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Supplementary appendix

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SUPPLEMENTARY MATERIAL

Supplement to: Appendicectomy plus standard medical therapy versus standard medical therapy alone for maintenance of remission in ulcerative colitis (ACCURE): a pragmatic, open-label, international, superiority randomised trial.

Contents

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2. SUPPLEMENTAL METHODS

List of study sites and investigators

Recruitment site	Principal investigator(s)	No. of patients recruited
Amsterdam UMC	Prof. dr. W.A. Bemelman, surgeon Dr. C.J. Buskens, surgeon	107
Sint Franciscus Gasthuis	Prof. G.R. D'Haens, gastroenterologist Dr. R. West, gastroenterologist Dr. G. Mannaerts, surgeon	14
Queen Elizabeth Hospital Birmingham	Dr. R. Cooney, gastroenterologist Dr. S. Pathmakanthan, gastroenterologist Prof. dr. T. Iqbal, gastroenterologist	14
Isala Hospital	Prof. dr. T.D. Pinkney, surgeon Dr. J. Vecht, gastroenterologist Dr. E.G.J.M. Pierik, surgeon	13
Slotervaart Hospital	Dr. A.C.T.M. Depla, gastroenterologist Dr. Y.I.Z. Acherman, surgeon	11
Meander Medical Center	Dr. M. Brink, gastroenterologist Dr. E. Consten, surgeon	6
Onze Lieve Vrouwe Gasthuis – Locatie Oost	Dr. J. Jansen, gastroenterologist Dr. M. Gerhards, surgeon	4
Onze Lieve Vrouwe Gasthuis – Locatie West	Dr. P. Stokkers, gastroenterologist Dr. B. Vrouenraets, surgeon	4
Gelre Hospital	Dr. H. Braat, gastroenterologist Dr. P. van Duijvendijk, surgeon	3
Queen Elizabeth University Hospital	Dr. J.P. Seenan, gastroenterologist Dr. G.A. Nicholson, surgeon	3
Amstelland Hospital	Dr. M.E. Gielen, gastroenterologist	2
St. Vincents Hospital	Dr. G. Doherty, gastroenterologist Prof. Dr. D. Winter, surgeon	2
Medway Maritime Hospital	Dr. G. Sipos, gastroenterologist Dr. C. Grimes, surgeon	2
Addenbrooke's Hospital	Dr. T. Raine, gastroenterologist Dr. J. Davies, surgeon	2
Conquest Hospital	Dr. S. Fong, gastroenterologist Dr. S.M. Shaw, surgeon	2
New Cross Hospital	Prof. dr. M. Brookes, gastroenterologist Dr. N. Yassin, surgeon	2
Amphia Hospital	Dr. T. Seerden, gastroenterologist Dr. R. Crolla, surgeon	1
Flevoziekenhuis	Dr. R. C. Mallant, gastroenterologist Dr. J.D.W. van der Bilt, surgeon	1
St Marks Hospital	Prof. dr. N. Arebi, gastroenterologist Prof. Dr. O.D. Faiz, surgeon	1
Queen's Medical centre	Dr. G. Moran, gastroenterologist Dr. J.P. Evans, surgeon	1
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Bristol Royal infirmary	Dr. E. Arthurs, gastroenterologist Dr. J. Shabbir, surgeon	1

Data monitoring and safety committee members

Member	Degree	Function	Affiliation
M.J.W. Koelemaij	MD, PhD	Medical specialist - Surgery, clinical epidemiologist	Amsterdam UMC
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J.T.M. van der Meer	MD, PhD	Medical specialist, Internal Medicine – Infectious Diseases	Amsterdam UMC
J.H.M. van den Brande	MD, PhD	Medical specialist – Gastroenterologist	Tergooi Hospital
K. Hood	PhD	Professor of Trials, Dean of Research & Innovation	Cardiff University

Critical event committee

Member	Degree	Department	Affiliation
Dr. R. Hompes	MD, PhD	Surgery	Amsterdam UMC
Dr. M. Duijvestein	MD, PhD	Gastroenterology and Hepatology	Radboud University Medical Center

Inclusion and exclusion criteria

2.0.1. INCLUSION CRITERIA

- Aged 18 years and older.
- Established diagnosis of ulcerative colitis according to ECCO guideline
- Disease relapse within 12 months of randomisation medically treated until remission
- Clinically confirmed remission at time of randomisation with partial Mayo score less than 3 and presumptive endoscopic Mayo subscore of 0 or 1, identified by either:
  - Colonoscopy (within 3 months) examining the full length of the colon and rectum
  - Sigmoidoscopy (within 3 months) examining the last part of the colon (sigmoid and rectum) with faecal calprotectin less than 150 µg/g
  - Faecal calprotectin less than 150 µg/g with a personal history of raised faecal calprotectin levels (>500 µg/g) during a previous disease flare-up at any stage
- Obtained written informed consent

2.0.2. EXCLUSION CRITERIA:

- Prior appendicectomy or other major abdominal surgery precluding safe appendicectomy
- (Suspicion of) Crohn's disease
- Disease recently treated with biologicals within 3 months prior to inclusion
- Partial Mayo score ≥3 or endoscopic Mayo score >1
- Medical comorbidity that increases perioperative morbidity

Standard operating procedure – laparoscopic appendicectomy

Patients randomised to the intervention arm undergo standard 3-port laparoscopic appendicectomy performed under general anaesthesia by or under direct supervision of a senior gastrointestinal surgeon with extensive experience in the procedure (>20 laparoscopic appendicectomies), as a planned day-case procedure.
This appendicectomy operation is undertaken within 9 weeks of randomisation.
The appendix is removed using a laparoscopic endostapler enabling a safe and complete appendicectomy with the cross-stapling line at the base of the appendix at the junction with the caecal pole. Furthermore, usual preoperative and postoperative care and discharge criteria are used, with no standard additional antibiotics prescribed post-operatively.

Relapse definition & data

Relapse is prespecified by the Trial Steering committee and defined as:

- Total Mayo score of 5 or higher, with a Mayo endoscopic subscore of 2 or 3
  OR
- In absence of endoscopy, based on review by the critical event committee with clinical information suggesting relapse:
  a. Exacerbation of symptoms (elevated stool-frequency subscore of 1 point or higher)
     AND
  b. Rectal bleeding (rectal-bleeding subscore of 1 or higher)
     OR
  c. Faecal calprotectin level of 150 µg/g or higher, more than four weeks after appendicectomy surgery
     OR
  d. Intensified medical therapy other than 5-aminosalicylic acid

Relapse data included the start date of clinical symptoms, Mayo score, symptoms of the suspected relapse, initiated treatment and diagnostic tests (blood test, CT scan, MRI scan, endoscopy, faecal calprotectin).

Additional details prespecified statistical analysis

2. In the general estimation equation (GEE) models to analyse the medication use over time within treatment groups, we considered time, treatment and the interaction between treatment and time as model parameters. Medication use at baseline (T0) was adjusted for as a fixed effect.
3. In the generalised mixed models (GLMM) to analyse the partial Mayo score, total Mayo score and health-related quality of life (EQ-5D-3L, Global Quality of Life, total inflammatory bowel disease questionnaire (IBDQ) scores and IBDQ domain scores) over time within treatment groups, we considered time, treatment and the interaction between treatment and time as model parameters. Scores at baseline (T0) were adjusted for as a fixed effect.
4. Minimal clinically important difference (MCID) and its calculation

COMPUTE Diff_totalIBDQ=T6_IBDQ_totalscore-T0_IBDQ_totalscore.
EXECUTE.

	Patients answered 'yes' to global change question (n=xxx)	**Patients answered 'no' to global change question (n=xxx)**	**Missing global change question (n=xxx)**
Difference total IBDQ score from baseline to 12-months follow-up	A (SD)	B (SD)	F (SD)
MCID change from baseline to 12-months	A−B		NA
Plus-minus values are means (SD). NA: Not applicable.			

5. Syntax and calculation health-related quality of life (HRQL):
   a. Utility index score 5Q-5D-3L:

```
RECODE EQ5D1 EQ5D2 EQ5D3 EQ5D4 EQ5D5 ('1'=1) ('2'=2) ('3'=3) (MISSING=9) INTO eq5dmob eq5dzlfz eq5ddgac eq5dpijn eq5dstem.
RENAME VARIABLES
(eq5dmob eq5dzlfz eq5ddgac eq5dpijn eq5dstem = mo sc ua pd ad).
COMPUTE MVH_A1 = 1.
VARIABLE LABELS MVH_A1 'Lamers NL tariff'.
DO IF (NVALID(mo, sc, ua, pd, ad) < 5 ).
RECODE
MVH_A1 (1 = SYSMIS).
END IF.
IF (MAX(mo, sc, ua, pd, ad) > 1) MVH_A1 = MVH_A1 -·071.
IF (mo = 2) MVH_A1 = MVH_A1 - 0·036.
IF (mo = 3) MVH_A1 = MVH_A1 - 0·161.
IF (sc = 2) MVH_A1 = MVH_A1 - 0·082.
IF (sc = 3) MVH_A1 = MVH_A1 - 0·152.
IF (ua = 2) MVH_A1 = MVH_A1 - 0·032.
IF (ua = 3) MVH_A1 = MVH_A1 - 0·057.
IF (pd = 2) MVH_A1 = MVH_A1 - 0·086.
IF (pd = 3) MVH_A1 = MVH_A1 - 0·329.
IF (ad = 2) MVH_A1 = MVH_A1 - 0·124.
IF (ad = 3) MVH_A1 = MVH_A1 - 0·325.
IF (MAX(mo, sc, ua, pd, ad) > 2) MVH_A1 = MVH_A1 - 0·234.
EXECUTE.
```

   b. Syntax global QoL:

```
QoL Raw score:    global_QoL_average_RS=(EORTC29+EORTC30)/2
QoL scale:        global_QoL_scale=((global_QoL_average_RS-1)/6)*100.
```

   c. Syntax total IBDQ

      Total IBDQ score is the sum of all questionnaires (questionnaire 1 through 32)
      Total IBDQ score average per item = total IBDQ score/32

   d. Syntax IBDQ per domain and number of items per domain

      i. IBDQ domain bowel symptoms score

```
IBDQ_bowelsymptoms=(SIBDQ1+SIBDQ5+SIBDQ9+SIBDQ13+SIBDQ17+SIBDQ20+SIBDQ22+SIBDQ26+ SIBDQ29)/10.
```

      ii. *IBDQ domain emotional function score*

```
IBDQ_emotionalfunction=(SIBDQ3+SIBDQ7+SIBDQ11+SIBDQ15+SIBDQ19+SIBDQ21+SIBDQ23+
SIBDQ25+SIBDQ27+SIBDQ30+SIBDQ31+SIBDQ32)/12.
```

iii. *IBDQ domain systemic symptoms score:*
IBDQ_systemicsymptoms=(SIBDQ2+SIBDQ6+SIBDQ10+SIBDQ14+SIBDQ18)/5.
iv. *IBDQ domain Social function score:*
IBDQ_socialfunction=(SIBDQ4+SIBDQ8+SIBDQ12+SIBDQ16+SIBDQ28)/5.

3. SUPPLEMENTAL ANALYSIS

Prespecified additional analysis primary outcome

v. Logistic regression on the one-year UC relapse rate was used to:

- Explore the interaction between treatment and disease extent as stratification factor during randomisation (Table S2).
- Adjust for following covariates: age at time of randomisation, sex, current smoker, disease extent, and time between start of most recent exacerbation of UC and randomisation (Table S3).

vi. Interaction between treatment and country (UK vs NL; Table S1).

Selected covariance structures in GLMM

Outcome	Selected covariance structure
Total Mayo score	Toeplitz
Partial Mayo score	Unstructured
EQ-5D-3L utility score	Auto Regressive 1
Global QoL score	Unstructured
Total IBDQ score	Unstructured
IBDQ: bowel symptoms	Unstructured
IBDQ: systemic symptoms	Toeplitz
IBDQ: social function	Unstructured
IBDQ: emotional function††	Unstructured
The optimal covariance structure for the repeated measures data was determined using visual inspection and Aikaike's information criterion values. Covariance structures evaluated: unstructured, auto regressive 1, Toeplitz, and compound symmetry.	

Cohort-specific minimum clinically important difference (MCID)

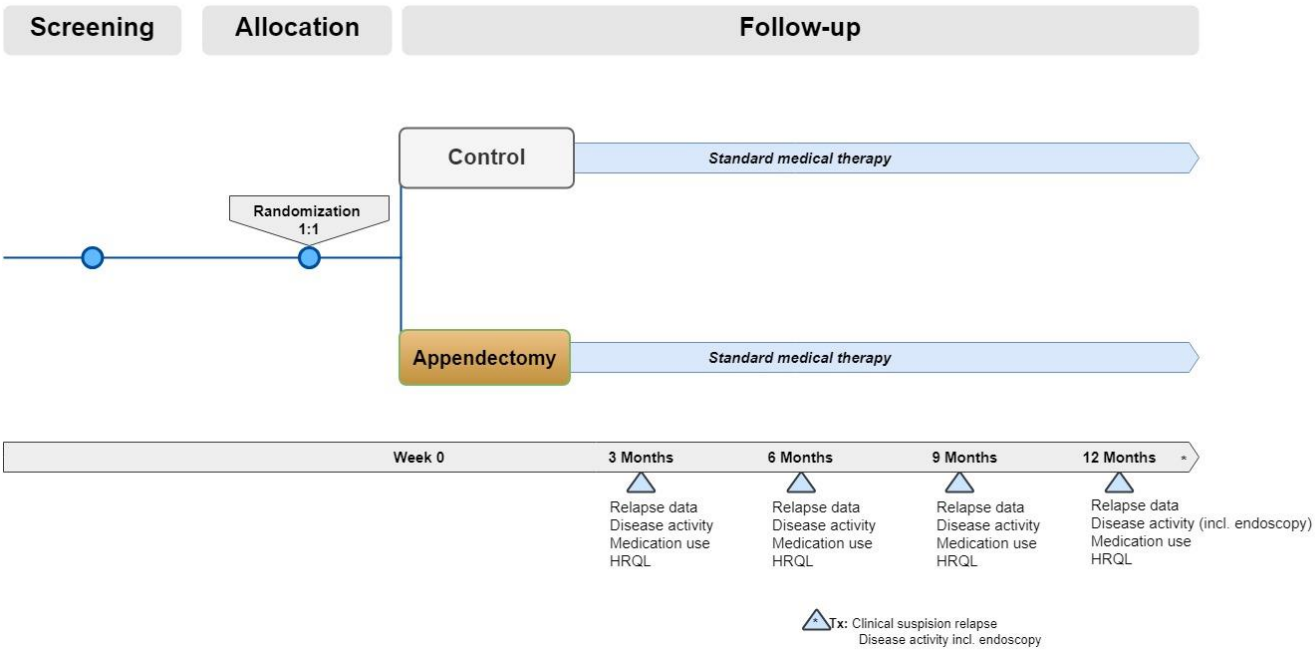
	Patients answered 'yes' to global change question (n=24)	Patients answered 'no' to global change question (n=25)	Missing global change question (n=83)
Difference total IBDQ score from baseline to 12-months follow-up	16·8 (16·5)	-1 (24·5)	1·5 (26·2)
MCID change from baseline to 12-months	17·83		NA
Data are mean (SD). NA: Not applicable.			

Correlation total IBDQ-score change and 'global-change question'

The Pearson correlation coefficient between the total IBDQ score change (from baseline to 12 months) was found to be r=0·398 (95% confidence interval 0·132–0·611, p=0·005)

4. SUPPLEMENTAL FIGURES

Figure S1: Study design of the ACCURE-trial



HRQL: Health-related quality of life

5. SUPPLEMENTAL TABLES

Table S1. Total relapse rate by country

Country	Appendicectomy n=98	Control n=97	p value for interaction	Odds ratio (95% confidence interval)
Netherlands	30/84 (35·7%)	48/82 (58·5%)	0·37	2·12 (0·42−10·80)
United-Kingdom	5/14 (35·7%)	6/15 (40·0%)		

Data are n/N (%).

