maeda et al., 2013; Thin et al., 2013). While there is evidence of effectiveness with InterStim and Solesta, these treatments can require additional follow-up, and InterStim can require complex management, surgical revision, and/or device replacement.

More recently, the FDA granted Humanitarian Use Device (HUD) approval for another FI device, the FENIX® magnetic artificial bowel sphincter (FDA News Release, Dec 2015). It is indicated for patients who have failed conservative therapies and less invasive therapy options like injectable bulking agents and SNS. Limited data (n=35) indicated effectiveness but, like Solesta and InterStim, 37% of patients were non-responders at 12 months.

Given limitations in existing device therapies, an unmet medical need remains for new, effective treatments of FI. The TOPAS system was designed based on extensive feedback from physicians who treat FI and expressed the need for additional effective device treatments that are also minimally

invasive, cost-effective, do not require on-going patient intervention, and have an acceptable risk profile and low reintervention rate. The TOPAS system meets all the aforementioned unmet medical needs. It is the only therapeutic option that anatomically provides support to the anorectum, offering clinicians and patients a treatment option that differs in potential mechanism of action from that with injectable bulking agents, SNS, radiofrequency energy delivery, or artificial bowel sphincters. Given that there is not one device option that works for all patients, TOPAS may be a successful, alternative option for women with FI.

1.2 TOPAS PMA STUDY DESIGN

The TOPAS PMA study is a prospective, multicenter, single-arm, open-label, two-stage, adaptive-design study enrolling female patients 18 years of age or older who had experienced FI symptoms for a minimum of 6 months and failed multiple conservative treatment modalities (dietary modification, pharmacological intervention, or pelvic floor muscle training). Patients who were pregnant and those who had inflammatory bowel disease, recent history of other gynecological or gastroenterological surgical repair procedures, or chronic watery diarrhea were not eligible to enroll in the clinical trial. Prior to each study visit, patients completed a 14 day bowel diary.

The primary clinical efficacy objective in the TOPAS PMA study was to determine if implantation with the TOPAS system results in a treatment response at 12 months in more than 50% of the study patients (i.e., treatment responders). Treatment responders were defined as patients who achieved at least a 50% reduction in the number of FI episodes from baseline to the 12 month post-operative visit.

Secondary effectiveness objectives included quantifying the long-term efficacy based on a reduction in the number of FI episodes and the responder rates at all follow-up time points up to 60 months; quantifying the reduction in the number of incontinence days and urge FI episodes through 60 months; and quantifying the change in patient reported outcomes (PROs) for FI symptom severity (by the Wexner Symptom Severity Score), FI QoL (by the FI Quality of Life Questionnaire [FIQoL]), pelvic floor distress and impact (by the Pelvic Floor Distress Inventory [PFDI-20] and Pelvic Floor Impact Questionnaire [PFIQ-7]), and sexual function (by the Pelvic Organ Prolapse/Urinary Incontinence Sexual Function Questionnaire [PISQ-12]) through 60 months.

At the time of study design, published data available on devices to treat FI were limited; therefore the expected treatment success rate at 12 months was unknown. This made it difficult to define the sample size. To address this issue, a two-stage adaptive design of Bauer and Köhne (1994) was selected to allow a mid-trial reassessment of sample size. Using this design, the TOPAS PMA study was conducted in two distinct and independent stages, with a different number of patients implanted in each stage. After Stage I was completed (i.e., after 80 patients had reached the 12 month time point), a pre-specified interim analysis on the primary endpoint was conducted.

The overall type 1 error was controlled at the 0.05 level using this two-stage design. A one-sided exact binomial test was used to test the hypothesis that the responder rate was greater than 50% FI episodes in each stage of the study. The interim analysis was conducted after 80 Stage I patients were implanted and completed 12 month follow-up. Based upon the findings in Stage I that no sample size adjustment was needed for Stage II, the sample size for Stage II remained at 72 (the required minimum for safety). As a result, a total of 152 patients were implanted with the TOPAS system in the study.

This Panel Pack provides 12 month follow-up data for all patients enrolled in the TOPAS PMA study as well as follow-up data from patients who had reached 24 months (N=132; 128 with bowel diary data), 36 months (N=115; 108 with bowel diary data), 48 months (N=32; 32 with bowel diary data) and 60 months (N=3; 3 with bowel diary data) as of the data cutoff date of 17 August 2015.

1.3 EFFECTIVENESS AND SAFETY IN THE TOPAS PMA STUDY

1.3.1 Effectiveness Results

The median number of FI episodes in a 14 day period was 18 (range 4 - 81) at baseline for all implanted patients and decreased by more than 50% at the first and subsequent follow-up visits (median = 5 FI episodes at months 3, 6, and 12). A similar reduction in median FI episodes was observed among Stage I patients (from 17 to 6, 4, and 6 at months 3, 6, and 12) and Stage II patients (from 19 to 5, 5, and 4 at months 3, 6, and 12). At the 12 month follow-up visit, 69.1% of all implanted patients were responders (defined as having at least a 50% decrease in FI episodes from baseline to 12 months post-operatively; Stage I: 65%, $p=0.0048$ and Stage II: 73.6%, $p<0.0001$).

The success rate found in the two independent stages demonstrated that the efficacy results are repeatable. In addition, in the absence of a control group, the sham control group in the Solesta PMA study provides context for these findings. The treatment response rate with the TOPAS system exceeded by two-fold the treatment response rate reported at 6 months with sham control (65.1% for TOPAS versus 32.1% for the Solesta Sham Group) in a very similar patient population that was evaluated using the same primary endpoint (Solesta SSED, 2011).

For the secondary effectiveness endpoint of long-term efficacy, the median number of FI episodes remained decreased at 12, 24, and 36 months. The responder rate at 36 months was 72.2% (78/108; observed case only). The mean number of incontinent days in a 14 day period decreased by more than 50% from baseline (9.5 days) to 3 months (4.7 days) and stayed at this decreased level through 36 months (4.4 days). The median number of urge FI episodes decreased from 4 at baseline to 0 at 3 months and remained at a median 0 through 36 months.

For the PRO objectives, including the Wexner Score, FIQoL, PFDI-20 and PFIQ-7, all improved by the 3 month visit and the improvements were maintained through 36 months in patients completing follow-

up. Treatment responder status and the percentage decrease in FI episodes were correlated with improvements in all PRO measures.

Since there are no anchor-based minimal clinically important differences (MCIDs) established for the change in the Wexner Score, FIQoL, and total PFDI-20 and PFIQ-7 scores, each was analyzed to determine whether the change exceeded ½ standard deviation (SD) that has been associated with clinical significance across a broad range of PROs (Norman, 2003). For the Wexner Score, FIQoL, and total PFDI-20 and PFIQ-7 scores, the change at 12, 24 and 36 months was greater than ½ SD, consistent with a clinical improvement noticeable to the patient. For the colo-rectal-anal subscales of the PFDI-20 (CRADI) and the PFDI-7 (CRAIQ), MCIDs have recently been established of -5 points and -8 for the CRADI and CRAIQ, respectively (Jelovsek et al., 2014). The change in CRADI and CRAIQ scores at 12, 24 and 36 months were all greater than 20 points indicating the TOPAS system had a clinically significant improvement in pelvic floor distress and impact in the colo-rectal-anal region.

1.3.2 Safety Results

The safety experience in the TOPAS PMA study was favorable with no device migration, revisions, erosions, extrusions, organ perforations, or UADEs in the 509 patient-years of follow-up. There were 677 adverse events (AEs), of which 17% were device- and/or procedure-related. The most commonly observed complications occurring in more than 5% of patients were pain (buttock, pelvic, groin) and incision site infection. The majority (92.2%) of all treatment-related AEs were either managed without therapy or with a non-surgical treatment.

There were 8 treatment-related serious adverse events (SAEs), none of which were life-threatening. There were no treatment-related deaths in the study, and no patients withdrew from the study from a treatment-related AE. Half (4/8) of treatment-related SAEs were due to the worsening of a pre-existing condition. One new onset SAE, methicillin-resistant *Staphylococcus aureus* infection (MRSA) of the left hand, was believed to be nosocomially acquired sometime during hospitalization for the implant procedure. Another new onset SAE (deep vein thrombosis) was determined by the Adverse Event Adjudication Committee (AEAC) to be due to the TOPAS implant procedure. The remaining two new onset SAEs were cases of de novo pelvic organ prolapse that were determined by the AEAC to be due to the TOPAS device.

1.3.3 Other Findings

The TOPAS system resulted in a decrease in health resource utilization such as reducing pad use, lost-work days, physician visits for FI, and caregiver support. In addition, based upon a patient surgical satisfaction questionnaire (n=86), 75% of treatment responders reported being satisfied/very satisfied with the results of the TOPAS surgery, 84% would have the surgery again, and 83% would recommend the TOPAS system to someone else.

1.4 BENEFIT RISK CONCLUSION

With the exception of colostomy, no surgical treatment option for FI will work in all patients, probably because of the multifactorial and complex etiology of FI. For example, in the studies leading to approval of InterStim and Solesta, 27% and 43% of patients receiving the device were non-responders at one year follow-up, respectively. Even with the PMA approval of the InterStim and Solesta devices and the recent HUD approval for the FENIX magnetic artificial bowel sphincter, significant unmet medical need remains for new treatments. For example, in their responses to ASTORA-sponsored surveys, physicians who treat FI affirmed the need for more treatment options, especially options that are minimally invasive, cost-effective, do not require ongoing patient intervention (e.g., retreatments, component replacement, or daily device interaction) and have an acceptable risk profile and low reoperation rate. In this regard, the TOPAS system, the first device providing anatomical support to the anorectum, meets all the aforementioned unmet medical needs for effective treatment of FI in women.

In the TOPAS PMA study, the TOPAS system substantially reduced FI episodes. At 12 months after surgical implantation, 69.1% of patients reported at least a 50% reduction in the number of FI episodes from baseline. More stringent definitions of treatment response were consistent with 42.1% of patients reporting at least a 75% reduction from baseline and 19.1% of patients reported complete continence at 12 months.

The robust findings for reduction in FI episodes at 12 months were associated with significant improvements in PROs including FI symptom severity, QoL, and pelvic floor distress and impact. The treatment responder rates and improvements in PROs were durable through 36 months in patients completing that visit. There was no negative impact on sexual function in sexually active patients through 36 months. The TOPAS system's benefits also include a decrease in health resource utilization.

The overall safety experience with the TOPAS system supports approval. The TOPAS system's unique anatomical placement does not require transvaginal incision, or any incision or modifications to the pelvic floor muscle, and thus has a different safety profile than transvaginal mesh devices that are implanted in a different anatomical location to treat different disease states.

ASTORA recognizes that a potential contributing factor to overall patient outcome and safety profile may be dependent on physician experience with surgical mesh implant procedures. Thus, a well-planned 3 phase physician training curriculum is proposed to educate on disease state, relevant anatomy, patient selection, and procedural requirements, with the intent of helping physicians utilize the TOPAS system in a safe and effective manner.

Although the TOPAS PMA study results were deemed to be generalizable, ASTORA is currently in ongoing discussions regarding a new post-market study with the TOPAS system. The study design and objectives have not yet been finalized, however, the study will likely focus on safety questions not addressed in the current TOPAS PMA Study. Furthermore, ASTORA will continue to follow the TOPAS

PMA study patients through five years (60 months) to monitor the long-term safety and efficacy of the device.

In summary, the TOPAS system offers clinicians a minimally invasive option for women that may be implanted after patients have failed more conservative therapies. ASTORA believes the benefits of the TOPAS system outweigh the risks, based on the following, and therefore commercial approval is warranted.

2 OVERVIEW OF THE TOPAS SYSTEM

ASTORA has significant experience in designing devices to treat patients with FI (i.e., the Acticon™ Neosphincter device, P010020), and using surgical mesh in transobturator suburethral slings to treat urinary incontinence (i.e., the Monarc™ Subfascial Hammock, K023516). The Acticon™ Neosphincter is an implantable device used to treat severe FI in males and females 18 years and older who have failed, or are not candidates for, less invasive forms of restorative therapy. To expand FI treatment to a less severe patient population, ASTORA intends the TOPAS system to be a minimally invasive option to treat FI for women that have failed more conservative therapies.

2.1 CLINICAL SAFETY OF IMPLANTED MESH

2.1.1 Introduction

One of the first clinical uses of polypropylene mesh was during hernia repair. The implantation of mesh provides scaffolding on which connective tissue can grow. The implanted mesh remains inert during long-term follow-up even in the presence of infection (Usher, 1970). Almost 700,000 herniorraphies are performed each year in the US with an estimated 80% of these hernia operations involving placement of a knitted polypropylene monofilament mesh (Di Vita, 2000). Other common uses of urogynecological surgical mesh include transvaginal or transabdominal placed mesh to treat pelvic organ prolapse (POP). A mesh sling is also used to treat stress urinary incontinence (SUI).

The TOPAS system uses Type I mesh, defined as macroporous with a pore size of >75 µm, which allows macrophages and fibroblasts to incorporate into the mesh (Baessler & Maher, 2006). A similar Type I polypropylene mesh is also currently used in other market-released ASTORA pelvic floor repairs products (Apogee, Elevate, and Perigee Pelvic Floor Repair Systems and the SPARC and Monarc urinary sling systems).

2.1.2 TOPAS System Unique Safety Profile

A different performance and safety profile is expected for the TOPAS implant compared to surgical meshes used in the treatment of SUI or POP due to TOPAS's anatomical placement, incisions, tissue interface, and product indications for use.

Table 1 summarizes placement and implantation location for the TOPAS system compared to other types of commercially-available pelvic floor surgical meshes. The TOPAS system implanted component is a surgical mesh which provides support to the anorectum as a means to treat FI. The TOPAS implant's placement does not require transvaginal incisions or incision or modification of the pelvic floor muscles. As observed in the TOPAS PMA study, in which there were no mesh erosions, extrusions, organ

perforations, device revisions, or UADEs, the TOPAS device has its own unique safety profile compared to other surgical mesh products.

Table 1: Description of Placement and Location of TOPAS System and Other Pelvic Floor Surgical Meshes

Surgical Meshes	TOPAS system	Transobturator slings for surgical repair of female SUI	Transvaginal Anterior POP repair systems	Transvaginal Posterior POP repair systems
Intended use	Permanent implant placed inferior to the anorectum and parallel to the puborectalis	Permanent implant between the vagina and the urethra (at the mid-urethra)	Permanent implant between the vagina and bladder	Permanent implant between the rectum and vagina
Indication	To treat women with fecal incontinence who have failed more conservative therapies	For the placement of a suburethral mesh for the treatment of female stress urinary incontinence (SUI) resulting from urethral hypermobility and/or intrinsic sphincter deficiency	Surgical mesh kit intended for transvaginal surgical treatment to correct anterior wall prolapse and vaginal apical prolapse	Surgical mesh kit intended for transvaginal surgical treatment to correct posterior wall prolapse and vaginal apical prolapse
Incision(s)	Buttock & thigh	Anterior wall of vagina and thigh	Anterior wall of vagina	Posterior wall of vagina
Implant Final Location	The implant is beneath the rectum, in a very distinguishable space: beneath the thick internal/external anal sphincter muscle (approximately1 cm) and puborectalis muscle (approximately 1cm thick) in adipose tissue space. The implant's elliptical section and the mesh arms are not in direct contact with the muscles directly next to the rectum or vagina.	The implant is in the tissue plane between the vagina and urethra.	The implant is in the tissue plane between the vagina and bladder. The apical arms are inserted into the sacrospinous ligament. The anterior arms are inserted into the obturator foramen.	The implant is in the tissue plane between the rectum and vagina. The apical arms are inserted into the sacrospinous ligament.
Construction of implant material	Type I polypropylene mesh	1st Generation AMS slings (Monarc and SPARC): Type I polypropylene mesh	AMS Anterior Repair System (Elevate Anterior): Intepro Lite (Type I polypropylene mesh)	AMS Posterior Repair System (Elevate Posterior): Intepro Lite (Type I polypropylene mesh)

2.2 DEVICE DESCRIPTION

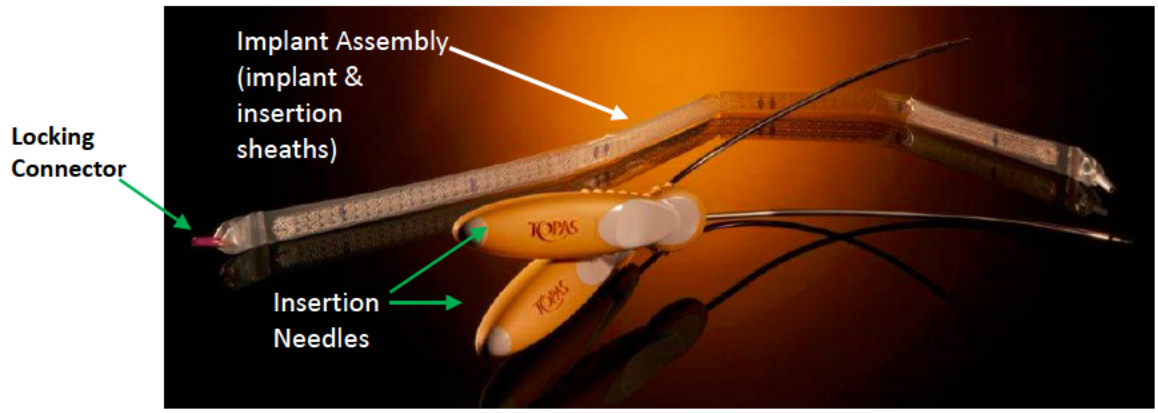
The TOPAS system is designed for minimally invasive implantation to provide support to the anorectum. Initially, fixation of the mesh implant provides physical anatomical support. After tissue in-growth occurs as part of the normal healing process, physical support is provided by both the mesh implant and tissue in-growth.

The TOPAS system is a sterile, single-use product consisting of two insertion needles and one mesh assembly (Figure 1). The assembly consists of mesh, covered by insertion sheaths with a needle tip connector on each end. The mesh implant is a single piece knitted, Type 1 polypropylene, monofilament mesh, 45 cm in length. The center portion of the mesh has an elliptical shape that is 5 cm in length and 2 cm wide. The arms extending from each side of the center mesh are 1.1 cm wide. The locking connectors, insertion sheath, and insertion needles are removed after the implant is properly positioned. The mesh is intended to remain in the body as a permanent implant and is magnetic resonance safe.

The mesh implant is covered by removable insertion sheaths, and one sheath covers the central portion of the mesh. At each end, the mesh arm is bonded to the insertion sheath, which is designed to facilitate the implant's passage through tissue. Markings on the insertion sheaths are designed to assist centering of the implant.

Locking connectors, color-coded for directionality, are attached to each insertion sheath. The locking connectors are designed to attach securely to the needle tips during passage of the mesh implant through the tissue and obturator foramen. Once snapped onto the needle tip, the locking connectors cannot be removed. The trimming process removes the insertion sheaths, the excess mesh remaining outside the body, the connectors, and the attached needles.

Figure 1: TOPAS Mesh Assembly and Stainless Steel Needles



The TOPAS mesh is implanted via the transobturator approach, where the insertion needle route is through the obturator membrane and parallel to the perineal body. Two small incisions are made on the

thighs following identification of the incision location by palpation. The incision locations facilitate prevention of injury to the artery and nerves at the obturator canal located on the opposite side of the obturator foramen during the needle insertion. Two additional small incisions are made on the buttocks, below the anus, for the introduction of the mesh assembly; there are no incisions made through the vagina or rectum. A tunnel is created from the patient's left side to the right side, posterior to the anal sphincter muscles and about 2 cm deep to the perianal skin. The end of a clamp is pushed through the left buttock incision and used to grab the pink connector of the mesh assembly. The mesh assembly is passed through the incision and is situated beneath the anorectum. The transobturator (insertion) needle is passed from the thigh incision to the left buttock incision, and the pink locking connector from the mesh assembly is attached to the insertion needle. The insertion needle is then retracted back through the tissue, and the same procedure is repeated with the second insertion needle on the other side. The mesh arms are then adjusted by pulling both together upward until gentle tension is palpable through the rectum. A slight ridge or "bump" should be felt but should not cause significant deformity or compression of the anal canal. The sheaths are removed after the initial tensioning by cutting below the locking connector and sliding the sheaths through the thigh incisions. Minor adjustments of the mesh can be done after sheath removal to complete tensioning. The excess mesh is then trimmed at the level of skin and thigh and buttocks incisions are closed.

2.3 MECHANISM OF ACTION

The mechanism of action of the TOPAS system is not completely understood but is believed to be due to providing support to the anorectum to compensate for loss of pelvic floor muscle function as a result of degradation in muscle tone or damage from obstetric injury. By doing so, ASTORA believes that the TOPAS system prevents the entry of stool into the anal canal.

At the time of development of the TOPAS PMA Study, preliminary evidence from earlier clinical work indicated that device implantation could have a significant effect on reducing FI episodes but the exact mechanism of action was not known. The TOPAS system was originally developed based on a theoretical mechanism of action relating to the role of the anorectal angle in rectal closure and the continence mechanism. Under normal conditions, the puborectalis muscle provides support under the anorectum, thereby creating an acute angle between the axis of the rectum and the anal canal of approximately 90 degrees (Palit et al., 2012). This acute anorectal angle is believed to keep stool in the rectum and maintains continence by creating a flap-valve mechanism in which the anterior rectal wall occludes the upper anal canal due to a rise in intra-abdominal pressure (Bannister et al., 1987; Parks 1975). Yet in a subset of study patients (n=33) in the TOPAS PMA Study, dynamic defecography measurements taken at baseline and 6 months post-implant have shown no difference in the anorectal angle at rest or evacuation or in anal canal length (see Section 4.6.3). It is unknown if failure to detect anatomical changes in this sub-study was real or due to variability with the measurement technique.

ASTORA's growing understanding of FI and experience with the TOPAS device suggest more is at play than can be explained by physical restoration of the anorectum. While the exact mechanism by which the TOPAS system is inducing a treatment response from patient to patient cannot be articulated, ASTORA believes there are some clinical and biological considerations that can help lay the foundation for explaining the mechanism of action of the TOPAS and its role in the complex FI continence mechanism.

In their Musco-Elastic Theory of Fecal Incontinence, Petros and Swash (2008) discuss similarities in the pathogenesis between urinary incontinence and FI and in the mechanisms of action to treat them. Based partly on this theory, ASTORA believes there are similarities in mechanism of action between mid-urethral slings and the TOPAS system especially as they relate to the importance of re-establishing support of urethra and anal canal respectively. DeLancey and Aston-Miller (2004) describe the urinary mechanism of action as relating to stiffness of supportive layer under the urethra which provides a backstop against which abdominal pressure compresses the urethra. The same may be at play with the TOPAS system where the sub-rectal mesh segment plays the role of the backstop or backboard against which abdominal forces act to provide cooptation of the anal canal.

ASTORA acknowledges that further work is needed to elucidate the mechanism of action of the TOPAS system and anticipates doing so in post-market studies.

2.4 NON-CLINICAL TESTING

Non-clinical studies included biocompatibility, shelf life, bench performance, sterility, package integrity, and cadaveric testing (Table 2). Bench testing was performed on the TOPAS system after ethylene oxide sterilization, environmental conditioning, distribution and shipping simulation, and aging. The TOPAS system met all design and performance requirements. As part of the design development of the TOPAS system, cadaver studies were performed that allowed an assessment of the procedure as well as the design of the product. All devices performed as intended and met the established customer requirements.

Table 2: Summary of Non-Clinical Testing

Test Name	Purpose	Results
Biocompatibility Testing – Implant		
Cytotoxicity (ISO 10993-5)	To evaluate whether an extract of the test article could cause cytotoxicity using the L929 mouse fibroblast cell culture.	Pass
Sensitization (ISO 10993-10)	To evaluate the allergenic potential or sensitizing capacity of the test article	Pass
Irritation (ISO 10993-10)	To evaluate local dermal irritation effects of leachables following intracutaneous injections.	Pass
Acute Systemic Toxicity (ISO 10993-11)	To evaluate acute systemic toxicity of leachables extracted from the test article following a single intravenous or intraperitoneal injection.	Pass
Pyrogenicity USP <151>; (ISO 10993-11)	To detect material-mediated pyrogenic reactions of extracts from the test article following intravenous administration.	Pass
Sub-Acute and Sub-chronic Toxicity (ISO 10993-11)	To assess the effects of multiple exposures to extracts of the test articles for a period not less than 24 hours and less than 14 days.	Pass
Genotoxicity (ISO 10993-3)	To evaluate the ability of an extract from the test article to cause mutagenic or chromosomal damage.	Pass
Implantation (ISO 10993-6)	To assess local pathological effects on living tissue at both gross and microscopic levels after implantation of a medical device/biomaterial.	Pass
Biocompatibility Testing - Temporary Contact Insertion Needles and Locking Connectors		
Cytotoxicity (ISO 10993-5)	To evaluate whether an extract of the test article could cause cytotoxicity using the L929 mouse fibroblast cell culture.	Pass
Sensitization (ISO 10993-10)	To evaluate the allergenic potential or sensitizing capacity of the test article.	Pass
Irritation (ISO 10993-10)	To evaluate local dermal irritation effects of leachables following intracutaneous injections.	Pass
Performance Testing – Bench		
Mesh Shelf Life	After aging and shipping conditions, the TOPAS system and the TOPAS packaging materials were subjected to bench testing and package integrity testing.	Pass
Mesh Elongation	To evaluate the ability of the implant to retain its integrity and resist undesired stretching under implantation (e.g., tensioning).	Pass
Mesh Tensile Strength	To evaluate the tensile strength of the implant (e.g., its ability to retain integrity during and immediately after implantation).	Pass
Mesh Implant Cycling	To evaluate the implant's ability to withstand repeated forces and stress events in the pelvic space during the tissue in-growth period.	Pass

Test Name	Purpose	Results
Handle to Needle Tensile Attachment Strength	To evaluate the ability of the insertion needle assembly to stay intact during device placement.	Pass
Handle to Needle Torsional Strength	To evaluate the torsional resistance of the insertion needle assembly during device placement.	Pass
Needle/Handle Interface Deflection	To evaluate the ability of the handle and needle shaft interface to withstand deflection without permanent deformation or breakage.	Pass
Sheath Tensile Strength	To evaluate the ability of the sheath to stay intact during device placement.	Pass
Sheath to Connector Attachment Strength	To evaluate the integrity of the attachment during device placement.	Pass
Sheath to Mesh Tack Bond Tensile Strength	To evaluate the integrity of the sheath to mesh bond strength during device placement.	Pass
Connector (Pink and White) to Needle Tip Pull Off	To evaluate the integrity of the connection between the locking connector and insertion needle.	Pass
Connector (Pink and White) to Needle Tip Push On	To evaluate the force required to attach the connector to the needle.	Pass
Performance Testing – Cadaver	To ensure the TOPAS system conforms to the user needs and intended use.	Pass
Sterilization Validation	To ensure the ethylene oxide sterilization cycle for the system consistently delivers a sterility assurance level (SAL) of 10-6 or better.	Currently in progress
Package Integrity		
Visual Inspection	Package integrity testing via visual inspection of product, bubble leak test, and tray/lid peel strength.	Pass
Bubble Leak Test		Pass
Tray/Lid Peel Strength		Pass

2.5 REGULATORY HISTORY

The TOPAS system is not commercially available in any country. In the US, a precursor version of the TOPAS system (the AMS Pelvic Floor Repair System) was cleared by the FDA in May 2007 (K070993). A small (n=29) post-market study was conducted to understand the outcomes of restoring pelvic floor support using the AMS Pelvic Floor Repair System (also referred to as PFR System) in women

(ClinicalTrials.gov #NCT00565136; Rosenblatt et al, 2014). The PFR system has not been further marketed in any country.

Because ASTORA wanted to introduce a novel treatment option to meet the unmet medical need that exists in treating FI in women, ASTORA continued to develop the TOPAS system to its final configuration and intended use to treat FI. Changes made to the PFR system were focused on improvement in physician usability based upon experience in the post-marketing study leading to the TOPAS system and culminating in the submission of the Investigational Device Exemption application to the FDA for the TOPAS PMA study in 2009 ((ClinicalTrials.gov #NCT01090739).

Key regulatory dates include:

- IDE (G090159) Approved (Conditional): 23 Sep 2009
- IDE (G090159) Approved (Full): 26 Mar 2010
- Study Initiation (First Enrollment): 17 Jun 2010
- First Patient Implanted: 14 Jul 2010
- Last Patient 12 Month Follow-up Visit: 08 Nov 2013
- PMA (P140006) Submitted: 17 Apr 2014
- PMA Deficiency Letter Received: 15 Jul 2014
- ASTORA Response to Deficiency Letter: 14 Jul 2015

3 TOPAS PMA STUDY DESCRIPTION

3.1 INTRODUCTION

The TOPAS PMA study is a single arm trial with an adaptive sample size design. This design was selected based on input from FDA and in consultation with the physician study advisory committee.

During the development of TOPAS PMA Study, ASTORA considered several potential comparative groups (including conservative treatment and a sham control arm) and concluded there was not an appropriate control treatment. For conservative treatment acting as a comparative group, patients in the TOPAS PMA Study needed to have failed conservative therapy to be eligible for study entry and it was considered unethical to require them to repeat conservative treatments as a potential control arm. In a sham design, patients would be required to undergo anesthesia and incisions without the potential benefit of a device implant. Both unnecessary anesthesia and incisions are associated with significant risks; therefore, a sham design was determined to be medically inappropriate for this type of intervention.

Based on these considerations, a single arm design was ultimately chosen whereby all patients were treated with the TOPAS system and utilized the patient as their own control for the measurement of the primary endpoint.

3.2 STUDY DESIGN

The TOPAS PMA study is a prospective, multicenter, single-arm, open-label, two-stage, adaptive study that enrolled female patients 18 years of age or older with FI symptoms for at least 6 months who had failed at least two conservative treatment modalities (e.g., dietary modification, pharmacological intervention, or pelvic floor muscle training). Failure of conservative therapy was determined from patient medical history and the judgment of the individual investigators; potential patients were not required to complete and fail a specific conservative therapy program in order to qualify for the study. For a complete list of inclusion and exclusion criteria, see Section 3.2.

The study was conducted at 15 centers in the US; 8 were led by Colorectal Surgeons and 7 centers by Urogynecologists. The primary endpoint was treatment responder status at 12 months with treatment response defined as at least a 50% reduction in number of FI episodes from baseline. Patients were evaluated acutely at 14-28 days post-implant and then at 3, 6, 12, 24, 36, 48, and 60 months post-implant (Table 3). The study was originally designed with a 36 month follow-up but was extended to 60 month follow-up in December 2013.

At baseline and prior to each follow-up visit, patients completed a 14 day bowel diary that provided information on the FI episodes and number of continent days. Patients also completed several PRO instruments that were used in secondary endpoint assessments, as discussed in the next section.

