Clinical Study Protocol
Full Protocol
2nd Stage Submission

The assessment of a clinical research protocol encompasses a 2-stage process. During the first stage applicants are called upon to provide a study synopsis including background, design, objectives, outcome parameters, major inclusion and exclusion criteria, statistics, and co-variates not exceeding 4 pages. Within 6 weeks from receipt, ClinCom will respond to the applicant with a preliminary review, either encouraging or declining the submission of a full protocol within 6 months of the first feed-back to the applicant. This full protocol will be subjected to a final review by ClinCom within 8 weeks of receipt.

PROJECT TITLE:

"Prophylactic versus endoscopy-driven treatment of Crohn's postoperative recurrence: A multicentric European study."

PRINCIPAL INVESTIGATOR:

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Comments ClinCom from 1st Stage (Point 1-7)

*Please list below and answer according to the points the 1st stage comments from ClinCom in order to facilitate the 2nd stage review***.**

1. BACKGROUND

Crohn's disease (CD) is a chronic and progressive disease with a high risk of surgical resection(1, 2). Moreover, the risk of endoscopic postoperative recurrence (POR) within 1 year after ileocecal resection is up to 73%. Because of the prognostic value of the Rutgeerts' endoscopic score(3, 4) it is universally recommended to perform an endoscopy 6-12 months after surgery to predict de disease course after ileocecal resection. Different risk factors for POR have been described such as prior intestinal surgery, penetrating disease, perianal location or small bowel extensive location(5, 6). Besides, smoking is the most accepted and consistent risk factor for POR in most of the studies(7).

Given that the majority of patients will have ePOR after ileocecal resection, different strategies have been proposed but there is currently no consensus or agreement for the most appropriated approach to prevent this ePOR, neither for the management of cPOR and sPOR at long term.

Among the different drugs that have been evaluated in this context, the aminosalycilates and budesonide have shown a very modest or even no benefit in this context(8-10). Nitroimidazoles have shown to be effective in the prevention of POR, but because of its side effects are not recommended as long term treatment(11, 12). Data about the efficacy of thiopurines to prevent POR are controversial(13-15). Overall, a Cochrane meta-analysis (16) showed that thiopurines were superior than 5-ASA to achieve ePOR at 1 year, although results are not so consistent for cPOR. Different studies have shown the efficacy of infliximab (IFX) to prevent ePOR(17-19). Results about its efficacy for cPOR are more controversial(20). With adalimumab, data is more limited but studies demonstrate its superiority against placebo to prevent POR (21-23). However, one randomized trial showed no superiority against AZA (24). Only one study has evaluated the efficacy of vedolizumab (VDZ) in this setting, showing lower rates of remission than IFX(25).

According to ECCO guidelines, prophylaxis is recommended in patients after ileocecal resection and at least one risk factor for POR(6). However, it is still not known which is the best medical treatment in this context and whether the systematic prophylactic treatment is more effective than the treatment according to the endoscopic activity after surgery. One study showed no benefit of systematically AZA after surgery compared to AZA only after diagnosis of endoscopic recurrence, although this study was statistically underpowered to achieve firm conclusions(26). The POCER study (27) showed that treatment according to clinical risk of recurrence, with early colonoscopy at 6 months and treatment step-up for recurrence, is better than conventional drug therapy alone without colonoscopy. Another group from Canada recently showed that thiopurines after surgery and addition of biologics guided by ePOR is the optimal strategy(28). Guo *et al.* have shown that thiopurines, when given systematically after surgery, reduce the risk of sPOR as compared to waiting for the endoscopic lesions to start them. However, after adjustment for risk factors there were no differences between groups(29).

Given the fact that the endoscopic lesions 6-12 months after ileocecal resection have prognostic value, it seems reasonable to look for strategies that "prevent" ePOR and not only "treat" ePOR. There is, however, no clear consensus in this context and the benefit of both strategies has not been compared. (30)

2. DESIGN

Retrospective observational multicenter superiority study including all CD patients undergoing their first ileocecal resection between January 2008 and April 2019 (in order to complete at least a 2 year follow-up before inclusion, by April 2021).
Cohort 1 (systematic prophylaxis): patients starting prophylactic immunomodulators (IMM) and/or biologics for POR after surgery (within the first 2 weeks after surgery).
Cohort 2 (endoscopically adjusted treatment): patients starting IMM and/or biologics according to endoscopic findings at the ileocolonoscopy 6-12 months after surgery.

