STUDY PROTOCOL WITH STATISTICAL ANALYSIS PLAN AND INFORMED CONSENT FORM

Prospective Comparative Evaluation of Different Surgical Techniques in the Treatment of Gynecomastia: A Multicenter Study

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Protocol Code:	175/2025
Document Type:	Study Protocol with Statistical Analysis Plan and Informed Consent Form
Document Date:	08 January 2026
Version:	1.0
Study Design:	Prospective Multi-center Cohort Study
Study Sites:	Antalya City Hospital, Antalya, Turkey Istanbul Bagcilar Training and Research Hospital, Istanbul, Turkey
Principal Investigator:	[Name withheld per ClinicalTrials.gov policy]
Ethics Committee:	Antalya City Hospital Scientific Research Ethics Committee Decision No: 20/175 – Date: 08 January 2026
Sponsor / Funder:	None (Investigator-initiated, no external funding)
Ethical Basis:	Declaration of Helsinki; ICH-GCP Guidelines

This document has been prepared for submission to ClinicalTrials.gov (U.S. National Library of Medicine) as a combined Study Protocol, Statistical Analysis Plan, and Informed Consent Form. Documents must be in English and PDF/A format as required by 42 CFR Part 11.

PART I — STUDY PROTOCOL

1. Study Identification

Official Title: Prospective Comparative Evaluation of Different Surgical Techniques in the Treatment of Gynecomastia: A Multicenter Study

Protocol Code: 175/2025 | **Document Date:** 08 January 2026 | **Version:** 1.0

Study Type: Prospective Multi-center Cohort Study (Non-interventional / Observational)

Study Setting: Hospital-based

Start Date: Immediately after ethics committee approval | **Duration:** Until 100 participants enrolled (50 study + 50 control)

2. Rationale and Background

Gynecomastia is a common condition defined as proliferation of mammary gland tissue in males, with a prevalence of 24–65% (EAA Guideline, 2023). Surgical treatment is the standard approach due to psychosocial distress (embarrassment, social isolation) and aesthetic concerns; however, differences in complications (NAC hypoesthesia 0–35%, scarring 10–20%) and satisfaction outcomes (BODY-Q scores 65–95) exist between endoscopic (minimally invasive, axillary incision) and open (periareolar incision) techniques (Diao et al., 2025, n=140; Xu et al., 2023, n=128).

Current literature (2023–2025, PubMed meta-analyses; Cao et al., n=1000+) highlights the advantages of endoscopic NSM in nerve preservation (0–5% permanent loss vs. 8–15%) and scar minimization (VSS 1.8 vs. 5.2); however, comparative cohorts in Turkey remain limited, with data deficiency in 40% of adolescent cases (Tukenmez et al., 2023, n=30). This gap necessitates clarification of national epidemiology. By integrating retrospective/prospective data with Propensity Score Matching (PSM), the study will provide evidence-based guidance, targeting quality of life (QoL) improvement (25–40%) and reduction in revision rates (5–15%). Ethical basis: Declaration of Helsinki, ICH-GCP; maximum benefit with minimal risk.

3. Objectives

3.1 Primary Objective

To objectively compare short- and long-term clinical efficacy, safety, and patient-centered outcomes of endoscopic nipple-areola complex (NAC)-preserving mastectomy (NSM) technique versus conventional open NSM technique in gynecomastia surgery, based on: surgical trauma minimization (nerve traction/transection), aesthetic preservation (scar and NAC symmetry), and functional recovery (sensory preservation).

3.2 Secondary Objectives

- Identify complication profiles and risk factors; verify potential 10–20% complication reduction of the endoscopic technique.
- Assess aesthetic and psychosocial outcomes using the BODY-Q Chest module (VAS) and Vancouver Scar Scale (VSS).
- Monitor NAC sensory loss up to 12 months using SWMT (Semmes-Weinstein monofilament test, 0.07–300 g/mm²); identify prognostic factors for revision rates and recurrence (prolactin level, hormonal ratios).

- Expand limited endoscopic cohorts in Turkey to provide input for clinical guidelines; correct baseline imbalances with PSM.
- Generate prospective data on endoscopic NSM for Grade II–III gynecomastia, and contribute to infrastructure for future randomized controlled trials.

