TOPAS™ Treatment for Fecal Incontinence

ASTORA Women's Health

Presentation to the
Gastroenterology-Urology Devices Panel
February 25, 2016

TOPAS

Tom Rasmussen

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ASTORA Women's Health

TOPAS Overview

- New, innovative, minimally invasive approach for women with Fecal Incontinence (FI)
- Uses surgical mesh to safely support a woman's natural anatomy
  - Reduces episodes of FI
  - Improves patient quality of life
- Not placed transvaginally

A Debilitating Condition

- FI causes shame, embarrassment, depression, poor self-esteem and self-imposed social isolation*
- An inability to control bowel movements
  - Ranges from occasional leakage to complete loss of bowel control
  - Mild, moderate, severe FI undefined
  - Patients may have multiple episodes weekly

* Landefeld et al., 2008; Minor, 2004; Norton, 2004

No One Treatment Works in All Patients

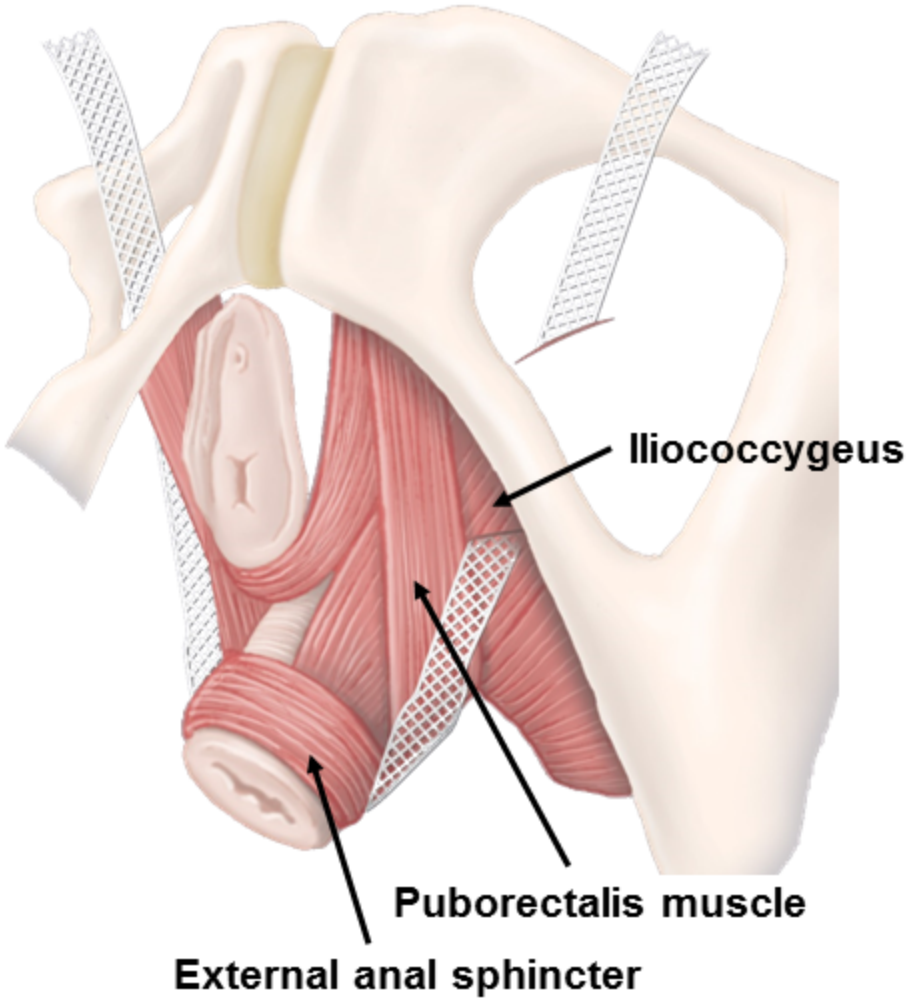
- Successful reduction in FI episodes does not eliminate concomitant treatment
- Some therapies result in additional burdens
  - Complex device management
  - Surgical revisions
  - Device replacement

TOPAS is a New Therapeutic Option

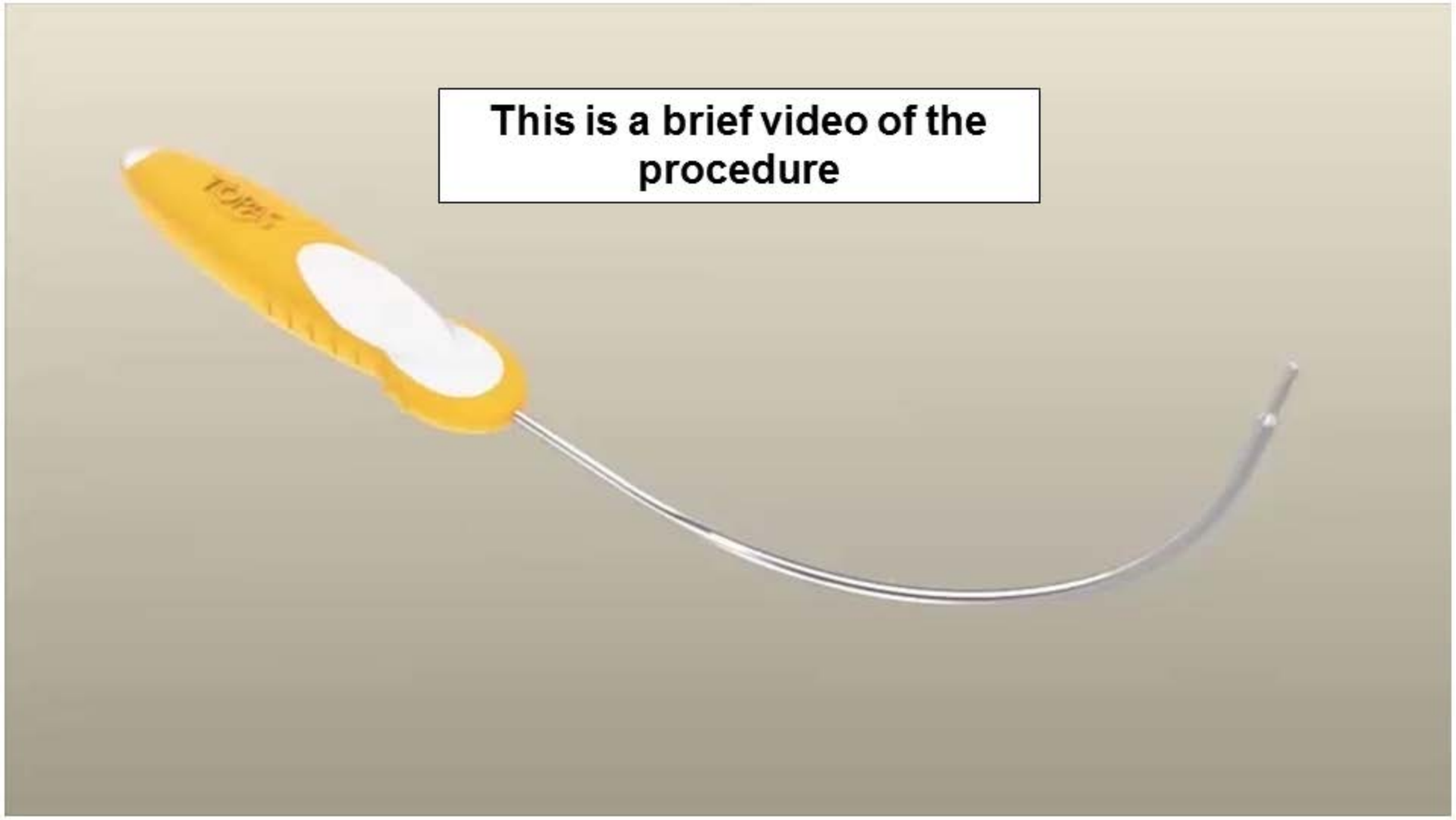
- Different potential MOA and implant location
- Support to the anorectum to compensate for the loss of pelvic floor muscle function

TOPAS Final Placement

- Goal is to place the synthetic mesh inferior to the anorectum and parallel with the puborectalis
- Mesh sits ~2 cm away from the anorectum



Outpatient Procedure Performed in ~30 Minutes With General Anesthesia



Indication for TOPAS

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.

Clinical Development Program

- Engaged physicians and statisticians in study design development
  - Single arm, adaptive study design
  - Required ≥ 152 patients
- Pre-market application submitted April 2014
- Not commercially available

TOPAS Meets Criteria for Valid Evidence

- Highest level of evidence are randomized controlled trials
- Valid scientific evidence includes objective trials without matched controls*
- Single arm studies provide valid scientific evidence to determine safety and effectiveness

* 21 CFR 860.7 (c)(2)

TOPAS Exceeded Primary Endpoint

- **Primary Endpoint:** > 50% achieve ≥ 50% reduction in number of FI episodes
  - 69% achieved ≥ 50% reduction in FI episodes versus baseline
  - Reduction was durable over 3-yr follow-up period
- Demonstrated improvements in QoL

TOPAS Demonstrated Favorable Mesh Safety Profile

- Not placed transvaginally
- No organ perforations
- 509 patient-years of follow-up, TOPAS has not seen
  - Erosions into vagina or rectum
  - Extrusions through incision sites
  - Bowel obstructions

Agenda

Unmet Need	**Mikio Nihira, MD** Professor of Obstetrics and Gynecology University of Oklahoma
Study Design & Efficacy	**Dee Fenner, MD** Professor of Obstetrics and Gynecology University of Michigan
Safety	**Mikio Nihira, MD**
Physician Education & Post-Approval	**Paul Below** Principal Clinical Research Specialist ASTORA Women's Health
Clinical Perspective	**Dee Fenner, MD**

Additional Experts

Massarat Zutshi, MD	TOPAS Study Investigator Staff, Colorectal Surgery Department Cleveland Clinic Foundation Cleveland, Ohio
Andy Mugglin, PhD	Statistical Consultant Paradigm Biostatistics, LLC, Minneapolis, Minnesota
Charlie Khamis	Director of Medical Science and Surgical Expertise ASTORA Women's Health
Ryan Casey	Senior Manager of Global Physician Training ASTORA Women's Health

Unmet Need for Women Living with Fecal Incontinence

Mikio Nihira, MD

Professor of Obstetrics and Gynecology
University of Oklahoma

Presentation Overview

- Pathophysiology
- Undertreated condition that is increasing
- Consequences of FI
- Treatment options

Several Mechanisms Necessary for Normal Fecal Continence

Mechanism	Normal Function
Innervation	Controlling rectal sensation
Pelvic Floor and Sphincter Muscles	Working properly
Stool Consistency	Not too soft to hold Not too hard to pass

Multiple Possible Contributing Factors

- Congenital, anatomic, neurologic, functional abnormalities
  - Obstetric trauma
  - Age
  - Diarrheal states
  - Inflammatory Bowel Disease
  - Neurologic conditions: Diabetic neuropathy, Multiple Sclerosis

Poor Correlation Between Diagnostic Tools, Causes and Outcomes

- Several tools to characterize FI
- Diagnostic tools may not be helpful to delineate
  - Pathophysiology
  - Potential treatment responses

FI in U.S. Women Expected to Increase

- 5-10% of women suffer ≥ 1 FI episode/month[1,2]
- In 2010, estimated that 10.6 million US women affected with FI[3]
- Increases with age

1. Markland et al, 2010, 2. Wu et al, 2014, 3. Wu et al, 2009

FI Negatively Affects Quality of Life

- FI limits lifestyle and ability to work
- Embarrassment, increased risk of depression
- Plan life around access to restrooms
- Social isolation

Landefeld et al., 2008; Minor, 2004; Norton, 2004

Treatment Barriers

- Lack of knowledge about available treatment options among patients and providers
- Patients embarrassed to seek medical advice
- < 3 in 10 patients discuss FI with their doctor
- Limited treatment options

Aitola et al, 2010; Harvie et al, 2011

Treatments Range from Non-Surgical to Major Interventions

- Dietary changes
- Medication
- Pelvic floor training

- Injectable bulking agent
- Sacral neuromodulation

- Sphincter repair surgery
- Colostomy

FDA Approved FI Devices

Device	Type	Ongoing Device Maintenance	MRI Compatible	Commercial Availability
Injectable Bulking Agent	Class III (PMA)	Required	Yes	Limited
Sacral Neuromodulator	Class III (PMA)	Required	No	Yes
Non-Permanent Vaginal Insert	Class II (510k)	Required	Yes	Limited
Magnetic Sphincter Augmentation Device	Class III (HDE)	No	No	Limited

Patients Need New, Accessible Treatment Options

- Ideal therapy
  - Efficacious and safe
  - Minimally invasive
  - Low maintenance
  - Improve patients' lives

Study Design

Dee Fenner, MD
Furlong Professor of Women's Health
Director of Gynecology
University of Michigan

Study Design

Design	Prospective Single Arm Open Label
Sites	15 US* 8 led by colorectal surgeons 7 led by urogynecologists

*One colorectal site closed prior to any patients implanted

Single Arm Study was Most Appropriate Design

- Study Advisory Committee determined randomization to conservative therapy inappropriate
- No comparable FDA-approved device available
- Benefit did not outweigh risk for sham arm
- Meets FDA standard for valid clinical evidence

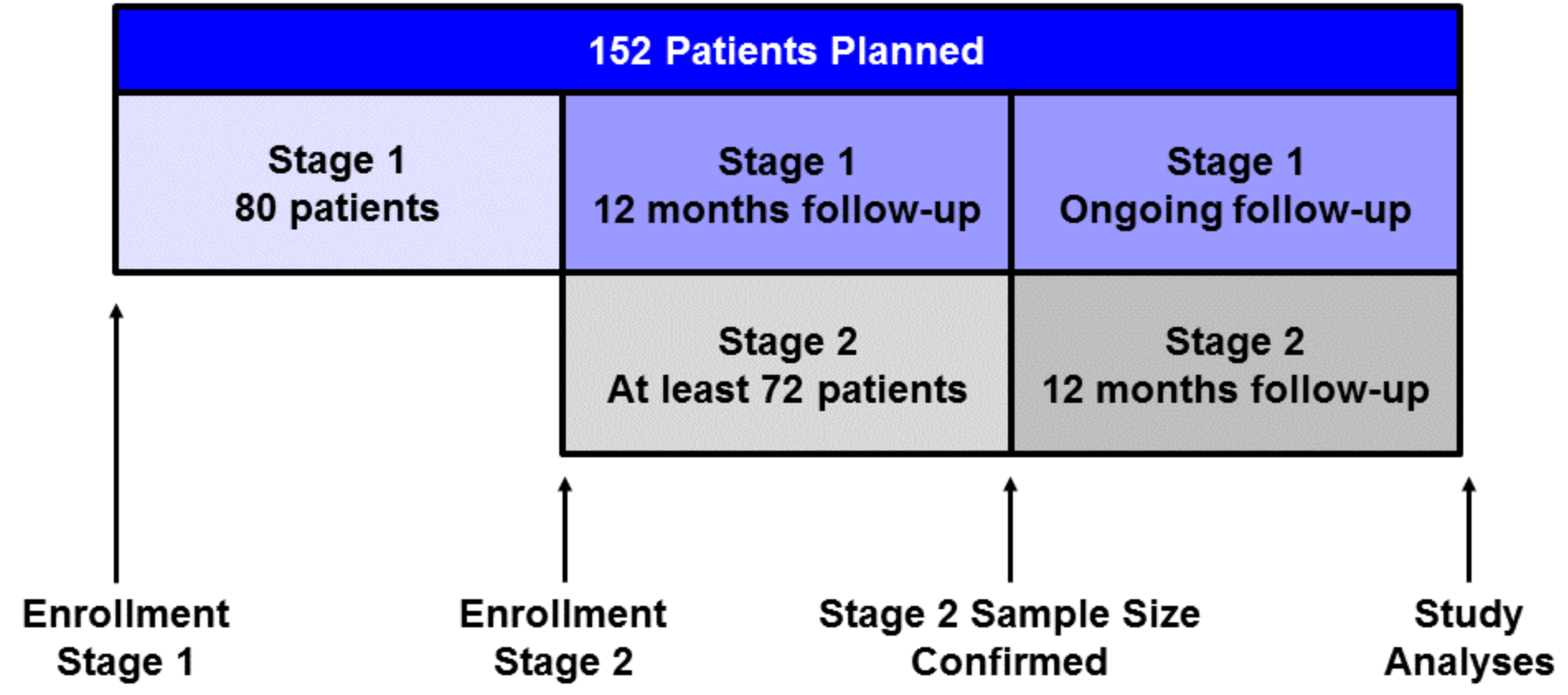
50% Reduction in FI Episodes is Standard Outcome = Responders

- Definition of responder
  - ≥ 50% reduction in FI episodes
- Study success criterion
  - > 50% of participants are responders
- Used in recent clinical device trials for FI*

* Wexner et al., 2011; Graf et al., 2011; Richter et al., 2015; Pakravan and Helmes, 2015

Adaptive Design Used

- Two-stage adaptive design
- Planned sample size re-estimation



Regular Follow-up Visits Measured Endpoints

Physical Exams / AE Assessment	2 - 4 weeks after surgery 3 & 6-month follow-up Annual thereafter, to 60 months
14-Day Bowel Diary	Baseline 3 & 6-month follow-up Annual thereafter, to 60 months
Health Questionnaires	

Patient Diary Collected Major Outcomes

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

Accident Urgency

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

Primary Efficacy Objective

Demonstrate that more than 50% of study participants could achieve at least a 50% reduction in fecal incontinent episodes from baseline to 12 months.

