STUDY PROTOCOL AND STATISTICAL ANALYSIS PLAN

Laparoscopic Nissen (Total) Versus Toupet (270°) Fundoplication for Gastroesophageal Reflux Management in Patients With Hiatal Hernia: A Patient- and Assessor-Blinded Randomized Controlled Trial

Short title: Nissen versus Toupet Fundoplication for Hiatal Hernia

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Item	Description
Sponsor/Institution	Sofiamed Hospital, Sofia, Bulgaria
Study location	Sofiamed Hospital, 16 G. M. Dimitrov Blvd., Sofia, Bulgaria
Principal investigator	Teodor Atanassov, Assoc. Prof. [confirm official spelling and title]
Co-investigators	Dr Katya Todorova; Dr Alexander Tsvetanov [confirm final author list]
Human subjects protection review	Ethics Committee approval number/date: [insert from approved document]
Estimated enrolment	200 participants, allocated 1:1 to two parallel groups
Study start date	29 May 2023
Estimated primary completion date	30 July 2026
Estimated study completion date	31 January 2027

Note: items in square brackets should be checked against the ethics approval document and institutional records before final upload.

1. Protocol Summary

This document describes the protocol and statistical analysis plan for a prospective, two-arm, parallel-group randomized controlled trial comparing laparoscopic Nissen fundoplication with laparoscopic Toupet fundoplication in patients undergoing laparoscopic surgical treatment for hiatal hernia associated with gastroesophageal reflux disease (GERD).

Participants will be randomly assigned in a 1:1 ratio to laparoscopic hiatal hernia repair with either complete 360° Nissen fundoplication or partial posterior 270° Toupet fundoplication. The trial is designed as a patient- and assessor-blinded study. The operating surgeon and operating room staff cannot be masked because of the nature of the surgical intervention.

2. Scientific Background and Rationale

Hiatal hernia is a common condition in which abdominal structures, most frequently the stomach, protrude through the esophageal hiatus into the thoracic cavity. It is often associated with gastroesophageal reflux symptoms and reduced quality of life. Surgical repair is considered in selected patients with symptomatic hiatal hernia and GERD, particularly when symptoms persist despite medical treatment or when anatomical repair is indicated.

Laparoscopic Nissen fundoplication is a complete 360° antireflux wrap and is widely used for reflux control. However, postoperative dysphagia and gas-bloat symptoms may occur after complete fundoplication. Laparoscopic Toupet fundoplication is a partial posterior 270° wrap designed to provide reflux control while potentially reducing functional side effects such as dysphagia and gas-bloat. The optimal fundoplication technique in patients undergoing hiatal hernia repair remains clinically relevant, particularly regarding the balance between durable reflux control and postoperative functional outcomes.

3. Study Objectives

3.1 Primary Objective

The primary objective is to compare clinical and functional outcomes after laparoscopic Nissen and Toupet fundoplication in patients undergoing laparoscopic hiatal hernia repair for hiatal hernia associated with GERD.

3.2 Secondary Objectives

- To compare early postoperative pain between the two intervention groups.
- To compare reflux-related health-related quality of life before and after surgery.
- To compare length of postoperative hospital stay.
- To compare recurrence of gastroesophageal reflux symptoms during follow-up.
- To compare operative time and time required to perform the fundoplication component of the procedure.
- To compare postoperative gas-bloat symptoms and postoperative complications.

4. Study Design

This is a prospective, randomized, patient- and assessor-blinded, two-arm, parallel-group controlled clinical trial. Participants will be allocated to one of two surgical intervention groups. Outcomes will be assessed at predefined postoperative time points and compared between groups.

Design element	Description
Study type	Interventional clinical trial
Allocation	Randomized
Intervention model	Parallel assignment
Masking	Participant and outcomes assessor masked; surgeon and operating room staff not masked
Primary purpose	Treatment
Number of arms	Two

Design element	Description
Estimated enrolment	200 participants

5. Study Population

5.1 Inclusion Criteria

- Patients aged 18 to 90 years.
- Patients diagnosed with primary hiatal hernia by fibrogastroscopy/upper gastrointestinal endoscopy and/or barium swallow examination.
- Patients with symptoms of gastroesophageal reflux disease.
- Patients scheduled for elective laparoscopic hiatal hernia repair with fundoplication.
- Patients able to provide written informed consent.

