Statistical analysis plan for the SPICY trial: Mesenteric SParIng versus extended mesentereCtomY in primary ileocolic resection for ileocaecal Crohn's disease – an international randomised controlled trial

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ABSTRACT

Background

Evidence suggest that the mesentery is involved in patients with Crohn's disease (CD). Data on the anti- or pro-inflammatory role of the mesentery are conflicting. It is suggested that extended mesenteric resection – removing an increased volume of mesentery – might result in decreased postoperative recurrence rates in patients undergoing ileocolic resection (ICR). The SPICY study was designed to analyse whether extended mesenterectomy is superior to mesenteric sparing ICR. This manuscript presents the statistical analysis plan (SAP) to evaluate the outcomes of the SPICY trial.

Design and methods: The trial was designed as an international randomised controlled superiority trial, allocating patients (1:1 ratio) to either group 1—mesenteric sparing ICR or group 2—extended mesenteric ICR, up to the level of the ileocolic trunk. To detect a clinically relevant difference of 25 per cent in endoscopic recurrence at 6 months, a total of 138 patients were required (including 10 per cent dropout). Patients aged ≥16 years with CD undergoing primary ICR were counselled for inclusion. Primary outcome is the 6-month postoperative endoscopic recurrence rate (modified Rutgeerts score ≥i2b), according to blinded central reading. Secondary outcomes were the centrally read degree of endoscopic recurrence, perioperative data, postoperative morbidity, histopathological outcomes and use of Crohn's medication postoperatively.

Discussion: The SPICY trial will provide comprehensive evidence whether mesenteric sparing resection or extended mesenterectomy is better in terms of recurrence rates in ileocolic Crohn's disease patients undergoing an ICR. Details of the statistical analysis are described in this SAP.

Registration number: NCT00287612 (http://www.clinicaltrials.gov)

Keywords: Statistical analysis plan, Crohn's disease, ileocolic, extended mesenteric resection, recurrence

INTRODUCTION

Background and rationale

Crohn's disease is a chronic inflammatory bowel disease (IBD) affecting the entire intestinal tract. Up to 75% of patients require surgery during the course of the disease.[1] Unfortunately, surgery is not curative. Despite all initiatives to reduce postoperative recurrence rates, recurrence of the disease is rather a rule than an exception. Today, the optimal anastomosis [2-6] and the role of the mesentery [7-11] are widely discussed topics in the field of surgery for patients undergoing ICR, aiming to reduce postoperative recurrence. As early as 1932, dr. Crohn described the 'creeping fat' – fat envelopment of the mesentery around inflamed parts of the bowel – as one of the hallmarks of CD and opted for extended resection as treatment of the disease. [12] Currently, data on the anti- or pro-inflammatory role of the mesentery are conflicting. There is increasing evidence that the mesentery is actively involved in CD and reports suggest that excision of the affected mesentery could reduce postoperative recurrence rates.[8, 9] However, prospective data of a randomised controlled trial are lacking.

The SPICY trial was designed as a randomised controlled international superiority trial to demonstrate superiority of an extended mesenteric resection in terms of postoperative recurrence rates. The trial protocol was previously published.[13] The present SAP focuses on outcomes up to six months of follow-up and adheres to the JAMA Guidelines for the content of statistical analysis plans in clinical trials of which the checklist is demonstrated in the Supplementary materials.[14] This document has been written based on the study protocol version 10, dated 03-04-2022 (approved 21-04-2022).

STUDY METHODS

Objectives

The aim of the SPICY study was to determine whether extended mesenteric resection results in reduced postoperative recurrence rates in CD patients undergoing ICR, compared to a mesenteric-sparing ICR. The primary outcome is the endoscopic recurrence rate at six months postoperatively, defined as a modified Rutgeerts score of ≥i2b, according to central reading.

The secondary outcomes are:

1. The degree of postoperative endoscopic recurrence (classified according to the modified Rutgeerts score), according to blinded central reading by two experts.
2. Perioperative data (i.e. operative time, per-operative blood loss, conversion rate)
3. Postoperative outcomes
    - Postoperative morbidity <30 days (length of hospital stay, anastomotic leakage and Clavien dindo score.
    - Histopathological data (length of resected colon, length of resected ileum, inflammation resection margins)
    - Postoperative medication (continuation Crohns' medication postoperatively, endoscopically guided start of Crohns' medication)

Framework

The SPICY trial was a superiority trial. The hypothesis for the primary analysis are as follows:

- Null hypothesis: There is no difference in the endoscopic recurrence rate between extended mesenteric resection and mesenteric sparing resection.
- Alternative hypothesis: There is a difference in the endoscopic recurrence rate between extended mesenteric resection and mesenteric sparing resection.