Handling of Missing Data

- Primary endpoint
  - Missing data as treatment failure
- Long-term follow up
  - Observed cases with missing data excluded

Secondary Objectives to Demonstrate Efficacy Focused on Sustained Results

- Long-term efficacy
- Reduced incontinent days, urge episodes, symptom severity
- Improvement in FI quality of life
- Quantify pelvic floor distress and impact to sexual function

Comprehensive Safety Objective

- Summarize all adverse events
- Quantify pelvic pain
- Known complications of surgical mesh used in pelvic floor reconstruction

Inclusion Criteria

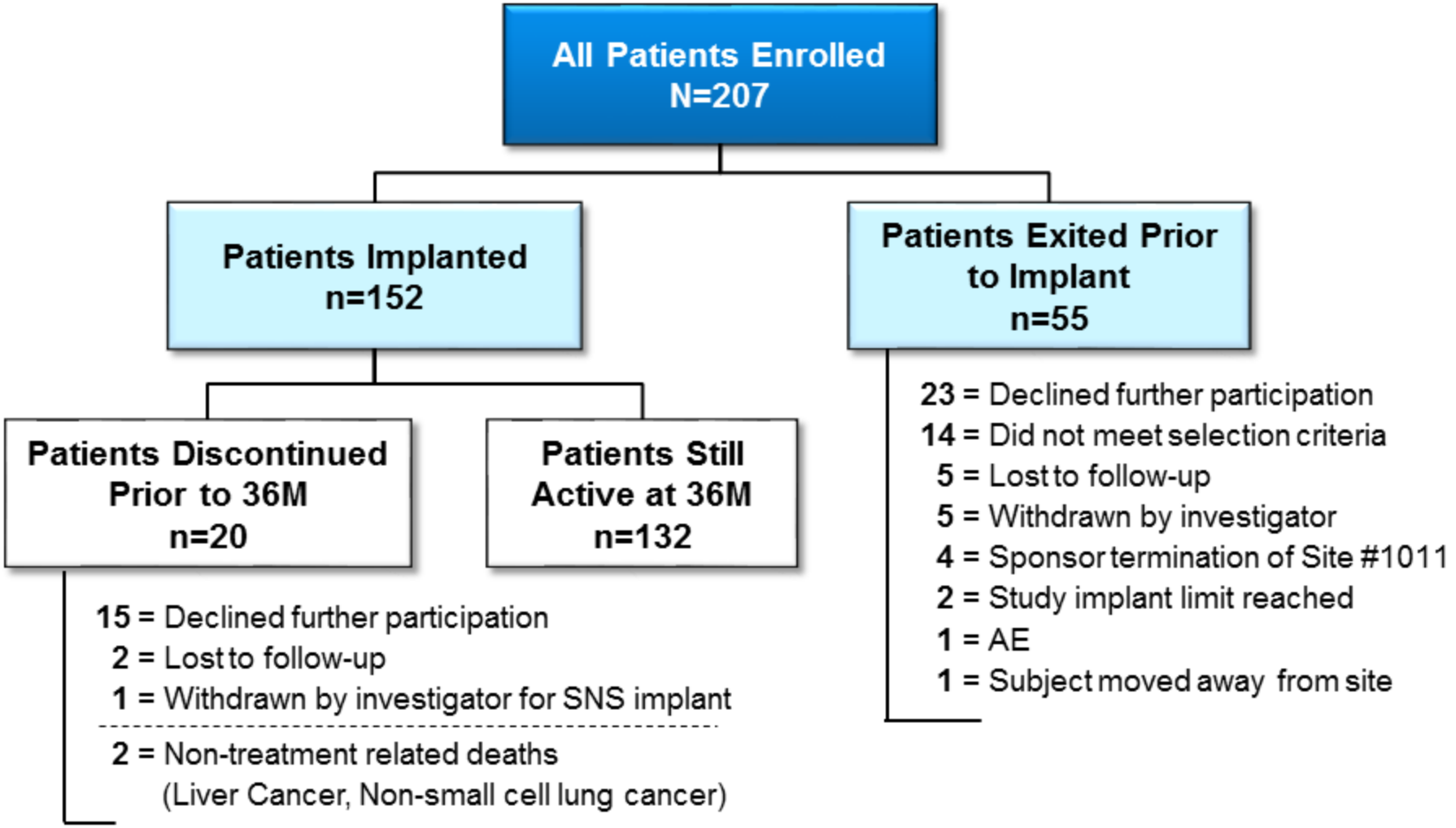
- ≥ 18 years of age
- Tried and failed ≥ 2 conservative therapies
- FI for ≥ 6 months
- ≥ 4 FI episodes in a 14-day period
- Met colon cancer screen guidelines

Exclusion Criteria

- Pregnant or planning future pregnancy
- Diagnosis of inflammatory bowel disease
- Chronic, watery diarrhea
- History of recent gynecologic or gastroenterologic surgical repair procedures

Study Results

Patient Status at 36 Months



Study Population Representative of Women with FI Seeking Treatment*

	N=152
Age (Mean ± SD)	59.6 ± 9.7
Duration of FI (Years) (Mean ± SD)	9.2 ± 9.5
Race	
Caucasian	90%
African American	7%
Other	3%
BMI (kg/m^2) (Mean ± SD)	27.8 ± 5.4
FI Episodes (14-day period)	
Mean ± SD	21.7 ± 15.4
Median	18
Etiology of FI	
Obstetric Trauma	57%
Idiopathic	41%
Other	7%

*Melville et al., 2005; Menees et al., 2013

Baseline Medical Characteristics

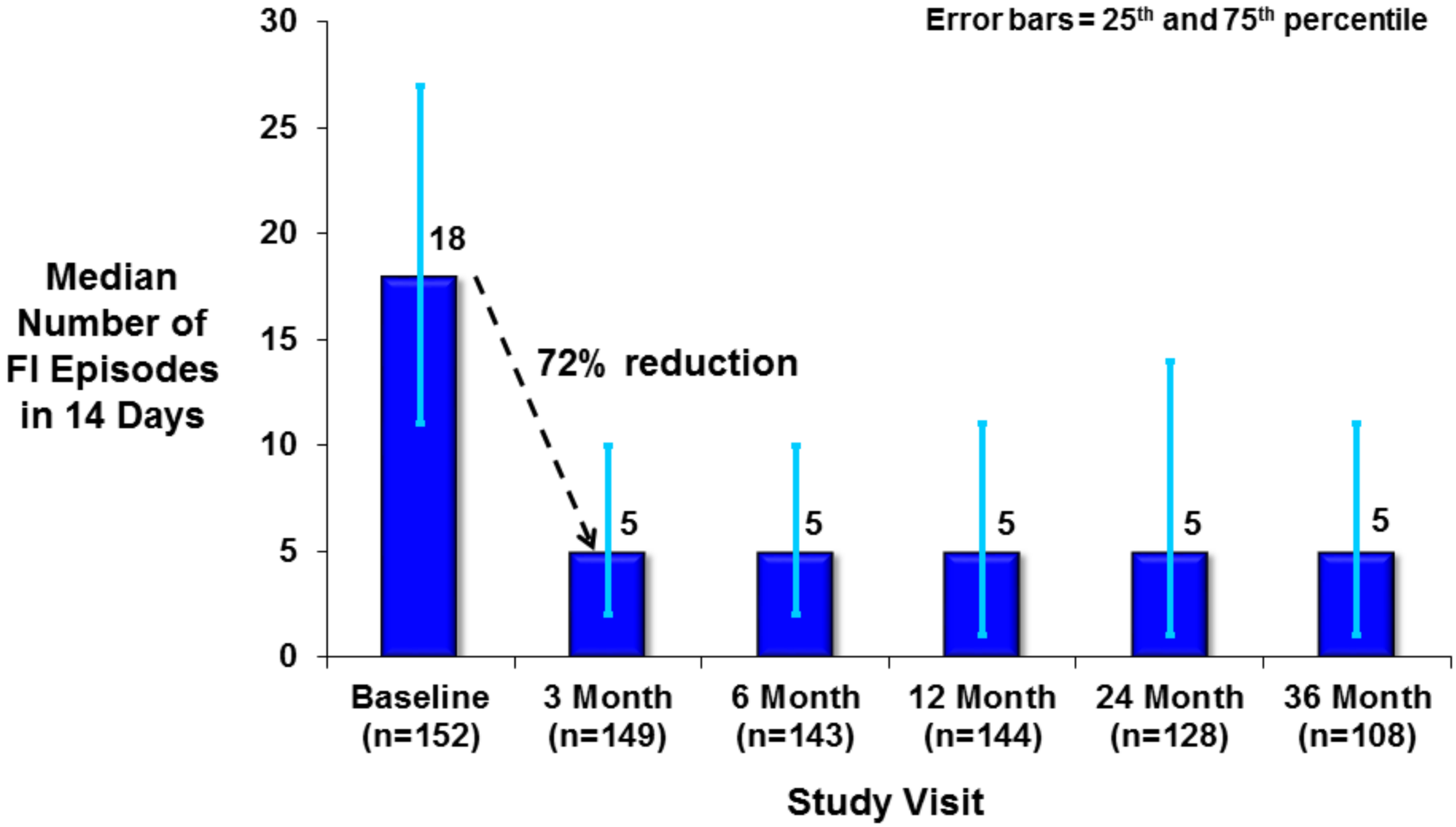
	N=152
Medical History	
Prior Hysterectomy and/or Oophorectomy	49%
Previous Prolapse and/or UI Repair	46%
Urinary Incontinence	26%
Previous Anal Sphincter Repair	20%
Vaginal Prolapse	5%
Rectal Prolapse	4%
Failed Conservative Treatment	
At Least Two	100%
All Three	40%

Study Met its Primary Endpoint of Reducing FI Episodes at 12 Months

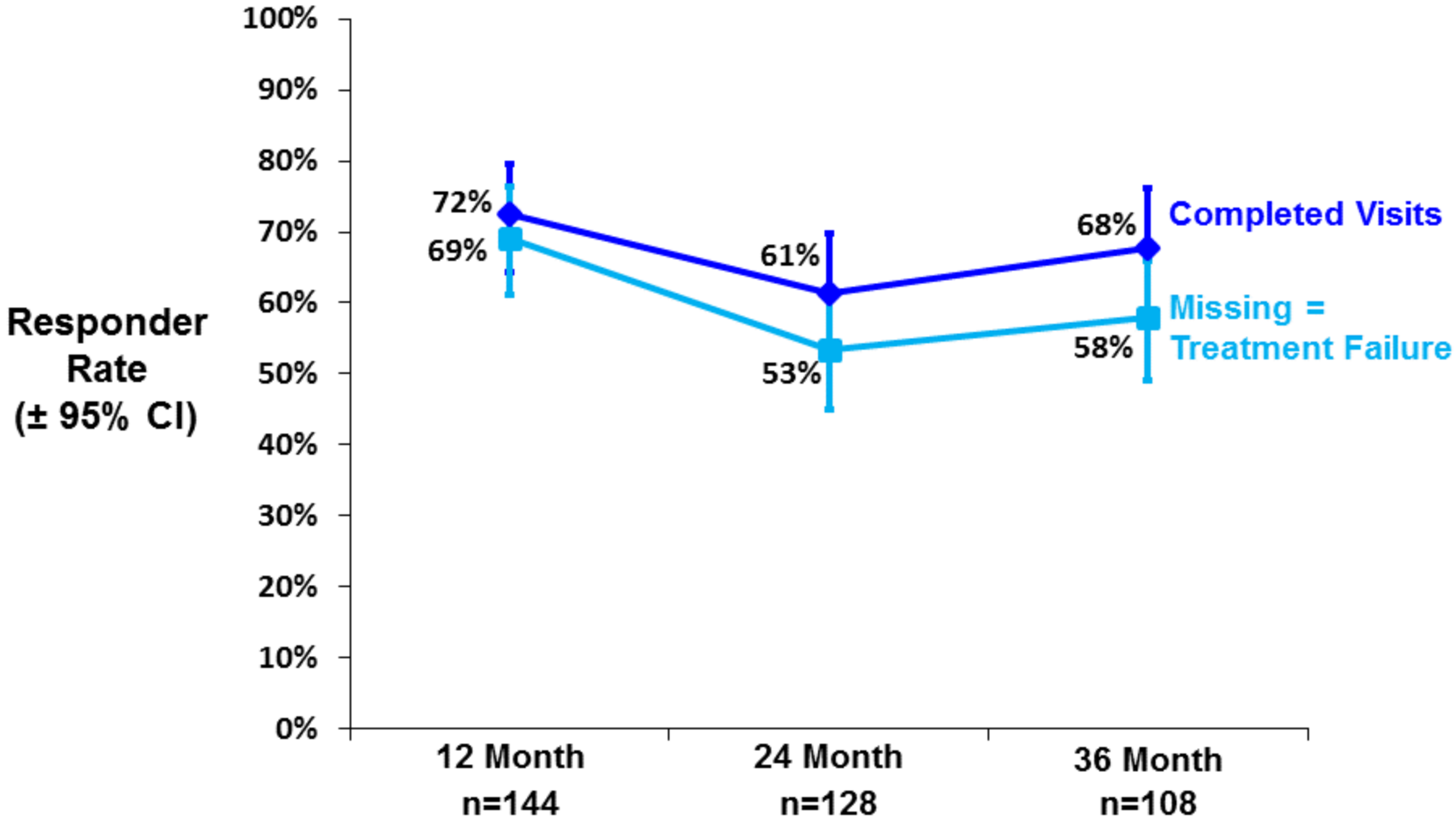
Subject Group	N	Treatment Success Rate % (95% CI)	P-Value
Stage I	80	**65%** (54, 75)	**0.0048**
Stage II	72	**74%** (62, 83)	**<0.0001**
All Implanted	152	**69%** (61, 76)	**NA**