Table S2. Logistic regression on the one-year relapse incidence to explore the interaction between treatment and disease extent as stratification factor.

	Odds ratio (95% confidence interval)	p value
Treatment group (appendicectomy vs control)	0·41 (0·16−1·02)	0·05
Disease extent		
Left-sided colitis vs proctitis	0·70 (0·28−1·73)	0·44
Pancolitis vs proctitis	1·08 (0·38−3·1)	0·88
Disease extent * treatment group		0·87
Left-sided colitis*appendicectomy	1·34 (0·36−5·07)	0·66
Pancolitis*appendicectomy	0·93 (0·22−4·04)	0·93

Table S3. Logistic regression between covariates as predictor for a relapse at 12 months

	Odds ratio (95% confidence interval)	p value
Treatment group (appendicectomy vs control)	0·40 (0·22−0·72)	**0·002**
Age, per year	1·01 (0·98−1·03)	0·60
Female sex	1·29 (0·70−2·36)	0·42
Current smoker	0·73 (0·30−1·77)	0·48
Disease extent		
Left-sided colitis vs proctitis	0·75 (0·38−1·49)	0·41
Pancolitis vs proctitis	1·10 (0·51−2·35)	0·81
Most recent exacerbation ulcerative colitis, per week	1·002 (0·99−1·02)	0·85

Table S4. Secondary outcome results*

	Baseline		3 months		6 months		9 months		12 months	
	Appendicectomy	Control	Appendicectomy	Control	Appendicectomy	Control	Appendicectomy	Control	Appendicectomy	Control
Relapses per patient										
1									29 (29·3%)	38 (38·8%)
2									7 (7·1%)	12 (12·2%)
3									0 (-)	5 (5·1%)
Time to first relapse, weeks									57 (27–69)	50† (14–57)
Mayo score‡										
Total Mayo score	1 (0–1)	0 (0–1)							1 (0–1)	1† (0–2)
Partial Mayo score	0 (0–1)	0 (0–0)	0 (0–2)	1 (0–2)	0 (0–2)	1 (0–2)	0 (0–1)	0 (0–2)	0 (0–1)	0 (0–1·5)
Colectomies within one year									0 (-)	0 (-)
HRQL										
EQ-5D-3L utility score ¶	0·84 (0·78–1·0)	1·0 (0·78–1·0)	0·81 (0·70–1·0)	0·84 (0·81–1·0)	0·84 (0·78–1·0)	0·84 (0·77–1·0)	0·84 (0·79–1·0)	0·84 (0·72–1·0)	0·84 (0·81–1·0)	0·84 (0·72–1·0)
Global QoL score ‖	75 (58–83)	75 (67–83)	75 (54–83)	75 (67–83)	75 (67–83)	83 (58–83)	83 (67–83)	75 (67–83)	83 (67–83)	83 (67–83)
Total IBDQ score**	188 (169–199)	191 (167–203)	185 (154–204)	191 (176–203)	188 (168–202)	191 (161–207)	193 (178–210)	187 (166–187)	198 (183–212)	187† (166–207)
IBDQ: bowel symptoms††	5·2 (4·8–5·7)	5·4 (4·7–5·9)	5·1 (4·5–5·7)	5·3 (4·8–5·9)	5·3 (4·7–5·7)	5·3 (4·6–5·9)	5·4 (4·9–6·0)	5·3 (4·4–5·9)	5·6 (5·0–6·0)	5·3† (4·7–5·8)
IBDQ: systemic symptoms††	5·2 (4·6–5·8)	5·4 (4·6–6·2)	5·4 (4·2–6·0)	5·5 (4·8–6·2)	5·2 (4·4–6·0)	5·4 (4·5–6·2)	5·6 (4·8–6·3)	5·6 (4·8–6.·0)	5·7 (5·0–6·4)	5·4 (4·6–5·4)
IBDQ: social function††	6·6 (5·8–7·0)	6·8 (6·1–7·0)	6·4 (5·7–7·0)	6.8 (6·2–7·0)	6·6 (6·0–7·0)	6·8 (5·6–7·0)	6·8 (6·2–7·0)	6·6 (6·2–7·0)	7·0 (6·6–7·0)	6·8 (6·0–7·0)
IBDQ: emotional function††	5·8 (5·2–6·3)	5·8 (5·0–6·3)	5·7 (4·7–6·4)	5·9 (5·3–6·4)	5·9 (5·1–6·4)	5·9 (5·0–6·5)	6·1 (5·3–6·5)	5·9 (5·2–6·3)	6·1 (5·5–6·5)	5·8 (5·2–6·9)

* Data are n (%) or median (IQR). Analyses for secondary outcomes were not adjusted and should be considered exploratory. In the generalised linear mixed models the baseline measurement was included as a fixed effect to adjust for initial differences between groups.

† $p<0·05$

‡ The Mayo score comprises four components: stool-frequency, rectal-bleeding, endoscopic subscore, and the physician's global assessment. Each component is rated on a 4-point scale ranging from 0 to 3, with the partial Mayo score ranging from 0 to 9 and the total Mayo score from 0 to 12; higher scores indicate more severe disease activity. The total Mayo score only differs from the partial Mayo score by including the Mayo endoscopic subscore as component. Data for total Mayo score were available for 73 in the appendicectomy group and 60 in the control group at 12 months. Data for partial Mayo score were available for 96 patients in the appendicectomy group and 93 in the control group at 3 months; 88 and 89, respectively, at 6 months; 90 and 85 at 9 months, 93 and 89 at 12 months.

¶ The utility score on the EuroQol 5-dimension 3-level questionnaire is an ordinal scale ranging from -0·329 to 1·00 to measure quality of life, with higher scores indicating better health status. Data for the utility score were available for 77 patients in the appendicectomy group and 73 in the control group at 3 months; 85 and 73, respectively, at 6 months; 85 and 74 at 9 months, 84 and 68 at 12 months.

‖The European Organisation for Research and Treatment of Cancer (EORTC) quality-of-life core (QLQ-C30) questionnaire is a scale ranging from 0 to 100 to measure global quality of life. A higher score indicates better global quality of life. Data for global quality of life were available for 77 patients in the appendicectomy group and 73 in the control group at 3 months; 86 and 73, respectively, at 6 months; 85 and 74 at 9 months, 84 and 68 at 12 months.

******The Inflammatory Bowel Disease Questionnaire (IBDQ) is a disease-specific scale containing four component subscales. Total score ranges from 32 to 224, with higher scores indicating better health-related quality of life. Data for total IBDQ scores were available for 76 patients in the appendicectomy group and 75 in the control group at 3 months; 87 and 73, respectively, at 6 months; 85 and 75 at 9 months, 82 and 67 at 12 months.

†† The IBDQ subscales, bowel symptoms, systemic symptoms, emotional function and social function scales ranges from 1 to 7, with higher scores indicating better health-related quality of life. Items per domain are 10, 12, 5 and 5, respectively.

Table S5. Generalised linear mixed models secondary endpoints*

	Coefficient (β) (95% confidence intervals)	p value
Total mayo score‡		
Treatment group (appendicectomy vs control)	-0·82 (-1·60−-0·05)	**0·04**
Baseline total mayo score	0·70 (0·11−1·29)	**0·02**
Partial Mayo score‡		
Treatment group (appendicectomy vs control)	-0·06 (-0·90−0·79)	0·90
Time	-0·13 (-0·28−0·02)	0·08
Treatment group (appendicectomy)*time	-0·07 (-0·27−0·14)	0·53
Baseline partial Mayo score	0·70 (0·36−1·04)	**<0·0001**
HRQL		
EQ-5D-3L utility score		
Treatment group (appendicectomy vs control)	-0·02 (-0·09−0·05)	0·56
Time	-0·001 (-0·02−0·02)	0·89
Treatment group (appendicectomy)*time	0·02 (-0·006−0·04)	0·14
Baseline EQ-5D-3L utility score	0·50 (0·40−0·60)	**<0·0001**
Global QoL		
Treatment group (appendicectomy vs control)	-4·8 (-11·27−1·59)	0·14
Time	0·55 (-0·97−2·07)	0·48
Treatment group (appendicectomy)*time	1·91 (-0·17−3·99)	0·07
Baseline global QoL	0·51 (0·41−0·62)	**<0·0001**
Total IBDQ score		
Treatment group (appendicectomy vs control)	-7·4 (-15·61−0·82)	0·08
Time	0·53 (-1·36−2·41)	0·58
Treatment group (appendicectomy)*time	3·80 (1·20−6·40)	**0·005**
Baseline total IBDQ score	0·69 (0·57−0·81)	**<0·0001**
IBDQ: bowel symptoms		
Treatment group (appendicectomy vs control)	-0·26 (-0·53−0·004)	0·05
Time	-0·03 (-0·09−0·04)	0·44
Treatment group (appendicectomy)*time	0·16 (0·06−0·25)	**0·001**
Baseline IBDQ: bowel symptoms	0·51 (0·40-0·62)	**<0·0001**
IBDQ: systemic symptoms		
Treatment group (appendicectomy vs control)	-0·25 (-0·61−0·12)	0·18
Time	0·04 (-0·04−0·12)	0·34
Treatment group (appendicectomy)*time	0·11 (-0·002−0·22)	0·05
Baseline IBDQ: systemic symptoms	0·66 (0·55−0·78)	**<0·0001**
IBDQ: social function		
Treatment group (appendicectomy vs control)	-0·26 (-0·60−0·07)	0·13
Time	0·04 (-0·03−0·11)	0·27
Treatment group (appendicectomy)*time	0·09 (-0·01−0·19)	0·08
Baseline IBDQ: social function	0·57 (0·45−0·69)	**<0·0001**
IBDQ: emotional function		
Treatment group (appendicectomy vs control)	-0·16 (-0·42−0·10)	0·23
Time	0·03 (-0·04−0·09)	0·39
Treatment group (appendicectomy)*time	0·08 (-0·003−0·17)	0·06
Baseline IBDQ: emotional function	0·72 (0·62−0·83)	**<0·0001**

* The baseline measurement was included as a fixed effect to adjust for initial differences between groups.
‡ Continuous variable in the model.

Table S6. Medication use‖

	Baseline		3 months		6 months		9 months		12 months	
Medication	**Appendicectomy**	**Control**	**Appendicectomy**	**Control**	**Appendicectomy**	**Control**	**Appendicectomy**	**Control**	**Appendicectomy**	**Control**
None	9 (9·1%)	4 (4·1%)	9 (9·3%)	5 (5·4%)	14 (15·7%)	6 (6·7%)	17 (18·7%)	8 (9·2%)	22 (23·4%)	7 (7·7%)
Topical therapy*	23 (23·2%)	22 (22·7%)	27 (27·8%)	24 (25·8%)	28 (31·5%)	23 (25·6%)	21 (23·1%)	18 (20·7%)	19 (20·2%)	19 (20·9%)
Oral 5-aminosalicylic acid	76 (76·8%)	81 (82·7%)	76 (78·4%)	82 (88·2%)	63 (70·8%)	73 (81·1%)	59 (64·8%)	68 (78·2%)	58 (61·7%)	73 (80·2%)
Systemic steroid†	1 (1·0%)	1 (1·0%)	4 (4·1%)	3 (3·2%)	5 (5·6%)	5 (5·6%)	6 (6·6)	3 (3·4%)	1 (1·1%)	4 (4·4%)
Immunomodulators‡	6 (6·1%)	12 (12·4%)	7 (7·2%)	12 (12·9%)	5 (5·6%)	10 (11·1%)	6 (6·6%)	12 (13·8%)	7 (7·4%)	13 (14·3%)
Biologic agents§	0 (-)	0 (-)	0 (-)	2 (2·2%)	0 (-)	4 (4·4%)	1 (1·1%)	4 (4·6%)	3 (3·2%)	5¶ (5·5%)

Data are n (%).

‖ In the generalised estimating equation the baseline measurement was included as a fixed effect to adjust for initial differences between groups. Data for medication use were available for 97 patients in the appendicectomy group and 93 in the control group at 3 months; 89 and 90, respectively, at 6 months; 91 and 87 at 9 months, 94 and 91 at 12 months.

*Topical therapy was defined as rectal enemas or suppositories

†Systemic steroids were oral corticosteroids (prednisone or equivalents or budesonide)

‡ Immunomodulators were azathioprine, methotrexate, thioguanine

§ Biologic agents were biological medication (anti-TNF, integrin antibody or small molecules such as janus kinase inhibitors)

¶ p=0·01

Table S7. General estimation equation medication use*

	Coefficient (β) (95% confidence interval)	p value
No medication		
Treatment group (appendicectomy vs control)	1·07 (0·31−3·62)	0·92
Time	1·15 (0·93−1·43)	0·19
Treatment group (appendicectomy)*time	1·27 (0·92−1·77)	0·15
Baseline no medication	9·3 (3·12−27·78)	**<0·0001**
Topical therapy		
Treatment group (appendicectomy vs control)	1·23 (0·52−2·91)	0·64
Time	0·89 (0·74−1·07)	0·21
Treatment group (appendicectomy)*time	0·95 (0·71−1·29)	0·76
Baseline topical therapy	5·63 (3·31−9·59)	**<0·0001**
Oral 5-aminosalicylic acid		
Treatment group (appendicectomy vs control)	0·87 (0·34−2·19)	0·76
Time	0·82 (0·69−0·97)	**0·02**
Treatment group (appendicectomy)*time	0·84 (0·66−1·08)	0·18
Baseline oral 5-aminosalicylic acid	13·52 (6·62−27·64)	**<0·001**
Systemic steroids		
Treatment group (appendicectomy vs control)	2·00 (0·44−9·09)	0·37
Time	1·10 (0·69−1·75)	0·68
Treatment group (appendicectomy)*time	0·77 (0·42−1·40)	0·39
Baseline systemic steroids	51·35 (6·59−399·85)	**0·00017**
Immunomodulators		
Treatment group (appendicectomy vs control)	0·38 (0·06−2·64)	0·33
Time	1·06 (0·67−1·67)	0·82
Treatment group (appendicectomy)*time	1·01 (0·43−2·39)	0·99
Baseline immunomodulators	425·37 (100·51−1800·19)	**<0·0001**
Biologic agents		
Treatment group (appendicectomy vs control)	0·003 (0·00−0·27)	**0·011**
Time	1·30 (0·96−1·76)	0·10
Treatment group(appendicectomy)*time	3·76 (1·31−10·83)	**0·014**
Baseline biologic agents	NA	NA

* The baseline measurement was included as a fixed effect to adjust for initial differences between groups. NA: Not applicable.

Table S8. Frequency of missing secondary endpoint data

	Baseline		3 months		6 months		9 months		12 months/end of study	
Variable	**Appendicectomy**	**Control**	**Appendicectomy**	**Control**	**Appendicectomy**	**Control**	**Appendicectomy**	**Control**	**Appendicectomy**	**Control**
Relapses per patient									0 (-)	0 (-)
Time to first relapse									0 (-)	0 (-)
Total Mayo score‡	20 (20·2%)	12 (12·2%)							26 (26·3%)	38 (38·8%)
Partial Mayo score	0 (-)	0 (-)	3 (3·0%)	5 (5·1%)	11 (11·1%)	9 (9·2%)	9 (9·1%)	13 (13·3%)	6 (6·1%)	9 (9·2%)
Colectomies within one year									0 (-)	0 (-)
HRQL§										
EQ-5D-3L score¶	11 (11·1%)	14 (14·3%)	22 (22·2%)	24 (24·5%)	14 (14·1%)	25 (25·5%)	14 (14·1%)	24 (24·5%)	15 (15·3%)	30 (30·6%)
Global QoL score‖	15 (15·3%)	21 (21·4%)	22 (22·2%)	25 (25·5%)	13 (13·1%)	25 (25·5%)	14 (14·1%)	24 (24·5%)	15 (15·3%)	30 (30·6%)
Total IBDQ score**	11 (11·1%)	14 (14·3%)	23 (23·2%)	23 (23·5%)	12 (12·1%)	25 (25·5%)	14 (14·1%)	23 (23·5%)	17 (17·2%)	31 (31·6%)
IBDQ: bowel symptoms††	11 (11·1%)	14 (14·3%)	22 (22·2%)	23 (23·5%)	12 (12·1%)	25 (25·5%)	14 (14·1%)	23 (23·5%)	15 (15·3%)	31 (31·6%)
IBDQ: systemic symptoms††	11 (11·1%)	14 (14·3%)	22 (22·2%)	22 (22·4%)	12 (12·1%)	25 (25·5%)	14 (14·1%)	23 (23·5%)	15 (15·3%)	31 (31·6%)
IBDQ: social function††	11 (11·1%)	14 (14·3%)	23 (23·2%)	23 (23·5%)	12 (12·1%)	25 (25·5%)	14 (14·1%)	23 (23·5%)	17 (17·2%)	31 (31·6%)
IBDQ: emotional function††	11 (11·1%)	14 (14·3%)	22 (22·2%)	23 (23·5%)	12 (12·1%)	25 (25·5%)	14 (14·1%)	23 (23·5%)	15 (15·3%)	31 (31·6%)

Data are n (%).