Trial design

The SPICY trial was a two-arm international randomised controlled superiority trial. Patients undergoing ICR for ileocolic Crohn disease were randomised for either group 1 - conventional mesenteric sparing resection or for group 2 - extended mesenteric resection.

In mesenteric sparing resection, the mesentery was divided close to the bowel, as currently advised in the ECCO guidelines. [15] In the extended mesenteric resection, the mesentery was removed up to the origin of the ileocolic trunk. After identification of the ileocolic junction, the lower edge of the ileal branch of the ileocolic artery was followed distally, figure 1. The rest of the operation remained identical in both groups. A video vignette of the surgical procedure was published and shared with all participating centres as an example.[16]

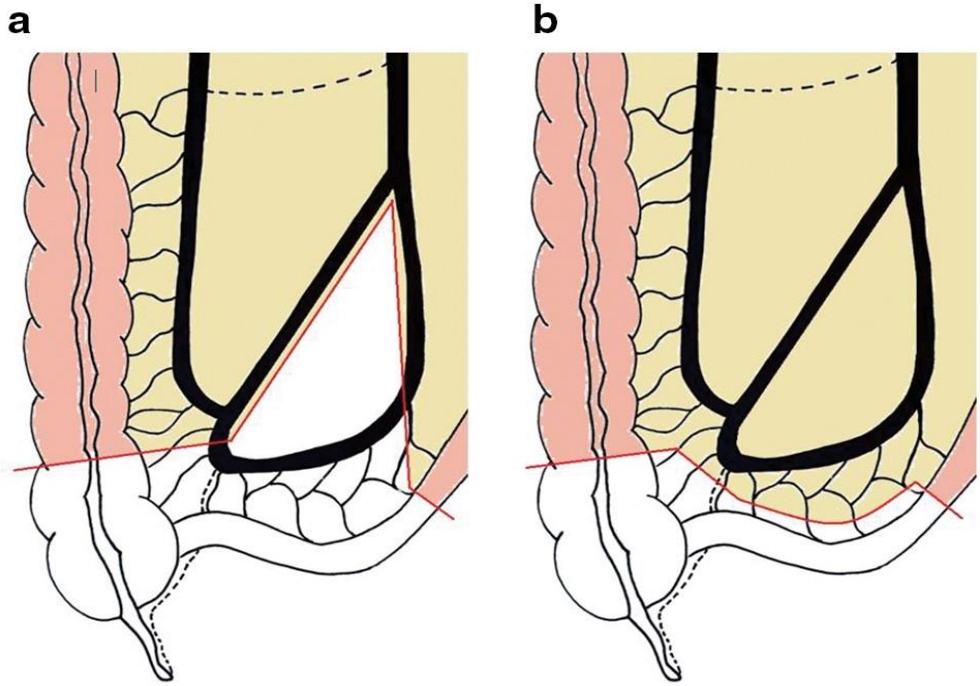

Figure 1. Surgical technique: a) Extended mesenteric resection following the lower edge of the ileocolic trunk; b) Mesenteric sparing ileocolic resection.

Both groups followed standard postoperative care. Six centres participated in this trial in the Netherlands and Italy. The SPICY trial was registered under registration number NCT04538638 on August 31th 2020.

STUDY POPULATION

Sample size

This study was powered to detect a clinically relevant difference of 25 per cent in endoscopic recurrence at 6 months between the two techniques: 60 per cent versus 35 per cent (a risk reduction of 45 per cent). Assuming a chi-square test for two independent proportions powered at 80 percent and a two-sided α-level of 0.05, a total of 62 patients in each surgical arm are required, for a total enrolment of 124 patients. Allowing for a 10 percent dropout, the aim was to enrol 138 patients.[13]

Screening for eligibility and recruitment

Patients were screened for eligibility using the inclusion and exclusion criteria, as reported in the study protocol. [13] The number of eligible patients who did not want to participate will be reported and presented in the CONSORT flow diagram, figure 2.

Randomisation

Eligible patients who consented were randomly assigned (1:1 ratio) to group 1 or group 2 by the research team, using CASTOR EDC randomisation software version 1.4. Randomisation was not stratified. In this study, patients, endoscopists and central readers were blinded to treatment allocation. Surgeons were not blinded.

