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A prospective, randomized, multicentre, open-label trial, designed to evaluate the best timing of closure of the temporary ileostomy (early versus late) in patients who underwent rectal cancer resection and with indication for adjuvant chemotherapy. The STOMAD (STOMa closure before or after ADjuvant therapy) randomized controlled trial.

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Title page:

A prospective, randomized, multicentre, open-label trial, designed to evaluate the best timing of closure of the temporary ileostomy (early versus late) in patients who underwent rectal cancer resection and with indication for adjuvant chemotherapy. The STOMAD (STOMa closure before or after ADjuvant therapy) randomized controlled trial.

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Abstract:

Introduction: Temporary ileostomy is a valuable aid in reducing the severity of complications related to rectal cancer surgery. However, it is still unclear what is the best timing of its closure in relation to the feasibility of an adjuvant treatment, especially considering patient-reported outcomes and health system costs. The aim of the study is to compare the results of an early versus late closure strategy in patients with indication to adjuvant chemotherapy after resection for rectal cancer.

Methods and analysis: This is a prospective multicentre randomized trial, sponsored by *Rete Oncologica Piemonte e Valle d'Aosta* (Oncology Network of Piedmont and Aosta Valley - Italy). Patients undergone to rectal cancer surgery with temporary ileostomy, aged >18 years, without evidence of anastomotic leak and with indication to adjuvant chemotherapy will be enrolled in 28 Network centres. An early closure strategy (between 30 and 40 days from rectal surgery) will be compared to a late one (after the end of adjuvant therapy). Primary endpoint will be the compliance to adjuvant chemotherapy with and without ileostomy. Complications associated with stoma closure as well as quality of life, costs, and oncological outcomes will be assessed as secondary endpoints.

Ethics and dissemination: The trial will engage the Network professional teams in a common effort to improve the treatment of rectal cancer by ensuring the best results in relation to the most correct use of resources. It will take into consideration both the patients' point of view (patient-reported outcome) and the health system perspective (costs analysis). The study has been approved by the Ethical Review Board of *Città della Salute e della Scienza* Hospital in Turin (Italy). The results of the study will be disseminated by the Network website, medical conferences and peer-reviewed scientific journals.

Trial registration: ClinicalTrials (www.clinicaltrials.gov) NCT04372992

Keywords: rectal cancer; temporary ileostomy; early closure; late closure; postoperative morbidity; adjuvant chemotherapy; randomized controlled trial.

Strengths and limitations of the study:

- STOMAD is a randomized trial aimed at improving the quality of life of patients with a temporary stoma while optimizing health system costs (value-based health care). It may contribute to boost interest in healthcare delivery research.
- The study will be conducted in the context of an oncology network that encompasses all the centres for the treatment of rectal cancer in the north-western area of Italy. The results of the experimentation could have an immediate impact on treatment protocols of the network centres and will have a high external validity given the large multicentric territorial setting.
- The results will be analysed taking into account the point of view of patients (patient-reported outcome analysis).
- The principal weakness of the study is the highly selected nature of the patient population. The strict inclusion criteria might slow the accrual rate.

INTRODUCTION

The temporary ileostomy is effective in reducing the severity of anastomotic complications in anterior resections for tumours of the rectum at risk of dehiscence and is therefore widely used, particularly after radiotherapy treatment. (1) In patients with indication for adjuvant chemotherapy, current practice consists of closing the stoma after the end of treatment.

The prolonged presence of the stoma can however favour the onset of stoma-related complications, such as prolapse, parastomal hernia, mechanical ileus, high-flow dehydration, and damage to kidney function. Ostomy-related complications may require unscheduled hospitalizations and result in increased costs. (2) In addition, the presence of the stoma impacts on patients' quality of life, causing alteration of the body image and imposing changes in the daily routine, lifestyle, and sexual sphere. (3, 4) Therefore, early closure of the ileostomy has been proposed in patients without signs of postoperative fistula.

The early closure (within one month of surgery) of the temporary ileostomy resulted not inferior to late closure (over 12 weeks) in 2 randomized studies that evaluated postoperative complications as an outcome. (5, 6) Early closure saves days of life with ileostomy for the patient and costs related to ostomy care for the health system and could represent the most desirable and convenient choice. (7) It was also associated with better long-term functional results in a secondary analysis of a randomized study. (8) However, in patients with indication for adjuvant therapy, it is not known what the best timing is for closing the stoma (before the start, during or at the end of the treatment) in terms of therapy tolerability, quality of life and overall costs. (9)

Both a start date delayed more than 8 weeks from surgery (10) and a received dose <70% of that planned (11) have been reported to reduce the effectiveness of adjuvant therapy in colorectal cancer patients. The presence of a stoma or the consequences of its early closure may interfere with an optimal delivery of chemotherapy. A recent multicentre retrospective study reported an increase

in gastrointestinal toxicity in chemo-treated patients with stoma, with significant reduction in treatment compliance. (12) On the other hand, early closure of the stoma could reveal an anterior resection syndrome (LARS) before chemotherapy, with a potential negative impact on the tolerability of the treatment itself, (13) or delay its initiation due to postoperative complications. (14)

This randomized study aims to identify the best timing for the stoma closure in relation to adjuvant therapy in terms of compliance to chemotherapy, complications, costs and quality of life (QoL).

METHODS AND ANALYSIS

STOMAD is a multicentre open-label randomized phase III trial designed to evaluate the best timing of the closure of temporary ileostomy in patients operated on for rectal cancer and with indication for adjuvant chemotherapy.

Objectives

1. Primary objective

   • To compare the compliance with adjuvant therapy between early and late closure of temporary ileostomy.

   The compliance with adjuvant chemotherapy in relation to the timing of ileostomy closure (before the start or after the end of treatment) will be assessed considering any therapeutic delay or dose reduction compared to the initially planned.

2. Secondary objectives

   To compare patients with early and late closure of temporary ileostomy in terms of:

   • Surgical morbidity

   • Chemotherapy toxicity

   • Patient-reported quality of life

- Costs
- Progression free survival (PFS)
- Overall survival (OS)

Target population and setting

Patients undergone to rectal resection (+/- neoadjuvant therapy) for cancer with protective ileostomy and candidates for adjuvant chemotherapy in the Centres for the treatment of colorectal neoplasms recognized by *Rete Oncologica Piemonte e Valle d'Aosta*.

The list of participating centres is reported in Table 1.