‡ The Mayo score comprises four components: stool-frequency, rectal-bleeding, endoscopic subscore, and the physician's global assessment. Each component is rated on a 4-point scale ranging from 0 to 3, with the partial Mayo score ranging from 0 to 9 and the total Mayo score from 0 to 12; higher scores indicate more severe disease activity. The total Mayo score only differs from the partial Mayo score by including the Mayo endoscopic subscore as component.

§ Health-related quality of life (HRQL) data were missing for 23 patients in the appendicectomy group and 30 in the control group.

¶ The utility score on the EuroQol 5-Dimension 3-Level questionnaire is an ordinal scale ranging from -0·329 to 1·00 to measure quality of life, with higher scores indicating better health status.

‖The European Organisation for Research and Treatment of Cancer (EORTC) quality-of-life core (QLQ-C30) questionnaire is a scale ranging from 0 to 100 to measure global quality of life. A higher score indicates better global quality of life.

**The Inflammatory Bowel Disease Questionnaire (IBDQ) is a disease-specific scale containing four component subscales. Total score ranges from 32 to 224, with higher scores indicating better health-related quality of life.

†† The IBDQ subscales, bowel symptoms, systemic symptoms, emotional function and social function scales ranges from 1 to 7, with higher scores indicating better health-related quality of life. Items per domain are 10, 12, 5 and 5, respectively.

Table S9. Safety (reported as-treated)

	Appendicectomy (n=96)	Control (n=101)	Absolute risk difference (95% CI)	p value
Serious adverse events	2 (2·1%)	0 (-)	2·1% (-0·77 to 4·9)	0·24
Adverse events	11 (11·5%)	10 (9·9%)	1·6% (-7·1 to 10·2)	0·72
Gastrointestinal (nonspecific)	*2 (2·1%)*	*2 (2·0%)*		
Gastrointestinal (IBD)	*3 (3·1%)*	*1 (1·0%)*		
Endocrine	*1 (1·0%)*			
Metabolism	*1 (1·0%)*	*1 (1·0%)*		
Infections	*2 (2·1%)*	*1 (1·0%)*		
Musculoskeletal	*1 (1·0%)*			
Neoplasms				
Low-grade appendiceal mucinous neoplasm (incidentally found in resected appendix specimens)	*2 (2·1%)*			
Renal and urinary disorders		*1 (1·0%)*		
Skin		*3 (3·0%)*		
Postoperative complications	5 (5·2%)			
Minor (Clavien-Dindo <III)	*3 (3·2%)*			
Major (Clavien-Dindo ≥III)	*2 (2·1%)*			

Data are n (%). IBD: inflammatory bowel disease.

Table S10. Serious adverse events (reported as-treated)

Group	Serious adverse event
Appendicectomy	Ischemia of the terminal ileum due to internal herniation requiring laparotomy and 60 cm small bowel resection with a side-to-side ileo-ascendostomy.
Appendicectomy	Postoperative bleed/hematoma, returned to theatre for laparoscopic washout of hematoma.

Table S11. Sensitivity analysis including patients with follow-up endoscopy only (n=159)

Outcome	Appendicectomy (n=85)	Control (n=174)	Relative risk (95% CI)	Risk difference (95% CI)	p value
Total relapse rate	30 (35·3%)	43 (58·1%)	60·7% (42·9% to 85·9%)	22·8% (7·7% to 38·0%)	0·004

A sensitivity analysis was performed by including patients with follow-up endoscopy only.

The effect of Appendectomy on the Clinical Course of UlceRativE colitis: A randomized multicenter trial (ACCURE-trial)

PROTOCOL TITLE:

The effect of Appendectomy on the Clinical Course of Ulcerative Colitis: a randomized multicenter trial

Short title	The effect of Appendectomy on the Clinical Course of Ulcerative Colitis
Acronym	ACCURE trial
Version	19
Date	18-05-2021
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	Hospital, Addenbrooke's Hospital, St Marks Hospital, Conquest Hospital, New Cross Hospital, Queen's Medical centre, Countess of Chester Hospital, Bristol Royal infirmary.
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Name	Signature	Date
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Overview Protocol Amendments ACCURE-trial

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version.

Amendment number	Date of amendment	Protocol version number	Type of amendment	Summary of amendment
01	07-11-2012	10	Substantial	• Clarification and removal of in- and exclusion criteria to improve the generalizability of the study population (no age limit, no limit on date of diagnosis prior to randomisation, no limitations on prior corticosteroid use, disease relapse within 12 months prior to randomisation). • Minor corrections..
02	06-12-2012	11	Substantial	• Update to study procedure (sigmoidoscopy with faecal calprotectin is accepted if colonoscopy could not be performed to define remission prior to randomisation). • Minor corrections.
03	01-08-2016	12	Substantial	• Clarification of inclusion criteria (negative stool culture). • Clarification of schema and patient flow. • Clarified who can undertake trial activities. • Update study procedure (faecal calprotectin as adequate and less invasive alternative measurement to colonoscopy three years after randomisation). • Minor corrections.
04	13-01-2017	13	Substantial	• Clarification and removal of exclusion criteria (disease treated with biologicals or immunomodulators for more than three months prior to inclusion). • Update study procedure (questionnaires via myIBDcoach application to increase response rate). • Minor corrections.
05	21-08-2018	14	Substantial	• Clarification and removal of exclusion criteria (immunomodulators). • Update study procedure (added faecal calprotectine measurement one week postoperatively to study symptoms postoperatively and FCP as marker) • Update secondary objectives (added ‘global change question’). • Inclusion of ACCURE-UK arm, increasing power from 80% to 90% • Minor corrections.
06	04-10-2018	15 + 16	Non-substantial	• Administrative changes including TMG, TSC and DMC members.
07	28-03-2018	17	Substantial	• Inclusion of critical event committee. • Administrative changes including updates to TMG, TSC and DMC members and participating centers.
08	24-08-2020	18	Substantial	• Inclusion of section on COVID-19 and measures addressing COVID-19 throughout. • Update to assessment schedule. • Administrative changes including updates to TMG, TSC and DMC members. • Minor corrections.
09	18-05-2021	19	Substantial	• Clarification of primary objective: criteria critical event committee. • Clarification of secondary objective: time to relapse definition added • Inclusion of process for obtaining informed consent remotely. • Minor corrections.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**ABR form (General Assessment and Registration form) is the application form that is required for submission to the accredited Ethics Committee (ABR = Algemene Beoordeling en Registratie)**
AE	**Adverse Event**
AR	**Adverse Reaction**
CA	**Competent Authority**
CCMO	**Central Committee on Research Involving Human Subjects**
CV	**Curriculum Vitae**
DSMB	**Data Safety Monitoring Board**
EU	**European Union**
EudraCT	**European drug regulatory affairs Clinical Trials GCP Good Clinical Practice**
IB	**Investigator's Brochure**
IC	**Informed Consent**
IMP	**Investigational Medicinal Product**
IMPD	**Investigational Medicinal Product Dossier**
METC	**Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)**
(S)AE	**Serious Adverse Event**
SPC	**Summary of Product Characteristics (in Dutch: officiële productinfomatie IB1-tekst)**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
Wbp	**Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)**
WMO	**Medical Research Involving Human Subjects Act (Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale: The annual incidence of ulcerative colitis (UC) amounts to 6-8 new cases per 100,000. Patients are intentionally treated medically and colitis refractory to medical management is treated surgically, mostly by means of an emergency colectomy or elective proctocolectomy with ileal J-pouch anastomosis. Over the past 10 years evidence has been accumulating indicating that the appendix has an immunomodulatory role in patients with UC reducing the need for medication and even colectomy. The concept that appendectomy may modulate the disease avoiding medical and surgical treatment, and costs is very appealing and exciting. This is especially true for appendectomy, as this is a relatively simple procedure that can be performed in day care.

Objective: The objective of this study is to evaluate the short-term and medium-term effectiveness of appendectomy to maintain remission in patients with an established diagnosis of ulcerative colitis treated for a relapse within 12 months prior to randomization.

Study design: The design of the study is a multicenter prospective randomized study.

Study population: In this study patients aged 18 years and older with an established diagnosis of UC (any extent of disease) and a disease relapse within 12 months of randomization, medically treated with 5-ASA (oral and/or topical), corticosteroids, immunomodulators, and/or after a washout period of at least 3 months after treatment with biologicals until clinically confirmed remission (partial Mayo score <3 confirmed by an endoscopic Mayo score of 0 or 1 or faecal calprotectin level below 150 µg/g) can be included.

Intervention: Patients will be randomized to laparoscopic appendectomy in day care setting or no appendectomy.

Main study parameters/endpoints: The primary endpoint is the one year UC relapse rate in both groups (defined as a total Mayo-score ≥5 with endoscopy subscore of 2 or 3 or clinically as an exacerbation of symptoms and rectal bleeding or FCP>150 µg/g (> 4 weeks after surgery) or intensified medical therapy other than 5-ASA therapy).

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Both groups of patients will be followed for one year by the medical staff and trial nurses in order to monitor morbidity of treatment, use of medication or necessity of surgery, disease activity as measured by endoscopy (at inclusion and after 12 months) and the non-invasive 9-point partial Mayo score (after 3, 6, 9 and 12 months), Health related Quality of life as measured by the EQ-5D, EORTC-QLQ-C30-QL and IBDQ questionnaires (at inclusion and every 3 months thereafter) and a 'global change question' at 12 months follow-up ("Since the start of the study, have your UC symptoms improved overall?", utilization of health care, direct medical and non-medical costs and friction costs related to leave from work. Patients will be contacted by telephone every 3 months by a trial nurse or the research resident to assess medication usage, complications, additional interventions, re-admissions, duration of hospital stay and visits to the outpatient clinic, number of days of sick leave and of social absence and to ensure completions of the questionnaires.

Patients will be followed up by the gastroenterologist or the research resident at the outpatient clinic or per telephone at 6 weeks and 3, 6, 9 and 12 months after inclusion, other visits are scheduled on indication. At the end of the study period, after 12 months, a second colonoscopy (or sigmoidoscopy with fecal calprotectin) will be performed to assess mucosal healing. In the 5 years following the study the gastroenterologists will be asked to measure the non-invasive 9-point partial Mayo score every 6 months during outpatient clinic appointments. Participants will have access to a telemedicine application (MyIBDcoach[1]) to fill out the Mayo score electronically when no outpatient clinic appointment is scheduled.

[1] Degens J, Romberg-Camps M, Cilissen M et al. DOP090. Results from a feasibility study with the telemedicine tool myIBDcoach in the Netherlands. ECCO 2014, DOP session 10 clinical practice.

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1. INTRODUCTION AND RATIONALE

1.1 Introduction

Ulcerative Colitis (UC) diffusely affects the mucosa of the colon, and is characterized by episodes of acute or chronic inflammation (1). UC should be regarded as a multifactorial disease involving an interaction between genetic and environmental factors that give rise to an inappropriate immunologic response (2). Disease activity is confined to the colon, and almost always involves the rectum. From there it may extent continuously to proximal. Patients can be classified as having proctitis (disease limited to the rectum), left-sided colitis (disease activity extending to proximal but not beyond the splenic flexure), or pancolitis (with disease activity extending from the rectum proximally to the cecum). The majority of UC patients can be treated effectively by medical therapy, applying 5-aminosalicylic acids (oral and/or topical) as first line therapy, but frequently (topical or systemic) corticosteroids are needed. More refractory patients need immunosuppression with thiopurines and/or TNF alpha blockers. Ulcerative colitis refractory to medical management is treated surgically, mostly by means of a proctocolectomy with ileal J-pouch anastomosis. Up to 20%-30% of patients with UC ultimately require surgery (3, 4). The procedure can be complicated by the development of anastomotic leakage requiring reoperation and later by pouchitis, high stool frequency, fecal incontinence and reduced fertility. A meta-analysis of complications showed pouch failure in 0.5-1% per year, pelvic sepsis in 9.5% and severe, mild and urge fecal incontinence in 3.7%, 17% and 7.3%, respectively (5).

The triggering factor for the development of UC is still unknown. However, cytokine imbalance and the production of inflammatory mediators by activated CD4+ T cells are considered to play an important role in the pathogenesis of UC. T-helper type 2 cells and their cytokines, particularly interleukin (IL)-4, have been suggested to enhance the development of UC (6). The cytokine production within the appendix has been proposed to trigger an immunological cascade in the colorectum (7, 8). The appendix is therefore suggested to be a priming site in the development of UC (9).

There is growing evidence in the literature linking prior appendectomy inversely with subsequent risk of the development of ulcerative colitis. This inverse association was first reported in 1987 as an unexpected finding in a study of childhood determinants of inflammatory bowel diseases (10). Only when another study (11) reported a low incidence of 0.6% of appendectomy in UC patients compared to an incidence of more than 25% in controls from orthopaedic clinics, this inverse relation drew major attention. Since then, various epidemiological and case control studies have investigated the association between appendicitis, appendectomy and the risk of developing UC.

Furthermore, a study with T-cell receptor α chain knockout mouse model of colitis showed that the development of inflammation is suppressed in those animals that undergo appendectomies, particularly at 3-5 weeks of age (12). Together with the findings that appendiceal inflammation with

cecal sparing occurs commonly as a skip lesion in UC, even in left-sided colitis (13-15), the appendix is suggested to be closely related to the pathogenesis of UC and considered as a treatment option.

If an appendectomy can protect UC patients from future use of medication or even surgery, the initial additional costs and potential side effects of appendectomy will be offset by substantial gain in health and reduction in costs later on. This is especially true for appendectomy, as this is a relatively simple procedure that can be performed in day care.

The annual incidence of ulcerative colitis (UC) amounts 6-8 new cases per 100,000, which means 1000-1300 new patients annually in the Netherlands. Naïve patients are generally treated until remission followed by tapering the medication. Over the past 10 years evidence has been accumulating indicating that appendectomy has an immunomodulatory role in patients with ulcerative colitis reducing the need for medication and even colectomy.

A systematic literature search of the electronic databases PubMed, the Cochrane library, and EMBASE was performed up to August 2nd, 2010 with both keywords and MeSH terms and consisted of: ulcerative colitis OR colitis, ulcerative [MESH] AND (appendix OR appendectomy OR appendicectomy OR appendiceal).

Studies designed to evaluate the effect of appendectomy on the clinical course in patients with UC were included. No limits were applied to the timing of appendectomy in UC patients. All controlled trials and observational studies designed to investigate this effect were selected. Inclusion was not otherwise restricted by study size, language, or publication type.

The methodological quality of the studies included was assessed using the Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. Study selection, quality assessment and data extraction was independently done by two reviewers. Primary endpoints were the number of relapses, the use of steroids, the number of hospital admissions and the number of colectomies.

Of the 4 outcome measurements, Naganuma *et al.* studied the relapse number of patients. In this study, a relapse was defined as hospitalization or increase in clinical activity of UC. This study found a lower relapse rate in patients who had an appendectomy before onset of UC (57.1%) compared with controls who did not undergo appendectomy (78.6%, absolute risk reduction (ARR) 21.5%; 95% confidence interval (CI) -1.71% - 45.92%).

