PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	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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VERSION 1 – REVIEW

REVIEWER	David Bock Institute of Medicine, Göteborg University
REVIEW RETURNED	16-Oct-2020

GENERAL COMMENTS	Good and clearly written manuscript. Very interesting and important topic. A few minor comments: 1. Sample size assessment. You state approx. 70% have adequate compliance among patients with closure after adjuvant therapy. Please add references. 2. Why is block size allowed to vary in a random way? 3. Statistical analysis of primary endpoint. You use a stratified Chi-square test to calculate a p-value. I encourage you to calculate a 95% confidence interval for the estimated treatment effect. Estimating treatment effect and 95% CI should be done for ALL endpoints. 4. Please consider alternative regressions models that t-test (e.g. quantile regression) in case the QoL score violates assumptions required for t-test/linear regression. 5. Please give a rational for not using a multiplicity correction due to multiple hypothesis tests.

REVIEWER	Yves Panis Beaujon Hospital, University of Paris, France
REVIEW RETURNED	18-Oct-2020

GENERAL COMMENTS	I am not sure that a randomized study with 3-year of inclusion, which is a big effort is necessary to answer this question. In others words, I am not sure that this question is crucial. For some people, the best timing to close the stoma is before chemotherapy, by early stoma closure (around 10 days after TME), for others is around 5-6 weeks, just before beginning of chemotherapy, and for some others, it is after 6 months of chemotherapy. But at the end, everybody get chemotherapy if needed. I agree that to have a strong answer for this voice will be interesting. However, in this case, a third group with early stoma closure is maybe necessary. Furthermore, to expect that compliance with chemotherapy which is 0.70 if done before stoma closure, will be increased by early stoma closure is very questionnable because of the very frequent bad functional results during the first weeks after stoma closure. For this reason, some others surgeons prefer give 2 courses of chemotherapy, then close the stoma, then finish chemotherapy for 10 additional courses. In conclusion, with this randomized study, the best expected results will be only that the compliance is better, but with a big risk that the study is negative. And at the end I am not sure that it will change the way people have decided to give chemo The last risk of this study is that anastomotic lea rate, frequently increased under chemo, is higher in the arm A.

VERSION 1 – AUTHOR RESPONSE

Response to Reviewer #1

1. Sample size assessment.

We have clarified the process of calculating the null hypothesis and added two more references.

2. Block size.

The complete random sequence was generated with a computerised procedure available in STATA 15 (RALLOC) that provides a sequence of treatments randomly permuted in blocks of varying size, where the size and order of the blocks are also random. This method of randomisation is strongly recommended to prevent predictability of assignment, with higher security than using a fixed block size or a constant order.

3. Confidence intervals

The calculation of 95% confidence intervals was planned for all study endpoints. We have clarified this point including a sentence in the statistical analysis paragraph.

4. Quantile regression models for QoL.

Thank for this suggestion. The choice of the most appropriate statistical model, including quantile regression, will be based on a careful evaluation of the distribution of the QoL score.

5. Multiplicity correction.

The study has only one primary hypothesis with a single endpoint and no multiplicity correction is due for this test. All secondary endpoints will be estimated with their 95% confidence intervals and statistical tests will not be used to claim superiority for them. According to the guidelines for SAP in clinical trials, justification for the absence of multiplicity adjustments for secondary outcomes is probably unnecessary unless a claim is to be made on them (Gamble, JAMA 2017).

Response to Reviewer #2

We were delighted to hear that our study was examined by one of the best-known European opinion leaders in colorectal surgery. We agree with Prof. Panis that we have embarked on a difficult task and

that the trial will not be easy-going. We would like to better explain the reasons that led to our decision.
We are members of an oncologic network the includes all the referral centres for cancer treatment in the north-west region of Italy. The aim of the network is to decrease the variability of cancer care and to disseminate good clinical practice among the network members. To this end, the centres representatives meet periodically to discuss the main criticalities of patients care pathways and issue consensus documents that are published on the network website.
The idea for the study was born during one of the network colorectal group meetings when we noticed that, although early stoma closure has been shown to be feasible and safe by randomized trials (and one by Prof. Panis' group), it is applied in few centres in our region. One of the main doubts of network members was related to the relationship between stoma closure and adjuvant chemotherapy with quite different opinions on this. As a network that analyses treatment pathways, we are interested not only in oncologic clinical research, but also in understanding the best way to organize care provision taking into account both patients point of view and health system costs (so-called cancer care delivery research). So, we decided to investigate that question by a randomized trial. We chose the two strategies that were the most accepted by the network centres and hence designed a two-arm study and sent the protocol for publication. In the meantime, the trial has been approved by all the Ethical Committees of the region and has started recruiting.
We thank Prof Panis for his valuable comments and, as we strongly believe in transparency of clinical trials, we hope to share our protocol with the medical community and shed new light on a rectal cancer treatment aspect that encompasses both patients well-being and good use of healthcare resources.

VERSION 2 – REVIEW

REVIEWER	David Bock Göteborg University
REVIEW RETURNED	20-Jan-2021

GENERAL COMMENTS	You misspelled "quantile regression" as "quartile regression" in the statistics section

REVIEWER	Yves Panis Beaujon Hospital
REVIEW RETURNED	30-Jan-2021

GENERAL COMMENTS	Authors answered correctly to queries paper can be published now in the revised form