Table 1. List of participating centres

Local PI	Local trial manager	Centre	Location
Paolo Millo	Elisa Ponte	AUSL Aosta – Surgical Unit – Parini Hospital	Aosta
Mario Morino	Massimiliano Mistrangelo	AOU Città Salute e Scienza – Academic Surgical Unit – Molinette Hospital	Torino
Paolo De Paolis	Mauro Santarelli	AOU Città Salute e Scienza – Surgical Unit – Molinette Hospital	Torino
Alessandro Ferrero	Paolo Massucco	AO Ordine Mauriziano – Surgical Unit – Umberto I Hospital (Coordineting centre)	Torino
Maurizio Degiuli	Rossella Reddavid	AOU S. Luigi Gonzaga – Academic Surgical Unit – S. Luigi Hospital	Orbassano (TO)
Roberto Saracco	Francesco Tomaselli	ASL Città Torino – Surgical Unit – Martini Hospital	Torino
Mauro Garino	Simone Birolo	ASL TO3 – Surgical Unit – Infermi Hospital	Rivoli (TO)
Andrea Muratore	Marcello Calabrò Nicoletta Pipitone	ASL TO3 – Surgical Unit – Agnelli Hospital	Pinerolo (TO)
Lodovico Rosato	Luca Panier Suffat	ASL TO4 – Surgical Unit – Civile Hospital	Ivrea (TO)
Eraldo Personnettaz	Monica Carrera	ASL TO4 – Surgical Unit – Ciriè Hospital	Ciriè (TO)
Pietro Cumbo	Francesco Potente	ASL TO5 – Surgical Unit – S. Croce Hospital	Moncalieri (TO)
Felice Borghi	Maria Carmela Giuffrida	AO S. Croce e Carle – Surgical Unit – S. Croce Hospital	Cuneo
Franco Bertolino	Marco Brunetti	ASL CN1 – Surgical Unit – SS. Annunziata Hospital	Savigliano (CN)
Andrea Gattolin	Roberto Rimonda	ASL CN1 – Surgical Unit – Regina Montis Regalis Hospital	Mondovì (CN)
Marco Calgaro	Vincenzo Adamo	ASL CN2 – Surgical Unit – S. Lazzaro Hospital	Alba (CN)
Fabio Priora	Igor Monsellato Domenico Piscioneri	AO SS. Antonio e Biagio e Cesare Arrigo - Surgical Unit – SS. Antonio e Biagio Hospital	Alessandria
Marco Amisano	Francesco Cravero	ASL AL – Surgical Unit – S. Spirito Hospital	Casale Monf.to (AL)
Alberto Serventi	Alberto Serventi	ASL AL – Surgical Unit – Mons. Galliano Hospital	Acqui Terme (AL)
Carmine Di Somma	Eliana Giaminardi	ASL AL – Surgical Unit – S. Giacomo Hospital	Novi Ligure (AL)
Vincenzo Sorisio	Luca Mazza	ASL AT – Surgical Unit – Cardinal Massaia Hospital	Asti
Sergio Gentilli	Paolo Bellora	AOU Maggiore Carità – Academic Surgical Unit – Maggiore Hospital	Novara
Raffaele Romito	Fabio Colli	AOU Maggiore Carità – Surgical Unit – Maggiore Hospital	Novara
Roberto Polastri	Roderto Perinotti	ASL BI – Surgical Unit – Infermi Hospital	Biella
Silvio Testa	Clemente De Rosa	ASL VC – Surgical Unit – S. Andrea Hospital	Vercelli
Sandro Zonta	Francesco Battafarano Renza Trapani	ASL VCO – Surgical Unit – S. Biagio Hospital ASL VCO – Surgical Unit – Castelli Hospital	Domodossola (VB) Verbania (VB)
Dario Ribero	Alfredo Mellano	FPO – Colorectal Surgical Unit – IRCCS	Candiolo (TO)
Renzo Leli	Paola Bellomo	Surgical Unit – Humanitas Gradenigo Hospital	Torino
Carlo Bima	Enrico Gibin	Surgical Unit – Cottolengo Hospital	Torino

Enrolment

Inclusion criteria

- Patients undergone to radical intestinal resection (R0) for rectal neoplasia with protective ileostomy.
- Age >= 18 years.
- Absence of fistula (enema and/or endoscopy)
- Indication to adjuvant chemotherapy
- Informed consent

Exclusion criteria

- ASA >3
- UICC stage IV
- ECOG Performance Status >=2
- Urgently closed stoma (before randomization) for stoma-related complications
- Severe and non-controlled systemic, oncologic, or infectious disease

Before enrolment, the patient shall not show signs of ongoing complications. The integrity of the colorectal anastomosis will be confirmed with an enema and/or endoscopy according to local standards starting 15 days after surgery.

The presence of a discontinuation of the anastomotic rhyme in endoscopy or of a spreading of any entity of the contrast medium on the enema will represent an exclusion criterion. All patients will simultaneously perform an oncological evaluation to establish the indication for adjuvant therapy in the presence of the definitive histological examination. Patients without signs of anastomotic complications and with indication for adjuvant therapy will be enrolled for study by the local investigators. Enrolment and randomization must take place within 21 days of the intervention.

The subjects who are eligible for the study, after the informed consent has been signed, will be stratified by previous neoadjuvant treatment (yes or no) and by the proposed adjuvant chemotherapy scheme (with or without platinum derivatives), and then randomized to one of the following arms:

- Arm A (experimental): closure of the stoma between 30 and 40 days after surgery on the rectum, before starting adjuvant therapy.

- Arm B (standard): closure of the stoma starting from 15 days and within 60 days from the end of the adjuvant therapy. The anastomosis instrumental evaluation will be repeated after the end of chemotherapy in this group.

Endpoint definition

1. Primary endpoint.

   Proportion of patients with adequate compliance with adjuvant treatment.

   Compliance with adjuvant therapy will be considered adequate if both of the following criteria are met:

   • start of adjuvant therapy within the 70th day (<= 10 weeks) after surgery on the rectum; and

   • total cumulative dose delivered, compared to the theoretical planned, >= 70%.

   Failure to adhere to at least 1 of the two criteria will correspond to a failure (inadequate compliance). Patients with missing or non-performed assessment of compliance for any reason will also be considered unsuccessful adherence.

2. Secondary endpoints.

   • Morbidity. Incidence of complications related to the presence or to the closure of the ileostomy, during hospitalization or after discharge, using the Clavien-Dindo classification. Individual patient events, hospitalizations and reoperations will be recorded.

- Chemotherapy toxicity. All adverse events according to CTCAE version 5.0 classification will be considered.
- QoL. Patient-reported quality of life will be measured at the baseline and at defined time points using validated questionnaires (EORTC C30 and CR29, EQ5D).
- Costs. The costs related to hospitalization, outpatient visits, ostomy care supplies and the management of complications and toxicity will be assessed.
- Progression free survival (PFS), defined as the time elapsed between the randomization date and the date of progression/death for any cause or the latest follow up available.
- Overall survival (OS), defined as the time elapsed between the randomization date and the date of death for any cause or the latest follow up available

Patients will be followed for the duration of the study, regardless of the clinical course, and will conclude the active follow-up with a final evaluation 12 months after randomization in both study arms. A longer follow-up, based only on routinely recorded data, will be conducted to assess long term overall survival. Enrolment is expected to start in September 2020.

The study flow diagram is depicted in Figure 1.

Surgical technique and medical therapy

Hospitalization will normally take place the day before or the morning of surgery. Antibiotic-prophylaxis (usually short-term with cefazoline within half an hour after skin incision) and thrombus-embolic prophylaxis will be performed according to national guidelines.

The stoma closure will be performed manually or mechanically according to the surgeon's judgment. The suture of the skin incision will be linear or purse-string according to the local standards.

The postoperative management will be based on the ERAS strategy (early feeding and mobilization). Discharge criteria will be passage of gas, adequate oral feeding, and good pain control.

Adjuvant chemotherapy will be administered, in terms of indications, drugs and schedules, according to the national guidelines (AIOM) and according to the consensus documents of the Colorectal Study Group of the Oncology Network (http://www.reteoncologica.it/area-operatori/gruppi-per-patologie/raccomandazioni-di-rete).

The ideal temporal target for the start of chemotherapy will be within 8 weeks of surgery on the rectum; the maximum time within 10 weeks. Randomized patients starting after this term are still followed up and evaluated until the end of follow-up for the evaluation of the other endpoints.

Endpoints assessment and follow-up

1. Morbidity

Complications related to stoma closure surgery, which occurred both during and after hospitalization, will be recorded according to the Clavien-Dindo classification. Their overall weight per patient will be calculated through the CCI. Management problems and complications from the stoma presence will also be recorded. All reinterventions and hospitalizations during the study period will be captured.

2. Adjuvant therapy

Chemotherapy toxicity will be evaluated according to the CTC-EORTC. Prophylaxis and treatment of side effects and dose reductions will be applied according to international standards (NCI-CTCAE criteria). Starting date of the treatment, dose reductions and therapeutic scheme variations, suspensions or interruptions will be recorded. In relation to the total dose and the total number of programmed cycles, the percentage of completeness of the adjuvant therapy will be calculated. Grade and type of adjuvant therapy toxicity will be recorded for each patient.