The study utilized two independent oversight committees: A Data Monitoring Committee (DMC) and Adverse Event Adjudication Committee (AEAC). Membership in both committees was restricted to individuals free of apparent significant conflicts of interest, which may have been financial, scientific and/or regulatory in nature. None of the committee members were investigators participating in the study.

The DMC was comprised of one statistician, three physicians and one patient advocate, all independent of the sponsor. The DMC was responsible for safeguarding the interests of trial participants, assessing the safety and efficacy of the interventions during the trial, and for monitoring the overall conduct of the clinical trial. The AEAC was comprised of the same three physicians that were members of the DMC. The AEAC was responsible for reviewing all adverse events and determining the correct assignment of codes, event seriousness, and relatedness to the study device and/or procedure.

Table 3: Study Visit Schedule

Activity	Screen #1	Screen #2	Implant T=0	Acute (14-28 days)	3 Mo (± 30 days)	6 Mo (± 30 days)	12 Mo (± 60 days)	24 Mo (± 60 days)	36 Mo (± 60 days)	48 Mo (± 60 days)	60 Mo (± 60 days
Review and Obtain Informed Consent Form	X										
Review Required Study Activities	X	X									
Confirm Patient Inclusion/Exclusion	X	X									
Collect Patient Medical History	X										
Conduct Digital Rectal Exam	X									X	X
Anal Manometry (Past 12 months)	X										
Conduct Endoanal Ultrasound/MRI (Past 12 months)	X										
Defecography[1]	X					X					
Conduct Urine Pregnancy Test (If applicable, patient of child-bearing potential)			X								
Distribute and Collect Patient Bowel Diary		X			X	X	X	X	X	X	X
Patient to Complete: Wexner Score, FIQoL, PFDI-20, PFIQ-7 & PISQ-12		X			X	X	X	X	X	X	X
Patient to Complete Health Resource Usage Questionnaire		X					X	X	X	X	X
Patient to Complete Numeric Pelvic Pain Scale (NPPS)[2]		X	X	X	X	X	X				
Patient to Complete Surgical Satisfaction Questionnaire (SSQ-8)[3]							X			X	X
Device Implantation			X								
Collect Procedure Data (estimated blood loss and length of procedure)			X								
End of Study[4]											X
Conduct Physical Examination of Surgical Area				X	X	X	X	X	X	X	X
Collect Adverse Events		X	X	X	X	X	X	X	X	X	X

1 - Defecography required at baseline (test results within 12 Months of consent date) and 180 day visit at a sub-set of study centers
2 - Patient received post-implant NPPS within 72 hours of implant
3 - SSQ-8 is optional and intended to be completed once between the 3 Month and 36 Month follow-up visit, and required at 48 and 60 Month visits
4 - End of Study visit is to be completed whenever a patient exits or completes the study

3.3 CLINICAL ENDPOINT ASSESSMENT

3.3.1 Primary and Secondary Endpoints

The primary clinical objective of the TOPAS PMA study was to determine if implantation with the TOPAS system produces a treatment response in more than 50% of the study patients. To be a treatment responder, at least a 50% reduction in the number of FI episodes from baseline to the 12 month post-operative visit was required by protocol.

Secondary effectiveness objectives were to quantify the following:

- Number of FI episodes and treatment responder rate through 60 months based on a 14 day bowel diary (see Appendix 3, Figure 16 for an example of the bowel diary used in the study).
- Number of incontinence days as measured by the number of days in the 14 day bowel diary when a patient had one or more FI episodes during a day
- Number of urge FI episodes as measured in the 14 day bowel diary
- FI symptom severity as measured by the Wexner Symptom Severity Score (Wexner Score)
- Disease-specific QoL as measured by the Fecal Incontinence Qulaity of Life Questionnaire (FIQoL)
- Pelvic floor distress and impact to the patient as measured by the Pelvic Floor Distress Inventory (PFDI-20) and Pelvic Floor Impact Questionnaire (PFIQ-7)
- Sexual function as measured by the Pelvic Organ Prolapse/Urinary. Incontinence Sexual Questionnaire (PISQ-12)

3.3.2 Quality of Life Assessments

There were five tools use to assess different aspects of changes in quality of life:

- **Wexner Score:** The Wexner Score is based upon assessment of three items about the type and frequency of incontinence (scored from 0 to 4) and two additional items on pad usage and lifestyle alteration (both scored from 0 to 4) (Jorge and Wexner, 1993). The total score of these five items ranges from 0 (complete continence) to 20 (complete incontinence). The Wexner Score correlates well with clinical assessment of the patient (0.87, $p<0.001$), has good test-retest reliability (0.75), and is sensitive to change in symptoms ($p<0.03$; Vaizey et al., 1999). The total score correlates closely with subjective perception of the FI severity by patients (Moo-Kyung Seong et al., 2011). See Appendix 3, Figure 17 for an example of the Wexner Score questionnaire used in the TOPAS PMA study.
- **FIQoL:** This tool was used to evaluate disease-specific QoL (Rockwood et al., 2000). The FIQoL consists of 29 questions within four domains (Coping, Lifestyle, Embarrassment, and Depression). Each domain is scored separately from 1 to 4, with a higher score indicating a

higher QoL. The internal consistency score (Cronbach alpha) was 0.8 or above for all four domains (Rockwood et al., 2000). See Appendix 3, Figure 18 for an example of the FIQoL questionnaire use in the study.

- **PFDI-20 and PFIQ-7:** The PFDI-20 and PFIQ-7 were used to evaluate pelvic floor distress and impact to the patient. Both instruments have been validated for use in women with disorders of the pelvic floor including urinary incontinence, POP, and FI (Barber et al., 2005). Both are scored on a 0 to 300 scale with higher scores indicting greater pelvic floor distress/impact. Both are composed of three subscales for prolapse (POPDI and POPIQ), urinary (UDI and UIQ), and colo-rectal-anal domains (CRADI and CRAIQ). Recently, MCIDs have been established for the CRADI and CRAIQ subscales of -5 points and -8 points, respectively (Jelovsek et al., 2014). See Appendix 3, Figures 19-20 for examples of the PFDI-20 and PFIQ-7 questionnaires used in the study.
- **PISQ-12:** Sexual function was assessed in sexually active patients with the PISQ-12, which has been validated for women with urinary incontinence and/or POP, but not specifically for those with FI (Rogers et al., 2003). The PISQ-12 is scored on a scale of 0 to 48, with higher scores indicating better sexual function. See Appendix 3, Figure 21 for an example of the PISQ-12 questionnaire used in the study.

3.4 INCLUSION AND EXCLUSION CRITERIA

The following are the inclusion and exclusion criteria for study enrollment.

- Inclusion Criteria:
  - An adult (≥18 years) female.
  - FI symptoms for a minimum of 6 months.
  - Failed two modalities of conservative therapies such as Dietary Modification, Pharmacologic Intervention, or Pelvic Floor Muscle Training.
  - <50 years old OR if ≥ 50 years old, had a negative cancer screening examination of the colon according to screening guidelines (colonoscopy or barium enema + flexible sigmoidoscopy) within the past three years prior to informed consent date. (Note: if not done, the investigating physician must have provided written justification for not having this exam and must have followed the American Cancer Society Guidelines, Levin et al., 2008).
  - FI episodes ≥4 in a 14 day period.
- Exclusion Criteria:
  - Was unable or unwilling to sign Informed Consent Form or comply with study requirements.
  - Currently enrolled in or plans to enroll in any concurrent drug and/or device study that may confound the results of this study as determined by sponsor.

- Allergic to polypropylene.
- Pregnant or planning a future pregnancy.
- Less than 12 months (365 days) postpartum.
- Pelvic prolapse ≥ 1 cm beyond the hymen (Stage III & IV).
- Had SUI or anterior repair within 3 months prior to TOPAS system implantation.
- Had a hysterectomy, sphincteroplasty, or posterior surgery within 6 months (180 days) prior to TOPAS system implantation.
- Had rectal surgery (such as rectopexy) within 12 months (365 days) of TOPAS system implantation.
- Was planning pelvic surgery within 12 months (365 days) post TOPAS system implantation.
- Current Grade III or IV hemorrhoids.
- Neurological or psychological condition as cause of FI such as multiple sclerosis, dementia, brain tumor.
- Diagnosed with Inflammatory Bowel Disease (for example, ulcerative colitis or Crohn's disease).
- Chronic, watery diarrhea, unmanageable by drugs or diet, as primary cause of FI.
- Severe chronic constipation, including obstructive defecatory disorder.
- External full thickness rectal prolapse.
- History of laxative abuse within the past five years.
- Previous rectal resection.
- Active pelvic infection, perianal or recto-vaginal fistula.
- Congenital anorectal malformations or chronic 4th degree lacerations and cloacae.
- History of therapeutic radiation for cancers of the pelvis.
- Currently implanted with a sacral nerve stimulator.
- Contraindicated for surgery or having any condition that would compromise wound healing.

3.5 STATISTICAL METHODOLOGY

The primary objective of the TOPAS PMA study was to show that the treatment responder rate to the TOPAS system was greater than 50% at 12 months. Because there was no experience to estimate the expected response with the TOPAS system in treating FI, a two-stage adaptive design was selected to allow for precise sample size estimation in Stage II (Bauer and Köhne, 1994). A pre-specified interim analysis was conducted after Stage I was complete without evaluation of any follow-up data in Stage II, thus keeping Stage II independent of Stage I. The study was designed to maintain study-wide Type I

error rate at 0.05. For the primary endpoint, all data from Stage I and II were analyzed separately, with no pooling of data between stages.

A one-sided exact binomial test was used to test the hypothesis that the treatment response rate was greater than 50% in each stage. At the conclusion of Stage I, the null hypothesis was to be rejected if the p-value for Stage I (p_1) was less than 0.0087, since ultimate success would be guaranteed ($T=p_1p_2 < 0.0087$ because $p2 \leq 1$). Table 4 shows the probability of rejecting the null hypothesis ("to be effective") at the end of Stage I, given various assumed true TOPAS system treatment response rates. If the null hypothesis was not rejected, Stage II would be conducted with a re-estimation of sample size to have adequate power to achieve $p_2 < 0.0087/p_1$.

Table 4: Probability (Power) of Stage I Conclusions for Various Assumed Treatment Response Rates

	True TOPAS System Treatment Response Rate						
	0.50	**0.58**	**0.59**	**0.60**	**0.61**	**0.62**	**0.63**
To be effective at Stage I (p_1<0.0087)	0.0048	0.123	0.164	0.213	0.270	0.334	0.403

Eighty patients were implanted and completed Stage I follow-up, 65% of whom were treatment responders (p=0.0048). Given that the primary objective was met with Stage I, it was unnecessary to adjust the sample size for Stage II. As such, ASTORA continued with enrollment and implantation of 72 patients in Stage II (152 total patients) for adequate safety assessment, as was pre-specified in the analysis plan.

The primary efficacy endpoint analyzed patients with missing 12 month follow-up data as treatment failures ("worst case" method). The impact of less extreme assumptions about missing data was also evaluated using the following:

- **Last Observation Carried Forward (LOCF):** Patients with missing 12 month diary data had the last available diary data substituted for the 12 month diary.
- **Modified Worst Case:** Patients with missing 12 month diary data were considered treatment failures unless there was a subsequent diary available (e.g., collected at the 24-month visit), which was then substituted for the 12 month. If there were multiple data points available beyond the 12 month follow-up visit, then data from the first available follow-up visit after the 12 month follow-up visit were used in the analysis.
- **Completed Cases Only:** Patients with missing 12 month bowel diary data were not included in the responder rate calculation.

Poolability of results was examined across study centers (centers with less than 5 patients treated were combined). The responder rate was summarized, and Fisher's Exact test was used to evaluate the center effect.

Descriptive statistics (mean, SD, median, and range) and 95% CIs were used to summarize the values of secondary efficacy objectives at baseline, 3, 6, 12, 24, 36, 48 and 60 month visits along with the change and/or percent change from baseline, when applicable. The change from baseline was calculated based on within patient change (i.e., at the patient level using matched pairs of data). Secondary endpoints were analyzed using data from all implanted patients (Stage I and Stage II combined) to determine the clinical significance of the primary findings without controlling type 1 error.

For the Wexner Score, FIQoL, and total PFDI-20 and PFIQ-7 scores, there are no established MCIDs. To evaluate the clinical significance of the change in each score, a ½ SD threshold for the change was defined based upon the experience of many PROs (Norman 2003). For the CRADI and CRAIQ subscales of the PFDI-20 and PFIQ-7, MCID point values have been recently established which were used to evaluate the clinical significance of the change in these subscores (Jelovsek et al., 2014).

4 RESULTS OF THE TOPAS PMA STUDY

4.1 SUMMARY

- The TOPAS PMA study significantly exceeded the performance goals for its primary objective. Overall, 69.1% of patients achieved at least a 50% reduction in FI episodes from baseline to 12 months.
    - In Stage I, 65% were treatment responders (p=0.0048) at 12 months.
    - In Stage II, 73.6% of patients were treatment responders (p<0.0001) at 12 months.
    - The treatment response was present as early as the 3 month follow-up visit and was sustained through 36 months of follow-up.
    - More than 42% of patients achieved at least a 75% decrease in FI episodes at 12 months.
    - 19.1% of patients reported complete continence at 12 months.
- Significant reductions in FI urge episodes and incontinent days were observed starting at the 3 month visit and continuing throughout the follow-up period.
- Patients had clinically important improvements in PRO measures.
    - For the Wexner Score, FIQoL, PFDI-20 and PFIQ-7, all improved by the 3 month visit and the improvements were maintained throughout the follow-up period.
    - Treatment responder status and the percentage decrease in FI episodes were correlated with improvements in all PRO measures.
- TOPAS system implantation resulted in a reduction in self-reported health resource utilization including a reduction in the use of pads, a reduction in number of physician visits due to FI, and a reduction in the number of days off from work due to FI.

4.2 PATIENT DISPOSITION AND BASELINE CHARACTERISTICS

The study enrolled 207 patients into screening, with 152 patients implanted with the TOPAS system. For the 55 patients enrolled but not implanted, the primary reasons that the implant was not performed were withdrawn consent (41.8%, 23/55) and not meeting study entry criteria (25.5%, 14/55) (Figure 2). Of the 23 patients that withdrew consent prior to the implant, 9 changed their mind about doing the study, 5 did not specify a reason, 4 wanted to continue their current FI treatment, 2 had family issues preventing participation, 2 had other health issues preventing participation, and 1 could not travel for the study visits. A detailed listing of all patients withdrawn prior to implant (n=55) is included in Appendix 1, Table 36. Of the 152 patients implanted, 94 patients are still active as of the data cutoff date of 17 Aug 2015 (Figure 2 and Figure 3).

Figure 2: Patient Enrollment Summary

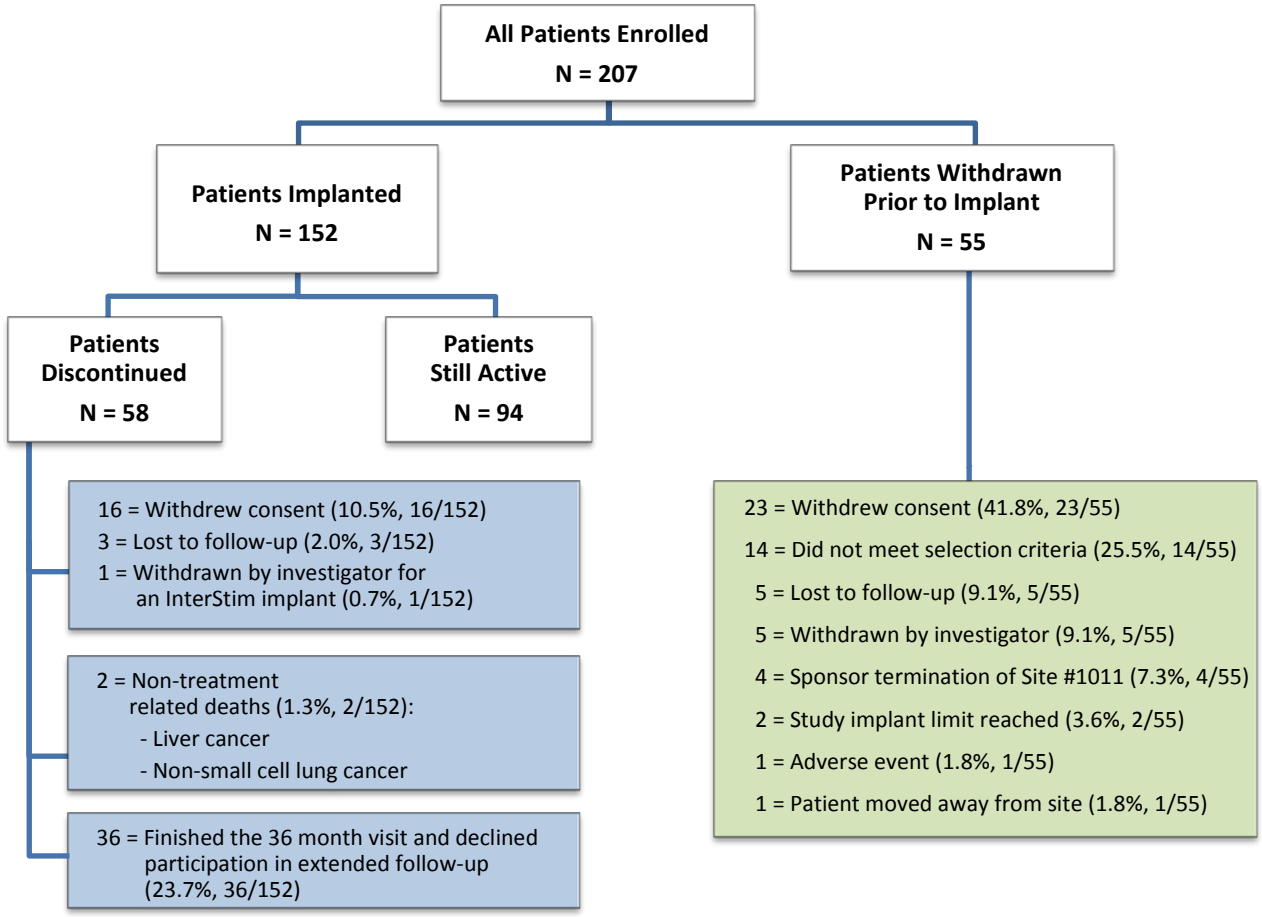
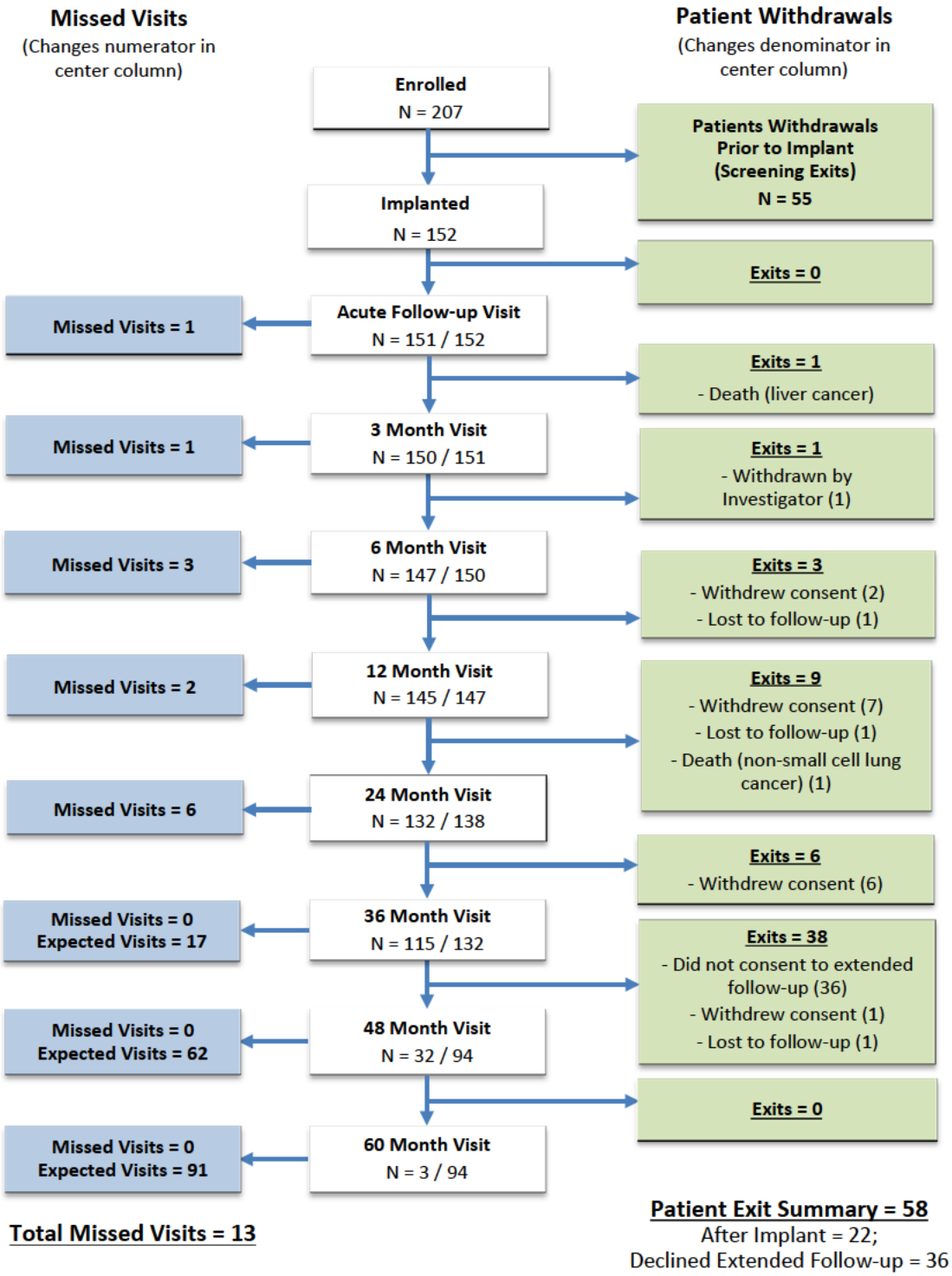


Figure 3: Patient Accountability



Thirty six patients completed the original 36 month study period and declined participation in the extended follow-up (Figure 2). 22 patients withdrew early for the following reasons: 16 withdrew consent, 3 were lost to follow-up, 1 was withdrawn by the investigator for an InterStim implant, and 2 died due to non-treatment related reasons.

Baseline demographic and medical characteristics of the implanted patients are summarized in Tables 5-9. Patients were about 60 years of age (59.6), postmenopausal (82.9%), and primarily Caucasian (90.1%). Obstetric trauma (57.2%) and idiopathic/unknown (40.8%) were the most common reasons given for FI. Overall, the mean Wexner Score at baseline was consistent with significant degree of severe symptoms (13.9). The mean FIQoL scores at baseline were 2.6 for lifestyle, 1.7 for coping, 2.4 for depression, and 1.6 for embarrassment, and are consistent with a significant impact on QoL.

The mean maximum resting anal and squeeze pressures (from anal manometry) were 31.5 ± 21.9 and 60.1 ± 42.6 mmHg, respectively. The majority (52.0%) had an external sphincter defect (mean size 95.3 ± 45.0 degrees) and 27.6% had internal sphincter defects (mean size 110.0 ± 53.7 degrees).

The most common medical history items were previous hysterectomy / oophorectomy (48.7%), previous prolapse and/or UI repair (46.1%), gastroesophageal reflux disease (42.8%), hypertension (39.5%), depressive disorder (36.8%), systemic pain condition (36.2%), hyperlipidemia (34.9%), and pelvic area pain (34.2%). The most common conservative therapies to treat FI tried by subjects prior to enrolling in the TOPAS PMS study were diet modification (86.8%), FI medications (67.8%), and pelvic floor muscle training (85.5%).

Table 5: Demographic and Clinical Characteristics for All Implanted Patients

Variable	Results*
Age (years)	59.6 ± 9.7 (60.0, 32.0 - 79.0)
Height (inches)	64.4 ± 2.5 (64.2, 59.0 - 70.0)
Weight (pounds)	163.6 ± 32.3 (160.0, 90.0 - 261.7)
BMI (kilograms/meter^2)	27.8 ± 5.4 (27.0, 17.0 - 44.5)
Race	
White/Caucasian	137 (90.1%)
Black or African American	10 (6.6%)
American Indian/First Nations/Alaska Native	0 (0.0%)
Asian	1 (0.7%)
Hispanic/Latina	3 (2.0%)
Native Hawaiian/Other Pacific Islander	0 (0.0%)
Other	1 (0.7%)
Obstetric History	
Gravidity	3.0 ± 1.8 (3.0, 0.0 - 9.0)
Parity	2.6 ± 1.4 (2.0, 0.0 - 8.0)
Number of Vaginal Deliveries	2.4 ± 1.5 (2.0, 0.0 - 8.0)
Number of Caesarean Deliveries	0.1 ± 0.5 (0.0, 0.0 - 4.0)
Menopausal Status	
Pre-menopausal	20 (13.2%)
Peri-menopausal	6 (3.9%)
Post-menopausal	126 (82.9%)

**Continuous variables: mean ± SD (median, range); Categorical variables: number of patients (%)*

Table 6: Baseline FI Characteristics for All Implanted Patients

FI Characteristic	Results*
Duration of FI (months)	110.0 ± 113.5 (n=152, 67.0, 8.0 - 712.0)
Etiology of FI	
Anorectal Trauma	6 (3.9%)
Obstetric Trauma	87 (57.2%)
Idiopathic/Unknown	62 (40.8%)
Congenital Abnormality	0 (0.0%)
Other	4 (2.6%)
Baseline Bowel Diary (14 Days)	
Number of All FI Episodes	21.7 ± 15.4 (n=152, 18.0, 4.0 - 81.0)
Number of Urge FI Episodes	6.1 ± 7.3 (n = 152, 4.0, 0.0 - 52.0)
Number of Incontinent Days	9.5 ± 3.2 (n = 152, 10.0, 3.0 - 14.0)
Wexner Score	13.9 ± 2.7 (n=150, 14.0, 5.0 - 20.0)
FIQoL	
Lifestyle	2.6 ± 0.8 (n = 152, 2.7, 1.0 - 4.0)
Coping	1.7 ± 0.6 (n = 152, 1.6, 1.0 - 3.6)
Depression	2.4 ± 0.6 (n = 151, 2.3, 1.0 - 3.9)
Embarrassment	1.6 ± 0.6 (n = 151, 1.7, 1.0 - 3.7)

**Continuous variables: mean ± SD (n, median, range); Categorical variables: number of patients (%)*

Table 7: Baseline Rectal Anatomy and Physiology Characteristics for All Implanted Patients

Variable	Results*
Digital Rectal Exam	
# Soft tissue scarring present (% yes)	26/152 (17.1%)
# Hemorrhoids present (% yes)	34/152 (22.4%)
# Anal resting tone present (% yes)	141/152 (92.8%)
Anorectal Manometry	
Mean Max Resting Pressure (mm Hg)	31.5 ± 21.9 (n=152, 30.0, 0.0 - 134.0)
Mean Max Squeeze Pressure (mm Hg)	60.1 ± 42.6 (n=152, 51.0, 0.0 - 245.0)
First Sensation (cc)	43.1 ± 30.9 (n=152, 40.0, 10.0 - 300.0)
Max Tolerate Volume (cc)	124.8 ± 61.9 (n=152, 117.5, 25.0 - 350.0)
Endoanal Ultrasound or MRI	
External Sphincter Defect? (% yes)	79/152 (52.0%)
External Sphincter Defect (degrees)	95.3 ± 45.0 (n=79, 90.0, 30.0 - 210.0)
Internal Sphincter Defect? (% yes)	42/152 (27.6%)
Internal Sphincter Defect (degrees)	110.0 ± 53.7 (n=42, 120.0, 0.0 - 270.0)

**Continuous variables: mean ± SD (n, median, range); Categorical variables: number of patients (%)*

Table 8: Baseline Medical History Characteristics for All Implanted Patients

Medical History Item	Number Patients (%)
Previous Hysterectomy and/or Oophorectomy	74 (48.7%)
Previous Prolapse and/or UI repair	70 (46.1%)
Gastroesophageal Reflux Disease	65 (42.8%)
Hypertension	60 (39.5%)
Depressive Disorder	56 (36.8%)
Systemic Pain	55 (36.2%)
Hyperlipidemia	53 (34.9%)
Pelvic Area Pain	52 (34.2%)
Diverticulitis	41 (27.0%)
Urinary Incontinence	39 (25.7%)
Hypothyroid	38 (25.0%)
Previous Cholecystectomy	38 (25.0%)
Hemorrhoids	36 (23.7%)
Irritable Bowel Syndrome	31 (20.4%)
Previous Anal Sphincter Repair	31 (20.4%)
Headaches	29 (19.1%)
Vaginal Atrophy	23 (15.1%)
Diabetes	19 (12.5%)
Vaginal Prolapse	8 (5.3%)
Rectal Prolapse	6 (3.9%)
Gallstones	2 (1.3%)

Table 9: Summary of Failed FI Conservative Therapies for All Implanted Patients

Failed Conservative Modality	Number Patients (%)
Diet Modification	132 (86.8%)
FI Medications	103 (67.8%)
Pelvic Floor Muscle Training	130 (85.5%)
Diet Modification Only	0 (0.0%)
FI Medications Only	0 (0.0%)
Pelvic Floor Muscle Training Only	0 (0.0%)
Diet Modification & FI Medications#	22 (14.5%)
Diet Modification & Pelvic Floor Muscle Training[#]	49 (32.2%)
FI Medications & Pelvic Floor Muscle Training[#]	20 (13.2%)
Diet Modification, FI Medication & Pelvic Floor Muscle Training[#]	61 (40.1%)
At Least Two Modalities of FI Treatments	152 (100.0%)

[#] *Mutually exclusive categories*

4.3 PROCEDURE SUMMARY

The TOPAS system procedure was completed, on average, in 33.4 ± 11.6 minutes (range 11.0 -71.0) and 98% of the cases (149 of 152) were completed in under 60 minutes. The length of procedure was similar for colorectal physicians (30.7 ± 11.1 min; range, 12.0 - 59.0) compared to urogynecology physicians 35.2 ± 11.6 min; range, 11.0 - 71.0). The majority of the implant procedures (78.9%) were completed under general anesthesia. Blood loss during the implant procedure was minimal (mean of 12.9 ± 10.5 mL) and patients were able to return home on average 10.9 ± 10.7 hours (range, 1.7 - 56.8) after the procedure.