The rate of ePOR will be assessed in the regular ileocolonoscopy at 6-12 months after surgery, and the time to cPOR and sPOR will be evaluated at long term.

Sample size: given that 65% of the population will present at least 1 risk factor (smoking, penetrant disease, perianal disease…) the ePOR at 6 months rate without prophylactic treatment would go up to 45% (26) and considering that a difference of 15% is clinically relevant, the expected ePOR for cohorts 1 and 2 would be 30% and 45% respectively. Therefore, 224 patients would be needed in each group (448 in total), with a significance level (alpha) of 5% and a power (1-beta) of 80%.
A sample of 163 CD patients per group (326 in total) will achieve at least 80% power to detect a difference of 15% in ePOR rate using a two-sided Chi-square test at the 5% significance level, when the highest ePOR rate at 6 months is estimated at 45% in the group without prophylactic treatment. (This sample size calculation was performed using SAS Power and Sample Size).

Definitions:
Endoscopic POR (ePOR): Rutgeerts score > i1.
Severe ePOR: Rutgeerts score i3-i4.
Endoscopic POR will be assessed according to the modified Rutgeerts' score, (31) specifying the proportion of patients with lesions at the anastomosis and less than 5 apthous lesions in neoileum (i2a) and of patients with more than 5 apthous lesions in neoileum , regardless the presence of lesions at the anastomosis(i2b).
Clinical POR (cPOR): symptoms and objective markers of disease activity (biochemical, endoscopic or radiological) leading to escalation in therapy.

a) Short-term clinical relapse: between surgery and the endoscopy
b) Long-term relapse: between endoscopy and the 2-3 y of FU

Surgical POR (sPOR): need of other ileal or ileocolic resection after the baseline ileocolonic resection of the patient which must be the first intestinal resection of the patient. Stricturoplasty and/or balloon dilatation will be also analysed.

3. OBJECTIVES

The primary objective is to find a difference in ePOR rate at 6-12 months after surgery between the group with systematic prophylaxis after ileocecal resection and the group with treatment only after adjustment to endoscopic findings after surgery.
As secondary outcomes, the time to clinical and surgical POR will be also evaluated for both strategies.
The risk factors for ePOR and sPOR as well as the efficacy and safety of the different medical regimens will be also analyzed.
Finally, differences of management according to the different hospitals/countries in Europe will be evaluated.

4. OUTCOME PARAMETERS

- Rate of ePOR at short term (at 6-12 months after surgery)
- Time to cPOR and sPOR
- Stenosis with pre-stenotic dilatation, intra-abdominal abscesses and perianal disease
- Rates of ePOR, cPOR and sPOR according to the different medical treatments and risk factors
- Rates of adverse events within the different drugs
- Most frequent strategy according to different hospitals and countries in Europe

5. MAJOR INCLUSION AND EXCLUSION CRITERIA

INCLUSION: adult (>18 years old), diagnosis of CD in the surgical specimen, first ileocecal or ileal resection, ileocolonoscopy within the 6-12 months after surgery, patients starting IMM and/or biologics immediately after surgery, patients starting IMM and/or biologics after the ileocolonoscopy at 6-12months.
EXCLUSION: ulcerative colitis, absence of endoscopy within 6-12 months after surgery, presence of remaining inflammation after surgery

6. STATISTICS

Descriptive statistics will be calculated as absolute frequencies and percentages for discrete data; and as mean and standard deviation or as medians with interquartile ranges (IQR) for continuous data, according to data distribution.

Simple (unadjusted) analyses
Simple logistic regression models for prevalence of ePOR at 6-12 months after surgery will be fitted.
The time to cPOR and time to sPOR will be compared between treatment groups using the log-rank test. Survival curves will be estimated using the Kaplan-Meier method.

Comparisons of continuous outcomes between two groups will be performed using Student's *t*–test for independent samples or the Mann-Whitney U test (according to the distribution of

data). Associations between categorical variables will be assessed using the Chi^2 test or the Fisher's exact test.

Multiple (adjusted) analyses

With a large number of covariates, there is a risk of finite sample bias in non-linear models. We will prevent extrapolation by refraining from modelling the association between outcome and confounders. Instead we will model the association between exposure (treatment) and confounders, by fitting a binary logistic regression model for prophylactic treatment. The propensity score expresses the conditional probability that a patient would have gotten prophylactic treatment on the basis of his/her covariates.

Next, we will fit a binary logistic regression model for ePOR at 6-12 months with treatment as explanatory variable and with adjustment for the propensity score. This will infer an effect measure for prophylactic treatment given that patients share the same propensity score.