5.2 Exclusion Criteria

- Patients younger than 18 years or older than 90 years.
- Patients with recurrent hiatal hernia.
- Patients who are not suitable for general anesthesia.
- Patients who prefer a surgical approach other than laparoscopic surgery.
- Patients unable or unwilling to provide informed consent or to complete postoperative follow-up assessments.

6. Randomization and Allocation

Eligible participants who provide informed consent will be randomized in a 1:1 ratio to one of the two intervention groups. Randomization will be performed before surgery according to a pre-specified allocation sequence. The allocation will determine whether the participant undergoes laparoscopic hiatal hernia repair with Nissen fundoplication or laparoscopic hiatal hernia repair with Toupet fundoplication.

The randomization process will be documented in the study records. Participants will be analyzed primarily according to the group to which they were randomized.

7. Masking

Participants and the postoperative outcomes assessor will be masked to the type of fundoplication performed. The operating surgeon and operating room staff cannot be masked because the surgical technique is visible and must be performed according to the randomized allocation. Operative details regarding the type of fundoplication will not be disclosed to the participant or the outcomes assessor before completion of the relevant postoperative assessments.

8. Interventions

8.1 Arm A: Laparoscopic Nissen Fundoplication

Participants assigned to Arm A will undergo laparoscopic hiatal hernia repair with Nissen fundoplication. The procedure includes a complete 360° fundoplication performed as part of standard laparoscopic antireflux surgery under general anesthesia.

8.2 Arm B: Laparoscopic Toupet Fundoplication

Participants assigned to Arm B will undergo laparoscopic hiatal hernia repair with Toupet fundoplication. The procedure includes a partial posterior 270° fundoplication performed as part of standard laparoscopic antireflux surgery under general anesthesia.

8.3 Concomitant Care

Perioperative care, anesthesia, postoperative analgesia, diet advancement, discharge criteria and follow-up will be provided according to institutional standard practice, unless otherwise specified in the study records. Any deviations from standard perioperative care that may influence outcomes will be documented.

9. Outcome Measures

9.1 Primary Outcome Measures

Outcome measure	Description	Time frame
Postoperative Pain Score at 24 Hours	Postoperative pain will be assessed 24 hours after surgery using the Visual Analog Scale (VAS). Higher scores indicate greater pain. The score will be used to compare early postoperative pain between the Nissen and Toupet groups.	24 hours after surgery
Postoperative Pain Score at 7 Days	Postoperative pain will be assessed 7 days after surgery using the VAS. The score will be used to evaluate and compare short-term postoperative pain between the two intervention groups.	7 days after surgery
Change in Health-Related Quality of Life After Surgery	Health-related quality of life will be assessed using the GERD-Health Related Quality of Life (GERD-HRQL) questionnaire. Preoperative scores will be compared with postoperative scores to evaluate changes in reflux-related symptoms and quality of life after surgery. Higher GERD-HRQL scores indicate worse reflux-related quality of life.	Preoperatively, 1 week, 4 weeks and 12 weeks after surgery
Postoperative Hospital Stay	Postoperative hospital stay will be measured as the number of days from the day of surgery until hospital discharge. Duration of stay will be compared between the Nissen and Toupet groups.	From the day of surgery until hospital discharge
Recurrence of Gastroesophageal Reflux Symptoms	Recurrence will be assessed as the presence or absence of recurrent gastroesophageal reflux symptoms during follow-up. Recurrent symptoms will be recorded and compared between the two intervention groups.	4 weeks, 6 months and 1 year after surgery