Missing = treatment failure

Reduction in Median FI Episodes



Responder Rate is Stable Over Time

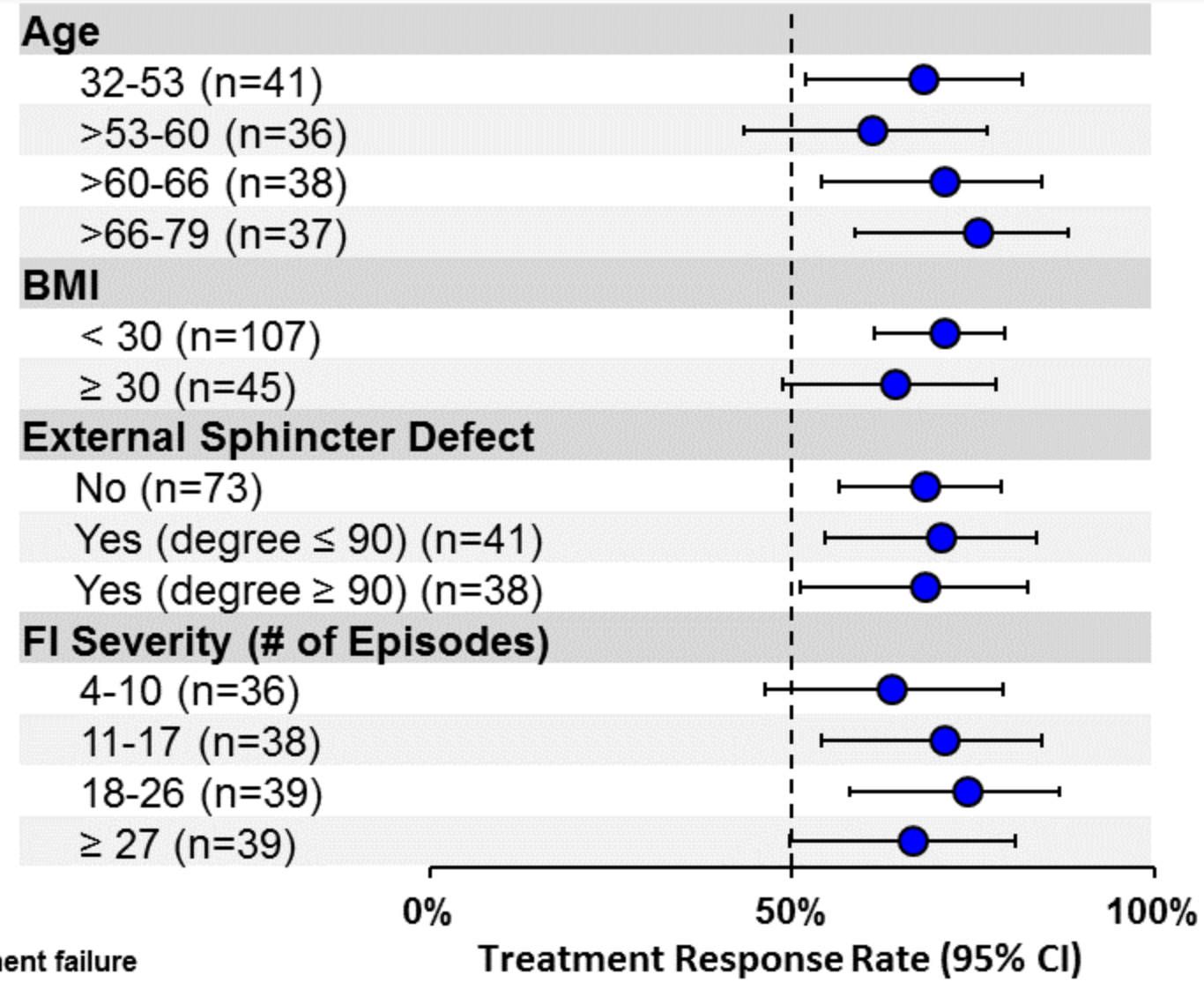


Improvement Categories at 12 Months

Change in FI Episodes From Baseline	Rate (95% CI)
Increase in Episodes	**12%** (7, 18)
No Change in Episodes	**7%** (4, 13)
Improvement in Episodes	
> 0% Improvement	**81%** (74, 87)
≥ 25% Improvement	**77%** (70, 83)
≥ 50% Improvement	**69%** (61, 76)
≥ 75% Improvement	**42%** (34, 50)
Complete Continence	**19%** (13, 26)

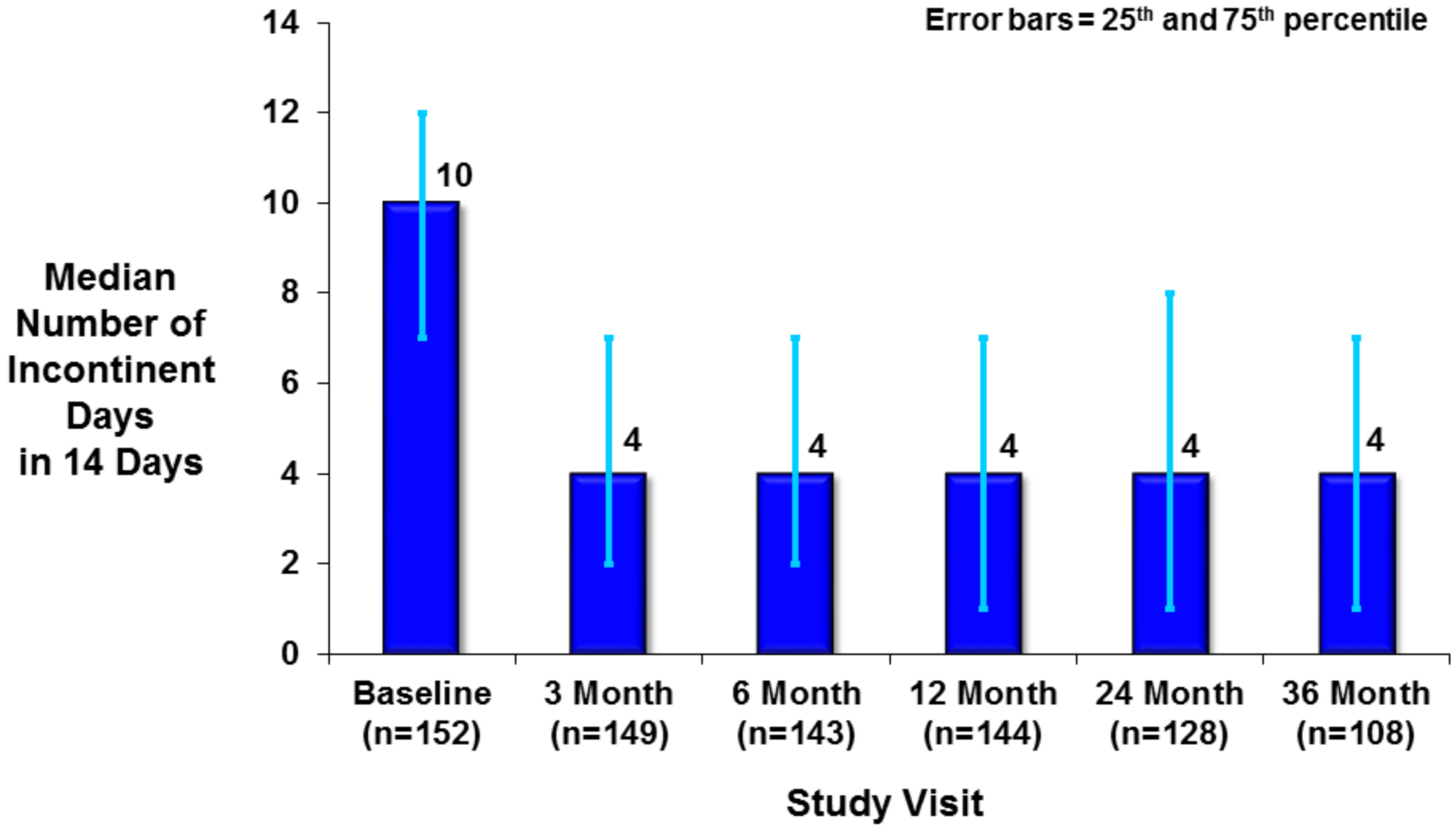
Missing = treatment failure

No Factors Found to Predict Results

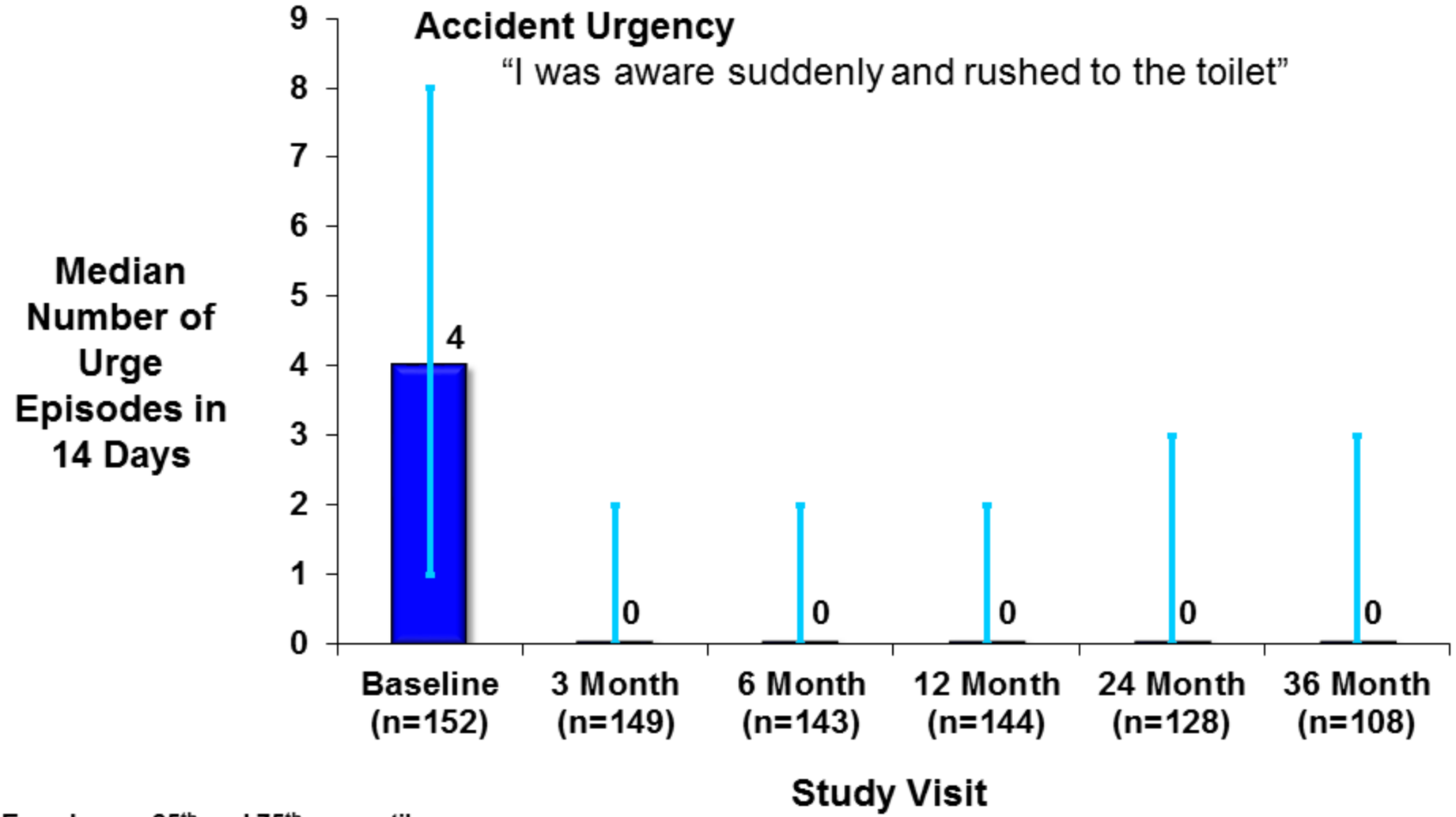


Missing = treatment failure

Median Number of Incontinent Days Decreased From Baseline



Number of Urge Episodes Decreased From Baseline



Error bars = 25th and 75th percentile

Improvements in Patient Reported Outcomes

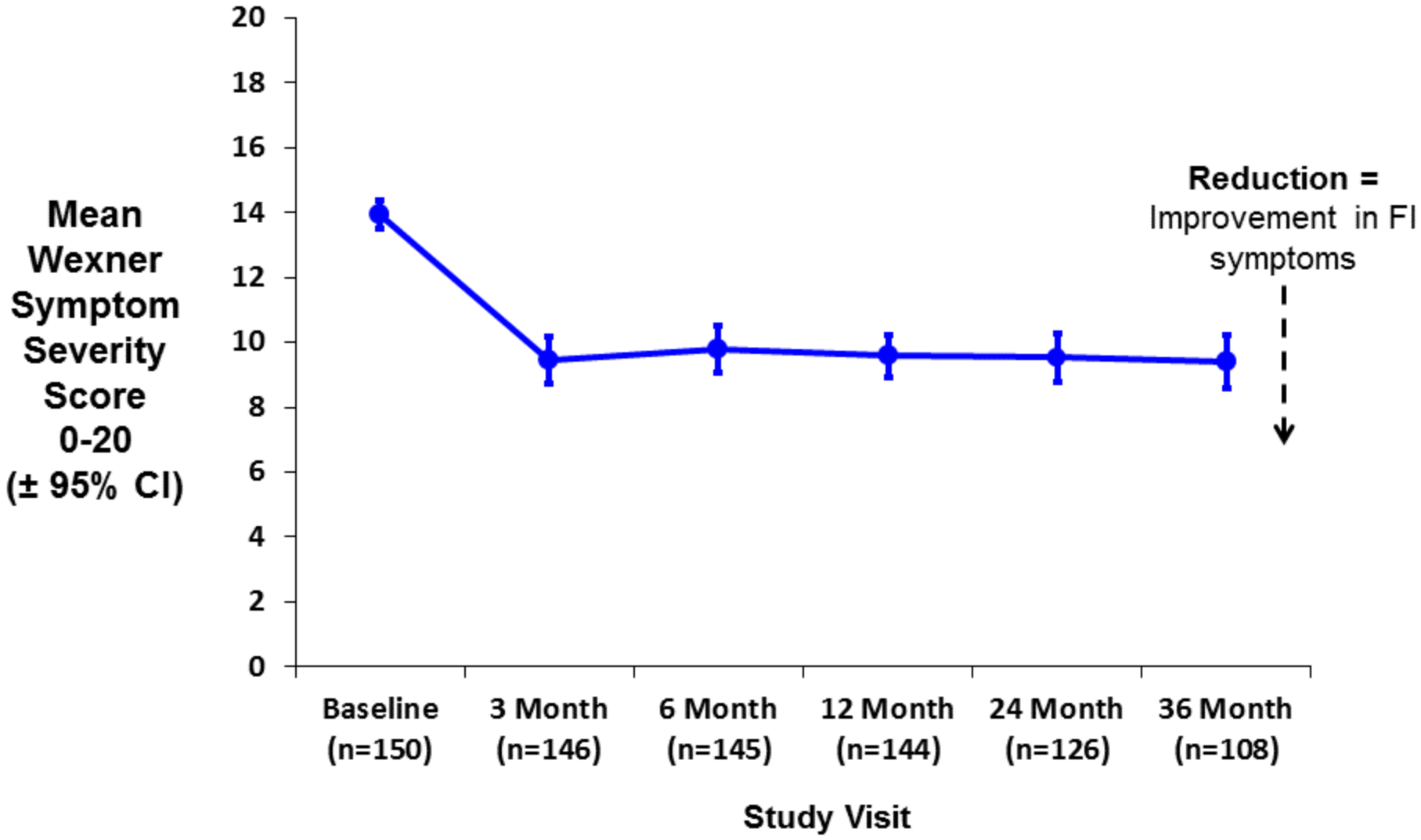
	Improvement
Wexner Symptom Severity Score	✓
Fecal Incontinence Quality of Life	✓
Pelvic Floor Distress Inventory	✓
CRADI Subscale	✓
Pelvic Floor Impact Questionnaire	✓
CRAIQ Subscale	✓
Sexual Function Questionnaire	No impact