In addition, we will fit a marginal structural model (using binary logistic regression upon weighting the data by the inverse of the propensity score) to infer the marginal treatment effect.

Likewise, Cox Proportional Hazards models will be fitted for time to cPOR and sPOR with adjustment for the propensity score.

All hypothesis testing will be performed at the two-sided 5% significance level.

7. CO-VARIATES

- Hospital
- Disease phenotype
- Smoking
- Use of antibiotics or mesalazine or probiotics
- Previous intestinal resection
- Length of resected small bowel
- Presence of endoscopic activity in colon in ileocolonoscopy after surgery
- Perianal disease
- Preoperative medical therapy (IMM, anti-TNF, VDZ, …)
- Reasons to stop medication (PNR, LOR, intolerance,toxicity, infections, malignancy…)
- B2, B3 phenotype
- Age at diagnosis

ENCOURAGING OR DECLINING THE SUBMISSION OF A FULL PROTOCOL

2nd Stage Review

1. SUMMARY

(brief and precise, outlining only the most relevant topics and the proposed objectives)
Maximum: 1 page

Ileocecal resection in patients with Crohn's disease (CD) is a common event which has particular implications in the management of the disease because of its nature of potential "reset" on the disease course. This theoretic "reset" leads to some clinicians to not re-start IBD medication after surgery; however, others do it systematically due to the high rate of postoperative recurrence (POR) in the absence of preventive treatment. For those patients at a very high risk of recurrence most clinicians will agree in starting prophylaxis. However, for the remaining (which are the majority) of patients, there is no consensus.
It is very well known that the majority of patients after surgery will develop endoscopic postoperative recurrence (ePOR) and that the severity of the endoscopic lesions in this context has a prognostic value. Nonetheless, there is still no consistent data to affirm which is the best strategy to avoid this ePOR at short term. In addition, it is unknown which strategy is the best to avoid surgical POR (sPOR) and clinical POR (cPOR) at long term.
The design of the available studies addressing this topic are heterogeneous since some of them analyze the efficacy of systematic prophylaxis whereas others evaluate the benefit of treating the endoscopic lesions. These are actually two very different concepts: *prevention* of ePOR vs. *treatment* of ePOR.
The aim of this study is to compare the incidence of POR with two different strategies: to start a preventive treatment systematically in all CD patients after an ileocecal resection *vs.* treating only those with ePOR (lesions after the ileocolonoscopy that is regularly performed in this context). A *proactive vs*. a *reactive* strategy thus.
All CD patients with their first ileocecal resection between 2008 and 2019 and having an ileocolonoscopy within 6-12 months after surgery will be included.
As secondary endpoints, the time to cPOR and sPOR will be also analyzed for both strategies at long term (from surgery). The efficacy and safety of the different medical regimens will be also evaluated as well as the differences in the management in between the different centers. With this purpose, the design of the study will be multicenter, observational and retrospective. Finally, a sub-analysis will be done after the stratification of patients according to their risk of recurrence.

2. INTRODUCTION

(including background information; there is no need to explain the basic nature of ulcerative colitis or Crohn's disease)

Crohn's disease (CD) is a chronic and progressive disease with a high risk of surgical resection(1, 2). Moreover, the risk of endoscopic postoperative recurrence (POR) within 1 year after ileocecal resection is up to 73%. Because of the prognostic value of the Rutgeerts' endoscopic score(3, 4) it is universally recommended to perform an endoscopy 6-12 months after surgery to predict de disease course after ileocecal resection. Different risk factors for POR have been described such as prior intestinal surgery, penetrating disease, perianal

location or small bowel extensive location(5, 6). Besides, smoking is the most accepted and consistent risk factor for POR in most of the studies(7).

Given that the majority of patients will have ePOR after ileocecal resection, different strategies have been proposed but there is currently no consensus or agreement for the most appropriated approach to prevent this ePOR, neither for the management of cPOR and sPOR at long term.

Among the different drugs that have been evaluated in this context, the aminosalycilates and budesonide have shown a very modest or even no benefit in this context (8-10). Nitroimidazoles have shown to be effective in the prevention of POR, but because of its side effects are not recommended as long term treatment (11, 12). Data about the efficacy of thiopurines to prevent POR are controversial (13-15). Overall, a Cochrane meta-analysis (16) showed that thiopurines were superior than 5-ASA to achieve ePOR at 1 year, although results are not so consistent for cPOR. Different studies have shown the efficacy of infliximab (IFX) to prevent ePOR (17-19). Results about its efficacy for cPOR are less consistent (20). With adalimumab, data is more limited but studies demonstrate its superiority against placebo to prevent POR (21-23). However, one randomized trial showed no superiority against AZA (24). Only one study has evaluated the efficacy of vedolizumab (VDZ) in this setting, showing lower rates of remission than IFX (25).