9.2 Secondary Outcome Measures

Outcome measure	Description	Time frame
Operative Time	Operative time will be measured in minutes from the beginning to the end of the laparoscopic surgical procedure. Total operative time will be compared between the two intervention groups.	Intraoperative
Fundoplication Time	Fundoplication time will be measured in minutes as the time required to perform the fundoplication component of the procedure. This measure will be used to compare the technical duration of Nissen and Toupet	Intraoperative

Outcome measure	Description	Time frame
	fundoplication.	
Gas-Bloat Symptoms	Postoperative gas-bloat symptoms will be assessed during follow-up. The presence or absence of symptoms such as bloating, inability to belch or increased gas-related abdominal discomfort will be recorded and compared between the two groups.	1 week, 4 weeks and 12 weeks after surgery
Postoperative Complications	Postoperative complications will be recorded according to type and frequency. The number and nature of postoperative complications will be compared between the Nissen and Toupet groups.	Up to 30 days after surgery

10. Follow-Up Schedule

Participants will be assessed preoperatively and postoperatively according to the study schedule. The planned postoperative follow-up time points are 24 hours, 7 days, 4 weeks, 12 weeks, 6 months and 1 year, depending on the outcome measure.

Time point	Assessments
Preoperative	Eligibility, informed consent, baseline GERD-HRQL, demographic and clinical variables
24 hours after surgery	VAS pain score, early postoperative clinical assessment
7 days after surgery	VAS pain score, GERD-HRQL, gas-bloat symptoms when applicable
4 weeks after surgery	GERD-HRQL, recurrent reflux symptoms, gas-bloat symptoms
12 weeks after surgery	GERD-HRQL, gas-bloat symptoms
6 months after surgery	Recurrent gastroesophageal reflux symptoms
1 year after surgery	Recurrent gastroesophageal reflux symptoms

11. Safety Assessment

All intraoperative and postoperative complications will be recorded in the study database. Postoperative complications will be collected up to 30 days after surgery for the prespecified outcome measure. Serious adverse events and clinically relevant complications will be managed according to institutional standards and reported according to applicable ethics committee and institutional requirements.

12. Data Collection and Confidentiality

Study data will be collected from clinical records, operative records, postoperative assessments and follow-up questionnaires. Data will be recorded in a study database using participant identifiers assigned by the study team. Personal identifying information will be protected according to institutional procedures and applicable data protection requirements.

Individual participant data will not be made publicly available. Trial results will be reported in anonymized and aggregated form only.

13. Statistical Analysis Plan

13.1 General Principles

The statistical analysis will compare outcomes between participants randomized to laparoscopic Nissen fundoplication and those randomized to laparoscopic Toupet fundoplication. All statistical tests will be two-sided. A p-value < 0.05 will be considered statistically significant. Statistical analyses will be performed using validated statistical software. The software package and version will be reported in the final study report.

Continuous variables will be summarized using mean, standard deviation, median, interquartile range, minimum and maximum, as appropriate. Categorical variables will be summarized using counts and percentages. Baseline characteristics will be presented by randomized group to describe group comparability.

13.2 Analysis Populations

The primary analysis population will be the intention-to-treat population, defined as all randomized participants analyzed according to their allocated intervention group. A per-protocol analysis may be performed as a sensitivity analysis including participants who received the allocated procedure and completed the relevant outcome assessment without major protocol deviations.

13.3 Baseline Characteristics

Baseline demographic and clinical characteristics will be summarized by study group. Variables may include age, sex, body mass index, clinical presentation, diagnostic findings, comorbidities and other clinically relevant baseline parameters available in the study database. No formal hypothesis testing of baseline characteristics is required for the primary interpretation, but descriptive comparison will be provided.