Wexner Symptom Severity Score

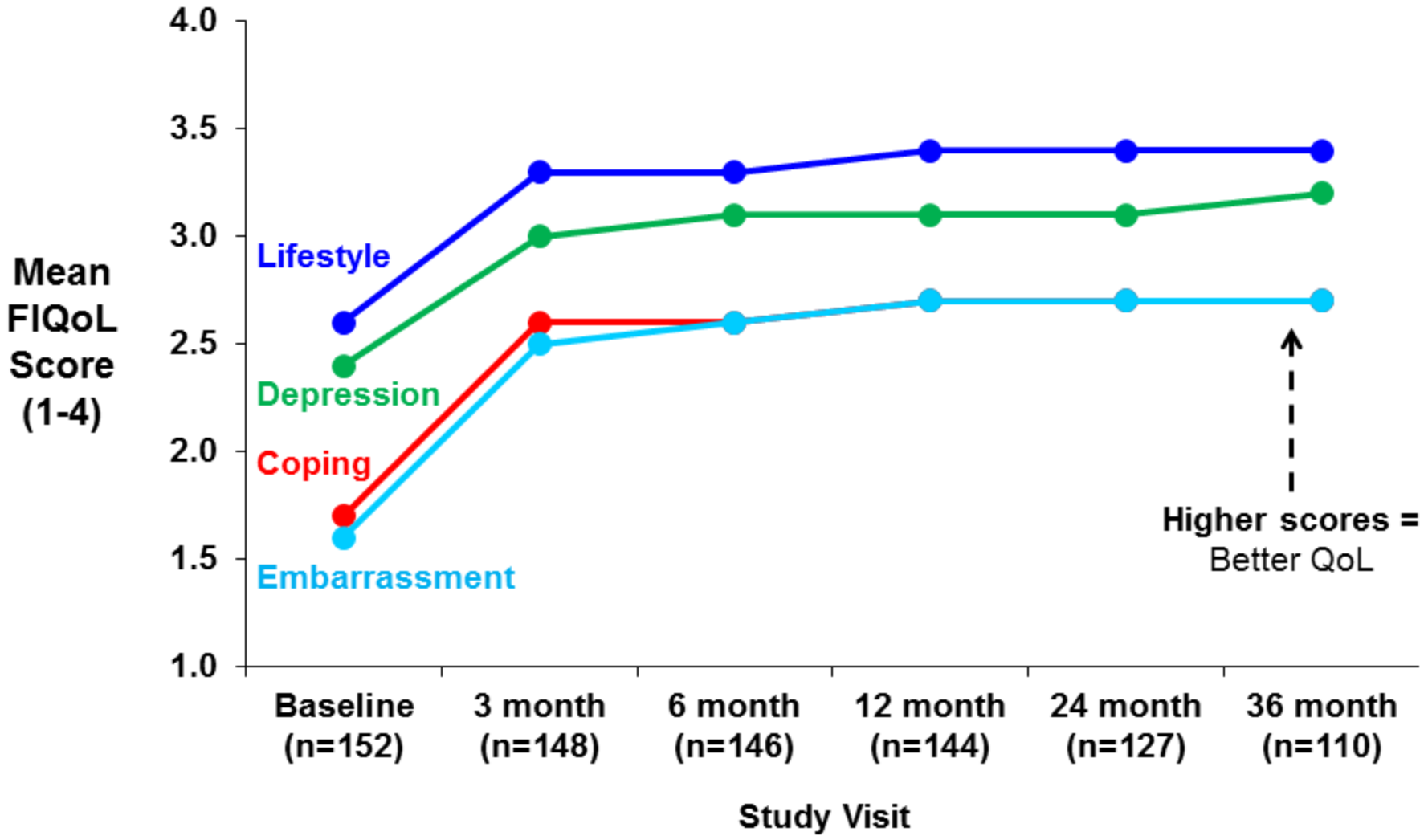
	Never	Rarely	Sometimes	Often	Always
Solid	☐ 0	☐ 1	☒ 2	☒ 3	☐ 4
Liquid	☐ 0	☐ 1	☒ 2	☐ 3	☐ 4
Gas	☐ 0	☐ 1	☐ 2	☒ 3	☐ 4
Wears pad	☐ 0	☐ 1	☒ 2	☐ 3	☒ 4
Lifestyle alteration	☒ 0	☐ 1	☐ 2	☒ 3	☐ 4
			Total=9	Total=15	

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

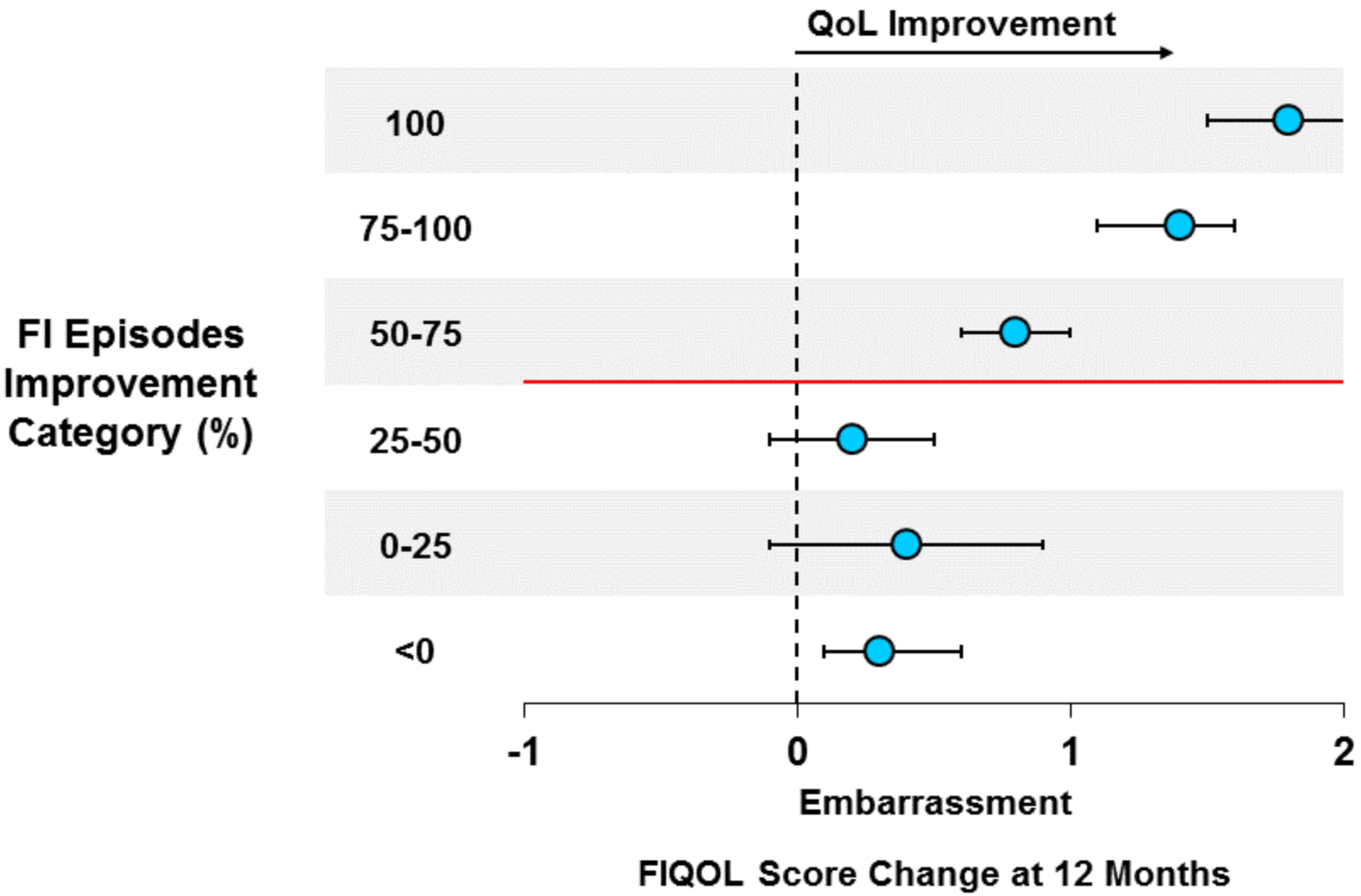
Meaningful Change in Wexner Score



Improvement in Fecal Incontinence Quality of Life Score (FIQoL)



Positive Correlation Between Treatment Response and QoL

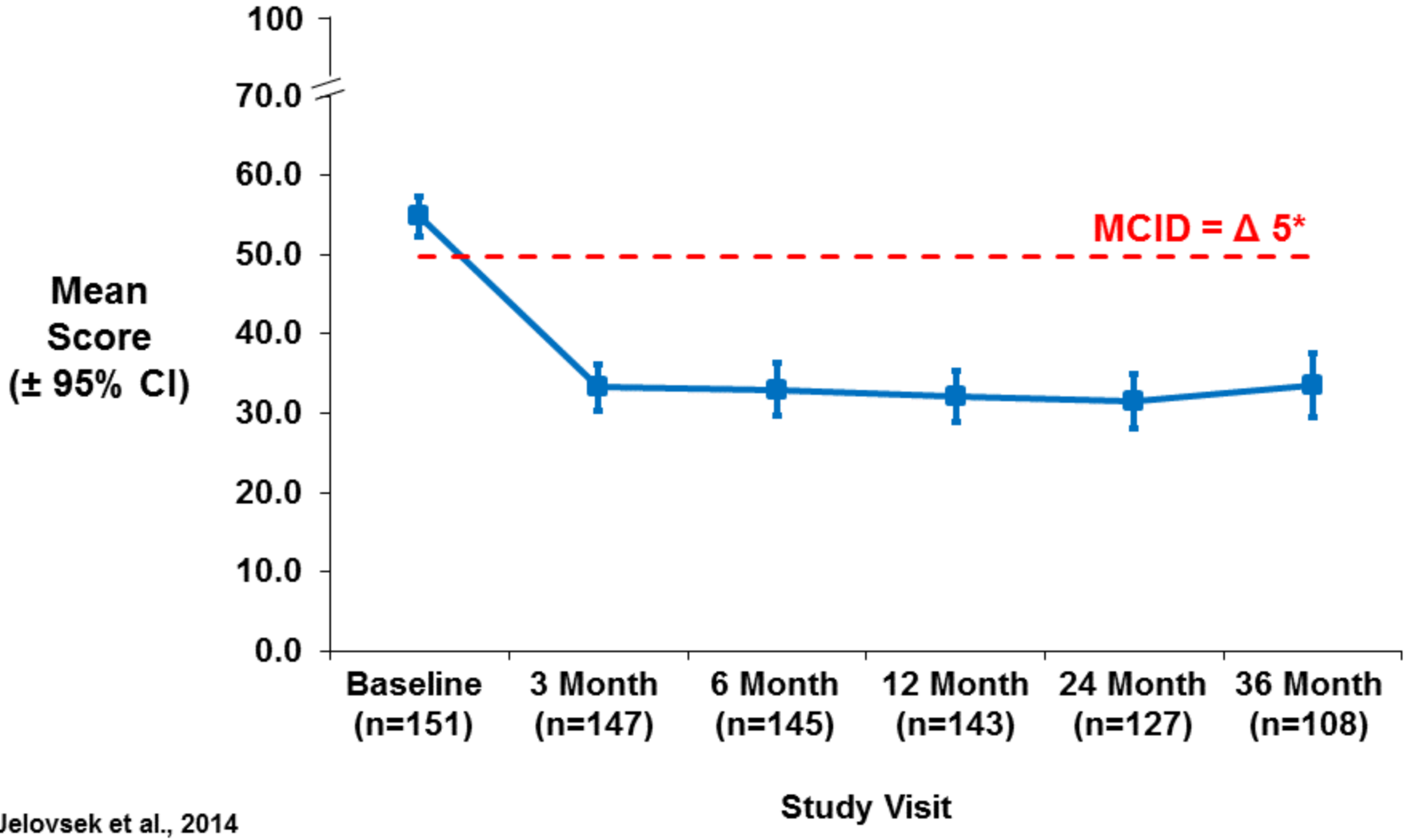


Colo-Rectal-Anal Distress Inventory (CRADI) and Impact Questionnaire (CRAIQ)

CRADI	CRAIQ
• Do you usually lose stool beyond your control if your stool is loose or liquid?	• Does your FI usually affect your ability to do household chores?
• Do you experience a strong sense of urgency and have to rush to the bathroom to have a bowel movement?	• Does your FI usually affect your ability to participate in social activities outside your home?

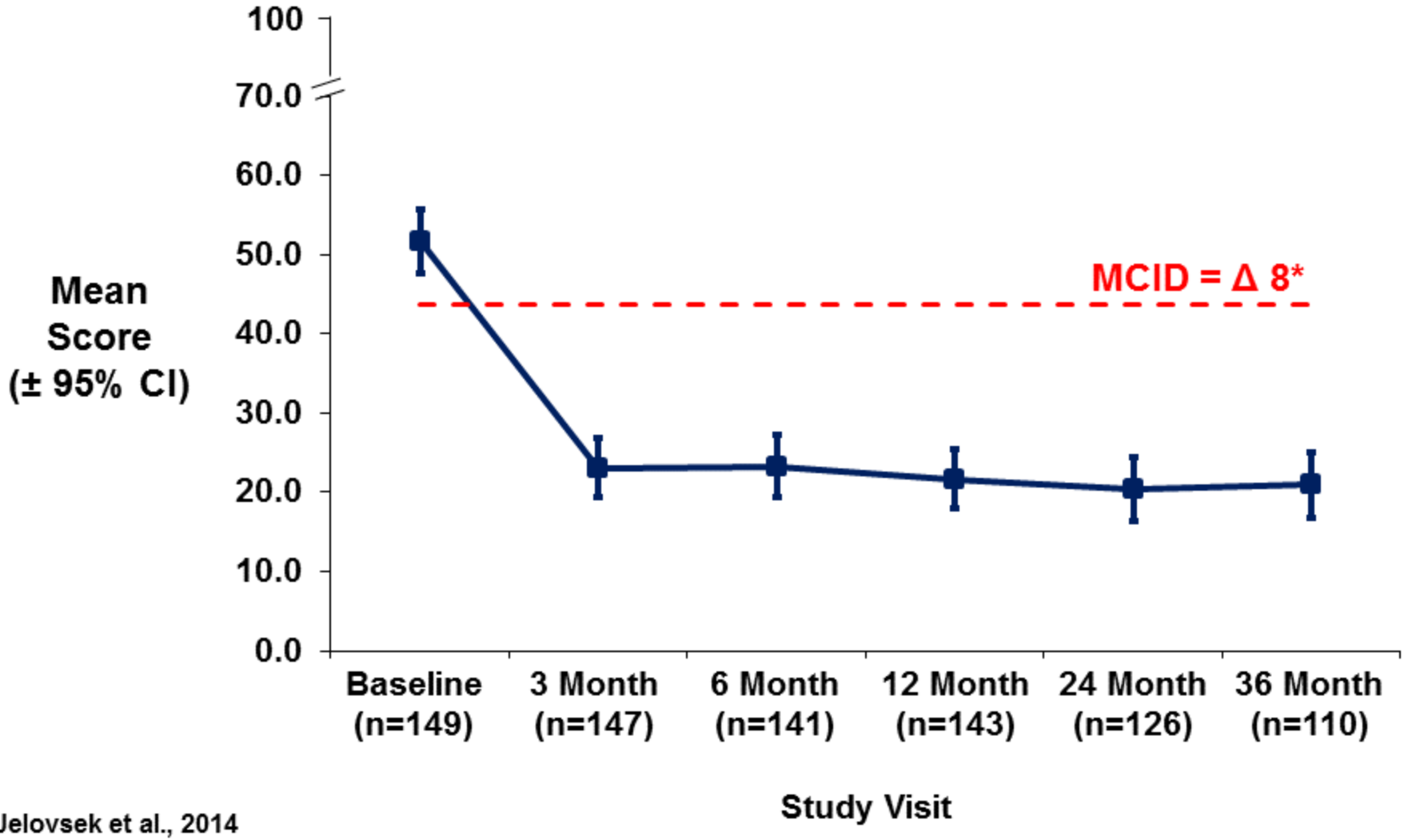
- Scores range from 0 - 100; lower scores = less distress or patient impact
- Established MCID values

Improved CRADI Score Exceeded MCID



*Jelovsek et al., 2014

Improved CRAIQ Score Exceeded MCID



*Jelovsek et al., 2014

Improvements in Other Tangible Measures

- Results when patients were asked, during the last year, aside from study procedure and study visit:

Question	Baseline (N=152)	36 Month (N=108)	% Change
# of pads per day taken for FI	2.4 ± 2.1	1.2 ± 1.6	-50%
Total # of health care provider visits due to FI	5.0 ± 7.6	0.3 ± 1.1	-94%
Total # of days taken off work due to FI	6.4 ± 34.0	0.9 ± 9.5	-86%

Data are mean ± SD

Positive Response to Surgical Satisfaction Questionnaire

Survey was offered on a one-time basis to all active patients between 3 and 36 months post-operatively (mean 26.7 +/- 8.8 months)

Question	All Patients (n=86)	Responders (n=63)	Non-Responders (n=23)
Looking back, if "had to do it all over again" would you have the surgery again?			
Satisfied or Very Satisfied	80.2%	84.1%	69.6%
Neutral	10.5%	12.7%	4.3%
Unsatisfied or Very Unsatisfied	9.3%	3.2%	26.1%
Would you recommend this surgery to someone else?			
Positive	80.2%	82.5%	73.9%
Neutral	14.0%	14.3%	13.0%
Negative	5.8%	3.2%	13.0%