According to ECCO guidelines, prophylaxis is recommended in patients after ileocecal resection and at least one risk factor for POR (6). However, it is still not known which is the best medical treatment in this context and whether the systematic prophylactic treatment is more effective than the treatment according to the endoscopic activity after surgery. One study showed no benefit of systematically AZA after surgery compared to AZA only after diagnosis of endoscopic recurrence, although this study was statistically underpowered to achieve firm conclusions (26). The POCER study (27) showed that treatment according to clinical risk of recurrence, with early colonoscopy at 6 months and treatment step-up for recurrence, is better than conventional drug therapy symptomatic-guided without colonoscopy. Another group from Canada recently showed that thiopurines after surgery and addition of biologics guided by ePOR is the optimal strategy (28). Guo *et al.* have shown that thiopurines, when given systematically after surgery, reduce the risk of sPOR as compared to waiting for the endoscopic lesions to start them. However, after adjustment for risk factors there were no differences between groups (29).

Given the fact that the endoscopic lesions 6-12 months after ileocecal resection have prognostic value, it seems reasonable to look for strategies that "prevent" ePOR ("***pro-active" approach***) and not only "treat" ePOR ("***reactive" approach***). There is, however, no clear consensus in this context and the benefit of both strategies has not been compared. (30)

3. HYPOTHESIS

The systematic prophylaxis ("***pro-active" approach***) after ileocecal resection is superior to no prophylaxis after surgery to prevent ePOR, cPOR and sPOR at short term; and also to the endoscopic-driven treatment ("***reactive" approach***) to prevent cPOR and sPOR at long term.

The probability of ePOR at 6-12 months is smaller with systematic prophylaxis ("***pro-active" approach***) compared to no prophylaxis.
The hazard of cPOR and sPOR is smaller with systematic prophylaxis ("***pro-active" approach***) compared to no prophylaxis or endoscopic-driven treatment ("***reactive" approach***).

4. STUDY POPULATION

All CD patients undergoing their first ileocecal resection between January 2008 and April 2019 (in order to complete at least a 2 year follow-up before inclusion, by April 2021).
Cohort 1 (systematic prophylaxis or ***"proactive approach"***): patients starting prophylactic immunomodulators (IMM)
and/or biologics for POR after surgery (within the first 2 weeks after surgery).
Cohort 2 (endoscopically adjusted treatment or ***"reactive approach"***): patients starting IMM and/or biologics according to endoscopic findings at the ileocolonoscopy 6-12 months after surgery.

5. DESIGN AND OBJECTIVE(S)

Retrospective observational multicenter superiority study.

Data will be collected using UR-CARE platform.

The rate of ePOR will be assessed in the regular ileocolonoscopy at 6-12 months after surgery, and the time to cPOR and sPOR since date of surgery will be evaluated at short term (until endoscopy at 6-12 months) and long term (at least 2 years of FU).

Sample size:
Given that 65% of the population will present at least 1 risk factor (smoking, penetrant disease, perianal disease…) the ePOR at 6 months rate without prophylactic treatment would go up to 45% (26) and considering that a difference of 15% is clinically relevant, the expected ePOR for cohorts 1 and 2 would be 30% and 45% respectively. Therefore, 224 patients would be needed in each group (448 in total), with a significance level (alpha) of 5% and a power (1-beta) of 80%.

Definitions:
Endoscopic POR (ePOR): Rutgeerts score > i1.

Severe ePOR: Rutgeerts score i3-i4.
Endoscopic POR will be assessed according to the modified Rutgeerts' score, (31) specifying the proportion of patients with lesions at the anastomosis and less than 5 apthous lesions in neoileum (i2a) and of patients with more than 5 apthous lesions in neoileum , regardless the presence of lesions at the anastomosis(i2b).

Clinical POR (cPOR): symptoms and objective markers of disease activity (biochemical, endoscopic or radiological) leading to escalation in therapy.

Surgical POR (sPOR): need of other ileal or ileocolic resection after the baseline ileocolonic resection of the patient which must be the first intestinal resection of the patient. Stricturoplasty and/or balloon dilatation will be also analysed.