4.4 EFFECTIVENESS RESULTS

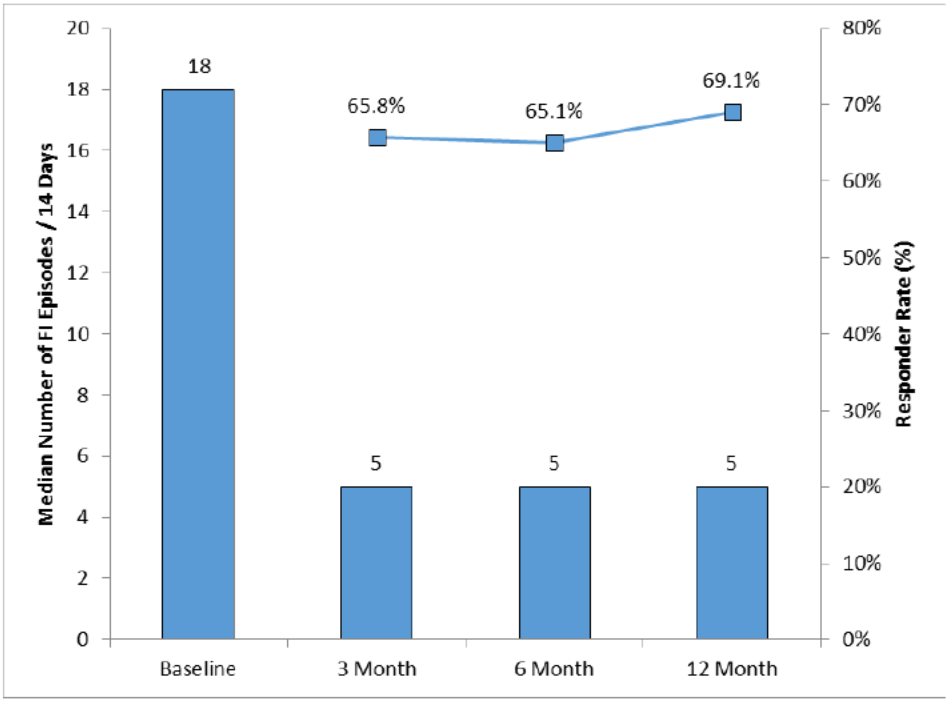
4.4.1 Primary Effectiveness Objective

The median number of FI episodes (14 day bowel diary period) was 18 (range 4 - 81) at baseline for all implanted patients and decreased by more than 50% at 3 month and all subsequent follow-up visits. The median number of FI episodes post-implant remained stable through 12 months (Table 10 and Figure 4).

Table 10: Summary of All FI Episodes (14 Day Period) Through 12 Months for All Implanted Patients and for Stage I and Stage II Patients

Study Visit	All Implanted Patients (N=152)		Stage I Patients (first 80 implanted)		Stage II Patients (last 72 implanted)	
	Median (range)	Mean ± SD (N)	Median (range)	Mean ± SD (N)	Median (range)	Mean ± SD (N)
BASELINE	18.0 (4 - 81)	21.7 ± 15.4 (N=152)	17.0 (5 - 81)	21.2 ± 15.2 (N=80)	19.0 (4 - 78)	22.1 ± 15.7 (N=72)
3 MONTH	5.0 (0 - 94)	9.2 ± 13.7 (N=149)	6.0 (0 - 94)	9.6 ± 13.8 (N=79)	5.0 (0 – 87)	8.7 ± 13.6 (N=70)
6 MONTH	5.0 (0 - 67)	8.2 ± 10.6 (N=143)	4.0 (0 – 67)	8.1 ± 11.7 (N=76)	5.0 (0 - 42)	8.3 ± 9.6 (N=67)
12 MONTH	5.0 (0 - 80)	9.3 ± 13.6 (N=144)	6.0 (0 - 80)	11.6 ± 16.6 (N=78)	4.0 (0 - 45)	6.6 ± 8.4 (N=66)

Figure 4: Median Number of All FI Episodes and Responder Rates through 12 Months for All Implanted Patients



At the 12 month visit, 69.1% (105/152) of all implanted patients were treatment responders, defined as having at least a 50% decrease in FI episodes from baseline to 12 months post-operatively (Table 11) (Stage I: 65.0% p=0.0048 and Stage II: 73.6%, p < 0.0001).

Table 11: Responder Rate at 12 Months for Stage I, Stage II, and All Implanted Patients

Patient Group	N	Responder Rate [95% CI]*	p-value
All Implanted	152	69.1% (105/152) [61.1%, 76.3%]	not applicable due to the two stage design
Stage I	80	65.0% (52/80) [53.5%, 75.3%]	0.0048
Stage II	72	73.6% (53/72) [61.9%, 83.3%]	<0.0001

** 95% CIs were calculated assuming a single-look fixed-sample-size design for all implanted*

4.4.1.1 Pre-specified Sensitivity Analyses

In the primary analysis of the responder rate at 12 months, there were only eight patients with missing data. Table 12 summarizes the findings from the pre-specified sensitivity analyses conducted to examine the impact of missing data. All findings were consistent with the robust responder rate observed in the pre-specified primary analysis.

Table 12: Responder Rates at 12 Months Calculated with Different Sensitivity Methods for All Implanted Patients and for Stage I and Stage II Patients

Missing Data Handling Method	All Implanted		Stage I Patients		Stage II Patients	
	N	Responder Rate [95% CI]*	N	Responder Rate [95% CI]*	N	Responder Rate [95% CI]*
Worst Case (Missing = Treatment Failure)	152	69.1% (105/152) [61.1%, 76.3%]	80	65.0% (52/80) [53.5%, 75.3%]	72	73.6% (53/72) [61.9%, 83.3%]
Modified Worst Case	152	69.1% (105/152) [61.1%, 76.3%]	80	65.0% (52/80) [53.5%, 75.3%]	72	73.6% (53/72) [61.9%, 83.3%]
Last Observation Carried Forward	152	70.4% (107/152) [62.5%, 77.5%]	80	67.5% (54/80) [56.1%, 77.6%]	72	73.6% (53/72) [61.9%, 83.3%]
Completed Cases Only	144	72.9% (105/144) [64.9%, 80.0%]	78	66.7% (52/78) [55.1%, 76.9%]	66	80.3% (53/66) [68.7%, 89.1%]

** 95% CIs were calculated assuming a single-look fixed-sample-size design*

4.4.1.2 Sensitivity Analyses Based upon Different Definitions to Define Response

The primary analyses defined response as a 50% reduction in FI at 12 months when compared to baseline. As shown in Table 13, most patients in the study had substantial reduction in FI from baseline. For example, of the 27 patients reporting from 15-20 FI episodes over the 14 day baseline period, only two had a frequency increase and 12 of 27 had reduced FI episodes to 4 or fewer over 14 days at the 12 month visit.

Table 13: Shift from Baseline to 12 Months in FI Episodes over 14 Days

	12 Month FI Frequency N (%)							
Baseline FI Frequency	**[0,4)**	**[4, 10]**	**(10, 15]**	**(15, 20]**	**(20, 30]**	**(30, 81]**	**Missing**	**Total**
[0,4]	NA	NA	NA	NA	NA	NA		
[4, 10]	22 (14.47)	7 (4.61)	2 (1.32)	2 (1.32)	0 (0.00)	0 (0.00)	3 (1.97)	36 (23.68)
(10, 15]	13 (8.55)	10 (6.58)	2 (1.32)	3 (1.97)	0 (0.00)	0 (0.00)	1 (0.66)	29 (19.08)
(15, 20]	12 (7.89)	9 (5.92)	2 (1.32)	1 (0.66)	1 (0.66)	1 (0.66)	1 (0.66)	27 (17.76)
(20, 30]	6 (3.95)	14 (9.21)	5 (3.29)	3 (1.97)	2 (1.32)	0 (0.00)	0 (0.00)	30 (19.74)
(30, 81]	6 (3.95)	4 (2.63)	3 (1.97)	3 (1.97)	3 (1.97)	8 (5.26)	3 (1.97)	30 (19.74)
Total	59 (38.82)	44 (28.95)	14 (9.21)	12 (7.89)	6 (3.95)	9 (5.92)	8 (5.26)	152 (100)

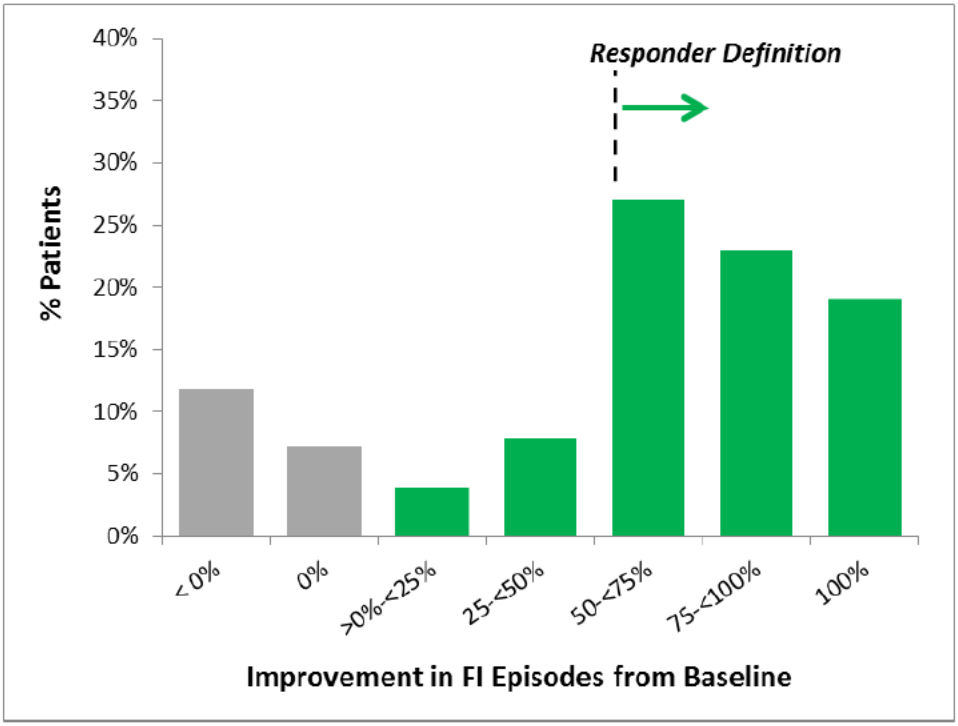
FI Categories were defined based upon baseline quintiles; NA=not applicable

To examine the clinical meaningfulness of the primary response rate definition, additional analyses were conducted using other definitions to define response (Table 14). At 12 months, 19.1% of all implanted patients (29/152) achieved complete continence and 23.0% (35/152) reported improvements in FI frequency of greater than 75% and <100% from baseline (Figure 5). This indicates that 42.1% (64/152) of the study patients had a large decrease in FI episodes of 75% or more (Table 14).

Table 14: Responder Rates at 12 Months Based upon Different Definitions to Define Response

Responder Definition	Responder Rate
> 0% reduction	80.9% (123/152)
≥ 25% reduction	77.0% (117/152)
≥ 50% reduction	69.1% (105/152)
≥ 75% reduction	42.1% (64/152)
100% reduction (complete continence)	19.1% (29/152)

Figure 5: Primary Efficacy Improvement Categories at 12 Months for All Implanted Patients



Note: 0% improvement category includes patients with missing data = 5.3%.

4.4.1.3 Responder Rate by Patient Subgroup

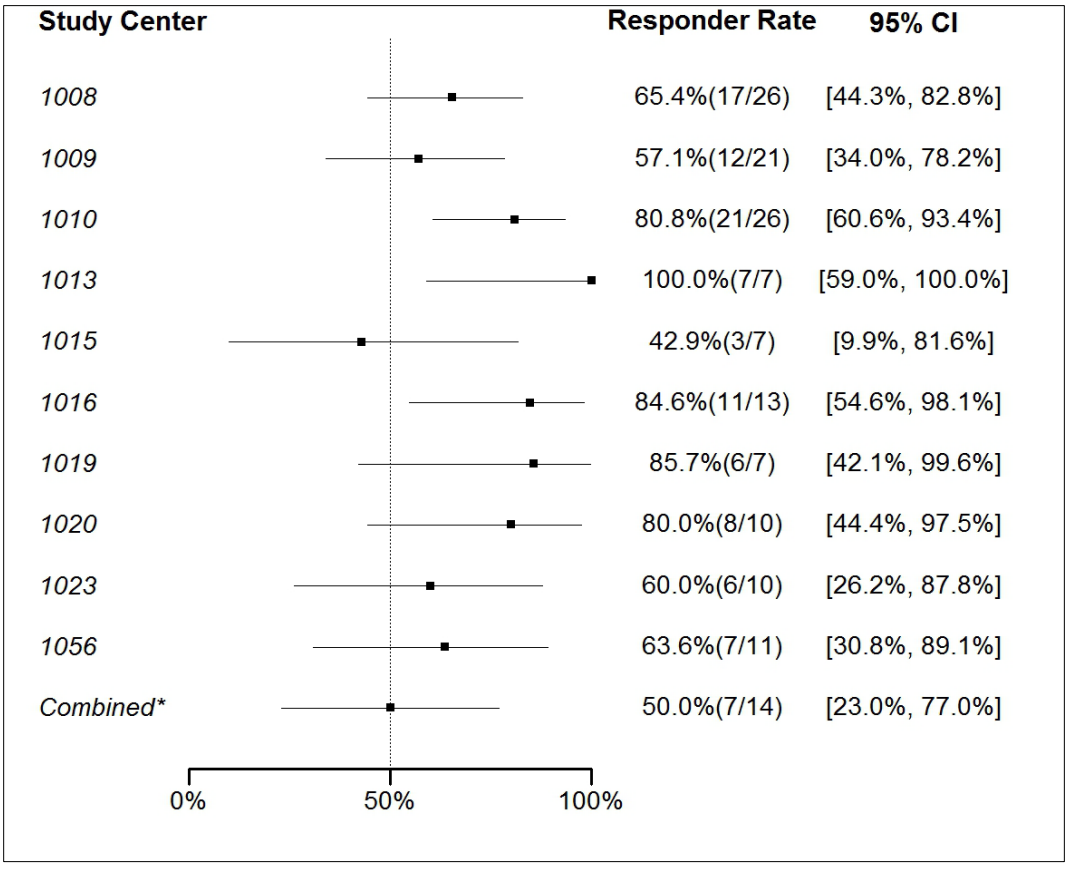
A logistic regression model was performed to examine the association of important baseline covariates with treatment success at 12 months including medical specialty, age, BMI, FI etiology, baseline frequency of FI episodes, number of vaginal deliveries, anorectal anatomy and physiology parameters, and medical history items. These analyses were considered exploratory in nature because the TOPAS PMA Study was not powered to perform these tests. The responder rate was consistent across all

subgroups and this analysis found no particular patient characteristics to be statistically significant and clinical meaningful in predicting treatment success with the TOPAS system (see Appendix 2 Table 37 for complete results).

4.4.1.4 Responder Rate by Study Center

Primary effectiveness data were examined by study center; centers with fewer than 5 treated patients were combined. According to Fisher's Exact test, there was no statistically significant difference in response rate among study centers at 12 months for all implanted patients (p=0.1540; Figure 6), for Stage I patients (p=0.9035), or Stage II patients (p=0.3754). Therefore, the primary efficacy data were poolable across centers.

Figure 6: Responder Rates by Study Center



4.4.1.5 FI Medication Use

FI medication use during the trial was not controlled. To examine if changes in FI medication use were associated with the primary efficacy results, FI medication usage (by total number of medications taken and by the number of subjects taking the medications) was assessed at baseline and 12 months. These data do not account for changes in medication dosages that may have occurred. For treatment responders, the number of subjects taking medications decreased slightly from baseline to 12 months (-3; Table 15) and did not change for non-responders (Table 16).

Table 15: FI Medication Usage for Responders (N=105)

FI Medication Class	Baseline		12 Month		Change	
	# of Meds	# of Subjects taking meds	# of Meds	# of Subjects taking meds	# of Meds	# of Subjects taking meds
Anti-Cholinergic Agents	3	2	4	3	1	1
Opioid Receptor Agents	21	19	20	18	-1	-1
Bulking Agents	17	16	19	16	2	0
Osmotic Laxatives	8	7	9	7	1	0
Bile Acid Sequestrants	3	3	2	2	-1	-1
Other	1	1	5	5	4	4
Total (Any of the Above)	**53**	**40***	**59**	**37***	**6**	**-3**

** Some subjects were taking multiple medications from the above medication classes so the total is not a sum for the column*

Table 16: FI Medication Usage for Non-Responders (N=47)

FI Medication Class	Baseline		12 Month		Change	
	# of Meds	# of Subjects taking meds	# of Meds	# of Subjects taking meds	# of Meds	# of Subjects taking meds
Anti-Cholinergic Agents	4	4	2	2	-2	-2
Opioid Receptor Agents	13	11	11	11	-2	0
Bulking Agents	7	6	10	9	3	3
Osmotic Laxatives	2	2	4	4	2	2
Bile Acid Sequestrants	0	0	1	1	1	1
Other	4	4	3	3	-1	-1
Total (Any of the Above)	**30**	**21***	**31**	**21***	**1**	**0**

** Some subjects were taking multiple medications from the above medication classes so the total is not a sum for the column*

Table 17: Number of Subjects Taking FI Medications at 12 Months by Responder Category

Variable	Responders (N=105)	Non-Responders (N=47)	p-value
Anti-Cholinergic Agents	3 (2.9%)	2 (4.3%)	0.616†
Bile Acid Sequestrants	2 (1.9%)	1 (2.1%)	1.000†
Bulking Agents	16 (15.2%)	9 (19.1%)	0.301*
Opioid Receptor Agents	18 (17.1%)	11 (23.4%)	0.163*
Osmotic Laxatives	7 (6.7%)	4 (8.5%)	0.496†
Other	5 (4.8%)	3 (6.4%)	0.685†
Total (Any of the Above)	**37 (35.2%)**	**21 (44.7%)**	**0.058***

† *Fisher Exact test;* * *Chi-square test with available data*

At 12 months, more non-responders (44.7%, 21/47) were taking an FI medication than responders (35.2%, 37/105), although the difference was not significant (p=0.058; Table 17). Opioid receptor medication use (i.e., antidiarrheals such as Loperamide or Atropine/Diphenoxylate) was not statistically different between the two groups (17.1% vs. 23.4% for responders and non-responders, respectively, p=0.163). These data suggest the reductions in FI episodes at 12 months in the responder group were not the result of more patients taking FI medications compared to the non-responders.

4.4.2 Secondary Effectiveness Objectives

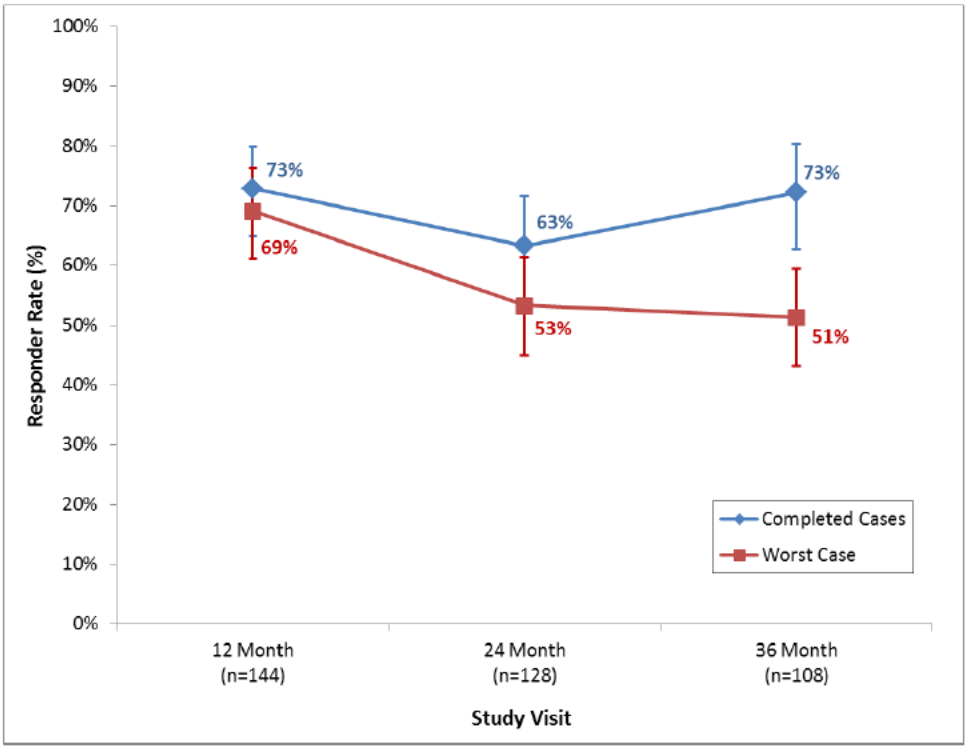
4.4.2.1 Responder Rate during Long-Term Follow-up

The reduction in the median number of FI episodes observed at 12 months was durable at 36 months in the 108 patients who had completed that visit (Table 18). Similarly, the responder rate at 36 months was 72.2% (completed cases only, Figure 7). Even when calculated with a worst case method (i.e., missing=treatment failure) the responder rate at 36 months was 51.3% and continued to exceed the 50% threshold for treatment success.

Table 18: Summary of All FI Episodes (14 day Period) Through 60 Months for All Implanted Patients

Study Visit	N	Median	Range	Mean ± SD
BASELINE	152	18.0	4 - 81	21.7 ± 15.4
12 MONTH	144	5.0	0 - 80	9.3 ± 13.6
24 MONTH	128	5.0	0 - 73	9.2 ± 11.6
36 MONTH	108	5.0	0 - 52	7.6 ± 9.3
48 MONTH	32	2.0	0 - 22	4.1 ± 5.4
60 MONTH	3	3.0	0 - 5	2.7 ± 2.5

Figure 7: Responder Rates through 36 Months for All Implanted Patients



4.4.2.2 Number of Incontinent Days

The mean number of incontinent days decreased by more than 50% from baseline (9.5 ± 3.2) to 3 months (4.7 ± 3.9) and remained at a similar level through 36 months (4.4 ± 3.8) indicating the effectiveness of the TOPAS system on reducing incontinent days is durable (Table 19).

Table 19: Summary of Incontinent Days (14 Day Period) Through 60 Months for All Implanted Patients

Study Visit	N	Mean ± SD (median, range)	Incontinent Days Responder Rate*
BASELINE	152	9.5 ± 3.2 (10.0, 3 - 14)	---
3 MONTHS	149	4.7 ± 3.9 (4.0, 0 - 14)	61.1% (91/149)
6 MONTHS	143	4.4 ± 3.7 (4.0, 0 - 14)	59.4% (85/143)
12 MONTHS	144	4.5 ± 3.9 (4.0, 0 - 14)	57.6% (83/144)
24 MONTHS	128	4.7 ± 4.1 (4.0, 0 - 14)	54.7% (70/128)
36 MONTHS	108	4.4 ± 3.8 (4.0, 0 - 14)	59.3% (64/108)
48 MONTHS	32	2.6 ± 2.9 (2.0, 0 - 11)	81.3% (26/32)
60 MONTHS	3	2.0 ± 1.7 (3.0, 0 - 3)	100.0% (3/3)

** Calculated with "Completed Cases Only" method.*

4.4.2.3 Number of Urge FI Episodes

The median number of urge FI episodes decreased from 4 (range, 0 - 52) at Baseline to 0 (range, 0 - 16) at 3 months and remained at a median of 0 through 36 months (range, 0 - 34; Table 20) indicating the effect of the TOPAS system on reducing urge FI episodes is durable.

Table 20: Summary of Urge FI Episodes (14 Day Period) for All Implanted Patients

Study Visit	N	Median (Mean ± SD, range)	Change from Baseline* Median (Q1, Q3)	% Change from Baseline* Median (Q1, Q3)
BASELINE	152	4.0 (6.1 ± 7.3, 0 - 52)	---	---
3 MONTH	149	0.0 (1.7 ± 2.7, 0 - 16)	-3.0 (-6.0 , 0.0)	-93.8 (-100.0 , -42.9)
6 MONTH	143	0.0 (1.9 ± 3.2, 0 - 18)	-3.0 (-6.0 , 0.0)	-86.6 (-100.0 , -50.0)
12 MONTH	144	0.0 (2.1 ± 4.1, 0 - 29)	-3.0 (-6.0 , 0.0)	-88.6 (-100.0 , -43.3)
24 MONTH	128	0.0 (2.5 ± 5.5, 0 - 39)	-2.0 (-6.0 , 0.0)	-86.6 (-100.0 , -51.6)
36 MONTH	108	0.0 (2.3 ± 4.6, 0 - 34)	-2.5 (-6.0 , 0.0)	-83.3 (-100.0 , -40.0)
48 MONTH	32	0.0 (0.9 ± 1.8, 0 - 8)	-3.5 (-8.0 , -1.0)	-100.0 (-100.0 , -80.0)
60 MONTH	3	0.0 (0.0 ± 0.0, 0 - 0)	-6.0 (-6.0 , -1.0)	-100.0 (-100.0 , -100.0)

** Change from baseline was calculated at the patient level with matched pairs of data.*

4.4.2.4 Wexner Score

The mean Wexner Score decreased from 13.9 ± 2.7 at baseline to 9.4 ± 4.3 at 3 months and remained below 10 through the 36 month visit (Table 21 and Figure 8). The MCID for change in the Wexner Score has not been established. For all follow-up visits, the change in the score approximates 1 SD, which exceeds the ½ SD threshold observed for MCIDs observed with many PRO scales (Norman 2003). Given the size of the change observed with the Wexner Score, which was greater in responders and correlated with percentage reduction in FI from baseline (Figure 9), the changes likely represent a strong clinical response.

Table 21: Wexner Score Summary for All Implanted Patients

Study Visit	N	Mean ± SD (median, range)	Change from Baseline* Mean [95% CI]	% Change from Baseline* Mean [95% CI]
BASELINE	150	13.9 ± 2.7 (14.0, 5.0 - 20.0)	---	---
3 MONTH	146	9.4 ± 4.3 (10.0, 0.0 - 20.0)	-4.4 [-5.1 , -3.8]	-32.3 [-37.1 , -27.5]
6 MONTH	145	9.8 ± 4.4 (10.0, 0.0 - 18.0)	-4.1 [-4.8 , -3.4]	-29.2 [-34.1 , -24.2]
12 MONTH	144	9.6 ± 3.9 (10.0, 0.0 - 17.0)	-4.3 [-4.9 , -3.6]	-30.0 [-34.7 , -25.2]
24 MONTH	126	9.5 ± 4.2 (10.0, 0.0 - 18.0)	-4.2 [-4.9 , -3.5]	-29.7 [-34.9 , -24.5]
36 MONTH	108	9.4 ± 4.3 (10.0, 0.0 - 18.0)	-4.3 [-5.1 , -3.5]	-30.3 [-36.4 , -24.3]
48 MONTH	31	8.1 ± 4.7 (7.0, 0.0 - 16.0)	-5.5 [-7.3 , -3.8]	-40.2 [-52.3 , -28.2]
60 MONTH	2	4.5 ± 3.5 (4.5, 2.0 - 7.0)	-11.0 [-74.5 , 52.5]	-67.5 [-339.0 , 204.0]

** Change from baseline was calculated at the patient level with matched pairs of data. Scale is 0-20 with higher score = more severe FI.*

Figure 8: Wexner Score by Study Visit for All Implanted Patients

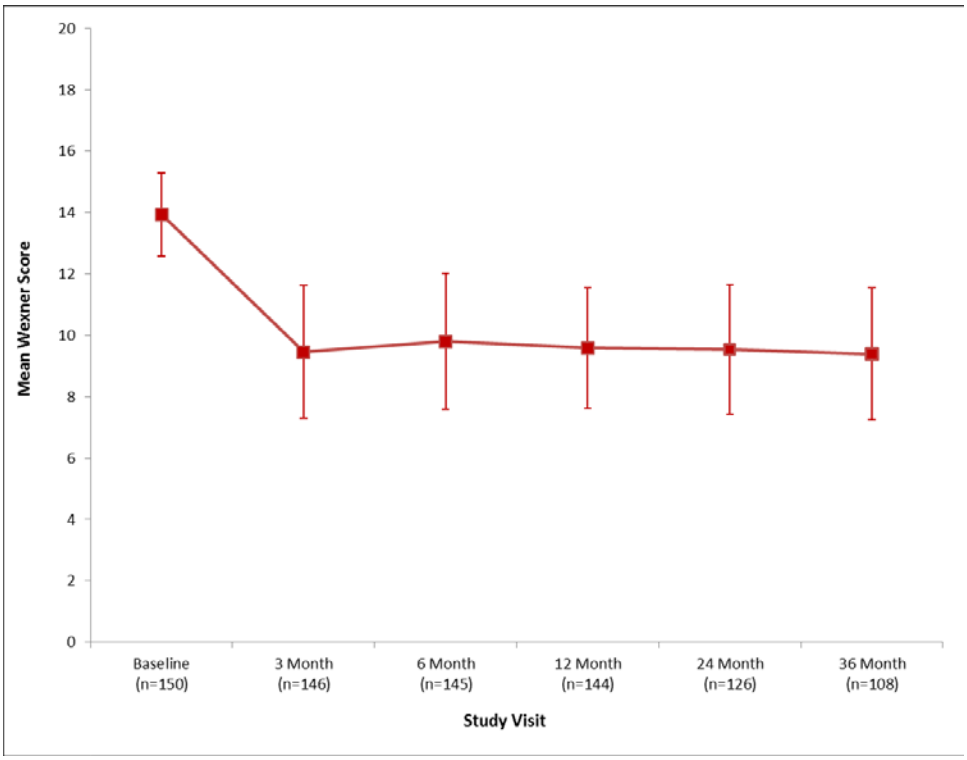
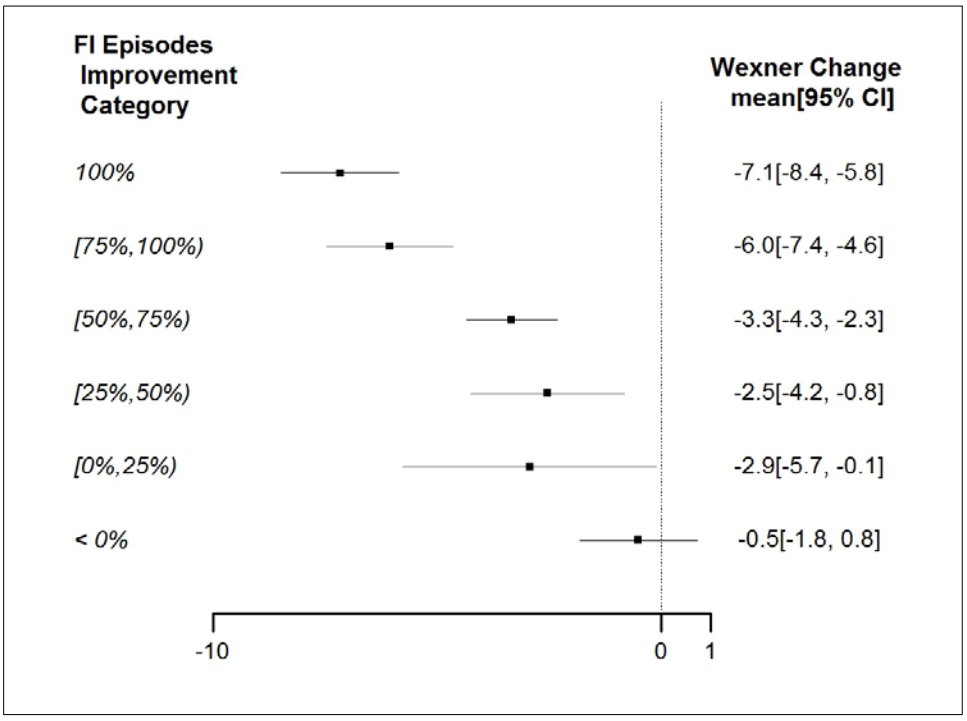


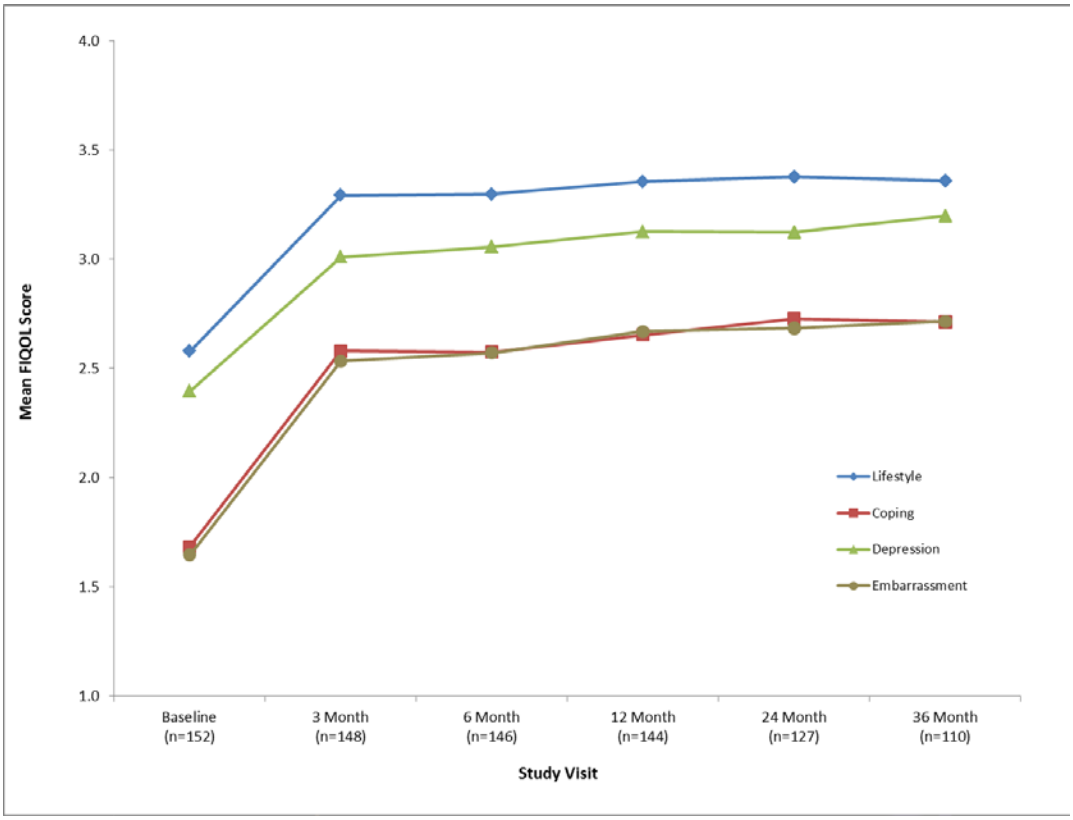
Figure 9: Change in Wexner Score by FI Improvement Category for All Implanted Patients, Mean (95% CI)



4.4.2.5 FIQoL Score

For all FIQoL domains, scores increased from baseline to 3 months and were maintained at improved levels throughout the rest of the follow-up period (Table 23 and Figure 10). There is also no MCID for the FIQoL. As with the Wexner Score, the change from baseline is about 1 SD and there was correlation of FIQoL to responder status and the percentage decrease in FI episodes. In Figure 11, the mean and 95% CI for the change from baseline for each of the FIQOL subscale scores is shown by the category of FI reduction. FI reduction of 50% or more was associated with a substantial improvement in FIQoL.