Primary Efficacy Conclusions

- Primary endpoint met
- 69% experienced at least a 50% reduction in fecal incontinent episodes

Secondary Efficacy Conclusions

- Secondary efficacy objective support TOPAS benefit
  - Sustained decrease in FI episodes
  - Decrease in FI urge episodes and incontinent days
  - Improvement in patient reported outcomes
- TOPAS treatment effect is immediate, consistent, durable, positive life changes

Safety

Mikio Nihira, MD, MPH

Professor of Obstetrics and Gynecology

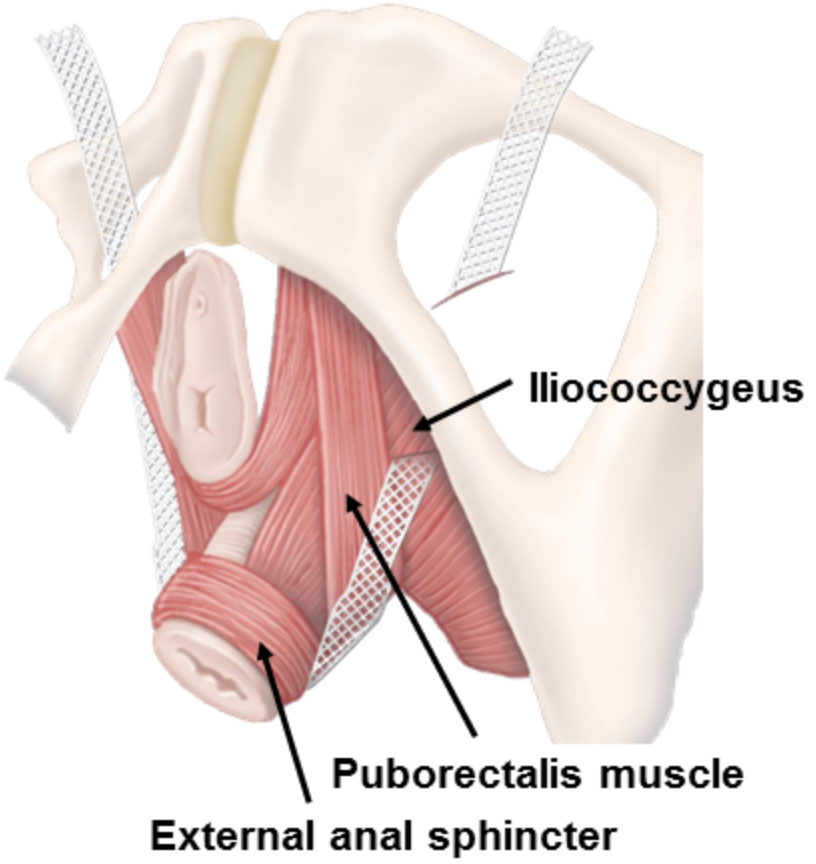
Division of Female Pelvic Medicine and Reconstructive Surgery, University of Oklahoma

Safety Overview

- Implant review
- Study safety objectives
- Data collection
- Treatment-related adverse events, serious adverse events, adverse events of special interest

TOPAS Has Unique Mesh Safety Profile

- Placed lateral to levator ani muscle and below anal sphincter
- ~2 cm tissue buffer between mesh and anus
- No transvaginal incisions



TOPAS Demonstrates Favorable Safety Profile in 509 Patient-Years

To date, TOPAS study has not seen

- Erosions
- Extrusions
- Organ perforations
- Bowel obstructions
- Device revisions
- Unanticipated adverse device effects (UADEs)

Safety Objective: Fully Characterize Safety Profile, Mesh-Related AEs

- Systematically collected all adverse events
- Mesh-related adverse events
  - Specified in protocol
  - Addressed in mandatory training
- Specified assessing patient for erosion, extrusion, infection, pelvic pain, leg pain and dyspareunia.

Adverse Events Assessed Throughout the Study

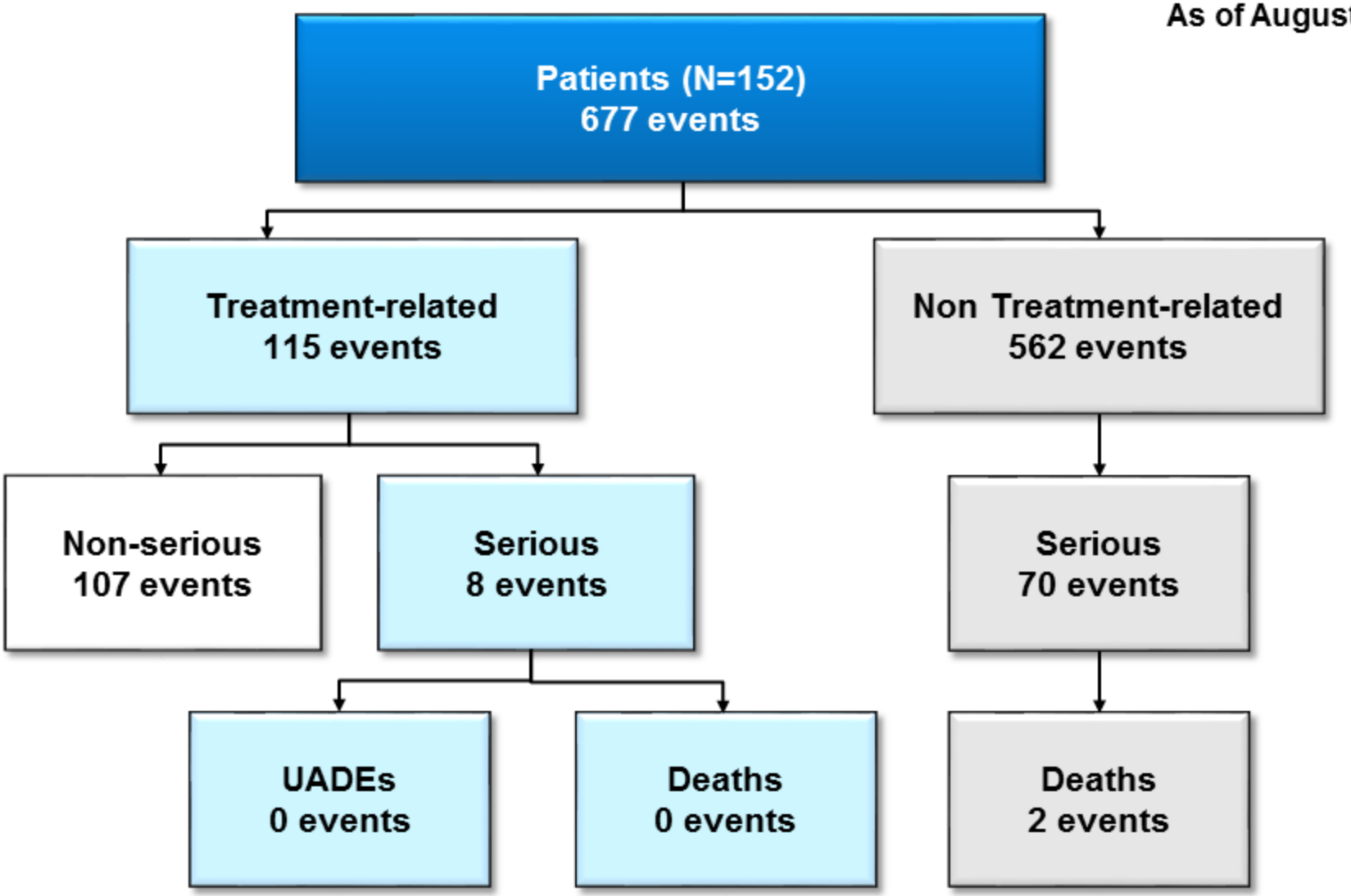
- Required at every follow-up visit
  - Physical exam
  - Patient questioning
- AEs assessed at all unscheduled visits
  - Patient-reported issues
- Standard of care assessments

All Adverse Events Reviewed by an Independent Expert Committee

- Adverse Event Adjudication Committee (AEAC)
  - Urogynecologist: Rebecca Rogers, MD
    - University of New Mexico
  - Gastroenterologist: Satish Rao, MD
    - University of Georgia
  - Colorectal Surgeon: Anthony Senagore, MD
    - Parma Medical Center, Ohio
- Data Monitoring Committee (DMC)
  - AEAC Members
  - Statistician: William Thomas, PhD
    - University of Minnesota
  - Patient Advocate: Nancy Norton
    - Founder, International Foundation for Functional GI Disorders

Treatment-Related AEs

As of August 2015



Majority of Treatment-Related Events Were Not Serious and Resolved

Treatment Related AE Type	All	Non-SAEs	SAEs	Resolved	
	Events (Patients)	Events	Events	Non-SAEs	SAEs
TOTAL	115 (72)	107	8	80%	88%
Pelvic Area Pain	50 (43)	49	1	82%	100%
Infection	25 (22)	24	1	100%	100%
Urinary Problems	8 (8)	8	0	63%	NA
Pelvic Organ Prolapse	13 (9)	10	3	30%	100%
Defecatory Disorder	4 (4)	4	0	50%	NA
Bleeding	1 (1)	1	0	100%	NA
Other	14 (14)	11	3	100%	67%

Majority of Treatment-Related Events Were Short in Duration

- 54% lasted ≤ 30 days
- Median duration of 25 days
- 81% resolved
- Unresolved events
  - Pelvic area pain (n=9)
  - Pelvic organ prolapse (n=7)
  - Urinary problems (n=3)
  - Other (n=3)

n=115

Status of Adverse Events

- Resolved events
  - Patient reported / physician assessment
  - Duration calculated from onset to resolution
- Ongoing events
  - Active participants
  - Patients who have exited study
  - Accumulated until resolution

92% Treatment-Related AEs Managed w/o Therapy or Received Non-Surgical Treatment

- Interventions included medication and physical therapy
- 8% required surgery (9 events)
  - 6 related to pre-existing conditions
    - 4 cases worsening pelvic organ prolapse
    - 1 case worsening sciatica
    - 1 case worsening urge incontinence
  - 3 cases de novo pelvic organ prolapse

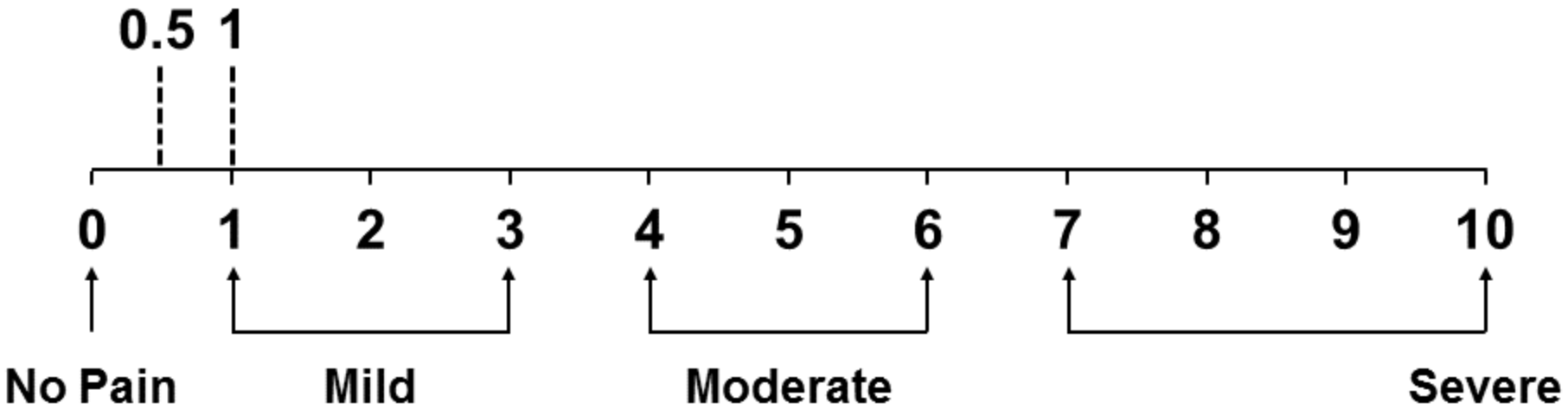
8 Treatment-Related SAEs; None Life-Threatening

- 4 SAEs related to pre-existing conditions
  - 1 PTSD case 1 week before surgery
  - 1 case COPD exacerbation
  - 1 case worsening sciatica
  - 1 case worsening pelvic organ prolapse
- 4 other SAEs
  - 1 case deep vein thrombosis
  - 1 case MRSA infection on left hand
  - 2 cases de novo pelvic organ prolapse
- All but PTSD resolved without reported sequela

82% Pelvic Area Pain Events Resolved

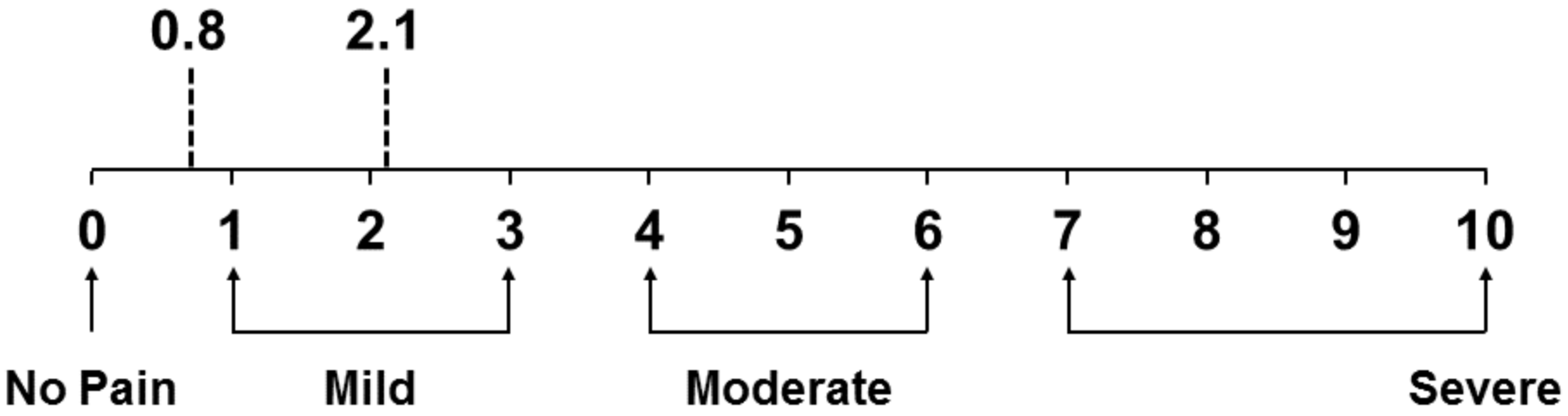
Pelvic Area Pain	50 Events
Patients	28% (43/152)
Duration	
Median days (range)	88 (0-1536)
≤ 30 days	21
31-120 days	8
> 121 days	21
Resolved	82% (41/50)
Treatment	
Surgical	1 (2%)
None	17 (34%)
Non-surgical	32 (64%)
Treatment Responders	67% (29/43)

Majority of Pelvic Area Pain Events Were Mild



Patients with Prolonged Pain had Average Pain Score in Mild Range

- 21 prolonged pain events in 18 patients



Prolonged Pain After 12 Months

- Question #20 of PFDI assessed pain
  - 67% (12/18) reported they did not usually experience pain
- 9 out of 18 patients resolved
  - 368 mean days to resolution
- 9 with ongoing pain
  - 5 exited the study, pain status unknown
  - 4 active patients continue to have ongoing pain as of August 2015

All Infections Resolved Without Reported Sequela

- 25 infection AEs
  - 9 incision site
    - Infection criteria quite liberal
  - 2 abscesses
  - 14 others (e.g. fungal, UTI, MRSA)
- All treated non-surgically
- Average duration < 30 days

Urinary Problems Were Infrequent

- Urinary problems (8 events)
  - 3 cases of urinary retention
  - 3 cases of worsening urinary incontinence
  - 1 case of new onset urinary incontinence
  - 1 case of dysuria

Rectal and Vaginal Prolapse

	Events (n=13)	
	Recurrent	DeNovo
Rectal (n=5)	**3**	**2**
Full	3	1
Mucosal	0	1
Vaginal (n=8)	**2**	**6**
Cystocele	1	1
Rectocele	1	4
Multi Compartment	0	1

- No adverse events of increased fecal retention or straining

Treatment-Related AEs Did Not Preclude Patients From Experiencing Benefits

	Reported Improvements at 12 Months	
	Patients (n=72) with Treatment-Related AEs	Patients (n=80) w/o Treatment-Related AEs
Fecal Incontinence Quality of Life Scores		
Lifestyle	82%	83%
Embarrassment	82%	90%
Coping	80%	87%
Depression	80%	84%
Responder Rate	65%	73%

No Observed Erosions, Extrusions, Perforations, Obstructions

TOPAS has not seen

- Erosions into vagina or rectum
- Extrusions through incision sites
- Perforations into vagina, bowel or bladder
- Bowel obstructions

AEAC Confirmed No Mesh Erosion or Obstructions

- FDA questions regarding possible events
  - Mesh erosion
  - Obstruction/straining
- Sponsor obtained all available medical records and interviewed treating surgeons
  - Repeated vaginal, rectal examinations performed
- AEAC concluded no mesh erosions or obstructions

Safety Conclusion

- TOPAS is well-tolerated and offers a safe treatment option
- Observed treatment-related adverse events were manageable
  - Majority were short in duration, mild, and resolved without reported sequelae
  - 8 SAEs
  - 92% were managed without therapy or received non-surgical treatment

Physician Education Program

Paul Below

Principal Clinical Research Specialist

ASTORA Women's Health

Comprehensive Education Program for Best Possible Patient Outcomes

- Modeled after successful TOPAS study training curriculum and input from Physician Advisory Committee
- Addresses disease state, relevant anatomy, patient selection, and procedural requirements

Education Program Open to Highly Qualified Physicians

- 3 requirements
  - Board certified in Female Pelvic Medicine and Reconstructive Surgery or Colon and Rectal Surgery;
  - Currently treating FI patients; and
  - Surgical experience implanting other FI devices or mesh in the pelvic floor.