The use of steroids in both the appendectomy and non-appendectomy patients was investigated in 4 of the 6 studies. Radford-Smith *et al.* and Florin *et al.* found a lesser requirement for immunosuppression (defined as therapy with azathioprine, 6-mercaptopurine, methotrexate or mycophenolate) in the UC patients who had an appendectomy (4.8 and 5.6%) compared to the controls (25% and 27%; ARR 20.2%; 95% CI 9.67% - 30.46% and ARR 21.4%; 95% CI 10.32%-32.97%, respectively). Selby *et al.* found no differences in ongoing immunosuppression requirement (defined as therapy with azathioprine, 6-mercaptopurine, or cyclosporine) between patients who had

an appendectomy before onset of UC (33.3%), patients who had an appendectomy after onset of UC (12.5%) or the control group (18%). The study of Cosnes *et al.* found no difference in the necessity for oral steroids in the appendectomised (67%) and non-appendectomised (70%) patients.

In the study by Hallas *et al.* the number of hospital admissions in patients with UC before and after the appendectomy compared to hospital admissions in controls before and after the index date were reported. The number of hospital admissions in the appendectomy group was 171 before and 117 after appendectomy (47% decrease). The number of admissions in the control group was 631 before and 424 after the index date (49% decrease).

In five studies the colectomy rate was investigated. Both Selby *et al.* and Hallas *et al.* found no differences in colectomy rates between the patients who had an appendectomy before onset of UC (12.5% and 4.5%, respectively), patients who had an appendectomy after onset of UC (16.7% in the study by Selby *et al.*) or the control group (8.8% and 5.2%, respectively). In the study by Cosnes *et al.* a higher proportion of appendectomised patients required colectomy (14.3%) compared to the non-appendectomised patients (5.6%, ARR for non-appendectomised patients 8.7%; 95% CI -1.29% - 18.66%). Radford-Smith *et al.* and Florin *et al.* both found a lower colectomy rate in the appendectomy group (0% and 5.3%, respectively) compared to the non-appendectomy group (21.4 and 24%, ARR 21.4%; 95% CI 13.17% - 28.79% and ARR 18.7%; 95% CI 7.50% - 29.97%, respectively).

Additionally, in a case series by Bolin *et al.* (27) 50 patients with ulcerative proctitis underwent appendectomy. The Simple Clinical Colitis Activity index (SCCAI) improved significantly from a median of 9 to a median of 2 ($p<0.0005$) in 40 patients (80%). From these patients, 15 patients (30%) had no need for continuing medical therapy. The index remained unchanged in 10 of 50 patients (20%). The initial clinical response has been maintained in 37 of 40 patients (93%) for up to three years.

Based on a review of the available evidence it is reasonable to assume that there will be a 50% reduction in relapse rate in patients treated by appendectomy. These patients will not need further remission induction treatment, thereby saving health care costs from medical therapy and surgery. The annual per-patient direct medical costs of ulcerative colitis range from €8949 to €10 395 in Europe. Based on these data, 1000 - 1300 new patients in the Netherlands will cost 10-13 mil. Euros annually. Appendectomy in day care costs 1300 Euros. If an appendectomy reduces the need for further treatment of ulcerative colitis by 50% a single investment of 1.3 - 1.7 mil. to perform the appendectomy will save 5 - 7.5 mil. Euros annually overall.

The available evidence points towards a therapeutic effect of appendectomy in UC. However, the available studies are most of limited quality and confounded by many factors. A randomized study must overcome these methodological problems.

1.2 Rationale

In this study patients with an established diagnosis of UC (any extent of disease) and a disease relapse within 12 months of randomization, medically treated until remission (with 5-ASA (oral and/or topical), corticosteroids, immunomodulators (azathioprine, 6-mercaptopurine, cyclosporine, tacrolimus or methotrexate) and/or after a washout period of at least 3 months after treatment with biologicals such as infliximab, adalimumab or vedolizumab) will be randomized to laparoscopic appendectomy or to no appendectomy. If an appendectomy can protect UC patients from future use of medication or even surgery, the initial additional costs and potential side effects of appendectomy will be offset by substantial gain in health and reduction in costs later on. This is especially true for appendectomy, as this is a relatively simple procedure that can be performed in day care.

Currently, no trials are being initiated on this issue as far as we know it. This study aims to answer the question if laparoscopic appendectomy will lower the relapse rate of patients with an established diagnosis of ulcerative colitis after remission has been achieved. Both the appendectomy group as well as the non-appendectomy group will be followed for one year by the medical staff and trial nurses in order to monitor morbidity of treatment, use of medication or necessity of surgery, disease activity as measured by endoscopy (at inclusion and after 12 months) and the Mayo score (at inclusion and after 3, 6, 9 and 12 months), quality of life as measured by the EQ-5D, EORTC-QLQ-C30-QL and IBDQ questionnaires (at inclusion and every 3 months thereafter) and a ‘global change question’ at 12 months follow- up (“Since the start of the study, have your UC symptoms improved overall?”, consumption of health care, direct costs and leave from work.

2. OBJECTIVES

The objective of this study is to evaluate the short-term and medium-term effectiveness of appendectomy to maintain remission in patients with an established diagnosis of ulcerative colitis treated for a relapse within 12 months prior to randomization.
Thus, we try to answer the following questions:

1. Does laparoscopic appendectomy lower the relapse rate of patients with an established diagnosis of UC and disease relapse within 12 months of randomization, after clinical and endoscopic remission has been achieved?
2. Does laparoscopic appendectomy prolong the time to relapse after remission?
3. Do patients treated with appendectomy have an overall better health related quality of life?
4. Is laparoscopic appendectomy a cost-effective strategy in the treatment of diagnosed UC in subgroup analysis?

Primary Objective:

1. The one year UC relapse rate (defined as a total Mayo-score ≥5 with endoscopy score of 2 or 3, or clinically as an exacerbation of symptoms and rectal bleeding or FCP>150 (> 4 weeks after surgery) or intensified medical therapy other than 5-ASA therapy).

Secondary Objectives:

1. Number of relapses per patient after 12 months
2. Time to first relapse, defined as the time between randomization in the control group or laparoscopic appendectomy in the intervention group and, the first day of clinical symptoms of an endoscopically or clinically confirmed relapse.
3. Disease activity, as measured with fecal calprotectin and the Mayo score.
4. Number of colectomies at one year follow-up
5. Medication usage (no medication, topical therapy, 5-ASA, systemic steroids, immunomodulators, biologicals, small molecules, trial medication) at baseline, 3, 6 9 and 12 months
6. Health related quality of life and costs (EQ-5D, EORTC-QLQ-C30-QL, IBDQ, and a ‘global change question’).

3. STUDY DESIGN

The study is designed as a multicenter randomized clinical trial aiming at patients with an established diagnosis of ulcerative colitis (any extent of disease) and a disease relapse, within 12 months of randomization, medically treated (with 5-ASA (oral and/or topical), corticosteroids, immunomodulators (azathioprine, 6-mercaptopurine, cyclosporine, tacrolimus or methotrexate), and/or after a wash out period of at least 3 months after treatment with biologicals such as infliximab, adalimumab or vedolizumab) until full clinical and endoscopic remission has been achieved as defined by the Mayo score. Patients eligible for this study are randomized to have a laparoscopic appendectomy done in day care setting (within nine weeks of randomization) as opposed to no appendectomy (unblinded). Patients will continue with all medical treatment as given prior to inclusion. Patients will be recruited in the outpatients IBD clinics of the participating medical centers. Centers (provisionally) agreed to participate in this project are listed on page 10. The total inclusion is scheduled to take place within 2 years.

Clinical remission is required for inclusion and is defined as a total Mayo score of 2 points or lower, with no individual subscore exceeding 1 point. Mucosal healing is defined as absolute subscore for endoscopy of 0 or 1. Relapse is defined both clinically and endoscopically as Mayo-score ≥5 with endoscopy score of 2 or 3. Clinically suspected relapses without endoscopic confirmation will be evaluated by a critical event committee (consisting of one independent colorectal surgeon and one IBD specialized gastroenterologist of a non-participating ACCURE-trial center). This committee will decide, based on clinical information, whether it should be considered as relapse.

Both patient groups will be followed for one year or until relapse by the medical staff and trial nurses.

At inclusion, a recent ileocolonoscopy is necessary to define remission (within 3 months). In case it is not possible to perform an ileocolonoscopy, a sigmoidscopy with the measurement of fecal calprotectin (< 150 ug/g) is sufficient. Patients will undergo an ileocolonoscopy with four colonic biopsies (two around (former) appendix opening and two at the most inflamed area) (or sigmoidoscopy with fecal calprotectin) after 12 months or at relapse (to assess histological appearance and mucosal appearance with the Mayo score, performed by a gastroenterologist blinded to the treatment allocation).

Patients will be followed up by the gastroenterologist or the research resident at the outpatient clinic or per telephone at 6 weeks and 3, 6, 9 and 12 months after inclusion, other visits are scheduled on indication. During these contacts the non-invasive 9-point partial Mayo score will be assessed.

Patients will fill in a health related quality of life questionnaires (EQ-5D, EORTC-QLQ-C30-QL and IBDQ) at inclusion and every 3 months thereafter for one year. Furthermore, a ‘global change question’ will be asked at 12 months follow- up (“Since the start of the study, have your UC symptoms improved overall?”) to assess the general impact. The questionnaires can be send

automatically via the MyIBDcoach application, this is an online telemedicine application developed by health care professionals to monitor disease activity, quality of life, medication compliance and side effects. Patients will be contacted by telephone every 3 months by a trial nurse or the research resident to assess medication usage, complications, additional interventions, re-admissions, duration of hospital stay and visits to the outpatient clinic, number of days of sick leave and of social in attendance and to ensure completions of the questionnaires.

In the 5 years following the study the gastroenterologists will be asked to measure the non-invasive 9-point partial Mayo score every 6 months during outpatient clinic appointments. When no outpatient clinic appointment is scheduled the Mayo score can be filled out electronically via the MyIBDcoach application. The resected appendices will be collected for further analysis (pathologic, cell subtyping, bacteriology).

4. STUDY POPULATION

4.1 Population (base)

Patients eligible for inclusion are patients with an established diagnosis of ulcerative colitis (any extent of disease) and a disease relapse, within 12 months of randomization, medically treated (with 5-ASA (oral and/or topical), corticosteroids, immunomodulators (azathioprine, 6-mercaptopurine, cyclosporine, tacrolimus or methotrexate) and/or biologicals such as infliximab, adalimumab or vedolizumab (for treatment with biologicals a wash out period of 3 months prior to inclusion is required) until full clinical (Mayo score <3) and endoscopic (Mayo score 0 or 1) remission has been achieved. Former biological use is only endorsed for patients with an insufficient response (primary non-responders) or adverse reaction during induction therapy, or prescribed for other indications (e.g. rheumatoid arthritis, ankylosing spondylitis, psoriasis) rather than secondary non-responders (due to severe disease). Patients included will continue medical treatment as given prior to inclusion during the study period of one year.

4.2 Inclusion criteria

- Aged 18 years and older.
- Established diagnosis of ulcerative colitis according to ECCO guideline
- Disease relapse within 12 months prior to randomization medically treated until remission
- Clinically confirmed remission at time of randomization with partial Mayo score less than 3 and presumptive endoscopic Mayo subscore of 0 or 1, identified by either:
    - Colonoscopy (within 3 months) examining the full length of the colon and rectum
    - Sigmoidoscopy (within 3 months) examining the last part of the colon (sigmoid and rectum) with faecal calprotectin less than 150 µg/g

- Faecal calprotectin less than 150 µg/g with a personal history of raised faecal calprotectin levels (>500 µg/g) during a previous disease flare-up at any stage

- Obtained written informed consent

4.3 Exclusion criteria

- Prior appendectomy or other major abdominal surgery precluding safe appendectomy
- (Suspicion of) Crohn's disease
- Disease recently treated with biologicals within 3 months prior to inclusion
- Partial Mayo score ≥3 or endoscopic Mayo score >1
- Medical comorbidity that increases perioperative morbidity
- Insufficient command of Dutch or cognitively unable to complete Dutch questionnaires

4.4 Sample size calculation

Group size calculations are based on a clinically relevant reduction in relapse rate under 2 grams of 5-ASA maintenance therapy from 40% in the control group to 20% in the appendectomy group. With a 5% two-sided significance level, 109 patients per study arm will be needed to achieve an 90% power to detect such a difference using a Chi-square test. Considering 12% patient drop out we expect to have to include 244 patients in order to analyze 218 patients. All data-analyses will be performed according to the intention-to-treat principle. Additional mixed-models repeated measures analysis of variance will be used to investigate whether there is a different pattern of change over time between the two study arms in the Mayo score and the EQ-5D, EORTC-QLQ-C30-QL and IBDQ (33). To assess clinical relevance of changes in the IBDQ, a clinical minimally important difference (MID) in IBDQ will be determined using a clinical anchor-based method. The MID will be calculated from the difference in IBDQ change scores of the patients answering “yes” and “no” to the ‘global change question’.

5. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment

Patients with an established diagnosis of ulcerative colitis (any extent of disease) and a disease relapse, within 12 months of randomization medically treated until remission will be randomized to laparoscopic appendectomy or to no appendectomy. Laparoscopic appendectomy will be performed within nine weeks of randomization.

The laparoscopic appendectomy is a relatively simple operation that can be done by most surgeons, in day care setting. The overall morbidity in laparoscopic appendectomy for (perforated) appendicitis is low (2.5-7.6%), and known to be related to the severity of the underlying disease (17-20). Wound

infections, intra-abdominal abscess, iatrogenic bowel perforation, pneumonia and thrombosis are known complications, which are rare. For this study fewer complications are expected in the participating patients in this trial, because the patients have no active disease and the appendix is not inflamed, and is therefore less susceptible to cause bleedings or (intra-abdominal) infections.
Patients randomly allocated to laparoscopic appendectomy will undergo surgery in the including center, Surgery will be performed under general anaesthesia. The appendix is removed using a laparoscopic endostapler enabling a safe and complete appendectomy with the cross stapling line at the base of the appendix with the cecal pole.

Laparoscopic appendectomy will be performed by a gastrointestinal surgeon with sufficient experience in laparoscopic appendectomies (>20). When participating centers lack a qualified surgeon the patient will be referred to the Academic Medical Center, the Queen Elizabeth Hospital Birmingham or a surgeon that has enough experience in a hospital nearby.

5.2 Use of co-intervention (if applicable)

In both patient groups the normal clinical course will be followed. In case of exacerbation, a measurement of fecal calprotectin will be performed and in case fecal calprotectin >150 ug/g an endoscopy will be performed and the Mayo score will be assessed by a gastroenterologist blinded to the treatment allocation.

6. METHODS

6.1 Study parameters/endpoints

6.1.1 Main study parameter/endpoint

The one year UC relapse rate (defined as a total Mayo-score ≥5 with endoscopy score of 2 or 3 or clinically as an exacerbation of symptoms and rectal bleeding or FCP>150 µg/g (> 4 weeks after surgery) or intensified medical therapy other than 5-ASA therapy).

6.1.2 Secondary study parameters/endpoints (if applicable)

-Number of relapses per patient after 12 months

-Time to first relapse, defined as time between randomization in the control group or laparoscopic appendectomy in the intervention group and, the first day of clinical symptoms of an endoscopically or clinically confirmed relapse.

- Disease activity, as measured with the Mayo score at baseline, 3, 6, 9 and 12 months.

- Number of colectomies at one-year follow-up.
- Medication usage at baseline, 3, 6, 9 and 12 months.
- Health related quality of life (EQ-5D, EORTC-QLQ-C30-QL,IBDQ and the 'global change question')

6.2 Randomization, blinding and treatment allocation

Randomization of consenting study participants will be done instantly through the study website. Patients will be randomized to one of two treatment strategies. Blinding of patients and physicians during treatment is unfeasible in this study. The endoscopic follow-up for recurrence will be scored by independent gastroenterologists.

6.3 Study procedures

Patients randomly allocated to laparoscopic appendectomy will undergo surgery in the including center. Patients will continue with medical treatment as given prior to inclusion. Both patient groups will be followed for one year by the medical staff and trial nurses. Patients will undergo an ileocolonoscopy with four colonic biopsies (two around (former) appendix opening and two at the most inflamed area) or sigmoidoscopy with a measurement of fecal calprotectin at inclusion (to define remission) and after 12 months or at relapse (to assess the Mayo score,).