Figure 10: FIQoL Score by Study Visit for All Implanted Patients



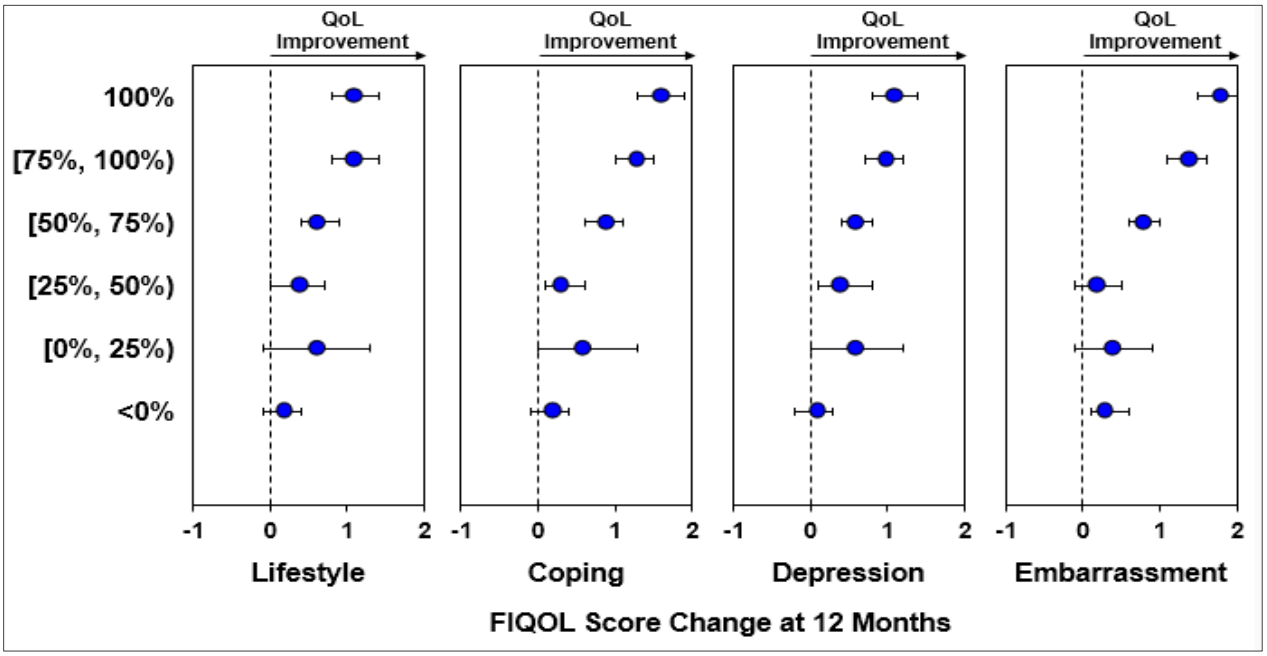
Note: Error bars have been omitted from Figure 10 for clarity. See Appendix 4, Figure 24 for line graphs of each FIQoL domain with error bars.

Table 22: FIQoL Score Summary for All Implanted Patients

Study Visit	N	Lifestyle Mean ± SD (median, range)	Change from Baseline* Mean [95% CI]	Coping Mean ± SD (median, range)	Change from Baseline* Mean [95% CI]	Depression Mean ± SD (median, range)	Change from Baseline* Mean [95% CI]	Embarrassment Mean ± SD (median, range)	Change from Baseline* Mean [95% CI]
BASELINE	152	2.6 ± 0.8 (2.7, 1.0 - 4.0)	---	1.7 ± 0.6 (1.6, 1.0 - 3.6)	---	2.4 ± 0.6 (2.3, 1.0 - 3.9)	---	1.6 ± 0.6 (1.7, 1.0 - 3.7)	---
3 MONTH	148	3.3 ± 0.7 (3.6, 1.0 - 4.0)	0.7 [0.6 , 0.8]	2.6 ± 0.8 (2.6, 1.0 - 4.0)	0.9 [0.8 , 1.0]	3.0 ± 0.7 (3.1, 1.1 - 4.0)	0.6 [0.5 , 0.7]	2.5 ± 0.9 (2.7, 1.0 - 4.0)	0.9 [0.7 , 1.0]
6 MONTH	146	3.3 ± 0.7 (3.5, 1.1 - 4.0)	0.7 [0.6 , 0.9]	2.6 ± 0.9 (2.6, 1.1 - 4.0)	0.9 [0.7 , 1.0]	3.1 ± 0.7 (3.1, 1.5 - 4.0)	0.7 [0.5 , 0.8]	2.6 ± 1.0 (2.7, 1.0 - 4.0)	0.9 [0.8 , 1.1]
12 MONTH	144	3.4 ± 0.7 (3.6, 1.0 - 4.0)	0.8 [0.6 , 0.9]	2.7 ± 0.9 (2.7, 1.0 - 4.0)	1.0 [0.8 , 1.1]	3.1 ± 0.7 (3.2, 1.1 - 4.0)	0.7 [0.6 , 0.8]	2.7 ± 0.9 (2.7, 1.0 - 4.0)	1.0 [0.9 , 1.2]
24 MONTH	127	3.4 ± 0.7 (3.7, 1.4 - 4.0)	0.8 [0.6 , 0.9]	2.7 ± 0.9 (2.8, 1.0 - 4.0)	1.0 [0.9 , 1.2]	3.1 ± 0.7 (3.3, 1.3 - 4.0)	0.7 [0.6 , 0.8]	2.7 ± 0.9 (2.7, 1.0 - 4.0)	1.0 [0.8 , 1.2]
36 MONTH	110	3.4 ± 0.7 (3.6, 1.5 - 4.0)	0.7 [0.6 , 0.9]	2.7 ± 0.9 (2.8, 1.1 - 4.0)	1.0 [0.8 , 1.1]	3.2 ± 0.7 (3.5, 1.1 - 4.0)	0.7 [0.6 , 0.9]	2.7 ± 0.9 (2.7, 1.0 - 4.0)	1.0 [0.8 , 1.1]
48 MONTH	31	3.5 ± 0.6 (3.8, 1.8 - 4.0)	0.9 [0.6 , 1.2]	2.9 ± 0.9 (3.1, 1.0 - 4.0)	1.3 [0.9 , 1.7]	3.3 ± 0.7 (3.6, 1.3 - 4.0)	0.8 [0.6 , 1.0]	2.8 ± 1.0 (3.0, 1.0 - 4.0)	1.1 [0.7 , 1.4]
60 MONTH	2	4.0 ± 0.0 (4.0, 4.0 - 4.0)	1.1 [-5.3 , 7.5]	3.7 ± 0.4 (3.7, 3.4 - 4.0)	2.3 [0.2 , 4.4]	3.5 ± 0.6 (3.5, 3.1 - 3.9)	0.9 [-1.5 , 3.3]	3.8 ± 0.2 (3.8, 3.7 - 4.0)	2.7 [-1.5 , 6.9]

** Change from baseline was calculated at the patient level with matched pairs of data; Scale is 1-4 for each domain with higher scores = better QOL.*

Figure 11: FIQoL Score Change at 12 Months by FI Improvement Category for All Implanted Patients, Mean (95% CI)



4.4.2.6 Pelvic Floor Distress Inventory (PFDI-20)

For the total PFDI-20 score and all subscales, values decreased from baseline to 3 months and were maintained at improved levels throughout the rest of the follow-up period (Table 23). The largest changes were observed in the colo-rectal-anal (CRADI) subscale, which contributed the most to the decreases in the overall PFDI-20 score. The mean change from baseline in the total PFDI-20 scores was more than ½ SD for all follow-up visits and the mean change from baseline in the CRADI score exceeded the MCID of -5 points established by Jelovsek et al. (2014) for all follow-up visits, indicating these decreases in pelvic floor distress were clinically important.

In Figure 12, the CRADI score is shown by category of FI episode reduction. FI episode reduction of ≥ 50% was associated with a substantial improvement in the CRADI score.

Figure 12: Change in CRADI Score by FI Improvement Category for All Implanted Patients, Mean (95% CI)

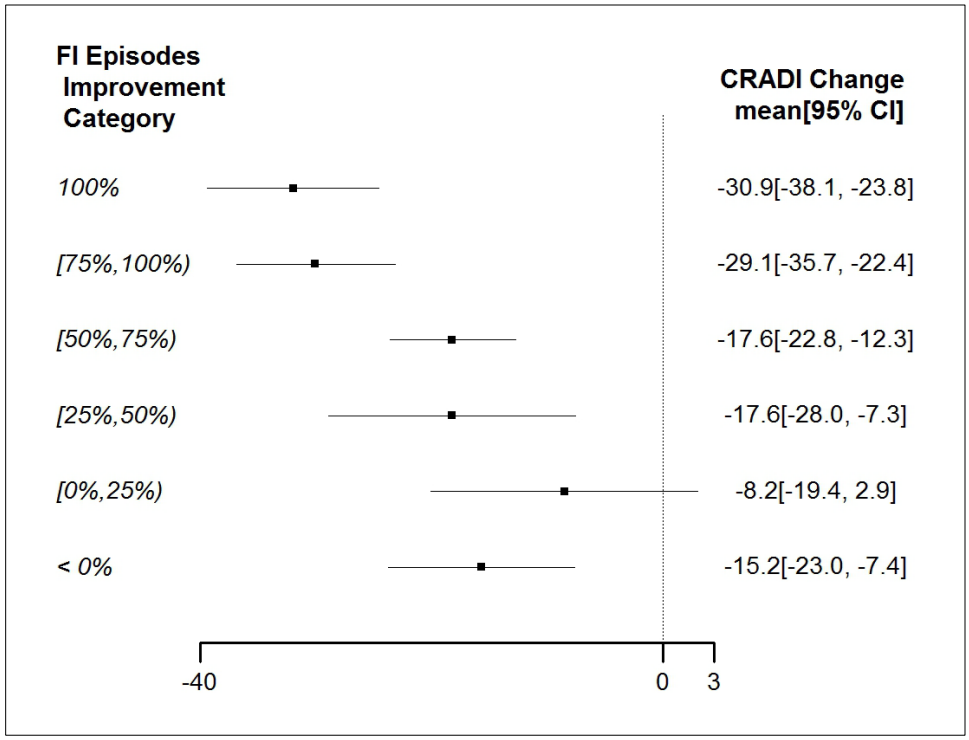


Table 23: PFDI-20 Score Summary for All Implanted Patients

Study Visit	N	CRADI Mean ± SD (median, range)	Change from Baseline* Mean [95% CI]	POPDI Mean ± SD (median, range)	Change from Baseline* Mean [95% CI]	UDI Mean ± SD (median, range)	Change from Baseline* Mean [95% CI]	Total Score Mean ± SD (median, range)	Change from Baseline* Mean [95% CI]
BASELINE	151	54.8 ± 16.2 (53.6, 6.3 - 100.0)	---	21.9 ± 19.5 (16.7, 0.0 - 83.3)	---	27.2 ± 25.1 (25.0, 0.0 - 100.0)	---	104.1 ± 47.4 (96.9, 22.9 - 245.8)	---
3 MONTH	147	33.3 ± 17.7 (34.4, 0.0 - 75.0)	-21.2 [-24.1 , -18.2]	14.9 ± 15.6 (8.3, 0.0 - 66.7)	-6.5 [-9.4 , -3.6]	21.4 ± 21.5 (16.7, 0.0 - 87.5)	-5.2 [-8.2 , -2.2]	69.7 ± 43.1 (63.6, 0.0 - 197.9)	-32.8 [-39.5 , -26.1]
6 MONTH	145	33.0 ± 19.8 (31.3, 0.0 - 96.9)	-21.8 [-25.2 , -18.3]	14.2 ± 14.9 (8.3, 0.0 - 54.2)	-7.8 [-10.8 , -4.8]	21.4 ± 22.7 (16.7, 0.0 - 95.8)	-5.9 [-9.4 , -2.5]	68.8 ± 45.9 (56.3, 0.0 - 215.6)	-35.5 [-43.2 , -27.9]
12 MONTH	143	32.1 ± 19.2 (31.3, 0.0 - 75.0)	-22.2 [-25.3 , -19.1]	12.8 ± 13.9 (8.3, 0.0 - 58.3)	-8.9 [-11.7 , -6.1]	21.5 ± 21.9 (16.7, 0.0 - 95.8)	-6.3 [-9.4 , -3.1]	66.7 ± 43.4 (57.1, 0.0 - 212.5)	-37.3 [-44.2 , -30.4]
24 MONTH	127	31.5 ± 19.7 (31.3, 0.0 - 87.5)	-22.2 [-25.7 , -18.7]	12.1 ± 13.8 (8.3, 0.0 - 70.8)	-9.0 [-12.1 , -5.9]	22.2 ± 22.1 (16.7, 0.0 - 100.0)	-5.6 [-9.1 , -2.0]	65.7 ± 43.9 (58.3, 0.0 - 258.3)	-36.8 [-44.2 , -29.3]
36 MONTH	108	33.5 ± 21.0 (33.3, 0.0 - 81.3)	-20.3 [-23. 9, -16.7]	13.8 ± 16.9 (8.3, 0.0 - 79.2)	-7.9 [-11.6 , -4.2]	22.6 ± 23.0 (16.7, 0.0 - 83.3)	-6.5 [-10.9 , -2.1]	70.3 ± 51.2 (54.7, 0.0 - 201.1)	-34.5 [-44.4, -24.6]
48 MONTH	31	29.9 ± 18.1 (28.6, 0.0 - 71.4)	-22.2 [-28.0 , -16.4]	14.9 ± 17.6 (8.3, 0.0 - 62.5)	-4.1 [-11.2 , 3.1]	26.9 ± 26.4 (16.7, 0.0 - 95.8)	-3.2 [-11.8 , 5.3]	71.7 ± 52.7 (64.3, 7.1 - 189.3)	-29.5 [-46.7 , -12.3]
60 MONTH	2	14.3 ± 20.2 (14.3, 0.0 - 28.6)	-37.5 [-105.6 , 30.6]	10.4 ± 14.7 (10.4, 0.0 - 20.8)	-6.3 [-85.7 , 73.2]	8.3 ± 0.0 (8.3, 8.3 - 8.3)	-4.2 [-163.0 , 154.7]	33.0 ± 34.9 (33.0, 8.3 - 57.7)	-47.9 [-354.3 , 258.4]

** Change from baseline was calculated at the patient level with matched pairs of data. PFDI-20 is composed of three subscales (CRADI, POPDI, UDI) scored on a scale of 0 to 100 and a total scored on a scale of 0 to 300. Higher values = greater pelvic floor distress.*

4.4.2.7 Pelvic Floor Impact Questionnaire (PFIQ-7)

Similar to the changes observed for the PFDI-20 scores, values for the total PFIQ-7 and all subscales decreased from baseline to 3 months and were maintained at improved levels for the remainder of the follow-up period. The largest changes were observed in the CRAIQ subscale, which contributed the most to the decreases in the overall PFIQ-7 score. The mean change from baseline in the total PFIQ scores was more than ½ SD for all follow-up visits and the mean change from baseline in the CRAIQ score exceeded the MCID of -8 points established by Jelovsek et al. (2014) for all follow-up visits, indicating that these decreases were clinically important (Table 24).

In Figure 13, the CRAIQ score is shown by category of FI episode reduction. FI episode reduction of ≥ 50% was associated with a substantial improvement in the CRAIQ score.

Figure 13: Change in CRAIQ Score by FI Improvement Category for All Implanted Patients, Mean (95% CI)

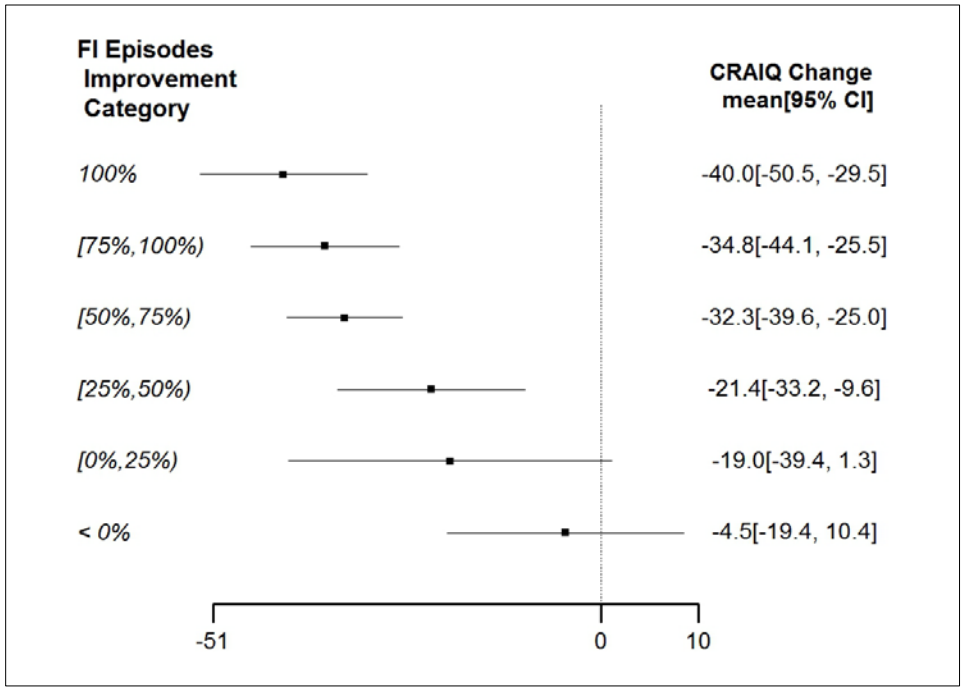


Table 24: PFIQ-7 Score Summary for All Patients

Study Visit	N	CRAIQ Mean ± SD (median, range)	Change from Baseline* Mean [95% CI]	POPIQ Mean ± SD (median, range)	Change from Baseline* Mean [95% CI]	UIQ Mean ± SD (median, range)	Change from Baseline* Mean [95% CI]	Total Score Mean ± SD (median, range)	Change from Baseline* Mean [95% CI]
BASELINE	149	51.7 ± 25.5 (54.8, 4.8 - 100.0)	---	9.8 ± 19.5 (0.0, 0.0 - 94.4)	---	18.5 ± 23.6 (4.8, 0.0 - 90.5)	---	79.6 ± 52.3 (71.4, 4.8 - 276.2)	---
3 MONTH	147	23.1 ± 22.7 (19.1, 0.0 - 100.0)	-28.5 [-32.8 , -24.2]	5.2 ± 11.8 (0.0, 0.0 - 90.5)	-4.2 [-7.4 , -1.0]	12.7 ± 19.8 (0.0, 0.0 - 95.2)	-5.2 [-8.6 , -1.8]	41.0 ± 43.5 (28.6, 0.0 - 257.2)	-37.7 [-45.3 , -30.1]
6 MONTH	141	23.3 ± 24.1 (14.3, 0.0 - 95.2)	-27.7 [-32.2 , -23.2]	5.8 ± 16.3 (0.0, 0.0 - 95.2)	-4.2 [-7.1 , -1.3]	10.8 ± 18.3 (0.0, 0.0 - 90.5)	-7.7 [-11.1 , -4.2]	39.6 ± 48.4 (23.8, 0.0 - 281.0)	-39.7 [-47.9 , -31.5]
12 MONTH	143	21.7 ± 22.6 (14.3, 0.0 - 100.0)	-29.3 [-33.9 , -24.8]	4.8 ± 12.7 (0.0, 0.0 - 71.4)	-5.4 [-8.4 , -2.3]	11.3 ± 18.1 (0.0, 0.0 - 90.5)	-7.7 [-11.0 , -4.3]	37.9 ± 43.5 (23.8, 0.0 - 223.8)	-42.3 [-50.7 , -33.9]
24 MONTH	126	20.4 ± 22.9 (14.3, 0.0 - 100.0)	-29.1 [-33.9 , -24.3]	4.5 ± 13.9 (0.0, 0.0 - 100.0)	-5.6 [-8.9 , -2.4]	10.4 ± 17.7 (0.0, 0.0 - 100.0)	-9.7 [-13.4 , -6.1]	35.2 ± 45.5 (23.8, 0.0 - 300.0)	-44.4 [-53.3 , -35.5]
36 MONTH	110	20.9 ± 22.1 (14.3, 0.0 - 85.7)	-28.2 [-33.1 , -23.3]	5.8 ± 14.5 (0.0, 0.0 - 71.4)	-4.2 [-7.7 , -0.6]	11.8 ± 19.6 (0.0, 0.0 - 71.4)	-8.6 [-12.5 , -4.7]	38.5 ± 48.5 (19.1, 0.0 - 214.3)	-40.7 [-50.3 , -31.2]
48 MONTH	30	15.1 ± 22.6 (7.1, 0.0 - 100.0)	-30.4 [-41.9 , -18.9]	4.1 ± 12.1 (0.0, 0.0 - 47.6)	-7.7 [-13.4 , -2.0]	12.5 ± 19.0 (0.0, 0.0 - 76.2)	-6.8 [-15.6 , 2.1]	31.6 ± 40.7 (19.0, 0.0 - 144.4)	-45.6 [-67.0 , -24.2]
60 MONTH	2	0.0 ± 0.0 (0.0, 0.0 - 0.0)	-33.3 [-396.3 , 329.7]	0.0 ± 0.0 (0.0, 0.0 - 0.0)	0.0 [--]	0.0 ± 0.0 (0.0, 0.0 - 0.0)	-2.4 [-32.6 , 27.9]	0.0 ± 0.0 (0.0, 0.0 - 0.0)	-35.7 [-368.5 , 297.1]

** Change from baseline was calculated at the patient level with matched pairs of data. PFIQ-7 is composed of three subscales (CRAIQ, POPIQ, UIQ) scored on a scale of 0 to 100 with the total scored on a scale of 0 to 300. Higher values = more negative pelvic floor impact.*

4.4.2.8 Pelvic Organ Prolapse/Urinary Incontinence Sexual Function Questionnaire (PISQ-12)

For all sexually active patients, the mean PISQ-12 score improved slightly from baseline during the follow-up period but these changes did not reach the ½ SD level in order to be noticeable by the patients. The baseline score and scores during follow-up are not suggestive of a population that has significant sexual dysfunction and improvement was not expected. Importantly, the findings indicate that the TOPAS system does not have a negative impact on sexual function (Table 25).

Table 25: PISQ-12 Total Score Summary for All Sexually Active Patients

Study Visit	N	Mean ± SD (median, range)	Change from Baseline* Mean [95% CI]	% Change from Baseline* Mean [95% CI]
BASELINE	95	32.2 ± 6.7 (33.0, 16.0 - 44.0)	---	---
3 MONTH	92	35.1 ± 6.1 (35.0, 23.0 - 48.0)	3.1 [2.2 , 4.0]	11.5 [7.9 , 15.1]
6 MONTH	88	35.0 ± 6.9 (35.0, 20.0 - 46.0)	2.7 [1.7 , 3.7]	10.1 [6.0 , 14.2]
12 MONTH	86	34.6 ± 7.1 (35.0, 14.0 - 48.0)	2.5 [1.2 , 3.7]	9.8 [4.7 , 15.0]
24 MONTH	80	33.9 ± 7.9 (34.5, 15.0 - 46.0)	2.1 [0.8 , 3.4]	8.3 [2.8 , 13.8]
36 MONTH	57	35.1 ± 7.8 (37.0, 17.0 - 47.0)	2.5 [0.9 , 4.2]	10.1 [3.0 , 17.1]
48 MONTH	16	35.1 ± 6.2 (33.5, 26.0 - 45.0)	1.7 [-1.0 , 4.3]	7.3 [-3.6 , 18.1]
60 MONTH	0	---	---	---

** Change from baseline was calculated at the patient level with matched pairs of data. Scored on a scale of 0-48 with higher scores = better sexual function*

4.5 SAFETY RESULTS

4.5.1 Summary

- In the 509 patient-years of follow-up, there were no erosions, extrusions, organ perforations, device revisions, or UADEs.
- There were 677 AEs, of which only 17% were device- and/or procedure (treatment)-related.
- The most commonly observed complications (occurring in more than 5% of patients) were pain (buttock, pelvic, groin) and incision site infection.
- The majority (92.2%) of all treatment-related AEs were either managed without therapy or with a non-surgical treatment.
- There were eight treatment-related SAEs. No SAEs were life-threatening, and there were no treatment-related deaths in the study.
- No patients withdrew from the study due to a treatment-related AE.

4.5.2 Overall Adverse Event Summary

There were 509 patient-years of follow-up with a mean follow-up of 40.2 months for all implanted patients. Overall, 677 AEs were reported in 152 implanted patients (Figure 13).

