STUDY PROTOCOL

Protocol ID: DSMU-GYN-PES-2024-01

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COVER PAGE

Official Title: Effectiveness and Safety of a Novel Volumetric Cross-Shaped Vaginal Pessary for the Management of Pelvic Organ Prolapse: a Prospective Multicenter Within-Subject Comparison Study

Short Title: CROSS-PES Study

Acronym: CROSS-PES

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Sponsor: Dnipro State Medical University

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1. PROTOCOL SUMMARY

1.1 Synopsis

Study Description: This prospective multicenter single-arm study evaluates the effectiveness and safety of a novel volumetric cross-shaped vaginal pessary in women with pelvic organ prolapse (POP) who have prior experience using a traditional vaginal pessary. The study uses a within-subject comparison design, with each participant serving as her own control by comparing outcomes achieved with the novel cross-shaped pessary against her documented outcomes with the previously used traditional pessary.

Objectives: To assess the continuation rate, anatomical correction of prolapse (POP-Q and Baden–Walker grading), patient-reported quality of life (PFDI-20, PFIQ-7), pain (VAS), global impression of improvement and severity (PGI-I, PGI-S), adverse events, and patient preference for the cross-shaped pessary compared with the participant's prior traditional pessary.

Primary Endpoint: Change in Pelvic Floor Distress Inventory (PFDI-20) score from baseline to 3 months.

Secondary Endpoints: Device continuation rate at 6 months; change in PFIQ-7 score; change in POP-Q stage; change in Baden–Walker grade; pain by Visual Analogue Scale (VAS); adverse events; Patient Global Impression of Improvement (PGI-I); Patient Global Impression of Severity (PGI-S); patient preference and satisfaction assessed by structured telephone interview.

Study Population: Women aged 18 years and older with pelvic organ prolapse (POP-Q stage ≥ II) who have been using a traditional vaginal pessary for at least 12 weeks.

Study Sites: Five medical centers across Ukraine (Poltava, Dnipro ×2, Kharkiv, Chervonohrad).

Enrollment: 51 participants.

Study Duration: September 2024 – March 2025 (6 months of active follow-up).

Participant Duration: 6 months per participant (visits at baseline, 1 month, 3 months, 6 months).

1.2 Schema

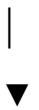
Screening & Enrollment (Visit 0)

Baseline Assessment (Visit 1, Day 0)

– Document current traditional pessary outcomes

– POP-Q, Baden–Walker, PFDI-20, PFIQ-7, VAS, PGI-S

– Fit cross-shaped pessary



Follow-up Visit 2 (Month 1 ± 1 week)

– POP-Q, Baden–Walker, VAS, adverse events

– Confirm correct positioning

Follow-up Visit 3 (Month 3 ± 2 weeks)

– POP-Q, Baden–Walker, PFDI-20, PFIQ-7, VAS

– PGI-I, PGI-S, adverse events

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Final Visit 4 / Telephone Interview (Month 6 ± 2 weeks)

– Continuation status

– PFDI-20, PFIQ-7, VAS, PGI-I, PGI-S

– Patient preference questionnaire

– Adverse events

– Study completion

1.3 Schedule of Activities

Procedure	**Screening**	**Visit 1 (Baseline)**	**Visit 2 (1 mo)**	**Visit 3 (3 mo)**	**Visit 4 (6 mo)**
Informed consent	✓				
Eligibility assessment	✓				
Demographics & medical history	✓				
Document prior pessary outcomes		✓			
POP-Q examination		✓	✓	✓	✓
Baden–Walker grading		✓	✓	✓	✓
PFDI-20		✓		✓	✓
PFIQ-7		✓		✓	✓
VAS pain		✓	✓	✓	✓
PGI-S		✓		✓	✓
PGI-I				✓	✓
Cross-shaped pessary fitting		✓			
Positioning check (standing + Valsalva)		✓	✓		
Adverse event assessment			✓	✓	✓
Patient preference questionnaire					✓

Procedure	Screening	Visit 1 (Baseline)	Visit 2 (1 mo)	Visit 3 (3 mo)	Visit 4 (6 mo)
Study completion					✓

2. INTRODUCTION

2.1 Study Rationale

Pelvic organ prolapse (POP) affects approximately 50% of parous women and significantly impairs quality of life. Vaginal pessaries remain the primary conservative treatment option, yet the fundamental designs available — ring, Gellhorn, cube, donut — have remained largely unchanged for decades. Despite wide use, pessary therapy is limited by high discontinuation rates (up to 60% within 24 months in the PEOPLE trial), suboptimal anatomical correction, difficulties with self-management, complications such as vaginal erosion and discharge, and need for regular clinic-based follow-up visits.