Patients will be followed up by the gastroenterologist or the research resident at the outpatient clinic or per telephone at 6 weeks and 3, 6, 9 and 12 months after inclusion, other visits are scheduled on indication. During these contacts the non-invasive 9-point partial Mayo score will be assessed.
Patients will fill in a health related quality of life questionnaires via the MyIBDcoach telemedicine application (EQ-5D, EORTC-QLQ-C30-QL and IBDQ) at inclusion and every 3 months thereafter for one year. Furthermore, a 'global change question' will be asked at 12 months follow- up ("Since the start of the study, have your UC symptoms improved overall?") to assess the general impact.
Patients will be contacted by telephone every 3 months by a trial nurse or the research resident to assess medication usage, complications, additional interventions, re-admissions, duration of hospital stay and visits to the outpatient clinic, number of days of sick leave and of social in attendance and to ensure completions of the questionnaires.

6.4 Questionnaire

Mayo score: The Mayo Score was introduced in a 1987 publication by Schroeder et al. Using this 12-point scoring system, disease activity is evaluated based on stool frequency, rectal bleeding, the physician's global assessment, and endoscopic appearance. Clinical response is defined as a decrease from baseline in the total Mayo score of at least 3 points and at least 30 percent, with an

accompanying decrease in the subscore for rectal bleeding of at least 1 point or an absolute subscore for rectal bleeding of 0 or 1.
Clinical remission is defined as a Total Mayo score of 2 points or lower, with no individual subscore exceeding 1 point. Mucosal healing is defined as an absolute subscore for endoscopy of 0 or 1.

To measure quality of life, several questionnaires will be used. These questionnaires will be send on fixed time points (every 3 months) via the MyIBDcoach application. Secured accounts will be facilitated for new patients and only the study coordinator will have access to the system. Alternatively, for patients with no internet connection, paper questionnaires will be send to the patients' house addresses, accompanied by a return envelope provided with postage stamps and the address of the hospital. The following questionnaires will be used:
EQ 5D (Euroqol): This questionnaire is a simple, generic instrument for describing and valuing health related quality of life. It includes 5 items (mobility, personal care, daily activities, pain, and anxiety-depression) that are answered on a 3-point scale ranging from no problems (level 1) to extreme problems (level 3) (31, 32).
Global quality of life (EORTC-QLQ-C30-QL): This sub questionnaire contains the 2 items of the global quality of life dimension of the EORTC-QLQ-C30 questionnaire.
Inflammatory Bowel Disease Questionnaire (IBDQ): A disease-specific questionnaire that measures quality of life in 4 domains (bowel symptoms, systemic symptoms, social function, and emotional function) (29-30).

6.5 Withdrawal of individual subjects

Patients can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

6.6 Premature termination of the study

An interim review will be performed at 25, 50,100, 150 and 200 included patients (of the total of 244 patients). At nine weeks after inclusion of these patients the trial's safety data will be evaluated. The DSMB will be supplied with the number of (serious) adverse events in both groups at the five mentioned time points. If there is a skewed distribution of the number of (serious) adverse events between the two groups an efficacy analysis can be performed at the discretion of the DSMB. Following these interim analyses the DSMB will advise the study steering committee upon continuation of the trial.

6.7 Section 10 WMO event

In accordance to section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited METC if anything occurs, on the basis of which it appears that the is advantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardise the subjects' health. The investigator will take care that all subjects are kept informed.

6.8 Adverse and serious adverse events

Adverse events are defined as any undesirable experience occurring to a subject during a clinical trial, whether or not considered related to the investigational procedure. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

A serious adverse event is any untoward medical occurrence or effect that at any dose results in death;

- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation (*the hospitalisation required to undergo laparoscopic appendectomy in those patients who were randomized to undergo an appendectomy, forms an exception to this category*);
- results in persistent or significant disability or incapacity;
- is a new event of the trial likely to affect the safety of the subjects, such as an unexpected outcome of an adverse reaction, lack of efficacy of an IMP used for the treatment of a life threatening disease, major safety finding from a newly completed animal study, etc.

If an SAE occurs, the principal investigator will be notified by email or telephone within 24 hours. Using the CCMO module 'ToetsingOnline', all SAEs will be reported to the CCMO and central MEC. The reporting will occur within 15 days after the investigator has first received information on the SAE. For fatal or life-threatening cases a preliminary report will be offered within 7 days followed by a complete report within 8 days.

A predefined list of SAE's will be reported periodically instead of individually using the CCMO-module 'toetsingOnline'. SAE's that will be listed and reported periodically are the following:

- complications after laparoscopic appendectomy
- disease recurrence in the follow-up year requiring hospitalisation
- SAE's that are classified by the steering group as 'not related to the trial'

6.8.1 Suspected unexpected serious adverse reactions (SUSAR)

The study does not investigate a medicinal product; therefore SUSARs are not applicable for this study and shall not be reported.

6.8.2 Annual safety report

The investigator will submit a safety report once a year to the central MEC and the competent authority until the follow-up of the last patients is completed. This safety report consists of:
- an aggregated summary table of all reported serious adverse events, ordered by organ system.

6.8.3 Follow-up of adverse events

All adverse events will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and or referral to the general physician or a medical specialist.

6.8.4 Data and safety monitoring

An independent research nurse from a different department, that is certified for monitoring according to GCP, will monitor the data. Three visits will be scheduled; the first after inclusion of the 60th patient; second visit after inclusion of the 120th patient and third visit after the end of the study. In all trial subjects the informed consent forms are assessed; source data verification will be performed in 10% of the population (n=18). The monitor also verifies whether all SAE's are appropriately reported within the time frames required by GCP, the protocol, the ethics committee, and the applicable regulatory requirement(s).

6.8.5 Data Safety Monitoring Board (DSMB)

This study is considered a low risk trial, in which in one study group a relatively simple and frequently performed operation is added to the common treatment for UC and compared to patients not undergoing this operation.

To assure proper data safety monitoring and relevance a DSMB will be installed. A data safety monitoring board will guard the safety of the included patients, give advice on continuation of the study upon superiority of one of the types of treatment, and will guard the methodological quality of the study. Also see the DSMB charter.

Furthermore, to keep insights in SAE's, the trial coordinator will communicate all SAE's to the independent monitor and to the steering committee (CJ Buskens, W.A. Bemelman, G.R. D'Haens,

MGW Dijkgraaf, TD Pinkney, S Pathmakanthan and EL Magill) of this study. The steering committee will comment on the reports. Every year also a cumulative list of all SAE's will be provided to the steering group and monitor.

CHARTER FOR DSMC ACCURE TRIAL

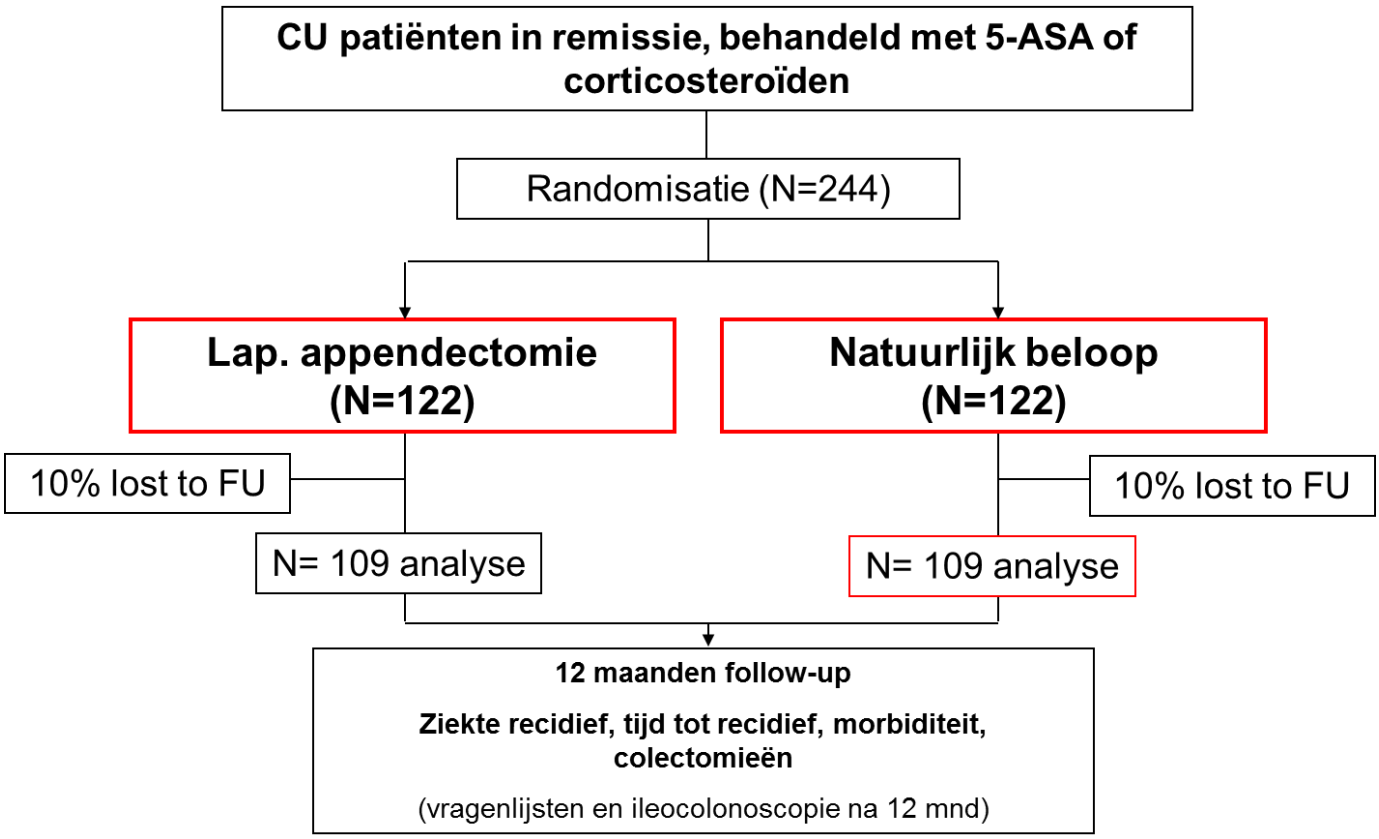
CONTENT	
1. Introduction	
Name of trial	ACCURE TRIAL
Objectives of trial, including interventions being investigated	The objective of this study is to evaluate the short-term and medium-term effectiveness of appendectomy in maintaining remission in patients with an established diagnosis of ulcerative colitis (any extent of disease) treated for a relapse within 12 months of randomization. Patients are included when remission is achieved by treatment with 5-ASA (oral and/or topical), corticosteroids, immunomodulators (azathioprine, 6-mercaptopurine, cyclosporine, tacrolimus or methotrexate) and/or after a wash out period of at least 3 months after treatment with biologicals such as infliximab, adalimumab or vedolizumab (Figure 1).
Outline of scope of charter	The purpose of this document is to describe the roles and responsibilities of the independent DSMC for the ACCURE trial, including the timing of meetings, methods of providing information to and from the DSMC, frequency and format of meetings, statistical issues and relationships with other committees.
2. Roles and responsibilities	
Statement of the aims of the committee	To safeguard the interests of trial participants and assess the safety of the appendectomy during the trial.
Terms of reference	The DSMC should receive and review the safety data of this trial. The DSMC should inform the Chair of the steering committee if, in their view: The number of (serious) adverse events is skewed between both groups to the prejudice of the patients in the appendectomy group.
Specific roles of DMC	Interim review at 25, 50, 100, 150 and 200 included patients (of the total of 244 patients). At 9 weeks after inclusion of these patients the trial's safety data should be evaluated. The DSMC will be supplied the number of (serious) adverse events in both groups at the three mentioned time points. It is at the discretion of the DSMC to meet early in the course of the trial and to discuss the protocol with the interim analysis plan, and to have the opportunity to clarify any aspects with the principal investigators. The DSMC will meet within one year of recruitment commencing.
3. Composition	
Membership and size of the DSMC	DSMC members register their assent by confirming (1) that they agree to be

CONTENT	
	on the DSMC and (2) that they agree with the contents of this Charter. The members are independent of the trial and have no competing interest that could impact on the trial. Also see the competing interest form (Annex 1). The members of the DSMC for this trial are: (1) M. Koelemay, MD, PhD, surgeon AMC, clinical epidemiologist (2) T. Karsten, MD, PhD, surgeon Onze Lieve Vrouwe Gasthuis (3) J. van der Meer, MD, PhD, internist AMC (4) J.H.M. van den Brande, MD, PhD, gastroenterologist, Tergooi Hospital. (5) K. Hood, PhD, Professor of Trials at Cardiff University The Chair will be chosen by the DMC members themselves. The Chair is expected to facilitate and summarise discussions. The trial statistician, MGW Dijkgraaf, will oversee the production of the report to the DSMC and will participate in DSMC meetings, guide the DSMC through the report and participate in DSMC discussions. The trial office team will provide input to the production of the DSMC report. The trial PI, may be asked, and will be available, to attend open sessions of the DSMC meeting. The other trial group members will not usually be expected to attend but can attend open sessions when necessary.
4. Relationships	
Clarification of DSMC role Competing interests	No payments or rewards will be awarded to the DSMC. Competing interests of DSMC members – financial matters, involvement in other trials or intellectual investment – should be disclosed (Annex 1). DSMC members should not use interim results to inform trading in pharmaceutical shares, and careful consideration should be given to trading in stock of companies with competing products.
5. Organisation of DMC meetings	
Expected frequency of DSMC meetings	The DSMC will meet at least yearly. The DSMC will perform an interim analysis at three time points; at 9 weeks after inclusion of the 25th, 50th,100th, 150th and 200rd patient. The meetings of the DSMC will be face-to-face to facilitate full discussion. All sessions are in principle open, although the DSMC can decide otherwise.
6. Trial documentation and procedures to ensure confidentiality and proper communication	
Intended content of material to be available in open sessions	Accumulated information relating to the trial's safety data will be presented. Other outcome measures (e.g. efficacy) may be presented, at the discretion of

CONTENT	
	the DSMC. The DSMC members will not be blinded to the treatment allocation.
Who will see the accumulating data and interim analysis	The DSMC will discuss the results of the interim analysis with the Trial Steering Committee (W.A. Bemelman, G.R.A.M. D'Haens, C.Y. Ponsioen, MGW Dijkgraaf, CJ Buskens, PJ Tanis, TD Pinkney, S Pathmakanthan and EL Magill). DMC members do not have the right to share confidential information with anyone outside the DSMC, other than the Trial Steering Committee.
External evidence	The PI and trial coordinator will identifying and circulate external evidence that can influence the trial.
To whom the DMC will communicate the decisions/ recommendations that are reached	The DSMC reports its recommendations in writing to the Trial Steering Committee. This will be copied to the trial coordinator in time for consideration at a TSC meeting. The DSMC members should store the papers safely after each meeting so they may check the next report against them. After the trial is reported, the DSMC members should destroy all interim reports.
7. Decision making	
Decisions/recommendations open to the DSMC	Possible recommendations: • No action needed, trial continues as planned • Early stopping due, for example, to clear benefit or harm of appendectomy, futility, or external evidence
Interim analysis	Interim review at 25, 50, 100, 150 and 200 included patients. At 9 weeks after inclusion of these patients the trial's safety data should be evaluated. The DSMC will be supplied the number of (serious) adverse events in both groups at the three mentioned time points.
Decisions or recommendations within the DSMC	Every effort should be made for the DSMC to reach a unanimous decision. If the DSMC cannot achieve this, a vote may be taken, although details of the vote should not be routinely included in the report to the TSC as these may inappropriately convey information about the state of the trial data. It is important that the implications (eg ethical, statisticial, practical, and financial) for the trial be considered before any recommendation is made. Effort should be made for all members to attend. The trial coordinator will try to ensure that a date is chosen to enable this. Members who cannot attend in person should be encouraged to attend by teleconference. If, at short notice, any DSMC members cannot attend at all then the DSMC may still meet if at least one statistician and one clinician, including the Chair (unless otherwise agreed), will be present. If the DSMC is considering recommending major action after such a meeting the DSMC Chair should talk with the absent members as soon after the meeting as possible to check they agree. If they do not, a further teleconference should be arranged with the full DSMC. If the report is circulated before the meeting, DSMC members who will not be

CONTENT	
	able to attend the meeting may pass comments to the DSMC Chair for consideration during the discussions. If a member does not attend a meeting, it should be ensured that the member is available for the next meeting. If a member does not attend a second meeting, they should be asked if they wish to remain part of the DSMC. If a member does not attend a third meeting, they should be replaced.
8. Reporting	
Recommendations/decisions of the DSMC	The DSMC will report their recommendations/decisions in a letter to the Trial Steering Committee, within 4 weeks after the meeting. A copy of this letter will be lodged with the trial coordinator.
Disagreement between the DSMC and TSC	If the DSMC has serious problems or concerns with the Trial Steering Committee decision a meeting of these groups should be held. The information to be shown would depend upon the action proposed and the DSMC's concerns. Depending on the reason for the disagreement confidential data will have to be revealed to all those attending such a meeting. The meeting will be chaired by a senior member of the trials office staff or an external expert who is not directly involved with the trial.
9. After the trial	
Publication of results	If requested by the DSMC, a meeting at the end of the trial will be held to allow the DSMC to discuss the final data with the principal trial investigators and give advice about data interpretation The DSMC will be given the opportunity to read and comment on any publications before submission, especially with respect to reporting of any DSMC recommendation regarding termination of a trial The DSMC may discuss issues from their involvement in the trial when permission is agreed with the overseeing committee.