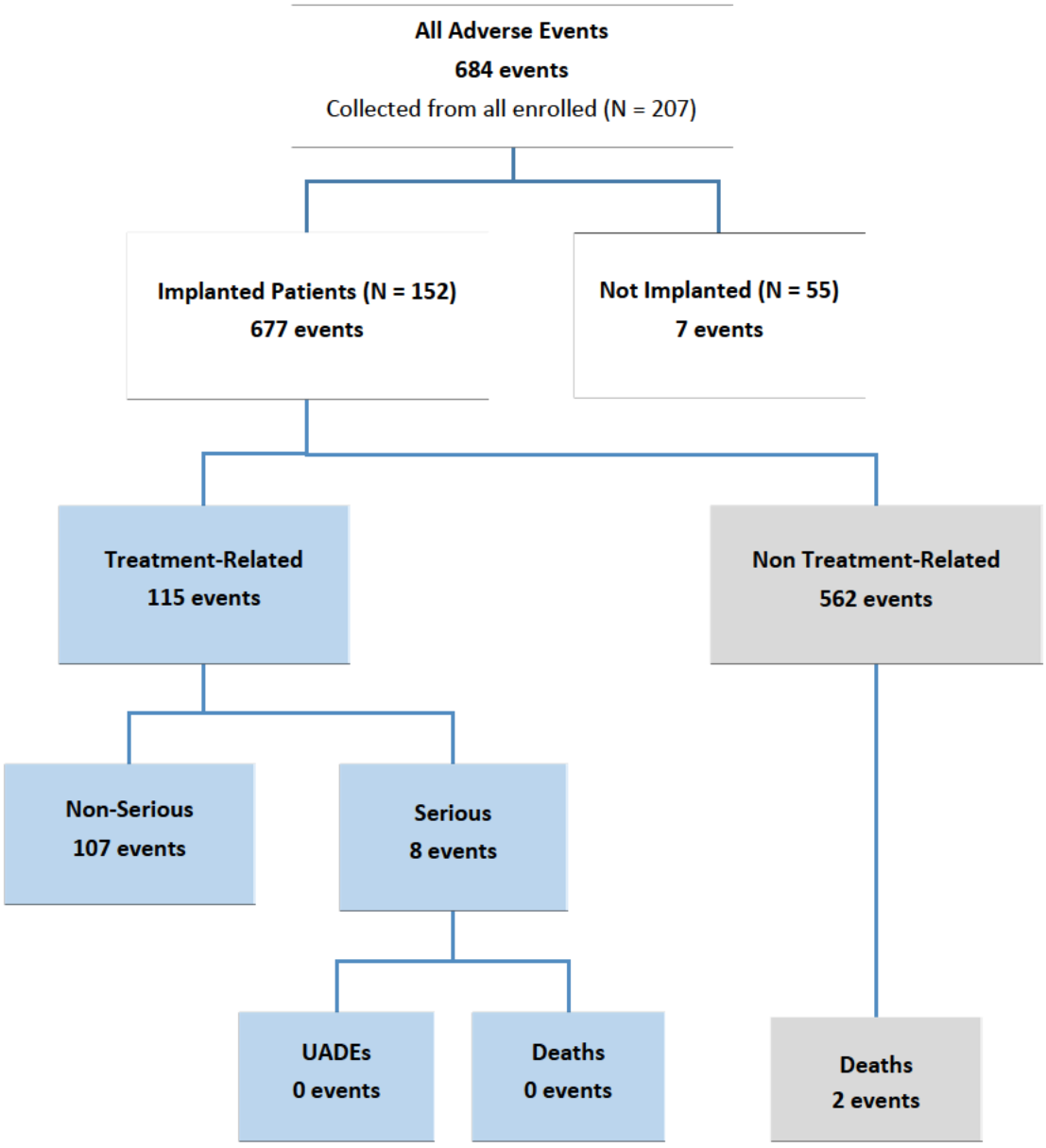
An AEAC reviewed all AE reports to adjudicate whether the event was procedure-, device- or procedure-/device-related. Of the 677 events, 562 (83.0%) were not related to the TOPAS system or implant procedure and 115 (17.0%) were treatment-related (described in Section 4.5.3). Overall, 47.4% (72/152) of patients had at least one treatment-related event. Of the treatment-related AEs, 65.2% (75/115) of the events were adjudicated by the AEAC as related to the procedure and not the device.

The majority (79.1%) of treatment-related AEs occurred within the first 120 days (3 months) post TOPAS implant and had a duration of less than 120 days from AE onset (66.1%). The majority (92.1%) of treatment-related AEs, regardless of duration, were managed without surgical intervention: either with no treatment or with medical intervention.

Eight out of 152 (5.3%) patients experienced treatment-related SAEs with four SAEs being device related. Half (50%, 4/8) of treatment-related SAEs were due to the worsening of a pre-existing condition. There were no treatment-related deaths.

No UADEs were observed, and there were no reports of mesh erosion, mesh extrusion, device revision, perforation of organs, foreign body reaction, or dyspareunia.

Figure 14: Summary Breakdown of All Adverse Events



4.5.3 Treatment-Related Adverse Events

The 115 treatment-related AEs included 75 procedure-related only events, 24 device-related only events, and 16 device and procedure-related events (Table 26 and Figure 15).

The most frequently reported treatment-related AEs (i.e., > 5% of patients) were pelvic pain/discomfort (8.6%; 13 events in 13 patients), buttock pain/discomfort (7.9%; 14 events in 12 patients), incision site infection (5.9%; 9 events in 9 patients), and groin pain/discomfort (5.3%; 9 events in 8 patients) (Table 27).

Table 26: Aggregated Summary of all AEs by Device and Procedure Relatedness

AE Category	Total AEs N	Not Treatment Related N (%)	Treatment-Related		
			Device Only N (%)	Procedure Only N (%)	Device and Procedure N (%)
Pelvic Area Pain	106	56 (52.8%)	11 (10.4%)	27 (25.5%)	12 (11.3%)
Infection	164	139 (84.8%)	1 (0.6%)	23 (14.0%)	1 (0.6%)
Incision Site	9	0 (0.0%)	0 (0.0%)	8 (88.9%)	1 (11.1%)
Abscess	3	1 (33.3%)	1 (33.3%)	1 (33.3%)	0 (0.0%)
Other Infections	152	138 (90.8%)	0 (0.0%)	14 (9.2%)	0 (0.0%)
Urinary Problems	27	19 (70.4%)	2 (7.4%)	6 (22.2%)	0 (0.0%)
De Novo Incontinence	5	4 (80.0%)	1 (20.0%)	0 (0.0%)	0 (0.0%)
Worsening Incontinence	13	10 (76.9%)	1 (7.7%)	2 (15.4%)	0 (0.0%)
Other	9	5 (55.6%)	0 (0.0%)	4 (44.4%)	0 (0.0%)
Pelvic Organ Prolapse	23	10 (43.5%)	10 (43.5%)	3 (13.0%)	0 (0.0%)
De Novo	13	5 (38.5%)	7 (53.8%)	1 (7.7%)	0 (0.0%)
Worsening	10	5 (50.0%)	3 (30.0%)	2 (20.0%)	0 (0.0%)
Bleeding	9	8 (88.9%)	0 (0.0%)	1 (11.1%)	0 (0.0%)
Defecatory Dysfunction	10	6 (60.0%)	0 (0.0%)	2 (20.0%)	2 (20.0%)
Defecatory Dysfunction	8	6 (75.0%)	0 (0.0%)	2 (25.0%)	0 (0.0%)
Worsening FI	2	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (100.0%)
Other	338	324 (95.9%)	0 (0.0%)	13 (3.8%)	1 (0.3%)
Erosion	0	0 (--%)	0 (--%)	0 (--%)	0 (--%)
Extrusion	0	0 (--%)	0 (--%)	0 (--%)	0 (--%)
Organ Perforation	0	0 (--%)	0 (--%)	0 (--%)	0 (--%)
TOTAL	**677**	**562 (83.0%)**	**24 (3.5%)**	**75 (11.1%)**	**16 (2.4%)**

Figure 15: Summary Breakdown of Treatment-Related AEs

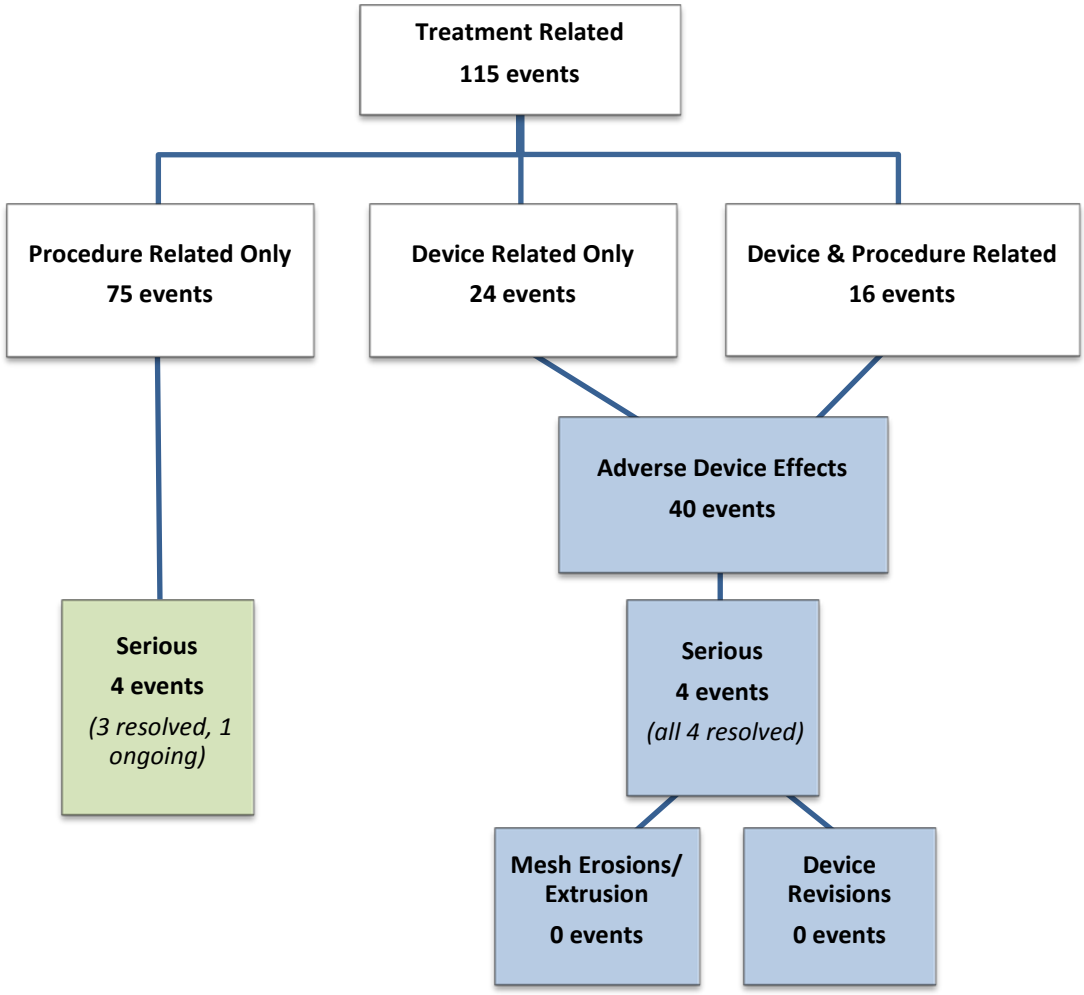


Table 27: Summary of Individual Treatment-Related AEs by Device and Procedure Relatedness

Adverse Event	Total AEs	Total Patients		Device Related Only		Procedure Related Only		Device and Procedure Related	
	N	N	%	N	%	N	%	N	%
Pain/Discomfort - Pelvic	13	13	8.6%	8	61.5%	0	0.0%	5	38.5%
Pain/Discomfort - Buttock	14	12	7.9%	0	0.0%	12	85.7%	2	14.3%
Infection - Incision Site	9	9	5.9%	0	0.0%	8	88.9%	1	11.1%
Pain/Discomfort - Groin	9	8	5.3%	0	0.0%	7	77.8%	2	22.2%
Prolapse - New	8	7	4.6%	7	87.5%	1	12.5%	0	0.0%
Pain/Discomfort - Leg	7	7	4.6%	1	14.3%	5	71.4%	1	14.3%
Infection(other than UTI): Fungal Infection	6	6	3.9%	0	0.0%	6	100.0%	0	0.0%
Pain/Discomfort - Urogenital	6	5	3.3%	1	16.7%	3	50.0%	2	33.3%
Prolapse - Worsening	5	3	2.0%	3	60.0%	2	40.0%	0	0.0%
Urinary Incontinence	3	3	2.0%	1	33.3%	2	66.7%	0	0.0%
Urinary Retention	3	3	2.0%	0	0.0%	3	100.0%	0	0.0%
Abscess	2	2	1.3%	1	50.0%	1	50.0%	0	0.0%
Allergic Reaction/Hypersensitivity Reaction	2	2	1.3%	0	0.0%	2	100.0%	0	0.0%
Constipation	2	2	1.3%	0	0.0%	2	100.0%	0	0.0%
Diarrhea	2	2	1.3%	0	0.0%	2	100.0%	0	0.0%
Erythema	2	2	1.3%	0	0.0%	2	100.0%	0	0.0%
Fecal Incontinence - Worsening	2	2	1.3%	0	0.0%	0	0.0%	2	100.0%
Other: Headache	2	2	1.3%	0	0.0%	2	100.0%	0	0.0%
Urinary Tract Infection (UTI)	2	2	1.3%	0	0.0%	2	100.0%	0	0.0%
Deep Venous Thrombosis	1	1	0.7%	0	0.0%	1	100.0%	0	0.0%
Dysuria	1	1	0.7%	0	0.0%	1	100.0%	0	0.0%

Adverse Event	Total AEs	Total Patients		Device Related Only		Procedure Related Only		Device and Procedure Related	
	N	N	%	N	%	N	%	N	%
Infection (other than UTI): C. Difficile Colitis	1	1	0.7%	0	0.0%	1	100.0%	0	0.0%
Infection(other than UTI): Genital Herpes	1	1	0.7%	0	0.0%	1	100.0%	0	0.0%
Infection (other than UTI): MRSA Infection	1	1	0.7%	0	0.0%	1	100.0%	0	0.0%
Infection (other than UTI): Yeast Infection	1	1	0.7%	0	0.0%	1	100.0%	0	0.0%
Other: Bleeding	1	1	0.7%	0	0.0%	1	100.0%	0	0.0%
Other: Chronic Obstructive Pulmonary Disease	1	1	0.7%	0	0.0%	1	100.0%	0	0.0%
Other: Nausea	1	1	0.7%	0	0.0%	1	100.0%	0	0.0%
Other: Post Traumatic Stress Disorder	1	1	0.7%	0	0.0%	1	100.0%	0	0.0%
Other: Rectal Discharge	1	1	0.7%	0	0.0%	1	100.0%	0	0.0%
Pain/Discomfort - Abdominal	1	1	0.7%	1	100.0%	0	0.0%	0	0.0%
Rectal Abnormality	1	1	0.7%	0	0.0%	1	100.0%	0	0.0%
Skin Irritation	1	1	0.7%	0	0.0%	0	0.0%	1	100.0%
Urinary Incontinence - De Novo Urge	1	1	0.7%	1	100.0%	0	0.0%	0	0.0%
Wound Dehiscence	1	1	0.7%	0	0.0%	1	100.0%	0	0.0%
TOTAL	**115**	**72**	**47.4%**	**24**	**20.9%**	**75**	**65.2%**	**16**	**13.9%**

The median time to onset for all treatment-related AEs was 12 days (mean 97.8 ± 207.0 days; range, -7 - 1004 days) with 91 events (79.1%) occurring within 120 days post-implant. Of the 24 events with later onset (i.e., >120 days post-implant), there were 12 cases of POP, 8 cases of pelvic area pain (i.e., 5 of pelvic pain, 2 of urogenital pain, and 1 of abdominal pain), 2 cases of urinary incontinence, and 1 case each of skin irritation and worsening FI (Table 28).

The majority (92.1%, 106/115) of treatment-related AEs, regardless of duration, required either no (27.8%, 32/115) or non-surgical treatment (64.33%, 74/115) with antibiotics, analgesics, bowel medications, diet modification, or physical therapy.

The 9 events required surgical treatment and included 4 cases of worsening POP (2 rectal prolapse and 1 each of rectocele and enterocele), 3 cases of de novo POP (1 each of cystocele/enterocele/rectocele, mucosal prolapse, and cystocele), 1 case of pelvic pain (exacerbated sciatica pain, treated with laminectomy, foraminotomy, and lateral fusion), and 1 case of worsening urge incontinence (treated with a TVT sling).

At the time of the data cutoff date (17 August 2015), 80.9% (93/115) of the treatment-related AEs had resolved. The unresolved treatment-related AEs (22/115, 19.1%) included 9 cases of pelvic pain, 7 cases of pelvic organ prolapse, 3 cases of urinary incontinence, 2 cases of worsening FI, and 1 case of worsening post-traumatic stress disorder.

Table 28: Aggregated Summary of Treatment-Related Adverse Events by Time to Onset, Duration, Treatment, and Resolution

AE Category	Total AEs N	Time to Onset				Duration				Treatment			Resolved N (%)
		Mean Days	<=30 Days	31-120 Days	121+ Days	Mean Days	0-30 Days	31-120 Days	121+ Days	None	Non-Surgical	Surgical	
Pelvic Pain	50	81.9 ± 196.0 (3.5, 0 - 1004)	34 (68.0%)	8 (16.0%)	8 (16.0%)	313.0 ± 454.9 (87.5, 0 - 1536)	21 (42.0%)	8 (16.0%)	21 (42.0%)	17 (34.0%)	32 (64.0%)	1 (2.0%)	41 (82.0%)
Buttock Pain/Discomfort	14	13.6 ± 31.0 (1.0, 0 - 113)	12 (85.7%)	2 (14.3%)	0 (0.0%)	144.4 ± 403.0 (17.5, 0 - 1536)	9 (64.3%)	2 (14.3%)	3 (21.4%)	3 (21.4%)	10 (71.4%)	1 (7.1%)	13 (92.9%)
Pelvic Pain/Discomfort	13	175.6 ± 236.7 (91.0, 0 - 862)	4 (30.8%)	4 (30.8%)	5 (38.5%)	567.2 ± 475.3 (487.0, 68 - 1314)	0 (0.0%)	4 (30.8%)	9 (69.2%)	7 (53.8%)	6 (46.2%)	0 (0.0%)	8 (61.5%)
Groin Pain/Discomfort	9	5.8 ± 11.6 (1.0, 0 - 36)	8 (88.9%)	1 (11.1%)	0 (0.0%)	217.7 ± 430.2 (14.0, 4 - 1264)	6 (66.7%)	1 (11.1%)	2 (22.2%)	0 (0.0%)	9 (100.0%)	0 (0.0%)	8 (88.9%)
Leg Pain/Discomfort	7	16.3 ± 36.7 (1.0, 0 - 99)	6 (85.7%)	1 (14.3%)	0 (0.0%)	181.7 ± 396.7 (22.0, 1 - 1076)	5 (71.4%)	0 (0.0%)	2 (28.6%)	4 (57.1%)	3 (42.9%)	0 (0.0%)	6 (85.7%)
Urogenital Pain/Discomfort	6	218.0 ± 402.8 (3.0, 0 - 1004)	4 (66.7%)	0 (0.0%)	2 (33.3%)	287.8 ± 309.7 (159.0, 4 - 824)	1 (16.7%)	1 (16.7%)	4 (66.7%)	3 (50.0%)	3 (50.0%)	0 (0.0%)	6 (100.0%)
Abdominal Pain/Discomfort	1	148.0 ± (148.0, 148 - 148)	0 (0.0%)	0 (0.0%)	1 (100.0%)	1297.0 ± (1297.0, 1297 - 1297)	0 (0.0%)	0 (0.0%)	1 (100.0%)	0 (0.0%)	1 (100.0%)	0 (0.0%)	0 (0.0%)
Infection	25	17.2 ± 14.3 (16.0, 1 - 58)	21 (84.0%)	4 (16.0%)	0 (0.0%)	19.2 ± 22.6 (15.0, 2 - 117)	22 (88.0%)	3 (12.0%)	0 (0.0%)	0 (0.0%)	25 (100.0%)	0 (0.0%)	25 (100.0%)
Incision Site	9	17.3 ± 10.2 (14.0, 7 - 33)	8 (88.9%)	1 (11.1%)	0 (0.0%)	11.1 ± 5.4 (12.0, 2 - 20)	9 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (100.0%)	0 (0.0%)	9 (100.0%)
Abscess	2	11.0 ± 11.3 (11.0, 3 - 19)	2 (100.0%)	0 (0.0%)	0 (0.0%)	11.5 ± 6.4 (11.5, 7 - 16)	2 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (100.0%)	0 (0.0%)	2 (100.0%)
Other Infections	14	18.1 ± 17.3 (17.5, 1 - 58)	11 (78.6%)	3 (21.4%)	0 (0.0%)	25.4 ± 28.7 (20.0, 2 - 117)	11 (78.6%)	3 (21.4%)	0 (0.0%)	0 (0.0%)	14 (100.0%)	0 (0.0%)	14 (100.0%)
Urinary Problems	8	176.6 ± 336.4 (0.0, 0 - 947)	5 (62.5%)	1 (12.5%)	2 (25.0%)	497.4 ± 533.8 (437.5, 0 - 1133)	4 (50.0%)	0 (0.0%)	4 (50.0%)	3 (37.5%)	4 (50.0%)	1 (12.5%)	5 (62.5%)
De Novo Incontinence	1	947.0 ± (947.0, 947 - 947)	0 (0.0%)	0 (0.0%)	1 (100.0%)	906.0 ± (906.0, 906 - 906)	0 (0.0%)	0 (0.0%)	1 (100.0%)	0 (0.0%)	1 (100.0%)	0 (0.0%)	0 (0.0%)
Worsening Incontinence	3	155.3 ± 190.6 (98.0, 0 - 368)	1 (33.3%)	1 (33.3%)	1 (33.3%)	1018.7 ± 141.1 (1062.0, 861 - 1133)	0 (0.0%)	0 (0.0%)	3 (100.0%)	1 (33.3%)	1 (33.3%)	1 (33.3%)	1 (33.3%)
Other Urinary Problems	4	0.0 ± 0.0 (0.0, 0 - 0)	4 (100.0%)	0 (0.0%)	0 (0.0%)	4.3 ± 6.6 (1.5, 0 - 14)	4 (100.0%)	0 (0.0%)	0 (0.0%)	2 (50.0%)	2 (50.0%)	0 (0.0%)	4 (100.0%)
Pelvic Organ Prolapse	13	350.9 ± 282.6 (223.0, 76 - 869)	0 (0.0%)	1 (7.7%)	12 (92.3%)	608.0 ± 463.4 (579.0, 0 - 1259)	1 (7.7%)	2 (15.4%)	10 (76.9%)	4 (30.8%)	2 (15.4%)	7 (53.8%)	6 (46.2%)

AE Category	Total AEs N	Time to Onset				Duration				Treatment			Resolved N (%)
		Mean Days	<=30 Days	31-120 Days	121+ Days	Mean Days	0-30 Days	31-120 Days	121+ Days	None	Non-Surgical	Surgical	
De Novo Prolapse	8	442.9 ± 322.6 (328.0, 128 - 869)	0 (0.0%)	0 (0.0%)	8 (100.0%)	695.6 ± 424.5 (597.5, 100 - 1259)	0 (0.0%)	1 (12.5%)	7 (87.5%)	4 (50.0%)	1 (12.5%)	3 (37.5%)	3 (37.5%)
Worsening Prolapse	5	203.8 ± 116.3 (190.0, 76 - 370)	0 (0.0%)	1 (20.0%)	4 (80.0%)	467.8 ± 537.5 (180.0, 0 - 1075)	1 (20.0%)	1 (20.0%)	3 (60.0%)	0 (0.0%)	1 (20.0%)	4 (80.0%)	3 (60.0%)
Bleeding	1	10.0 ± (10.0, 10 - 10)	1 (100.0%)	0 (0.0%)	0 (0.0%)	11.0 ± (11.0, 11 - 11)	1 (100.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)
Defecatory Problems	4	103.8 ± 155.7 (42.0, 0 - 331)	2 (50.0%)	1 (25.0%)	1 (25.0%)	509.5 ± 586.5 (458.5, 4 - 1117)	2 (50.0%)	0 (0.0%)	2 (50.0%)	2 (50.0%)	2 (50.0%)	0 (0.0%)	2 (50.0%)
Worsening Fecal Incontinence	2	205.0 ± 178.2 (205.0, 79 - 331)	0 (0.0%)	1 (50.0%)	1 (50.0%)	1012.0 ± 148.5 (1012.0, 907 - 1117)	0 (0.0%)	0 (0.0%)	2 (100.0%)	2 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Defecatory Dysfunction	2	2.5 ± 3.5 (2.5, 0 - 5)	2 (100.0%)	0 (0.0%)	0 (0.0%)	7.0 ± 4.2 (7.0, 4 - 10)	2 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (100.0%)	0 (0.0%)	2 (100.0%)
Other	14	23.1 ± 47.0 (2.5, -7 - 168)	11 (78.6%)	2 (14.3%)	1 (7.1%)	138.7 ± 423.5 (9.0, 0 - 1600)	11 (78.6%)	1 (7.1%)	2 (14.3%)	5 (35.7%)	9 (64.3%)	0 (0.0%)	13 (92.9%)
TOTAL	**115**	**97.8 ± 207.0 (12.0, -7 - 1004)**	**74 (64.3%)**	**17 (14.8%)**	**24 (20.9%)**	**278.3 ± 441.1 (25.0, 0 - 1600)**	**62 (53.9%)**	**14 (12.2%)**	**39 (33.9%)**	**32 (27.8%)**	**74 (64.3%)**	**9 (7.8%)**	**93 (80.9%)**

Continuous variable: Mean ± SD (median, min-max); Categorical variable: N (%) - based on events.

Eight treatment-related AEs (7.0%, 8/115) were adjudicated as SAEs (Table 29). Three of the SAEs (POP) were adjudicated as device-related only, 1 was adjudicated as device- and procedure-related (buttock pain) and the remaining 4 SAEs were all adjudicated as procedure-related only.

Table 29: Listing of All Treatment-Related Serious Adverse Events

Event ID	AEAC Adjudication	Days from Implant	Duration Days	Device Related	Procedure Related	Intervention	Event Status
(b) (6)	Pain/Discomfort – Buttock (exacerbation of sciatic pain)	113	131	Yes	Yes	Other: Pelvic floor physical therapy, caudal performed Surgery: L3 L4 L5 SI laminectomy, lateral recess decompression foraminotomy, L3 L4 L5 B/L lateral fusion	Resolved without sequelae
	Worsening Pelvic Organ Prolapse (recurrent rectal prolapse)	122	55	Yes	No	Surgery: Robotic assisted laparoscopic rectopexy	Resolved without sequelae
	De Novo Pelvic Organ Prolapse (mild cystocele / enterocele / rectocele)	433	100	Yes	No	Surgery: Supracervical hysterectomy with bilateral salpingectomy, sacrocolpopexy and cystoscopy	Resolved without sequelae
	Exacerbated Post Traumatic Stress Disorder	-7	1600*	No	Yes	Medication: Clonidine, tegratol Other: Inpatient rehabilitation therapy for ~ 3 months	Ongoing
	Deep Vein Thrombosis	21	10	No	Yes	Medication: Enoxaparin, warfarin	Resolved without sequelae
	Worsening Chronic Obstructive Pulmonary Disease	1	1	No	Yes	Medication: Furosemide, salbutomal, ipratropium, solumedrol	Resolved without sequelae
	De Novo Pelvic Organ Prolapse (mucosal prolapse)	128	579	Yes	No	Surgery: Delorme procedure excision rectal procedencia with anastomosis	Resolved without sequelae
	MRSA Infection (left hand)	58	117	No	Yes	Medication: Clindamycin, IV morphine, Valtrex, vancomycin, calcium channel blocker, topical nitroglycerin, antibiotics	Resolved without sequelae

(b) (6)

A summary of the treatment-related SAEs follows:

- Pelvic area pain (worsening sciatic pain) (b) (6) was adjudicated as both device and procedure-related. The patient had a prior history of sciatica pain that had been ongoing since 2010, with a treatment of physical therapy. The event had an onset of 113 days post TOPAS system implant and was diagnosed during a physical exam (results: pain at sciatica). The event required surgical intervention (laminectomy, foraminotomy, lateral fusion) and in-patient hospitalization. Upon treatment, this event resolved without sequelae, 131 days after onset.
- Worsening pelvic organ prolapse (recurrent rectal prolapse) (b) (6) was adjudicated as device-related only. The patient had a prior history of rectal prolapse that was surgically treated in 2010 (laparoscopic sigmoidectomy and suture rectopexy). This event had an onset of 122 days post TOPAS system implant and was diagnosed during a pelvic exam (results: rectal prolapse) by the study center. This event was adjudicated as an SAE because it involved a surgical intervention (laparoscopic rectopexy) and in-patient hospitalization. Upon treatment, this event resolved without sequelae, 55 days after onset.
- De novo pelvic organ prolapse (mild cystocele/enterocele/rectocele) (b) (6) was adjudicated as device-related only. The patient did not have a prior history of vaginal prolapse. The event had an onset of 433 days post TOPAS system implant and was diagnosed by the study center as a mild pelvic organ prolapse (results: cystocele / enterocele / rectocele) through a pelvic exam. The event involved an outpatient procedure and was adjudicated as an SAE because of the surgical intervention (supracervical hysterectomy with bilateral salpingectomy, sacrocolpopexy and cystoscopy). Upon treatment, this event resolved without sequelae, 100 days after onset.
- Worsening post-traumatic stress disorder (b) (6)) was adjudicated as procedure-related only and had an onset seven days prior to receiving the TOPAS system implant. The patient had a prior history of PTSD dating back to 1975 that was previously treated with medications (Buspar, Minipress, Cymbalta). The study center did not report any diagnostics for this event. This event was adjudicated as an SAE because it involved an in-patient hospitalization. This event is still ongoing with a duration of 1600 days at the time of the report cutoff date.
- Deep vein thrombosis (b) (6)) was adjudicated as procedure-related and had an onset 21 days post TOPAS system implant. The study center diagnosed this event through a spiral CT (results: negative) and by Doppler ultrasound of lower extremity (results: DVT of lower extremity). The implant procedure lasted 59 minutes for this patient, compared to the study mean of 33.4 minutes (range, 11.0 - 71.0 minutes). This event was adjudicated as an SAE

because it involved an in-patient hospitalization. The patient was treated with anticoagulants (levonox and warfarin) and the event resolved with no sequelae, 10 days after onset.

- Worsening chronic obstructive pulmonary disease ([redacted]) was adjudicated as procedure-related and had an onset 1 day post TOPAS system implant. The patient had a prior history of COPD (onset date unknown). The study center diagnosed the event through blood work (results: hypercapnic and hypoxemia) and by chest x-ray (results: mild chronic interstitial changes). This event was adjudicated as an SAE because it involved an in-patient hospitalization. This event resolved with no sequelae, 1 day after onset.
- De novo pelvic organ prolapse (mucosal prolapse) ([redacted]) was adjudicated as device-related only. The patient did not have a prior history of rectal prolapse. The event had an onset of 128 days post TOPAS system implant and the method of diagnosis is unknown. The event required surgical intervention (Delorme procedure excision rectal procedencia with anastomosis) and an in-patient hospitalization. Upon treatment, this event resolved without sequelae, 579 days after onset. At the last available follow-up visit for the study (12 Month), the patient was a treatment responder (68.4% decline in FI episodes from baseline).
- Methicillin-resistant *Staphylococcus aureus* infection (left hand) ([redacted]) was adjudicated as procedure-related and had an onset 58 days post TOPAS system implant. The study center completed diagnostics of lab tests (result: MRSA infection), basic metabolic panel (results: normal), and MRI (results: inflammation and ulcers but no osteomyelitis or abscess). This event was adjudicated as an SAE because it involved an in-patient hospitalization. This event resolved with no sequelae, 117 days after onset.

4.5.4 Adverse Device Effects

Adverse device effects (ADEs) were predefined as device-related only or device- and procedure-related and included erosion, infection, pelvic pain, defecatory dysfunction, and hematoma. Of the 115 treatment-related AEs in the study, 40 events (34.8%) were adjudicated as ADEs (Table 30).