A novel volumetric cross-shaped vaginal pessary has been developed to address these limitations. The device consists of two intersecting medical-grade silicone rings (toruses) arranged at approximately right angles around a shared center of symmetry, creating a three-dimensional spherical structure. This design is intended to provide multi-vector pelvic floor support (addressing anterior, posterior, and apical compartment prolapse simultaneously), improved retention due to the volumetric configuration, better vaginal drainage through its open architecture, and easier self-management by patients.

The device is the subject of international patent application WO2025159727A1.

This study was designed to evaluate the effectiveness and safety of the cross-shaped pessary under real-world clinical conditions, using each participant's experience with her prior traditional pessary as an internal control.

2.2 Background

The PEOPLE randomized trial (van der Vaart et al., JAMA 2022; n = 440) compared pessary therapy with surgery for POP and demonstrated a 54.1% crossover rate from pessary to surgery, with approximately 60% of women discontinuing pessary use within 24 months. These findings underscore the need for improved pessary designs.

The TOPSY randomized controlled trial (Hagen et al., EClinicalMedicine 2023; 66:102326; n = 340) compared pessary self-management with clinic-based care and found no significant difference in quality of life (PFIQ-7: 32.3 vs. 32.5 at 18 months), while self-management was associated with fewer complications (16.7% vs. 22.0%) and lower costs. These findings suggest that device designs facilitating self-management may improve long-term outcomes.

Literature on pessary continuation rates shows wide variation: approximately 80% at 1 year, declining to 46–64% at 2 years and 33.5% at 10 years depending on pessary type and patient population.

2.3 Risk/Benefit Assessment

2.3.1 Known Potential Risks. The cross-shaped pessary is made of medical-grade silicone, a material with an established safety profile in vaginal pessary use. Anticipated risks are comparable to those of standard vaginal pessaries: vaginal discharge, vaginal erosion or abrasion, discomfort or pain, urinary symptoms (new or worsened stress incontinence, difficulty voiding), difficulty with insertion or removal, and pessary expulsion. No additional risks specific to the cross-shaped design have been identified in preliminary clinical use.

2.3.2 Known Potential Benefits. Potential benefits include improved anatomical correction of prolapse across multiple compartments, higher continuation rates due to improved comfort and self-management capability, improved quality of life as measured by validated instruments (PFDI-20, PFIQ-7), and reduced need for clinic-based pessary changes.

2.3.3 Assessment of Potential Risks and Benefits. The risks of the cross-shaped pessary are anticipated to be no greater than those of standard vaginal pessaries, which have an established safety profile over decades of clinical use. The potential benefits — improved anatomical correction, better tolerability, and easier self-management — outweigh the known risks. All participants in this study have prior pessary experience and are familiar with pessary-related adverse effects.

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3. OBJECTIVES AND ENDPOINTS

	Objective	Endpoint	Justification
Primary	To evaluate the effect of the cross-shaped pessary on pelvic floor symptom distress	Change in PFDI-20 score from baseline to 3 months	PFDI-20 is a validated, widely used measure of symptom distress in POP; MCID = 15.3 points
Secondary	To assess device continuation	Proportion of participants continuing use at 6 months (with 95% CI)	Continuation rate is the most clinically meaningful indicator of pessary acceptability
Secondary	To evaluate impact on quality of life	Change in PFIQ-7 from baseline to 3 and 6 months	PFIQ-7 captures functional impact of pelvic floor disorders; MCID = 15.0 points
Secondary	To assess anatomical correction	Change in POP-Q stage and Baden–Walker grade at 1, 3, and 6 months	POP-Q is the standardized system for prolapse staging
Secondary	To evaluate pain	Change in VAS (0–10) at 1, 3, and 6 months	VAS is a validated, simple pain assessment tool

	Objective	Endpoint	Justification
Secondary	To assess safety	Incidence, type, and severity of adverse events through 6 months	Standard safety reporting
Secondary	To assess global patient-reported outcomes	PGI-I (7-point Likert) and PGI-S (4-point Likert) at 3 and 6 months	Validated global impression instruments used in urogynecology trials
Secondary	To assess patient preference	Proportion preferring cross-shaped pessary over previous traditional pessary; satisfaction scores (5-point Likert) at 6 months	Preference reflects composite patient experience beyond individual endpoint scores

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4. STUDY DESIGN

4.1 Overall Design

This is a prospective, multicenter, open-label, single-arm study with a within-subject comparison design conducted at five medical centers in Ukraine. Each participant serves as her own control: outcomes achieved with the novel cross-shaped pessary are compared with the participant's documented outcomes using her prior traditional pessary.