STATISTICAL PRINCIPLES

Analyses methods

All statistical tests will be two-sided and results will be presented with 95% confidence intervals. P-values of less than 0.05 will be considered statistically significant. Missing data in baseline characteristics or outcomes will be reported.

Baseline patient characteristics

Baseline characteristics of the included patients will be reported by randomisation group and presented in table 1. Categorical variables will be summarised as numbers and percentages in each category. These data will be analysed using the chi-square or Fisher's exact test, depending on cell count. Continuous variables that are normally distributed will be summarised by mean and standard deviation; median and interquartile range in case of non-normal distribution. The distribution is checked using histograms and boxplots. Analysis of continuous variables will be performed using the Student's t-test and the Mann-Whitney U-test. Differences between study arms will be reported.

Outcomes

The primary endpoint, endoscopic recurrence rates, will be compared between two groups with Chi square testing (table 2). Secondary outcomes will be analysed using chi-Square or Fisher's exact test, as appropriate (table 3, 4). The degree of endoscopic recurrence, centrally read, will be presented in a bar chart, figure 3.

The latest available version (currently v.28) of the statistical program SPSS® (IBM, Armonk, New York, USA) will be used to perform analyses.

Additional analyses not mentioned in this analysis plan, but performed in response to journal reviewers will explicitly be qualified as post hoc.

Adherence and protocol deviations

Protocol deviation and violation

Protocol deviations were predefined as follows:

- Not receiving the surgical treatment as assigned by randomisation, whether or not due to technical reasons.
- No endoscopy postoperatively.

Protocol violations are predefined as follows:

- Postoperative diagnosis other than Crohn's disease.
- Not receiving an anastomosis (in case of a (definitive-) stoma).

Handling protocol deviations and violations, lost to follow up and withdrawal

For each group the number of patients with protocol violation and deviation will be reported and specified with reasons. In case of withdrawal of consent and lost to follow-up, the number of patients will be reported, figure 2.

- In case of protocol violation, patient data will not be available for analyses and patients will be excluded from the trial.
- In case of protocol deviation patients will be included in the ITT analysis
    - Not receiving the surgical treatment as assigned by randomisation, whether or not due to technical reasons → patients will be included in the ITT analysis according to the originally assigned study arm at baseline
    - No endoscopy postoperatively → if a patient meets the 6 months follow up, but endoscopy could not be performed due to patients specific reasons (i.e. pregnancy), or the quality was insufficient to score endoscopic recurrence, MR or ultrasound to define recurrence will be accepted for the ITT analysis.
- In case of withdrawal of consent, patient data will not be available for analysis and patients will be excluded from the trial.
- Patients who are lost to follow up prior to the primary endpoint will be excluded from all outcome analyses. Baseline data will be reported.

Analysis populations

Data analyses will be conducted according to the intention-to-treat (ITT) principle. All included patients will be analysed according to their originally assigned study arm at baseline.

Two additional analyses will be considered:

- Per protocol analysis:

  In the case of > 5% protocol deviations, a per-protocol analysis will be performed for patients who received endoscopy with a central reading score. All patients with a protocol deviation will excluded from this analysis.

- As treated analysis:

  In the case >5% patients not receiving their intervention as indicated by randomisation, an additional 'as treated' analysis will be presented with patients analysed in the study arm of the received treatment.

Timing of final analyses

The SPICY trial was considered a low-risk trial by the Medical Ethical Committee of the Amsterdam UMC. Therefore, no data safety monitoring board was set up and no interim analysis was planned.

The statistical analysis of the primary (endoscopic recurrence) and secondary outcomes as previously described, will be performed and presented in the initial manuscript when every patient has reached six months follow-up, data entry and cleaning has been completed.