No mesh-related erosions, extrusions, organ perforations, device revisions, or UADEs were reported in the study up to the data cutoff date. In addition, no patients withdrew from the study as a result of an ADE. Based on Kaplan-Meier survival estimates at 12 months, the event rate for ADEs was 17.2%, representing the probability that a patient implanted with the TOPAS system will experience an ADE within the first 12 months of implant. Four ADEs (3 POP and 1 pelvic area/buttock pain) were adjudicated as SAEs.

Table 30: Summary of Adverse Device Effects

Adverse Event Category	Total AEs	Total Patients		Serious AEs		UADE		Continuing AEs		Resolved AEs		KM Event Rate with 95% CI at 12 Month
	N	N	% Total	N	% AEs	N	% AEs	N	% AEs	N	% AEs	
Pelvic Area Pain	23	21	13.8 %	1	4.3%	0	0.0%	9	39.1%	14	60.9%	12.6% (7.1%, 17.7%)
Infection[#]	2	2	1.3%	0	0.0%	0	0.0%	0	0.0%	2	100.0 %	1.3% (0.0%, 3.1%)
Incision Site	1	1	0.7%	0	0.0%	0	0.0%	0	0.0%	1	100.0 %	0.7% (0.0%, 1.9%)
Abscess	1	1	0.7%	0	0.0%	0	0.0%	0	0.0%	1	100.0 %	0.7% (0.0%, 1.9%)
Urinary Problems	2	2	1.3%	0	0.0%	0	0.0%	2	100.0 %	0	0.0%	0.0% (0.0%, 2.4%)*
De Novo Incontinence	1	1	0.7%	0	0.0%	0	0.0%	1	100.0 %	0	0.0%	0.0% (0.0%, 2.4%)*
Worsening Incontinence	1	1	0.7%	0	0.0%	0	0.0%	1	100.0 %	0	0.0%	0.0% (0.0%, 2.4%)*
Pelvic Organ Prolapse	10	7	4.6%	3	30.0%	0	0.0%	6	60.0%	4	40.0%	2.6% (0.1%, 5.2%)
De Novo Prolapse	7	6	3.9%	2	28.6%	0	0.0%	4	57.1%	3	42.9%	1.3% (0.0%, 3.1%)
Worsening Prolapse	3	2	1.3%	1	33.3%	0	0.0%	2	66.7%	1	33.3%	1.3% (0.0%, 3.1%)
Other	3	3	2.0%	0	0.0%	0	0.0%	2	66.7%	1	33.3%	2.0% (0.0%, 4.2%)
Hematoma	0	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0.0% (0.0%, 2.4%)*
Defecatory Dysfunction	0	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0.0% (0.0%, 2.4%)*
Erosion	0	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0.0% (0.0%, 2.4%)*
Extrusion	0	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0.0% (0.0%, 2.4%)*
TOTAL	**40**	**33**	**21.7%**	**4**	**10.0%**	**0**	**0.0%**	**19**	**47.5%**	**21**	**52.5%**	**17.2% (11.0%, 23.0%)**

** Exact Binomial 95% CI used. There were no "Other infections" or "Other urinary problems" reported as ADEs so these categories were not included here.*

4.5.5 Deaths Occurring During Study

Two deaths were reported in the study; both were adjudicated as not treatment-related (Table 31).

Table 31: Listing of Deaths during the Study

Patient ID	SAE Name	Surgery Date	Death Date	Days Post Procedure	Device Related	Procedure Related	Serious	UADE
(b) (6)	Liver Cancer	10/10/2011	11/29/2011	50	No	No	Yes	No
	Non-Small Cell Lung Cancer	07/08/2011	04/24/2013	656	No	No	Yes	No

The following are descriptions of deaths during the study:

- Liver Cancer: (b) (6) had a reoccurrence of breast cancer 50 days post TOPAS system implant. The patient had a prior history of breast cancer (dating back to 2001) that had been in remission. The patient complained of abdominal pain, which was assessed by the study center to be liver cancer ((b) (6)) that was attributed to the patient's prior history of breast cancer. The patient was hospitalized, underwent a liver biopsy, and received non-surgical interventions (morphine, dilaudid, cefazolin, and metronidazole). The patient died approximately 1 week after the onset of the event.
- Non-Small Cell Lung Cancer: (b) (6) died from respiratory failure 656 days post TOPAS system implantation due to a reported case of non-small cell lung cancer (b) (6) The patient had a prior history of interstitial lung disease (onset unknown) with no prior history of cancer. The patient was hospitalized, underwent palliative radiation, and received additional medication (levaquin, robaxin, decadron, and vancomycin) before going into hospice care. The patient died approximately 3 weeks after onset of the event.

4.5.6 Pelvic Pain

A secondary safety objective of the study was to quantify patient-reported pelvic pain in the previous 24 hours as measured by a Numeric Pelvic Pain Scale (NPPS) from baseline through 12 months post-operatively. The NPPS was adapted from a Numerical Rating Scale (NRS) described by McCafferty and Pasero (1999) and is scored on a 0-10 scale, with higher scores indicating more severe pain (see Appendix 3, Figure 23 for an example of the NPPS questionnaire used in the study. The NPPS was added to the study on 15 September 2010 and, therefore, was not completed by all patients at the baseline visit.

For all patients who completed baseline assessments, the mean baseline NPPS score was 0.8 ± 1.7 (Table 32), which corresponds to the low end of the "mild" category (pain = nagging, annoying, interfering little with activities of daily living). The mean NPPS score increased at the procedure visit to 3.2 ± 2.5 (corresponding to the low end of the "moderate" category). By the acute follow-up visit (14 - 28 days), mean NPPS scores had decreased to 1.0 ± 1.9 and remained below 1.0 through 12 months. This suggests the pain associated implantation with the TOPAS system is minimal and decreases to baseline levels within 3 months of the procedure.

Table 32: NPPS Score Summary by Visit

	All Patients		Patients with Baseline NPPS scores		
Study Visit	N	Mean ± SD (median, range)	N	Mean ± SD (median, range)	Change from Baseline* Mean [95% CI]
BASELINE	103	0.8 ± 1.7 (0.0, 0.0 - 8.0)	103	0.8 ± 1.7 (0.0, 0.0 - 8.0)	---
PROCEDURE	110	3.3 ± 2.4 (3.0, 0.0 - 10.0)	102	3.2 ± 2.5 (3.0, 0.0 - 10.0)	2.4 [1.9 ,2.9]
ACUTE FU	113	1.1 ± 2.0 (0.0, 0.0 - 8.0)	101	1.0 ± 1.9 (0.0, 0.0 - 8.0)	0.2 [-0.3 ,0.7]
3 MONTH	125	0.5 ± 1.3 (0.0, 0.0 - 6.0)	99	0.4 ± 1.1 (0.0, 0.0 - 5.0)	-0.3 [-0.6 ,0.1]
6 MONTH	135	0.8 ± 2.0 (0.0, 0.0 - 10.0)	98	0.7 ± 1.8 (0.0, 0.0 - 10.0)	-0.1 [-0.6 ,0.4]
12 MONTH	137	0.5 ± 1.5 (0.0, 0.0 - 10.0)	91	0.6 ± 1.6 (0.0, 0.0 - 10.0)	-0.2 [-0.6 ,0.3]

** Change from baseline is calculated at the patient level with matched pairs of data. NPPS Score is rated on a 0-10 with higher scores = worse pain. The NPPS Score was not collected beyond the 12 month visit.*

4.6 OTHER FINDINGS IN THE TOPAS PMA STUDY

4.6.1 Health Resource Utilization

A summary of patient-reported health resource usage questionnaire responses at baseline through 36 months for all implanted patients are presented in Table 33. For all implanted patients, TOPAS system treatment resulted in a reduction in the use of pads (2.4 pads/day at baseline to 1.2 pads/day at 36 months), a reduction in doctor visits due to FI (5.0 visits at baseline to 0.3 at 36 months), and a reduction in having to take time off from work due to FI (6.4 days off at baseline to 0.9 at 36 months).

Table 33: Health Resource Usage Summary for All Implanted Patients

During the last year, aside from study procedure and study visit:	Baseline	12 Month	24 Month	36 Month
Does patient use pads or diapers? (% yes)	83.8% (124/148)	58.2% (82/141)	54.0% (68/126)	53.6% (59/110)
# of pads per day patient took for FI	2.4 ± 2.1 (2.0, - 10)	1.4 ± 1.8 (1.0, 0 - 8)	1.1 ± 1.5 (1.0, 0.0 - 8.0)	1.2 ± 1.6 (1.0, 0.0 - 8.0)
Have you spent any days in the hospital due to FI? (% yes)	4.7% (7/148)	2.1% (3/141)	0.8% (1/126)	0.0% (0/110)
Total # of days in hospital due to FI	0.1 ± 0.6 (0.0, 0 - 5)	0.1 ± 0.5 (0.0, 0 - 5)	0.0 ± 0.1 (0.0, 0.0 - 1.0)	0.0 ± 0.0 (0.0, 0.0 - 0.0)
Have you been to see your doctor or had surgery due to FI? (% yes)	91.2% (135/148)	17.0% (24/141)	17.5% (22/126)	16.4% (18/110)
Total # of visits due to FI	5.0 ± 7.6 (3.0, 0 - 70)	0.4 ± 1.4 (0.0, 0 - 9)	0.5 ± 1.8 (0.0, 0.0 - 12.0)	0.3 ± 1.1 (0.0, 0.0 - 8.0)
Have you had to take time off work due to FI? (% yes)	21.5% (31/144)	4.3% (6/141)	7.2% (9/125)	0.9% (1/110)
Total # of days patient took off work due to FI	6.4 ± 34.0 (0.0, 0 - 365)	1.3 ± 9.9 (0.0, 0 - 100)	4.5 ± 35.4 (0.0, 0.0 - 365.0)	0.9 ± 9.5 (0.0, 0.0 - 100.0)
Has a relative or friend taken time off work to look after you due to FI? (% yes)	5.4% (8/148)	0.0% (0/141)	0.8% (1/126)	0.0% (0/110)
Total # of days friend/relative took off to take care of patient due to FI	0.2 ± 1.3 (0.0, 0 - 10)	0.0 ± 0.0 (0.0, 0 - 0)	0.0 ± 0.3 (0.0, 0.0 - 3.0)	0.0 ± 0.0 (0.0, 0.0 - 0.0)

Continuous data are mean ± SD (median, range)

4.6.2 Surgical Satisfaction

Surgical satisfaction was assessed with the SSQ-8 (Murphy et al., 2008; See Appendix 3, Figure 22 for an example of the SSQ-8 questionnaire used in the study. The SSQ-8 was added to the study on 22 Jan 2013 and was offered on an optional one-time basis to all active patients between 3 and 36 months (mean 26.7 ± 8.8) post-operatively. 75% of treatment responders reported being satisfied/very satisfied with the results of the TOPAS surgery, 84% would have the surgery again, and 83% would recommend the TOPAS system to someone else (Table 34).

Table 34: SSQ-8 Summary by Treatment Responder Status at the One-Time Optional Assessment

Question	All Patients	Responders	Non-Responders
#1 How satisfied are you with how your pain was controlled in the hospital after surgery?			
Satisfied or Very Satisfied	87.1% (74/85)	85.7% (54/63)	90.9% (20/22)
Neutral	3.5% (3/85)	3.2% (2/63)	4.5% (1/22)
Unsatisfied or Very Unsatisfied	9.4% (8/85)	11.1% (7/63)	4.5% (1/22)
#2 How satisfied are you with how your pain was controlled when you returned home after surgery?			
Satisfied or Very Satisfied	83.5% (71/85)	84.1% (53/63)	81.8% (18/22)
Neutral	7.1% (6/85)	6.3% (4/63)	9.1% (2/22)
Unsatisfied or Very Unsatisfied	9.4% (8/85)	9.5% (6/63)	9.1% (2/22)
#3 How satisfied are you with the amount of time it took for you to return to your daily activities, for example housework or social activities outside the home?			
Satisfied or Very Satisfied	80.0% (68/85)	82.3% (51/62)	73.9% (17/23)
Neutral	8.2% (7/85)	8.1% (5/62)	8.7% (2/23)
Unsatisfied or Very Unsatisfied	11.8% (10/85)	9.7% (6/62)	17.4% (4/23)
#4 How satisfied are you with the amount of time it took for you to return to work?			
Satisfied or Very Satisfied	60.7% (51/84)	67.7% (42/62)	40.9% (9/22)
Neutral	3.6% (3/84)	3.2% (2/62)	4.5% (1/22)
Unsatisfied or Very Unsatisfied	4.8% (4/84)	1.6% (1/62)	13.6% (3/22)
Not Applicable	31.0% (26/84)	27.4% (17/62)	40.9% (9/22)
#5 How satisfied are you with the amount of time it took for you to return to your normal exercise routine?			
Satisfied or Very Satisfied	68.6% (59/86)	71.4% (45/63)	60.9% (14/23)
Neutral	10.5% (9/86)	9.5% (6/63)	13.0% (3/23)
Unsatisfied or Very Unsatisfied	11.6% (10/86)	9.5% (6/63)	17.4% (4/23)
Not Applicable	9.3% (8/86)	9.5% (6/63)	8.7% (2/23)
#6 How satisfied are you with the results of your surgery?			
Satisfied or Very Satisfied	66.3% (57/86)	74.6% (47/63)	43.5% (10/23)
Neutral	19.8% (17/86)	17.5% (11/63)	26.1% (6/23)

Question	All Patients	Responders	Non-Responders
Unsatisfied or Very Unsatisfied	14.0% (12/86)	7.9% (5/63)	30.4% (7/23)
#7 Looking back, if "had to do it all over again" would you have the surgery again?			
Satisfied or Very Satisfied	80.2% (69/86)	84.1% (53/63)	69.6% (16/23)
Neutral	10.5% (9/86)	12.7% (8/63)	4.3% (1/23)
Unsatisfied or Very Unsatisfied	9.3% (8/86)	3.2% (2/63)	26.1% (6/23)
#8 Would you recommend this surgery to someone else?			
Positive	80.2% (69/86)	82.5% (52/63)	73.9% (17/23)
Neutral	14.0% (12/86)	14.3% (9/63)	13.0% (3/23)
Negative	5.8% (5/86)	3.2% (2/63)	13.0% (3/23)

4.6.3 Defecography Data

To study the mechanism of action of the TOPAS system, dynamic defecography was performed at a subset of four study centers (N=33 patients) at baseline and 6 months post-implant. Descriptive statistics for defecography variables are presented in Table 35. No differences from baseline to 6 months were observed in the anorectal angle at rest or at evacuation. A small increase (0.5 cm) in anal canal length was noted, but this is not statistically significant and is observed only in a small sample size (n=8).

Table 35: Defecography Changes from Baseline

Variable	Baseline Mean ± SD (n, median, range)	6 Month Mean ± SD (n, median, range)	Change from Baseline* Mean [95% CI], n
Anorectal Angle at Rest (degrees)	133.5 ± 17.7 (n=26, 132.0, 107.0 - 172.0)	132.4 ± 16.6 (n=26, 132.0, 99.0 - 165.0)	-3.7 [-7.8 , 0.5] n=20
Anorectal Angle at Evacuation (degrees)	141.0 ± 20.1 (n=21, 144.0, 98.0 - 174.0)	143.2 ± 16.4 (n=22, 143.0, 98.0 - 168.0)	1.4 [-5.7 , 8.5] n=15
Length of Anal Canal (cm)	2.5 ± 0.6 (n=14, 2.4, 1.7 - 4.0)	3.1 ± 0.9 (n=15, 2.8, 2.2 - 5.1)	0.5 [-0.1 , 1.0] n=8

** Change from baseline was calculated on a patient level using matched pairs of data*

As discussed in Section 2.3 (Mechanism of Action), it was originally theorized that the TOPAS system works by providing support to the puborectalis thereby helping to maintain the anorectal angle and anal canal length. The results from this defecography sub-study do not provide evidence to support this theory. Patients did have an obtuse anorectal angle at rest (i.e., more than 90 degrees but less than 180 degrees) but there was no change following TOPAS system implantation. These data also do not support the idea that TOPAS system implantation results in severe increases in the anorectal angle that could cause obstructed defecation.

The inability to detect differences following TOPAS system implantation in this sub-study may be due to high inter- and intra-observer inconsistency in measuring the anorectal angle with this technique (Jorgensen et al., 1993; Yang et al., 1994). Further studies are needed to explore the mechanism of action of the TOPAS system and may necessitate the use of different measurement techniques including dynamic MRI and/or 3D anal ultrasound.

5 SUMMARY OF PROPOSED LABELING

The proposed indication for the TOPAS™ System is to treat women with FI (also referred to as accidental bowel leakage) who have failed more conservative therapies.

The following contraindications will be included in labeling:

- Do not use the TOPAS system in pregnant patients or those planning a future pregnancy.
- Do not implant the TOPAS device in patients with pre-existing conditions that pose an unacceptable surgical risk, such as but not limited to, active infection or signs of tissue necrosis.
- Do not implant the TOPAS device in patients with known sensitivity or allergy to polypropylene mesh products.
- Do not implant the TOPAS device in patients who are unwilling to abstain from receptive anal intercourse.

The following warnings will be included in labeling:

- Do not proceed with implantation of the TOPAS device if the bowel is perforated during the procedure.
- Surgical revision or removal of the TOPAS device may involve multiple surgeries. Complete removal of the mesh may not be possible and may not result in complete resolution of the symptoms or complications.
- Avoid excessive tensioning of the mesh assembly during final positioning to avoid potential temporary or permanent defecatory obstruction or other AEs.

The following precautions will be included in labeling:

- General precautions
    - Physician credentialing, institutional requirements, and operating room permission for the TOPAS procedure is the responsibility of the institution.
    - ASTORA recommends successful completion of the ASTORA TOPAS Physician Training Program and/or maintenance of procedural proficiency for all implanting physicians. Use of this device without prior completion of the training program is not recommended.
    - Prophylactic antibiotics and deep vein thrombosis prevention protocols should be administered according to institutional guidelines. Any infection should be resolved prior to the TOPAS procedure.
    - Prior to the procedure, perform a digital rectal examination to evaluate rectal anatomy to avoid possible rectal perforation.
    - Perform a digital rectal examination during routine patient follow-up visits.

- Patient related precautions
    - Patients with pelvic anatomical abnormalities, pre-existing conditions (e.g. blood coagulation disorders, inflammatory bowel disease, myofascial pelvic pain, etc.) or planning future pregnancies may not be appropriate surgical candidates; the risks and benefits should be carefully considered.
    - In patients with compromised immune systems or other conditions that would compromise healing, the risks and benefits should be carefully considered.
    - Previous operation(s) or trauma in the pelvic region may compromise the outcome of the TOPAS procedure; the risks and benefits should be carefully considered.
    - Caution should be used in patients who have received radiation treatment in the implantation area.
    - Treatment of FI with the TOPAS system may unmask pre-existing incontinence and/or pelvic organ prolapse.
- Treatment-related precautions
    - The TOPAS procedure should be performed with over-gloving and care should be taken to follow all steps in use of removing the over-glove. Change gloves frequently when contaminated, or if there is any suspicion of contamination.
    - Perform an endoscopic evaluation of the bowel prior to the procedure as clinically indicated.
    - Follow procedural instructions to avoid vessel perforation or nerve damage when passing the needle.
    - Use digital palpation when passing the needle near the vagina and rectum to avoid perforation.
    - Observe the patient for any signs of significant bleeding.
    - During pre-operative preparation, physical therapy stretching or other exercise may be appropriate. Special care should be taken in patients with conditions that may be aggravated by placement in the dorsal lithotomy position.
    - Use caution not to contaminate the mesh with fecal matter or contact the mesh with any staples, clips or other instruments that may damage the device.

Detailed directions for use will be included in labeling. Post-procedure patient monitoring instructions and management will be included and are as follows:

- Take steps to reduce and/or minimize an increase in intra-abdominal pressure after the procedure (e.g. inform anesthesia staff that coughing could impact mesh fixation).
- Post-operative antibiotic use should be determined by the physician.
- Patients should be advised to take a stool softener or laxative as needed to prevent constipation.

- Patients should be counseled to abstain from heavy lifting, exercise and intercourse for approximately 6 weeks. Patients can return to other normal daily activities at the physician's discretion.
- If bleeding, painful defecation or other problems occur, patients should be instructed to contact the surgeon immediately.
- Prior to discharge from the hospital, patients should be informed of appropriate self-monitoring activity and action to take if a potential AEs occurs.
- Treat infected surgical wounds according to standard practice.

The TOPAS system Instructions for Use provides physicians with appropriate indications for prescription use of the device, and step-by-step implantation procedure instructions intend to minimize procedural errors and associated patient-related risks. ASTORA also recognizes that a potential contributing factor to overall patient outcome and safety profile may be dependent on physician experience with surgical mesh implant procedures. Thus, ASTORA has created a proposed product training program that will be required for physicians to complete prior to use (see Section 6.2).

6 POST-APPROVAL PLANS

6.1 POST-MARKET STUDIES

ASTORA will follow patients currently enrolled in the TOPAS PMA Study through 5 years (60 months) of follow-up to monitor the long-term performance and safety of the TOPAS system. The TOPAS PMA Study was originally designed with a 3 year follow-up period but was extended to 5 years in December 2013 following discussions with the FDA. A long-term safety endpoint has been proposed to measure if the proportion of study patients experiencing at least one treatment-related SAE is lower than 25% at 60 months of follow-up (this is still under evaluation by the FDA). As part of this study extension, ASTORA will continue providing annual updates on safety and performance data to the FDA until the study is completed at the end of 2017.

ASTORA is currently in ongoing discussions on the design of a new post-market study with the TOPAS system. The study design and objectives have not yet been finalized but the study will likely focus on safety questions not addressed in the current TOPAS PMA Study. The most up-to-date information on the post-market study will be presented by ASTORA at the Advisory Committee meeting.

In addition, for the commercialization of the TOPAS system, ASTORA Product Surveillance personnel will monitor all physician and patient complaints to monitor for any new complaint types or existing types occurring at higher than predicted levels.

6.2 PHYSICIAN TRAINING PROGRAM

ASTORA has also designed a well-planned physician training program (based on the training done in the TOPAS PMA Study) with the intent of helping physicians utilize the TOPAS system in a safe and effective manner. The proposed training program will have three phases including:

- An online introductory course with curriculum focusing on FI and it's etiology, pelvic anatomy relevant to FI and the TOPAS procedure, product information and labeling, patient selection, and complications management,
- A hands-on component including additional didactic training and experience implanting the TOPAS device with a pelvic model and cadavers, and
- A surgical experience overseen by a qualified proctor (at least two cases).

The training program will also include an optional refresher course for physicians who have completed the three-phases described above.

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APPENDIX 1: LISTING OF STUDY WITHDRAWALS

Table 36: Listing of Study Withdrawals (Screening Exits) for All Patients Enrolled but not Implanted

Patient ID	Enrollment Date	Implant Date	Exit Date	Complete Study?	Exit Reason	Comments
(b) (6)	29JUN10	N/A	17MAR11	No	Patient withdrawal of consent	Patient using metamucil to decrease FI episodes. No longer interested in study. Pt. did not complete bowel diary as per her report.
	16AUG10	N/A	13JAN11	No	Patient withdrawal of consent	Not having fi anymore per patient's report. Patient did not complete bowel diary.
	24AUG10	N/A	26AUG10	No	Patient withdrawal of consent	Patient stated she is no longer interested in the study because she travels often and does not want to travel to England shortly after implant and be at risk for an infection.
	07SEP10	N/A	25FEB11	No	Patient withdrawal of consent	Patient withdrew consent due to recent breast cancer diagnosis.
	01OCT10	N/A	07FEB11	No	Patient lost to follow-up	Certified letter sent 2/3/11.
	05JAN11	N/A	27JAN11	No	Did not meet selection criteria	Did not meet inclusion criteria 5. Patient states her 14 day bowel diary was a typical 14 days for her.
	30MAR11	N/A	07MAY11	No	Did not meet selection criteria	Did not meet inclusion criteria #5. Patient states she had a typical 14 days when she completed her bowel diary. She stopped her supplements and said her FI stopped as well, patient mailed in bowel diary and did not return to sign updated ICF.
	13APR11	N/A	31OCT11	No	Did not meet selection criteria	Entire colon was unable to be visualized during colonoscopy dated 9/13/11, therefore cancer could not be ruled out.
	04OCT11	N/A	07MAY12	No	Patient lost to follow-up	Multiple messages left for patient regarding status of study participation. All unanswered. Certified letter sent 4/25/12. Delivery confirmation retained. No response.
	04OCT11	N/A	22MAR12	No	Patient lost to follow-up	Multiple messages left for patient regarding status of study participation. All unanswered. Certified letter sent 3/8/12. Delivery confirmation retained. No response.

Patient ID	Enrollment Date	Implant Date	Exit Date	Complete Study?	Exit Reason	Comments
(b) (6)	15MAY12	N/A	31MAY12	No	Patient withdrawal of consent	Patient is unable to participate in study, her sister is morbidly ill and patient is in Texas for the foreseeable future to care for her.
	30SEP10	N/A	02NOV10	No	Patient withdrawal of consent	Patient changed mind about procedure, withdrew consent.
	26OCT10	N/A	03AUG11	No	Withdrawal of patient by investigator	
	18NOV10	N/A	30MAY11	No	Patient withdrawal of consent	Patient decided that she no longer wants to have surgery.
	07JUN11	N/A	22SEP11	No	Patient withdrawal of consent	Patient changed mind and decided to have a sacral nerve stimulator implanted.
	11AUG11	N/A	24AUG11	No	Patient withdrawal of consent	Patient withdrew from the study prior to her screening #2 visit because she felt apprehensive about participating in a research trial / having a procedure with an investigational device.
	29SEP11	N/A	06OCT11	No	Patient withdrawal of consent	Patient felt that her condition had improved since her visit and did not want to proceed with surgery at that time.
	02FEB12	N/A	08MAR12	No	Patient withdrawal of consent	Patient is having other health / personal issues and does not want to treat FI at this time. She noted that pectin helped more than anything she tried prior. She had 4 episodes since enrolling, down from 4/day, and is okay with this amount.
	07SEP12	N/A	05OCT12	No	Withdrawal of patient by investigator	
	19OCT10	N/A	02NOV10	No	Patient withdrawal of consent	Patient decided not to have surgery.
	05MAR12	N/A	22MAR12	No	Withdrawal of patient by investigator	
	05AUG10	N/A	19OCT10	No	Sponsor termination of site	
	05AUG10	N/A	19OCT10	No	Sponsor termination of site	
	02SEP10	N/A	19OCT10	No	Sponsor termination of site	
	27SEP10	N/A	22OCT10	No	Sponsor termination of site	

Patient ID	Enrollment Date	Implant Date	Exit Date	Complete Study?	Exit Reason	Comments
(b) (6)	18APR11	N/A	05AUG11	No	Did not meet selection criteria	Patient did not meet inclusion criteria #5. Spoke with patient over the phone following completion of the bowel diary. Patient did not actually come to office for SV #2 since she clearly did not meet criteria.
	09MAY11	N/A	05AUG11	No	Did not meet selection criteria	Patient did not meet inclusion criteria #5.
	16MAR12	N/A	18APR12	No	Patient withdrawal of consent	
	18OCT12	N/A	01NOV12	No	Study implant threshold reached	
	18APR12	N/A	11SEP12	No	Patient withdrawal of consent	
	10JUL12	N/A	15AUG12	No	Patient withdrawal of consent	
	09NOV10	N/A	26NOV10	No	AE made further follow-up inappropriate	AE number one resulted in colostomy for patient.
	07DEC10	N/A	07FEB11	No	Patient withdrawal of consent	Patient decided not to have implant.
	12NOV10	N/A	29MAR11	No	Patient withdrawal of consent	Patient could not make up her mind regarding any type of treatment.
	22DEC10	N/A	25FEB11	No	Did not meet selection criteria	Exclusion criteria #16: Rectal prolapse found on defecography exam 17 FEB 2011
	17JAN11	N/A	31MAR11	No	Did not meet selection criteria	Patient reported FI episodes had decreased to < 2 per week. Inclusion Criterion #5 . Patient was exited over the phone and did not reconsent to ICF version 1.7.
	19APR11	N/A	12MAY11	No	Did not meet selection criteria	Patient exclusion criterion # 16 full thickness rectal prolapse.
	20MAR12	N/A	20MAR12	No	Withdrawal of patient by investigator	Patient was previously enrolled in the trial in Utah with Dr. Eyring.
	20OCT10	N/A	11FEB11	No	Patient withdrawal of consent	Patient wanted to continue conservative treatments.
	10OCT11	N/A	10OCT11	No	Patient withdrawal of consent	Patient wanted to continue conservative treatment (biofeedback therapy); not considering TOPAS as a future option.
	02FEB12	N/A	09MAR12	No	Did not meet selection criteria	Excl. criteria # 4 (pelvic prolapse > 1 cm).