3-Phase Physician Training Program

Phase One

E-Learning Introductory Course

Phase Two

Classroom Course with Hands-on Component

Phase Three

Surgical Experience Overseen by Qualified Proctor

Phase One: Framework for Treating FI

E-Learning Introductory Course

- E-Learning Curriculum
  - Module 1: FI Overview, Epidemiology
  - Module 2: Anatomy & Physiology
  - Module 3: FI Therapies & TOPAS
  - Module 4: Clinical Evidence
  - Module 5: Patient Preparation
  - Module 6: TOPAS Procedure
  - Module 7: Managing Complications
- Demonstrate understanding of material before advancing to next phase

Phase Two: Hands On With Device

Classroom Course with Hands-on Component

- Classroom Curriculum:
  - Review of e-learning topics
  - Case studies on patient selection and managing complications
- Hands-on experience implanting TOPAS in a pelvic model and cadavers

Phase Three: Proctored Surgical Experience

Surgical Experience Overseen by Qualified Proctor

- Perform the procedure with oversight of physician proctor
- Demonstrate ability to perform all steps of the procedure
- 2 proctored cases required
- Receive record of training completion from ASTORA

ASTORA to Provide Ongoing Physician Support

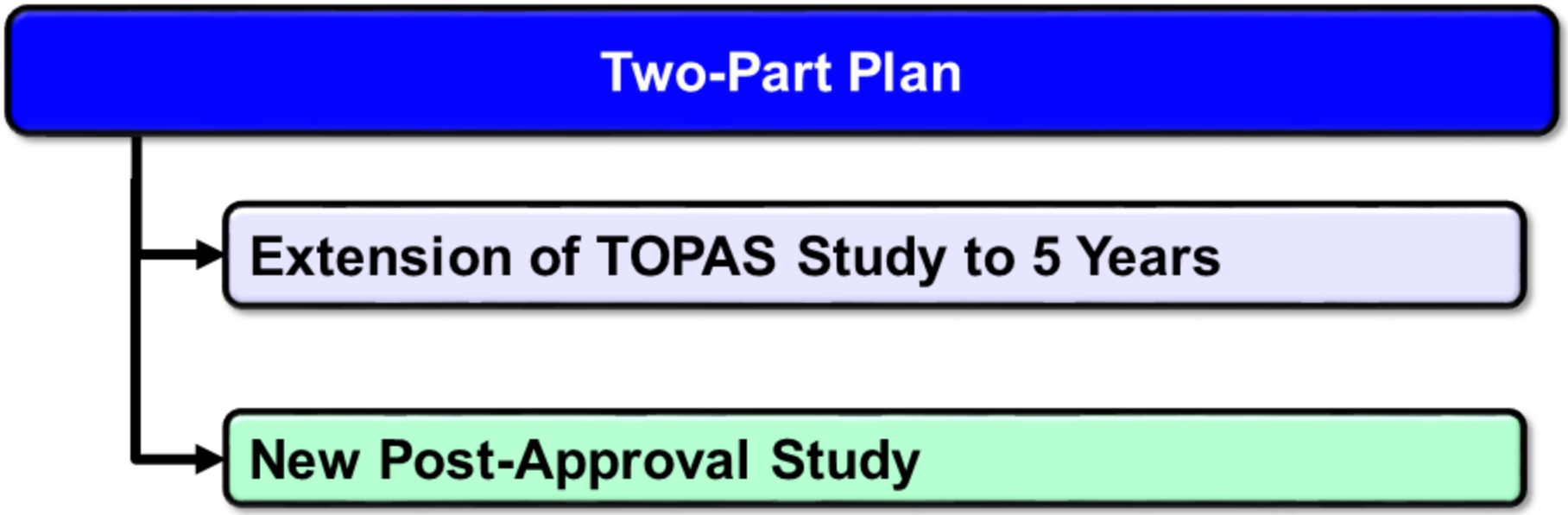
- Refresher course available for all TOPAS-trained physicians
  - Repeat e-learning modules and pelvic model hands-on training
  - Option of additional cadaver training and proctoring
  - Required for those who have not completed ≥ 8 cases annually

ASTORA to Provide Ongoing Physician Support

- Physician Advisory Committee to advise on managing complication cases
- Ongoing collaboration with physician advisors and FDA on program development
- Proper training is key to successful outcomes and improving quality of life for patients with FI

Post-Approval

Comprehensive, Proactive, Long-Term Surveillance Program for TOPAS



Ongoing Evaluation of Long-Term Safety and Performance

Extension of TOPAS Study to 5 Years

- 5 years follow-up in clinical trial
  - Annual safety and efficacy updates to FDA
  - Updates include:
    - Monitoring all AEs
    - 60 month safety endpoint of <25% SAEs
    - Digital rectal exam at 48 and 60 month follow-up visits
    - Continue patient bowel diaries, QoL surveys

Post-Approval Study to Enroll New Cohort of Patients to Monitor Safety

New Post-Approval Study

- New cohort of patients
- Draft study protocol detailed in FDA's Executive Summary
- Primary objective will focus on safety
- ASTORA will continue working with agency on study design

Additional Safety Assessments in the Post-Approval Study

New Post-Approval Study

- Collection of additional bowel habit information in the patient diary
- Assessment of pelvic organ prolapse at baseline and post-operatively
- Detailed assessment of pelvic pain
- Additional imaging techniques to study anorectal changes

Comprehensive Safety and Performance Monitoring Plan

- Long-term surveillance plan

1. **Extension of TOPAS Study to 5 Years**

2. **New Post-Approval Study**

- Limited launch to previous TOPAS study implanters and investigators in new post-approval study
- Physician education + post-approval study monitoring will mitigate risk, prepare doctors

Clinical Perspective

Dee Fenner, MD

Furlong Professor of Women's Health

Director of Gynecology

University of Michigan

Demonstrates Favorable Benefit-Risk Profile for Women Living with FI

- Unique anatomical placement
- Offers important new treatment option to patients

New FI Treatment Options Needed

- No single treatment works for all FI patients
- Even with new therapies, significant unmet need persists
- TOPAS is first device providing anatomical support to the anorectum
- Need treatments not requiring multiple therapeutic adjustments

Study Limitations

- Single arm study
- Caucasian population > 30 years of age
- Not powered for predictors of efficacy
- No restrictions on medications and diet changes
- Mechanism of action not fully understood

Study Strengths

- Both colorectal and urogynecology surgeons
- > 500 patient-years of follow-up
- Objective and subjective endpoints
- Validated disease-specific questionnaires

TOPAS Study Met Primary Endpoint and Demonstrated QoL Improvements

- 69% of patients experienced ≥ 50% reduction in number of FI episodes
- Secondary efficacy objectives demonstrated improvements in FI symptom severity and quality of life
- Reduced healthcare resource utilization

Safe, Manageable Treatment Option

- Observed pain events generally mild
- Prolapse cases manageable
- Infections were treatable and resolved
- 8 treatment-related SAEs
  - 4 due to pre-existing conditions
  - 7 resolved without reported sequelae
- No mesh erosions, extrusions, perforations, dyspareunia, foreign body reaction, or surgical revisions

TOPAS Benefits Outweigh Risks

- Almost 70% achieved ≥ 50% reduction in FI episodes
- Patients experiencing any decrease in FI episodes reported improved QoL
- TOPAS is well tolerated
- Offers safe treatment option

Favorable Benefit-Risk Profile

- Study results demonstrate that TOPAS is a viable, safe, effective option for patients
- TOPAS should be an option for patients

TOPAS™ Treatment for Fecal Incontinence

ASTORA Women's Health

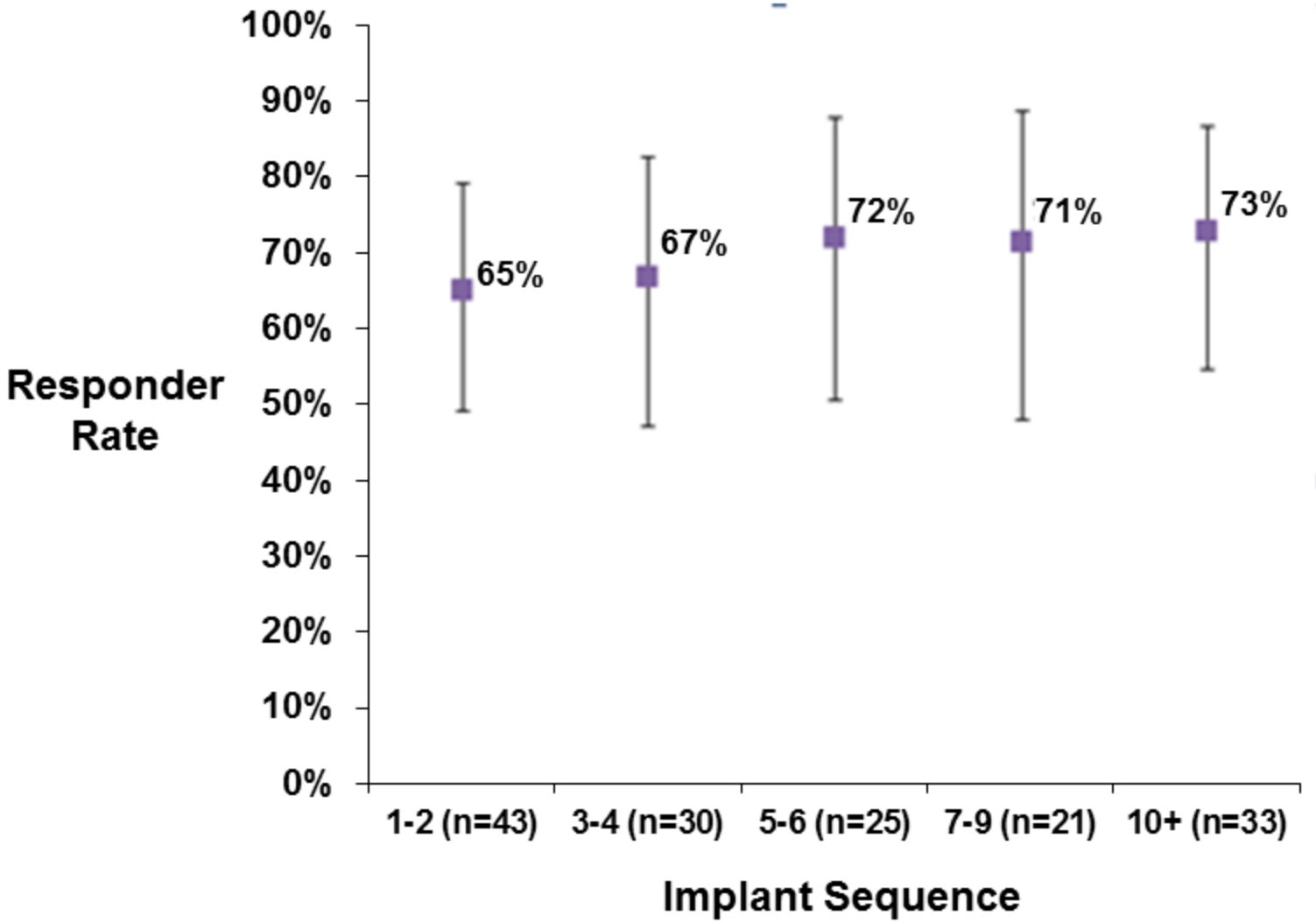
Presentation to the
Gastroenterology-Urology Devices Panel
February 25, 2016

ONSCREEN
BACK-UP SLIDES

Rationale for One-Sided Test

- For a single-arm trial, there is no clinical meaning attached to the concept that the treatment may be significantly worse than a pre-specified performance goal or objective performance criterion.
- Efficacy is only proven if it can be established that the treatment is better than the performance goal.
- Given that this is the only meaningful tail of the null distribution, a 1-sided test appropriate for this study.

No Learning Effect on Efficacy Response



Defecography Data

Variable	Baseline Mean ± SD (n, median, range)	6 Month Mean ± SD (n, median, range)	Δ from Baseline* Mean [95% CI], n
Anorectal Angle at Rest (degrees)	133.5 ± 17.7 (n=26, 132, 107-172)	132.4 ± 16.6 (n=26, 132, 99-165)	-3.7 [-7.8, 0.5] n=20
Anorectal Angle at Evacuation (degrees)	141.0 ± 20.1 (n=21, 144, 98-174)	143.2 ± 16.4 (n=22, 143, 98-168)	1.4 [-5.7, 8.5] n=15
Length of Anal Canal (cm)	2.5 ± 0.6 (n=14, 2.4, 1.7- 4)	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 subject level using matched pairs of data

Pelvic Area Pain Risk Factors – Medical Specialty

Pelvic Area Pain Rates by Specialty

- Colorectal: 45.0% (27/60 subjects)
- Urogynecology: 17.4% (16/92 subjects)