3. QoL

Quality of life will be measured using the EORTC C30, CR29 and EQ5D validated questionnaires. The questionnaires will be administered, in both arms, upon enrolment (baseline), at the beginning of the 4th cycle of adjuvant therapy and at 12 months after the intervention on rectal cancer.

The LARS score will be used to evaluate intestinal and sphincter function at 12 months after the rectal intervention in both arms (in the control group if ostomy closed since at least 2 months).

4. Costs

The costs will be estimated considering the days of hospitalization related to the closure of the stoma, the treatment of complications or toxicity, the outpatient visits during the study period and the amount of supplies for stoma care. Regional averages costs will be used as the basic cost unit.

Statistical considerations

1. Sample size

The sample size was calculated in relation to the main objective. Based on the available literature data, the null hypothesis (proportion of patients with adequate compliance to the adjuvant treatment in patients with closure of the stoma after treatment) is equal to 0.70. The alternative hypothesis is an increase in the proportion up to 0.85, with an absolute increase of 0.15. This increase is considered clinically relevant. With a two-tailed alpha error of 0.05 and a power of 0.80, the sample size required is at least 242 patients (121 for each treatment arm). Taking into account a maximum drop-out rate of approximately 10%, the total number of patients enrolled and randomized will be 270. The estimated study duration is 36 months.

2. Randomization

The randomization list, stratified by neoadjuvant therapy (yes/no) and by type of planned adjuvant chemotherapy (fluoropyrimidine +/- platinum derivatives) will be generated by the Clinical Epidemiology Unit of *Città della Salute e della Scienza* University Hospital in Turin, using a block procedure of variable length in random order, completely concealed to clinicians. The 1:1

randomization will be done online. After entering the inclusion/exclusion criteria and the stratification variables into the database, the patient will be randomized and registered in arm A or B. The computerized randomization system will be accessible continuously.

3. Analysis

The principal analyses will be carried out on all subjects randomized according to the assigned treatment arm (intention to treat principle). The demographic and baseline characteristics will be described for the whole study population and for each treatment arm. Discrete variables will be summarized by frequencies and percentages. The continuous variables will be summarized with the use of standard measures of central tendency and dispersion (mean and standard deviation or median deviation and interquartile range). The analysis of the primary endpoint will be based on the comparison of treatment compliance between the two arms by means of a stratified chi-square test. As a sensitivity analysis, further potential confounders detected at the baseline will be included in a logistic regression model. OS and PFS, calculated from the randomization date, will be assessed with the Kaplan-Meier method and the differences in survival (overall and disease-free) will be tested using the stratified Log-rank test. The Hazard Ratios (HR), adjusted for the stratification criteria and the main prognostic factors, and the relative confidence intervals (95% CI) will be estimated using the Cox model. Planned subgroup analyses will be carried out for the two stratification factors of the randomization (neoadjuvant treatment and adjuvant chemotherapy) and by age (divided into 3 classes according to the tertiles). The incidence of individual adverse events during hospitalization will be compared using the chi square test or the exact Fischer test, as appropriate. The comparison on the quality of life will be evaluated by comparing the average score between the two groups with the Student's T test (or with a non-parametric test, if necessary) and with generalized linear mixed model to take into account the repeated measurements over time on the same subjects. Per protocol analyses will be performed for exploratory purposes.

Data collection

The data will be collected in each participating centre by filling in an electronic CRF (eCRF). A local study manager will be identified for each participating centre. The completeness and congruity of the data will be checked periodically by a central study monitor and overviewed the study's Steering Committee. The central monitor and Steering Committee will refer to the local managers for any request for clarification.

ETHICS AND DISSEMINATION

The *Rete Oncologica Piemonte e Valle d'Aosta* is a multidisciplinary organization that includes specialists involved in the treatment of cancer disease in the north-western territory of Italy. The aim of the Oncology Network is to reduce the variability of treatments, guarantee uniform access to and improve the quality of cancer care. To this end, the Network issues recommendations, drafted through a peer review process by its members, and defines the criteria for the designation as referral centres for cancer specific procedures.

STOMAD is a non-profit study conducted within the Network centres and is part of the research branch aimed at improving the healthcare delivery system. It is proposed to investigate which is the best adjuvant treatment delivery strategy in relation to the presence of the stoma for patients operated on for rectal cancer, taking into consideration both the patient's point of view (patients reported outcome) and the health system perspective (costs analysis).

The study will be conducted according to the principles of the Helsinki Declaration and the ICH Guideline for Good Clinical Practice. It will be approved by the reference Ethics Committee of each participating centre. Each enrolled patient must express a written consent. Consent can be revoked at any time. Patients data will be collected on an existing online platform created by the Clinical Epidemiology Unit of the main centre in the region, which will also be responsible for all statistical

analyses. The data collected for the study will be processed in accordance with current national legislation (Personal Data Protection Code). The trial Steering Committee may request the premature termination of the study in case of adverse events with severity and frequency significantly higher than expected or if the primary end point in the experimental group is significantly worse than the control group before the end of the study. For these evaluations, the Steering Committee will not use pre-defined statistical criteria (statistical stopping rules) but will base the decision on a careful quantitative and qualitative evaluation of the events that will be discussed in scheduled meetings.

This trial will engage the Network professional teams in a common effort to improve the treatment of rectal cancer by ensuring the best results in relation to the most correct use of resources (value-based health care). Other positive effects could be the strengthening of collaboration relationships between the Network centres and the definition of a common platform for future Network research.

The results of this study will be presented at national and international meetings and reported in the Network website. A manuscript with the final results will be submitted for publication in a peer-reviewed journal.

Abbreviations:

AIOM: Associazione Italiana Oncologia Medica
ERAS: Enhanced Recovery After Surgery protocol
ASA: American Society of Anesthesiologists
ECOG PS: Eastern Cooperative Oncology Group – Performance Status
UICC: Union for International Cancer Control
CCI: Comprehensive Complication Index
CTC-EORTC: Common Toxicity Criteria – European Organization for Research and Treatment of Cancer
NCI-CTCAE: National Cancer Institute – Common Terminology Criteria for Adverse Events
OS: Overall survival
PFS: Progression Free Survival
QoL: Quality of Life
LARS: Low Anterior Resection Syndrome
e-CRF: electronic Case Report Form
ICH: International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use

Figure legend:

Figure 1. Study flow diagram

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Declarations:

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Authors' contributions

PM proposed the conception and design of the study protocol. APF, MM, SP, GC, CG, MCG, DM, IM, MKP, RP, PR, CM and FS contributed to the initial conception, design, and the drafting of the protocol and represent the trial Steering Committee. EP, MM, MS, FT, RR, SB, MC, NSP, LPS, MC, FP, MB, RR, VA, DP, FC1, AS, EG1, LM, PB1, FC2, CDR, FB, RT, AM, EG2 and PB2 evaluated and approved the protocol and will be responsible for local patient accrual and data registration. All authors have approved the final submitted manuscript.

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Ethics approval
The study has been approved by the Ethical Review Board of *Azienda Ospedaliera Universitaria Città della Salute e della Scienza,* Turin (Italy).

Funding
STOMAD is a non-profit clinical trial sponsored by *Rete Oncologica Piemonte e Valle d'Aosta,* Italy (http://www.reteoncologica.it/). It will not receive external funding.

Competing interests
The authors declare that they have no competing interests.

Data availability
Anonymized trail data will be available for 36 months after the results publication upon request to the principal investigator. Data will be provided in electronic dataset format containing deidentified participant files by the Unit of Epidemiology of the *Azienda Ospedaliera Universitaria Città della Salute e della Scienza,* Turin (Italy) after evaluation and approval of the request by the trial steering committee.

Patients and Public involvement
Patients organizations were not involved in the conception and drafting of the trial. Hoverer, the endpoints were specifically designed to include patient-reported outcomes and validated quality of life questionnaires will be applied throughout the trial timeline.