Figure 2. CONSORT FLOW diagram SPICY, intention to analysis for primary outcome parameter

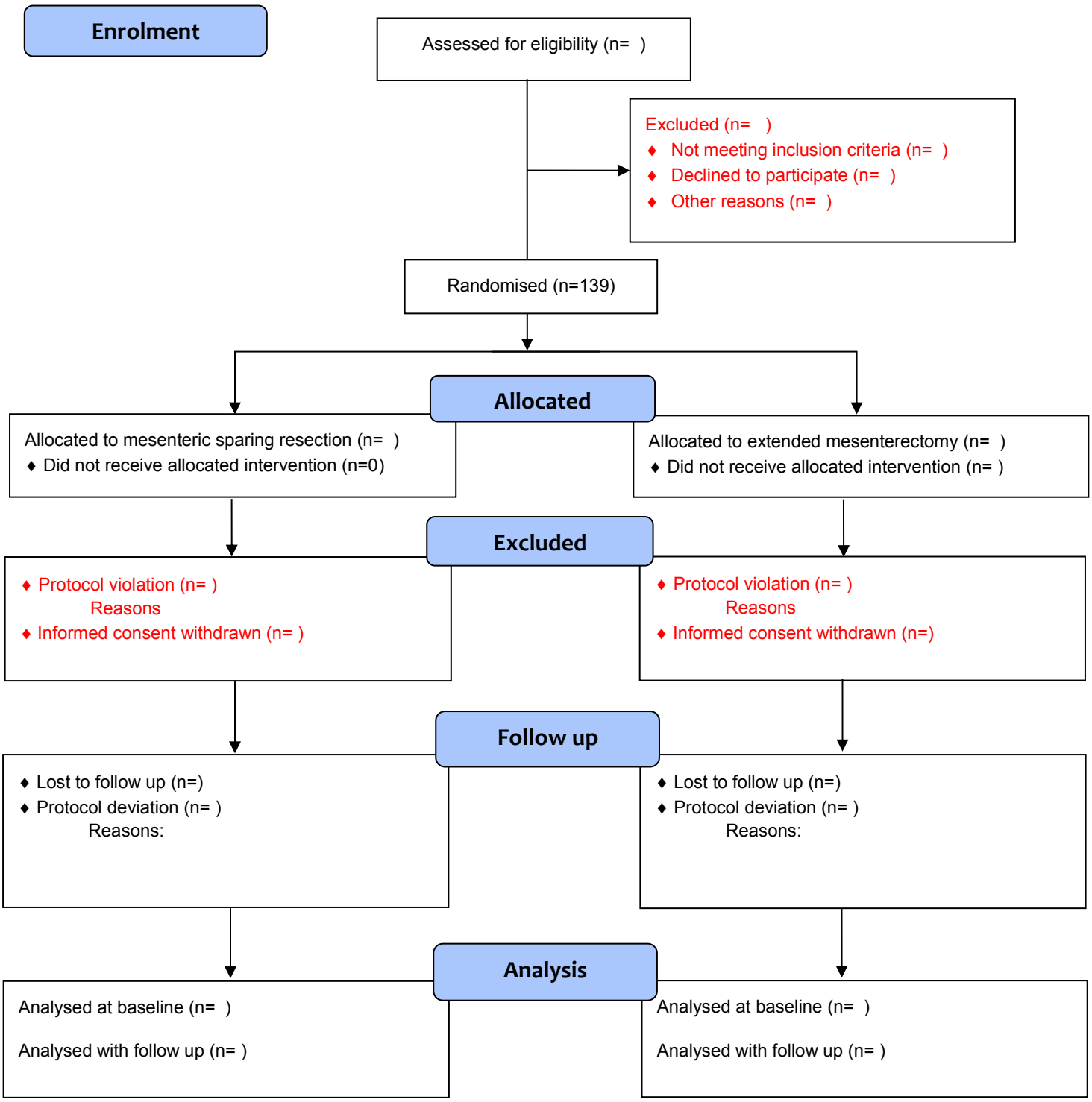

Table 1 Baseline characteristics			
n (%), median (IQR)	*Extended mesenterectomy (n=)*	*Mesenteric sparing (n=)*	*p-value*
Age at surgery, *years*			
Sex (male)			
Disease duration at surgery, *months*			
Smoker			
Active			
Ex-smoker			
BMI (kg/m^2)			
Age at onset			
A1, ≤16 years			
A2, 16-40 years			
A3, ≥40 years			
Behaviour of disease			
B1, inflammatory			
B2, stricturing			
B3, penetrating			
Perianal disease			
Location of disease			
L1, terminal ileum			
L3, ileocolic			
Crohns' medication <12weeks before operation			
No medication			
Thiopurines			
Steroids			
Biologicals			
Small molecules			
BMI: body mass index			

Table 2. Primary outcome			
n%, median (IQR)	*Extended mesenterectomy (n=)*	*Mesenteric sparing (n=)*	*P* value
Endoscopic recurrence rate,			
Time between surgery and endoscopy, *months*			

Table 3. Secondary outcomes Outcomes central reading			
n (%)	*Extended mesenterectomy (n=)*	*Mesenteric sparing (n=)*	*P* value
Endoscopic recurrence rate, according to the modified Rutgeerts score			

**Degree of recurrence, according to tmodified Rutgeerts score will be presented in a bar chart, figure 3*

Table 4. Secondary outcomes Perioperative outcomes			
n%, median (IQR)	*Extended mesenterectomy (n=)*	*Mesenteric sparing (n=)*	*P* value
Per-operative data			
Operating time, *hours*			
Operative blood loss, *cc*			
Conversion rate			
Postoperative morbidity <30 days			
Length of hospital stay, *days*			
Anastomotic leakage			
Clavien Dindo score			
Histopathological data			
Radical resection			
Both sides no inflammation			
Distal inflammation			
Proximal inflammation			
Inflammation on both sides			
Length of resected ileum, *cm*			
Length of resected colon, *cm*			
Postoperative medication			
Continuation of Crohn medication immediately after surgery			
No medication			
Thiopurines			
Biologicals			
Small molecules (JAK)			
Endoscopically guided start of postoperative Crohn medication			
No medication			
Thiopurines			
Biologicals			
Small molecules (JAK)			
Total on medication after 6 months			

Harms

Serious Adverse Events (SAEs) are registered at the Central Committee on Research Involving Human Subjects (CCMO) and will be presented in the manuscript. All postoperative complications and needed re-interventions will be reported as secondary outcome parameter in postoperative morbidity.

MANUSCRIPT AND AUTHORSHIP

The SPICY study group will share the results irrespective of the outcomes. The manuscript will be submitted on behalf of the SPICY study group, the coordinating study team will be mentioned as co-authors. The coordinating investigator and principal investigator will be respectively first and senior author on the manuscript. Members of the SPICY study group will be mentioned in alphabetical order.

DISCUSSION

This SAP describes the intended analyses of data collected throughout the study upon completion of follow-up of the respective outcome. By publishing the SAP, we aim to increase the transparency of data analyses.

Challenges

The main challenge of the SPICY study was conducting the study and ensuring adequate follow-up during the COVID pandemic. In the published protocol, the primary endpoint was defined as endoscopic recurrence after six months. ECCO guidelines recommend surveillance endoscopy between 6 months and 1 year after surgery. Therefore, endoscopies performed later, due to longer waiting lists, were accepted (maximum median of 1 year per group is accepted).

Another challenge in designing the SPICY study concerned defining the eligible population. For this study, external validity was considered more important than internal validity because there are too many confounding factors during the perioperative phase (i.e. surgical procedure, anastomotic configuration and type of anastomosis, radicality of resection, presence of a perianal fistula and use of postoperative medication for other reasons). Therefore, a more heterogeneous group representative of the target population undergoing ICR surgery was included.

Finally, all patients in whom a recurrence was assessed around 6 months postoperatively were included in the ITT analysis. The aim of this study was to analyse whether extended mesenterectomy lowers the risk of developing postoperative recurrence (objectified by endoscopy, MR or ultrasonography). In the context of external validity, we present all results from patients with completed follow-up (ITT analysis). The percentages and degree of endoscopic recurrences, according to central reading, is presented separately.

Funding

The SPICY trial is an investigator study, with funding from TKI-LSH with no influence on protocol writing, data collection and interpretation or access to data.

Author's contribution

Van der Does de Willebois, Buskens, Bemelman and van Dieren have made substantial contributions to the concept and design of the SAP and have been involved in drafting this manuscript. Van Dieren elaborated to the considerations of the statistical analyses. All other authors participated in the critical revision of the manuscript for intellectual content and approved the final version.

Ethics approval and consent to participate

This study has been approved by the Amsterdam UMC Medical Ethical Committee. The protocol is registered by the Dutch Central Committee on Research Involving Human Subjects (NL61632.018.18). For all other participating centres, approval of the local ethical committee and/or board of directors was obtained. This study has been performed in accordance with the principles of Good Clinical Practice.

Availability of data and materials

The data that support the findings of this study are available, upon reasonable request.

Competing interests

None to declare.

List of abbreviations

BMI – Body mass index; CCMO - Central Committee on Research Involving Human Subjects; CD – Crohn's disease; ECCO – European Crohns and Colitis Organisation; ICR – ileocolic resection; ITT – intention to treat; IQR – interquartile range; SAE - Serious Adverse Events; SAP – statistical analysis plan

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