Figure summarizing trial



7. STATISTICAL ANALYSIS

7.1 Statistics

The relapse rate, medication usage and time to relapse of the two groups will be compared with Chi-square testing, Mann Whitney U-testing and survival analysis using the statistical program SPSS.
Differences in quality of life, disease activity and morbidity will be analyzed using mixed-models analysis of variance for repeated measures, accounting for differences in survival between groups.

7.2 Interim analysis

An interim review will be performed at 25, 50, 100, 150 and 200 included patients. At 9 weeks after inclusion of these patients the trial's safety data should be evaluated. The DSMC will be supplied the number of (serious) adverse events in both groups at the three mentioned time points.
If there is a skewed distribution of the number of (serious) adverse events between the two groups an efficacy analysis can be performed at the discretion of the DSMC.

7.3 Economic evaluation

The economic evaluation will be performed from a societal perspective as a cost-effectiveness and cost-utility analysis. Primary outcomes in the economic evaluation are costs per patient related to the appendectomy and the non-surgical treatment and costs per QALY gained. Additional one way sensitivity analyses will determine how changing treatment costs might impact the results. Standard unit prices will be used when available, complemented by results from cost calculations where needed. The cumulative total costs will be calculated for the 12 month study period. Furthermore the cost effectivity (costs per prevented relapse) will be calculated.
Direct medical costs and indirect costs arising from losses in productivity will be assessed.

8. ETHICAL CONSIDERATIONS

8.1 Regulation statement

This trial will be conducted according to the principles of the declaration of Helsinki (version of 2008) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and other European guidelines, regulations and acts. Data management, monitoring and reporting of the study will be carried out in accordance with the ICH GCP guidelines.

8.2 Recruitment and consent

It will be the responsibility of the Investigator to obtain informed consent for each participant prior to performing any trial related procedure. Consent may be taken by the PI or delegate (consultants, registrars, research nurses) as captured on the ACCURE Site Signature and Delegation Log. All those delegated to take consent must have undertaken Good Clinical Practice (GCP) training.

Investigators or delegate will ensure that they adequately explain the aim, trial treatment, anticipated benefits and potential hazards of taking part in the trial to the participant. They will also stress that participation is voluntary and that the participant is free to refuse to take part and may withdraw from the trial at any time. The participant will be given adequate time to read the patient information form (PIF) and to discuss their participation with others outside of the site research team. The participant will be given the opportunity to ask questions before completing Informed Consent Form (ICF).

If the participant expresses an interest in participating in the trial they will be asked to complete the latest version of the ICF. The ICF will be completed using one of the following processes:

- **By post**

The ICF is posted to the participant, or emailed and then printed by the participant, along with the PIF. During the remote discussion with the person consenting the participant, the participant will initial, sign and date the ICF. The PI or delegated will document this in the participants medical notes. The participant will post the partially completed ICF back to the site. The PI or delegate consenting the participant will then sign and date the ICF. Only after the PI or delegate has countersigned the returned ICF is consent considered to be obtained. A copy of the completed ICF will be posted back to the participant, and the original placed in the investigator site file.

- **By email**

The ICF is posted to the participant, or emailed and then printed by the participant, along with the PIF. During the remote discussion with the person consenting the participant, the participant will initial, sign and date the paper ICF. The participant will email a copy (photograph or scan) of the partially

completed ICF back to the site. The PI or delegate consenting the participant will then sign and date the ICF. Only after the PI or delegate has countersigned the electronic ICF is consent considered to be obtained. A copy of the completed ICF will be emailed back to the participant, and the original (with wet-ink signature of person taking consent) placed in the investigator site file. Copies of email from the participant with the attached partially completed ICF and the email from the person talking consent with the fully completed ICF attached are to be printed and stored with the ICF.

- **Face-to-face**

The ICF is given to the participant and they will initial, sign and date the ICF. The PI or delegate consenting the participant will then sign and date the ICF. Only after the PI or delegate has countersigned the ICF is consent considered to be obtained. A copy of the completed ICF will be posted back to the participant, and the original placed in the investigator site file.

The participant must give explicit consent for the regulatory authorities, members of the research team and or representatives of the sponsor to be given direct access to the participant's medical records.
Once the participant is entered into the trial, the participant's trial number will be entered on the ICF maintained in the investigator site file. Details of the informed consent discussions will be recorded in the participant's medical notes. This will include date of discussion, the name of the trial, summary of discussion, version number of the PIF given to participant and version number of ICF signed, consent process followed (post, email, or face-to-face) and date consent received.

At each visit (including follow-up conducted remotely) the participant's willingness to continue in the trial will be ascertained and documented in the medical notes. Throughout the trial the participant will have the opportunity to ask questions about the trial. Any new information that may be relevant to the participant's continued participation will be provided. Where new information becomes available which may affect the participants' decision to continue, participants will be given time to consider and if happy to continue will be re-consented. Re-consent will be documented in the medical notes. The participant's right to withdraw from the trial will remain.

8.3 Objection by minors or incapacitated subjects (if applicable)

Minors and legally incompetent adults are excluded from the trial.

8.4 Compensation for injury

The AMC Medical Research BV has insurance, which is in accordance with the legal requirements in The Netherlands (Article 7 WMO and the Measure regarding Compulsory Insurance for Clinical

Research in Humans of June 23, 2003). This insurance provides cover for damage to research subjects through injury or death caused by the trial:
- € 450.000,-- (i.e. four hundred and fifty thousand Euro) for death or injury for each subject who participates in the research;
- € 3.500.000,-- (i.e. three million five hundred thousand Euro) for death or injury for all subjects who participate in the research;
- € 5.000.000,-- (i.e. five million Euro) for the total damage incurred by the organization for all damage disclosed by scientific research for the AMC as 'Sponsor (verrichter)' in the meaning of said Act in each year of insurance coverage.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the trial.

8.5 Incentives (if applicable)

Enrolled patients will not receive any special incentives, compensation or treatment through participation in this trial.

9. ADMINISTRATIVE ASPECTS AND PUBLICATION

9.1 Handling and storage of data and documents

Every randomized patient will be assigned a five digit study number. Communication occurs only with this number. The full name and birth date of the patient will only be recorded on the informed consent form.

A study coordinator coordinates the study, monitors patient inclusion and protocol steps, data collection, data entry, preparation and performs analyses and will report the data. Continuous data monitoring, and data collection on a CRF will guarantee complete and real-time prospective recording of data. Data will be collected and stored at the AMC in a separate, closed room.

9.2 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

All substantial amendments will be notified to the METC and to the competent authority.

Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

9.3 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

9.4 End of study report

The investigator will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.

In case the study is ended prematurely, the investigator will notify the accredited METC, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

9.5 Public disclosure and publication policy

Patients are entitled to public disclosure of the results of the trial on the basis of their participation in it. The results of research will be submitted for publication to peer-reviewed scientific journals.

Agreements with respect to participation in publication will be made before the start of the trial. Only participating doctors from other centers will participate in publication if a substantial contribution to the trial (e.g. patient accrual, full completion of CRF or intellectual input) is made. The manuscript will be submitted on behalf of the ACCURE study group in alphabetical order. The coordinating investigator and principal investigator will be first and senior authors, respectively.

10. ANCILLARY STUDIES

As ancillary studies, a part of the resected appendices (1cm2 mid-appendix, and 1cm2 cecal/appendicular base, as was decided in collaboration with the department of pathology) will be stored in -80 for further fundamental analyses:

1. Pre-operative periappendicular endoscopic biopsies will be used to determine if histological inflammation in the appendix resection specimens can be reliably predicted. Histological findings in the resection specimens will be correlated to clinical and pathological response after appendectomy.

2. To analyse the immunological make-up of UC appendices, mucosa from resection specimens and will be collected. Lamina propria mononuclear cells (LPMCs) are freshly isolated and connective and adipose tissue is removed. The tissue will be washed followed by removal of the mucus layer and epithelial cells by Dithiothreitol (DTT) and Beta-mercaptoethanol. Cells will be isolated by enzymatic digestion using a mix of collagenase, protease and DNase. These methods have been established and verified not to affect expression of critical markers. The phenotype of LPMCs will be analyzed by flow cytometry with markers associated with adaptive and innate immune cells: CD45, CD3, CD4, CD8, CD127 (IL-7), RORC, IL23R, IL-1BR, NKp44, NKp46, NKp30, CCR6 and CXC3. Flow cytometry will be performed to unravel the functional characteristics of these cells in the intestine, populations are sorted from the isolated LPMCs with FACSAria. Thereby, gene expression of freshly sorted cells will be compared using real-time polymerase chain reaction (RT-PCR)..

3. Inflammation in the colonic biopsies will be classified according to the validated Geboes score (grade 0-5: architectural changes, increase of chronic inflammatory infiltrate, increase of eosinophils in the lamina propria, increase of neutrophils in the lamina propria, involvement of neutrophils in the epithelium (cryptitis), crypt destruction, and erosion or ulcerations).(26) Histological characteristics from the pre- and postoperative colonoscopies will be compared to quantify pathological response. Results will be compared to findings in the appendicular resection specimens (see ancillary studies 1 and 2) to determine appendicular features predictive of pathological response with the aim to possibly identify a patient group most likely to respond to appendectomy.

4. For microbiota analysis representative sections of mucosa will be chosen for Laser Capture Microdissection system (LCM). Using LCM, specific microenvironmental spaces, i.e. apical side epithelial barrier and lamina propria will be dissected and captured on previously UV-irradiated PALM Membrane Slides (PALM Microlaser Technologies AG, Bernried, Germany). Since the bacterial diversity in these samples is unknown, samples will be screened for diversity by Denaturing Gradient Gel Electrophoresis of 16S rRNA genes first, and subsequently analysed by the HITChip. The HITChip is a custom-made Agilent microarray targeting all currently known (approximately 1140 at present) gastrointestinal tract bacteria. It is a dynamic microarray in the sense that whenever new sequences are published these can instantly be added to the microarray. In addition to its qualitative

properties, the HITChip has also shown to have quantitative power to allow for detection of certain adherent invasive *E. coli* strains, specific probes for these microbes will be incorporated in the HITChip (Claesson 2009, Rajilic 2009)

11. TIME SCHEDULE

2nd half 2011:

Obtaining Ethic Committee Approval AMC and other participating centers

Accrual of participating centers

Site initiation visits according to GCP

Start clinical study

2012 - 2022

Inclusion of patients

Follow up of included patients

Data management

Periodical update including centers

2022-2023

Follow-up of included patients for one year

Data management

2023-2024

Analysis of data, writing report

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The effect of appendectomy on the clinical course of ulcerative colitis:

A randomized multicenter trial (ACCURE-trial)

Trial Registration: NTR2883, ISRCTN60945764

Statistical Analysis Plan

SAP Version Number	Protocol Version Number
4.1 Date: 28 August 2023	19

Name of Author:	E. Visser	Role:	Trial coordinator	Affiliation:	Amsterdam University Medical Centre
Signature of Author:	[redacted]	Date:	28 August 2023		
Name of Reviewers:	Kelly Handley	Role:	Senior Statistician	Affiliation:	University of Birmingham Clinical Trials Unit
		Date:	28 August 2023		
	Apostolos Fakis	Role:	Trial Statistician	Affiliation:	University of Birmingham Clinical Trials Unit
		Date:	28 August 2023		
Name of Chief Investigator:	C.J. Buskens	Role:	Chief Investigator	Affiliation:	Amsterdam University Medical Centre
Signature of Chief Investigator:	[redacted]	Date:	28 August 2023		
This Statistical Analysis Plan has been reviewed and approved by:					
Name of Approver:	M.G.W. Dijkgraaf	Role:	Senior Statistician	Affiliation:	Amsterdam University Medical Centre
Signature of Approver:	[redacted]	Date:	28 August 2023		

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ABBREVIATIONS

5-ASA:	5-aminosalicylic acids
AE:	Adverse event
ASA:	American Society of Anaesthesiologists
AT:	As-treated
BMI:	Body mass index
CEC:	Critical event committee
CONSORT:	Consolidated Standards of Reporting Trials
CRC:	Colorectal cancer
DSMC:	Data Monitoring and Safety Committee
ECCO:	European Crohn's and Colitis Organisation
EORTC:	European Organisation for Research and Treatment of Cancer
EQ-VAS:	EuroQol visual analogue scale
FCP:	Faecal calprotectin
HGD:	High-grade dysplasia
HRQL:	Health-related quality of life
IBD:	Inflammatory bowel disease
IBDQ:	Inflammatory Bowel Disease Questionnaire
IQR:	interquartile range
ITT:	Intention-to-treat
NL:	The Netherlands
pMS:	partial Mayo Score
PSC:	Primary sclerosing cholangitis
QoL:	*Quality of life*
RS:	Raw score
SAE:	Serious adverse event
SAP:	Statistical analysis plan
UC:	Ulcerative colitis
UK:	United Kingdom

ABSTRACT

Background: The primary treatment of ulcerative colitis (UC) is medical therapy using a standard step-up approach. An appendectomy might modulate the clinical course of UC, decreasing the incidence of relapses and reducing need for medication. The objective of the ACCURE trial is to assess the efficacy of laparoscopic appendectomy in addition to standard medical treatment in maintaining remission in UC patients. This article presents the statistical analysis plan to evaluate the outcomes of the ACCURE trial.

Design and methods: The ACCURE trial was designed as a multicentre, randomised controlled trial. UC patients with a new diagnosis or a disease relapse within the past 12 months, treated with 5-ASA, corticosteroids, or immunomodulators until complete clinical and endoscopic remission (defined as total Mayo score <3 with endoscopic subscore of 0 or 1), were counselled for inclusion. Also, patients previously treated with biologicals who had a washout period of at least 3 months were considered for inclusion. Patients were randomised (1:1) to laparoscopic appendectomy plus maintenance treatment or a control group (maintenance therapy only). The primary outcome is the one-year UC relapse rate (defined as a total Mayo-score ≥5 with endoscopic subscore of 2 or 3, or clinically as an exacerbation of symptoms and rectal bleeding or FCP>150 or intensified medical therapy other than 5-ASA therapy). Secondary outcomes include number of relapses per patient, time to first relapse, disease activity, number of colectomies, medication usage and health-related quality of life.

Discussion: The ACCURE trial will provide comprehensive evidence whether adding an appendectomy to maintenance treatment is superior to maintenance treatment only in maintaining remission in UC patients.

Trial registration: NTR, NTR2883. Registered 3 May 2011, https://onderzoekmetmensen.nl/en/trial/22414.