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Patient Population

Curative resection for rectal neoplasm with temporary ileostomy and indication to adjuvant therapy

ACCRUAL

EXCLUSION CRITERIA

- ❑ ASA >3
- ❑ IV stage
- ❑ ECOG Performance Status >=2
- ❑ Severe non-controlled systemic, oncological or infectious disease

INCLUSION/EXCLUSION CRITERIA EVALUATION

INCLUSION CRITERIA

- ❑ >= 18 years
- ❑ No fistula (enema and/or endoscopy)
- ❑ Indication to adjuvant therapy
- ❑ Consent signed

ENDOSCOPY/ENEMA

ANASTOMOTIC LEAK

RANDOMIZATION

TREATMENT

ARM A
experimental

EARLY ILEOSTOMY CLOSURE

ADJUVANT THERAPY

ARM B
standard

ADJUVANT THERAPY

ENDOSCOPY/ENEMA

ANASTOMOTIC LEAK

LATE ILEOSTOMY CLOSURE

FOLLOW - UP

FOLLOW UP
(12 months from randomization)

FOLLOW UP
(12 months from randomization)

LOST TO FOLLOW UP

DATA ANALYSIS

FINAL ANALYSIS

Primary endpoint: adjuvant therapy compliance

Secondary endpoints: complications, costs, QoL, oncological outcome

Section/item	ItemNo	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	1
Protocol version	3	Date and version identifier	NA
Funding	4	Sources and types of financial, material, and other support	17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	16
	5b	Name and contact information for the trial sponsor	17
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	NA

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	16
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3
	6b	Explanation for choice of comparators	4
Objectives	7	Specific objectives or hypotheses	
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	4
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	NA

	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	NA
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	14
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	NA
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9, 10
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9, 10
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	NA

	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	NA
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	13
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	17
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	17
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	12
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA

Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	12
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	17
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	13
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	13
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NA
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

BMJ Open

A prospective, randomized, multicentre, open-label trial, designed to evaluate the best timing of closure of the temporary ileostomy (early versus late) in patients who underwent rectal cancer resection and with indication for adjuvant chemotherapy. The STOMAD (STOMa closure before or after ADjuvant therapy) randomized controlled trial.

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Title page:

A prospective, randomized, multicentre, open-label trial, designed to evaluate the best timing of closure of the temporary ileostomy (early versus late) in patients who underwent rectal cancer resection and with indication for adjuvant chemotherapy. The STOMAD (STOMa closure before or after ADjuvant therapy) randomized controlled trial.

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Word count: 2754

Abstract:

Introduction: Temporary ileostomy is a valuable aid in reducing the severity of complications related to rectal cancer surgery. However, it is still unclear what is the best timing of its closure in relation to the feasibility of an adjuvant treatment, especially considering patient-reported outcomes and health system costs. The aim of the study is to compare the results of an early versus late closure strategy in patients with indication to adjuvant chemotherapy after resection for rectal cancer.

Methods and analysis: This is a prospective multicentre randomized trial, sponsored by *Rete Oncologica Piemonte e Valle d'Aosta* (Oncology Network of Piedmont and Aosta Valley - Italy). Patients undergone to rectal cancer surgery with temporary ileostomy, aged >18 years, without evidence of anastomotic leak and with indication to adjuvant chemotherapy will be enrolled in 28 Network centres. An early closure strategy (between 30 and 40 days from rectal surgery) will be compared to a late one (after the end of adjuvant therapy). Primary endpoint will be the compliance to adjuvant chemotherapy with and without ileostomy. Complications associated with stoma closure as well as quality of life, costs, and oncological outcomes will be assessed as secondary endpoints.

Ethics and dissemination: The trial will engage the Network professional teams in a common effort to improve the treatment of rectal cancer by ensuring the best results in relation to the most correct use of resources. It will take into consideration both the patients' point of view (patient-reported outcome) and the health system perspective (costs analysis). The study has been approved by the Ethical Review Board of *Città della Salute e della Scienza* Hospital in Turin (Italy). The results of the study will be disseminated by the Network website, medical conferences and peer-reviewed scientific journals.

Trial registration: ClinicalTrials (www.clinicaltrials.gov) NCT04372992

Keywords: rectal cancer; temporary ileostomy; early closure; late closure; postoperative morbidity; adjuvant chemotherapy; randomized controlled trial.

Strengths and limitations of the study:

- The study will involve all the referral centres for the treatment of colorectal cancer in the north-western area of Italy in a joint effort to improve the quality of rectal cancer care.
- It will have a high external validity given the large multicentric territorial context and the pragmatic approach with large inclusion criteria.
- The results will be analysed taking into account both the point of view of patients (patient-reported outcome analysis) and the costs for the health system.
- The main weakness of the study is the relative rarity of the patient population that could slow the accrual rate.

INTRODUCTION

The temporary ileostomy is effective in reducing the severity of anastomotic complications in anterior resections for tumours of the rectum at risk of dehiscence and is therefore widely used, particularly after radiotherapy treatment. (1) In patients with indication for adjuvant chemotherapy, current practice consists of closing the stoma after the end of treatment.

The prolonged presence of the stoma can however favour the onset of stoma-related complications, such as prolapse, parastomal hernia, mechanical ileus, high-flow dehydration, and damage to kidney function. Ostomy-related complications may require unscheduled hospitalizations and result in increased costs. (2) In addition, the presence of the stoma impacts on patients' quality of life, causing alteration of the body image and imposing changes in the daily routine, lifestyle, and sexual sphere. (3, 4) Therefore, early closure of the ileostomy has been proposed in patients without signs of postoperative fistula.

The early closure (within one month of surgery) of the temporary ileostomy resulted not inferior to late closure (over 12 weeks) in 2 randomized studies that evaluated postoperative complications as an outcome. (5, 6) Early closure saves days of life with ileostomy for the patient and costs related to ostomy care for the health system and could represent the most desirable and convenient choice. (7) It was also associated with better long-term functional results in a secondary analysis of a randomized study. (8) However, in patients with indication for adjuvant therapy, it is not known what the best timing is for closing the stoma (before the start, during or at the end of the treatment) in terms of therapy tolerability, quality of life and overall costs. (9)

Both a start date delayed more than 8 weeks from surgery (10) and a received dose <70% of that planned (11) have been reported to reduce the effectiveness of adjuvant therapy in colorectal cancer patients. The presence of a stoma or the consequences of its early closure may interfere with

an optimal delivery of chemotherapy. A recent multicentre retrospective study reported an increase in gastrointestinal toxicity in chemo-treated patients with stoma, with significant reduction in treatment compliance. (12) On the other hand, early closure of the stoma could reveal an anterior resection syndrome (LARS) before chemotherapy, with a potential negative impact on the tolerability of the treatment itself, (13) or delay its initiation due to postoperative complications. (14)

This randomized study aims to identify the best timing for the stoma closure in relation to adjuvant therapy in terms of compliance to chemotherapy, complications, costs and quality of life (QoL).

METHODS AND ANALYSIS

STOMAD is a multicentre open-label randomized phase III trial designed to evaluate the best timing of the closure of temporary ileostomy in patients operated on for rectal cancer and with indication for adjuvant chemotherapy.

Objectives

1. Primary objective

   • To compare the compliance with adjuvant therapy between early and late closure of temporary ileostomy.

   The compliance with adjuvant chemotherapy in relation to the timing of ileostomy closure (before the start or after the end of treatment) will be assessed considering any therapeutic delay or dose reduction compared to the initially planned.

2. Secondary objectives

   To compare patients with early and late closure of temporary ileostomy in terms of:

   • Surgical morbidity

- Chemotherapy toxicity
- Patient-reported quality of life
- Costs
- Progression free survival (PFS)
- Overall survival (OS)

Target population and setting

Patients undergone to rectal resection (+/- neoadjuvant therapy) for cancer with protective ileostomy and candidates for adjuvant chemotherapy in the Centres for the treatment of colorectal neoplasms recognized by *Rete Oncologica Piemonte e Valle d'Aosta*.