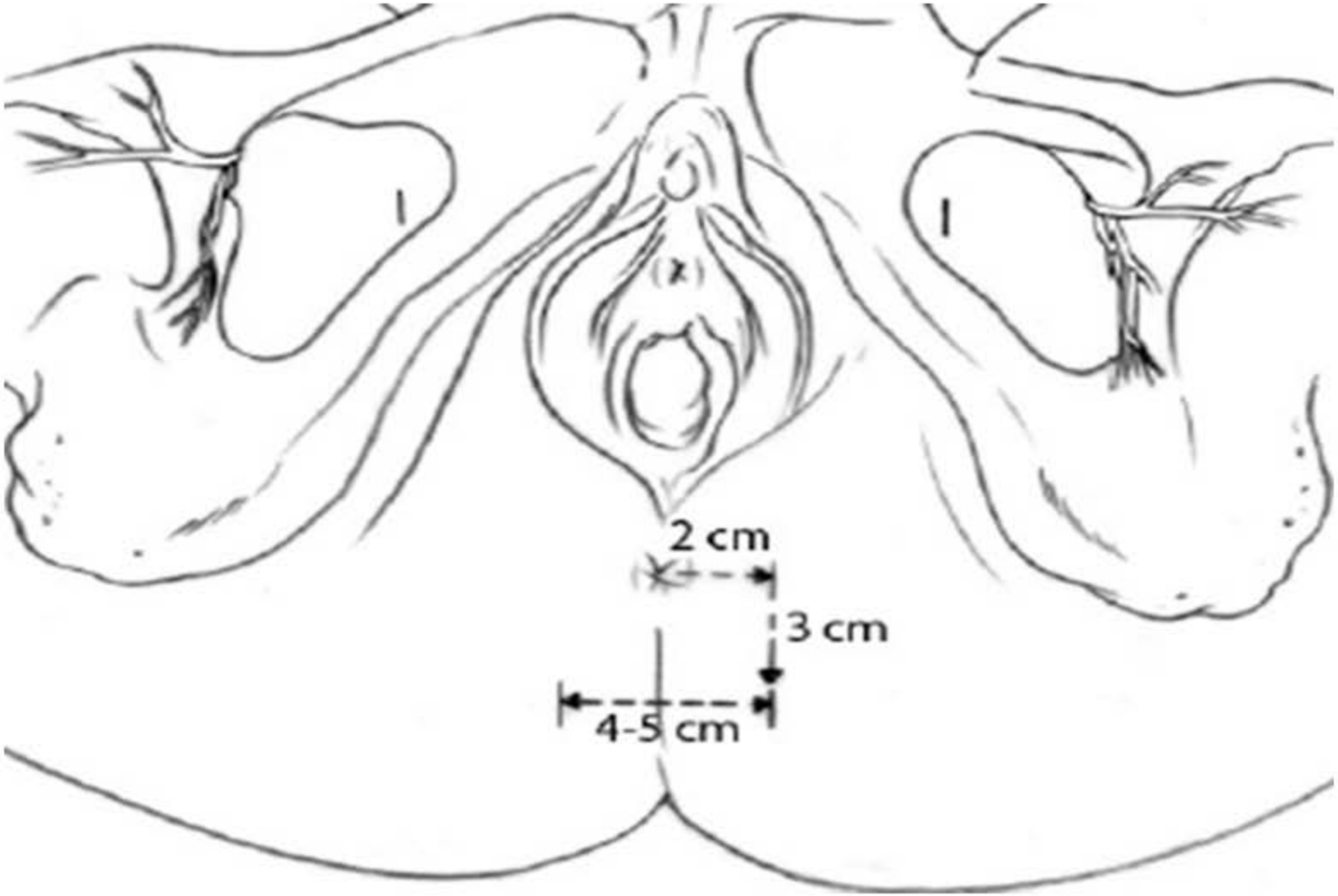
No Predictive Patient Factors for Pelvic Area Pain

Univariate logistic regression model for the following covariates

- Age, BMI, parity
- Medical Hx (including systemic & pelvic pain)
- QoL scores
- Responder rates at 12 months
- Medical specialty*

* Medical specialty originally showed up as significant due to a center difference (sites 1008 & 1010).

Buttock Incisions

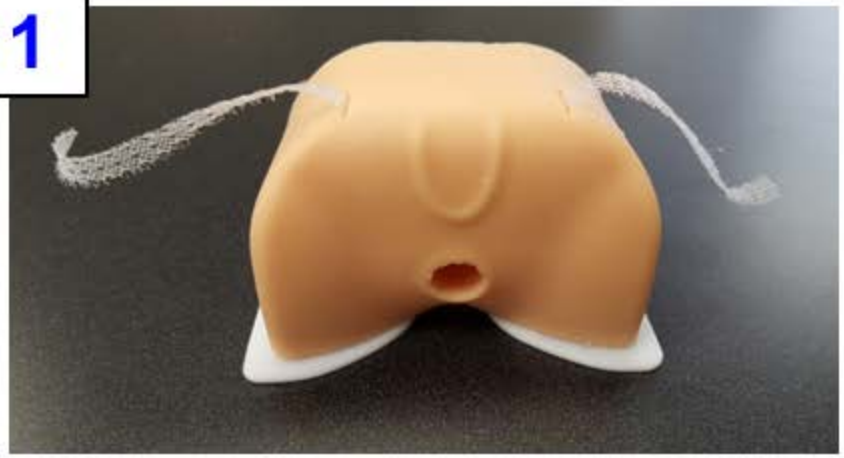


Instructions for Optimal Mesh Tensioning

- The implanter is instructed to conduct rectal palpation during tensioning so that a slight ridge or bump can be felt
- Should not cause significant deformity or compression of the anal canal

Standardized Tensioning Training

1



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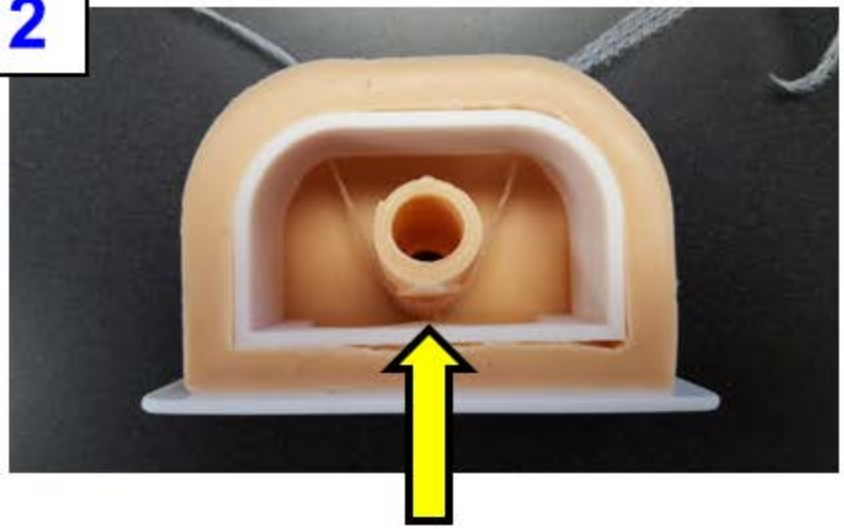

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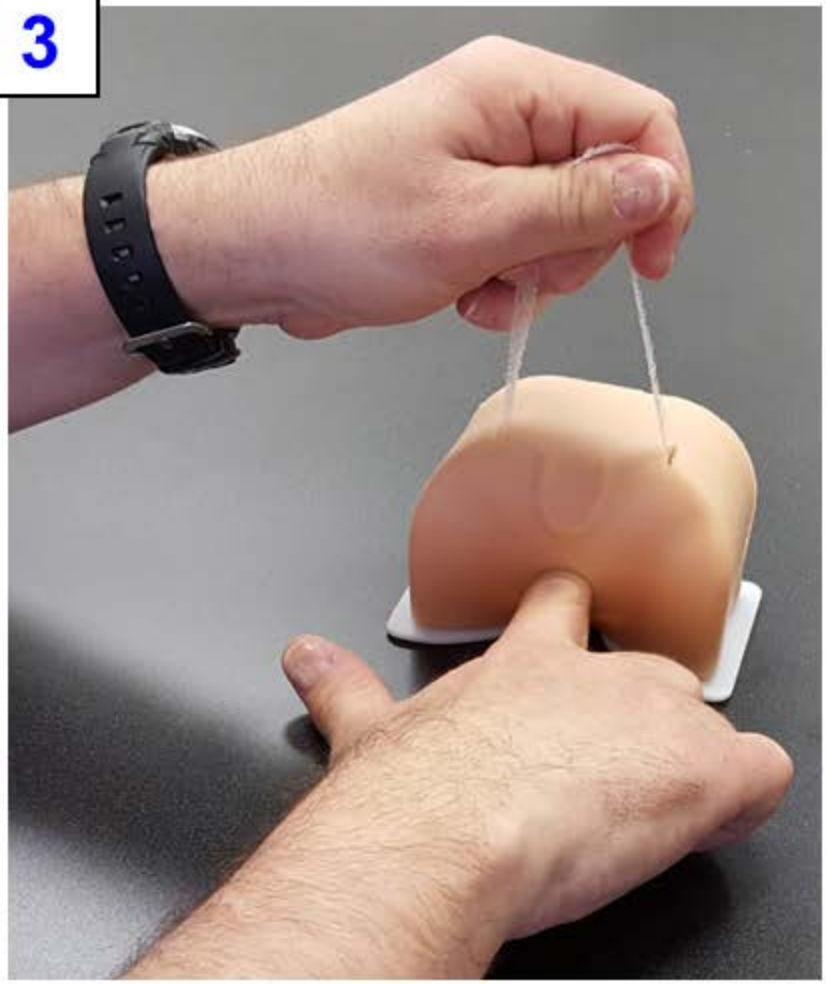
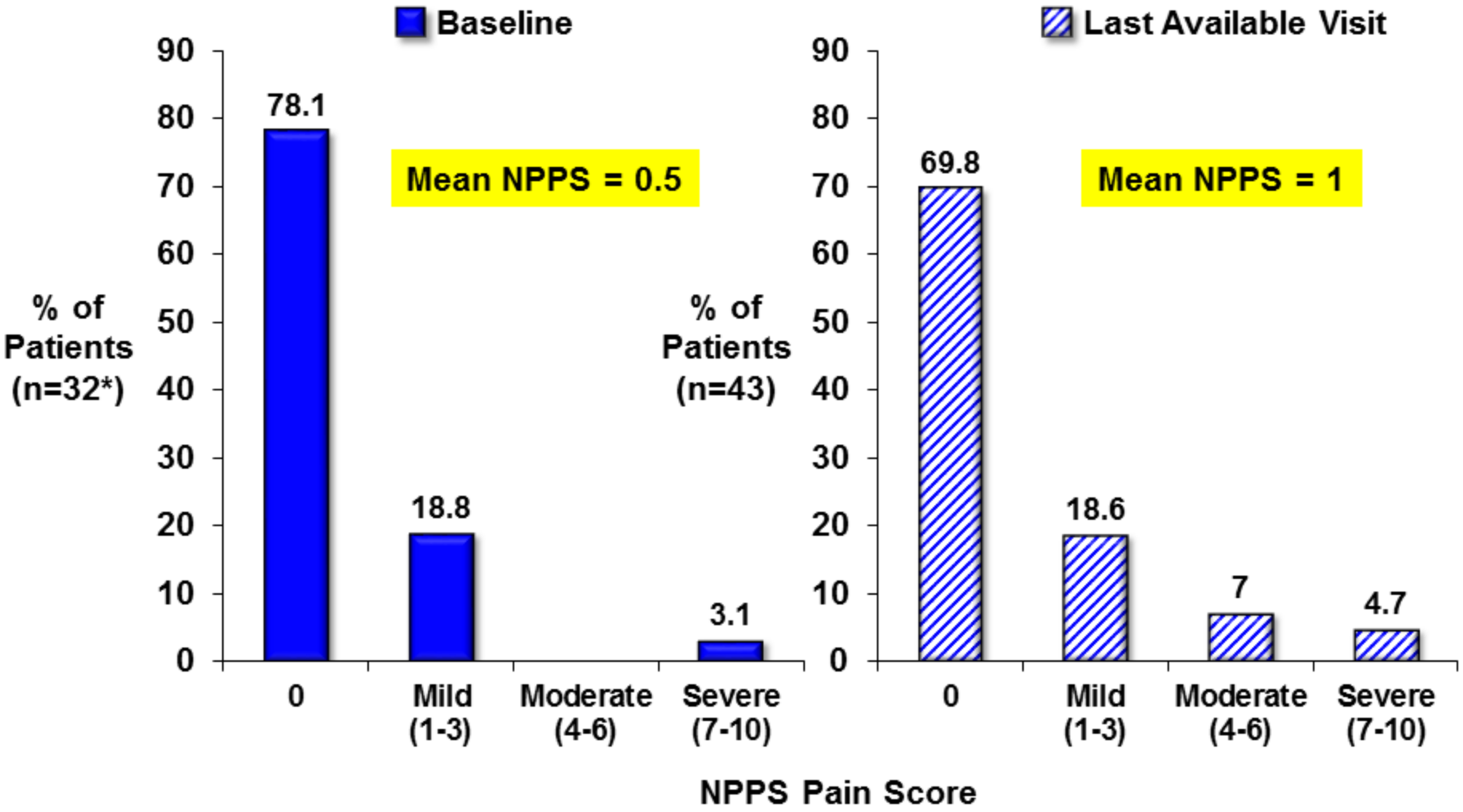


Diversity in Patient Population

- No reason to believe there are racial differences from an anatomical position
- Centers were intentionally selected in diverse geographic locations; including regions with high percentages of minorities
- Patient sub-groups were not stratified to ensure patient diversity. Study sites were dependent on patients who sought participation in the trial
- Didn't advertise for patients

Majority of Pelvic Area Pain Patients Reported No to Mild Pain at Last Visit



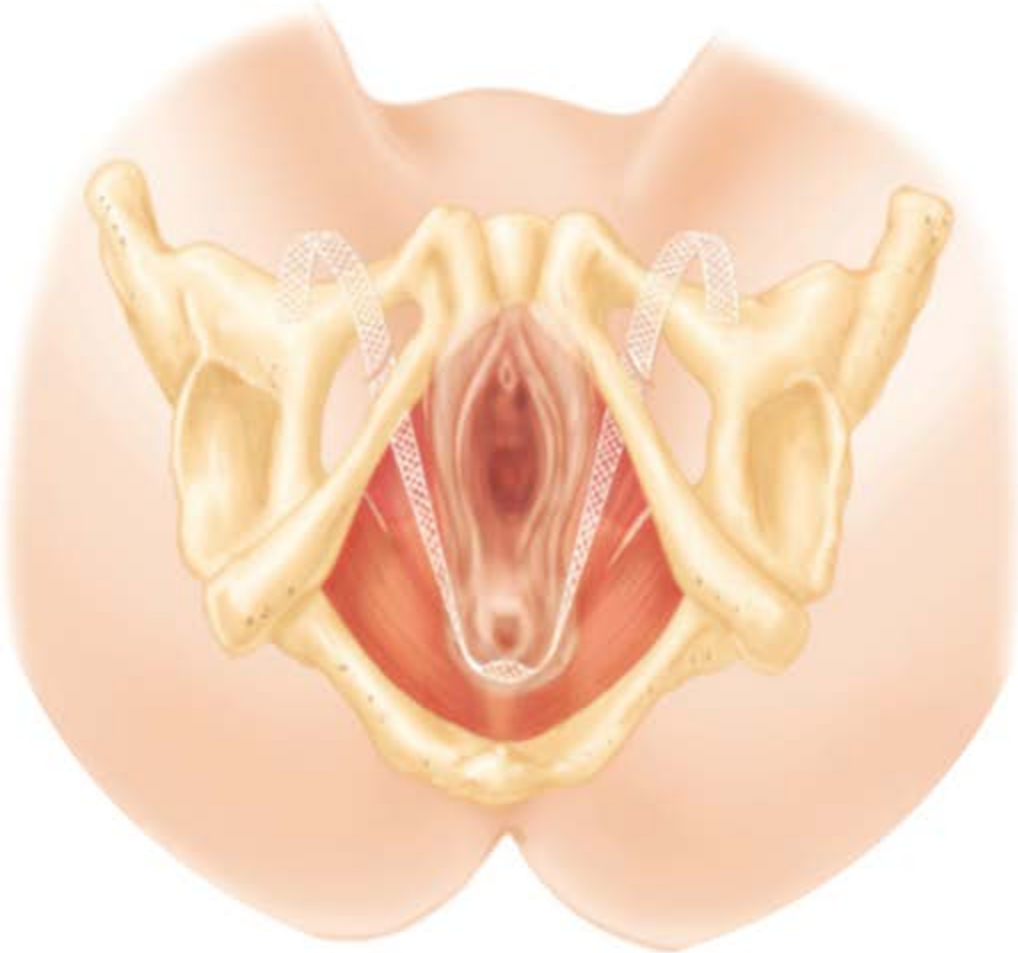
*11 patients had no pain score at baseline