Patient ID	Enrollment Date	Implant Date	Exit Date	Complete Study?	Exit Reason	Comments
(b) (6)	31MAY12	N/A	09JUL12	No	Patient withdrawal of consent	
	23MAR11	N/A	20APR11	No	Patient withdrawal of consent	Patient withdrew consent prior to implant.
	29NOV10	N/A	17MAR11	No	Patient lost to follow-up	
	03DEC10	N/A	08NOV11	No	Patient withdrawal of consent	Patient changed her mind about participation in study after family health issues.
	15DEC10	N/A	03JAN11	No	Did not meet selection criteria	Patient's bowel regimen was successful in treating her FI. She no longer qualifies for the study.
	18MAR11	N/A	11APR11	No	Did not meet selection criteria	Patient started fiber regimen that resolved her FI symptoms. No longer having FI episodes.
	04APR11	N/A	01AUG11	No	Did not meet selection criteria	Patient only had 2 FI episodes in 2 weeks. No longer qualified for study.
	15JUL11	N/A	15JUL11	No	Did not meet selection criteria	Patient's frequency of BMs ranging from 4-12/day with incontinence only of liquid stool is consistent with an underlying etiology of her bowel motility disorder. Not a candidate for the TOPAS PMA study.
	22AUG11	N/A	22AUG11	No	Withdrawal of patient by investigator	
	29AUG11	N/A	23JAN12	No	Patient moved away from site location	
	08DEC11	N/A	12JAN12	No	Patient withdrawal of consent	Patient decided to pursue other options
	10JAN12	N/A	16JUL12	No	Study implant threshold reached	Unable to meet surgical deadline
	07FEB12	N/A	07FEB12	No	Did not meet selection criteria	Patient did not meet inclusion criteria number 3.
	07FEB12	N/A	27APR12	No	Patient lost to follow-up	

APPENDIX 2: RESPONDER RATE BY PATIENT SUBGROUP

Table 37: Subgroup Analysis for the Treatment Response Rate Using Logistic Regression

Covariate	Responder Rate at 12 Month	Comparison	Logistic Regression Model	
			Odds Ratio [95% CI]	p-value
Medical Specialty				**0.216**
Colorectal Surgeon	63.3% (38/60)	Colorectal Surgeon vs. Urogynecologist	0.64 [0.32 , 1.29]	
Urogynecologist	72.8% (67/92)	REFERENCE	---	
Age (years)				**0.592**
[32-53]	68.3% (28/41)	REFERENCE	---	
(53-60]	61.1% (22/36)	(53-60] vs. [32-53]	0.73 [0.29 , 1.87]	
(60-66]	71.1% (27/38)	(60-66] vs. [32-53]	1.14 [0.44 , 2.98]	
(66-79]	75.7% (28/37)	(66-79] vs. [32-53]	1.44 [0.53 , 3.92]	
BMI (kg/m^2)				**0.324**
< 27	72.7% (56/77)	<27 vs. ≥ 27	1.42 [0.71 , 2.82]	
≥ 27	65.3% (49/75)	REFERENCE	---	
Baseline FI Episodes (number in 14 days)				**0.768**
[4-10]	63.9% (23/36)	REFERENCE	---	
[11-17]	71.1% (27/38)	[11-17] vs. [4-10]	1.39 [0.52 , 3.68]	
[18-26]	74.4% (29/39)	[18-26] vs. [4-10]	1.64 [0.61 , 4.41]	
≥ 27	66.7% (26/39)	≥ 27 vs. [4-10]	1.13 [0.44 , 2.93]	
Vaginal Deliveries (number)				**0.069**
0	100.0% (12/12)	0 vs. [1,2]	12.88 [0.65 , 253.84]	
[1,2]	66.2% (51/77)	REFERENCE	---	
> 2	66.7% (42/63)	> 2 vs. [1,2]	1.02 [0.50 , 2.06]	
FI Etiology				**0.102**
Trauma	64.1% (59/92)	REFERENCE	---	
Idiopathic/Other	76.7% (46/60)	Idiopathic/Other vs. Trauma	1.84 [0.88 , 3.83]	

Covariate	Responder Rate at 12 Month	Comparison	Logistic Regression Model	
			Odds Ratio [95% CI]	p-value
External Sphincter Defect (present/degree)				**0.965**
No	68.5% (50/73)	No vs. Yes with degree > 90	1.00 [0.43 , 2.33]	
Yes w/degree ≤ 90	70.7% (29/41)	Degree ≤ 90 vs. > 90	1.12 [0.43 , 2.91]	
Yes w/ degree > 90	68.4% (26/38)	REFERENCE	---	
Internal Sphincter Defect (present/degree)				**0.708**
No	70.9% (78/110)	No vs. Yes with degree > 90	1.28 [0.54 , 3.06]	
Yes w/degree ≤ 90	61.5% (8/13)	Degree ≤ 90 vs. > 90	0.84 [0.22 , 3.26]	
Yes w/ degree > 90	65.5% (19/29)	REFERENCE	---	
Mean Max Squeeze Pressure (mmHg)				**0.585**
[0, 31.5]	73.7% (28/38)	REFERENCE	---	
(31.5, 51]	69.2% (27/39)	(31.5, 51] vs. [0, 31.5]	0.80 [0.30 , 2.17]	
(51, 83]	73.0% (27/37)	(51, 83] vs. [0, 31.5]	0.96 [0.35 , 2.68]	
(83, 245]	60.5% (23/38)	(83, 245] vs. [0, 31.5]	0.55 [0.21 , 1.45]	
Mean Max Resting Pressure (mmHg)				**0.306**
[0, 16]	76.9% (30/39)	REFERENCE	---	
(16, 30]	68.4% (26/38)	(16, 30] vs. [0, 16]	0.65 [0.24 , 1.79]	
(30, 43]	57.9% (22/38)	(30, 43] vs. [0, 16]	0.41 [0.15 , 1.10]	
(43, 134]	73.0% (27/37)	(43, 134] vs. [0, 16]	0.81 [0.29 , 2.29]	
Rectal First Sensation (cc)				**0.700**
[10, 20]	67.5% (27/40)	REFERENCE	---	
(20, 40]	64.0% (32/50)	(20, 40] vs. [10, 20]	0.86 [0.36 , 2.06]	
(40, 51.5]	75.0% (18/24)	(40, 51.5] vs. [10, 20]	1.44 [0.46 , 4.50]	
(51.5, 300]	73.7% (28/38)	(51.5, 300] vs. [10, 20]	1.35 [0.51 , 3.59]	
Maximum Tolerated Volume (cc)				**0.736**
[25, 80]	66.7% (28/42)	REFERENCE	---	
(80, 117.5]	67.6% (23/34)	(80, 117.5] vs. [25, 80]	1.05 [0.40 , 2.74]	
(117.5, 159]	65.8% (25/38)	(117.5, 159] vs. [25, 80]	0.96 [0.38 , 2.43]	
(159, 350]	76.3% (29/38)	(159, 350] vs. [25, 80]	1.61 [0.60 , 4.31]	

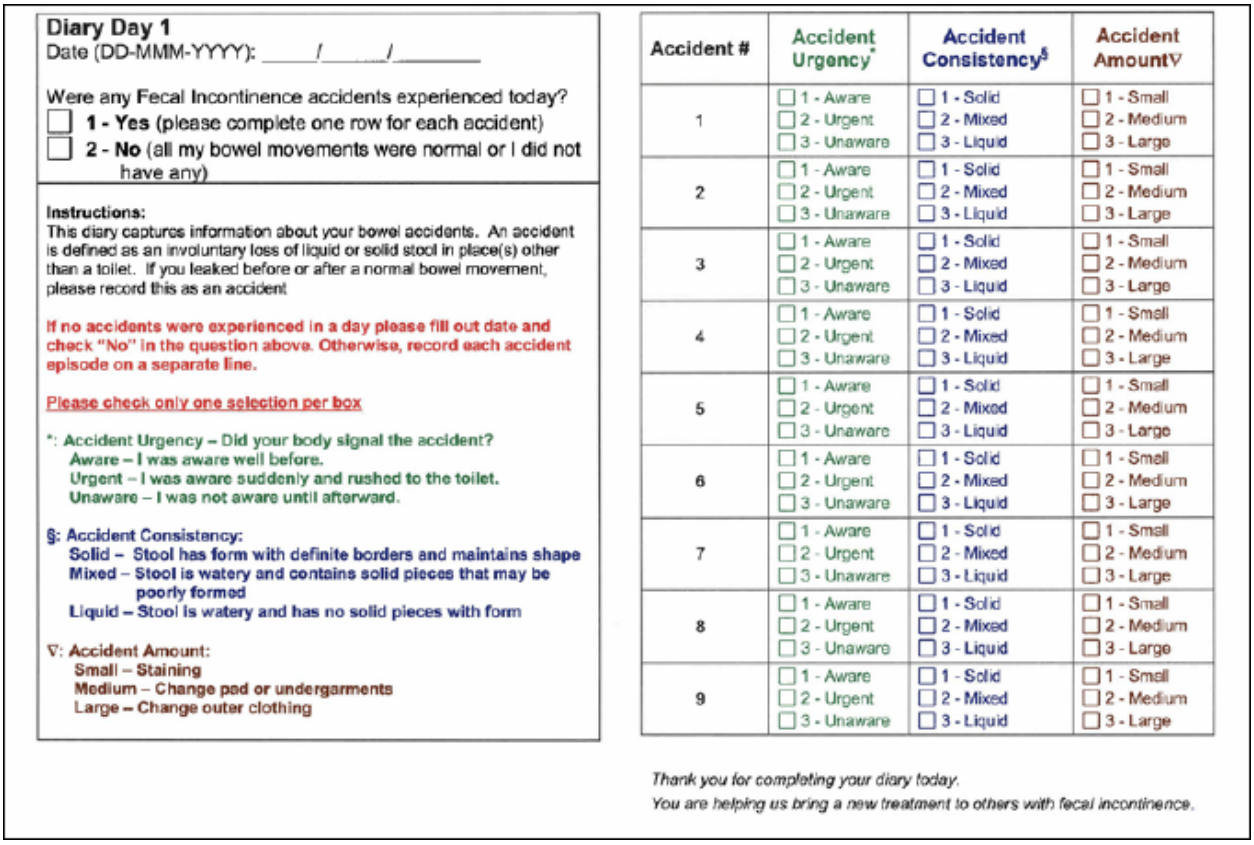
Covariate	Responder Rate at 12 Month	Comparison	Logistic Regression Model	
			Odds Ratio [95% CI]	p-value
Smoked Within the Past 6 Months?				**0.710**
Yes	75.0% (6/8)	REFERENCE	---	
No	68.8% (99/144)	No vs. Yes	0.73 [0.14 , 3.78]	
Diabetes Medical History				**0.320**
Yes	78.9% (15/19)	REFERENCE	---	
No	67.7% (90/133)	No vs. Yes	0.56 [0.17 , 1.78]	
Hypertension Medical History				**0.485**
Yes	72.4% (42/58)	REFERENCE	---	
No	67.0% (63/94)	No vs. Yes	0.77 [0.38 , 1.59]	
Previous Cholecystectomy Surgical History				**0.612**
Yes	65.8% (25/38)	REFERENCE	---	
No	70.2% (80/114)	No vs. Yes	1.22 [0.56 , 2.67]	
Depressive Disorder Medical History*				**0.998**
Yes	69.1% (38/55)	REFERENCE	---	
No	69.1% (67/97)	No vs. Yes	1.00 [0.49 , 2.04]	
Previous Prolapse and/or UI Repair Surgical History				**0.352**
Yes	72.9% (51/70)	REFERENCE	---	
No	65.9% (54/82)	No vs. Yes	0.72 [0.36 , 1.44]	
Systemic Pain Medical History^				**0.464**
Yes	72.7% (40/55)	REFERENCE	---	
No	67.0% (65/97)	No vs. Yes	0.76 [0.37 , 1.58]	

** Depressive disorder includes the following medical history conditions: depression, anxiety*

^ Systemic pain includes the following medical history conditions: lupus, rheumatoid arthritis, fibromyalgia

APPENDIX 3: PATIENT-REPORTED QUESTIONNAIRES

Figure 16: Patient Bowel Diary Daily Record Page



Diary Day 1
Date (DD-MMM-YYYY): _____/_____/_____

Were any Fecal Incontinence accidents experienced today?
☐ **1 - Yes** (please complete one row for each accident)
☐ **2 - No** (all my bowel movements were normal or I did not have any)

Instructions:
This diary captures information about your bowel accidents. An accident is defined as an involuntary loss of liquid or solid stool in place(s) other than a toilet. If you leaked before or after a normal bowel movement, please record this as an accident

If no accidents were experienced in a day please fill out date and check "No" in the question above. Otherwise, record each accident episode on a separate line.

Please check only one selection per box

*: Accident Urgency – Did your body signal the accident?
Aware – I was aware well before.
Urgent – I was aware suddenly and rushed to the toilet.
Unaware – I was not aware until afterward.

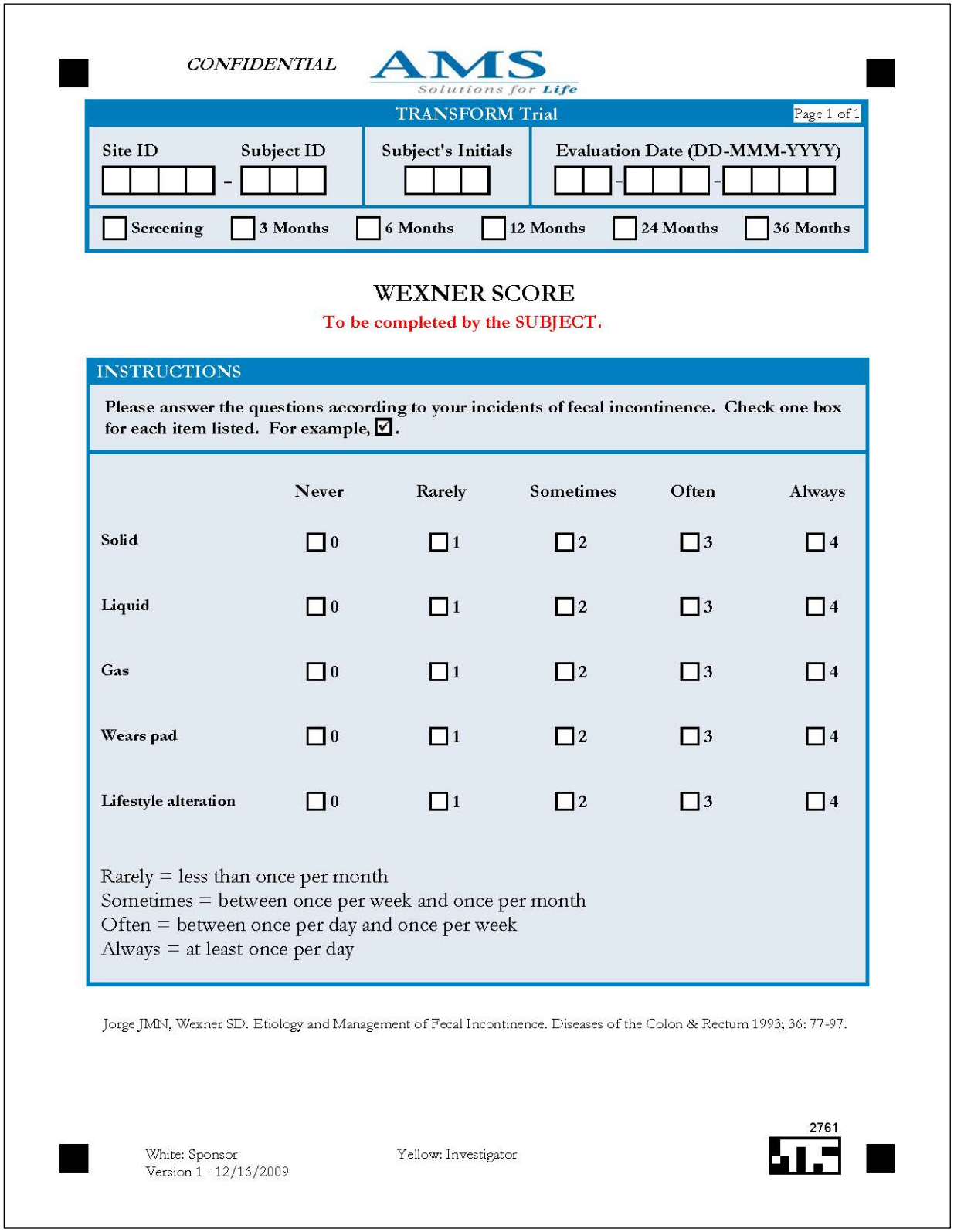
§: Accident Consistency:
Solid – Stool has form with definite borders and maintains shape
Mixed – Stool is watery and contains solid pieces that may be poorly formed
Liquid – Stool is watery and has no solid pieces with form

∇: Accident Amount:
Small – Staining
Medium – Change pad or undergarments
Large – Change outer clothing

Accident #	Accident Urgency*	Accident Consistency§	Accident Amount∇
1	☐ 1 - Aware ☐ 2 - Urgent ☐ 3 - Unaware	☐ 1 - Solid ☐ 2 - Mixed ☐ 3 - Liquid	☐ 1 - Small ☐ 2 - Medium ☐ 3 - Large
2	☐ 1 - Aware ☐ 2 - Urgent ☐ 3 - Unaware	☐ 1 - Solid ☐ 2 - Mixed ☐ 3 - Liquid	☐ 1 - Small ☐ 2 - Medium ☐ 3 - Large
3	☐ 1 - Aware ☐ 2 - Urgent ☐ 3 - Unaware	☐ 1 - Solid ☐ 2 - Mixed ☐ 3 - Liquid	☐ 1 - Small ☐ 2 - Medium ☐ 3 - Large
4	☐ 1 - Aware ☐ 2 - Urgent ☐ 3 - Unaware	☐ 1 - Solid ☐ 2 - Mixed ☐ 3 - Liquid	☐ 1 - Small ☐ 2 - Medium ☐ 3 - Large
5	☐ 1 - Aware ☐ 2 - Urgent ☐ 3 - Unaware	☐ 1 - Solid ☐ 2 - Mixed ☐ 3 - Liquid	☐ 1 - Small ☐ 2 - Medium ☐ 3 - Large
6	☐ 1 - Aware ☐ 2 - Urgent ☐ 3 - Unaware	☐ 1 - Solid ☐ 2 - Mixed ☐ 3 - Liquid	☐ 1 - Small ☐ 2 - Medium ☐ 3 - Large
7	☐ 1 - Aware ☐ 2 - Urgent ☐ 3 - Unaware	☐ 1 - Solid ☐ 2 - Mixed ☐ 3 - Liquid	☐ 1 - Small ☐ 2 - Medium ☐ 3 - Large
8	☐ 1 - Aware ☐ 2 - Urgent ☐ 3 - Unaware	☐ 1 - Solid ☐ 2 - Mixed ☐ 3 - Liquid	☐ 1 - Small ☐ 2 - Medium ☐ 3 - Large
9	☐ 1 - Aware ☐ 2 - Urgent ☐ 3 - Unaware	☐ 1 - Solid ☐ 2 - Mixed ☐ 3 - Liquid	☐ 1 - Small ☐ 2 - Medium ☐ 3 - Large

Thank you for completing your diary today.
You are helping us bring a new treatment to others with fecal incontinence.

Figure 17: Example Wexner Symptom Severity Score Questionnaire



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☐ Screening ☐ 3 Months ☐ 6 Months ☐ 12 Months ☐ 24 Months ☐ 36 Months

WEXNER SCORE

To be completed by the SUBJECT.

INSTRUCTIONS

Please answer the questions according to your incidents of fecal incontinence. Check one box for each item listed. For example, ☑.

	Never	Rarely	Sometimes	Often	Always
Solid	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Liquid	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Gas	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Wears pad	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Lifestyle alteration	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

Rarely = less than once per month
Sometimes = between once per week and once per month
Often = between once per day and once per week
Always = at least once per day

Jorge JMN, Wexner SD. Etiology and Management of Fecal Incontinence. Diseases of the Colon & Rectum 1993; 36: 77-97.

2761

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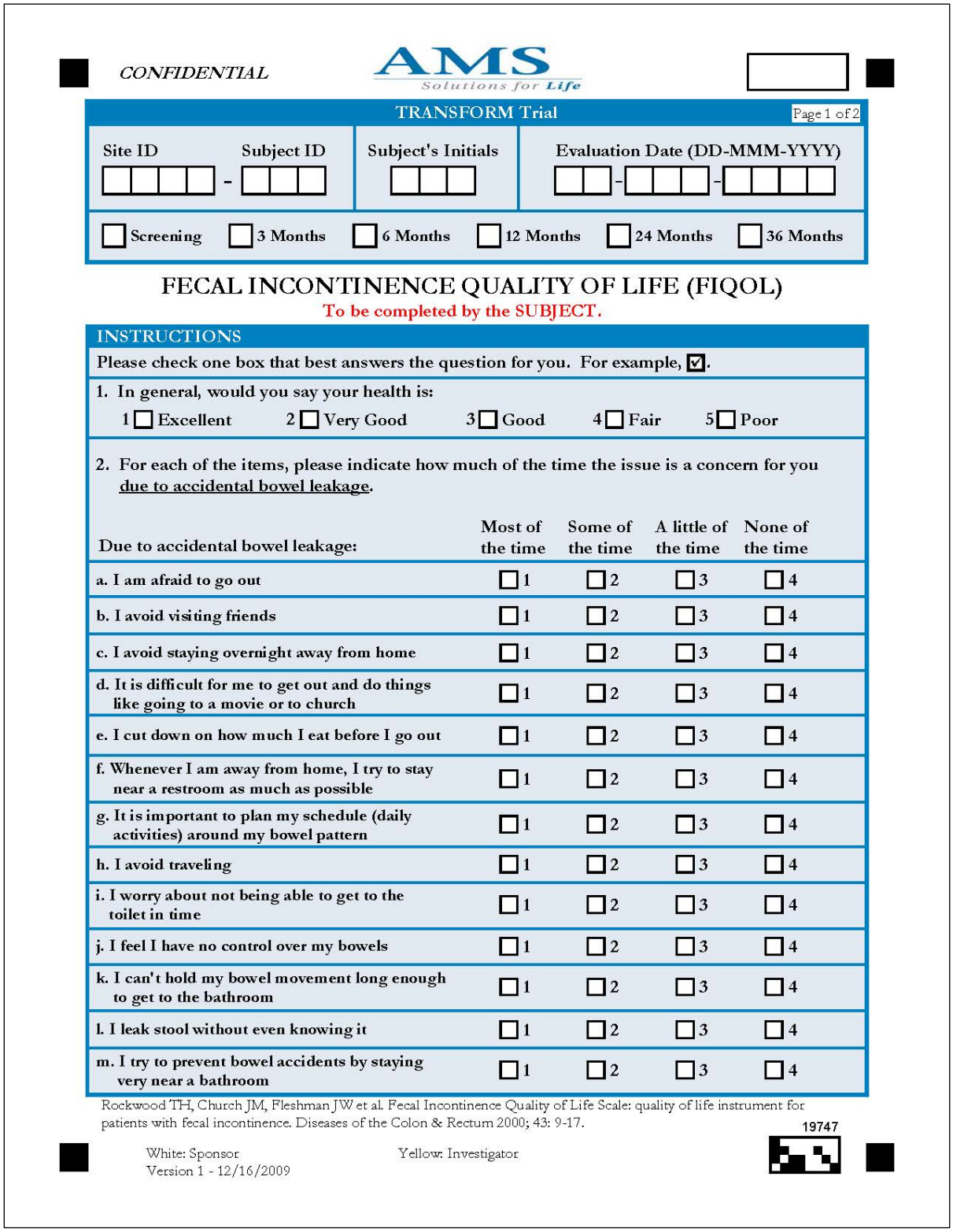
Figure 18: Example FIQoL Questionnaire



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Site ID - Subject ID | Subject's Initials | Evaluation Date (DD-MMM-YYYY)

☐ Screening ☐ 3 Months ☐ 6 Months ☐ 12 Months ☐ 24 Months ☐ 36 Months

FECAL INCONTINENCE QUALITY OF LIFE (FIQOL)

To be completed by the SUBJECT.

INSTRUCTIONS

Please check one box that best answers the question for you. For example, ☑.

1. In general, would you say your health is:

1 ☐ Excellent 2 ☐ Very Good 3 ☐ Good 4 ☐ Fair 5 ☐ Poor

2. For each of the items, please indicate how much of the time the issue is a concern for you due to accidental bowel leakage.

Due to accidental bowel leakage:	Most of the time	Some of the time	A little of the time	None of the time
a. I am afraid to go out	☐ 1	☐ 2	☐ 3	☐ 4
b. I avoid visiting friends	☐ 1	☐ 2	☐ 3	☐ 4
c. I avoid staying overnight away from home	☐ 1	☐ 2	☐ 3	☐ 4
d. It is difficult for me to get out and do things like going to a movie or to church	☐ 1	☐ 2	☐ 3	☐ 4
e. I cut down on how much I eat before I go out	☐ 1	☐ 2	☐ 3	☐ 4
f. Whenever I am away from home, I try to stay near a restroom as much as possible	☐ 1	☐ 2	☐ 3	☐ 4
g. It is important to plan my schedule (daily activities) around my bowel pattern	☐ 1	☐ 2	☐ 3	☐ 4
h. I avoid traveling	☐ 1	☐ 2	☐ 3	☐ 4
i. I worry about not being able to get to the toilet in time	☐ 1	☐ 2	☐ 3	☐ 4
j. I feel I have no control over my bowels	☐ 1	☐ 2	☐ 3	☐ 4
k. I can't hold my bowel movement long enough to get to the bathroom	☐ 1	☐ 2	☐ 3	☐ 4
l. I leak stool without even knowing it	☐ 1	☐ 2	☐ 3	☐ 4
m. I try to prevent bowel accidents by staying very near a bathroom	☐ 1	☐ 2	☐ 3	☐ 4

Rockwood TH, Church JM, Fleshman JW et al. Fecal Incontinence Quality of Life Scale: quality of life instrument for patients with fecal incontinence. Diseases of the Colon & Rectum 2000; 43: 9-17.

19747

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☐ Screening ☐ 3 Months ☐ 6 Months ☐ 12 Months ☐ 24 Months ☐ 36 Months

FECAL INCONTINENCE QUALITY OF LIFE (FIQOL)

3. Due to accidental bowel leakage, indicate the extent to which you AGREE or DISAGREE with each of the following items.

Due to accidental bowel leakage:	Strongly Agree	Somewhat Agree	Somewhat Disagree	Strongly Disagree
a. I feel ashamed	☐ 1	☐ 2	☐ 3	☐ 4
b. I can not do many of things I want to do	☐ 1	☐ 2	☐ 3	☐ 4
c. I worry about bowel accidents	☐ 1	☐ 2	☐ 3	☐ 4
d. I feel depressed	☐ 1	☐ 2	☐ 3	☐ 4
e. I worry about others smelling stool on me	☐ 1	☐ 2	☐ 3	☐ 4
f. I feel like I am not a healthy person	☐ 1	☐ 2	☐ 3	☐ 4
g. I enjoy life less	☐ 1	☐ 2	☐ 3	☐ 4
h. I have sex less often than I would like to	☐ 1	☐ 2	☐ 3	☐ 4
i. I feel different from other people	☐ 1	☐ 2	☐ 3	☐ 4
j. The possibility of bowel accidents is always on my mind	☐ 1	☐ 2	☐ 3	☐ 4
k. I am afraid to have sex	☐ 1	☐ 2	☐ 3	☐ 4
l. I avoid traveling by plane or train	☐ 1	☐ 2	☐ 3	☐ 4
m. I avoid going out to eat	☐ 1	☐ 2	☐ 3	☐ 4
n. Whenever I go someplace new, I specifically locate where the bathrooms are	☐ 1	☐ 2	☐ 3	☐ 4

4. During the past month, have you felt so sad, discouraged, hopeless, or had so many problems that you wondered if anything was worthwile?

1 ☐ Extremely so - To the point that I have just about given up
2 ☐ Very much so
3 ☐ Quite a bit
4 ☐ Some - Enough to bother me
5 ☐ A little bit
6 ☐ Not at all

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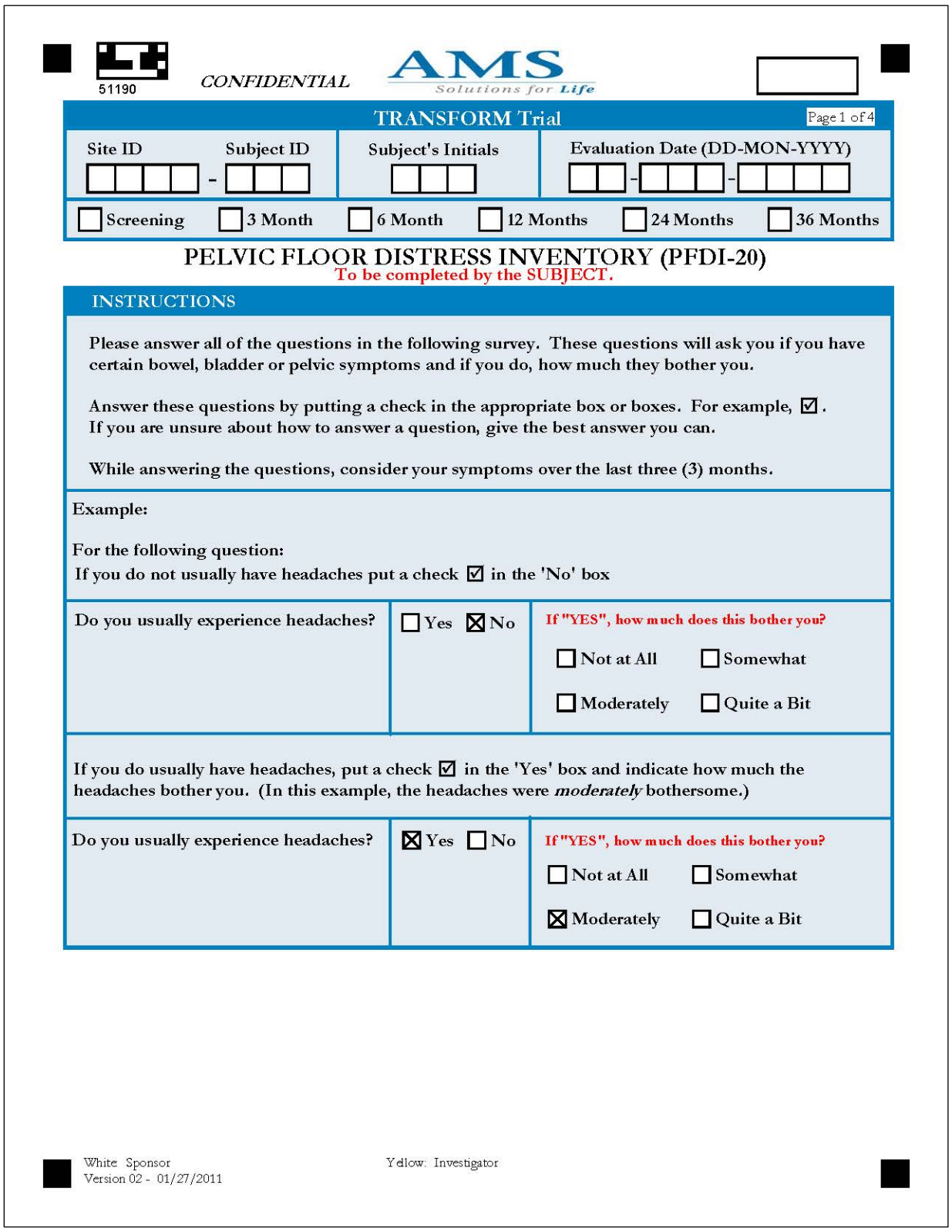
Figure 19: Example PFDI-20 Questionnaire



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Site ID ☐☐☐☐ - Subject ID ☐☐☐ | Subject's Initials ☐☐☐ | Evaluation Date (DD-MON-YYYY) ☐☐-☐☐☐-☐☐☐☐

☐ Screening ☐ 3 Month ☐ 6 Month ☐ 12 Months ☐ 24 Months ☐ 36 Months

PELVIC FLOOR DISTRESS INVENTORY (PFDI-20)

To be completed by the SUBJECT.

INSTRUCTIONS

Please answer all of the questions in the following survey. These questions will ask you if you have certain bowel, bladder or pelvic symptoms and if you do, how much they bother you.

Answer these questions by putting a check in the appropriate box or boxes. For example, ☑.
If you are unsure about how to answer a question, give the best answer you can.

While answering the questions, consider your symptoms over the last three (3) months.