The list of participating centres is reported in Table 1.

Table 1. List of participating centres

Local PI	Local trial manager	Centre	Location
Paolo Millo	Elisa Ponte	AUSL Aosta – Surgical Unit – Parini Hospital	Aosta
Mario Morino	Massimiliano Mistrangelo	AOU Città Salute e Scienza – Academic Surgical Unit – Molinette Hospital	Torino
Paolo De Paolis	Mauro Santarelli	AOU Città Salute e Scienza – Surgical Unit – Molinette Hospital	Torino
Alessandro Ferrero	Paolo Massucco	AO Ordine Mauriziano – Surgical Unit – Umberto I Hospital (Coordineting centre)	Torino
Maurizio Degiuli	Rossella Reddavid	AOU S. Luigi Gonzaga – Academic Surgical Unit – S. Luigi Hospital	Orbassano (TO)
Roberto Saracco	Francesco Tomaselli	ASL Città Torino – Surgical Unit – Martini Hospital	Torino
Mauro Garino	Simone Birolo	ASL TO3 – Surgical Unit – Infermi Hospital	Rivoli (TO)
Andrea Muratore	Marcello Calabrò Nicoletta Pipitone	ASL TO3 – Surgical Unit – Agnelli Hospital	Pinerolo (TO)
Lodovico Rosato	Luca Panier Suffat	ASL TO4 – Surgical Unit – Civile Hospital	Ivrea (TO)
Eraldo Personnettaz	Monica Carrera	ASL TO4 – Surgical Unit – Ciriè Hospital	Ciriè (TO)
Pietro Cumbo	Francesco Potente	ASL TO5 – Surgical Unit – S. Croce Hospital	Moncalieri (TO)
Felice Borghi	Maria Carmela Giuffrida	AO S. Croce e Carle – Surgical Unit – S. Croce Hospital	Cuneo
Franco Bertolino	Marco Brunetti	ASL CN1 – Surgical Unit – SS. Annunziata Hospital	Savigliano (CN)
Andrea Gattolin	Roberto Rimonda	ASL CN1 – Surgical Unit – Regina Montis Regalis Hospital	Mondovì (CN)
Marco Calgaro	Vincenzo Adamo	ASL CN2 – Surgical Unit – S. Lazzaro Hospital	Alba (CN)
Fabio Priora	Igor Monsellato Domenico Piscioneri	AO SS. Antonio e Biagio e Cesare Arrigo - Surgical Unit – SS. Antonio e Biagio Hospital	Alessandria
Marco Amisano	Francesco Cravero	ASL AL – Surgical Unit – S. Spirito Hospital	Casale Monf.to (AL)
Alberto Serventi	Alberto Serventi	ASL AL – Surgical Unit – Mons. Galliano Hospital	Acqui Terme (AL)
Carmine Di Somma	Eliana Giaminardi	ASL AL – Surgical Unit – S. Giacomo Hospital	Novi Ligure (AL)
Vincenzo Sorisio	Luca Mazza	ASL AT – Surgical Unit – Cardinal Massaia Hospital	Asti
Sergio Gentilli	Paolo Bellora	AOU Maggiore Carità – Academic Surgical Unit – Maggiore Hospital	Novara
Raffaele Romito	Fabio Colli	AOU Maggiore Carità – Surgical Unit – Maggiore Hospital	Novara
Roberto Polastri	Roderto Perinotti	ASL BI – Surgical Unit – Infermi Hospital	Biella
Silvio Testa	Clemente De Rosa	ASL VC – Surgical Unit – S. Andrea Hospital	Vercelli
Sandro Zonta	Francesco Battafarano Renza Trapani	ASL VCO – Surgical Unit – S. Biagio Hospital ASL VCO – Surgical Unit – Castelli Hospital	Domodossola (VB) Verbania (VB)
Dario Ribero	Alfredo Mellano	FPO – Colorectal Surgical Unit – IRCCS	Candiolo (TO)
Renzo Leli	Paola Bellomo	Surgical Unit – Humanitas Gradenigo Hospital	Torino
Carlo Bima	Enrico Gibin	Surgical Unit – Cottolengo Hospital	Torino

Enrolment

Inclusion criteria

- Patients undergone to radical intestinal resection (R0) for rectal neoplasia with protective ileostomy.

- Age >= 18 years.

- Absence of fistula (enema and/or endoscopy)

- Indication to adjuvant chemotherapy

- Informed consent

Exclusion criteria

- ASA >3

- UICC stage IV

- ECOG Performance Status >=2

- Severe and non-controlled systemic, oncologic, or infectious disease

Before enrolment, the patient shall not show signs of ongoing complications. The integrity of the colorectal anastomosis will be confirmed with an enema and/or endoscopy according to local standards starting 15 days after surgery.

The presence of a discontinuation of the anastomotic rhyme in endoscopy or of a spreading of any entity of the contrast medium on the enema will represent an exclusion criterion. All patients will simultaneously perform an oncological evaluation to establish the indication for adjuvant therapy in the presence of the definitive histological examination. Patients without signs of anastomotic complications and with indication for adjuvant therapy will be enrolled for study by the local investigators. Enrolment and randomization must take place within 21 days of the intervention.

The subjects who are eligible for the study, after the informed consent has been signed, will be stratified by previous neoadjuvant treatment (yes or no) and by the proposed adjuvant chemotherapy scheme (with or without platinum derivatives), and then randomized to one of the following arms:

- Arm A (experimental): closure of the stoma between 30 and 40 days after surgery on the rectum, before starting adjuvant therapy.

- Arm B (standard): closure of the stoma starting from 15 days and within 60 days from the end of the adjuvant therapy. The anastomosis instrumental evaluation will be repeated after the end of chemotherapy in this group.

Endpoint definition

1. Primary endpoint.

   Proportion of patients with adequate compliance with adjuvant treatment.

   Compliance with adjuvant therapy will be considered adequate if both of the following criteria are met:

   • start of adjuvant therapy within the 70th day (<= 10 weeks) after surgery on the rectum; and

   • total cumulative dose delivered, compared to the theoretical planned, >= 70%.

   Failure to adhere to at least 1 of the two criteria will correspond to a failure (inadequate compliance). Patients with missing or non-performed assessment of compliance for any reason will also be considered unsuccessful adherence.

2. Secondary endpoints.

   • Morbidity. Incidence of complications related to the presence or to the closure of the ileostomy, during hospitalization or after discharge, using the Clavien-Dindo classification. Individual patient events, hospitalizations and reoperations will be recorded.

   • Chemotherapy toxicity. All adverse events according to CTCAE version 5.0 classification will be considered.

   • QoL. Patient-reported quality of life will be measured at the baseline and at defined time points using validated questionnaires (EORTC C30 and CR29, EQ5D). Bowel function will be evaluated at 12 months from randomization by means of the LARS score.

• Costs. The costs related to hospitalization, outpatient visits, ostomy care supplies and the management of complications and toxicity will be assessed.

• Progression free survival (PFS), defined as the time elapsed between the randomization date and the date of progression/death for any cause or the latest follow up available.

• Overall survival (OS), defined as the time elapsed between the randomization date and the date of death for any cause or the latest follow up available

Patients will be followed for the duration of the study, regardless of the clinical course, and will conclude the active follow-up with a final evaluation 12 months after randomization in both study arms. A longer follow-up, based only on routinely recorded data, will be conducted to assess long term overall survival. Enrolment is expected to start in September 2020.

The study flow diagram is depicted in Figure 1.

Surgical technique and medical therapy

Hospitalization will normally take place the day before or the morning of surgery. Antibiotic-prophylaxis (usually short-term with cefazoline within half an hour after skin incision) and thrombus-embolic prophylaxis will be performed according to national guidelines.