Both for cPOR and sPOR the following will be analysed:

a) Short-term cPOR and/or sPOR: between surgery and the endoscopy
b) Long-term cPOR and/or sPOR: between surgery and at least 2 years of FU

Objectives

- Prymary objective: to evaluate whether the systematic prophylaxis after ileocecal resection is superior to no prophylaxis to prevent ePOR within de first 6-12 months after surgery (primary endpoint).
- Secondary objectives:
  - To assess whether systematic prophylaxis is superior to endoscopically adjusted treatment with respect to time to clinical and surgical POR at short and long term.
  - To explore the differences of management according to the different hospitals/countries in Europe.
    To analyse the treatment burden and safety of both strategies.

6. ENDPOINTS, CO-VARIATES AND VARIABLES

Primary and secondary endpoints

- Rate of ePOR at 6-12 months after surgery
- Time to cPOR since date of surgery
- Time to sPOR since date of surgery

Variables

- Endoscopic post-operative recurrence (ePOR) at short term (during ileocolonoscopy at 6-12 months after surgery)
- Clinical and surgical post-operative recurrence (cPOR and sPOR) at short term (from surgery up to the endoscopy)
- Clinical and surgical post-operative recurrence (cPOR and sPOR) at long term (from endoscopy until the end of FU which will be at least of 2 years)
- Adverse events within the different drugs

Co-variates

- Hospital
- Age at diagnosis
- Disease phenotype
- EIM
- Smoking
- Pre-operative medical therapy (5-ASA, corticosteroids, IMM, biologics)
- Post-operative medical therapy (5-ASA, corticosteroids, IMM, biologics)
- Need of biological optimization (re-induction and/or intensification)
- Reason for stopping IMM and/of biologic before and after surgery

- Adverse events of medications after surgery
- Complications after surgery
- Number of abdominal surgeries
- Number of abdominal resections
- Length of resected small bowel
- Number of stricturoplasties
- Endoscopic dilatation of stenosis
- Hospitalizations because of disease flare after surgery
- Mortality

7. INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria: adult (>18 years old), diagnosis of CD in the surgical specimen, first ileocecal or ileal resection, ileocolonoscopy within the 6-12 months after surgery, at least 2 year FU after surgery

Exclusion criteria: ulcerative colitis, absence of endoscopy within 6-12 months after surgery, presence of remaining inflammation after surgery, surgery because of malignancy

8. PRIOR, PROHIBITED AND CONCOMITANT MEDICATION

Prior medication to inclusion: 5-ASA, corticosteroids, IMM, biologics
Prohibited medication: none
Concomitant medication: 5-ASA, antibiotics, corticosteroids, IMM, biologics