Similar Efficacy Results for Both Medical Specialties

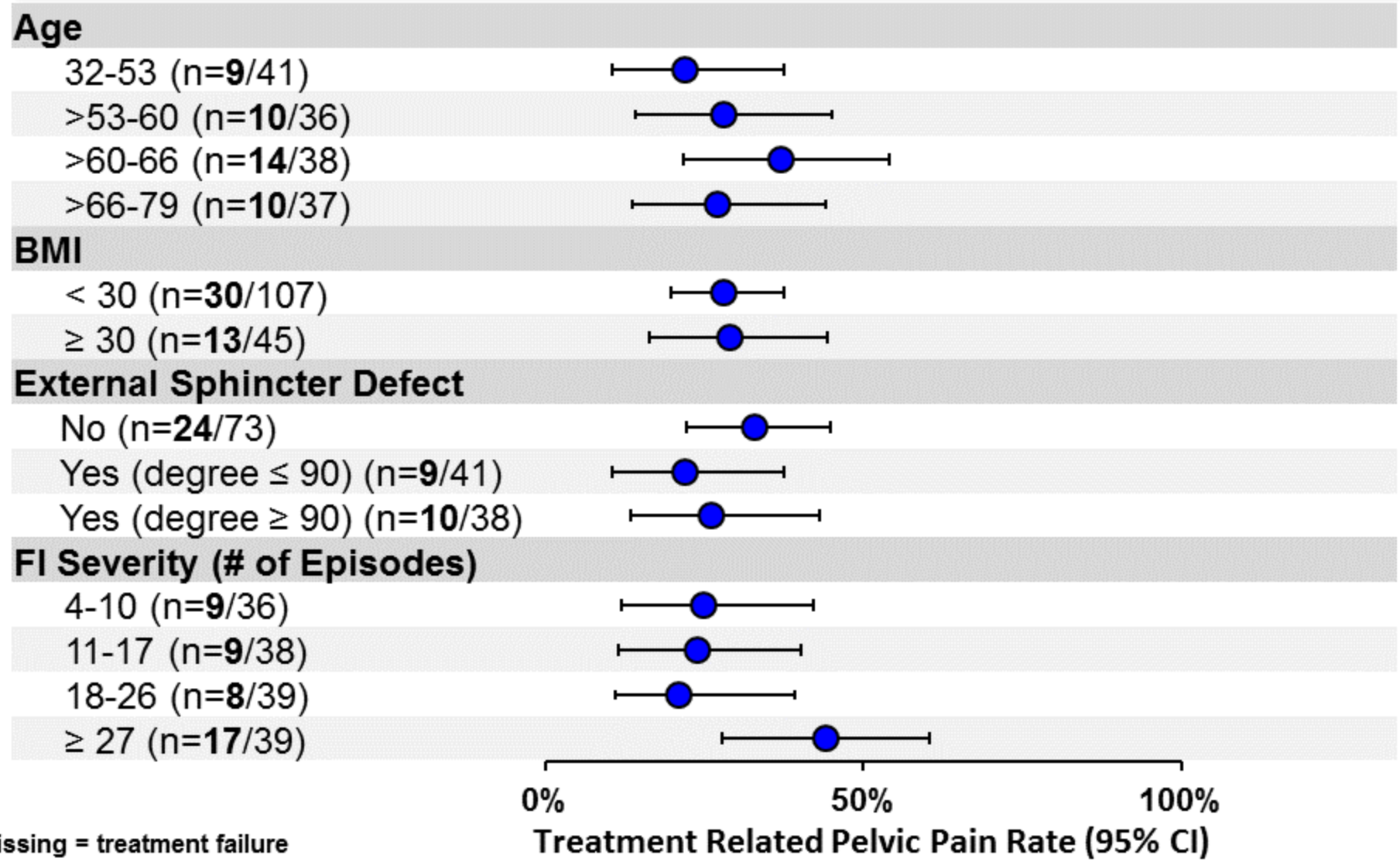
Medical Specialty	Treatment Success Rate %
Colorectal	63.3% (36/60)
Urogynecology	72.8% (67/92)
p-value*	0.216

Missing = treatment failure
*Chi-squared test

Coronal View of TOPAS System

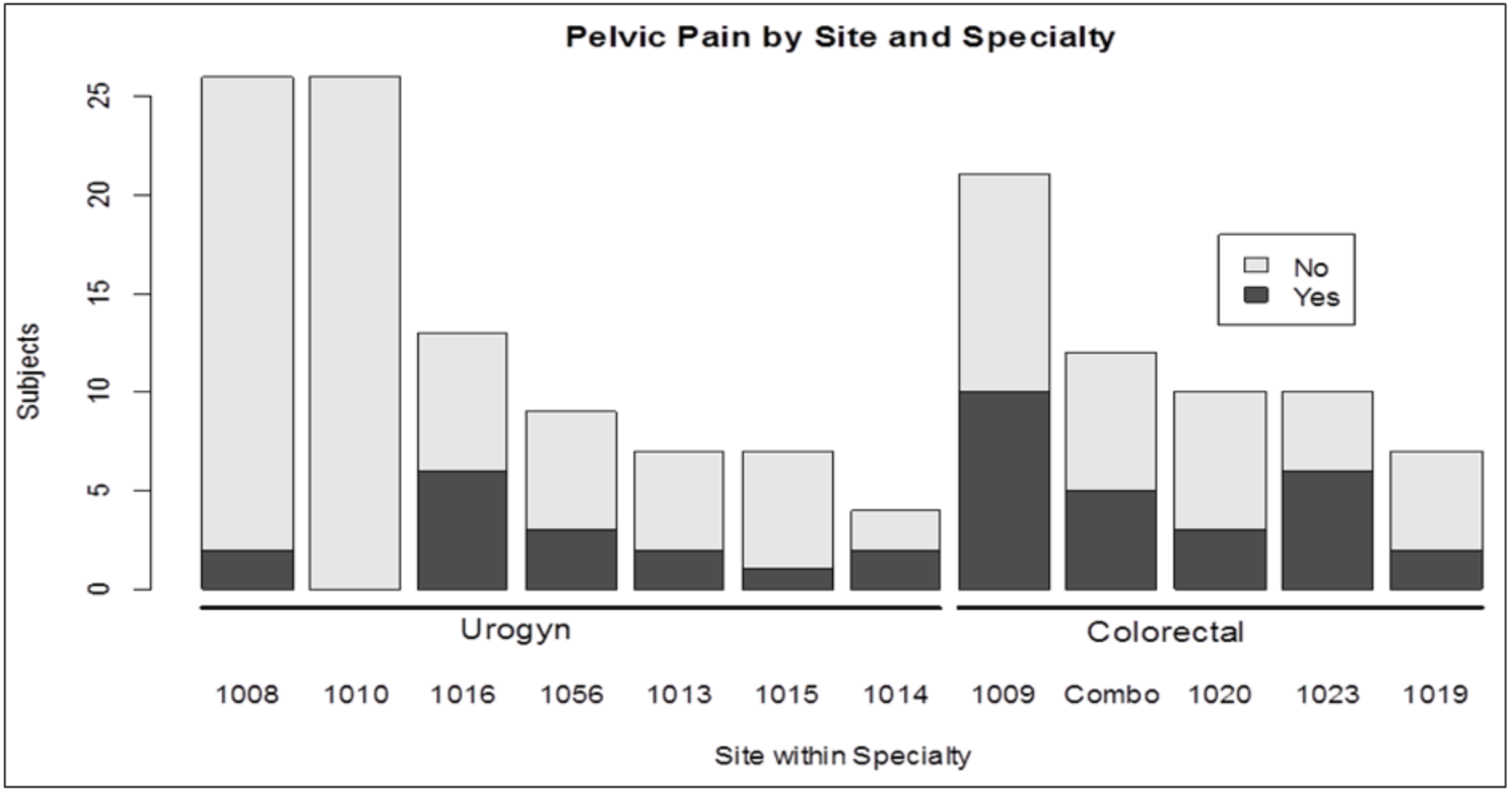


Treatment Related Pelvic Area Pain Events (n=43)

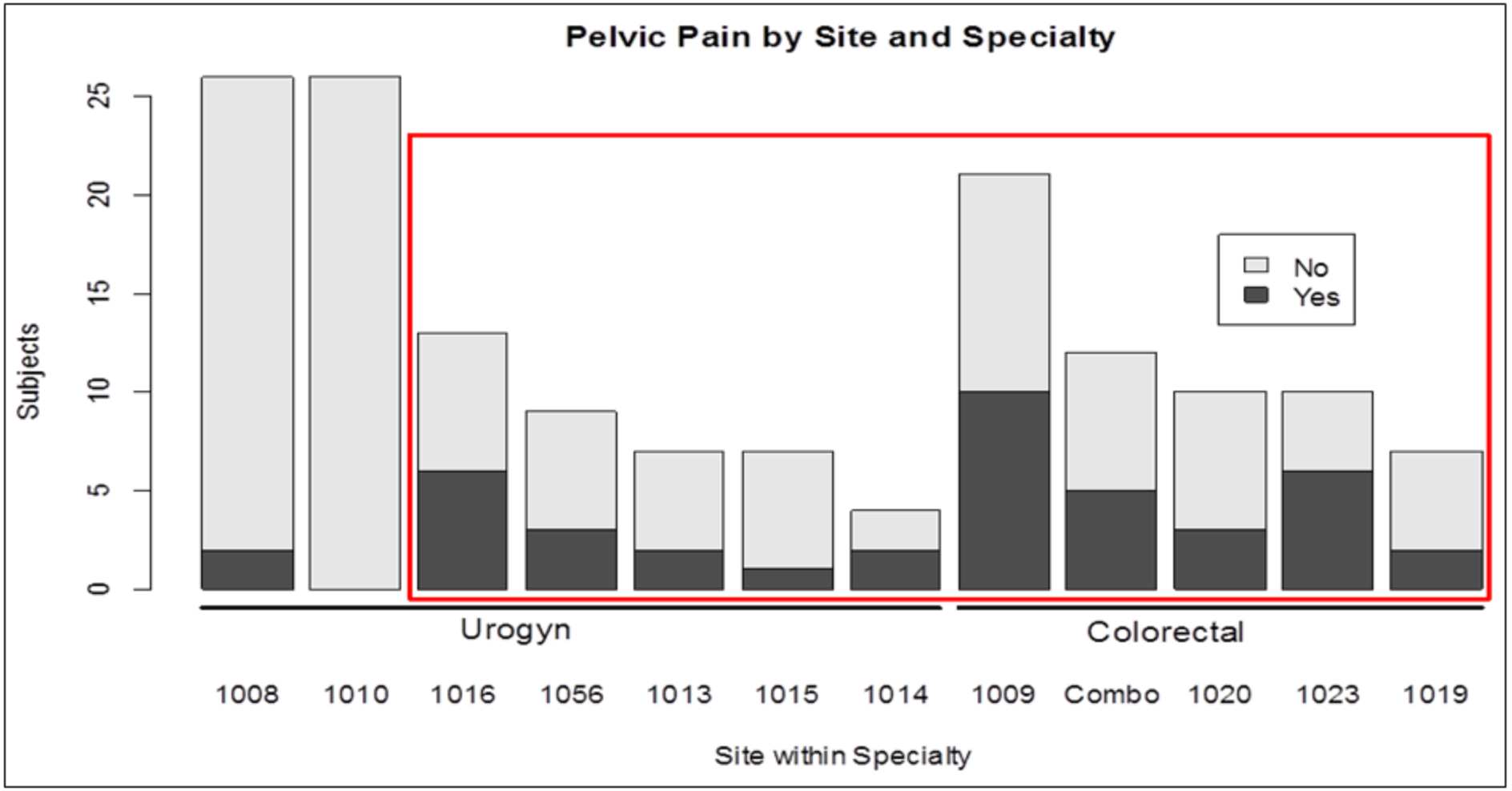


Missing = treatment failure

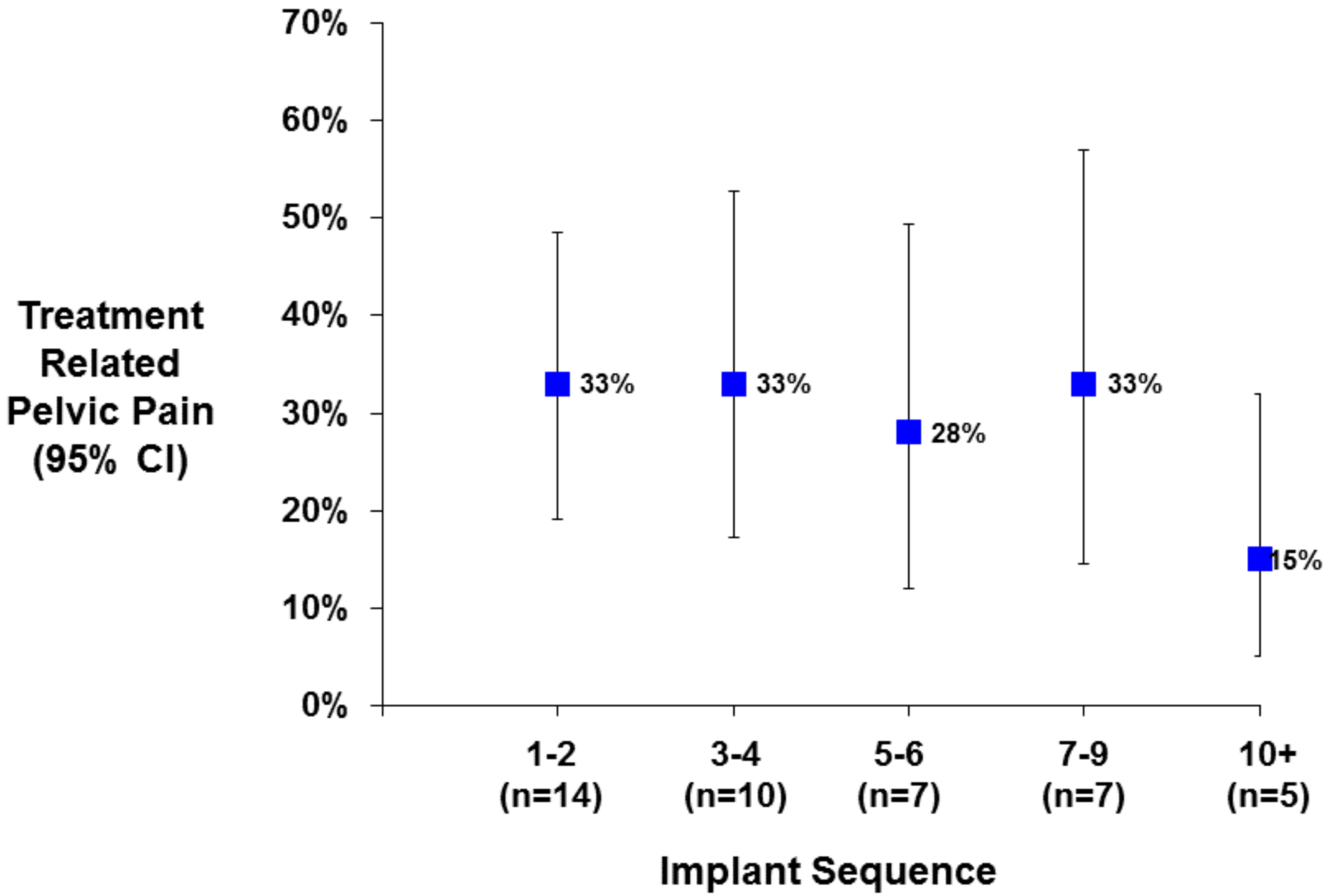
Pelvic Area Pain Risk Factors – Medical Specialty



Pelvic Area Pain Risk Factors – Medical Specialty



Treatment Related Pelvic Area Pain: Implant Sequence



Rectal Prolapse Events

Event ID	De Novo / Recurrent	Symptoms	Diagnosis	Treatment	Days to onset	Resolution Status
1008-025-AE02	Recurrent	rectal prolapse/ bulge outside of her rectum when straining	Rectal Exam: Full Thickness Rectal	robotic assisted laparoscopic rectopexy	122	Resolved 55 days
1008-025-AE03	Recurrent	c/o feeling something protruding from the rectum c/o rectal bleeding and mucous discharge	Rectal Exam: Prolapsed Lip	2 doses of sclerotherapy	261	Ongoing 1075 days
1008-035-AE01	Recurrent	rectal prolapse felt when bearing down	Rectal Exam: Full Thickness Rectal	anterior rectopexy	76	Ongoing 1029 days
1020-011-AE06	De Novo	No Signs / Symptoms Reported	Defecography: Internal Rectal prolapse	None	159	Ongoing 1104 days
1022-003-AE08	De Novo	Participants fells like a grape size skin coming out of the anus after shower	Rectal Exam	Delorme procedure excision rectal procedencia with anastomosis	128	Resolved 579 days

Baseline and Follow-Up

Cohen Kappa = 0.01

		Last Available Follow-Up	
		Yes	No
Baseline	Yes	24	60
	No	19	49