The stoma closure will be performed manually or mechanically according to the surgeon's judgment.

The suture of the skin incision will be linear or purse-string according to the local standards.

The postoperative management will be based on the ERAS strategy (early feeding and mobilization).

Discharge criteria will be passage of gas, adequate oral feeding, and good pain control.

Adjuvant chemotherapy will be administered, in terms of indications, drugs and schedules, according to the national guidelines (AIOM) and according to the consensus documents of the Colorectal Study Group of the Oncology Network (http://www.reteoncologica.it/area-operatori/gruppi-per-patologie/raccomandazioni-di-rete).

The ideal temporal target for the start of chemotherapy will be within 8 weeks of surgery on the rectum; the maximum time within 10 weeks. Randomized patients starting after this term are still followed up and evaluated until the end of follow-up for the evaluation of the other endpoints.

Endpoints assessment and follow-up

1. Morbidity

Complications related to stoma closure surgery, which occurred both during and after hospitalization, will be recorded according to the Clavien-Dindo classification. Their overall weight per patient will be calculated through the CCI. Management problems and complications from the stoma presence will also be recorded. All reinterventions and hospitalizations during the study period will be captured.

2. Adjuvant therapy

Chemotherapy toxicity will be evaluated according to the CTC-EORTC. Prophylaxis and treatment of side effects and dose reductions will be applied according to international standards (NCI-CTCAE criteria). Starting date of the treatment, dose reductions and therapeutic scheme variations, suspensions or interruptions will be recorded. In relation to the total dose and the total number of programmed cycles, the percentage of completeness of the adjuvant therapy will be calculated. Grade and type of adjuvant therapy toxicity will be recorded for each patient.

3. QoL

Quality of life will be measured using the EORTC C30, CR29 and EQ5D validated questionnaires. The questionnaires will be administered, in both arms, upon enrolment (baseline), at the beginning of the 4th cycle of adjuvant therapy and at 12 months after the intervention on rectal cancer.

The LARS score will be used to evaluate intestinal and sphincter function at 12 months after the rectal intervention in both arms (in the control group if ostomy closed since at least 2 months).

4. Costs

The costs will be estimated considering the days of hospitalization related to the closure of the stoma, the treatment of complications or toxicity, the outpatient visits during the study period and the amount of supplies for stoma care. Regional averages costs will be used as the basic cost unit.

Statistical considerations

1. Sample size

The sample size was calculated in relation to the main objective. The null hypothesis (proportion of patients with adequate compliance to the adjuvant treatment in patients with closure of the stoma after treatment) was inferred from data of randomized trials of adjuvant chemotherapy after rectal cancer resection (15, 16) and studies on chemotherapy toxicity directly related to the presence of an ostomy (12), and was set at 0.70. The alternative hypothesis is an increase in the proportion up to 0.85, with an absolute increase of 0.15. This increase is considered clinically relevant. With a two-tailed alpha error of 0.05 and a power of 0.80, the sample size required is at least 242 patients (121 for each treatment arm). Taking into account a maximum drop-out rate of approximately 10%, the total number of patients enrolled and randomized will be 270. The estimated study duration is 36 months.

2. Randomization

The randomization list, stratified by neoadjuvant therapy (yes/no) and by type of planned adjuvant chemotherapy (fluoropyrimidine +/- platinum derivatives) will be generated by the Clinical Epidemiology Unit of *Città della Salute e della Scienza* University Hospital in Turin, using a block procedure of variable length in random order, completely concealed to clinicians. The 1:1 randomization will be done online. After entering the inclusion/exclusion criteria and the

stratification variables into the database, the patient will be randomized and registered in arm A or B. The computerized randomization system will be accessible continuously.

3. Analysis

The principal analyses will be carried out on all subjects randomized according to the assigned treatment arm (intention to treat principle). The demographic and baseline characteristics will be described for the whole study population and for each treatment arm. Discrete variables will be summarized by frequencies and percentages. The continuous variables will be summarized with the use of standard measures of central tendency and dispersion (mean and standard deviation or median deviation and interquartile range). The analysis of the primary endpoint will be based on the comparison of treatment compliance between the two arms by means of a stratified chi-square test. As a sensitivity analysis, further potential confounders detected at the baseline will be included in a logistic regression model. OS and PFS, calculated from the randomization date, will be assessed with the Kaplan-Meier method and the differences in survival (overall and disease-free) will be tested using the stratified Log-rank test. The 95% confidence intervals (95% CI) will be calculated for all the study endpoints. Hazard Ratios (HR), adjusted for the stratification criteria and the main prognostic factors, will be estimated using the Cox model. Planned subgroup analyses will be carried out for the two stratification factors of the randomization (neoadjuvant treatment and adjuvant chemotherapy) and by age (divided into 3 classes according to the tertiles) using interaction terms between treatment arm and the subgroup variable in the regression models. Multiplicity adjustments for secondary outcomes and subgroup analyses will not be performed because these results will be considered exploratory and no claims will be made on them. The incidence of individual adverse events during hospitalization will be compared using the chi square test or the exact Fischer test, as appropriate. The comparison on the quality of life will be evaluated by comparing the average score between the two groups with the Student's T test (or with a non-

parametric test and quartile regression, if necessary) and with generalized linear mixed model to take into account the repeated measurements over time on the same subjects. Per protocol analyses will be performed for exploratory purposes.

Data collection

The data will be collected in each participating centre by filling in an electronic CRF (eCRF). A local study manager will be identified for each participating centre. The completeness and congruity of the data will be checked periodically by a central study monitor and overviewed the study's Steering Committee. The central monitor and Steering Committee will refer to the local managers for any request for clarification.

ETHICS AND DISSEMINATION

The *Rete Oncologica Piemonte e Valle d'Aosta* is a multidisciplinary organization that includes specialists involved in the treatment of cancer disease in the north-western territory of Italy. The aim of the Oncology Network is to reduce the variability of treatments, guarantee uniform access to and improve the quality of cancer care. To this end, the Network issues recommendations, drafted through a peer review process by its members, and defines the criteria for the designation as referral centres for cancer specific procedures.

STOMAD is a non-profit study conducted within the Network centres and is part of the research branch aimed at improving the healthcare delivery system. It is proposed to investigate which is the best adjuvant treatment delivery strategy in relation to the presence of the stoma for patients operated on for rectal cancer, taking into consideration both the patient's point of view (patients reported outcome) and the health system perspective (costs analysis).

The study will be conducted according to the principles of the Helsinki Declaration and the ICH Guideline for Good Clinical Practice. It will be approved by the reference Ethics Committee of each participating centre. Each enrolled patient must express a written consent (the consent form in original language is provided as Supplemental Material). Consent can be revoked at any time. Patients data will be collected on an existing online platform created by the Clinical Epidemiology Unit of the main centre in the region, which will also be responsible for all statistical analyses. The data collected for the study will be processed in accordance with current national legislation (Personal Data Protection Code). The trial Steering Committee may request the premature termination of the study in case of adverse events with severity and frequency significantly higher than expected or if the primary end point in the experimental group is significantly worse than the control group before the end of the study. For these evaluations, the Steering Committee will not use pre-defined statistical criteria (statistical stopping rules) but will base the decision on a careful quantitative and qualitative evaluation of the events that will be discussed in scheduled meetings.

This trial will engage the Network professional teams in a common effort to improve the treatment of rectal cancer by ensuring the best results in relation to the most correct use of resources (value-based health care). Other positive effects could be the strengthening of collaboration relationships between the Network centres and the definition of a common platform for future Network research.

The results of this study will be presented at national and international meetings and reported in the Network website. A manuscript with the final results will be submitted for publication in a peer-reviewed journal.