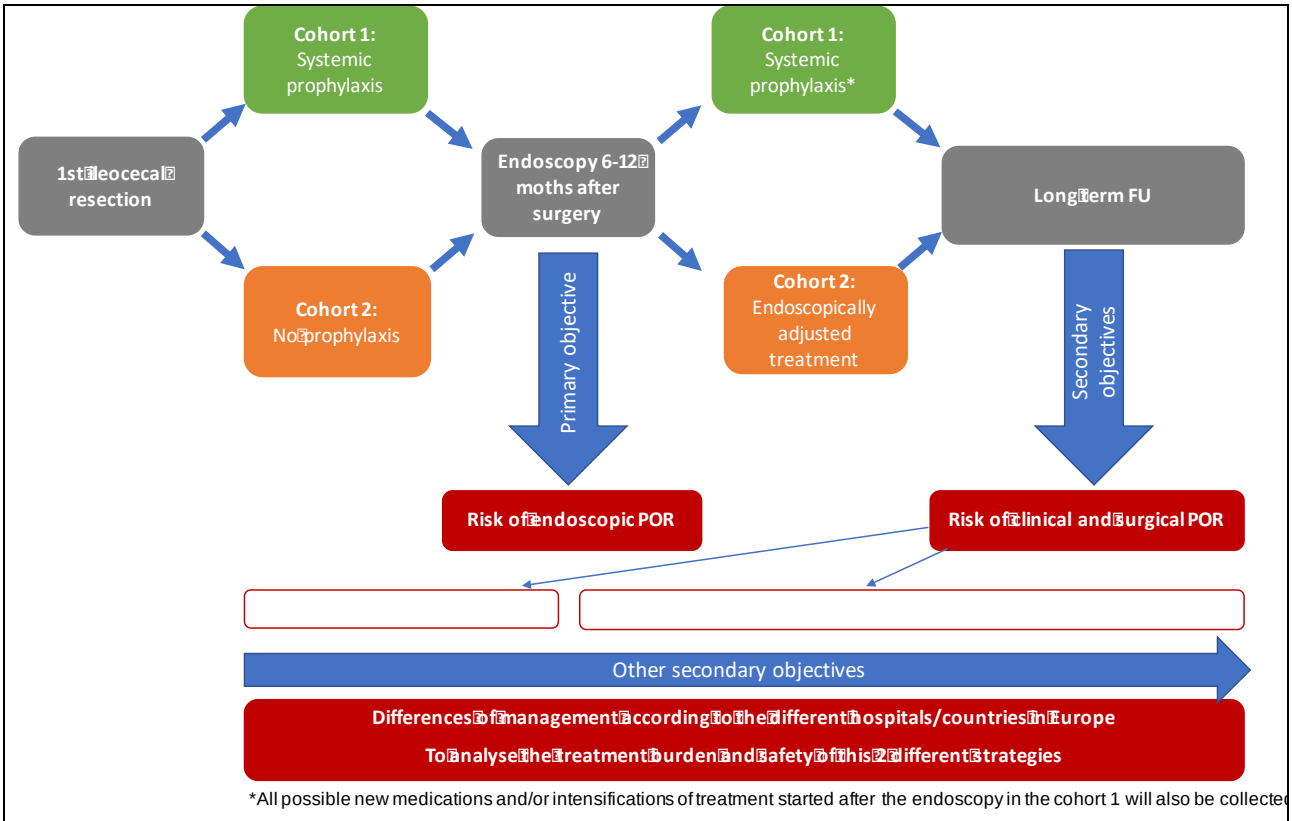
9. EFFICACY AND SAFETY MEASURES, STUDY PROCEDURES, STUDY FLOW-CHART

Efficacy measures:

- ePOR rate at short term (6-12 months after surgery)
- Time to cPOR and sPOR at long term (from surgery)
- Treatment burden (number of IMM and/or biologics during the follow-up, including the start date and stop date of every IMM and/or biologics)

Safety measures:

- Adverse events of medications after surgery
- Complications after surgery
- Number of abdominal surgeries
- Number of abdominal resections
- Length of resected small bowel
- Hospitalizations because of disease flare after surgery
- Mortality



10.STATISTICAL CONSIDERATIONS

Descriptive statistics will be calculated as absolute frequencies and percentages for discrete data; and as mean and standard deviation or as medians with interquartile ranges (IQR) for continuous data, according to data distribution.

Simple (unadjusted) analyses

Simple logistic regression models for prevalence of ePOR at 6-12 months after surgery will be fitted.

The time to cPOR and time to sPOR will be compared between treatment groups using the log-rank test. Survival curves will be estimated using the Kaplan-Meier method.

Comparisons of continuous outcomes between two groups will be performed using Student's *t*–test for independent samples or the Mann-Whitney U test (according to the distribution of data). Associations between categorical variables will be assessed using the Chi^2 test or the Fisher's exact test.

Multiple (adjusted) analyses

With a large number of covariates, there is a risk of finite sample bias in non-linear models. We will prevent extrapolation by refraining from modelling the association between outcome and confounders. Instead we will model the association between exposure (treatment) and confounders, by fitting a binary logistic regression model for prophylactic treatment. The propensity score expresses the conditional probability that a patient would have gotten prophylactic treatment on the basis of his/her covariates.

Next, we will fit a binary logistic regression model for ePOR at 6-12 months with treatment as explanatory variable and with adjustment for the propensity score. This will infer an effect measure for prophylactic treatment given that patients share the same propensity score.
In addition, we will fit a marginal structural model (using binary logistic regression upon weighting the data by the inverse of the propensity score) to infer the marginal treatment effect.
Likewise, Cox Proportional Hazards models will be fitted for time to cPOR and sPOR with adjustment for the propensity score.

All hypothesis testing will be performed at the two-sided 5% significance level.

11. CONSIDERATIONS ON SAFETY REPORTING, ETHICS, FEASIBILITY AND LOGISTICS

Data collection will be done by using RED-Cap (Research Electronic Data Capture), an electronic data base that has been already used for other ECCO studies. Given the exhaustive data needed regarding treatment periods and different outcomes along the FU, this electronic database can ensure the quality of this data collection in a comprenhensive way.

The study protocol will need to approved by the ethics committees of each participant centre.

12. APPENDICES

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