Example:

For the following question:
If you do not usually have headaches put a check ☑ in the 'No' box

Do you usually experience headaches?	☐ Yes ☒ No	If "YES", how much does this bother you? ☐ Not at All ☐ Somewhat ☐ Moderately ☐ Quite a Bit

If you do usually have headaches, put a check ☑ in the 'Yes' box and indicate how much the headaches bother you. (In this example, the headaches were *moderately* bothersome.)

Do you usually experience headaches?	☒ Yes ☐ No	If "YES", how much does this bother you? ☐ Not at All ☐ Somewhat ☒ Moderately ☐ Quite a Bit

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Site ID ____ - Subject ID ____ Subject's Initials ____

☐ Screening ☐ 3 Month ☐ 6 Month ☐ 12 Months ☐ 24 Months ☐ 36 Months

PELVIC FLOOR DISTRESS INVENTORY (PFDI-20)

To be completed by the SUBJECT.

INSTRUCTIONS

Answer these questions by putting a check in the appropriate box or boxes. For example, ☑.

If you are unsure about how to answer a question, give the best answer you can. While answering the questions, consider your symptoms over the last three (3) months.

1. Do you usually experience pressure in the lower abdomen?	☐ Yes ☐ No	If "YES", how much does this bother you? ☐ Not at All ☐ Somewhat ☐ Moderately ☐ Quite a Bit
2. Do you usually experience heaviness or dullness in the pelvic area?	☐ Yes ☐ No	If "YES", how much does this bother you? ☐ Not at All ☐ Somewhat ☐ Moderately ☐ Quite a Bit
3. Do you usually have a bulge or something falling out that you can see or feel in the vaginal area?	☐ Yes ☐ No	If "YES", how much does this bother you? ☐ Not at All ☐ Somewhat ☐ Moderately ☐ Quite a Bit
4. Do you usually have to push on the vagina or around the rectum to have or complete a bowel movement?	☐ Yes ☐ No	If "YES", how much does this bother you? ☐ Not at All ☐ Somewhat ☐ Moderately ☐ Quite a Bit
5. Do you usually experience a feeling of incomplete bladder emptying?	☐ Yes ☐ No	If "YES", how much does this bother you? ☐ Not at All ☐ Somewhat ☐ Moderately ☐ Quite a Bit
6. Do you ever have to push up on a bulge in the vaginal area with your fingers to start or complete urination?	☐ Yes ☐ No	If "YES", how much does this bother you? ☐ Not at All ☐ Somewhat ☐ Moderately ☐ Quite a Bit
7. Do you feel you need to strain too hard to have a bowel movement?	☐ Yes ☐ No	If "YES", how much does this bother you? ☐ Not at All ☐ Somewhat ☐ Moderately ☐ Quite a Bit

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☐ Screening ☐ 3 Month ☐ 6 Month ☐ 12 Months ☐ 24 Months ☐ 36 Months

PELVIC FLOOR DISTRESS INVENTORY (PFDI-20)

8. Do you feel you have not completely emptied your bowels at the end of a bowel movement?	☐ Yes ☐ No	If "YES", how much does this bother you? ☐ Not at All ☐ Somewhat ☐ Moderately ☐ Quite a Bit
9. Do you usually lose stool beyond your control if your stool is well formed?	☐ Yes ☐ No	If "YES", how much does this bother you? ☐ Not at All ☐ Somewhat ☐ Moderately ☐ Quite a Bit
10. Do you usually lose stool beyond your control if your stool is loose or liquid?	☐ Yes ☐ No	If "YES", how much does this bother you? ☐ Not at All ☐ Somewhat ☐ Moderately ☐ Quite a Bit
11. Do you usually lose gas from the rectum beyond your control?	☐ Yes ☐ No	If "YES", how much does this bother you? ☐ Not at All ☐ Somewhat ☐ Moderately ☐ Quite a Bit
12. Do you usually have pain when you pass your stool?	☐ Yes ☐ No	If "YES", how much does this bother you? ☐ Not at All ☐ Somewhat ☐ Moderately ☐ Quite a Bit
13. Do you experience a strong sense of urgency and have to rush to the bathroom to have a bowel movement?	☐ Yes ☐ No	If "YES", how much does this bother you? ☐ Not at All ☐ Somewhat ☐ Moderately ☐ Quite a Bit
14. Does a part of your bowel ever pass through the rectum and bulge outside during or after a bowel movement?	☐ Yes ☐ No	If "YES", how much does this bother you? ☐ Not at All ☐ Somewhat ☐ Moderately ☐ Quite a Bit
15. Do you usually experience frequent urination?	☐ Yes ☐ No	If "YES", how much does this bother you? ☐ Not at All ☐ Somewhat ☐ Moderately ☐ Quite a Bit

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Site ID ____ - Subject ID ____ Subject's Initials ____

☐ Screening ☐ 3 Month ☐ 6 Month ☐ 12 Months ☐ 24 Months ☐ 36 Months

PELVIC FLOOR DISTRESS INVENTORY (PFDI-20)

16. Do you usually experience urine leakage associated with a feeling of urgency, that is a strong sensation of needing to go to the bathroom?	☐ Yes ☐ No	If "YES", how much does this bother you? ☐ Not at All ☐ Somewhat ☐ Moderately ☐ Quite a Bit
17. Do you usually experience urine leakage related to coughing, sneezing, or laughing?	☐ Yes ☐ No	If "YES", how much does this bother you? ☐ Not at All ☐ Somewhat ☐ Moderately ☐ Quite a Bit
18. Do you usually experience small amounts of urine leakage (that is, drops)?	☐ Yes ☐ No	If "YES", how much does this bother you? ☐ Not at All ☐ Somewhat ☐ Moderately ☐ Quite a Bit
19. Do you usually experience difficulty emptying your bladder?	☐ Yes ☐ No	If "YES", how much does this bother you? ☐ Not at All ☐ Somewhat ☐ Moderately ☐ Quite a Bit
20. Do you usually experience pain or discomfort in the lower abdomen or genital region?	☐ Yes ☐ No	If "YES", how much does this bother you? ☐ Not at All ☐ Somewhat ☐ Moderately ☐ Quite a Bit

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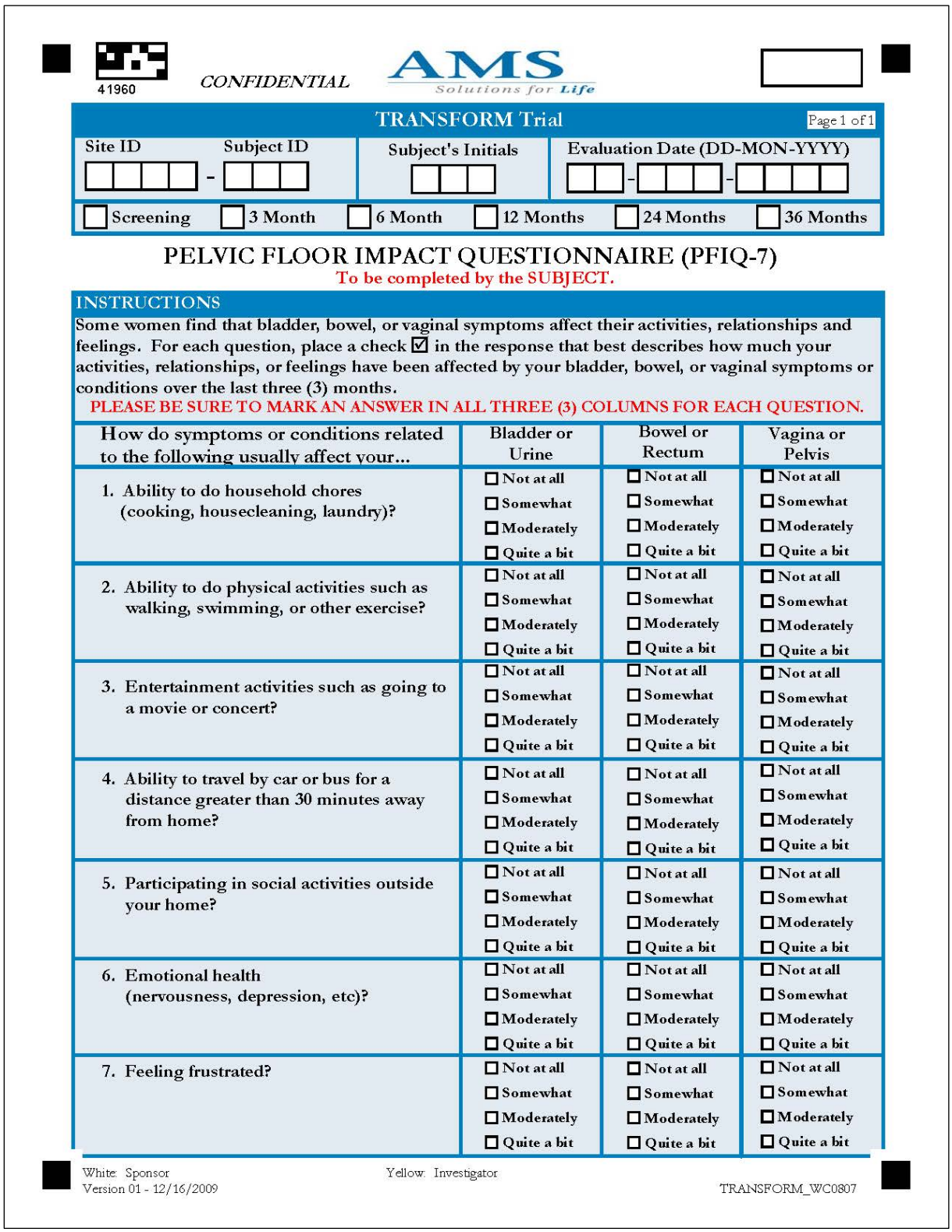
TRANSFORM_WC0807

Figure 20: Example PFIQ-7 Questionnaire



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Subject's Initials ☐☐☐

Evaluation Date (DD-MON-YYYY) ☐☐-☐☐☐-☐☐☐☐

☐ Screening ☐ 3 Month ☐ 6 Month ☐ 12 Months ☐ 24 Months ☐ 36 Months

PELVIC FLOOR IMPACT QUESTIONNAIRE (PFIQ-7)

To be completed by the SUBJECT.

INSTRUCTIONS

Some women find that bladder, bowel, or vaginal symptoms affect their activities, relationships and feelings. For each question, place a check ☑ in the response that best describes how much your activities, relationships, or feelings have been affected by your bladder, bowel, or vaginal symptoms or conditions over the last three (3) months.

PLEASE BE SURE TO MARK AN ANSWER IN ALL THREE (3) COLUMNS FOR EACH QUESTION.

How do symptoms or conditions related to the following usually affect your...	Bladder or Urine	Bowel or Rectum	Vagina or Pelvis
1. Ability to do household chores (cooking, housecleaning, laundry)?	☐ Not at all ☐ Somewhat ☐ Moderately ☐ Quite a bit	☐ Not at all ☐ Somewhat ☐ Moderately ☐ Quite a bit	☐ Not at all ☐ Somewhat ☐ Moderately ☐ Quite a bit
2. Ability to do physical activities such as walking, swimming, or other exercise?	☐ Not at all ☐ Somewhat ☐ Moderately ☐ Quite a bit	☐ Not at all ☐ Somewhat ☐ Moderately ☐ Quite a bit	☐ Not at all ☐ Somewhat ☐ Moderately ☐ Quite a bit
3. Entertainment activities such as going to a movie or concert?	☐ Not at all ☐ Somewhat ☐ Moderately ☐ Quite a bit	☐ Not at all ☐ Somewhat ☐ Moderately ☐ Quite a bit	☐ Not at all ☐ Somewhat ☐ Moderately ☐ Quite a bit
4. Ability to travel by car or bus for a distance greater than 30 minutes away from home?	☐ Not at all ☐ Somewhat ☐ Moderately ☐ Quite a bit	☐ Not at all ☐ Somewhat ☐ Moderately ☐ Quite a bit	☐ Not at all ☐ Somewhat ☐ Moderately ☐ Quite a bit
5. Participating in social activities outside your home?	☐ Not at all ☐ Somewhat ☐ Moderately ☐ Quite a bit	☐ Not at all ☐ Somewhat ☐ Moderately ☐ Quite a bit	☐ Not at all ☐ Somewhat ☐ Moderately ☐ Quite a bit
6. Emotional health (nervousness, depression, etc)?	☐ Not at all ☐ Somewhat ☐ Moderately ☐ Quite a bit	☐ Not at all ☐ Somewhat ☐ Moderately ☐ Quite a bit	☐ Not at all ☐ Somewhat ☐ Moderately ☐ Quite a bit
7. Feeling frustrated?	☐ Not at all ☐ Somewhat ☐ Moderately ☐ Quite a bit	☐ Not at all ☐ Somewhat ☐ Moderately ☐ Quite a bit	☐ Not at all ☐ Somewhat ☐ Moderately ☐ Quite a bit

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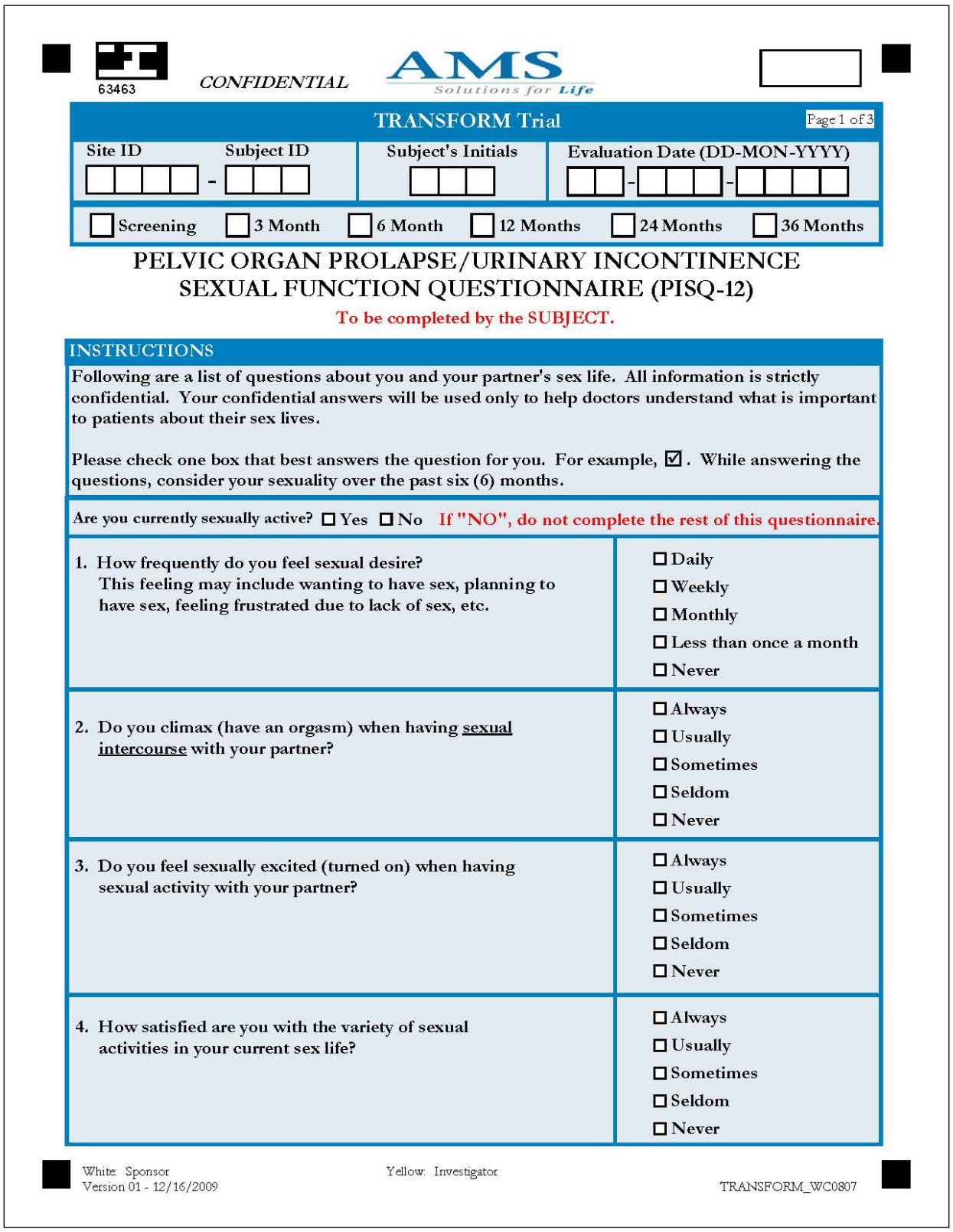
Figure 21: Example PISQ-12 Questionnaire



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Site ID ____ - Subject ID ____ | Subject's Initials ____ | Evaluation Date (DD-MON-YYYY) __ - ____ - ____

☐ Screening ☐ 3 Month ☐ 6 Month ☐ 12 Months ☐ 24 Months ☐ 36 Months

PELVIC ORGAN PROLAPSE/URINARY INCONTINENCE SEXUAL FUNCTION QUESTIONNAIRE (PISQ-12)

To be completed by the SUBJECT.

INSTRUCTIONS

Following are a list of questions about you and your partner's sex life. All information is strictly confidential. Your confidential answers will be used only to help doctors understand what is important to patients about their sex lives.

Please check one box that best answers the question for you. For example, ☑. While answering the questions, consider your sexuality over the past six (6) months.

Are you currently sexually active? ☐ Yes ☐ No If "NO", do not complete the rest of this questionnaire.

1. How frequently do you feel sexual desire? This feeling may include wanting to have sex, planning to have sex, feeling frustrated due to lack of sex, etc.	☐ Daily ☐ Weekly ☐ Monthly ☐ Less than once a month ☐ Never
2. Do you climax (have an orgasm) when having sexual intercourse with your partner?	☐ Always ☐ Usually ☐ Sometimes ☐ Seldom ☐ Never
3. Do you feel sexually excited (turned on) when having sexual activity with your partner?	☐ Always ☐ Usually ☐ Sometimes ☐ Seldom ☐ Never
4. How satisfied are you with the variety of sexual activities in your current sex life?	☐ Always ☐ Usually ☐ Sometimes ☐ Seldom ☐ Never

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Site ID	Subject ID	Subject's Initials	
☐☐☐☐ -	☐☐☐	☐☐☐	

☐ Screening ☐ 3 Month ☐ 6 Month ☐ 12 Months ☐ 24 Months ☐ 36 Months

PELVIC ORGAN PROLAPSE/URINARY INCONTINENCE SEXUAL FUNCTION QUESTIONNAIRE (PISQ-12)

5. Do you feel pain during sexual intercourse?	☐ Always ☐ Usually ☐ Sometimes ☐ Seldom ☐ Never
6. Are you incontinent of urine (leak urine) with sexual activity?	☐ Always ☐ Usually ☐ Sometimes ☐ Seldom ☐ Never
7. Does fear of incontinence (either stool or urine) restrict your sexual activity?	☐ Always ☐ Usually ☐ Sometimes ☐ Seldom ☐ Never
8. Do you avoid sexual intercourse because of bulging in the vagina (either the bladder, rectum or vagina falling out)?	☐ Always ☐ Usually ☐ Sometimes ☐ Seldom ☐ Never
9. When you have sex with your partner, do you have negative emotional reactions such as fear, disgust, shame or guilt?	☐ Always ☐ Usually ☐ Sometimes ☐ Seldom ☐ Never

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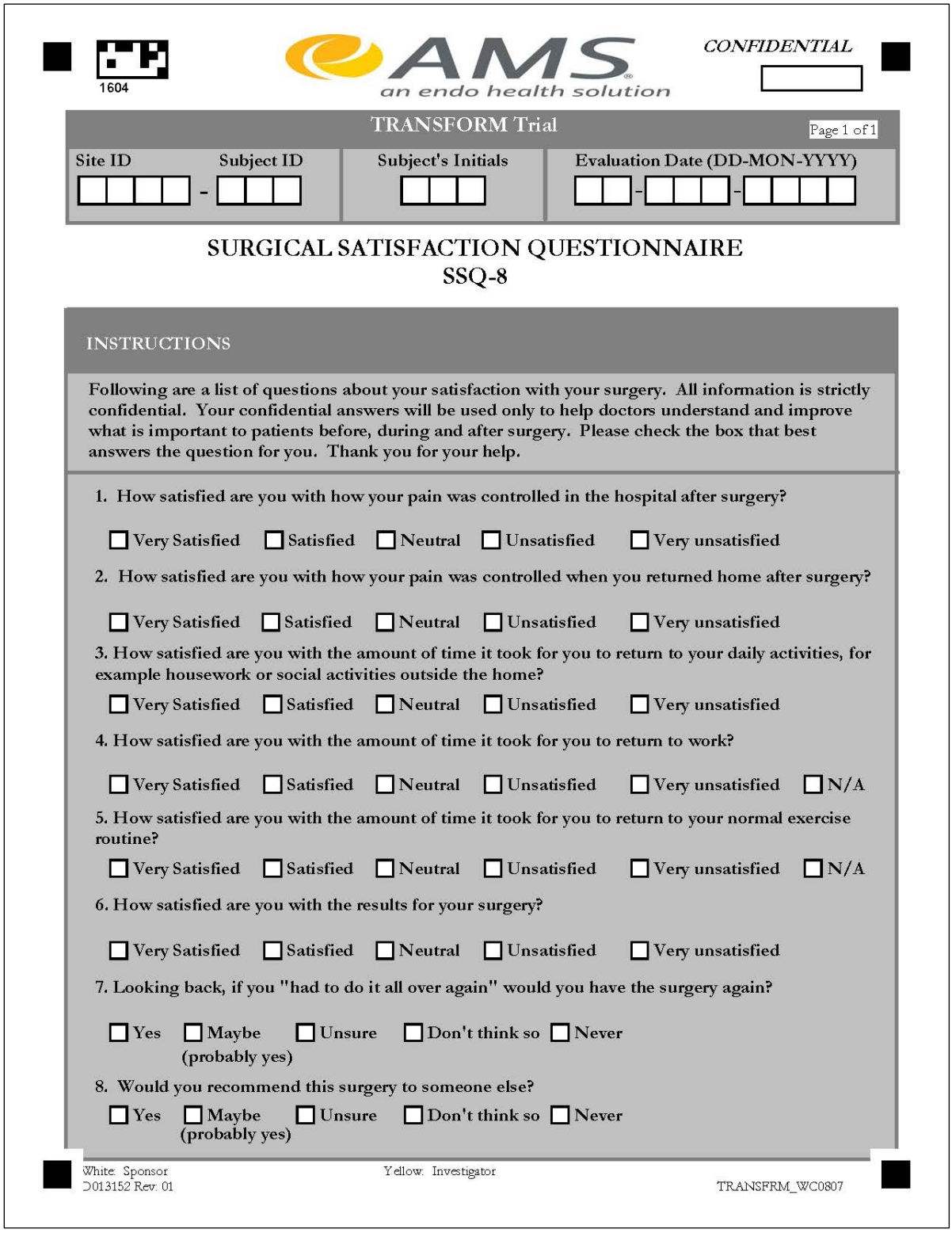
Subject's Initials ☐☐☐

☐ Screening ☐ 3 Month ☐ 6 Month ☐ 12 Months ☐ 24 Months ☐ 36 Months

PELVIC ORGAN PROLAPSE/URINARY INCONTINENCE SEXUAL FUNCTION QUESTIONNAIRE (PISQ-12)

10. Does your partner have a problem with <u>erections</u> that affects your sexual activity?	☐ Always ☐ Usually ☐ Sometimes ☐ Seldom ☐ Never
11. Does your partner have a problem with premature ejaculation that affects your sexual activity?	☐ Always ☐ Usually ☐ Sometimes ☐ Seldom ☐ Never
12. Compared to orgasms you have had in the past, how intense are the orgasms you have had in the past six (6) months?	☐ Much less intense ☐ Less intense ☐ Same intensity ☐ More intense ☐ Much more intense

Figure 22: Example SSQ-8 Questionnaire



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Site ID ____ - Subject ID ___ | Subject's Initials ___ | Evaluation Date (DD-MON-YYYY) __-___-____

SURGICAL SATISFACTION QUESTIONNAIRE
SSQ-8

INSTRUCTIONS

Following are a list of questions about your satisfaction with your surgery. All information is strictly confidential. Your confidential answers will be used only to help doctors understand and improve what is important to patients before, during and after surgery. Please check the box that best answers the question for you. Thank you for your help.

1. How satisfied are you with how your pain was controlled in the hospital after surgery?

☐ Very Satisfied ☐ Satisfied ☐ Neutral ☐ Unsatisfied ☐ Very unsatisfied

2. How satisfied are you with how your pain was controlled when you returned home after surgery?

☐ Very Satisfied ☐ Satisfied ☐ Neutral ☐ Unsatisfied ☐ Very unsatisfied

3. How satisfied are you with the amount of time it took for you to return to your daily activities, for example housework or social activities outside the home?

☐ Very Satisfied ☐ Satisfied ☐ Neutral ☐ Unsatisfied ☐ Very unsatisfied

4. How satisfied are you with the amount of time it took for you to return to work?

☐ Very Satisfied ☐ Satisfied ☐ Neutral ☐ Unsatisfied ☐ Very unsatisfied ☐ N/A

5. How satisfied are you with the amount of time it took for you to return to your normal exercise routine?

☐ Very Satisfied ☐ Satisfied ☐ Neutral ☐ Unsatisfied ☐ Very unsatisfied ☐ N/A

6. How satisfied are you with the results for your surgery?

☐ Very Satisfied ☐ Satisfied ☐ Neutral ☐ Unsatisfied ☐ Very unsatisfied

7. Looking back, if you "had to do it all over again" would you have the surgery again?

☐ Yes ☐ Maybe (probably yes) ☐ Unsure ☐ Don't think so ☐ Never

8. Would you recommend this surgery to someone else?

☐ Yes ☐ Maybe (probably yes) ☐ Unsure ☐ Don't think so ☐ Never

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D013152 Rev: 01

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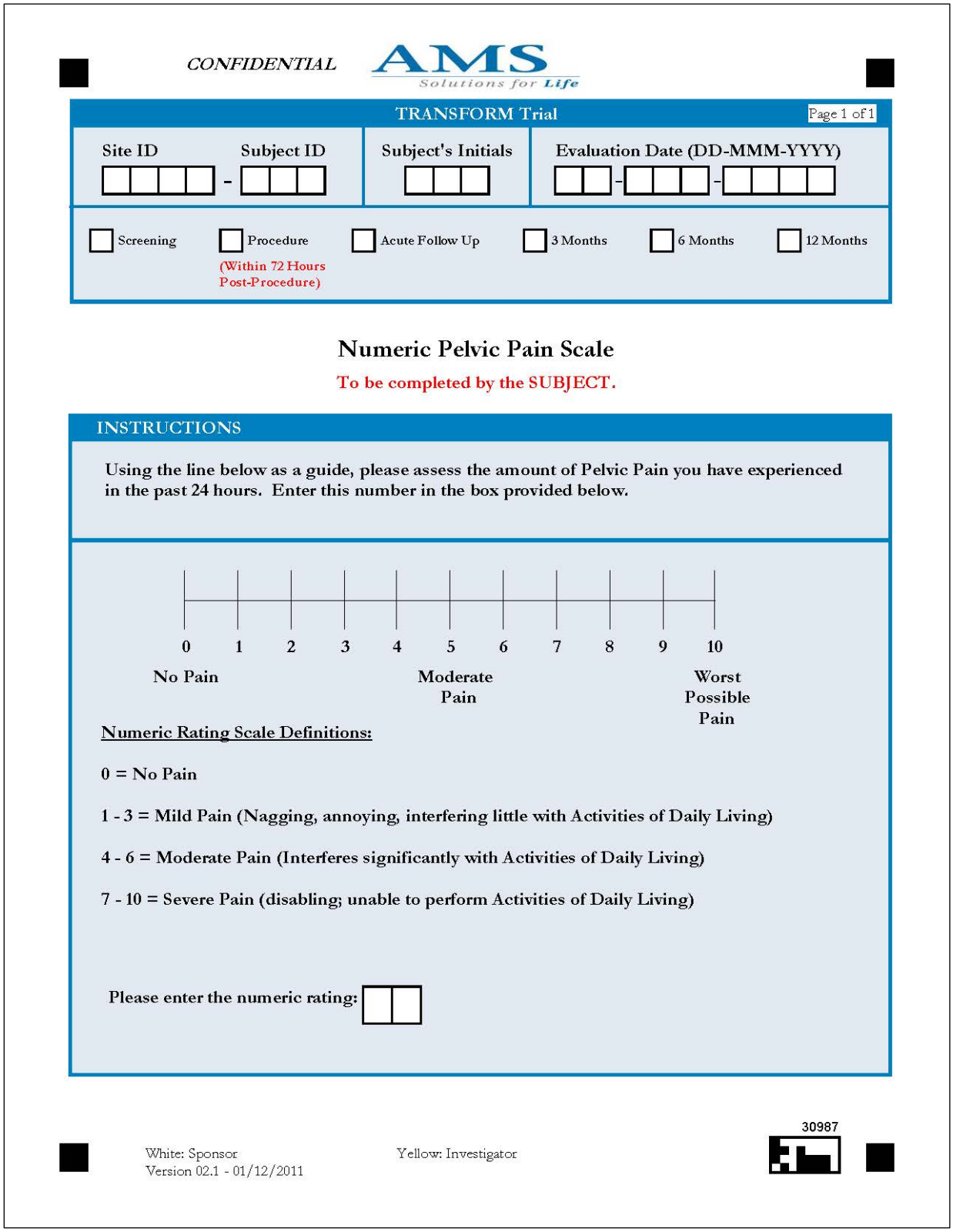
Figure 23: Example NPPS Questionnaire



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Site ID ☐☐☐☐ - Subject ID ☐☐☐ | Subject's Initials ☐☐☐ | Evaluation Date (DD-MMM-YYYY) ☐☐-☐☐☐-☐☐☐☐

☐ Screening ☐ Procedure (Within 72 Hours Post-Procedure) ☐ Acute Follow Up ☐ 3 Months ☐ 6 Months ☐ 12 Months

Numeric Pelvic Pain Scale

To be completed by the SUBJECT.

INSTRUCTIONS

Using the line below as a guide, please assess the amount of Pelvic Pain you have experienced in the past 24 hours. Enter this number in the box provided below.

0 1 2 3 4 5 6 7 8 9 10

No Pain — Moderate Pain — Worst Possible Pain

Numeric Rating Scale Definitions:

0 = No Pain

1 - 3 = Mild Pain (Nagging, annoying, interfering little with Activities of Daily Living)

4 - 6 = Moderate Pain (Interferes significantly with Activities of Daily Living)

7 - 10 = Severe Pain (disabling; unable to perform Activities of Daily Living)

Please enter the numeric rating: ☐☐

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APPENDIX 4: INDIVIDUAL FIQOL DOMAIN GRAPHS

Figure 24: Individual FIQOL Domain Graphs with Error Bars