Abbreviations:

AIOM: Associazione Italiana Oncologia Medica
ERAS: Enhanced Recovery After Surgery protocol
ASA: American Society of Anesthesiologists
ECOG PS: Eastern Cooperative Oncology Group – Performance Status
UICC: Union for International Cancer Control
CCI: Comprehensive Complication Index
CTC-EORTC: Common Toxicity Criteria – European Organization for Research and Treatment of Cancer
NCI-CTCAE: National Cancer Institute – Common Terminology Criteria for Adverse Events
OS: Overall survival
PFS: Progression Free Survival
QoL: Quality of Life
LARS: Low Anterior Resection Syndrome
e-CRF: electronic Case Report Form
ICH: International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use

Figure legend:

Figure 1. Study flow diagram

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Declarations:

Authors' contributions

PM proposed the conception and design of the study protocol. AF, MM, SP, GC, CG, MCG, DM, IM, MKP, RP, PR, CM and FS contributed to the initial conception, design, and the drafting of the protocol and represent the trial Steering Committee. EP, MM, MS, FT, RR, SB, MC, NP, LPS, MC, FP, MB, RR, VA, DP, FC1, AS, EG1, LM, PB1, FC2, CDR, FB, RT, AM, EG2 and PB2 evaluated and approved the protocol and will be responsible for local patient accrual and data registration. All authors have approved the final submitted manuscript.

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Ethics approval

The study has been approved by the Ethical Review Board of *Azienda Ospedaliera Universitaria Città della Salute e della Scienza,* Turin (Italy).

Funding

STOMAD is a non-profit clinical trial sponsored by *Rete Oncologica Piemonte e Valle d'Aosta,* Italy (http://www.reteoncologica.it/). It will not receive external funding.

Competing interests

The authors declare that they have no competing interests.

Data availability

Anonymized trail data will be available for 36 months after the results publication upon request to the principal investigator. Data will be provided in electronic dataset format containing deidentified participant files by the Unit of Epidemiology of the *Azienda Ospedaliera Universitaria Città della Salute e della Scienza,* Turin (Italy) after evaluation and approval of the request by the trial steering committee.

Patients and Public involvement

Patients organizations were not involved in the conception and drafting of the trial. Hoverer, the endpoints were specifically designed to include patient-reported outcomes and validated quality of life questionnaires will be applied throughout the trial timeline.

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Patient Population

Curative resection for rectal neoplasm with temporary ileostomy and indication to adjuvant therapy

ACCRUAL

EXCLUSION CRITERIA

- ❑ ASA >3
- ❑ IV stage
- ❑ ECOG Performance Status >=2
- ❑ Severe non-controlled systemic, oncological or infectious disease

INCLUSION/EXCLUSION CRITERIA EVALUATION

INCLUSION CRITERIA

- ❑ >= 18 years
- ❑ No fistula (enema and/or endoscopy)
- ❑ Indication to adjuvant therapy
- ❑ Consent signed

ENDOSCOPY/ENEMA

ANASTOMOTIC LEAK

RANDOMIZATION

TREATMENT

ARM A
experimental

EARLY ILEOSTOMY CLOSURE

ADJUVANT THERAPY

ARM B
standard

ADJUVANT THERAPY

ENDOSCOPY/ENEMA

ANASTOMOTIC LEAK

LATE ILEOSTOMY CLOSURE

FOLLOW - UP

FOLLOW UP
(12 months from randomization)

FOLLOW UP
(12 months from randomization)

LOST TO FOLLOW UP

DATA ANALYSIS

FINAL ANALYSIS

Primary endpoint: adjuvant therapy compliance

Secondary endpoints: complications, costs, QoL, oncological outcome

Su carta intestata del centro partecipante

FOGLIO INFORMATIVO
E MODULO DI CONSENSO INFORMATO PER IL PAZIENTE

Studio prospettico randomizzato sul timing di chiusura dell'ileostomia temporanea nei pazienti operati per neoplasia rettale e con indicazione a chemioterapia adiuvante.
The STOma closure before or after ADjuvant therapy trial - STOMAD TRIAL

Gentile Signore/a,

Le è stato chiesto di partecipare ad una sperimentazione clinica, promossa dalla Rete Oncologica Piemonte e Valle d'Aosta.
I ricercatori studiano i casi come il suo, al fine di migliorare i metodi diagnostici, le terapie e la cura. Questo tipo di approccio si definisce ricerca clinica.
Prima di dare il Suo consenso a partecipare a questo studio, è bene che Lei sia a conoscenza dei rischi e dei benefici ad esso correlati. La Sua partecipazione a questa ricerca è assolutamente volontaria e Le sarà concesso il tempo sufficiente per decidere se partecipare. Questo processo è noto con il nome di consenso informato.
Nelle pagine seguenti, troverà i dettagli della sperimentazione clinica, di cui potrà discutere con il Suo medico. Le raccomandiamo di leggere queste informazioni con attenzione. Se c'è qualcosa che non capisce o di cui desidererebbe sapere di più, non esiti a chiederlo.
Prima di decidere di partecipare, Le consigliamo di parlarne con un familiare, un amico o il Suo medico di medicina generale.

Quando avrà compreso la natura dello studio clinico e se desidera parteciparvi, Le chiederemo di firmare il modulo per il consenso informato del paziente. Le sarà consegnata una copia del presente foglio informativo e del modulo per il consenso informato del paziente, che Le consigliamo di conservare.

Finalità della ricerca e Descrizione della sperimentazione clinica

La invitiamo a prendere parte a questo studio in quanto Le è stato diagnosticato un tumore rettale, per il quale è stato trattato con un intervento chirurgico di resezione rettale con confezione di una ileostomia.
Nei pazienti che, come lei, devono essere sottoposti a successiva chemioterapia adiuvante, l'attuale prassi prevede la chiusura della stomia dopo il termine del trattamento farmacologico, il che avviene in genere dopo almeno 3 mesi dall'intervento.
E' stato rilevato però che la presenza prolungata della stomia può favorire l'insorgenza di complicanze che potrebbero richiedere anche un secondo ricovero. La presenza della stomia inoltre incide sulla qualità di vita imponendo cambiamenti importanti nella routine quotidiana, nello stile di vita e nella sfera sessuale.

Alcuni studi hanno dimostrato che la chiusura precoce dell'ileostomia è altrettanto sicura rispetto alla chiusura tardiva e quindi preferibile sia dal punto di vista del paziente che per quanto riguarda la spesa sanitaria.
Non è tuttavia ancora noto quale sia il momento migliore per chiudere la stomia in relazione alla tollerabilità della chemioterapia.
Per dirimere tale quesito, questo studio prevede di coinvolgere i pazienti operati per tumore del retto nei centri della Rete Oncologica Piemonte e Valle d'Aosta. Lo studio prevede per metà dei partecipanti la chiusura della stomia a 30-40 giorni dall'intervento (gruppo di studio) e per l'altra metà a circa 15 gg dal termine della terapia adiuvante (gruppo di controllo).
L'assegnazione dei pazienti ad un gruppo o all'altro non è a discrezione degli sperimentatori, ma avviene attraverso un meccanismo computerizzato casuale chiamato randomizzazione.
Il presente studio clinico è condotto ai sensi del diritto nazionale applicabile e delle linee guida internazionali, ed è stato approvato dal Comitato Etico del centro coordinatore (AO Ordine Mauriziano - Torino), nonché dal Comitato Etico Indipendente del Suo centro.

Sono tenuto a prendere parte a questo progetto di ricerca?

La Sua partecipazione a questo studio di ricerca è assolutamente volontaria. Se dovesse decidere di non partecipare, non ci sarà alcuna ripercussione sulla sua assistenza medica. Qualora cominciasse lo studio, avrà la possibilità di ritirarsi in qualsiasi momento e senza doverne specificare la ragione. Questa decisione non influirà in alcun modo sull'assistenza medica futura.
Qualora si dovesse ritirare dallo studio, solo i dati già raccolti saranno usati ai fini dell'analisi. Qualora dovesse ritirare il consenso ma dare la Sua approvazione, il Suo medico di riferimento per lo studio potrà raccogliere informazioni sul Suo stato di salute da fonti disponibili quali ad esempio cartelle cliniche o registri pubblici.