13.4 Analysis of Primary Outcomes

Primary outcome	Planned analysis
Postoperative pain score at 24 hours	VAS pain scores at 24 hours will be compared between groups. If data are approximately normally distributed, an independent-samples t-test will be used. If normality assumptions are not met, the Mann-Whitney U test will be used. Mean or median differences with confidence intervals will be reported when appropriate.
Postoperative pain score at 7 days	VAS pain scores at 7 days will be analyzed using the same approach as the 24-hour pain outcome.
Change in GERD-HRQL score	GERD-HRQL scores will be summarized at each time point. Within-group change from baseline and between-group differences in change will be assessed. Depending on data structure and distribution, repeated-measures analysis, mixed-effects modelling, or non-parametric methods may be used. The main comparison will focus on the difference in postoperative improvement between the Nissen and Toupet groups.
Postoperative hospital stay	Length of postoperative hospital stay in days will be compared between groups using an independent-samples t-test or Mann-Whitney U test, depending on distribution.
Recurrence of gastroesophageal reflux symptoms	The presence of recurrent reflux symptoms at each follow-up time point will be summarized as counts and percentages and compared between groups using the chi-square test or Fisher exact test, as appropriate.

13.5 Analysis of Secondary Outcomes

Secondary outcome	Planned analysis
Operative time	Total operative time in minutes will be compared between groups using an independent-samples t-test or Mann-Whitney U test, depending on distribution.
Fundoplication time	Fundoplication time in minutes will be compared between groups using an independent-samples t-test or Mann-

Secondary outcome	Planned analysis
	Whitney U test, depending on distribution.
Gas-bloat symptoms	Gas-bloat symptoms will be summarized as counts and percentages at each follow-up time point and compared between groups using the chi-square test or Fisher exact test, as appropriate. If severity scoring is available, scores may be compared using parametric or non-parametric methods according to distribution.
Postoperative complications	Postoperative complications up to 30 days will be summarized by type and frequency. Overall complication rates will be compared between groups using the chi-square test or Fisher exact test, as appropriate. Serious or clinically relevant complications will be described individually in the final report.

13.6 Missing Data

The amount and pattern of missing data will be described for each outcome. The primary analysis will be based on available observed data for each outcome and time point. Participants with missing data for a specific outcome will be excluded from that specific analysis but retained in analyses for which data are available. If the amount of missing data is substantial, sensitivity analyses may be performed and the potential impact of missing data will be discussed in the final report.

13.7 Multiplicity

This study includes several clinical and functional outcomes. No formal adjustment for multiplicity is planned. Results will be interpreted in the context of the prespecified outcome hierarchy, clinical relevance, effect size and confidence intervals, not only p-values.

13.8 Interim Analysis

No formal interim efficacy analysis is planned. Safety issues will be monitored continuously according to standard clinical and institutional procedures.

13.9 Sample Size Considerations

The planned enrolment is 200 participants, with approximately 100 participants randomized to each intervention group. This sample size is intended to provide clinically useful comparative data on postoperative pain, reflux-related quality of life, recurrence of reflux symptoms and postoperative functional outcomes after the two fundoplication techniques. Rare complications may not be detected with sufficient precision in a study of this size.

14. Ethical Considerations

The study will be conducted in accordance with the principles of the Declaration of Helsinki, applicable national requirements, institutional policies and the approval of the relevant human subjects protection review board/ethics committee. Written informed consent will be obtained from all participants before enrolment. Participants will be informed about the study purpose, the randomized allocation to surgical technique, potential benefits, potential risks, confidentiality protections and the right to withdraw from the study according to applicable requirements.

15. Dissemination of Results

The results of the trial may be submitted for publication in peer-reviewed journals and presented at scientific meetings. Results will be reported in aggregated form. No publicly shared report will include information that directly identifies individual participants.

16. Protocol Amendments

Any substantive amendment to the protocol or statistical analysis plan will be documented, dated and submitted for ethics committee/institutional approval when required. The final version used for ClinicalTrials.gov results reporting should include all amendments approved before the time of results submission that apply to all clinical trial facility locations.

17. References

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6. Rantanen TK, Salo JA, Salminen JT, Kellokumpu IH. Functional outcome after laparoscopic or open Nissen fundoplication: a follow-up study. Arch Surg. 1999;134:240-244.
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18. Document Control

Version	Date	Description	Approval/Initials
1.0	19 June 2026	Initial integrated study protocol and statistical analysis plan prepared for trial registration/results documentation.	[insert]