ISRCTN, ISRCTN60945764. Registered 12 August 2019, https://www.isrctn.com/ISRCTN60945764.

1. INTRODUCTION

This document is the Statistical Analysis Plan (SAP) for the ACCURE-trial, and should be read in conjunction with the current trial protocol. This SAP details the proposed analyses and presentation of the data for the main paper(s) reporting the results for the ACCURE-trial.

The results reported in these papers will follow the strategy set out here. Subsequent analyses of a more exploratory nature will not be bound by this strategy, though they are expected to follow the broad principles laid down here. The principles are not intended to curtail exploratory analysis (e.g. to decide cut-points for categorisation of continuous variables), nor to prohibit accepted practices (e.g. transformation of data prior to analysis), but they are intended to establish rules that will be followed, as closely as possible, when analysing and reporting data.

1.1 Background and rationale

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) affecting the mucosa of the colon and rectum, with an annual incidence of 6-8 new cases per 100,000.(1) The primary treatment is medical therapy consisting of step-up approach starting with 5-aminosalicylic acids (5-ASA), followed by immunomodulators, biologicals, small molecules, and trial medication. Most patients will remain on long-term medication to prevent exacerbations and preserve quality of life. Despite the expanding medical armamentarium and declining emergent UC colectomy rates, the overall incidence of (procto)colectomy in UC patients has remained unchanged over the years.(2) Nevertheless, up to 20% of the patients require surgery.(3, 4)

There is increasing evidence suggesting an immunomodulatory role of the appendix in patients with UC.(5, 6) We hypothesise that an appendectomy has a beneficial effect on the UC disease course; decreasing the number of relapses and reducing the need for (upscaling) medication. The ACCURE trial

is a randomised, international, multicentre trial to assess the efficacy of appendectomy to maintain remission in patients with UC.(7) From September 2012 to September 2022, 201 patients were randomised. Analyses will commence in 2023 following completion of 1-year follow-up for the last patient, data cleaning checks, and data lock.

1.2 Objectives

The objective of the ACCURE trial was to determine the efficacy of appendectomy in addition to standard medical treatment to maintain remission in patients with UC, and to establish the acceptability of the intervention compared to standard treatment only. The trial protocol was previously published.(7) The present manuscript is the proposed statistical analysis plan (SAP), which follows the JAMA Guidelines for the content of statistical analysis plans in clinical trials.(8)

2. STUDY METHODS

2.1 Trial design

The ACCURE trial was an investigator-initiated two-arm, multicentre, randomised controlled superiority trial. UC patients in complete clinical and endoscopic remission (defined as Mayo score <3 with endoscopic subscore 0 or 1) who were treated for a relapse within the past 12 months (with 5-ASA, corticosteroids, immunomodulators or after a washout period of at least 3 months after treatment with biologicals) were randomised into two groups. The intervention group underwent laparoscopic appendectomy in day care setting plus maintenance medical therapy. The appendix was removed including the cecal base to include the orifice of the appendix using a laparoscopic endostapler. The control group continued maintenance therapy at the discretion of the treating gastroenterologist.

The ACCURE trial included two trial registrations. The ACCURE trial (NL) was registered at the Netherlands National Trial Register (NTR2883) on May 3rd 2011. Ten centres were involved in the trial in the Netherlands (NL) and Ireland. The ACCURE-UK-2 (ISCRCTN60945764) is the UK arm of the ACCURE trial (NL) and was registered on 12 August 2019. The study was conducted in 10 hospitals in the United Kingdom (UK). The ACCURE trial (NL) and ACCURE-UK-2 shared a matched overall study design and form the definitive trial (the ACCURE trial) for the final analysis.

2.2 Randomisation

Eligible patients were randomly assigned (1:1 ratio) by the research team with ALEA randomisation software. Randomisation was stratified by disease localisation (rectum, left-sided colitis, pancolitis). Patients and physicians were not blinded during treatment.

2.3 Sample size

The ACCURE trial (NL) was powered on a clinically relevant reduction in relapse rate from an expected 40% in the control group to 20% in the intervention group.(7) With a 5% two-sided significance level, 82 patients per study arm were needed to achieve 80% power to detect such a difference using chi-square test. Considering 10% patient dropouts we aimed to include 184 patients in order to analyse 164 patients.

In September 2019, the ACCURE trial was started in the United Kingdom (ACCURE-UK-2) to improve recruitment and increase statistical power. The aim was to include 244 patients intending to analyse 218 patients (109 per study arm) to reach 90% power in demonstrating superiority of appendectomy. However, the study was closed after the inclusion of 201 patients in September 2022 due to prolonged accrual (related to the COVID-19 pandemic).

2.4 Framework

The ACCURE trial was a superiority trial. The hypotheses for the primary analysis were as follows:

- Null hypothesis: there is no difference in the one-year cumulative relapse rate between laparoscopic appendectomy plus maintenance therapy versus maintenance therapy only.
- Alternative hypothesis: there is a difference in the one-year cumulative relapse rate between laparoscopic appendectomy plus maintenance therapy versus maintenance therapy only.

2.5 Statistical interim analysis and stopping guidance

According to the protocol, no planned interim analysis was scheduled. However, during the inclusion period, a few manuscripts were published suggesting a relation between appendectomy and the development of high-grade dysplasia (HGD) and colorectal cancer (CRC) in UC patients.(9) Therefore, an interim analysis for safety was performed at the discretion of the Data Monitoring and Safety Committee (DSMC) after inclusion of 153 patients in March 2021. In addition to the number of (serious) adverse events in both groups at one year, the interim analysis for confirmation of safety also addressed the number of patients with HGD and CRC in both groups during long-term follow-up. For safety regarding neoplasia, the following rules were defined: when the absolute number of patients with HGD/CRC in the intervention group was higher by 1: continuation of the trial; higher by 2: assessment of potential underlying risk factors for HGD/CRC (i.e. onset before adulthood, disease duration >10 years, concomitant PSC); higher by 3: continuation of the trial was at the discretion of the DSMC. When the absolute number of patients with HGD/CRC was higher in the control group (standard care), assessment of cases could be conducted at the discretion of the DSMC. Conditional on appendectomy being considered safe, the interim analysis was proceeded with a stopping rule for superiority (Haijbittle-Peto boundary $p<0.001$). In this analysis, no overwhelming efficacy could be demonstrated. The DSMC did not share the outcome results with the research group but communicated that there was no need for early termination of the trial.

2.6 Timing of final analysis

The analyses will be performed when the last patient has reached one year follow-up, data entry has been completed, the collected patient data have been monitored, and after this SAP has been accepted for publication.

2.7 Timing of outcome assessments

Outpatient clinic visits or telephone consults were performed at 6 weeks and 3, 6, 9 and 12 months after appendectomy or in the control group after randomisation. During these contacts, the partial Mayo Score (pMS), medication use, complications, readmissions, hospital stay and visits to outpatient clinic, were assessed.(10) Health-related quality of life (HRQL) questionnaires (EQ-5D, EORTC-QLQ-C30-QL and IBDQ) (11-13) were completed at inclusion and every 3 months thereafter during the first year. In the Netherlands, the questionnaires were sent via the MyIBDcoach application or could be completed online. In the UK, hard copies of the questionnaires were completed by the participant on site at the baseline visit or at home and returned by post if an in-person visit was not possible, and at all subsequent time points, the questionnaires were posted out by the central trial team. An endoscopy was performed at the time of suspected relapse or at the end of the 12-month study period (12 months after appendectomy in the intervention group and after randomisation in the control group) to objectively assess mucosal appearance and determine the full Mayo score.

3. STATISTICAL PRINCIPLES

3.1 Confidence intervals and *P* values

All statistical tests will be two-sided. P values of less than 0.05 will be considered statistically significant. The presented confidence intervals will be 95% and two-sided.

3.2 Adherence and Protocol violation

Protocol violation in eligibility was defined as randomisation of a patient who did not qualify for inclusion or who met an exclusion criterion. These patients were excluded from intervention and further follow-up.

Predefined as a major protocol violation with a direct impact on the primary outcome was UC relapse during the waiting period for appendectomy in the intervention group. These patients were not excluded, but the number (and percentage) of patients with a protocol violation will be summarised by group with details of the type of deviation provided and reported in a patient flow diagram according to the Consolidated Standards of Reporting Trials (CONSORT, Figure. 1).

3.3 Analysis populations

All primary analyses (primary and secondary outcomes) will be based on the intention-to-treat (ITT) principle. All randomised patients will be included in the analyses according to their initially assigned study arm at baseline, regardless of whether they actually received the allocated intervention or not. Patients with a protocol violation concerning eligibility will be excluded from analysis. Safety data will be reported by treatment arm, and an as-treated (AT) analysis will be performed. In the AT analysis, patients will be analysed according to the treatment they actually received, rather than the study arm they were initially assigned.

4. TRIAL POPULATION

4.1 Screening and eligibility

Patients were screened for eligibility using the inclusion and exclusion criteria according to the most recent version of the study protocol. The number of excluded patients after randomisation and reasons for ineligibility will be reported and illustrated in the CONSORT flow diagram (Figure. 1).

Inclusion criteria:

- Aged ≥ 18 years.
- Established diagnosis of UC according to ECCO guideline.(14)
- Disease relapse within 12 months prior to randomisation medically treated until remission.
- Clinically confirmed remission at time of randomisation, with pMS <3 and presumptive endoscopic Mayo subscore of 0 or 1, identified by either:
    - Colonoscopy (within 3 months) examining the full length of the colon and rectum
    - Sigmoidoscopy (within 3 months) examining the last part of the colon (sigmoid and rectum) with faecal calprotectin (FCP) <150 µg/g
    - FCP <150 µg/g with a personal history of raised FCP levels (>500 µg/g) during a previous disease flare-up at any stage.
- Obtained informed consent

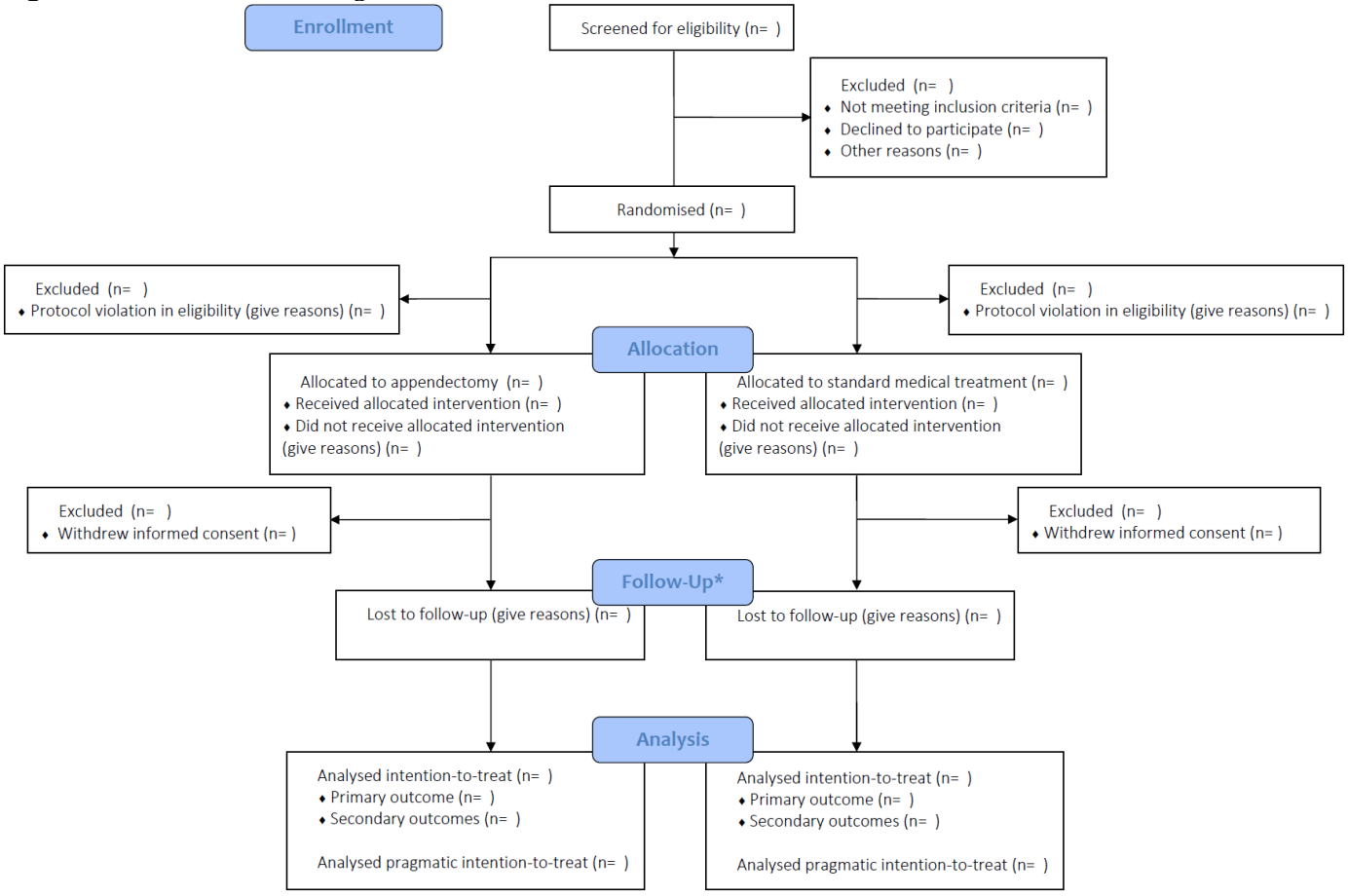
Exclusion criteria:

- Prior appendectomy or major abdominal surgery precluding safe appendectomy.
- (Suspicion of) Crohn's disease.
- Disease recently treated with biologicals (within 3 months prior to inclusion).
- pMS ≥3 or endoscopic Mayo score >1.
- Medical comorbidity that increases perioperative morbidity .

4.2 Recruitment

Informed consent was obtained from the patients according to the ACCURE trial protocol. For both treatment arms, the numbers of patients who were randomised, received the intended treatment, and were analysed for the primary outcome will be presented in the CONSORT flow diagram (Figure 1).

Figure 1. CONSORT flow diagram



*All patients are included according to the intention-to-treat principle. Patients not evaluable for primary outcome analysis are included in analyses for evaluable secondary outcomes.

4.3 Withdrawal/ Follow-up

For each group, withdrawal and loss to follow-up will be reported and specified with reasons at each time point (Figure 1). These outcomes will be explored as per other missing responses.

4.4 Baseline patient characteristics

The baseline characteristics of the included patients will be reported per randomisation group and shown in a baseline table (Table 1). Categorical variables will be summarised by numbers and percentages in each category. Continuous variables will be summarised by mean and standard deviation or median and

interquartile range, as appropriate. Tests of statistical significance will not be undertaken, nor will confidence intervals be presented.(15)

Table 1. Baseline characteristics of the patients included in the trial (intention to treat)		
Characteristic	*Appendectomy (N=)*	*Control (N=)*
Age (years)		
Age at diagnosis (years)		
Gender, female, *n (% n/N)*		
Disease duration (years)		
Smoking status, *n (% n/N)*		
Current		
Former		
BMI (kg/m^2)		
ASA physical status classification grade >II, *n (% n/N)*		
PSC, *n (% n/N)*		
Family history of IBD, *n (% n/N)*		
Medication at baseline		
No medication, *n (% n/N)*		
Topical therapy, *n (% n/N)*		
5-ASA, *n (% n/N)*		
Systemic steroids, *n (% n/N)*		
Immunomodulators, *n (% n/N)*		
Extent of disease		
Proctitis, *n (% n/N)*		
Left-sided colitis, *n (% n/N)*		
Pancolitis, *n (% n/N)*		
Start of most recent exacerbation UC before randomisation (weeks)		
Abbreviations: BMI: body mass index; ASA: American Society of Anaesthesiologists; PSC: primary sclerosing cholangitis; IBD: inflammatory bowel disease; 5-ASA: 5-aminosalicylic acid; UC: ulcerative colitis.		