The study is not randomized and not blinded. The within-subject design was chosen because it eliminates inter-subject variability in anatomy, prolapse severity, and baseline quality of life, thereby increasing statistical power with a smaller sample size. The open-label design was necessitated by the obvious physical difference between the cross-shaped pessary and traditional pessary types.

Nineteen gynecologists from 16 medical institutions were trained in the fitting technique prior to the start of enrollment. Participants were recruited from five clinical sites.

No interim analysis was planned. No Data Monitoring Committee was established, given the low-risk nature of the intervention and the short study duration.

4.2 Scientific Rationale for Study Design

A randomized controlled trial comparing the cross-shaped pessary with standard pessary types would represent the highest level of evidence; however, such a trial was considered premature at this stage of device development. The within-subject comparison design was selected as the most efficient first-in-human clinical evaluation because it controls for individual patient factors, requires a smaller sample size, and provides robust preliminary evidence of efficacy and safety to inform the design of a subsequent randomized trial.

4.3 End of Study Definition

A participant is considered to have completed the study upon completion of the 6-month follow-up visit (Visit 4) or the structured telephone interview at 6 months. The end of the study is defined as the date of the last participant's last study contact.

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5. STUDY POPULATION

5.1 Inclusion Criteria

1. Female, aged 18 years or older.
2. Pelvic organ prolapse POP-Q stage ≥ II (any compartment).
3. Current use of a traditional vaginal pessary (ring, Gellhorn, cube, donut, or other) for at least 12 consecutive weeks prior to enrollment.
4. Willing and able to provide written informed consent.
5. Able to attend scheduled follow-up visits or participate in telephone interviews.

5.2 Exclusion Criteria

1. Active vaginal or pelvic infection at the time of enrollment.
2. Pregnancy or planned pregnancy during the study period.
3. History of pelvic radiation therapy.
4. Severe vaginal atrophy with active erosion preventing pessary use.
5. Planned surgical treatment for POP during the study period.
6. Cognitive impairment or psychiatric condition precluding informed consent or protocol compliance.
7. Known allergy to silicone.

5.3 Strategies for Recruitment and Retention

Participants were recruited by their treating gynecologists at each of the five study sites from among existing pessary users presenting for routine follow-up. Retention was supported by scheduled visit reminders and the option of telephone follow-up for the 6-month assessment.

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6. STUDY INTERVENTION

6.1 Study Intervention Description

The investigational device is a volumetric cross-shaped vaginal pessary consisting of two closed rings (toruses) of medical-grade silicone that intersect at two diametrically opposite points in planes at approximately right angles, sharing a common center of symmetry. The resulting three-dimensional structure is approximately spherical. Outer diameter: 55 mm. The device is compressible for insertion (squeezed into an oblong or X-shaped configuration) and expands to its full shape once positioned in the vagina.

Patent: International application WO2025159727A1 (inventors: Sultanov S.A., Dolzhenko A.M., Kornilovska I.M.; priority date 22 January 2024). No study author has financial or intellectual property ties to the device or its inventors.

6.2 Administration

The cross-shaped pessary is fitted by a trained gynecologist during a clinical visit. After insertion, correct positioning is confirmed with the participant in the standing position during a Valsalva maneuver. Participants receive standardized instructions on self-removal, reinsertion, and daily hygiene.

6.3 Study Intervention Compliance

Compliance is defined as continued use of the cross-shaped pessary. Discontinuation, temporary removal, and reasons for discontinuation are documented at each follow-up visit.

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7. STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

Participants may discontinue use of the cross-shaped pessary at any time for any reason. Reasons for discontinuation are documented and include: inadequate symptom relief, discomfort or pain, adverse event, desire for surgery, loss of the device (expulsion), or personal preference.

7.2 Participant Withdrawal

Participants may withdraw from the study at any time without penalty. Participants who discontinue the cross-shaped pessary are encouraged to remain in follow-up for collection of outcome data (intention-to-treat principle). A participant is considered lost to follow-up after three unsuccessful attempts to establish contact.

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8. STUDY ASSESSMENTS AND PROCEDURES

8.1 Efficacy Assessments

POP-Q Examination: Standardized quantitative assessment of prolapse stage (0–IV) performed at each visit by the site investigator.

Baden–Walker Grading: Complementary grading system (0–4) applied at each visit.

PFDI-20 (Pelvic Floor Distress Inventory – Short Form 20): A validated 20-item questionnaire assessing symptom distress across three domains: Pelvic Organ Prolapse Distress Inventory (POPDI-6), Colorectal-Anal Distress Inventory (CRADI-8), and Urinary Distress Inventory (UDI-6). Score range 0–300; higher scores indicate greater distress. MCID = 15.3 points.

PFIQ-7 (Pelvic Floor Impact Questionnaire – Short Form 7): A validated 7-item questionnaire assessing the impact of pelvic floor disorders on daily activities, relationships,

and emotions across three domains. Score range 0–300; higher scores indicate greater impact. MCID = 15.0 points.

VAS Pain: A 10-cm visual analogue scale (0 = no pain, 10 = worst imaginable pain) for assessment of pessary-related discomfort.

PGI-I (Patient Global Impression of Improvement): A 7-point Likert scale from 1 (very much better) to 7 (very much worse).

PGI-S (Patient Global Impression of Severity): A 4-point Likert scale from 1 (no problems) to 4 (severe problems).

Patient Preference Questionnaire: A structured telephone interview at 6 months assessing preference for the cross-shaped pessary versus previous traditional pessary, overall satisfaction (5-point Likert from 1 = very dissatisfied to 5 = very satisfied), perceived effectiveness, quality of life change, ease of use, and convenience.

8.2 Safety Assessments

Adverse events are assessed at each follow-up visit (Months 1, 3, 6) and include: vaginal discharge, vaginal erosion/abrasion, bleeding, pain, urinary symptoms (incontinence, voiding difficulty), pessary expulsion, infection, fistula formation, and any other unanticipated event. Each event is graded for severity (mild, moderate, severe) and relationship to the device (related, possibly related, unrelated).

8.3 Adverse Events

8.3.1 Definition of Adverse Event (AE). Any untoward medical occurrence in a study participant, which does not necessarily have a causal relationship with the study intervention.

8.3.2 Definition of Serious Adverse Event (SAE). Any adverse event that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

8.3.3 Adverse Event Reporting. All adverse events are documented in the case report form at each visit. Serious adverse events are reported to the Principal Investigator within 24 hours of awareness and to the ethics committee within 7 days. In this study, zero serious adverse events were reported.

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9. STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

Primary hypothesis: The cross-shaped pessary produces a clinically and statistically significant improvement in PFDI-20 score compared with baseline (i.e., compared with the participant's scores while using her prior traditional pessary). The minimal clinically important difference (MCID) for PFDI-20 is 15.3 points.

Secondary hypotheses: The cross-shaped pessary achieves a 6-month continuation rate exceeding 80%; the cross-shaped pessary produces significant improvements in PFIQ-7,

POP-Q stage, Baden–Walker grade, VAS pain, PGI-I, and PGI-S compared with baseline/prior pessary.

9.2 Sample Size Determination

Based on published data showing a mean PFDI-20 change of approximately 45 points (SD ≈ 50) in pessary studies, a sample of 45 participants provides >90% power to detect a change of 15.3 points (MCID) with a two-sided paired t-test at $\alpha = 0.05$. To account for a 10–15% dropout rate, 51 participants were enrolled.

9.3 Populations for Analysis

Intention-to-treat (ITT) population: All enrolled participants who had the cross-shaped pessary fitted (n = 51).

Per-protocol (PP) population: All participants who completed the 3-month visit with no major protocol deviations.

9.4 Statistical Analyses

9.4.1 General Approach. Continuous variables are presented as mean ± SD or median (IQR) depending on distribution. Categorical variables are presented as frequencies (%). Within-subject comparisons are analyzed using paired t-tests or Wilcoxon signed-rank tests as appropriate. A two-sided p-value < 0.05 is considered statistically significant. The Kaplan–Meier method is used for continuation rate estimation. 95% confidence intervals are reported for all primary and secondary endpoints.

9.4.2 Analysis of Primary Endpoint. Change in PFDI-20 from baseline to 3 months, analyzed by paired t-test in the ITT population. Results are reported as mean difference with 95% CI.

9.4.3 Analysis of Secondary Endpoints. Continuation rate at 6 months: Kaplan–Meier estimate with 95% CI. PFIQ-7, VAS, PGI-I, PGI-S: paired comparisons as for primary endpoint. POP-Q and Baden–Walker: McNemar's test or Wilcoxon signed-rank test. Patient preference: descriptive statistics (proportions with 95% CI).

9.4.4 Safety Analysis. Adverse events are summarized descriptively by type, severity, and relationship to the device in the safety population (all participants who received the device).

9.4.5 Missing Data. For the primary endpoint, sensitivity analyses will be performed using last observation carried forward (LOCF) and worst-case imputation. Participants who discontinue the cross-shaped pessary are classified as treatment failures in the continuation rate analysis.

9.5 Software

Statistical analyses are performed using SPSS version 28.0 (IBM Corp., Armonk, NY, USA) and R version 4.3 (R Foundation for Statistical Computing, Vienna, Austria).

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10. REGULATORY, ETHICAL, AND STUDY OVERSIGHT

10.1 Ethical Considerations

The study protocol was reviewed and approved by the Ethics Committee of Dnipro State Medical University (Approval No. 2024-05-PES, dated 15 May 2024). The study is conducted in accordance with the Declaration of Helsinki (2013 revision), the principles of Good Clinical Practice (ICH-GCP), and applicable Ukrainian legislation on clinical research.

10.2 Informed Consent

Written informed consent is obtained from each participant prior to enrollment. The consent form describes the study purpose, procedures, potential risks and benefits, alternatives to participation, and the right to withdraw at any time without penalty. Participants are given adequate time to consider participation and to ask questions.

10.3 Confidentiality and Privacy

All participant data are de-identified using a unique study code. Personal identifying information is stored separately from study data in a locked location accessible only to the Principal Investigator. Data are managed in accordance with Ukrainian data protection laws.

10.4 Study Governance

The Principal Investigator (M.V. Medvediev) has overall responsibility for study conduct. Each site investigator is responsible for protocol compliance, data collection, and adverse event reporting at their respective center.

10.5 Conflict of Interest

No study author has financial, intellectual property, or other conflicts of interest related to the cross-shaped pessary or its manufacturers/patent holders. The study was investigator-initiated and received no external funding.

10.6 Funding

This study was investigator-initiated and self-funded. No external grants, industry funding, or other financial support was received.

10.7 Data Handling and Record Keeping

Source data are recorded in standardized case report forms (paper and electronic). All study records will be retained for a minimum of 5 years following study completion. The Principal Investigator is the custodian of all study data.

10.8 Protocol Amendments

Any amendments to this protocol require approval from the Ethics Committee before implementation, except where immediate action is necessary to protect participant safety.

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11. STUDY SITES AND INVESTIGATORS

Site #	Facility	City	Principal Site	Phone	Email

			Investigator		
1	Regional Clinical Hospital, Poltava Regional Council	Poltava	Olga V. Kanivets, MD	+380-50-757-34-06	Olgakanivec681@gmail.com
2	Clinical Hospital of Emergency Medical Care, Dnipro City Council	Dnipro	Nataliya Kovalenko, MD	+380-97-367-65-37	nk0973676537@gmail.com
3	City Out-Patient Clinic No. 18, Kharkiv City Council	Kharkiv	Olga S. Novikova, MD	+380-57-725-12-89	mrsdoktor@gmail.com
4	State Interdistrict Screening Center	Chervonohrad	Iryna Samsin, MD	+380-66-157-36-20	Irunka1985@i.ua
5	City Clinical Hospital No. 6, Dnipro City Council	Dnipro	Galyna Spodobets, MD	+380-98-708-46-51	spodobec.gala@gmail.com

12. REFERENCES

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4. Hagen S, Glazener C, Sinclair L, et al. Clinical effectiveness of vaginal pessary self-management vs clinic-based care for pelvic organ prolapse: the TOPSY randomised controlled superiority trial. EClinicalMedicine. 2023;66:102326.
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13. ABBREVIATIONS

AE — Adverse Event; CI — Confidence Interval; GCP — Good Clinical Practice; ICH — International Conference on Harmonisation; IRB — Institutional Review Board; ITT — Intention to Treat; MCID — Minimal Clinically Important Difference; PGI-I — Patient Global Impression of Improvement; PGI-S — Patient Global Impression of Severity; PFDI-20 — Pelvic Floor Distress Inventory–Short Form 20; PFIQ-7 — Pelvic Floor Impact Questionnaire–Short Form 7; POP — Pelvic Organ Prolapse; POP-Q — Pelvic Organ Prolapse Quantification; PP — Per Protocol; SAE — Serious Adverse Event; SD — Standard Deviation; VAS — Visual Analogue Scale.

PROTOCOL AMENDMENT HISTORY

Version	Date	Section(s)	Summary of Changes	Rationale
1.0	15 May 2024	—	Original protocol	—