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4. Study Population

4.1 Sample Size

Estimated number of patient participants: **50** (endoscopic group) | Age range: 18–60 years

Estimated number of control participants: **50** (open technique group) | Age range: 18–60 years

Total estimated enrollment: 100 participants

4.2 Inclusion Criteria

Applicable to both groups:

- Clinically/ultrasonographically confirmed primary gynecomastia (palpable gland ≥2 cm, Simon Grade II–III); male patients aged 18–60 years.
- Cases requesting surgery due to cosmetic/psychosocial distress (VAS >4/10 dissatisfaction).
- Technical eligibility: Minimal skin excess for endoscopic group (Grade <IV); any grade for open group. Bilateral/unilateral cases included.
- Patients providing informed written consent, compliant with 12-month follow-up (telephone/examination).

4.3 Exclusion Criteria

- Secondary gynecomastia (hormonal disorder, drug-induced, hypogonadism, suspected thyroid/malignancy; testosterone/oestrogen ratio <5); pseudo-gynecomastia (lipomastia only, no glandular tissue).
- Age <18 or >60 years; severe comorbidities: cardiac failure NYHA>II, diabetes HbA1c>8, active smoking >20 pack-years, BMI>35.
- Previous chest/breast surgery, radiation, or trauma; active infection or hematological disorder (abnormal coagulation test).
- Fertility problems of reproductive age with positive hormone test; immunodeficiency (active HIV/HBV).
- Refusal of consent, mental incapacity (MMSE<24), or geographical access problem making follow-up impossible.

4.4 Control Group

Patients who underwent conventional open NSM technique will serve as controls against the endoscopic NSM group. Balance between groups will be ensured by Propensity Score Matching (PSM) (age, grade, BMI). Control group patients will be males aged 18–60 years, predominantly Simon Grade II–III, with BMI 25–30.

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5. Study Design and Procedures

5.1 Surgical Procedures

Endoscopic Group: Liposuction and tissue excision through a single axillary incision (endoscopic NAC-preserving mastectomy – NSM technique).

Open Group (Control): Subcutaneous mastectomy through a periareolar incision (conventional open NSM technique). This is the standard clinical practice comparator.

No additional interventions beyond standard treatment procedures will be applied to patients within the scope of the study.

5.2 Follow-up Schedule

12-month follow-up by examination and/or telephone at 1, 3, 6, and 12 months postoperatively. Complications (hypoesthesia, scarring) will be recorded at each visit.

5.3 Data Collection

Patient data will be collected anonymously from hospital electronic medical records with ethics committee approval. Questionnaires (BODY-Q Chest module, VAS) are patient-oriented and administered equally to both groups. Data will be stored in a secure encrypted electronic system; patient confidentiality will be maintained at every stage.

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6. Outcome Measures

6.1 Primary Outcomes

- Complication rate: NAC hypoesthesia rate (0–35%), scarring rate (10–20%), assessed at 1, 3, 6, and 12 months postoperatively.
- Rate of permanent NAC sensory loss measured by SWMT at 12 months.
- Scar quality: Vancouver Scar Scale (VSS) score.

6.2 Secondary Outcomes

- Patient satisfaction: BODY-Q Chest module score and Visual Analogue Scale (VAS).
- Quality of life (QoL) score at 3, 6, and 12 months postoperatively.
- Revision rates and recurrence rates at 12 months.
- Hormonal prognostic factors: prolactin level, testosterone/oestrogen ratio.

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7. Study Sites

Site 1: General Surgery Clinic, Antalya City Hospital, Gocerler Mahallesi, 5379 Sokak, 07080 Kepez/Antalya, Turkey

Site 2: General Surgery Clinic, Istanbul Bagcilar Training and Research Hospital, Istanbul, Turkey

Preoperative and postoperative physical examination findings, VSS scar evaluation, VAS pain scoring, and patient satisfaction questionnaire will be conducted at both sites. No additional laboratory investigation is planned beyond routine preoperative examinations and pathological evaluation of excised tissue.

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8. Ethical Considerations

This study is conducted in accordance with the Declaration of Helsinki and ICH-GCP guidelines. Ethics committee approval was obtained from the Antalya City Hospital Scientific Research Ethics Committee (Decision No: 20/175, Date: 08 January 2026, Protocol Code: 175/2025). All patients will provide written informed consent prior to participation. The study involves no additional interventions beyond standard surgical care.

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9. References

- EAA Guideline, 2023. European Academy of Andrology guideline on gynecomastia evaluation and management.
- Diao et al., 2025 (n=140). Endoscopic versus open NSM for gynecomastia: a prospective comparative study.
- Xu et al., 2023 (n=128). Outcomes of endoscopic nipple-areola complex-sparing mastectomy in gynecomastia.
- Cao et al. (n=1000+). Meta-analysis of endoscopic versus open techniques for gynecomastia surgery. PubMed, 2023–2025.
- Tukenmez et al., 2023 (n=30). Endoscopic approach for gynecomastia in Turkey: a preliminary cohort study.

PART II — STATISTICAL ANALYSIS PLAN (SAP)

10. Statistical Analysis Plan

10.1 Overview

This Statistical Analysis Plan (SAP) describes the planned statistical approach for analyzing data collected in the prospective multi-center cohort study comparing endoscopic NSM versus open NSM techniques for gynecomastia treatment.

10.2 Software

Data will be analyzed using **Statistical Package for the Social Sciences (SPSS) version 15.0** (SPSS, Inc., Chicago, IL, USA).

10.3 Assessment of Normality

Before statistical testing, the conformity of all continuous variables to normal distribution will be assessed using the **Shapiro-Wilk test**.

10.4 Comparison of Continuous Variables

- **Normally distributed variables:** One-way Analysis of Variance (ANOVA) will be used for group comparisons.
- **Non-normally distributed variables:** Kruskal-Wallis test will be used.

Post-hoc tests will be applied where appropriate to identify specific group differences following significant omnibus tests.

10.5 Comparison of Categorical Variables

- **Chi-square test** will be applied for categorical variables with sufficient expected cell frequencies (≥5).
- **Fisher's exact test** will be used when expected cell frequencies are <5.

10.6 Significance Level

All statistical tests will be **two-tailed**. A p-value of **<0.05** will be considered statistically significant.

10.7 Propensity Score Matching (PSM)

To correct for baseline imbalances between the endoscopic and open technique groups, **Propensity Score Matching (PSM)** will be applied. Matching variables will include: age, Simon grade, and BMI. The matching ratio and caliper width will be defined prior to analysis.

10.8 Primary Analysis

The primary analysis will compare complication rates (NAC hypoesthesia, scarring) between the endoscopic and open NSM groups using chi-square or Fisher's exact test as appropriate. Relative risk (RR) and 95% confidence intervals will be calculated.

10.9 Secondary Analyses

- BODY-Q Chest module scores and VAS scores will be compared between groups using the appropriate test based on distribution (ANOVA or Kruskal-Wallis).
- VSS scar scores will be compared between groups at each time point.

- SWMT filament threshold values at 12 months will be used to assess permanent NAC sensory loss; Mann-Whitney U test will be applied.
- Kaplan-Meier curves will be used for time-to-revision analysis; log-rank test for group comparison.
- Logistic regression will be used to identify independent prognostic factors (prolactin level, hormonal ratios, BMI, grade) for complications and recurrence.

10.10 Handling of Missing Data

Missing data will be reported descriptively. Where applicable, multiple imputation or last observation carried forward (LOCF) methods will be considered. Sensitivity analyses will be performed to assess the impact of missing data.

PART III — INFORMED CONSENT FORM (STUDY GROUP)

11. Informed Consent Form

Code: KU.FR.40 | Publication Date: 28.11.2024 | Revision No: — | Page: 3/3

T.C. MINISTRY OF HEALTH

ANTALYA CITY HOSPITAL

TO THE CHAIR OF THE SCIENTIFIC RESEARCH ETHICS COMMITTEE

You are invited to participate in a study titled **"Prospective Comparative Evaluation of Different Surgical Techniques in the Treatment of Gynecomastia: A Multicenter Study."** This study is being conducted for research purposes. We recommend that you join this research. Participation in the study is voluntary. Before deciding whether to participate, it is important that you know the purpose and procedures of the study, how information about you will be used, and what the study involves. Please read the following information carefully and ask for clear answers to your questions. Once you are fully informed and your questions have been answered, you will be asked to sign this form if you wish to participate.

11.1 What are the aims and rationale of the study, and how many other people will participate?

- The primary aim of this study is to objectively compare the short- and long-term clinical effectiveness, safety, and patient-centered outcomes of the endoscopic nipple-areola complex (NAC)-preserving mastectomy (NSM) technique versus the conventional open NSM technique in gynecomastia surgery.
- Secondary aims include: identifying complication profiles and risk factors; verifying the potential 10–20% complication reduction of the endoscopic technique.
- The research is planned to last 1 year with approximately 100 patients.

11.2 Should I participate in this study?

Whether or not you participate in this study is entirely your decision. If you decide to participate, you will be given this written informed consent form to sign. Even if you sign this form now, you are free to withdraw at any time without giving any reason. If you do not wish to participate or if you withdraw, there will be no change in the treatment provided to you by your doctor. You also have the right to withdraw your consent at any stage of the study.

11.3 What will happen if I participate in this study?

No additional interventions beyond standard treatment procedures will be applied to patients within the scope of the study. Preoperative and postoperative physical examination findings, scar evaluation with VSS, pain scoring with VAS, and patient satisfaction questionnaire will be conducted at the General Surgery Clinics of Antalya City Hospital and Istanbul Bagcilar Training and Research Hospital, Istanbul, Turkey. No additional laboratory investigation is planned beyond routine preoperative examinations and pathological evaluation of the excised tissue.

11.4 What are the benefits of participating in the study?

There is no direct medical benefit expected from this research for the participant. This study is conducted solely for research purposes.

11.5 What is the cost of participating in this study?

You will not incur any financial cost by participating, and no payment will be made to you.

11.6 How will my personal information be used?

Your investigator will use your personal information to conduct the research and statistical analyses, and your identifying information will be kept confidential throughout the study. At the end of the study, you have the right to request information about the research outcomes. Without your written permission, information about you cannot be viewed or disclosed by anyone else. Study results may be used in scientific publications upon completion of the study, but your identity will not be revealed.

11.7 Contact Information

If you have any questions or need additional information about the study, please contact:

Name: [Principal Investigator - name withheld per ClinicalTrials.gov policy]

Role: General Surgery Specialist

Institution: Antalya City Hospital

11.8 Participant Declaration

I was informed by Dr. …… at the Department/Clinic of General Surgery that a medical research study will be conducted and the **above information** was conveyed to me, and I have read the relevant text. After this information, I was invited as a 'participant' in such a research study.

I fully understand all the explanations made to me. Under these conditions, I voluntarily agree to participate in this clinical study with my own consent, without any pressure or coercion.

- I was informed that I have the right to refuse participation. I also know that this will not harm my medical care or my relationship with my physician.
- I am aware that I may withdraw from this study at any time without giving any reason, provided I notify the responsible investigator/physician. I know that refusal or later withdrawal will not place me under any liability, and will not affect the medical care I need now or in the future.
- The investigator/physician conducting the study may remove me from the study without my consent, provided no harm is done to my medical condition due to non-compliance with the study program.
- The results of the study may be presented at scientific meetings or publications. However, in such cases, my identity will be strictly kept confidential.
- I will not be held financially responsible for any expenses related to the research, nor will any payment be made to me.
- A signed copy of this form will be provided to me.

Participant	Witness to Interview	Informing Investigator
Name – Surname:	Name – Surname, Title:	Name – Surname:

Address:	Address:	Address:
Tel: Signature: Date:	Tel: Signature: Date:	Tel: Signature: Date:

Note: Guardianship/custody arrangements will be made and consent of parent/guardian obtained where applicable. The 'Witness to Interview' section is mandatory for psychiatric and pediatric studies. The participant declaration and signature must appear on the same page; they must NOT be on different pages.

End of Document — Study Protocol with SAP and ICF