5. ANALYSIS

5.1 Outcome definitions

5.1.1 PRIMARY OUTCOME

The primary outcome measure is the one-year total UC relapse rate, defined as:

- Both clinically and endoscopically with a total Mayo-score ≥5 and endoscopic subscore of 2 or 3.
- OR clinically in absence of endoscopy, based on review by an independent critical event committee (see below).

Relapse data was collected at the 3-, 6-, 9- and 12-month follow-up forms and the end of study form. Clinically suspected relapses without endoscopic confirmation were evaluated by a critical event Committee (CEC), consisting of an independent IBD surgeon and gastroenterologist blinded to the allocation group. The CEC members were the same for both the NL and the UK. The decision will be based on clinical information suggesting relapse (exacerbation of abdominal symptoms, increased bowel frequency and rectal bleeding) or FCP>150 (> 4 weeks after surgery) or intensified medical therapy other than 5-ASA therapy.

5.1.2 SECONDARY OUTCOMES

Secondary outcomes include:

1. Number of relapses per patient after 12 months.
2. Time to first relapse defined as the time between randomisation in the control group or laparoscopic appendectomy in the intervention group and the first day of clinical symptoms of an endoscopically or clinically confirmed relapse.
3. Disease activity measured with the total Mayo score at baseline and 12 months and the pMS assessed at 3, 6 and 9 months.(10) The total Mayo score consists of four components stool frequency, rectal bleeding, endoscopic appearance and physician's global assessment (Table 2). These items are rated from 0 to 3, resulting in a total Mayo score ranging from 0 to 12 and a pMS without endoscopic assessment ranging from 0 to 9. In the Mayo score, clinical remission is defined as a total Mayo score of 2 points or lower, with no individual subscore exceeding 1 point. Mucosal healing is defined as an absolute subscore for endoscopy of 0 or 1.
4. Number of colectomies at the one-year follow-up.
5. Medication usage (no medication, topical therapy, 5-ASA, systemic steroids, immunomodulators, biologicals, small molecules, trial medication) at baseline, 3, 6, 9 and 12 months.

6. HRQL measured by the EQ-5D health status questionnaire (12), the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30-QL (11) and the Inflammatory Bowel Disease Questionnaire (IBDQ), at baseline, 3, 6, 9 and 12 months (13, 16). The EQ-5D is a generic standardised measure of HRQL at the day of completion consisting of the EQ-5D descriptive system and the EuroQol visual analogue scale (EQ-VAS). The EQ-5D comprises 5 problem areas (mobility, self-care, daily activities, pain/discomfort, mood) with patients indicating whether they experience no, some or extreme problems. The EQ-VAS is a vertical scale grading overall health status, ranging from 0 (worst imaginable health state) to 100 (best imaginable health state). Global quality of life (QoL) is assessed using two items of the global QoL dimension (items 29 and 30 in version 3.0) of the EORTC-QLQ-C30-QL that reflect overall health and QoL on the day of completion. These two items are 7-point response scales, ranging from 1 (very poor) to 7 (excellent). The average of these two items is estimated, which is the raw score (RS). The global QoL is scored by transforming the RS to a standardised 0-100 final scale score. If one or both items are missing, the global QoL is scored as missing. The IBDQ is a disease-specific questionnaire measuring QoL in 4 domains (bowel symptoms, systemic symptoms, social function and emotional function) over two weeks preceding completion. The IBDQ consists of 32 questions rated on a scale of 1–7, resulting in a total score ranging from 32 to 224. The score per domain is also estimated. If one or more items are missing, a domain and the total IBDQ are scored as missing. After inclusion of 79 patients, the protocol was amended to include a ‘global change question’ after 12 months: “Since the start of the study, have your UC symptoms improved overall?”.

5.1.3 HANDLING MISSING ITEMS

If one or more items are missing to determine the outcome score (e.g. stool frequency to determine the partial and total Mayo score), the outcome (e.g. pMS) is scored as missing.

Table 2. Components of the Mayo Score	
Stool frequency	0 = Normal no. of stools for this patient 1 = 1 to 2 stools per day more than normal 2 = 3 to 4 stools per day more than normal 3 = ≥ 5 stools per day more than normal
Rectal bleeding	0 = No blood seen 1 = Streaks of blood with stool less than half the time 2 = Obvious blood with stool most of the time 3 = Blood alone passes
Mucosal appearance at endoscopy*	0 = Normal or inactive disease 1 = Mild disease (erythema, decreased vascular pattern, mild friability) 2 = Moderate disease (marked erythema, absent vascular pattern, friability, erosions) 3 = Severe disease (spontaneous bleeding, ulceration)
Physician rating of disease activity	0 = Normal 1 = Mild disease 2 = Moderate disease 3 = Severe disease
*Not included in the partial Mayo Score	

5.2 Analysis methods

5.2.1 PRIMARY OUTCOME ANALYSIS

The one-year UC relapse rate will be compared between the intervention and control groups with chi-square testing (Table 3).

Table 3. Primary outcome results				
	Appendectomy N=	Control group N=	*P* value[1]	*Adjusted P value*[2]
Total relapse rate, *n (% n/N)*				
[1]chi-square test [2]Logistic Regression				

5.2.2 ADDITIONAL ANALYSIS PRIMARY OUTCOME:

5.2.2.1 Stratified analysis, covariate adjustment, subgroup analysis

Logistic regression on the one-year UC relapse rate will be used to (i) explore the interaction between treatment and disease location as stratification factor during randomisation and (ii) adjust for the following covariates: age at time of randomisation, gender, smoking status, extent of disease and time

between start of most recent exacerbation of UC and randomisation.(17) In addition, the interaction between treatment and country (UK vs. NL) will be exploratively addressed (Table 4).

Table 4. Subgroup analysis for primary outcome			
	Appendectomy N=	Control group N=	*P* value for interaction
NL total relapse rate, *n (% n/N)*			
UK total relapse rate, *n (% n/N)*			
Abbreviations: NL: the Netherlands; UK: United Kingdom			

5.2.2.2 Pragmatic ITT analysis

As described in the published study protocol, T0 lies at different time points in both groups (i.e. intervention group: T0 date of appendectomy; control group: T0 date of randomisation). To provide a pragmatic worst-case scenario for daily clinical practice, we will perform an additional analysis in which relapses occurring between dates of randomisation and appendectomy will be included as well. In this 'pragmatic' ITT analysis, T0 will be the randomisation date in both groups. Consequently, the follow-up time in the intervention group will be longer compared to the control group (i.e. time between randomisation date and appendectomy plus one year follow-up versus one year follow-up only).

5.2.3 SECONDARY OUTCOMES ANALYSIS

The number of relapses per patient will be compared between groups with Poisson regression (Table 5), time to first relapse with Kaplan-Meier survival analysis including log-rank testing, and number of colectomies with chi-square testing (Table 5). If covariate adjustment substantially affected the primary outcome contrast, covariate adjustment will also be applied for these secondary outcomes with Poisson regression, Cox-regression and logistic regression, respectively. If the assumption of proportional hazards seems invalid given the data, the time to first relapse will be analysed in distinct strata. Use of medication over time and by group will be descriptively reported by number and percentages. (Table 6) General estimation equation will be utilised to examine the impact of intervention on medication use over time within treatment, time and the interaction between treatment and time as model parameters.

Table 5. Secondary outcome results										
	Baseline		3 months		6 months		9 months		12 months	
	A N=	C N=	A N=	C N=	A N=	C N=	A N=	C N=	A N=	C N=
Number of relapses per patient, median (IQR)										
Time to first relapse, median, (IQR)										
HRQL, median (IQR) EQ-5D score Global QoL score Total IBDQ score IBDQ: Bowel symptoms IBDQ: Systemic symptoms IBDQ: Social function IBDQ: Emotional function										
Mayo score, median (IQR) Total Mayo score Partial Mayo score										
Number of colectomies at 1 year, *n (% n/N)*										
Abbreviations: A: appendectomy; C: control; IQR: interquartile range; HRQL: Health-Related Quality of Life; QoL: quality of life; IBDQ: Inflammatory Bowel Disease Questionnaire *p<0.05										

Table 6. Medication usage [1]										
	Baseline		3 months		6 months		9 months		12 months	
	A N=	C N=	A N=	C N=	A N=	C N=	A N=	C N=	A N=	C N=
No medication, *n (% n/N)*										
Topical therapy, *n (% n/N)*										
5-ASA, *n (% n/N)*										
Systemic steroids, *n (% n/N)*										
Immunomodulators, *n (% n/N)*										
Biologicals, *n (% n/N)*										
Trial medication, *n (% n/N)*										
Abbreviations: A: appendectomy; C: control; 5-ASA: 5-aminosalicylic acid [1]General estimation equation										

Additional generalised linear mixed models will be applied to investigate whether a different pattern of change over time exists between the two study arms in the Mayo score and the IBDQ, EQ-5D, EQ-VAS and EORTC-QLQ-C30-QL.(18) Best fitting covariance structures among repeated data will be based on visual inspection and Akaike's information criterion. Baseline scores will be included as covariates in the models of repeated data.

To assess the clinical relevance of changes in the IBDQ, a clinical minimally important difference in IBDQ will be determined using a clinical anchor-based method. The minimally important difference will be calculated from the difference in IBDQ change scores of the patients answering "yes" and "no" to the 'global change question'. Furthermore, the correlation coefficient between the IBDQ score and the global change question will be calculated by Pearson's correlation method; a minimum correlation of at least 0.30 will be regarded as acceptable.

The critical P value of 0.05 will not be adjusted for multiple testing and all analyses of secondary outcomes should be considered exploratory. Additional analyses not mentioned in this analysis plan but performed in response to journal reviewers will explicitly be qualified as post hoc.

5.3 Missing data

Missing data on outcome data will not be imputed. Based on the sample size calculation, a total of 164 evaluable patients (82 per study arm) are needed. Patients are evaluable if they were not excluded due to protocol violation in eligibility or consent, and if the primary outcome is available. To reach the appropriate sample size and target power in the study, patients not fulfilling these evaluability criteria were replaced. Generalised linear mixed modelling of repeated data allows for missing data. Patients without any follow-up data for an outcome will not be included in the analysis of that outcome, with the reasons for this missingness counted by group and overall.

5.4 Harms

The number and percentage of participants experiencing any adverse events (AEs) or serious adverse events (SAEs) will be presented by treatment group, and safety AT analysis will be performed (Table 7). AEs and SAEs between randomisation/surgery and 3-month follow-up will be registered. SAEs will be followed up at least until the final consequences have become clear, even if it implies that the follow-

up continues beyond the planned follow-up period. For patients undergoing appendectomy, in-hospital stay (N nights), postoperative complications and reinterventions will be reported. Complications of laparoscopic appendectomy will be classified according the Clavien-Dindo classification.(19)

Table 7. Safety[1]			
	Arm A N=	Arm B N=	P value[2]
Total SAE, *n (% n/N)*			
Total AE, *n (% n/N)*			
Abbreviations: A: appendectomy plus maintenance therapy; B: maintenance therapy; SAE: serious adverse event; AE: adverse event [1]Reported as-treated [2]chi-square test			

5.5 Statistical software

Analyses will be carried out using the latest version of SPSS statistics (IBM Corp.) at the time of analysis.

Manuscript and authorship

The steering committee of the ACCURE trial will share the results irrespective of the outcomes. The manuscript will be submitted on behalf of the ACCURE study group in alphabetical order. The coordinating investigator and principal investigator will be first and senior authors, respectively. The steering committee, other local principal investigators, physician assistants and research nurses who were responsible for significant patient recruitment and data collection, will be listed in the ACCURE study group.

6. DISCUSSION

The ACCURE trial is an investigator-initiated two-arm, multicentre, non-blinded, randomised controlled superiority trial in UC patients in complete clinical and endoscopic remission with the aim to assess whether the efficacy of laparoscopic appendectomy in addition to standard medical treatment is beneficial in maintaining remission in UC patients.

7.1 Challenges

In the design of the trial we faced several challenges mostly regarding accrual of the trial, which was slower than anticipated. First, accrual might have been challenging due to the narrow eligibility criteria of the trial; originally, only patients in remission treated with 5-ASA were eligible. To improve inclusion rates, the criteria were amended in 2018, by also including patients who were in remission on immunomodulators and patients who were previously treated with biologicals (>3 months prior to inclusion). Second, when including patients in remission, the motivation for patients to participate in a trial is probably lower compared to patients with active UC. Furthermore, in daily practice, surgeons and gastroenterologists might also be less encouraged to counsel/include patients without active disease in a trial. Third, when comparing a surgical intervention with standard therapy in a randomised controlled setting, the majority of patients participating in the trial might opt for an appendectomy because they are already receiving the standard treatment. Randomised controlled trials are still seen as the gold standard. However, to increase accrual and prevent selection bias, a patient preference model might have been more suitable when comparing a surgical intervention versus medical therapy. Fourth, during the COVID pandemic the trial was paused for almost a year.

Another problem was that not all patients underwent endoscopy after one year of follow-up. According to the published protocol, the primary outcome is the one-year UC relapse rate, defined both clinically and endoscopically as a Mayo-score ≥5 with an endoscopy score of 2 or 3. This issue was especially pronounced in patients without symptoms, making it difficult to persuade them to undergo colonoscopy. However, for patients presenting symptoms of a flare, it was not always possible to perform a colonoscopy. In the meeting on November 20th 2018, the DSMC advised to install a CEC to evaluate clinically suspected relapses without endoscopic confirmation. The advice was submitted to the Medical Ethics Review Committee for permission and granted on November 13th, 2019. In addition to endoscopically proven relapses, the CEC also evaluated all clinically suspected relapses based on clinical information. To qualify as relapse, an exacerbation of symptoms and rectal bleeding or FCP>150

(> 4 weeks after surgery) had to be observed, or medical therapy other than 5-ASA therapy had to be intensified. Finally, as the trial ran for a long period of time, daily clinical practice might have changed during the years. However, most developments were in the field of biologics, and these patients were not eligible for this trial.

7.2 Future perspectives

This update contains the predefined SAP for the ACCURE trial. By publishing the SAP, we aim to increase the transparency of data analyses. The outcomes of this study will provide insight into the role of appendectomy in the clinical course of UC. For this study, an IBD team was identified in every participating hospital, which could lead to improved communication and collaboration between different hospitals in future research. This will facilitate future research projects, and we have learned during this project that close collaborations are indispensable to carry out large projects aiming to improve the treatment of UC.

7.3 Trial status

Recruitment and randomisation concluded in September 2022. The final follow-up of participants is scheduled for completion in November 2023.

7. DECLARATIONS

8.1 Funding

The Dutch arm of this investigator initiated study was funded by a grant from the charity fund: Nuts-Ohra (FNO 1202-008). The ACCURE-UK 2 was funded by the Efficacy and Mechanism Evaluation Programme branch of the National Institute for Health Research (IRAS project ID: 254954). The funders

had no role in designing the study and data collection, nor will they influence the analysis and writing process of the manuscript.

8.2 Contributors

Visser, Heuthorst, Pinkney and Buskens have made substantial contributions to the concept and design of the SAP and have been involved in drafting this manuscript. Visser and Heuthorst contributed equally to the work. Dijkgraaf, Handley and Fakis elaborated on the considerations of statistical analyses. All other authors participated in the critical revision of the manuscript for intellectual content and approved the final version.

8.3 Ethics approval and consent to participate

Ethics approval for ACCURE-NL (NTR2883) was granted at the Institutional Review Board of the Academic Medical Centre, Amsterdam, April 12th 2012. Ethics approval for the ACCURE-UK 2 (ISCRCTN60945764) was obtained via the National Research Ethics System on July 29th 2019. This study was performed in accordance with the principles of Good Clinical Practice, the Dutch Agreement on Medical Treatment Act and the European General Data Protection Regulation.

8.4 Consent for publication

Not applicable.

8.5 Availability of data and materials

Details regarding protocol amendments for the ACCURE trial can be provided upon request.

8.6 Competing interests

The authors declare that they have no competing interests.

8.7 Acknowledgements

We would like to express our gratitude to the trial steering committee, trial management group, CEC and local principal investigators for their contribution in the design, management and implementation of the study. Furthermore, we acknowledge the members of the DSMC for their expertise and recommendations throughout the trial.

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