Quali sono le alternative alla mia partecipazione?

Qualora Lei decidesse di non prendere parte al presente studio, lei verrà trattato secondo la attuale pratica clinica che prevede la chiusura della stomia al termine della chemioterapia adiuvante.

Procedure

Una volta firmato il modulo di consenso informato il medico svolgerà le opportune valutazioni per assicurarsi della Sua idoneità alla partecipazione allo studio.
All'atto dell'arruolamento le sarà chiesto di compilare un Questionario atto a valutare la qualità di vita (QoL).
Il personale le chiederà di compilare dei questionari simili in altri due diversi momenti del percorso di cura:

- al quarto ciclo del programma di chemioterapia;
- dopo circa 12 mesi dall'intervento.

Visite ed esami previsti nel corso della terapia di studio

Dal momento che la Sua partecipazione allo studio si inserisce nella cura della Sua problematica clinica, le visite e gli esami previsti fanno parte del normale approccio terapeutico garantito dal suo ospedale.

Quali sono i possibili benefici della partecipazione allo studio?

Ad oggi non è possibile sapere quale sia il momento migliore per la chiusura della stomia, quindi non è certo che questo studio possa darLe un beneficio diretto.
Questa ricerca però, aiuterà i ricercatori a comprendere la migliore strategia di trattamento chirurgico per aiutare altri pazienti con la Sua stessa malattia in futuro.

Quali sono i possibili rischi legati alla partecipazione allo studio?

Lo studio non comporta rischi aggiuntivi rispetto alla corrente pratica clinica per i pazienti che rientreranno nel gruppo di studio, in quanto trattasi di tecnica chirurgica comunemente utilizzata.

Qual è il costo per la partecipazione allo studio?

Tutte le spese, ad esempio gli esami standard di routine, saranno gestiti come se Lei stesse ricevendo un'assistenza medica normale, senza partecipare ad alcun studio clinico. Non Le saranno addebitati costi aggiuntivi.
La partecipazione al presente studio non è retribuita.

Che cosa succederà alle informazioni che mi riguardano?

I ricercatori dovranno raccogliere informazioni personali quali l'età, il sesso e le altre informazioni mediche richieste. Tutte le informazioni relative alla raccolta dei Suoi dati personali saranno cifrate in modo tale che senza una chiave non sarà possibile farle risalire alla persona interessata.
Qualsiasi informazione personale o medica raccolta sarà strettamente privata e riservata. La conservazione delle informazioni avverrà in modo sicuro. Solo le persone autorizzate potranno accedervi, in quanto perfettamente al corrente della loro natura strettamente riservata. Né il Suo nome né qualsiasi altra informazione identificativa compariranno in alcun rapporto di studio reso disponibile al pubblico.
I rappresentanti del promotore dello studio (Rete Oncologica Piemonte e Valle d'Aosta), le agenzie per i farmaci o i Comitati Etici potranno richiedere l'accesso alle informazioni personali o mediche contenute nella Sua cartella clinica, al fine di verificare le procedure e/o i dati di studio. In caso di sinistri relativi a problemi o danni

medici, anche i rappresentanti dell'assicurazione avranno accesso ai Suoi dati medici attraverso il Suo ricercatore e solo nella misura necessaria per la gestione del sinistro. Il promotore dello studio garantisce il rispetto delle linee guida nazionali e internazionali sulla protezione dei dati.
I Suoi dati personali saranno trattati, nei limiti e con le modalità indicate nel presente documento e in conformità al Codice in Materia di Protezione dei Dati Personali (D.Lgs 196 del 30/06/2003) e al Regolamento (UE) 2016/679 sulla protezione dei dati personali (GDPR).

Cosa succederebbe se dovessero sorgere nuove informazioni durante lo studio?

Lei ha il diritto di essere informato dei progressi dello studio di ricerca e dei suoi risultati finali. Inoltre, ha il diritto di essere informato riguardo a eventuali altri risultati di altri studi che potrebbero rivelarsi importanti per il Suo trattamento o influire sulla Sua disponibilità a proseguire questo studio.

A chi devo rivolgermi in caso di dubbi?

Se ha bisogno di ulteriori informazioni su questo studio prima di decidere di parteciparvi, si rivolga al Suo medico di riferimento per lo studio. Qualora dovesse decidere di partecipare, si rivolga allo stesso medico di riferimento qualora si verificassero gravi effetti indesiderati causati dalla terapia.

Responsabile locale per lo studio – Dott: .....
Recapito: .....

Su carta intestata del centro partecipante

CONSENSO INFORMATO DEL PAZIENTE ALLA PARTECIPAZIONE ALLA SPERIMENTAZIONE CLINICA

Studio prospettico randomizzato sul timing di chiusura dell'ileostomia temporanea nei pazienti operati per neoplasia rettale e con indicazione a chemioterapia adiuvante.
The stoma closure before or after adjuvant therapy trial - STOMAD TRIAL

DICHIARAZIONE DEL PAZIENTE

Con la firma sottostante attesto che:

- Il medico citato di seguito mi ha spiegato oralmente e per iscritto gli obiettivi, la procedura dello studio, gli effetti attesi, i possibili vantaggi e svantaggi e i potenziali rischi. Se desidero ulteriori informazioni su questo studio, posso rivolgermi al medico dello studio.
- Ho letto e compreso il modulo di informazioni per i pazienti prodotto per questo studio. Le mie domande relative alla partecipazione allo studio hanno ricevuto una risposta soddisfacente. Posso conservare il modulo informativo e riceverò una copia del mio consenso informato firmato.
- Ho avuto tempo a sufficienza per prendere la mia decisione.
- La mia partecipazione a questo studio è volontaria. Posso ritirare la mia partecipazione in ogni momento senza addurre alcuna motivazione e senza nessuna ripercussione sulla prosecuzione dell'assistenza medica.
- Riceverò una copia del modulo di informazione del paziente e una copia del modulo di consenso firmato.

NOME E COGNOME _____

FIRMA _____DATA:_____

TESTIMONE IMPARZIALE (Solo nel caso in cui il paziente non sia in grado di leggere o scrivere) – Compilare solo se applicabile

Confermo di non essere in relazione con lo studio, di aver partecipato al processo del consenso e di aver letto le informazioni dello studio.

NOME E COGNOME
DEL TESTIMONE IMPARZIALE:_____

FIRMA
DEL TESTIMONE IMPARZIALE:_____DATA: _____

DICHIARAZIONE DEL MEDICO RICHIEDENTE IL CONSENSO INFORMATO

Dichiaro di aver spiegato in modo esauriente il presente studio al paziente.
A mio giudizio e secondo il paziente le informazioni fornite, anche riguardo a rischi e benefici, sono state sufficienti per una decisione informata.

NOME E COGNOME DEL MEDICO CHE HA OTTENUTO IL CONSENSO:
_____

FIRMA DEL MEDICO CHE HA OTTENUTO IL CONSENSO:
_____
_____

DATA: _____

Section/item	ItemNo	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	1
Protocol version	3	Date and version identifier	NA
Funding	4	Sources and types of financial, material, and other support	17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	16
	5b	Name and contact information for the trial sponsor	17
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	NA

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	16
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3
	6b	Explanation for choice of comparators	4
Objectives	7	Specific objectives or hypotheses	
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	4
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	NA

	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	NA
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	14
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	NA
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9, 10
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9, 10
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	NA

	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	NA
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	13
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	17
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	17
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	12
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA

Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	12
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	17
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	13
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	13
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NA
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA