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RISK-STRATIFIED RANDOMISED CONTROLLED TRIAL IN PAEDIATRIC CROHN'S DISEASE: METHOTREXATE VERSUS AZATHIOPRINE OR ADALIMUMAB FOR MAINTAINING REMISSION IN PATIENTS AT LOW OR HIGH RISK FOR AGGRESSIVE DISEASE COURSE, RESPECTIVELY – A TREATMENT STRATEGY: THE REDUCE-RISK IN CD PIBD TRIAL

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3 **RISK-STRATIFIED RANDOMISED CONTROLLED TRIAL IN PAEDIATRIC**
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5 **CROHN'S DISEASE: METHOTREXATE VERSUS AZATHIOPRINE OR**
6
7 **ADALIMUMAB FOR MAINTAINING REMISSION IN PATIENTS AT LOW OR HIGH**
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9 **RISK FOR AGGRESSIVE DISEASE COURSE, RESPECTIVELY – A TREATMENT**
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11 **STRATEGY: THE REDUCE-RISK IN CD PIBD TRIAL**
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23 **consortium and PIBDnet**
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56 Disease, Immunomodulators

ABSTRACT

Introduction

Immunomodulatory medications such as thiopurines (azathioprine (AZA)/6-mercaptopurine (6MP)), methotrexate (MTX) and adalimumab (ADA) are well established for maintenance of remission within paediatric Crohn's disease (CD). It remains unclear which maintenance medication should be used first-line in specific patient groups.

Aims

To compare the efficacy of maintenance therapies in newly diagnosed CD based upon stratification into high and low risk groups for severe CD evolution; MTX versus AZA/6MP in low-risk and MTX versus ADA in high-risk patients. Primary end point: sustained remission at 12 months (weighted paediatric Crohn's disease activity index ≤ 12.5 and C-reactive protein ≤ 1.5 -fold upper limit) without relapse or ongoing requirement for EEN/steroids 12 weeks after treatment initiation.

Methods and Analysis

REDUCE-RISK in CD is an international multicentre open-label prospective randomised controlled trial funded by EU within the Horizon2020 framework (grant number 668023). Eligible patients (aged 6-17 years, new-onset receiving steroids or EEN for induction of remission for luminal +/- perianal CD; are stratified into low and high-risk groups based upon phenotype and response to induction therapy.

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3 Participants are randomised to one of two treatment arms within their risk group: low-
4 risk patients to weekly subcutaneous MTX or daily oral AZA/6MP, and high-risk
5 patients to weekly subcutaneous MTX or fortnightly ADA. Patients are followed up
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8 for 12 months at pre-specified intervals. Electronic case report forms are completed
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11 prospectively. The study aims to recruit 312 participants (176 low-risk; 136 high-risk).
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17 **Ethics and Dissemination**

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19 ClinicalTrials.gov Identifier: (NCT02852694), authorisation and approval from local
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21 ethics committees have been obtained prior to recruitment. Individual informed
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23 consent will be obtained prior to participation in the study. Results will be published
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25 in a peer-reviewed journal with open access.
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31 **Registration Details**

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33 NCT02852694; pre-results.
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38 **Article Summary**

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40 • This study is the first international prospective RCT comparing three different
41 immunomodulatory medications for maintenance of remission in newly
42 diagnosed CD based upon a risk stratification protocol.
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46 • This study may better define the most appropriate first-line immunomodulatory
47 medication to be used in specific subsets of CD patients requiring
48 immunomodulatory maintenance therapy.
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52 • An ancillary study will compare outcomes in ADA treated patients from
53 inclusion (TOP-Down) versus patients switched to ADA due to failure of
54 immunomodulator therapy (STEP-Up).
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- Therapeutic efficacy will be supported by drug levels, pharmacogenomics and microbiome analysis as secondary outcomes.
- Inability to blind patients, their relatives or treating physicians to treatment due to ethical issues and differences between medication administration routes serves as a limitation to this study.
- Blinding of an alternative clinician to assess disease activity during study visits may prove practically difficult in smaller centres.

INTRODUCTION

Crohn's disease (CD) the most common form of inflammatory bowel disease (IBD) in children is a chronic disorder with the potential to affect the whole gastrointestinal tract. The aim of CD treatment is to control active inflammation and achieve bowel healing; chronic and uncontrolled CD results in poor outcomes for patients, including

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3 reduced quality of life, recurrent hospitalisation and potential need for surgical
4 intervention.¹ Treatments for CD are categorised into those which induce remission
5 (such as steroids^{1,2} or exclusive enteral nutrition (EEN)^{1,3} and those which maintain
6 remission. Immunomodulatory medications are a mainstay of maintenance treatment
7 in IBD; with the efficacy of thiopurines (e.g. azathioprine (AZA) and 6-
8 mercaptopurine (6MP))^{4,5,6} and methotrexate (MTX)^{7,8,9,10} well established. Anti-
9 tumour necrosis factor (anti-TNF) therapies (infliximab^{11,12} and adalimumab
10 (ADA)^{13,14}) including their biosimilars are used in those patients refractory to
11 “traditional” induction or maintenance treatment.
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13
14 Due to a lack of treatment strategy trials within the paediatric IBD (PIBD) population
15 however, it remains unclear which of the aforementioned maintenance therapies
16 should be used first-line in individual patients. Randomised controlled trials
17 comparing the use of MTX with thiopurines for maintenance of remission failed to
18 show a significant difference in efficacy between the two.^{15,16, 17} A Cochrane review
19 in adults with quiescent CD highlighted the lack of adequately powered trials
20 necessary in order to determine the efficacy and safety of thiopurines compared to
21 other maintenance therapies^{4, 10}. The RISK study demonstrated improved clinical
22 and growth-based outcomes at 1 year with anti-TNF monotherapy in comparison
23 with immunomodulatory monotherapy; however further investigation into which
24 specific patients are most likely to benefit from these therapies is still required.¹⁸

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26 There is a clear disparity between North America and Europe in terms of which form
27 of immunosuppression first with both concerns about efficacy and safety lying behind
28 these thus there is an urgent need for a head to head study in children to help inform
29 the first choice of immunosuppression.
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3 Stratifying patients by risk for complex or severe CD may allow pre-emptive direction
4 of maintenance strategy and potentially an early reduction in disease burden with
5 subsequent improvement in long-term outcomes. The adult IBD Ahead initiative
6 highlighted young age at diagnosis as a risk factor for severity of CD evolution¹⁹; all
7 patients diagnosed within paediatric services would therefore be considered 'high
8 risk'. Paediatric consensus guidelines suggest that paediatric CD patients at 'high
9 risk for poor outcome' should receive early therapy optimisation to modify
10 progression of their disease.¹ The guidelines list specific features which may be
11 considered predictive for poor outcome in paediatric CD (see Table 1).¹ Patients
12 deemed at high risk for complex disease or poor outcome may benefit from a 'Top-
13 down' approach as the TISKids aims to investigate²¹.

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15 Therefore the PIBDnet consortium recognised the urgent need to investigate the
16 efficacy and safety of immunomodulatory medications and to stratify whether a top-
17 down approach was superior to a traditional 'step-up' for paediatric patients deemed
18 at high risk for rapidly complicated disease course. REDUCE-RISK in CD is a
19 randomised controlled trial (RCT) which aims to compare the effectiveness of
20 immunomodulatory medications for maintenance of remission in newly diagnosed
21 CD based upon risk stratification specifically, the effectiveness of MTX versus
22 AZA/6MP for maintenance of remission who are low risk for rapidly progressive
23 disease and the effectiveness of MTX versus ADA in a high risk group.

24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 **METHODS AND ANALYSIS**

50 51 52 53 54 **Study Design**

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3 We designed an international multicentre open-label prospective RCT with 4
4 treatment arms as shown in Figure 1. Following screening and consent, eligible
5 patients are stratified into low and high-risk groups based upon phenotype and
6 disease response to induction therapy (Table 1). Patients are then randomised to
7 one of two arms within their risk group: with low risk patients receiving either weekly
8 subcutaneous MTX or daily oral AZA/6MP, and high-risk patients receiving either
9 weekly subcutaneous MTX or fortnightly subcutaneous ADA.
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24 **Study End Points**

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28 Patients are followed up for 12 months post randomisation. The primary end point of
29 the study is sustained steroid or EEN-free remission at 12 months, defined as
30 weighted Paediatric Crohn's Disease Activity Index (wPCDAI) ≤ 12.5 and C-reactive
31 protein (CRP) ≤ 1.5 -fold upper limit without a relapse or need for EEN/steroids since
32 week 12.
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42 Secondary end points include comparison of time to first relapse, remission at 12
43 weeks, growth, adverse events, health related quality of life and patient reported
44 outcomes between the two treatment arms within each risk group, but also between
45 low and high risk MTX treated patients. The study also aimed to evaluate clinical
46 predictors for response, including genomic and serological markers and results of
47 drug monitoring (MTX and ADA concentrations) metabolites (6-thioguanine (6-TG)
48 and 6-methylmercaptopurine (6-MMP) in AZA/6MP) and anti-drug antibodies (ADA)
49 in relation to adherence, toxicity and response. The ancillary study additionally aimed
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3 to evaluate the efficacy of ADA in patients treated from inclusion (Top-down) versus
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5 patients switched to ADA due to immunomodulator failure (Step-up). Further
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7 outcome measures are detailed in Box 1.
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Box 1: Study endpoints

Primary Endpoint

- Sustained steroid/EEN-free remission at month 12, where sustained remission is defined as wPCDAI \leq 12.5 and CRP \leq 1.5 times the upper limit without a relapse or need for EEN/steroids since week 12.

Secondary Endpoints:

Comparing the following within 1) the two treatment arms per risk group; 2) methotrexate treatment between high and low risk groups; and 3) TOP-Down adalimumab (high risk group) versus STEP-Up adalimumab (ancillary study):

- Rate of clinical remission at month 12 (physician global assessment (PGA), wPCDAI, paediatric Crohn's disease activity index (PCDAI))
- Relapse free remission with normal CRP at month 12
- Relapse free remission with normal CRP and faecal calprotectin $<$ 300 at month 12
- Remission at week 12
- Time to first relapse after week 12
- Faecal calprotectin values at visits 1, 2, 4 and 6 (respectively at month 0, 2, 6 and 12)
- Dropout rates
- Adverse drug event rate
- Height velocity and z-score at baseline and 52 weeks
- Quality of life as measured by the IMPACT 3 questionnaire completed at each study visit
- Health economic evaluation at all visits (forms EQ-5D-Y proxy 1, EQ-5D-Y and EQ-5D-5L, WPAI:CD Caregiver, School Attendance start of the research and follow up visits)

Eligibility Criteria and Recruitment

56 Full eligibility criteria for the study are listed in Box 2. Patients are eligible if aged 6-
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58 17 years with new-onset ($<$ 6 months) treatment naïve luminally active and/or
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3 perianal fistulising CD diagnosed as per revised Porto criteria²² receiving steroids or
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5 EEN for induction of remission with wPCDAI >40 or CRP >2 times upper limit of
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7 normal at diagnosis. Informed consent from must be obtained prior to participation in
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9 the study. Patients are excluded in cases of previous use of IBD related medications;
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11 pregnancy or refusal to use contraceptives; disease requiring surgery;
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13 contraindications to study medication; exposure to live vaccine within 3 weeks; oral
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15 anticoagulant or anti-malarial use; current or previous malignancy; significant
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17 infection; or significant comorbidity.
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Box 2: Eligibility criteria**Inclusion Criteria**

- Patients aged 6-17 years with new-onset (<6 months) treatment naïve active luminal and/or perianal fistulising Crohn's disease diagnosed using established criteria²² requiring steroids or EEN for induction of remission
- wPCDAI >40 or CRP >2 times upper limit of normal at diagnosis
- Luminal active Crohn's disease (B1) with or without B2 and/or B3 disease behaviour as per Paris classification²³
- Signed informed consent

Exclusion Criteria

- wPCDAI <42.5 at diagnosis, except where CRP >2 times upper normal limit
- Lack of induction therapy with steroids or EEN
- Previous therapy with any IBD-related medication other than induction therapy as detailed within this protocol with the exception of 5-aminosalicylic acid (5ASA) preparations
- Pregnancy or refusal to use contraceptives during the study period in pubertal patients unless absolute abstinence is confirmed at each study visit
- Lactating mothers
- Perianal fistulising disease requiring surgical therapy
- Patients homozygous for thiopurine methyltransferase (TPMT) mutations or those with TPMT activity <6 nmol/h/ml erythrocytes or <9nmol 6MTG/g Hb/h, unless they qualify as high-risk patients
- Evidence of un-drained and un-controlled abscess/phlegmon
- Contraindication to any drugs used in the trial (including intolerance/hypersensitivity or allergy to study drugs (thiopurines, methotrexate or adalimumab))
- Current or previous malignancy
- Serious comorbidities (e.g. renal insufficiency, hepatitis, respiratory insufficiency) which may interfere with drug therapy or interpretation of outcome parameters or will make it unlikely that the patient will complete the trial.
- Infection with mycobacterium tuberculosis, hepatitis B or C, human immunodeficiency virus (HIV)
- Moderate to severe heart failure (New York Heart Association class III/IV)
- Oral anticoagulant therapy, anti-malarial therapy
- Live vaccine exposure (including yellow fever) less than 3 weeks prior to inclusion

Screening Visit (Visit 0)

The screening visit allows for assessment of eligibility for inclusion in the study, evaluation of the patient's response to induction therapy if already commenced,

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3 commencement of induction therapy where not commenced, and acquisition of
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5 consent and assent.
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10 11 12 *Induction Therapy* 13

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15 All enrolled patients receive either corticosteroids or exclusive enteral nutrition (EEN)
16 as induction as determined by the clinical team and the patient/caregiver. For EEN
17 any balanced formula (polymeric or elemental) administered orally or via nasogastric
18 tube is permitted and should be prescribed for 6-8 weeks. Tapering of steroids is at
19 the discretion of the prescribing clinician. Adaptation of induction therapy (e.g. dose
20 increase of steroids or return to EEN) or crossover from one induction therapy to the
21 other is permitted in order to achieve remission, however patients must have
22 discontinued their induction therapy by week 12. If induction therapy is not
23 discontinued by week 12 the patient is considered a treatment failure, with protocol
24 for this detailed below.
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45 Inclusion Visit and Risk Group Allocation (week 5 +/- 3 weeks; visit 1) 46 47 48

49 In order to incorporate response to initial induction therapy within the risk
50 stratification criteria, inclusion and risk group allocation is performed at week 5 +/- 3
51 weeks of induction therapy. Data from the screening visit is reviewed with ineligible
52 patients excluded, and patients are then stratified into the high or low risk group
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54 (Table 1) based upon the ECCO/ESPGHAN consensus guidelines¹. Patients with
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perianal fistulising disease at diagnosis are auto-allocated to the high-risk group regardless of other factors at inclusion visit. All other patients are allocated to the low risk group. Patients with low thiopurine methyltransferase (TPMT) activity or homozygous mutations are excluded should they be categorised as low risk.

DEFINING HIGH RISK CROHN'S DISEASE PATIENTS	
ECCO/ESPGHAN CONSENSUS GUIDELINES¹	MODIFIED STUDY CRITERIA
Severe perianal disease	Complex perianal fistulising disease phenotype
Extensive (pan-enteric) disease; deep colonic ulcers on endoscopy	Panenteric disease phenotype (defined as L3 with L4b as per Paris classification ²³ or L3 with deep ulcers in the duodenum, stomach or oesophagus not related to non-steroidal anti-inflammatory medications or <i>Helicobacter pylori</i>)
	Overall cumulative disease extent of ≥ 60 cm
Stricturing and penetrating disease at onset	B2, B3 or B2B3 disease behaviour ²¹
Marked growth retardation > -2.5 height Z scores	Severe growth impairment (height z-score < -2 or crossing ≥ 2 centiles) likely related to Crohn's disease
Persistent severe disease despite adequate induction therapy	Hypoalbuminemia (< 30 g/L), elevated CRP (at least 2 times upper limit of normal range), or wPCDAI > 12.5 despite at least 3 weeks of optimized induction therapy with steroids or EEN
Severe osteoporosis	Not included

Table 1 – Definition of high-risk patients based upon ECCO/ESPGHAN consensus guidelines¹ (ECCO – European Crohn's and Colitis Organisation; ESPGHAN – European Society for Paediatric Gastroenterology, Hepatology and Nutrition; CRP – C-reactive protein; wPCDAI – weighted Paediatric Crohn's Disease Activity Index; EEN – exclusive enteral nutrition)

Randomisation and Treatment Allocation

Randomisation is undertaken following allocation to high or low risk group at week 5 +/- 3 weeks. This process utilises an integrated module within the electronic case report form (CRF) system. Within both the high and low risk groups patients are 1:1 randomised to MTX versus ADA or AZA/6MP respectively in blocks of four stratified by EEN or steroid induction therapy. Code for randomisation is prepared and held by the central coordinating site and site co-ordinators are then informed of the results. Immunomodulator or biologic therapy should be commenced within 2 weeks of randomisation as per the protocol outlined in Table 2.

AZA/6MP and MTX are prescribed and dispensed according to local guidelines. ADA (Humira ®) is provided by AbbVie. Co-interventions are prohibited.

	Therapy	Route	Dose	Notes
LOW RISK PROTOCOL	Methotrexate	SC	15mg/m ² body surface area weekly (max dose 25mg)	Ondansetron 4-8mg orally 1 hour pre injection and folic acid 15mg (5mg in patients <20kg) 3 days post injection are recommended for all patients
	VERSUS			
	Azathioprine	PO	2.5mg/kg (rounded down to nearest 12.5mg)	Half calculated dose for TPMT heterozygotes/activity 6-9nmol/h/ml
HIGH RISK PROTOCOL	OR			
	6-Mercaptopurine	PO	1.5mg/kg (rounded down to nearest 12.5mg)	Half calculated dose for TPMT heterozygotes/activity 6-9nmol/h/ml
	Methotrexate	SC	15mg/m ² body surface area weekly (max dose 25mg)	Ondansetron 4-8mg orally 1 hour pre injection and folic acid 15mg (5mg in patients <20kg) 3 days post injection are recommended for all patients
HIGH RISK PROTOCOL	VERSUS			
	Adalimumab (Humira ®)	SC	160mg then 80mg after 2 weeks then 40mg every 2 weeks thereafter (patients >35kg) 120mg then 80mg after 2 weeks then 40mg every 2 weeks thereafter (patients 25-35kg) 80mg then 40mg after 2 weeks and 20mg every 2 weeks thereafter (patients <25kg)	

Table 2: Medication protocol for low and high-risk patients following randomisation (TPMT – thiopurine methyltransferase)

Follow Up Visits (Visit 2, 3, 4, 5 and 6)

Patients are followed up at pre-specified intervals (Figure 1) with a window of +/- 2 weeks. A telephone call is undertaken at week 4 following initiation of induction in order to support patient compliance with induction regime and advise weaning where appropriate. Data as described in Box 3 are collected at each consultation. Patients' compliance with therapy is determined at each face-to-face follow up visit by pill and vial counts plus by patients' reporting.

Box 3: Standard requirements for each study visit

- An explicit history of illness since last visit, including review of symptoms, medications (including compliance check) and adverse events.
- Physical examination
- wPCDAI, PGA and PCDAI scoring
- Anthropometrics (height measured using a calibrated wall mounted stadiometer)
- Blood tests
 - White blood cells
 - Absolute neutrophil count
 - Haemoglobin
 - Haematocrit
 - Platelet count
 - Erythrocyte sedimentation rate (ESR)
 - C-reactive protein (CRP)
 - Amylase
 - Albumin
 - Aspartate transaminase (AST)
 - Alanine transaminase (ALT)
 - Conjugated bilirubin
 - Gamma glutamyl transferase (GGT)
- Stool samples for faecal calprotectin and microbiome analysis
- Health economic parameters (EQ-5D-Y proxy 1; EQ-5D-Y; EQ-5D-5L; WPAI:CD; school attendance questionnaire)
- Quality of life evaluation (IMPACT 3)
- Urine human chorionic gonadotropin (hCG) in all female patients of child-bearing potential
- Confirmation of contraception use or of absolute abstinence in all patients

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Remission is defined as wPCDAI \leq 12.5, normal CRP (\leq 1.5 times upper normal range) and being free of steroids or EEN. Once remission is achieved and induction therapy is discontinued, a patient is considered to be failing treatment or experiencing a relapse in the following circumstances:

- wPCDAI $>$ 40
- CRP $>$ 2 times upper normal limit in the absence of any clear infectious process
- wPCDAI $>$ 12.5 but $<$ 40 and/or CRP $>$ 1.5 times but $<$ 2 times over upper normal limit at 2 consecutive visits within 2-8 weeks
- Development of CD related complications e.g. fistulisation
- Requirement for additional CD-specific medication/surgery since last study visit

A patient will also be considered a treatment failure should induction therapy be continued at week 12. In addition, the treating clinician may escalate treatment at any time point independent of wPCDAI score if it is felt that the patient is experiencing a relapse.

Dose Optimisation and Therapeutic Drug Monitoring

Drug monitoring is undertaken as detailed below. In addition to this, samples for drug monitoring should be collected at the time of medication cessation in the event of drug discontinuance due to adverse effect or loss of response. Potential adaptations to therapies which may be made at specific follow up visits are detailed in Box 4.

Box 4 – Potential adaptations to therapies at follow up visits

Month 2 (Visit 2)

- Failure to discontinue induction therapy by week 12
 - Offer switch to the ancillary study (ADA STEP-up) to those prescribed MTX or AZA/6MP, or an increase in dose frequency to weekly in those prescribed ADA
 - Alternatively, the patient may leave the study and receive therapies as per the discretion of the treating clinician.

Months 4, 6, 9 and 12 (Visits 3, 4, 5 and 6)

- Thiopurine non response
 - Protocol as per metabolite levels (detailed in Table 3)
- Thiopurine intolerance (except pancreatitis)
 - Switch to alternate thiopurine (AZA to 6MP or vice versa) or split dose to provide twice daily (BD) dosing
- Thiopurine failure (any exacerbation despite dose optimisation/pancreatitis/cytopaenia)
 - Offer switch to ancillary study (ADA STEP-up) or exit study
- MTX intolerance or failure (any exacerbation or elevation of liver enzymes as detailed below)
 - Offer switch to ancillary study (ADA STEP-up) or exit study
- ADA failure (any exacerbation)
 - Increase frequency to weekly dosing

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7 *Azathioprine*
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RESULT	ACTION
6-TG <150	Consider non-compliance; repeat sample at subsequent visit and increase dose if low 6-TG confirmed (+25mg or +12.5mg if dose <50mg)
6-TG 150-800	No adaptation
6-TG >800	Decrease dose if repeat sample at subsequent visit confirms high 6-TG (-25mg or -12.5mg if dose <50mg)
6-MMP >8000 or signs of hepatotoxicity	Stop medication – switch to ancillary study Erythrocyte lysate sample frozen at -80C and shipped to central lab at end of study for thiopurine nucleotides

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30 *Table 3 – Azathioprine dose adjustments based upon metabolite levels*
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37 TPMT genotype or phenotype at screening determines the initial dose of AZA/6MP;
38 and measurement of thiopurine metabolites (6-thioguanine (6-TG) and 6-
39 methylmercaptopurine (6-MMP)) at visit 2 determines requirement for subsequent
40 dose adjustment performed according to the recommendations in Table 3. Where
41 possible thiopurine metabolites are measured locally; central lab measurements are
42 provided for centres where this is unavailable.
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51 At visit 2 a urine sample for TPMT metabolite determination and an erythrocyte
52 lysate sample for quantification of Thiopurine Nucleotides by Liquid
53 Chromatography-Tandem Mass Spectrometry should be frozen at -80°C and
54 shipped on dried ice to the central lab at the end of the study. At each visit from visit
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3 2 to 6, an additional EDTA blood sample will be collected for further 6-TG and 6-
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5 MMP testing and frozen at -80C.
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11 12 *Methotrexate*

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16 Washed erythrocyte for MTX levels will be obtained at visits 2, 4 and 6 and stored
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18 frozen at local centres. These samples will be sent on dry ice for central analysis to
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20 evaluate response to therapy and adverse effects in relation to drug levels.
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27 28 *Adalimumab*

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31 Adalimumab trough levels are measured after 3 injections of maintenance therapy
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33 (e.g. at visit 2) within the local laboratory (central lab testing available if local lab
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35 testing is unavailable). Dosing interval may be shortened to weekly in the event of
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37 low ADA levels (<8 mcg/ml) and negative ADA antibodies. Further samples should
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39 be obtained at visits 3, 4, 5 and 6 and should be frozen for later analysis within the
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41 central lab.
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49 50 *Pharmacogenetics*

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53 DNA for pharmacogenetics should be taken from patients randomised to MTX or
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55 AZA/6MP for multiplex genotyping of polymorphism related to drug metabolism to
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57 evaluate safety and response to therapy. Analysis will be performed at the end of the
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59 study, or earlier in those patients showing toxicity.
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Ancillary Study

Patients unable to discontinue induction therapy or those randomised to thiopurine or MTX therapy who experience treatment failure may be invited to participate in the ancillary study (STEP-up ADA) until visit 5. Any initial maintenance therapy will be stopped and induction and maintenance regime for ADA as previously described will be commenced. Up to 3 additional study visits at 3-month intervals will be offered to these patients in order to obtain 12 months of follow up. A maximum of 68 patients can participate in this ancillary study allowing a 1:1 comparison of TOP-down ADA to STEP-up ADA therapy.

Unscheduled Visits

Unscheduled visits may be arranged based upon clinical requirements. As for scheduled visits per protocol treatment adaptations are possible if intolerance or failure of the study drug is detected. Subsequent scheduled visits will not be changed after an unscheduled visit.

Treatment Discontinuation

Patients who discontinue treatment before completing 12 months of study drug within either the main study or the ancillary study will receive a single follow-up visit. This will be either 12 months after the commencement of study treatment or at the point of inclusion in the ancillary study.

Modifications to the protocol while the study is being conducted will be relayed to all site staff by email and then onto their relevant ethical and regulatory boards. The current manuscript is based on protocol 5.1 last modified 28th May 2019.

Allocation Concealment and Blinding

For ethical reasons we decided against a double dummy design for blinding the patient, parents and care givers. Due to the differences in medication administration route and the significant nausea commonly associated with MTX blinding of the allocation to the patients, their families or their physicians is not possible. Where possible however, blinding of an alternative clinician to score the wPCDAI, PCDAI and PGA at each study visit should occur (prospective randomized open blind end-point (PROBE) evaluation).

Safety

The external and independent Advisory Board of PIBDSETQuality serves as an independent Data and Safety Monitoring Board; it meets at pre-specified intervals with access to all data within the study. The principal investigator at each site is responsible for reporting any safety issues (adverse events, serious adverse events (SAEs), suspected unexpected serious adverse reactions), drop-outs, or any new information which may impact the study in any way. The principal investigator shall report to the sponsor all SAEs experienced by a study subject receiving an Adalimumab(Humira) within 24 hours of learning of the event regardless of the relationship of the event to the product. All SAEs are immediately sent to AbbVie pharmacovigilance by the sponsor. SAEs will be followed from the date of patient's signature of informed consent, until complete resolution or 30 days after the end of the study/patient's final study visit.

Box 5 – Criteria for premature termination of study treatment or participation

- Pregnancy at any stage
- Treatment failure as per protocol
- Failure to tolerate allocated treatment or alternatives as listed within the protocol
- Significant drug related side effects manifesting as significantly abnormal bloods results or adverse effects based upon the clinical judgement of the treating physician
- Request of participant to be withdrawn from treatment
- The judgement of the treating physician being that it is in the best interests of the participant to withdraw from study treatment
- Loss of participant to follow up
- Patient death

Participants may withdraw consent for further participation or data collection at any time without giving reason and without prejudicing further care or treatment; and will be permanently withdrawn from study treatment in the event of any of the situations outlined in Box 5. Patients should be provided with a study alert card for use in the event of an emergency.

Biochemical markers are monitored with a clearly defined protocol for adjustments to therapy based on abnormal results (e.g. neutropenia, pancreatitis, elevated liver enzymes).

Data Collection, Management and Monitoring

Patient CRFs are completed in a prospective manner using an electronic web-based system designed specifically by PIBDnet for this trial. In order to maintain data

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2
3 security and integrity, the web-based data entry will be linked to a password secured
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5 Microsoft Access database, where data will be stored until time of analysis. Files will
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7 be saved on a code secured net-drive and backed-up following each data entry on a
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9 disk locked in a cabinet. Patients will be identified only by a study code assigned at
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11 the point of enrolment. Code of patient identifiers will be kept at each participating
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13 site. Handling of patient-identifiable is compliant with the legislation of each
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15 participating centre and the European General Data Protection Regulation (GDPR).
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17 Investigators will be invited to fax or email the paper source document to the
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19 coordinating site on a random basis to allow appropriate monitoring. Access to data
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21 with detailed information on study outcomes will be made available to other research
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23 groups on request and at the discretion of the principal investigators.
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30 Monitoring arrangements are in place for all sites after initial site initiation. The
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32 monitoring visits will occur regularly partly dependant on recruitment rate at
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34 individual sites. The monitoring is performed usually by someone external to the
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36 clinical team.
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40 **Analysis and Statistical Methods**

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43 Descriptive statistics (mean, median, standard deviation, standard error, quartiles,
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45 minimum, maximum, and two-sided 95% confidence limits of mean and median) will
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47 be presented for each treatment of the low and high risk paediatric CD groups and,
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49 where applicable, for the paired difference of each patient. Frequency tables will be
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51 presented where applicable.
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60 **Primary Analysis**

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Difference in the 12-month steroid/EEN free sustained remission rates between the treatment groups will be undertaken using Chi square test. Mantel Haenzel test will be used to combine data from all participating sites.

Secondary Analyses

Chi-square tests or Fisher's exact tests will be used to compare rates of remission, steroid intake, dropout and serious adverse events between the two arms of each risk group and between the low and high risk MTX groups. Logistic regression analyses may be performed to adjust for any imbalances in baseline covariates. To compare time to disease flare between the arms of each risk group and between high and low risk MTX groups, a Kaplan–Meier survival estimate will be used and the log-rank test of equality over strata. A Cox proportional hazard model will be constructed to obtain a hazard ratio after validation of the proportionality assumption and adjusting for possible confounding variables (including age and disease duration). Student's t tests or Wilcoxon rank sum tests will be used to compare growth, steroid dose, adverse events, changes in quality of life and patient reported outcomes between the two arms of each risk group and between the high and low risk MTX groups. The predictive value of faecal calprotectin levels, CRP, serum tests or other clinical predictors for response (including genomic and serological markers) will be assessed for each arm of the study using sensitivity, specificity, negative and positive predictive values or area under the ROC curve. Multivariate logistic regression analyses will then be performed.

Analyses will be performed using the R software (<http://cran.r-project.org>). All comparisons will be made using a 2-sided significance level of 0.05.

Sample Size Considerations

Estimated remission rates are based on recent analysis from the RISK study¹⁸, indicating an advantage of early anti-TNF introduction over immunomodulator therapy. For the low risk group, it was hypothesized that 48% of children will be in remission at 12 months for the AZA/6MP arm versus 70% for the MTX arm. On the basis of this data with an alpha risk of 5% and a power of 80% a sample requirement of 88 patients per arm was calculated assuming a 10% loss of follow up. For the high-risk group, it was hypothesised that 40% of children will be in remission at 12 months for the MTX arm versus 65% for the adalimumab arm. To detect this difference with an alpha risk of 5% and a power of 80%, a sample size of 68 participants is necessary, again assuming a 10% loss of follow-up. In total 312 participants will be included in the study (176 low-risk group; 136 high risk group).

Patient and Public Involvement

Patients were not involved in the development of this study; however, the French patient charity AFA Crohn, RCH, France was involved in study design and critically reviewed and commented upon all aspects of the trial.

Discussion

REDUCE-RISK in CD is the first multicentre international RCT aiming to compare three different medication strategies for maintenance of remission in newly diagnosed CD based upon a risk stratification protocol. During the 12-month follow up period the effects of the differing management strategies will be assessed via data collected and outcome measures as defined above in order to analyse the efficacy and safety of each medication and better define the most appropriate first-line maintenance immunomodulatory medication to be used in specific subsets of CD patients. As a group we speculatively hypothesise that MTX will be superior to thiopurines for maintaining remission in CD in the low risk group although in the absence of head to head studies prior to this one this study will provide data to address this. We also hypothesise that ADA will be superior to MTX in the high-risk group based upon the results from the RISK study.¹⁸ In addition to this, the ancillary study will compare outcomes in ADA treated patients from inclusion (Top-down) versus patients switched to ADA due to failure of immunomodulator therapy (Step-up), with the potential to stratify which patients might benefit from such a top-down treatment strategy.

The design and completion of interventional studies in PIBD is a recognised challenge between rigorous study design methodology and pragmatic considerations around feasibility and completion within a paediatric dataset.²⁴ This particular study is limited by the inability to blind the treatment allocation to the patients, their families

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3 or their treating physician due to the differences in medication administration route
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5 and the side effects commonly associated with the study medication. Although the
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7 protocol advises that where possible blinding of an alternative clinician to score
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9 disease assessment at each study visit should occur in order to obtain prospective
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11 randomized open blind end-point (PROBE) evaluation this may be practically difficult
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13 in smaller centres where staff are familiar with the majority of their patient cohort.
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22 **ETHICS AND DISSEMINATION**

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25 The study is being conducted according to the principles of the Declarations of
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27 Helsinki and to date has been approved by all participating sites as listed within
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29 supplementary Table 1. Clinical trials authorisation and ethics approval has been
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31 obtained from the local ethics review committees of these participating nations and
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33 centres. The Standard Protocol Items: Recommendations for Interventional Trials
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35 (SPIRIT) guidelines²⁵ were adhered to in the production of the protocol for this trial
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37 (see uploaded material for details).
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46 **Consent**

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49 Patients and their caregivers are provided with study-specific information including
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51 an explicit description of the study outline and alternatives for participation. It is made
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53 clear to all patients approached that declining to participate in the study will not
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55 jeopardize the quality of subsequent care received. After a period of consideration, if
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57 agreeable, the patient's parent or caregiver is asked to sign consent forms with age-
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3 appropriate assent obtained from the child where relevant (see appendix 1 for model
4 consent forms). The signed forms are filed within the patient's medical record with a
5 copy provided to the participant and their caregiver. Consent will be obtained by site
6 staff with the relevant training and who are identified as assigned on the delegation
7 log. Participants taking part in the ancillary study will not be re-consented.
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19 **Dissemination**

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22 Results of the study will be submitted for publication within a peer-reviewed journal.
23 In accordance with the H2020 general grant agreement, the dissemination process
24 will ensure open access to the scientific publications resulting from this project.
25 Journal authorship guidelines will be adhered to and there are no plans to use
26 professional writers.
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37 **AUTHOR CONTRIBUTIONS**

38
39 **R. Harris** prepared the manuscript with comments and review from all authors.

40
41 **RKR** and **FMR** assisted in developing the original study protocol and provided
42 critical review of the manuscript.
43
44

45
46 **All authors have assisted in developing the original study protocol and**
47 **approved the uploaded draft.**
48
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51 As sponsor PIBDnet has full responsibility and control for the original study design,
52 collection, management, analysis, and interpretation of data, including writing of the report
53 and the decision where to submit the report for publication,
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57 **FUNDING**

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4 Bowel Diseases Network for Safety, Efficacy, Treatment and Quality improvement of
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6 Innovation Framework Programme (grant number 668023). ADA (Humira ®) is
7 provided by AbbVie.
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13
14 The main study sponsor is PIBDNet. PIBDNet is the EU legal representative for the
15 study. The specific contact for the sponsor is Frank Ruemmele (Service de Gastro-
16 entérologie, Hôpital Necker Enfants Malades, 149 rue de Sèvres, 75015 Paris,
17 France).
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26 **COMPETING INTERESTS**

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28 **RKR** is supported by an NHS Research Scotland Senior Research Fellowship, and
29 has received speaker's fees, travel support, and/or participated in medical board
30 meetings with Nestle, MSD Immunology, AbbVie, Dr Falk, Takeda, Napp, Mead
31 Johnson, Nutricia & 4D Pharma. FMR has received speaker fees from Shering-
32 Plough, Nestlé, MeadJohnson, Ferring, MSD, Johnson & Johnson, Centocor, AbbVie;
33 has served as a board member for SAC:DEVELOP (Johnson & Johnson), CAPE
34 (AbbVie), LEA (AbbVie); and has been invited to MSD France, Nestlé Nutrition
35 Institute, Nestlé Health Science, Danone, MeadJohnson, Takeda, Celgene, Biogen,
36 Shire, Pfizer, and Therakos. DT received consultation fee, research grant, royalties,
37 or honorarium from Janssen, Pfizer, Hospital for Sick Children, Ferring, Abbvie,
38 Takeda, Biogen, Atlantic Health, Shire, Celgene, Lilly, Neopharm, Roche. LdR
39 received consultation fee, research grant, or honorarium from ZonMw, ECCO, Shire,
40 Malinckrodt, Nestlé, Celltrion, Abbvie and Pfizer. MA received consultation fee and
41 honorarium from Abbvie. SK received consultation fee, research grant, or
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3 honorarium from Danone, Nestec-Nutrition, Abbvie, Takeda, Celgene, Shire, Pfizer,
4
5 Biogaia, Janssen, Berlin-Chemie; Mead Johnson, Vifor, Pharmacosmos,
6
7 ThermoFisher
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12 **Remaining authors:** nil competing interests declared.
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16 **FIGURE LEGENDS**

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21 *Figure 1 – Study Design of the REDUCE-RISK in CD trial*
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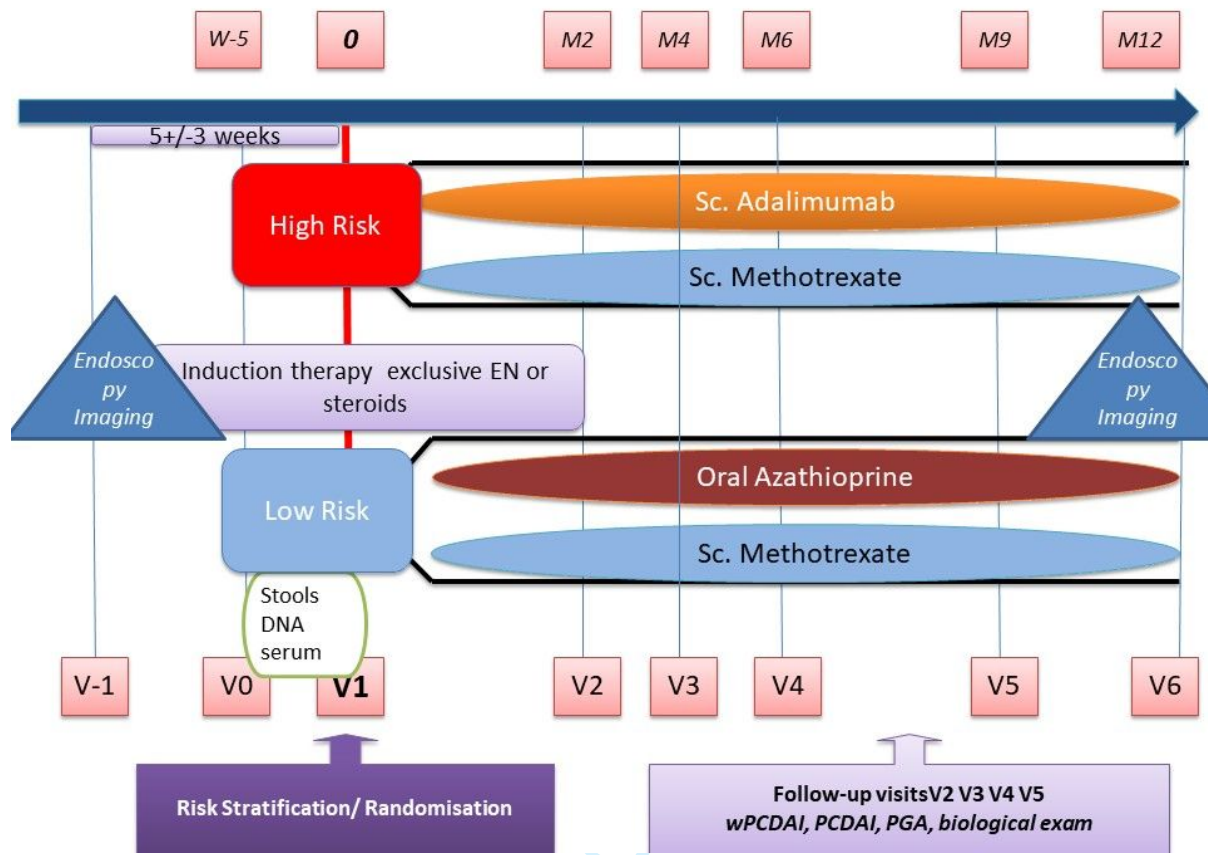


Figure 1 – Study Design of the REDUCE-RISK in CD trial

Participating Sites – REDUCE-RISK in CD Study		
Country	City	Site
Belgium	Brussels	Universitair Ziekenhuis
	Brussels	Clinique Saint Luc UCL
	Liège	Clinique de l'Espérance
	Brussels	HUDERF
Canada	Toronto	SickKids
Czech Republic	Prague	FN Motol
	Plzeň	FN Plzeň
	Prague	First Medical Faculty
France	Paris	Hôpital Necker Enfants Malades
	Paris	Hôpital Robert Debré
	Paris	Hôpital Armand Trousseau
	Le Havre	Hôpital Jacques Monod
	Nancy	Hôpitaux de Brabois
	Toulouse	Hôpital des Enfants
	Tours	Hôpital Clocheville
	Caen	CHU Caen Côte de Nacre
	Marseille	Hôpital de la Timone
Germany	Munich	Childrens Hospital
	Ulm	Universitätsklinikum
	Hannover	MHH Kinderklinik
	Giessen	UKGM
	Berlin	Charite Hospital
Greece	Athens	Children's Hospital "AGIA SOFIA"
Israel	Jerusalem	Shaare Zedek Medical Center
	Tel Aviv	Wolfson Medical Center
	Petah Tikva	Schneider Children's Medical Center
	Ramat Gan	Sheba Medical Center
	Haifa	Rambam Medical Center
Italy	Rome	Università degli Studi di Roma La Sapienza
	Bologna	Maggiore Hospital
	Florence	Azienda Ospedaliero Universitaria
	Parma	Azienda Ospedaliero
	Rome	Opsedale Pediatrico Bambino Gesù
Netherlands	Rotterdam	Erasmus Medical Center
Poland	Warsaw	Centrum Zdrowia MDM
	Białystok	Uniwersytecki Dziecięcy Szpital Kliniczny
	Łódź	Instytut Centrum Zdrowia Matki Polki
United Kingdom	Glasgow	The Royal Hospital for Children
	London	Royal London Children's Hospital, Barts Health NHS Trust
	Edinburgh	Sick Children's Hospital
	Birmingham	Children's Hospital
	Oxford	John Radcliffe Hospital

Supplementary Table 1 – Sites participating in REDUCE-RISK in CD



INFORMED CONSENT FORM

Parents/Guardian Informed Consent Form for Participation of a Minor in a Clinical Trial

Risk-stratified randomized controlled trial in paediatric Crohn's Disease: Methotrexate versus azathioprine or adalimumab for maintaining remission in patients at low or at high risk for aggressive disease course, respectively – a treatment strategy.

Dear parents,

Your child's doctor, Dr....., working at Hospital, propose your child to participate in a clinical trial related to its disease.

It is important to read this note carefully before taking any decision. Do not hesitate to ask the physician all the questions you may have about it.

The participation of your child is based on volunteering. Therefore, your child can refuse to participate or stop its participation in the trial at any time, all of this without prejudice to the patient's right to receive the standard treatment.

If you refuse your child to participate, he/she will still receive the best medical support.

Purpose of the research and trial's objectives

Your child has just been diagnosed with Crohn's disease. The disease is characterised by chronic inflammation of the digestive track (bowel/colon). This disease changes over between remission period and relapse period. There are efficient drugs able to prevent relapse and to maintain remission. In order to reduce the likelihood of long-term complications, induction treatment has already been prescribed to your child. This first treatment has to be followed up by a maintenance treatment that will be introduced to avoid the inflammation from returning. Consensus guidelines of ECCO / ESPGHAN (french and european IBD specialized organizations) recommend 3 efficient treatments: either immunosuppressive treatment with Thiopurines (azathioprine and 6-mercaptopurine), or Methotrexate or anti TNF (adalimumab).

So far, no clinical trial has been conducted to compare those 3 treatments in children with Crohn's disease and to answer the following question: "Which treatment is the most efficient, for which patient and/or in which situation?"

Progression of Crohn's disease is not the same for all patients. That's why this study will first classified all children in high and low risk groups based on more or less severe course of Crohn's disease. The lower risk group will be randomized (which is like tossing a coin) to receive either thiopurines or methotrexate as maintenance treatment. The high risk group will be randomized to receive either methotrexate or adalimumab. Results will show whether there is different efficiency between the 3 drugs for patients with a more or less severe disease.

Sponsor

PIBD-Net (www.pibd-net.org) is a global, international and non-profit organisation gathering physicians and researchers specialised in inflammatory bowel diseases. The acronym stands for Pediatric Inflammatory Bowel Diseases Network and it is present in 31 countries (Europe, North America, Australia and Japan). This organisation is dedicated in improving the medical care of children with inflammatory bowel disease through the establishment of clinical researches.

PIBD-Net and partners received funding from European Commission for Horizon 2020 program (project no.668023) in order to perform this research.

The approximate number of participants and duration of follow-up

A total of 312 new-onset children with Crohn's disease (136 in that high-risk group and 176 in the low risk) will be enrolled in many sites around the world. The period of recruitment is 45 months and your child will be followed up for 12 months after enrolment.



What will happen to your child during the trial?

If you agree to have your child participating in this study, your child will be first directed into one of two groups based on certain predictors of its disease (such as its location and severity). You will know which group your child is in. Next, your child will be randomized to receive maintenance treatment namely:

- **METHOTREXATE or AZATHIOPRINE for the low risk group ;**
- **METHOTREXATE or ADALIMUMAB for the high risk group ;**

You cannot choose the treatment group but you will know which drug your child will receive.

You will not be asked to come to clinic just because of this study which is designed to mirror regular follow-up in clinic. After signing the informed consent allowing your child to be part of this research, your child will have clinic visit every 2 months during the first 6 months and then every 3 months during the last 6 months. At each visit, a clinic examination is performed and blood, urine and stool samples are collected (this process follows our standard clinical practices of our patients not involved in this protocole).

Your doctor, your child and yourself will be asked to complete short questionnaires to evaluate the quality of life of your child. Most of the recorded data for this study is needed anyway as part of a regular visit but there might be a few more questions we will ask you for this study.

We will also contact you over the phone at week 4 to ask how your child feels regarding its Crohn's disease, whether your child has any bad reactions to the medications your child will receive and check your child compliance to the treatment.

To optimize the medications we prescribe, we will draw 12 ml (3-4 teaspoons) of blood at inclusion visit, 10ml at visit V2, and then 5ml at each next study visits to measure the level of the medications your child will receive. A urine sample will be collected at inclusion visit and a DNA sample (either 5ml of blood or buccal swab) will be collected at the beginning of the study, and also in case of drug intolerance.

We will also collect your child stool (poop) six times during the year to measure the amount of inflammation in its bowel as well as bacteria flora in its intestine.

We will evaluate whether the drugs work based on

- completed questionnaires
- clinic examination
- results of biological samples

Optional Ancillary study (« ADA STEP-up »)

In case of failing (intolerance or relapse) of your child immunomodulator therapy (: either azathioprine/6MP or methotrexate), your child will be invited to participate in the ancillary study. If you agree, your child will be prescribed adalimumab during 12 months.

This adalimumab treatment can increase the study duration by a maximum of 9 months, meaning a maximum of 3 additional visits. Those visits are identical to the regular follow up study visits.

The expected benefits to the participant or to others because of the trial

The medications your child will receive in this study are not experimental and thus there are no direct benefit for using these drugs that are available outside of the study. However, your child will be monitored closely to ensure optimization of the treatment by adapting drug amounts based on new analyses (urine, DNA, blood and stool samples). In addition, patients involved in this study have access to molecular analyses in order to better understand why a patient is less responsive than expected. That might result in a more tight control of the disease and better monitoring of the treatment of your child.



After study completion, we will have the required data to recommend how to use these medications in new children who develop Crohn's disease.

Risks added by the research

As previously mentioned, all medications used in this trial are not experimental and are being used very often in clinical practice in children/adolescents and adults with Crohn's disease. There is no additional risk compares to regular clinical practices. The known risks and discomfort that may be anticipated are listed below.

Known risks and discomfort that may be anticipated

The medications yourchild will receive in this study are not experimental but used in regular practices. They can also be associated with side effects (all described in the corresponding drug information sheet).

- ✗ **METHOTREXATE: weekly subcutaneous (under the skin)** This drug may be associated with side effects mainly in the day of the injection including flu-like symptoms, nausea, vomiting, headache or fatigue. Your child will be asked to take a vitamin called folic acid which will reduce these non-dangerous side effects. This injection may cause slight discomfort.METHOTREXATE may cause reduced blood counts, especially white blood cells and elevated liver enzymes. Thoses parameters will be checked regularly. In this study, molecular analyses will be performed to screen patients who can't tolerate METHOTREXATE..This drug causes an unusual sensitiveness to the sun (however, there is no data stating that it increases the risk of cancer or lymphoma). METHOTREXATE can cause foetal abnormalities so pregnancy is not allowed and efficient contraceptive is essential (for both male and female).
- ✓ **AZATHIOPRINE (or 6MP): to be taken orally.** THIOPURINES may cause reduced blood counts, especially white blood cells and elevated liver enzymes. Thoses parameters will be checked regularlyIn this study, molecular analyses will be done in order to screen patients who can't tolerate those drugs. In some rare cases (<3%), the drug may cause inflammation in the pancreas which is usually mild and not dangerous. As all drugs, THIOPURINES can't be tolerated by some patients due to allergy. Approximately 10% of children will not tolerate the drug because of nausea, vomiting, tummy pain, diarrhea, headaches or fever..THIOPURINES are associated with an increased infectious risk (about 1%). Infections are likely cause by viruses. In rare cases, THIOPURINES may increase risk for blood cancer called lymphoma (especially for patients > 65 year old).-This drug causes an unusual sensitiveness to the sun and can be associated with skin cancer in case of significant sun exposure.

ADALIMUMAB: subcutaneous (under the skin) injections every 2 weeks Adalimumab is associated with minor pain during the injection and local reactions could appear with minimal significance..ADALIMUMAB is associated with an increased infectious risk. However, serious infections are uncommon. Before starting ADALIMUMAB treatment, tuberculosis must be excluded. With time, the effect of adalimumab may wain as a result of the development of antibodies against the drug. Skin inflammatory damages (such as « psoriasis ») were observed in some patients. Anti TNF drugs have been closely monitored since their use as standard treatment. Those drugs may be responsible of heart failure for patients with severe heart disease, hepatitis, decreasing blood cells, demyelinating neurologic disease, or lupus (without affecting main organs). In addition, some cases of cancer have been notified in patient treated by ADALIMUMAB, but risks of cancer is slightly increased only for melanoma. Number of cancer seems not to be increased compared to patients with Crohn's diseases and without being treated with those drugs.

Circumstances under which participation in the medical trial may be discontinued in accordance with the decision of the investigator or the Sponsor:

- a. The doctor has the right to take your child out of the study at any time. This will be made after clinical considerations, your child's side effects from the drugs, intolerance to the drugs or lose of response.
- b. Regulatory authorities (Ministry of Health or Ethics committee), may stop your child participating in the study.



An explanation of alternative treatments, their advantages and disadvantages, if any, for the participant:

The current standard therapy for maintenance therapy in Crohn's disease is either METHOTREXATE or thiopurines or anti-TNF biologics for the more severe Crohn diseases. This is exactly the medications given also as part of this study. The difference is that instead letting you and the doctor choose between the options, the choice is standardized based on predictive variables of your disease and randomization. If you choose not to have your child participating in the study, your child will likely receive anyway one or more of these three drugs. The only exception would be that if anti-TNF is prescribed, either adalimumab or infliximab can be given and as part of this study your child will receive adalimumab only. However, your child will not have access to molecular analyses described in this protocol with a close monitoring of drug safety. Indeed, those 'new' analyses are not done in the standard clinical practice of Crohn's disease.

If you participate in this study, what will you have to do more than usual ?

If you agree to have your child participating in this study, please make sure to follow the listed points below. Please come at your appointments with your child. If not possible, please inform its physician as soon as possible

- Please ensure that your child takes the treatment as instructed by its doctor
- Please inform the physician involved in the study of any event happening during the research (such as hospitalization,...)
- Your child must not participate in any other clinical trial that involves the use of an investigational product throughout the course of this trial. It is to avoid accidents such as possible interactions between medicines.

Biological samples collected during this research project

If you agree to have your child participating in this research, additional blood, urine and stool samples will be collected at the same time as our standard clinic samplings. Please see below:

- ✓ 10ml of blood during inclusion visit (on randomisation day).
- ✓ 5ml of blood (PAX tube) during inclusion visit for RNA analyses
- ✓ 10ml of blood at follow up visits M2 (2 months after inclusion)
- ✓ 5 ml of blood at follow up visits M4, M6, M9 and M12 (4, 6, 9, 12 months after inclusion)
- ✓ Stool sample at inclusion visit and follow up visits M2, M4, M6, M9 and M12 (2, 4, 6, 9, 12 months after inclusion visit).
- ✓ A DNA sample will be collected at inclusion visit and in case of intolerance of one of the drugs for DNA analyses.
- ✓
- ✓ Urine sample (15ml) will be collected at M2 visit (2 months after inclusion).

Those samples will be sent to specialized laboratories in order to be used to perform specific studies such as adalimumab, methotrexate, thiopurine analyses and serology, genetic (both DNA and RA), microbiology studies. They will also be re-used for further testing on Crohn's disease, its diagnosis and its treatment as well as efficacy and tolerance by molecular ("omic") analyses.

At any time, you can request to your clinician to have those biological samples destroyed or not to be used for further researches.

Confidentiality

As part of biomedical research in which PIBD-Net sponsor proposes your child's participation, treatment of personal data will be set up to analyse results of this research based on its aim. Therefore, your child medical data and quality of life will be transferred to PIBD-Net sponsor. Those data will be anonymous and identified by a coded number and its initials. Those confidential data could be transferred to local and foreign authorities. If your child has to be withdrawn for any reasons, collected data prior its withdrawal will be used unless you do not want them to.



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3 Then, you will have to inform the physician accordingly.
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5 According to the EU General Data Protection Regulation (GDPR) dated on 26May2018, you have the right to access
6 to your child and your personal data, modify them and oppose the use of your child and your data. You have also
7 the right to request that your child and your personal data are erased, are limited in use, and to ask for a complete
8 copy of all data collected from you and your child for the study. You can contact the Data Privacy Officer (DPO) of
9 the sponsor at any time at dpo@pibd-net.org for any request regarding your child and your personal data.
10

11 Data collected for the study are transferred outside of the EU, as our database is based in Israel. However, we
12 guarantee that data protection will be as strict as requested by GDPR.
13

14 **Voluntary participation**

15 Your participation in this research is entirely voluntary. It is your choice whether to have your child participating or
16 not, all the services your child receives at this hospital will continue and nothing will change. If you choose not to
17 participate in this research project, your child will be offered the treatment that is routinely offered in this hospital
18 for Crohn's disease. You may change your mind later and stop participating even if you agreed earlier.
19

20 **Right to refuse or withdraw**

21 Your child does not have to take part in this research if you do not wish to do so and refusing to participate will not
22 affect its treatment in any way. Your child will still have all the benefits that it would otherwise have at this hospital.
23 You may stop participating in the research at any time that you wish without losing any of its rights as a patient
24 here. Its treatment at this hospital will not be affected in any way.
25

26 **Alternatives to participating**

27 If you do not wish that your child takes part in the research, your child will be provided with the established standard
28 treatment available at this hospital.
29

30 **Reimbursement**

31 There is no reimbursement for participating in this study. There are no special visits to the hospital excepted during
32 this study. All DNA, blood, urine and stool samples will be taken at the time of a routine clinic visit.
33

34 **This proposal has been reviewed and approved by [name of the local IRB], which is a committee whose**
35 **task it is to make sure that research participants are protected from harm.**
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Informed consent form

We, the undersigned :

M, Miss, (*name, first name of parent/legal guardian*)

M, Miss, (*name, first name of parent/legal guardian*)

I, M, Miss,(*name, first name of parent*) hereby declare that my consent below has been given voluntarily and that I have understood all of the above. I undertake to also inform the child's father/mother (*please cross off as appropriate*) of my consent for the participation of our child in the clinical trial. If the child's father/mother (*please cross off as appropriate*) does not agree to affix his/her consent to mine, I undertake to inform the physician in-charge and to withdraw my consent for the participation of my child in the clinical trial. I have also received a lawfully and dated copy of this informed consent form

I agree that my child (*name, first name of the child*).....**takes part of the study named** "*Risk-stratified randomized controlled trial in paediatric Crohn's Disease : Methotrexate versus azathioprine or adalimumab for maintaining remission in patients at low or at high risk for aggressive disease course, respectively – a treatment strategy* ", managed by PIBD Net. It has been explained to us by (*name, first name of explaining investigator /sub investigator, phone,*).....

.....physician in this clinical trial.

- We hereby declare that we agree for our child to participate in the clinical trial as detailed in this document
- Our child has been informed and agreed to take part of this clinical trial.
- We had the opportunity to ask all the questions we had to the physician who explained potential risks and constraints linked to our child participation in this clinical trial.
- We received appropriate answers to all our questions
- We hereby declare that at the time of signing this document, our child is not participating in another clinical trial that involves the use of any investigational product, and that we undertake that our child will not participate in any other clinical that involves the use of an investigational product throughout the course of this trial.
- We declare that our child has a health insurance.
- .We hereby declare that we are free to choose that our child will not participate in the clinical trial, and that we are free to stop our child participation in the trial at any time, and all of this without prejudice to our child's right to receive the standard treatment. Then, we will inform the physician whether data collected prior our decision can be used or not.
- We have been informed that the doctor has the right to take our child out of the study at any time, if needed.
- That in case of completing a questionnaire – we are entitled not to answer all or some of the questions in the questionnaire.
- We are informed that samples collected during this clinical trial will be kept and used for further testing on Crohn's disease. We can decide at any time not to have those samples used by informing our child physician.
- That we are guaranteed confidentiality concerning the identity of the patient and that of the parents/guardians. This confidentiality will be kept by all those concerned with and involved in the clinical trial, and their identity will not be disclosed in any publication.
- That the Medical Institution has arranged for appropriate insurance coverage of the investigators, physicians and medical staff involved in the clinical trial, against claims filed by clinical trial participants and/or third party claims related to the clinical trial, either during the course of the trial or thereafter. This is without prejudice to our rights under the law.
- That in case of pregnancy during the course of the clinical trial, the girl/woman will be counselled (by the principal investigator) concerning the possible effects on the foetus and the fate of the pregnancy, including



the possibility of discontinuing the pregnancy.

- We hereby declare that our below consent has been given voluntarily and that we have understood all of the above mentioned. We also received a lawfully signed and dated copy of this informed consent.
- By signing this consent form, we authorize the sponsor of the clinical trial, the Institutional Helsinki Committee, the auditing entity at the Medical Institute and the Ministry of Health direct access to the patient's medical file, to verify the clinical trial methods and the clinical data. This access to our child medical information will be performed with confidentiality maintained, according to the laws and procedures of maintaining confidentiality.
- We declare that we are informed and give our approval to receive all information related to our child participation in this clinical trial. We know that data will only be used for treatment and follow up cares
- We hereby declare that we know and agree to have the information on our child's participation in the clinical trial provided to his/her attending physician at the HMO/Health care Services with which our child is insured, in case the clinical trial involved the provision of services : performing medical examinations or supplying devices or products or implants. We know that the HMO will not use this information for purposes other than medical treatment and follow up

I agree to have my child participating in the ancillary study (« ADA STEP-up »)

Yes

No

[please tick]

<u>Signature of parents or guardians/representatives of the patient</u>	<u>Signature of the child</u>
Name, First Name : _____ Date : _____ Signature : _____ Name, First Name : _____ Date : _____ Signature : _____	Name, First Name : _____ Date : _____ Signature : _____

Declaration of the Investigator/Sub-Investigator : This consent was obtained by me after I have explained all the above mentioned to the parents (or guardians) of the clinical trial participant and ensure that all my explanations were understood by them.

Investigator/Sub-investigator' Signature :

Name, First Name: _____

Date: _____ Signature : _____

This is a triplicate document. First / original copy to be kept by the investigator for 15 years, second copy to be given to parents or legal guardians, third copy to be kept in Investigator files (under sealed envelope).



Informed consent for Genetic Analyses

Hereby declare that we agree for genetic examinations of our child to study genes involved in tolerance / non tolerance of the drugs by molecular (“omic”) analyses and analyses of drug efficacy in Crohn disease’s patients.

Hereby declare that we agree that all recorded data collected during this trial including genetic data can be processed by the sponsor or acting as sponsor. I understand that, as stipulated in the General Data Protection Regulation, I can access, modify, erase or ask for a copy of my child’s personal data and my personal data at any time, by asking to the investigator who will contact the sponsor.

We can decide not to participate anymore in the genetic part of the trial by informing our doctor who will inform the sponsor.

Yes No *[please tick]*

Hereby declare that we agree that all biological samples collected during this trial can be used for future genetic research on Crohn’s disease.

Yes No *[please tick]*

Parents/guardians Signature:

Investigator Signature:

Name, First name:

Name, First name:

Date : Signature :

Date : Signature :

Name, First name:

Date : Signature :

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. *Ann Intern Med.* 2013;158(3):200-207

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	Throughout manuscript
Protocol version	#3	Date and version identifier	21
Funding	#4	Sources and types of financial, material, and other support	30
Roles and responsibilities:	#5a	Names, affiliations, and roles of protocol contributors	1,2,30

1 contributorship

2 Roles and [#5b](#) Name and contact information for the trial sponsor 29
 3 responsibilities:
 4 sponsor contact
 5 information
 6
 7

8
 9 Roles and [#5c](#) Role of study sponsor and funders, if any, in study 30
 10 responsibilities: design; collection, management, analysis, and
 11 sponsor and funder interpretation of data; writing of the report; and the
 12 decision to submit the report for publication,
 13 including whether they will have ultimate authority
 14 over any of these activities
 15
 16
 17

18
 19 Roles and [#5d](#) Composition, roles, and responsibilities of the 23,30
 20 responsibilities: coordinating centre, steering committee, endpoint
 21 committees adjudication committee, data management team,
 22 and other individuals or groups overseeing the trial,
 23 if applicable (see Item 21a for data monitoring
 24 committee)
 25
 26
 27

28 Introduction

29
 30
 31 Background and [#6a](#) Description of research question and justification for 6-8
 32 rationale undertaking the trial, including summary of relevant
 33 studies (published and unpublished) examining
 34 benefits and harms for each intervention
 35
 36
 37

38 Background and [#6b](#) Explanation for choice of comparators 6-7
 39 rationale: choice of
 40 comparators
 41
 42

43 Objectives [#7](#) Specific objectives or hypotheses 8-10
 44

45 Trial design [#8](#) Description of trial design including type of trial (eg,
 46 parallel group, crossover, factorial, single group),
 47 allocation ratio, and framework (eg, superiority,
 48 equivalence, non-inferiority, exploratory)
 49
 50
 51

52 Methods:

53 **Participants,**
 54 **interventions, and**
 55 **outcomes**
 56
 57
 58

1	Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Supplemental table 1
2				
3				
4				
5				
6				
7				
8	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	10-12
9				
10				
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14	Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	15-16
15				
16				
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18				
19				
20	Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	18, 19,22
21				
22				
23				
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26				
27	Interventions: adherence	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	19-21
28				
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31				
32	Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	13,23
33				
34				
35				
36	Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-10
37				
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49	Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	See figure 1 8,12,15,16-19
50				
51				
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54				
55	Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions	27
56				
57				
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supporting any sample size calculations

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2
3 Recruitment [#15](#) Strategies for achieving adequate participant enrolment to reach target sample size Not listed
4
5

6 **Methods:**

7 **Assignment of**
8 **interventions (for**
9 **controlled trials)**
10
11

12
13 Allocation: sequence [#16a](#) Method of generating the allocation sequence (eg, 15,16,22
14 generation computer-generated random numbers), and list of
15 of any factors for stratification. To reduce predictability
16 of a random sequence, details of any planned
17 restriction (eg, blocking) should be provided in a
18 separate document that is unavailable to those who
19 enrol participants or assign interventions
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23
24 Allocation [#16b](#) Mechanism of implementing the allocation 22
25 concealment sequence (eg, central telephone; sequentially
26 mechanism numbered, opaque, sealed envelopes), describing
27 any steps to conceal the sequence until
28 interventions are assigned
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33 Allocation: [#16c](#) Who will generate the allocation sequence, who will 15
34 implementation enrol participants, and who will assign participants
35 to interventions
36
37

38 Blinding (masking) [#17a](#) Who will be blinded after assignment to 22
39 interventions (eg, trial participants, care providers,
40 outcome assessors, data analysts), and how
41
42

43 Blinding (masking): [#17b](#) If blinded, circumstances under which unblinding is N/A
44 emergency permissible, and procedure for revealing a
45 unblinding participant's allocated intervention during the trial
46
47

48 **Methods: Data**
49 **collection,**
50 **management, and**
51 **analysis**
52
53

54
55 Data collection plan [#18a](#) Plans for assessment and collection of outcome, 24-25
56 baseline, and other trial data, including any related
57 processes to promote data quality (eg, duplicate
58
59

1		measurements, training of assessors) and a	
2		description of study instruments (eg, questionnaires,	
3		laboratory tests) along with their reliability and	
4		validity, if known. Reference to where data	
5		collection forms can be found, if not in the protocol	
6			
7			
8	Data collection plan:	#18b Plans to promote participant retention and complete	Not listed
9	retention	follow-up, including list of any outcome data to be	
10		collected for participants who discontinue or deviate	
11		from intervention protocols	
12			
13			
14			
15	Data management	#19 Plans for data entry, coding, security, and storage,	25
16		including any related processes to promote data	
17		quality (eg, double data entry; range checks for data	
18		values). Reference to where details of data	
19		management procedures can be found, if not in the	
20		protocol	
21			
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25	Statistics: outcomes	#20a Statistical methods for analysing primary and	25-26
26		secondary outcomes. Reference to where other	
27		details of the statistical analysis plan can be found,	
28		if not in the protocol	
29			
30			
31			
32	Statistics: additional	#20b Methods for any additional analyses (eg, subgroup	26-27
33	analyses	and adjusted analyses)	
34			
35			
36	Statistics: analysis	#20c Definition of analysis population relating to protocol	26
37	population and	non-adherence (eg, as randomised analysis), and	
38	missing data	any statistical methods to handle missing data (eg,	
39		multiple imputation)	
40			
41			
42	Methods:		
43	Monitoring		
44			
45			
46	Data monitoring:	#21a Composition of data monitoring committee (DMC);	23
47	formal committee	summary of its role and reporting structure;	
48		statement of whether it is independent from the	
49		sponsor and competing interests; and reference to	
50		where further details about its charter can be found,	
51		if not in the protocol. Alternatively, an explanation of	
52		why a DMC is not needed	
53			
54			
55			
56			
57	Data monitoring:	#21b Description of any interim analyses and stopping	23
58			
59			
60			

1	interim analysis		guidelines, including who will have access to these	
2			interim results and make the final decision to	
3			terminate the trial	
4				
5	Harms	#22	Plans for collecting, assessing, reporting, and	23
6			managing solicited and spontaneously reported	
7			adverse events and other unintended effects of trial	
8			interventions or trial conduct	
9				
10				
11				
12	Auditing	#23	Frequency and procedures for auditing trial conduct,	24
13			if any, and whether the process will be independent	
14			from investigators and the sponsor	
15				
16				
17	Ethics and			
18	dissemination			
19				
20				
21	Research ethics	#24	Plans for seeking research ethics committee /	4
22	approval		institutional review board (REC / IRB) approval	
23				
24				
25	Protocol	#25	Plans for communicating important protocol	22
26	amendments		modifications (eg, changes to eligibility criteria,	
27			outcomes, analyses) to relevant parties (eg,	
28			investigators, REC / IRBs, trial participants, trial	
29			registries, journals, regulators)	
30				
31				
32				
33	Consent or assent	#26a	Who will obtain informed consent or assent from	29-30
34			potential trial participants or authorised surrogates,	
35			and how (see Item 32)	
36				
37				
38				
39	Consent or assent:	#26b	Additional consent provisions for collection and use	No additional
40	ancillary studies		of participant data and biological specimens in	consent see
41			ancillary studies, if applicable	page 30
42				
43				
44	Confidentiality	#27	How personal information about potential and	24
45			enrolled participants will be collected, shared, and	
46			maintained in order to protect confidentiality before,	
47			during, and after the trial	
48				
49				
50				
51	Declaration of	#28	Financial and other competing interests for principal	30
52	interests		investigators for the overall trial and each study site	
53				
54				
55	Data access	#29	Statement of who will have access to the final trial	Not provided
56			dataset, and disclosure of contractual agreements	
57			that limit such access for investigators	
58				
59				
60				

1	Ancillary and post	#30	Provisions, if any, for ancillary and post-trial care,	N/A
2	trial care		and for compensation to those who suffer harm from	
3			trial participation	
4				
5				
6	Dissemination policy:	#31a	Plans for investigators and sponsor to communicate	29
7	trial results		trial results to participants, healthcare professionals,	
8			the public, and other relevant groups (eg, via	
9			publication, reporting in results databases, or other	
10			data sharing arrangements), including any	
11			publication restrictions	
12				
13				
14				
15				
16	Dissemination policy:	#31b	Authorship eligibility guidelines and any intended	29
17	authorship		use of professional writers	
18				
19				
20	Dissemination policy:	#31c	Plans, if any, for granting public access to the full	Not planned
21	reproducible		protocol, participant-level dataset, and statistical	
22	research		code	
23				
24				
25	Appendices			
26				
27	Informed consent	#32	Model consent form and other related	Appendix 1
28	materials		documentation given to participants and authorised	
29			surrogates	
30				
31				
32				
33	Biological specimens	#33	Plans for collection, laboratory evaluation, and	Not provided
34			storage of biological specimens for genetic or	
35			molecular analysis in the current trial and for future	
36			use in ancillary studies, if applicable	
37				
38				
39				

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BMJ Open

A MULTI-NATIONAL RISK-STRATIFIED RANDOMISED CONTROLLED TRIAL IN PAEDIATRIC CROHN'S DISEASE : METHOTREXATE VERSUS AZATHIOPRINE OR ADALIMUMAB FOR MAINTAINING REMISSION IN PATIENTS AT LOW OR HIGH RISK FOR AGGRESSIVE DISEASE COURSE, RESPECTIVELY – A TREATMENT STRATEGY PROTOCOL FOR: THE REDUCE-RISK IN CD PIBD TRIAL

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Keywords:	Inflammatory bowel disease < GASTROENTEROLOGY, Paediatric gastroenterology < GASTROENTEROLOGY, Clinical trials < THERAPEUTICS

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3 **A MULTI-NATIONAL RISK-STRATIFIED RANDOMISED CONTROLLED TRIAL IN**
4
5 **PAEDIATRIC CROHN'S DISEASE: METHOTREXATE VERSUS AZATHIOPRINE**
6
7 **OR ADALIMUMAB FOR MAINTAINING REMISSION IN PATIENTS AT LOW OR**
8
9 **HIGH RISK FOR AGGRESSIVE DISEASE COURSE, RESPECTIVELY – A**
10
11 **TREATMENT STRATEGY PROTOCOL FOR THE REDUCE-RISK IN CD PIBD**
12
13 **TRIAL**
14
15

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17
18
19 **Rachel E. Harris¹; Marina Aloï²; Lissy de Ridder³; Nicholas M Croft⁴; Sibylle**
20
21 **Koletzko^{5,6}; Arie Levine⁷; Dan Turner⁸; Gigi Veereman⁹; Mattias Neyt¹⁰ Laetitia**
22
23 **Bigot¹¹; Frank M. Ruemmele^{12,13*}; Richard K. Russell^{1*}; on behalf of the PIBD**
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25 **SETQuality consortium and PIBDnet**
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1
2
3 **Key Words:** Paediatric Gastroenterology, Inflammatory Bowel Disease, Crohn's
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5 Disease, Immunomodulators
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11 **ABSTRACT**

12 **Introduction**

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14
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16
17 Immunomodulators such as thiopurines (azathioprine (AZA)/6-mercaptopurine
18 (6MP)), methotrexate (MTX) and biologics such as adalimumab (ADA) are well
19 established for maintenance of remission within paediatric Crohn's disease (CD). It
20 remains unclear however which maintenance medication should be used first-line in
21 specific patient groups.
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33 **Aims**

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35 To compare the efficacy of maintenance therapies in newly diagnosed CD based
36 upon stratification into high and low risk groups for severe CD evolution; MTX versus
37 AZA/6MP in low-risk and MTX versus ADA in high-risk patients. Primary end point:
38 sustained remission at 12 months (weighted paediatric Crohn's disease activity index
39 ≤ 12.5 and C-reactive protein ≤ 1.5 -fold upper limit) without relapse or ongoing
40 requirement for EEN/steroids 12 weeks after treatment initiation.
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53 **Methods and Analysis**

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55 REDUCE-RISK in CD is an international multicentre open-label prospective
56 randomised controlled trial funded by EU within the Horizon2020 framework (grant
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1
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3 number 668023). Eligible patients (aged 6-17 years, new-onset disease receiving
4 steroids or EEN for induction of remission for luminal +/- perianal CD are stratified
5 into low and high-risk groups based upon phenotype and response to induction
6 therapy. Participants are randomised to one of two treatment arms within their risk
7 group: low-risk patients to weekly subcutaneous MTX or daily oral AZA/6MP, and
8 high-risk patients to weekly subcutaneous MTX or fortnightly ADA. Patients are
9 followed up for 12 months at pre-specified intervals. Electronic case report forms are
10 completed prospectively. The study aims to recruit 312 participants (176 low-risk;
11 136 high-risk).

26 **Ethics and Dissemination**

27
28 ClinicalTrials.gov Identifier: (NCT02852694), authorisation and approval from local
29 ethics committees have been obtained prior to recruitment. Individual informed
30 consent will be obtained prior to participation in the study. Results will be published
31 in a peer-reviewed journal with open access.

40 **Registration Details**

41
42 NCT02852694; pre-results.

47 **Strengths and limitations**

- 48 • This is the 1st international prospective RCT comparing 3 different i
49 medications for maintenance of remission in newly diagnosed CD
50
- 51 • This study may better define the most appropriate first-line immunomodulators
52 based upon a risk stratification protocol. .
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- Therapeutic efficacy will be supported by drug levels, pharmacogenomics and microbiome analysis as secondary outcomes.
- Inability to blind participants or treating physicians serves as a limitation to this study.
- Blinding of an alternative clinician to assess disease activity during study visits may prove practically difficult in smaller centres.

For peer review only

INTRODUCTION

Crohn's disease (CD) the most common form of inflammatory bowel disease (IBD) in children is a chronic disorder with the potential to affect the whole gastrointestinal tract. The aim of CD treatment is to control active inflammation and achieve bowel healing. Chronic and uncontrolled CD results in poor outcomes for patients, including reduced quality of life, recurrent hospitalisation and potential need for surgical

1
2
3 intervention.¹ Treatments for CD are categorised into those which induce remission
4
5 (such as steroids^{1,2} or exclusive enteral nutrition (EEN)^{1,3} and those which maintain
6
7 remission. Immunomodulators are a mainstay of maintenance treatment in IBD, with
8
9 the efficacy of thiopurines (e.g. azathioprine (AZA) and 6-mercaptopurine (6MP))^{4,5,6}
10
11 and methotrexate (MTX)^{7,8,9,10} well established. Anti-tumour necrosis factor (anti-
12
13 TNF) therapies (infliximab^{11,12} and adalimumab (ADA)^{13,14}) including their biosimilars
14
15 were used in those patients refractory to “traditional” induction or maintenance
16
17 treatment. More recently in clinical practice patients deemed as high risk have been
18
19 treated with a biologic without the need for prior use of an immunomodulator.
20
21 Due to a lack of treatment strategy trials within the paediatric IBD (PIBD) population
22
23 however, it remains unclear which of the aforementioned maintenance therapies
24
25 should be used first-line in individual patients. Randomised controlled trials
26
27 comparing the use of MTX with thiopurines for maintenance of remission failed to
28
29 show a significant difference in efficacy between the two.^{15,16, 17} A Cochrane review
30
31 in adults with quiescent CD highlighted the lack of adequately powered trials
32
33 necessary in order to determine the efficacy and safety of thiopurines compared to
34
35 other maintenance therapies^{4, 10}. The RISK study (observational, non-randomised
36
37 study) demonstrated improved clinical and growth-based outcomes at 1 year with
38
39 anti-TNF monotherapy in comparison with immunomodulators; however further
40
41 investigation into which specific patients are most likely to benefit from these
42
43 therapies is still required.¹⁸ There is a clear disparity between North America and
44
45 Europe in terms of which form of immunosuppression is used initially with both
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47 concerns about efficacy and safety lying behind these differences, thus there is an
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49 urgent need for a head to head study in children to help objectively inform the
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51 primary choice of immunosuppression.
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3 Stratifying patients by risk for complex or severe CD may allow pre-emptive direction
4 of maintenance strategy and potentially an early reduction in disease burden with
5 subsequent improvement in long-term outcomes. The adult IBD Ahead initiative
6 highlighted young age at diagnosis as a risk factor for severity of CD evolution¹⁹; all
7 patients diagnosed within paediatric services would therefore be considered 'high
8 risk'. Paediatric consensus guidelines suggest that paediatric CD patients at 'high
9 risk for poor outcome' should receive early therapy optimisation to modify
10 progression of their disease.¹ The guidelines list specific features which may be
11 considered predictive for poor outcome in paediatric CD (see Table 1).¹ Patients
12 deemed at high risk for complex disease or poor outcome may benefit from a 'Top-
13 down' approach as the TISKids (a randomised controlled trial from disease diagnosis)
14 aims to investigate²⁰.

15
16 Therefore the PIBDnet consortium recognised the urgent need to investigate the
17 efficacy and safety of immunomodulators and to investigate whether a top-down
18 approach was superior to a traditional 'step-up' for paediatric patients deemed at
19 high risk for rapidly complicated disease course. REDUCE-RISK in CD is a
20 randomised controlled trial (RCT) which aims to compare the effectiveness of
21 immunomodulators for maintenance of remission in newly diagnosed CD based
22 upon risk stratification specifically, the effectiveness of MTX versus AZA/6MP for
23 maintenance of remission who are low risk for rapidly progressive disease and the
24 effectiveness of MTX versus ADA in a high risk group.

25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 **METHODS AND ANALYSIS**

54 55 56 57 58 **Study Design**

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5 We designed an international multicentre open-label prospective RCT with 4
6
7 treatment arms as shown in Figure 1. Following screening and consent, eligible
8
9 patients are stratified into low and high-risk groups based upon phenotype and
10
11 disease response to induction therapy (Table 1). Patients are then randomised to
12
13 one of two arms within their risk group, with low risk patients receiving either weekly
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15 subcutaneous MTX or daily oral AZA/6MP and high-risk patients receiving either
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17 weekly subcutaneous MTX or fortnightly subcutaneous ADA.
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26 **Study End Points**

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31 Patients are followed up for 12 months post randomisation. The primary end point of
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33 the study is sustained steroid or EEN-free remission at 12 months, defined as
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35 weighted Paediatric Crohn's Disease Activity Index (wPCDAI) ≤ 12.5 and C-reactive
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37 protein (CRP) ≤ 1.5 -fold upper limit without a relapse or need for EEN/steroids since
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39 week 12.
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45 Secondary end points include comparison of time to first relapse, remission at 12
46
47 weeks, growth, adverse events, health related quality of life and patient reported
48
49 outcomes between the two treatment arms within each risk group but also between
50
51 low and high risk MTX treated patients. The study also aimed to evaluate clinical
52
53 predictors for response, including genomic and serological markers and results of
54
55 drug monitoring (MTX and ADA concentrations) metabolites (6-thioguanine (6-TG)
56
57 and 6-methylmercaptopurine (6-MMP) in AZA/6MP) and anti-drug antibodies (ADA)
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3 in relation to adherence, toxicity and response. The ancillary study additionally aimed
4
5 to evaluate the efficacy of ADA in patients treated from inclusion (Top-down) versus
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7 patients switched to ADA due to immunomodulator failure (Step-up). Further
8
9 outcome measures are detailed in Box 1.
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Box 1: Study endpoints

Primary Endpoint

- Sustained steroid/EEN-free remission at month 12, where sustained remission is defined as wPCDAI \leq 12.5 and CRP \leq 1.5 times the upper limit without a relapse or need for EEN/steroids since week 12.

Secondary Endpoints:

Comparing the following within 1) the two treatment arms per risk group; 2) methotrexate treatment between high and low risk groups; and 3) TOP-Down adalimumab (high risk group) versus STEP-Up adalimumab (ancillary study):

- Rate of clinical remission at month 12 (physician global assessment (PGA), wPCDAI, paediatric Crohn's disease activity index (PCDAI))
- Relapse free remission with normal CRP at month 12
- Relapse free remission with normal CRP and faecal calprotectin $<$ 300 at month 12
- Remission at week 12
- Time to first relapse after week 12
- Faecal calprotectin values at visits 1, 2, 4 and 6 (respectively at month 0, 2, 6 and 12)
- Dropout rates
- Adverse drug event rate
- Height velocity and z-score at baseline and 52 weeks
- Quality of life as measured by the IMPACT 3 questionnaire completed at each study visit
- Health economic evaluation at all visits (forms EQ-5D-Y proxy 1, EQ-5D-Y and EQ-5D-5L, WPAI:CD Caregiver, School Attendance start of the research and follow up visits)

Eligibility Criteria and Recruitment

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3 Full eligibility criteria for the study are listed in Box 2. Patients are eligible if aged 6-
4
5 17 years with new-onset (<6 months) treatment naïve luminally active and/or
6
7 perianal fistulising CD diagnosed as per revised Porto criteria²¹ receiving steroids or
8
9 EEN for induction of remission with wPCDAI >40 or CRP >2 times upper limit of
10
11 normal at diagnosis. Informed consent from must be obtained prior to participation in
12
13 the study. Patients are excluded in cases of previous use of IBD related medications,
14
15 pregnancy or refusal to use contraceptives; disease requiring surgery,
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17 contraindications to study medication, exposure to live vaccine within 3 weeks, oral
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19 anticoagulant or anti-malarial use, current or previous malignancy, significant
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21 infection or significant comorbidity.
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26 The planned start date for the study is 01.2017 with planned end 06/2022.
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Box 2: Eligibility criteria**Inclusion Criteria**

- Patients aged 6-17 years with new-onset (<6 months) treatment naïve active luminal and/or perianal fistulising Crohn's disease diagnosed using established criteria²¹ requiring steroids or EEN for induction of remission
- wPCDAI >40 or CRP >2 times upper limit of normal at diagnosis
- Luminal active Crohn's disease (B1) with or without B2 and/or B3 disease behaviour as per Paris classification²²
- Signed informed consent

Exclusion Criteria

- wPCDAI <42.5 at diagnosis, except where CRP >2 times upper normal limit
- Lack of induction therapy with steroids or EEN
- Previous therapy with any IBD-related medication other than induction therapy as detailed within this protocol with the exception of 5-aminosalicylic acid (5ASA) preparations
- Pregnancy or refusal to use contraceptives during the study period in pubertal patients unless absolute abstinence is confirmed at each study visit
- Lactating mothers
- Perianal fistulising disease requiring surgical therapy
- Patients homozygous for thiopurine methyltransferase (TPMT) mutations or those with TPMT activity <6 nmol/h/ml erythrocytes or <9nmol 6MTG/g Hb/h, unless they qualify as high-risk patients
- Evidence of un-drained and un-controlled abscess/phlegmon
- Contraindication to any drugs used in the trial (including intolerance/hypersensitivity or allergy to study drugs (thiopurines, methotrexate or adalimumab))
- Current or previous malignancy
- Serious comorbidities (e.g. renal insufficiency, hepatitis, respiratory insufficiency) which may interfere with drug therapy or interpretation of outcome parameters or will make it unlikely that the patient will complete the trial.
- Infection with mycobacterium tuberculosis, hepatitis B or C, human immunodeficiency virus (HIV)
- Moderate to severe heart failure (New York Heart Association class III/IV)
- Oral anticoagulant therapy, anti-malarial therapy
- Live vaccine exposure (including yellow fever) less than 3 weeks prior to inclusion

Screening Visit (Visit 0)

The screening visit allows for assessment of eligibility for inclusion in the study, evaluation of the patient's response to induction therapy if already commenced,

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3 commencement of induction therapy where not commenced, and acquisition of
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5 consent and assent.
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11 *Induction Therapy*

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15 All enrolled patients receive either corticosteroids or exclusive enteral nutrition (EEN)
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17 as induction as determined by the clinical team and the patient/caregiver. For EEN
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19 any balanced formula (polymeric or elemental) administered orally or via nasogastric
20
21 tube is permitted and should be prescribed for 6-8 weeks. Tapering of steroids is at
22
23 the discretion of the prescribing clinician. Adaptation of induction therapy (e.g. dose
24
25 increase of steroids or return to EEN) or crossover from one induction therapy to the
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27 other is permitted in order to achieve remission, however patients must have
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29 discontinued their induction therapy by week 12. If induction therapy is not
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31 discontinued by week 12 the patient is considered a treatment failure, with the
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33 protocol for this detailed below.
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45 Inclusion Visit and Risk Group Allocation (week 5 +/- 3 weeks; visit 1)

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49 In order to incorporate response to initial induction therapy within the risk
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51 stratification criteria, inclusion and risk group allocation is performed at week 5 +/- 3
52
53 weeks of induction therapy. Data from the screening visit is reviewed with ineligible
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55 patients excluded and patients are then stratified into the high or low risk group
56
57 (Table 1) based upon the ECCO/ESPGHAN consensus guidelines¹. Patients with
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60

perianal fistulising disease at diagnosis are auto-allocated to the high-risk group regardless of other factors at inclusion visit. All other patients are allocated to the low risk group. Patients with low thiopurine methyltransferase (TPMT) activity or homozygous mutations are excluded should they be categorised as low risk.

DEFINING HIGH RISK CROHN'S DISEASE PATIENTS	
ECCO/ESPGHAN CONSENSUS GUIDELINES	MODIFIED STUDY CRITERIA
Severe perianal disease	Complex perianal fistulising disease phenotype
Extensive (pan-enteric) disease; deep colonic ulcers on endoscopy	Panenteric disease phenotype (defined as L3 with L4b as per Paris classification ²³ or L3 with deep ulcers in the duodenum, stomach or oesophagus not related to non-steroidal anti-inflammatory medications or <i>Helicobacter pylori</i>)
	Overall cumulative disease extent of ≥ 60 cm
Strictureing and penetrating disease at onset	B2, B3 or B2B3 disease behaviour ²⁰
Marked growth retardation > -2.5 height Z scores	Severe growth impairment (height z-score < -2 or crossing ≥ 2 centiles) likely related to Crohn's disease
Persistent severe disease despite adequate induction therapy	Hypoalbuminemia (< 30 g/L), elevated CRP (at least 2 times upper limit of normal range), or wPCDAI > 12.5 despite at least 3 weeks of optimized induction therapy with steroids or EEN
Severe osteoporosis	Not included

Table 1 – Definition of high-risk patients based upon ECCO/ESPGHAN consensus guidelines¹ (ECCO – European Crohn's and Colitis Organisation; ESPGHAN – European Society for Paediatric Gastroenterology, Hepatology and Nutrition; CRP – C-reactive protein; wPCDAI – weighted Paediatric Crohn's Disease Activity Index; EEN – exclusive enteral nutrition)

Randomisation and Treatment Allocation

Randomisation is undertaken following allocation to high or low risk group at week 5 +/- 3 weeks. This process utilises an integrated module within the electronic case report form (CRF) system. Within both the high and low risk groups patients are 1:1 randomised to MTX versus ADA or AZA/6MP respectively in blocks of four stratified by EEN or steroid induction therapy. Code for randomisation is prepared and held by the central coordinating site and site co-ordinators are then informed of the results. Immunomodulator or biologic therapy should be commenced within 2 weeks of randomisation as per the protocol outlined in Table 2.

AZA/6MP and MTX are prescribed and dispensed according to local guidelines. ADA (Humira ®) is provided by AbbVie. Co-interventions are prohibited.

	Therapy	Route	Dose	Notes
LOW RISK PROTOCOL	Methotrexate	SC	15mg/m ² body surface area weekly (max dose 25mg)	Ondansetron 4-8mg orally 1 hour pre injection and folic acid 15mg (5mg in patients <20kg) 3 days post injection are recommended for all patients
	VERSUS			
	Azathioprine	PO	2.5mg/kg (rounded down to nearest 12.5mg)	Half calculated dose for TPMT heterozygotes/activity 6-9nmol/h/ml
HIGH RISK PROTOCOL	OR			
	6-Mercaptopurine	PO	1.5mg/kg (rounded down to nearest 12.5mg)	Half calculated dose for TPMT heterozygotes/activity 6-9nmol/h/ml
	Methotrexate	SC	15mg/m ² body surface area weekly (max dose 25mg)	Ondansetron 4-8mg orally 1 hour pre injection and folic acid 15mg (5mg in patients <20kg) 3 days post injection are recommended for all patients
HIGH RISK PROTOCOL	VERSUS			
	Adalimumab (Humira ®)	SC	160mg then 80mg after 2 weeks then 40mg every 2 weeks thereafter (patients >35kg) 120mg then 80mg after 2 weeks then 40mg every 2 weeks thereafter (patients 25-35kg) 80mg then 40mg after 2 weeks and 20mg every 2 weeks thereafter (patients <25kg)	

Table 2: Medication protocol for low and high-risk patients following randomisation

(TPMT – thiopurine methyltransferase)

Follow Up Visits (Visit 2, 3, 4, 5 and 6)

Patients are followed up at pre-specified intervals (Figure 1) with a window of +/- 2 weeks. A telephone call is undertaken at week 4 following initiation of induction in order to support patient compliance with induction regime and advise weaning where appropriate. Data as described in Box 3 are collected at each consultation. Patients' compliance with therapy is determined at each face-to-face follow up visit by pill and vial counts plus by patients' reporting.

Box 3: Standard requirements for each study visit

- An explicit history of illness since last visit, including review of symptoms, medications (including compliance check) and adverse events.
- Physical examination
- wPCDAI, PGA and PCDAI scoring
- Anthropometrics (height measured using a calibrated wall mounted stadiometer)
- Blood tests
 - White blood cells
 - Absolute neutrophil count
 - Haemoglobin
 - Haematocrit
 - Platelet count
 - Erythrocyte sedimentation rate (ESR)
 - C-reactive protein (CRP)
 - Amylase
 - Albumin
 - Aspartate transaminase (AST)
 - Alanine transaminase (ALT)
 - Conjugated bilirubin
 - Gamma glutamyl transferase (GGT)
- Stool samples for faecal calprotectin and microbiome analysis
- Health economic parameters (EQ-5D-Y proxy 1; EQ-5D-Y; EQ-5D-5L; WPAI:CD; school attendance questionnaire)
- Quality of life evaluation (IMPACT 3)
- Urine human chorionic gonadotropin (hCG) in all female patients of child-bearing potential
- Confirmation of contraception use or of absolute abstinence in all patients

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7 Remission is defined as wPCDAI \leq 12.5, normal CRP (\leq 1.5 times upper normal
8 range) and being free of steroids or EEN. Once remission is achieved and induction
9 therapy is discontinued, a patient is considered to be failing treatment or
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14 experiencing a relapse in the following circumstances:

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17 • wPCDAI $>$ 40
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19 • CRP $>$ 2 times upper normal limit in the absence of any clear infectious
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21 process
- 22
23 • wPCDAI $>$ 12.5 but $<$ 40 and/or CRP $>$ 1.5 times but $<$ 2 times over upper
24
25 normal limit at 2 consecutive visits within 2-8 weeks
- 26
27 • Development of CD related complications e.g. fistulisation
- 28
29 • Requirement for additional CD-specific medication/surgery since last study
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31
32
33 visit

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37 A patient will also be considered a treatment failure should induction therapy be
38 continued at week 12. In addition, the treating clinician may escalate treatment at
39
40 any time point independent of wPCDAI score if it is felt that the patient is
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42
43
44 experiencing a relapse.

Dose Optimisation and Therapeutic Drug Monitoring

Drug monitoring is undertaken as detailed below. In addition to this, samples for drug monitoring should be collected at the time of medication cessation in the event of drug discontinuance due to adverse effect or loss of response. Potential adaptations to therapies which may be made at specific follow up visits are detailed in Box 4.

Box 4 – Potential adaptations to therapies at follow up visits

Month 2 (Visit 2)

- Failure to discontinue induction therapy by week 12
 - Offer switch to the ancillary study (ADA STEP-up) to those prescribed MTX or AZA/6MP, or an increase in dose frequency to weekly in those prescribed ADA
 - Alternatively, the patient may leave the study and receive therapies as per the discretion of the treating clinician.

Months 4, 6, 9 and 12 (Visits 3, 4, 5 and 6)

- Thiopurine non response
 - Protocol as per metabolite levels (detailed in Table 3)
- Thiopurine intolerance (except pancreatitis)
 - Switch to alternate thiopurine (AZA to 6MP or vice versa) or split dose to provide twice daily (BD) dosing
- Thiopurine failure (any exacerbation despite dose optimisation/pancreatitis/cytopaenia)
 - Offer switch to ancillary study (ADA STEP-up) or exit study
- MTX intolerance or failure (any exacerbation or elevation of liver enzymes as detailed below)
 - Offer switch to ancillary study (ADA STEP-up) or exit study
- ADA failure (any exacerbation)
 - Increase frequency to weekly dosing

Azathioprine

RESULT	ACTION
6-TG <150	Consider non-compliance; repeat sample at subsequent visit and increase dose if low 6-TG confirmed (+25mg or +12.5mg if dose <50mg)
6-TG 150-800	No adaptation
6-TG >800	Decrease dose if repeat sample at subsequent visit confirms high 6-TG (-25mg or -12.5mg if dose <50mg)
6-MMP >8000 or signs of hepatotoxicity	Stop medication – switch to ancillary study Erythrocyte lysate sample frozen at -80C and shipped to central lab at end of study for thiopurine nucleotides

Table 3 – Azathioprine dose adjustments based upon metabolite levels

TPMT genotype or phenotype at screening determines the initial dose of AZA/6MP; and measurement of thiopurine metabolites (6-thioguanine (6-TG) and 6-methylmercaptopurine (6-MMP)) at visit 2 determines requirement for subsequent dose adjustment performed according to the recommendations in Table 3. Where possible thiopurine metabolites are measured locally; central lab measurements are provided for centres where this is unavailable.

At visit 2 a urine sample for TPMT metabolite determination and an erythrocyte lysate sample for quantification of Thiopurine Nucleotides by Liquid Chromatography-Tandem Mass Spectrometry should be frozen at -80°C and shipped on dried ice to the central lab at the end of the study. At each visit from visit

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3 2 to 6, an additional EDTA blood sample will be collected for further 6-TG and 6-
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5 MMP testing and frozen at -80C.
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10 11 12 *Methotrexate* 13

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16 Washed erythrocyte for MTX levels will be obtained at visits 2, 4 and 6 and stored
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18 frozen at local centres. These samples will be sent on dry ice for central analysis to
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20 evaluate response to therapy and adverse effects in relation to drug levels.
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27 *Adalimumab* 28

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31 Adalimumab trough levels are measured after 3 injections of maintenance therapy
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33 (e.g. at visit 2) within the local laboratory (central lab testing available if local lab
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35 testing is unavailable). Dosing interval may be shortened to weekly in the event of
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37 low ADA levels (<8 mcg/ml) and negative ADA antibodies. Further samples should
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39 be obtained at visits 3, 4, 5 and 6 and should be frozen for later analysis within the
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41 central lab.
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49 *Pharmacogenetics* 50

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53 DNA for pharmacogenetics should be taken from patients randomised to MTX or
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55 AZA/6MP for multiplex genotyping of polymorphism related to drug metabolism to
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57 evaluate safety and response to therapy. Analysis will be performed at the end of the
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59 study, or earlier in those patients showing toxicity.
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Ancillary Study

Patients unable to discontinue induction therapy or those randomised to thiopurine or MTX therapy who experience treatment failure may be invited to participate in the ancillary study (STEP-up ADA) until visit 5. Any initial maintenance therapy will be stopped and induction and maintenance regime for ADA as previously described will be commenced. Up to 3 additional study visits at 3-month intervals will be offered to these patients in order to obtain 12 months of follow up. A maximum of 68 patients can participate in this ancillary study allowing a 1:1 comparison of TOP-down ADA to STEP-up ADA therapy.

Unscheduled Visits

Unscheduled visits may be arranged based upon clinical requirements. As for scheduled visits per protocol treatment adaptations are possible if intolerance or failure of the study drug is detected. Subsequent scheduled visits will not be changed after an unscheduled visit.

Treatment Discontinuation

Patients who discontinue treatment before completing 12 months of study drug within either the main study or the ancillary study will receive a single follow-up visit. This will be either 12 months after the commencement of study treatment or at the point of inclusion in the ancillary study.

Modifications to the protocol while the study is being conducted will be relayed to all site staff by email and then onto their relevant ethical and regulatory boards. The current manuscript is based on protocol 5.1 last modified 28th May 2019.

Allocation Concealment and Blinding

For ethical reasons we decided against a double dummy design for blinding the patient, parents and care givers. Due to the differences in medication administration route and the significant nausea commonly associated with MTX blinding of the allocation to the patients, their families or their physicians is not possible. Where possible however, blinding of an alternative clinician to score the wPCDAI, PCDAI and PGA at each study visit should occur (prospective randomized open blind end-point (PROBE) evaluation).

Safety

The external and independent Advisory Board of PIBDSETQuality serves as an independent Data and Safety Monitoring Board which meets at pre-specified intervals with access to all data within the study. The principal investigator at each site is responsible for reporting any safety issues (adverse events, serious adverse events (SAEs), suspected unexpected serious adverse reactions), drop-outs, or any new information which may impact the study in any way. The principal investigator shall report to the sponsor all SAEs experienced by a study subject receiving an Adalimumab (Humira) within 24 hours of learning of the event regardless of the relationship of the event to the product. All SAEs are immediately sent to AbbVie pharmacovigilance by the sponsor. SAEs will be followed from the date of patient's signature of informed consent, until complete resolution or 30 days after the end of the study/patient's final study visit.

Box 5 – Criteria for premature termination of study treatment or participation

- Pregnancy at any stage
- Treatment failure as per protocol
- Failure to tolerate allocated treatment or alternatives as listed within the protocol
- Significant drug related side effects manifesting as significantly abnormal bloods results or adverse effects based upon the clinical judgement of the treating physician
- Request of participant to be withdrawn from treatment
- The judgement of the treating physician being that it is in the best interests of the participant to withdraw from study treatment
- Loss of participant to follow up
- Patient death

Participants may withdraw consent for further participation or data collection at any time without giving reason and without prejudicing further care or treatment. Patients will be permanently withdrawn from study treatment in the event of any of the situations outlined in Box 5. Patients should be provided with a study alert card for use in the event of an emergency.

Biochemical markers are monitored with a clearly defined protocol for adjustments to therapy based on abnormal results (e.g. neutropenia, pancreatitis, elevated liver enzymes).

Data Collection, Management and Monitoring

Patient CRFs are completed in a prospective manner using an electronic web-based system designed specifically by PIBDnet for this trial. In order to maintain data

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3 security and integrity, the web-based data entry will be linked to a password secured
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5 Microsoft Access database, where data will be stored until time of analysis. Files will
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7 be saved on a code secured net-drive and backed-up following each data entry on a
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9 disk locked in a cabinet. Patients will be identified only by a study code assigned at
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11 the point of enrolment. Code of patient identifiers will be kept at each participating
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13 site. Handling of patient-identifiable is compliant with the legislation of each
14
15 participating centre and the European General Data Protection Regulation (GDPR).
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17 Investigators will be invited to fax or email the paper source document to the
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19 coordinating site on a random basis to allow appropriate monitoring. Access to data
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21 with detailed information on study outcomes will be made available to other research
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23 groups on request and at the discretion of the principal investigators.
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30 Monitoring arrangements are in place for all sites after initial site initiation. The
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32 monitoring visits will occur regularly partly dependant on recruitment rate at
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34 individual sites. The monitoring is performed usually by someone external to the
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36 clinical team.
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40 **Analysis and Statistical Methods**

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43 Descriptive statistics (mean, median, standard deviation, standard error, quartiles,
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45 minimum, maximum, and two-sided 95% confidence limits of mean and median) will
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47 be presented for each treatment of the low and high risk paediatric CD groups and
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49 where applicable, for the paired difference of each patient. Frequency tables will be
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51 presented where applicable.
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60 **Primary Analysis**

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Difference in the 12-month steroid/EEN free sustained remission rates between the treatment groups will be undertaken using Chi square test. Mantel Haenzel test will be used to combine data from all participating sites.

Secondary Analyses

Chi-square tests or Fisher's exact tests will be used to compare rates of remission, steroid intake, dropout and serious adverse events between the two arms of each risk group and between the low and high risk MTX groups. Logistic regression analyses may be performed to adjust for any imbalances in baseline covariates. To compare time to disease flare between the arms of each risk group and between high and low risk MTX groups, a Kaplan–Meier survival estimate will be used and the log-rank test of equality over strata. A Cox proportional hazard model will be constructed to obtain a hazard ratio after validation of the proportionality assumption and adjusting for possible confounding variables (including age and disease duration). Student's t tests or Wilcoxon rank sum tests will be used to compare growth, steroid dose, adverse events, changes in quality of life and patient reported outcomes between the two arms of each risk group and between the high and low risk MTX groups. The predictive value of faecal calprotectin levels, CRP, serum tests or other clinical predictors for response (including genomic and serological markers) will be assessed for each arm of the study using sensitivity, specificity, negative and positive predictive values or area under the ROC curve. Multivariate logistic regression analyses will then be performed.

Analyses will be performed using the R software (<http://cran.r-project.org>). All comparisons will be made using a 2-sided significance level of 0.05.

Sample Size Considerations

Estimated remission rates are based on recent analysis from the RISK study¹⁸, indicating an advantage of early anti-TNF introduction over immunomodulator therapy. For the low risk group, it was hypothesized that 48% of children will be in remission at 12 months for the AZA/6MP arm versus 70% for the MTX arm. On the basis of this data with an alpha risk of 5% and a power of 80% a sample requirement of 88 patients per arm was calculated assuming a 10% loss of follow up. For the high-risk group, it was hypothesised that 40% of children will be in remission at 12 months for the MTX arm versus 65% for the adalimumab arm. To detect this difference with an alpha risk of 5% and a power of 80%, a sample size of 68 participants is necessary, again assuming a 10% loss of follow-up. In total 312 participants will be included in the study (176 low-risk group; 136 high risk group).

Patient and Public Involvement

Patients were not involved in the development of this study; however, the French patient charity AFA Crohn, RCH, France was involved in study design and critically reviewed and commented upon all aspects of the trial.

Discussion

REDUCE-RISK in CD is the first multicentre international RCT aiming to compare three different medication strategies for maintenance of remission in newly diagnosed CD based upon a risk stratification protocol. During the 12-month follow up period the effects of the differing management strategies will be assessed via data collected and outcome measures as defined above in order to analyse the efficacy and safety of each medication and better define the most appropriate first-line maintenance immunomodulators to be used in specific subsets of CD patients. As a group we speculatively hypothesise that MTX will be superior to thiopurines for maintaining remission in CD in the low risk group although in the absence of head to head studies prior to this one this study will provide randomised data to address this. We also hypothesise that ADA will be superior to MTX in the high-risk group based upon the results from the RISK study.¹⁸ In addition to this, the ancillary study will compare outcomes in ADA treated patients from inclusion (Top-down) versus patients switched to ADA due to failure of immunomodulators (Step-up), with the potential to stratify which patients might benefit from such a top-down treatment strategy. We acknowledge that comparison of the ancillary group with the group randomised from baseline to ADA is not randomised and may be subject to selection bias noting the ancillary group have failed or been intolerant to initial therapy. However we feel it is important to include this to allow us to compare the trial with studies which have allocated patients directly to anti-tnf (RISK, TISKids) and to see how many patients benefit from “rescue therapy” after failure of their initial allocation.

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5 The design and completion of interventional studies in PIBD is a recognised
6 challenge between rigorous study design methodology and pragmatic considerations
7 around feasibility and completion within a paediatric dataset.²³ This particular study
8 is limited by the inability to blind the treatment allocation to the patients, their families
9 or their treating physician due to the differences in medication administration route
10 and the side effects commonly associated with the study medication. Although the
11 protocol advises that where possible blinding of an alternative clinician to score
12 disease assessment at each study visit should occur in order to obtain prospective
13 randomized open blind end-point (PROBE) evaluation this may be practically difficult
14 in smaller centres where staff are familiar with the majority of their patient cohort.
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33 **ETHICS AND DISSEMINATION**

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36 The study is being conducted according to the principles of the Declarations of
37 Helsinki and to date has been approved by all participating sites as listed within
38 supplementary Table 1. Clinical trials authorisation and ethics approval has been
39 obtained from the local ethics review committees of these participating nations and
40 centres. The Standard Protocol Items: Recommendations for Interventional Trials
41 (SPIRIT) guidelines²⁴ were adhered to in the production of the protocol for this trial
42 (see uploaded material for details).
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57 **Consent**

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3 Patients and their caregivers are provided with study-specific information including
4 an explicit description of the study outline and alternatives for participation. It is made
5 clear to all patients approached that declining to participate in the study will not
6 jeopardize the quality of subsequent care received. After a period of consideration, if
7 agreeable, the patient's parent or caregiver is asked to sign consent forms with age-
8 appropriate assent obtained from the child where relevant (see appendix 1 for model
9 consent forms). The signed forms are filed within the patient's medical record with a
10 copy provided to the participant and their caregiver. Consent will be obtained by site
11 staff with the relevant training and who are identified as assigned on the delegation
12 log. Participants taking part in the ancillary study will not be re-consented.
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31 **Dissemination**

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34 Results of the study will be submitted for publication within a peer-reviewed journal.
35 In accordance with the H2020 general grant agreement, the dissemination process
36 will ensure open access to the scientific publications resulting from this project.
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38 Journal authorship guidelines will be adhered to and there are no plans to use
39 professional writers.
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49 **AUTHOR CONTRIBUTIONS**

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51 RH prepared the draft manuscript with comments and review from all authors.
52
53 RKR, MA, LR, NC, SK, AL, DT, GV, MN and LB and FMR were involved in the
54 conception, design, planning and then drafting of the original research protocol and
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3 RKR, RH, MA, LR, NC, SK, AL, DT, GV, MN and LB and FMR provided critical
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5 review of the manuscript and approved the final uploaded draft.
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8 As sponsor PIBDnet has full responsibility and control for the original study design,
9
10 collection, management, analysis, and interpretation of data, including writing of the report
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12 and the decision where to submit the report for publication,
13

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15
16 This work was supported as part of the PIBD-SETQuality (Paediatric Inflammatory
17
18 Bowel Diseases Network for Safety, Efficacy, Treatment and Quality improvement of
19
20 care) project funded by the European Commission Horizon 2020 - Research and
21
22 Innovation Framework Programme (grant number 668023). ADA (Humira ®) is
23
24 provided by AbbVie.
25
26

27
28 The main study sponsor is PIBDNet. PIBDNet is the EU legal representative for the
29
30 study. The specific contact for the sponsor is Frank Ruemmele (Service de Gastro-
31
32 entérologie, Hôpital Necker Enfants Malades, 149 rue de Sèvres, 75015 Paris,
33
34 France).
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37 **COMPETING INTERESTS**

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40 **RKR** is supported by an NHS Research Scotland Senior Research Fellowship, and
41
42 has received speaker's fees, travel support, and/or participated in medical board
43
44 meetings with Nestle, MSD Immunology, AbbVie, Dr Falk, Takeda, Napp, Mead
45
46 Johnson, Nutricia & 4D Pharma. FMR has received speaker fees from Shering-
47
48 Plough, Nestlé, MeadJohnson, Ferring, MSD, Johnson & Johnson, Centocor, AbbVie;
49
50 has served as a board member for SAC:DEVELOP (Johnson & Johnson), CAPE
51
52 (AbbVie), LEA (AbbVie); and has been invited to MSD France, Nestlé Nutrition
53
54 Institute, Nestlé Health Science, Danone, MeadJohnson, Takeda, Celgene, Biogen,
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3 Shire, Pfizer, and Therakos. DT received consultation fee, research grant, royalties,
4 or honorarium from Janssen, Pfizer, Hospital for Sick Children, Ferring, Abbvie,
5 Takeda, Biogen, Atlantic Health, Shire, Celgene, Lilly, Neopharm, Roche. LdR
6 received consultation fee, research grant, or honorarium from ZonMw, ECCO, Shire,
7 Malinckrodt, Nestlé, Celltrion, Abbvie and Pfizer. MA received consultation fee and
8 honorarium from Abbvie. SK received consultation fee, research grant, or
9 honorarium from Danone, Nestec-Nutrition, Abbvie, Takeda, Celgene, Shire, Pfizer,
10 Biogaia, Janssen, Berlin-Chemie; Mead Johnson, Vifor, Pharmacosmos,
11 ThermoFisher
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26 **Remaining authors:** nil competing interests declared.
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29 30 31 **FIGURE LEGENDS**

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35 *Figure 1 – Study Design of the REDUCE-RISK in CD trial*
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37 *M2 = Month 2, V2 = visit 2.*
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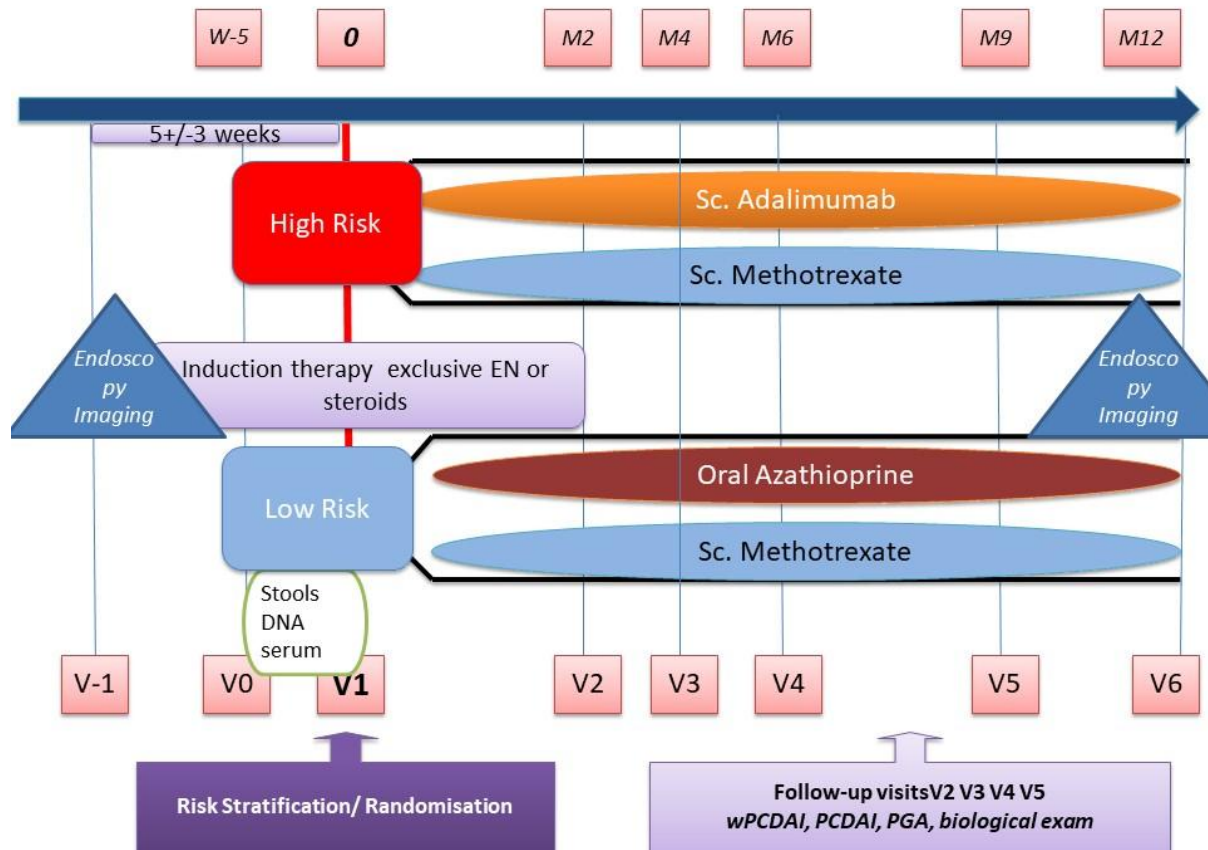


Figure 1 – Study Design of the REDUCE-RISK in CD trial

Participating Sites – REDUCE-RISK in CD Study			
Country	City	Site	Ethics committee
Belgium	Brussels	Universitair Ziekenhuis	Commissie Ethiek, UZ Brussel
	Brussels	Clinique Saint Luc UCL	
	Liège	Clinique de l'Espérance	
	Brussels	HUDERF	
Canada	Toronto	SickKids	SickKids Research Ethics Board, Toronto
Czech Republic	Prague	FN Motol	Eticka Komise, Plzen Eticka Komise, VFN Praha Eticka Komise, FN Motol Praha
	Plzeň	FN Plzeň	
	Prague	First Medical Faculty	
France	Paris	Hôpital Necker Enfants Malades	CPP Hôpital Necker, Paris
	Paris	Hôpital Robert Debré	
	Paris	Hôpital Armand Trousseau	
	Le Havre	Hôpital Jacques Monod	
	Nancy	Hôpitaux de Brabois	
	Toulouse	Hôpital des Enfants	
	Tours	Hôpital Clocheville	
	Caen	CHU Caen Côte de Nacre	
	Marseille	Hôpital de la Timone	
Germany	Munich	Childrens Hospital	Ethikkommission LMU, München
	Ulm	Universitätsklinikum	
	Hannover	MHH Kinderklinik	
	Giessen	UKGM	
	Berlin	Charite Hospital	
Greece	Athens	Children's Hospital "AGIA SOFIA"	Ethics Committee, Athens
Israel	Jerusalem	Shaare Zedek Medical Center	Helsinki Committee, Schneider Medical Center, Petah Tikva Ethics and Research Committee, Wolfson Medical Center, Tel Aviv Institutional Review Board, SZMC, Jerusalem
	Tel Aviv	Wolfson Medical Center	
	Petah Tikva	Schneider Children's Medical Center	
	Ramat Gan	Sheba Medical Center	
	Haifa	Rambam Medical Center	
Italy	Rome	Università degli Studi di Roma La Sapienza	Comitato Etico dell'Universita' "SAPIENZA", Roma Comitato Etico Regionale per la Sperimentazione Clinica della Regione Toscana Sezione, Firenze Comitato Etico, Servizio Sainuario Regionale, Bologna
	Bologna	Maggiore Hospital	
	Florence	Azienda Ospedaliero Universitaria	
	Parma	Azienda Ospedaliero	
	Rome	Opsedale Pediatrico Bambino Gesù	
Netherlands	Rotterdam	Erasmus Medical Center	Medische Etische Toetsings Commissie, Erasmus MC,

			Rotterdam
Poland	Warsaw	Centrum Zdrowia MDM	Bioethical Commission at the Institute of Polish Mother's Health Center, Lodz
	Białystok	Uniwersytecki Dziecięcy Szpital Kliniczny	
	Łódź	Instytut Centrum Zdrowia Matki Polki	
United Kingdom	Glasgow	The Royal Hospital for Children	North West - Liverpool East Research Ethics Committee, NHS, Manchester
	London	Royal London Children's Hospital, Barts Health NHS Trust	
	Edinburgh	Sick Children's Hospital	
	Birmingham	Children's Hospital	
	Oxford	John Radcliffe Hospital	

Supplementary Table 1 – Sites participating in REDUCE-RISK in CD



INFORMED CONSENT FORM

Parents/Guardian Informed Consent Form for Participation of a Minor in a Clinical Trial

Risk-stratified randomized controlled trial in paediatric Crohn's Disease: Methotrexate versus azathioprine or adalimumab for maintaining remission in patients at low or at high risk for aggressive disease course, respectively – a treatment strategy.

Dear parents,

Your child's doctor, Dr....., working at Hospital, propose your child to participate in a clinical trial related to its disease.

It is important to read this note carefully before taking any decision. Do not hesitate to ask the physician all the questions you may have about it.

The participation of your child is based on volunteering. Therefore, your child can refuse to participate or stop its participation in the trial at any time, all of this without prejudice to the patient's right to receive the standard treatment.

If you refuse your child to participate, he/she will still receive the best medical support.

Purpose of the research and trial's objectives

Your child has just been diagnosed with Crohn's disease. The disease is characterised by chronic inflammation of the digestive track (bowel/colon). This disease changes over between remission period and relapse period. There are efficient drugs able to prevent relapse and to maintain remission. In order to reduce the likelihood of long-term complications, induction treatment has already been prescribed to your child. This first treatment has to be followed up by a maintenance treatment that will be introduced to avoid the inflammation from returning. Consensus guidelines of ECCO / ESPGHAN (french and european IBD specialized organizations) recommend 3 efficient treatments: either immunosuppressive treatment with Thiopurines (azathioprine and 6-mercaptopurine), or Methotrexate or anti TNF (adalimumab).

So far, no clinical trial has been conducted to compare those 3 treatments in children with Crohn's disease and to answer the following question: "Which treatment is the most efficient, for which patient and/or in which situation?"

Progression of Crohn's disease is not the same for all patients. That's why this study will first classified all children in high and low risk groups based on more or less severe course of Crohn's disease. The lower risk group will be randomized (which is like tossing a coin) to receive either thiopurines or methotrexate as maintenance treatment. The high risk group will be randomized to receive either methotrexate or adalimumab. Results will show whether there is different efficiency between the 3 drugs for patients with a more or less severe disease.

Sponsor

PIBD-Net (www.pibd-net.org) is a global, international and non-profit organisation gathering physicians and researchers specialised in inflammatory bowel diseases. The acronym stands for Pediatric Inflammatory Bowel Diseases Network and it is present in 31 countries (Europe, North America, Australia and Japan). This organisation is dedicated in improving the medical care of children with inflammatory bowel disease through the establishment of clinical researches.

PIBD-Net and partners received funding from European Commission for Horizon 2020 program (project no.668023) in order to perform this research.

The approximate number of participants and duration of follow-up

A total of 312 new-onset children with Crohn's disease (136 in that high-risk group and 176 in the low risk) will be enrolled in many sites around the world. The period of recruitment is 45 months and your child will be followed up for 12 months after enrolment.



What will happen to your child during the trial?

If you agree to have your child participating in this study, your child will be first directed into one of two groups based on certain predictors of its disease (such as its location and severity). You will know which group your child is in. Next, your child will be randomized to receive maintenance treatment namely:

- **METHOTREXATE or AZATHIOPRINE for the low risk group ;**
- **METHOTREXATE or ADALIMUMAB for the high risk group ;**

You cannot choose the treatment group but you will know which drug your child will receive.

You will not be asked to come to clinic just because of this study which is designed to mirror regular follow-up in clinic. After signing the informed consent allowing your child to be part of this research, your child will have clinic visit every 2 months during the first 6 months and then every 3 months during the last 6 months. At each visit, a clinic examination is performed and blood, urine and stool samples are collected (this process follows our standard clinical practices of our patients not involved in this protocole).

Your doctor, your child and yourself will be asked to complete short questionnaires to evaluate the quality of life of your child. Most of the recorded data for this study is needed anyway as part of a regular visit but there might be a few more questions we will ask you for this study.

We will also contact you over the phone at week 4 to ask how your child feels regarding its Crohn's disease, whether your child has any bad reactions to the medications your child will receive and check your child compliance to the treatment.

To optimize the medications we prescribe, we will draw 12 ml (3-4 teaspoons) of blood at inclusion visit, 10ml at visit V2, and then 5ml at each next study visits to measure the level of the medications your child will receive. A urine sample will be collected at inclusion visit and a DNA sample (either 5ml of blood or buccal swab) will be collected at the beginning of the study, and also in case of drug intolerance.

We will also collect your child stool (poop) six times during the year to measure the amount of inflammation in its bowel as well as bacteria flora in its intestine.

We will evaluate whether the drugs work based on

- completed questionnaires
- clinic examination
- results of biological samples

Optional Ancillary study (« ADA STEP-up »)

In case of failing (intolerance or relapse) of your child immunomodulator therapy (: either azathioprine/6MP or methotrexate), your child will be invited to participate in the ancillary study. If you agree, your child will be prescribed adalimumab during 12 months.

This adalimumab treatment can increase the study duration by a maximum of 9 months, meaning a maximum of 3 additional visits. Those visits are identical to the regular follow up study visits.

The expected benefits to the participant or to others because of the trial

The medications your child will receive in this study are not experimental and thus there are no direct benefit for using these drugs that are available outside of the study. However, your child will be monitored closely to ensure optimization of the treatment by adapting drug amounts based on new analyses (urine, DNA, blood and stool samples). In addition, patients involved in this study have access to molecular analyses in order to better understand why a patient is less responsive than expected. That might result in a more tight control of the disease and better monitoring of the treatment of your child.



After study completion, we will have the required data to recommend how to use these medications in new children who develop Crohn's disease.

Risks added by the research

As previously mentioned, all medications used in this trial are not experimental and are being used very often in clinical practice in children/adolescents and adults with Crohn's disease. There is no additional risk compares to regular clinical practices. The known risks and discomfort that may be anticipated are listed below.

Known risks and discomfort that may be anticipated

The medications yourchild will receive in this study are not experimental but used in regular practices. They can also be associated with side effects (all described in the corresponding drug information sheet).

- ✗ **METHOTREXATE: weekly subcutaneous (under the skin)** This drug may be associated with side effects mainly in the day of the injection including flu-like symptoms, nausea, vomiting, headache or fatigue. Your child will be asked to take a vitamin called folic acid which will reduce these non-dangerous side effects. This injection may cause slight discomfort.METHOTREXATE may cause reduced blood counts, especially white blood cells and elevated liver enzymes. Thoses parameters will be checked regularly. In this study, molecular analyses will be performed to screen patients who can't tolerate METHOTREXATE..This drug causes an unusual sensitiveness to the sun (however, there is no data stating that it increases the risk of cancer or lymphoma). METHOTREXATE can cause foetal abnormalities so pregnancy is not allowed and efficient contraceptive is essential (for both male and female).
- ✓ **AZATHIOPRINE (or 6MP): to be taken orally.** THIOPURINES may cause reduced blood counts, especially white blood cells and elevated liver enzymes. Thoses parameters will be checked regularlyIn this study, molecular analyses will be done in order to screen patients who can't tolerate those drugs. In some rare cases (<3%), the drug may cause inflammation in the pancreas which is usually mild and not dangerous. As all drugs, THIOPURINES can't be tolerated by some patients due to allergy. Approximately 10% of children will not tolerate the drug because of nausea, vomiting, tummy pain, diarrhea, headaches or fever..THIOPURINES are associated with an increased infectious risk (about 1%). Infections are likely cause.. by viruses. In rare cases, THIOPURINES may increase risk for blood cancer called lymphoma (especially for patients > 65 year old).—This drug causes an unusual sensitiveness to the sun and can be associated with skin cancer in case of significant sun exposure.

ADALIMUMAB: subcutaneous (under the skin) injections every 2 weeks Adalimumab is associated with minor pain during the injection and local reactions could appear with minimal significance..ADALIMUMAB is associated with an increased infectious risk. However, serious infections are uncommon. Before starting ADALIMUMAB treatment, tuberculosis must be excluded. With time, the effect of adalimumab may wain as a result of the development of antibodies against the drug. Skin inflammatory damages (such as « psoriasis ») were observed in some patients. Anti TNF drugs have been closely monitored since their use as standard treatment. Those drugs may be responsible of heart failure for patients with severe heart disease, hepatitis, decreasing blood cells, demyelinating neurologic disease, or lupus (without affecting main organs). In addition, some cases of cancer have been notified in patient treated by ADALIMUMAB, but risks of cancer is slightly increased only for melanoma. Number of cancer seems not to be increased compared to patients with Crohn's diseases and without being treated with those drugs.

Circumstances under which participation in the medical trial may be discontinued in accordance with the decision of the investigator or the Sponsor:

- a. The doctor has the right to take your child out of the study at any time. This will be made after clinical considerations, your child's side effects from the drugs, intolerance to the drugs or lose of response.
- b. Regulatory authorities (Ministry of Health or Ethics committee), may stop your child participating in the study.



An explanation of alternative treatments, their advantages and disadvantages, if any, for the participant:

The current standard therapy for maintenance therapy in Crohn's disease is either METHOTREXATE or thiopurines or anti-TNF biologics for the more severe Crohn diseases. This is exactly the medications given also as part of this study. The difference is that instead letting you and the doctor choose between the options, the choice is standardized based on predictive variables of your disease and randomization. If you choose not to have your child participating in the study, your child will likely receive anyway one or more of these three drugs. The only exception would be that if anti-TNF is prescribed, either adalimumab or infliximab can be given and as part of this study your child will receive adalimumab only. However, your child will not have access to molecular analyses described in this protocole with a close monitoring of drug safety. Indeed, those 'new' analyses are not done in the standardclinical practise of Crohn's disease.

If you participate in this study, what will you have to do more than usual ?

If you agree to have your child participating in this study, please make sure to follow the listed points belowPlease come at your appointments with your child. If not possible, please inform its physician as soon as possible

- Please ensure that your child takes the treatment as instructed by its doctor
- Please inform the physician involved in the study of any event happening during the research (such as hospitalization,...)
- Your child must not participate in any other clinical trial that involves the use of an investigational product throughout the course of this trial. It is to avoid accidents such as possible interactions between medicines.

Biological samples collected during this research project

If you agree to have your child participating in this research, additional blood, urine and stool samples will be collected at the same time as our standard clinic samplings. Please see below:

- ✓ 10ml of blood during inclusion visit (on randomisation day).
- ✓ 5ml of blood (PAX tube) during inclusion visit for RNA analyses
- ✓ 10ml of blood at follow up visits M2 (2 months after inclusion)
- ✓ 5 ml of blood at follow up visits M4, M6, M9 and M12 (4, 6, 9, 12 months after inclusion)
- ✓ Stool sample at inclusion visit and follow up visits M2, M4, M6, M9 and M12 (2, 4, 6, 9, 12 months after inclusion visit).
- ✓ A DNA sample will be collected at inclusion visit and in case of intolerance of one of the drugs for DNA analyses.
- ✓
- ✓ Urine sample (15ml) will be collected at M2 visit (2 months after inclusion).

Those samples will be sent to specialized laboratories in order to be used to perform specific studies such as adalimumab, methotrexate, thiopurine analyses and serology, genetic (both DNA and RA), microbiology studies. They will also be re-used for further testing on Crohn's disease, its diagnosis and its treatment as well as efficacy and tolerance by molecular ("omic") analyses.

At any time, you can request to your clinician to have those biological samples destroyed or not to be used for further researches.

Confidentiality

As part of biomedical research in which PIBD-Net sponsor proposes your child's participation, treatment of personal data will be set up to analyse results of this research based on its aim. Therefore, your child medical data and quality of life will be transferred to PIBD-Net sponsor. Those data will be anonymous and identified by a coded number and its initials. Those confidential data could be transferred to local and foreign authorities. If your child has to be withdrawn for any reasons, collected data prior its withdrawal will be used unless you do not want



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3 them to. Then, you will have to inform the physician accordingly.

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5 According to the EU General Data Protection Regulation (GDPR) dated on 26May2018, you have the right to
6 access to your child and your personal data, modify them and oppose the use of your child and your data. You
7 have also the right to request that your child and your personal data are erased, are limited in use, and to ask for
8 a complete copy of all data collected from you and your child for the study. You can contact the Data Privacy
9 Officer (DPO) of the sponsor at any time at dpo@pibd-net.org for any request regarding your child and your
10 personal data.
11

12 Data collected for the study are transferred outside of the EU, as our database is based in Israel. However, we
13 guarantee that data protection will be as strict as requested by GDPR.
14

15 **Voluntary participation**

16 Your participation in this research is entirely voluntary. It is your choice whether to have your child participating or
17 not, all the services your child receives at this hospital will continue and nothing will change. If you choose not to
18 participate in this research project, your child will be offered the treatment that is routinely offered in this hospital
19 for Crohn's disease. You may change your mind later and stop participating even if you agreed earlier.
20
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22 **Right to refuse or withdraw**

23 Your child does not have to take part in this research if you do not wish to do so and refusing to participate will not
24 affect its treatment in any way. Your child will still have all the benefits that it would otherwise have at this
25 hospital. You may stop participating in the research at any time that you wish without losing any of its rights as a
26 patient here. Its treatment at this hospital will not be affected in any way.
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29 **Alternatives to participating**

30 If you do not wish that your child takes part in the research, your child will be provided with the established
31 standard treatment available at this hospital.
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33 **Reimbursement**

34 There is no reimbursement for participating in this study. There are no special visits to the hospital excepted
35 during this study. All DNA, blood, urine and stool samples will be taken at the time of a routine clinic visit.
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40 **This proposal has been reviewed and approved by [name of the local IRB], which is a committee whose**
41 **task it is to make sure that research participants are protected from harm.**
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Informed consent form

We, the undersigned :

M, Miss, (*name, first name of parent/legal guardian*)

M, Miss, (*name, first name of parent/legal guardian*)

I, M, Miss,(*name, first name of parent*) hereby declare that my consent below has been given voluntarily and that I have understood all of the above. I undertake to also inform the child's father/mother (*please cross off as appropriate*) of my consent for the participation of our child in the clinical trial. If the child's father/mother (*please cross off as appropriate*) does not agree to affix his/her consent to mine, I undertake to inform the physician in-charge and to withdraw my consent for the participation of my child in the clinical trial. I have also received a lawfully and dated copy of this informed consent form

I agree that my child (*name, first name of the child*).....**takes part of the study named** "*Risk-stratified randomized controlled trial in paediatric Crohn's Disease : Methotrexate versus azathioprine or adalimumab for maintaining remission in patients at low or at high risk for aggressive disease course, respectively – a treatment strategy* ", managed by PIBD Net. It has been explained to us by (*name, first name of explaining investigator /sub investigator, phone,*).....

.....physician in this clinical trial.

- We hereby declare that we agree for our child to participate in the clinical trial as detailed in this document
- Our child has been informed and agreed to take part of this clinical trial.
- We had the opportunity to ask all the questions we had to the physician who explained potential risks and constraints linked to our child participation in this clinical trial.
- We received appropriate answers to all our questions
- We hereby declare that at the time of signing this document, our child is not participating in another clinical trial that involves the use of any investigational product, and that we undertake that our child will not participate in any other clinical that involves the use of an investigational product throughout the course of this trial.
- We declare that our child has a health insurance.
- .We hereby declare that we are free to choose that our child will not participate in the clinical trial, and that we are free to stop our child participation in the trial at any time, and all of this without prejudice to our child's right to receive the standard treatment. Then, we will inform the physician whether data collected prior our decision can be used or not.
- We have been informed that the doctor has the right to take our child out of the study at any time, if needed.
- That in case of completing a questionnaire – we are entitled not to answer all or some of the questions in the questionnaire.
- We are informed that samples collected during this clinical trial will be kept and used for further testing on Crohn's disease. We can decide at any time not to have those samples used by informing our child physician.
- That we are guaranteed confidentiality concerning the identity of the patient and that of the parents/guardians. This confidentiality will be kept by all those concerned with and involved in the clinical trial, and their identity will not be disclosed in any publication.
- That the Medical Institution has arranged for appropriate insurance coverage of the investigators, physicians and medical staff involved in the clinical trial, against claims filed by clinical trial participants and/or third party claims related to the clinical trial, either during the course of the trial or thereafter. This is



without prejudice to our rights under the law.

- That in case of pregnancy during the course of the clinical trial, the girl/woman will be counselled (by the principal investigator) concerning the possible effects on the foetus and the fate of the pregnancy, including the possibility of discontinuing the pregnancy.
- We hereby declare that our below consent has been given voluntarily and that we have understood all of the above mentioned. We also received a lawfully signed and dated copy of this informed consent.
- By signing this consent form, we authorize the sponsor of the clinical trial, the Institutional Helsinki Committee, the auditing entity at the Medical Institute and the Ministry of Health direct access to the patient's medical file, to verify the clinical trial methods and the clinical data. This access to our child medical information will be performed with confidentiality maintained, according to the laws and procedures of maintaining confidentiality.
- We declare that we are informed and give our approval to receive all information related to our child participation in this clinical trial. We know that data will only be used for treatment and follow up cares
- We hereby declare that we know and agree to have the information on our child's participation in the clinical trial provided to his/her attending physician at the HMO/Health care Services with which our child is insured, in case the clinical trial involved the provision of services : performing medical examinations or supplying devices or products or implants. We know that the HMO will not use this information for purposes other than medical treatment and follow up

I agree to have my child participating in the ancillary study (« ADA STEP-up »)

Yes

No

[please tick]

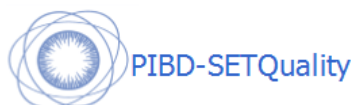
<u>Signature of parents or guardians/representatives of the patient</u>	<u>Signature of the child</u>
Name, First Name : _____	Name, First Name : _____
Date : _____	Date : _____ Signature : _____
Name, First Name : _____	
Date : _____ Signature : _____	

Declaration of the Investigator/Sub-Investigator : This consent was obtained by me after I have explained all the above mentioned to the parents (or guardians) of the clinical trial participant and ensure that all my explanations were understood by them.

Investigator/Sub-investigator' Signature :

Name, First Name: _____

Date: _____
Signature : _____



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3 **This is a triplicate document. First / original copy to be kept by the investigator for 15 years, second copy**
4 **to be given to parents or legal guardians, third copy to be kept in Investigator files (under sealed**
5 **envelope).**
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For peer review only



Informed consent for Genetic Analyses

Hereby declare that we agree for genetic examinations of our child to study genes involved in tolerance / non tolerance of the drugs by molecular (“omic”) analyses and analyses of drug efficacy in Crohn disease’s patients.

Hereby declare that we agree that all recorded data collected during this trial including genetic data can be processed by the sponsor or acting as sponsor. I understand that, as stipulated in the General Data Protection Regulation, I can access, modify, erase or ask for a copy of my child’s personal data and my personal data at any time, by asking to the investigator who will contact the sponsor.

We can decide not to participate anymore in the genetic part of the trial by informing our doctor who will inform the sponsor.

Yes No *[please tick]*

Hereby declare that we agree that all biological samples collected during this trial can be used for future genetic research on Crohn’s disease.

Yes No *[please tick]*

Parents/guardians Signature:

Investigator Signature:

Name, First name:

Name, First name:

Date : Signature :

Date : Signature :

Name, First name:

Date : Signature :

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. *Ann Intern Med.* 2013;158(3):200-207

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	Throughout manuscript
Protocol version	#3	Date and version identifier	21
Funding	#4	Sources and types of financial, material, and other support	30
Roles and responsibilities:	#5a	Names, affiliations, and roles of protocol contributors	1,2,30

1 contributorship

2 Roles and [#5b](#) Name and contact information for the trial sponsor 29
 3 responsibilities:
 4 sponsor contact
 5 information
 6
 7

8
 9 Roles and [#5c](#) Role of study sponsor and funders, if any, in study 30
 10 responsibilities:
 11 sponsor and funder design; collection, management, analysis, and
 12 interpretation of data; writing of the report; and the
 13 decision to submit the report for publication,
 14 including whether they will have ultimate authority
 15 over any of these activities
 16
 17

18
 19 Roles and [#5d](#) Composition, roles, and responsibilities of the 23,30
 20 responsibilities:
 21 coordinating centre, steering committee, endpoint
 22 adjudication committee, data management team,
 23 and other individuals or groups overseeing the trial,
 24 if applicable (see Item 21a for data monitoring
 25 committee)
 26
 27

28 Introduction

29
 30
 31 Background and [#6a](#) Description of research question and justification for 6-8
 32 rationale undertaking the trial, including summary of relevant
 33 studies (published and unpublished) examining
 34 benefits and harms for each intervention
 35
 36
 37

38 Background and [#6b](#) Explanation for choice of comparators 6-7
 39 rationale: choice of
 40 comparators
 41
 42

43 Objectives [#7](#) Specific objectives or hypotheses 8-10
 44

45 Trial design [#8](#) Description of trial design including type of trial (eg,
 46 parallel group, crossover, factorial, single group),
 47 allocation ratio, and framework (eg, superiority,
 48 equivalence, non-inferiority, exploratory)
 49
 50
 51

52 Methods:

53 **Participants,**
 54 **interventions, and**
 55 **outcomes**
 56
 57
 58
 59
 60

1	Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Supplemental table 1
2				
3				
4				
5				
6				
7				
8	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	10-12
9				
10				
11				
12				
13				
14				
15	Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	15-16
16				
17				
18				
19				
20	Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	18, 19,22
21				
22				
23				
24				
25				
26				
27	Interventions: adherence	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	19-21
28				
29				
30				
31				
32	Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	13,23
33				
34				
35				
36	Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-10
37				
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39				
40				
41				
42				
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44				
45				
46				
47				
48				
49	Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	See figure 1 8,12,15,16-19
50				
51				
52				
53				
54				
55	Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions	27
56				
57				
58				
59				
60				

supporting any sample size calculations

1
2
3 Recruitment [#15](#) Strategies for achieving adequate participant enrolment to reach target sample size Not listed
4
5

6 **Methods:**

7 **Assignment of**
8 **interventions (for**
9 **controlled trials)**
10
11

12
13 Allocation: sequence [#16a](#) Method of generating the allocation sequence (eg, 15,16,22
14 generation computer-generated random numbers), and list of
15 of any factors for stratification. To reduce predictability
16 of a random sequence, details of any planned
17 restriction (eg, blocking) should be provided in a
18 separate document that is unavailable to those who
19 enrol participants or assign interventions
20
21

22
23
24 Allocation [#16b](#) Mechanism of implementing the allocation 22
25 concealment sequence (eg, central telephone; sequentially
26 mechanism numbered, opaque, sealed envelopes), describing
27 any steps to conceal the sequence until
28 interventions are assigned
29
30

31
32
33 Allocation: [#16c](#) Who will generate the allocation sequence, who will 15
34 implementation enrol participants, and who will assign participants
35 to interventions
36
37

38 Blinding (masking) [#17a](#) Who will be blinded after assignment to 22
39 interventions (eg, trial participants, care providers,
40 outcome assessors, data analysts), and how
41
42

43 Blinding (masking): [#17b](#) If blinded, circumstances under which unblinding is N/A
44 emergency permissible, and procedure for revealing a
45 unblinding participant's allocated intervention during the trial
46
47

48 **Methods: Data**
49 **collection,**
50 **management, and**
51 **analysis**
52
53

54
55 Data collection plan [#18a](#) Plans for assessment and collection of outcome, 24-25
56 baseline, and other trial data, including any related
57 processes to promote data quality (eg, duplicate
58
59

1		measurements, training of assessors) and a	
2		description of study instruments (eg, questionnaires,	
3		laboratory tests) along with their reliability and	
4		validity, if known. Reference to where data	
5		collection forms can be found, if not in the protocol	
6			
7			
8			
9	Data collection plan:	#18b Plans to promote participant retention and complete	Not listed
10	retention	follow-up, including list of any outcome data to be	
11		collected for participants who discontinue or deviate	
12		from intervention protocols	
13			
14			
15	Data management	#19 Plans for data entry, coding, security, and storage,	25
16		including any related processes to promote data	
17		quality (eg, double data entry; range checks for data	
18		values). Reference to where details of data	
19		management procedures can be found, if not in the	
20		protocol	
21			
22			
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24			
25	Statistics: outcomes	#20a Statistical methods for analysing primary and	25-26
26		secondary outcomes. Reference to where other	
27		details of the statistical analysis plan can be found,	
28		if not in the protocol	
29			
30			
31			
32	Statistics: additional	#20b Methods for any additional analyses (eg, subgroup	26-27
33	analyses	and adjusted analyses)	
34			
35			
36	Statistics: analysis	#20c Definition of analysis population relating to protocol	26
37	population and	non-adherence (eg, as randomised analysis), and	
38	missing data	any statistical methods to handle missing data (eg,	
39		multiple imputation)	
40			
41			
42	Methods:		
43	Monitoring		
44			
45			
46	Data monitoring:	#21a Composition of data monitoring committee (DMC);	23
47	formal committee	summary of its role and reporting structure;	
48		statement of whether it is independent from the	
49		sponsor and competing interests; and reference to	
50		where further details about its charter can be found,	
51		if not in the protocol. Alternatively, an explanation of	
52		why a DMC is not needed	
53			
54			
55			
56			
57			
58	Data monitoring:	#21b Description of any interim analyses and stopping	23
59			
60			

1	interim analysis		guidelines, including who will have access to these	
2			interim results and make the final decision to	
3			terminate the trial	
4				
5	Harms	#22	Plans for collecting, assessing, reporting, and	23
6			managing solicited and spontaneously reported	
7			adverse events and other unintended effects of trial	
8			interventions or trial conduct	
9				
10				
11				
12	Auditing	#23	Frequency and procedures for auditing trial conduct,	24
13			if any, and whether the process will be independent	
14			from investigators and the sponsor	
15				
16				
17	Ethics and			
18	dissemination			
19				
20				
21	Research ethics	#24	Plans for seeking research ethics committee /	4
22	approval		institutional review board (REC / IRB) approval	
23				
24				
25	Protocol	#25	Plans for communicating important protocol	22
26	amendments		modifications (eg, changes to eligibility criteria,	
27			outcomes, analyses) to relevant parties (eg,	
28			investigators, REC / IRBs, trial participants, trial	
29			registries, journals, regulators)	
30				
31				
32				
33	Consent or assent	#26a	Who will obtain informed consent or assent from	29-30
34			potential trial participants or authorised surrogates,	
35			and how (see Item 32)	
36				
37				
38				
39	Consent or assent:	#26b	Additional consent provisions for collection and use	No additional
40	ancillary studies		of participant data and biological specimens in	consent see
41			ancillary studies, if applicable	page 30
42				
43				
44	Confidentiality	#27	How personal information about potential and	24
45			enrolled participants will be collected, shared, and	
46			maintained in order to protect confidentiality before,	
47			during, and after the trial	
48				
49				
50				
51	Declaration of	#28	Financial and other competing interests for principal	30
52	interests		investigators for the overall trial and each study site	
53				
54				
55	Data access	#29	Statement of who will have access to the final trial	Not provided
56			dataset, and disclosure of contractual agreements	
57			that limit such access for investigators	
58				
59				
60				

1	Ancillary and post	#30	Provisions, if any, for ancillary and post-trial care,	N/A
2	trial care		and for compensation to those who suffer harm from	
3			trial participation	
4				
5				
6	Dissemination policy:	#31a	Plans for investigators and sponsor to communicate	29
7	trial results		trial results to participants, healthcare professionals,	
8			the public, and other relevant groups (eg, via	
9			publication, reporting in results databases, or other	
10			data sharing arrangements), including any	
11			publication restrictions	
12				
13				
14				
15				
16	Dissemination policy:	#31b	Authorship eligibility guidelines and any intended	29
17	authorship		use of professional writers	
18				
19				
20	Dissemination policy:	#31c	Plans, if any, for granting public access to the full	Not planned
21	reproducible		protocol, participant-level dataset, and statistical	
22	research		code	
23				
24				
25	Appendices			
26				
27	Informed consent	#32	Model consent form and other related	Appendix 1
28	materials		documentation given to participants and authorised	
29			surrogates	
30				
31				
32				
33	Biological specimens	#33	Plans for collection, laboratory evaluation, and	Not provided
34			storage of biological specimens for genetic or	
35			molecular analysis in the current trial and for future	
36			use in ancillary studies, if applicable	
37				
38				
39				

40 None The SPIRIT checklist is distributed under the terms of the Creative Commons Attribution
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BMJ Open

PROTOCOL FOR A MULTI-NATIONAL RISK-STRATIFIED RANDOMISED CONTROLLED TRIAL IN PAEDIATRIC CROHN'S DISEASE: METHOTREXATE VERSUS AZATHIOPRINE OR ADALIMUMAB FOR MAINTAINING REMISSION IN PATIENTS AT LOW OR HIGH RISK FOR AGGRESSIVE DISEASE COURSE

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3 **PROTOCOL FOR A MULTI-NATIONAL RISK-STRATIFIED RANDOMISED CONTROLLED TRIAL IN**
4 **PAEDIATRIC CROHN'S DISEASE: METHOTREXATE VERSUS AZATHIOPRINE OR ADALIMUMAB**
5 **FOR MAINTAINING REMISSION IN PATIENTS AT LOW OR HIGH RISK FOR AGGRESSIVE DISEASE**
6 **COURSE**
7
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9

10
11 **Rachel E. Harris¹; Marina Aloï²; Lissy de Ridder³; Nicholas M Croft⁴; Sibylle**
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13 **Bigot¹¹; Frank M. Ruemmele^{12,13*}; Richard K. Russell^{1*}; on behalf of the PIBD**
14 **SETQuality consortium and PIBDnet**
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49
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51 **Key Words:** Paediatric Gastroenterology, Inflammatory Bowel Disease, Crohn's
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53 Disease, Immunomodulators
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ABSTRACT

Introduction

Immunomodulators such as thiopurines (azathioprine (AZA)/6-mercaptopurine (6MP)), methotrexate (MTX) and biologics such as adalimumab (ADA) are well established for maintenance of remission within paediatric Crohn's disease (CD). It remains unclear however which maintenance medication should be used first-line in specific patient groups.

Aims

To compare the efficacy of maintenance therapies in newly diagnosed CD based upon stratification into high and low risk groups for severe CD evolution; MTX versus AZA/6MP in low-risk and MTX versus ADA in high-risk patients. Primary end point: sustained remission at 12 months (weighted paediatric Crohn's disease activity index ≤ 12.5 and C-reactive protein ≤ 1.5 -fold upper limit) without relapse or ongoing requirement for EEN/steroids 12 weeks after treatment initiation.

Methods and Analysis

REDUCE-RISK in CD is an international multicentre open-label prospective randomised controlled trial funded by EU within the Horizon2020 framework (grant number 668023). Eligible patients (aged 6-17 years, new-onset disease receiving steroids or EEN for induction of remission for luminal +/- perianal CD) are stratified into low and high-risk groups based upon phenotype and response to induction therapy. Participants are randomised to one of two treatment arms within their risk

1
2
3 group: low-risk patients to weekly subcutaneous MTX or daily oral AZA/6MP, and
4
5 high-risk patients to weekly subcutaneous MTX or fortnightly ADA. Patients are
6
7 followed up for 12 months at pre-specified intervals. Electronic case report forms are
8
9 completed prospectively. The study aims to recruit 312 participants (176 low-risk;
10
11
12 136 high-risk).
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17 **Ethics and Dissemination**

18
19 ClinicalTrials.gov Identifier: (NCT02852694), authorisation and approval from local
20
21 ethics committees have been obtained prior to recruitment. Individual informed
22
23 consent will be obtained prior to participation in the study. Results will be published
24
25 in a peer-reviewed journal with open access.
26
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30 **Registration Details**

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33 NCT02852694; pre-results.
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38 **Strengths and limitations**

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- This is the 1st international prospective RCT comparing 3 different i medications for maintenance of remission in newly diagnosed CD
 - This study may better define the most appropriate first-line immunomodulators based upon a risk stratification protocol. .
 - Therapeutic efficacy will be supported by drug levels, pharmacogenomics and microbiome analysis as secondary outcomes.
 - Inability to blind participants or treating physicians serves as a limitation to this study.

- Blinding of an alternative clinician to assess disease activity during study visits may prove practically difficult in smaller centres.

INTRODUCTION

Crohn's disease (CD) the most common form of inflammatory bowel disease (IBD) in children is a chronic disorder with the potential to affect the whole gastrointestinal tract. The aim of CD treatment is to control active inflammation and achieve bowel healing. Chronic and uncontrolled CD results in poor outcomes for patients, including reduced quality of life, recurrent hospitalisation and potential need for surgical intervention.¹ Treatments for CD are categorised into those which induce remission (such as steroids^{1,2} or exclusive enteral nutrition (EEN)^{1,3} and those which maintain remission. Immunomodulators are a mainstay of maintenance treatment in IBD, with the efficacy of thiopurines (e.g. azathioprine (AZA) and 6-mercaptopurine (6MP))^{4,5,6}

1
2
3 and methotrexate (MTX)^{7,8,9,10} well established. Anti-tumour necrosis factor (anti-
4 TNF) therapies (infliximab^{11,12} and adalimumab (ADA)^{13,14}) including their biosimilars
5
6 were used in those patients refractory to “traditional” induction or maintenance
7
8 treatment. More recently in clinical practice patients deemed as high risk have been
9
10 treated with a biologic without the need for prior use of an immunomodulator.
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12

13
14 Due to a lack of treatment strategy trials within the paediatric IBD (PIBD) population
15
16 however, it remains unclear which of the aforementioned maintenance therapies
17
18 should be used first-line in individual patients. Randomised controlled trials
19
20 comparing the use of MTX with thiopurines for maintenance of remission failed to
21
22 show a significant difference in efficacy between the two.^{15,16, 17} A Cochrane review
23
24 in adults with quiescent CD highlighted the lack of adequately powered trials
25
26 necessary in order to determine the efficacy and safety of thiopurines compared to
27
28 other maintenance therapies^{4, 10}. The RISK study (observational, non-randomised
29
30 study) demonstrated improved clinical and growth-based outcomes at 1 year with
31
32 anti-TNF monotherapy in comparison with immunomodulators; however further
33
34 investigation into which specific patients are most likely to benefit from these
35
36 therapies is still required.¹⁸ There is a clear disparity between North America and
37
38 Europe in terms of which form of immunosuppression is used initially with both
39
40 concerns about efficacy and safety lying behind these differences, thus there is an
41
42 urgent need for a head to head study in children to help objectively inform the
43
44 primary choice of immunosuppression.
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51 Stratifying patients by risk for complex or severe CD may allow pre-emptive direction
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53 of maintenance strategy and potentially an early reduction in disease burden with
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55 subsequent improvement in long-term outcomes. The adult IBD Ahead initiative
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57 highlighted young age at diagnosis as a risk factor for severity of CD evolution¹⁹; all
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3 patients diagnosed within paediatric services would therefore be considered 'high
4 risk'. Paediatric consensus guidelines suggest that paediatric CD patients at 'high
5 risk for poor outcome' should receive early therapy optimisation to modify
6 progression of their disease.¹ The guidelines list specific features which may be
7 considered predictive for poor outcome in paediatric CD (see Table 1).¹ Patients
8 deemed at high risk for complex disease or poor outcome may benefit from a 'Top-
9 down' approach as the TISKids (a randomised controlled trial from disease diagnosis)
10 aims to investigate²⁰.

11
12 Therefore the PIBDnet consortium recognised the urgent need to investigate the
13 efficacy and safety of immunomodulators and to investigate whether a top-down
14 approach was superior to a traditional 'step-up' for paediatric patients deemed at
15 high risk for rapidly complicated disease course. REDUCE-RISK in CD is a
16 randomised controlled trial (RCT) which aims to compare the effectiveness of
17 immunomodulators for maintenance of remission in newly diagnosed CD based
18 upon risk stratification specifically, the effectiveness of MTX versus AZA/6MP for
19 maintenance of remission who are low risk for rapidly progressive disease and the
20 effectiveness of MTX versus ADA in a high risk group.

21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 **METHODS AND ANALYSIS**

46 47 48 49 **Study Design**

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53 We designed an international multicentre open-label prospective RCT with 4
54 treatment arms as shown in Figure 1. Following screening and consent, eligible
55 patients are stratified into low and high-risk groups based upon phenotype and
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3 disease response to induction therapy (Table 1). Patients are then randomised to
4
5 one of two arms within their risk group, with low risk patients receiving either weekly
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7 subcutaneous MTX or daily oral AZA/6MP and high-risk patients receiving either
8
9 weekly subcutaneous MTX or fortnightly subcutaneous ADA.
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17 **Study End Points**

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21 Patients are followed up for 12 months post randomisation. The primary end point of
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23 the study is sustained steroid or EEN-free remission at 12 months, defined as
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25 weighted Paediatric Crohn's Disease Activity Index (wPCDAI) ≤ 12.5 and C-reactive
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27 protein (CRP) ≤ 1.5 -fold upper limit without a relapse or need for EEN/steroids since
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29 week 12.
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36 Secondary end points include comparison of time to first relapse, remission at 12
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38 weeks, growth, adverse events, health related quality of life and patient reported
39
40 outcomes between the two treatment arms within each risk group but also between
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42 low and high risk MTX treated patients (a full list of secondary endpoints can be
43
44 found in box 1). The TUMMY CD (Patient related outcome measure) was originally
45
46 included as a secondary end point but has been withdrawn as the original timetable
47
48 of development and validation of the score has not been met so it was not ready in
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50 time to be included. The study also aimed to evaluate clinical predictors for response,
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52 including genomic and serological markers and results of drug monitoring (MTX and
53
54 ADA concentrations) metabolites (6-thioguanine (6-TG) and 6-methylmercaptopurine
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56 (6-MMP) in AZA/6MP) and anti-drug antibodies (ADA) in relation to adherence,
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3 toxicity and response. The ancillary study additionally aimed to evaluate the efficacy
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5 of ADA in patients treated from inclusion (Top-down) versus patients switched to
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7 ADA due to immunomodulator failure (Step-up). Further outcome measures are
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9 detailed in Box 1.
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15 16 **Box 1: Study endpoints**

17 18 **Primary Endpoint**

- 19 - Sustained steroid/EEN-free remission at month 12, where sustained remission is
20 defined as wPCDAI \leq 12.5 and CRP \leq 1.5 times the upper limit without a relapse or
21 need for EEN/steroids since week 12.
22
23

24 **Secondary Endpoints:**

25 Comparing the following within 1) the two treatment arms per risk group; 2) methotrexate
26 treatment between high and low risk groups; and 3) TOP-Down adalimumab (high risk
27 group) versus STEP-Up adalimumab (ancillary study):
28

- 29 • Rate of clinical remission at month 12 (physician global assessment (PGA),
30 wPCDAI, paediatric Crohn's disease activity index (PCDAI))
- 31 • Relapse free remission with normal CRP at month 12
- 32 • Relapse free remission with normal CRP and faecal calprotectin $<$ 300 at month 12
- 33 • Remission at week 12 (measured by wPCDAI \leq 12.5 and normal CRP and being off
34 steroids/exclusive enteral nutrition)
- 35 • Time to first relapse after week 12
- 36 • Predictive value of faecal calprotectin values at visits 1, 2, 4 and 6 (respectively at
37 month 0, 2, 6 and 12)
- 38 • Dropout rates
- 39 • Adverse drug event rate including pharmacogenomics for toxicity and response to
40 therapy
- 41 • Height velocity and z-score at baseline and 52 weeks
- 42 • Quality of life as measured by the IMPACT 3 questionnaire completed at each study
43 visit
- 44 • Health economic evaluation at all visits (forms EQ-5D-Y proxy 1, EQ-5D-Y and EQ-
45 5D-5L, WPAI:CD Caregiver, School Attendance start of the research and follow up
46 visits)
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Eligibility Criteria and Recruitment

Full eligibility criteria for the study are listed in Box 2. Patients are eligible if aged 6-17 years with new-onset (<6 months) treatment naïve luminally active and/or perianal fistulising CD diagnosed as per revised Porto criteria²¹ receiving steroids or EEN for induction of remission with wPCDAI >40 or CRP >2 times upper limit of normal at diagnosis. Eligible definitions of disease behaviour were derived from the Paris classification.²² Informed consent from must be obtained prior to participation in the study. Patients are excluded in cases of previous use of IBD related medications, pregnancy or refusal to use contraceptives; disease requiring surgery, contraindications to study medication, exposure to live vaccine within 3 weeks, oral anticoagulant or anti-malarial use, current or previous malignancy, significant infection or significant comorbidity.

The planned start date for the study is 01.2017 with planned end 06/2022.

Box 2: Eligibility criteria**Inclusion Criteria**

- Patients aged 6-17 years with new-onset (<6 months) treatment naïve active luminal and/or perianal fistulising Crohn's disease diagnosed using established criteria²¹ requiring steroids or EEN for induction of remission
- wPCDAI >40 or CRP >2 times upper limit of normal at diagnosis
- Luminal active Crohn's disease (B1) with or without B2 and/or B3 disease behaviour as per Paris classification²²
- Signed informed consent

Exclusion Criteria

- wPCDAI <42.5 at diagnosis, except where CRP >2 times upper normal limit
- Lack of induction therapy with steroids or EEN
- Previous therapy with any IBD-related medication other than induction therapy as detailed within this protocol with the exception of 5-aminosalicylic acid (5ASA) preparations
- Pregnancy or refusal to use contraceptives during the study period in pubertal patients unless absolute abstinence is confirmed at each study visit
- Lactating mothers
- Perianal fistulising disease requiring surgical therapy
- Patients homozygous for thiopurine methyltransferase (TPMT) mutations or those with TPMT activity <6 nmol/h/ml erythrocytes or <9nmol 6MTG/g Hb/h, unless they qualify as high-risk patients
- Evidence of un-drained and un-controlled abscess/phlegmon
- Contraindication to any drugs used in the trial (including intolerance/hypersensitivity or allergy to study drugs (thiopurines, methotrexate or adalimumab))
- Current or previous malignancy
- Serious comorbidities (e.g. renal insufficiency, hepatitis, respiratory insufficiency) which may interfere with drug therapy or interpretation of outcome parameters or will make it unlikely that the patient will complete the trial.
- Infection with mycobacterium tuberculosis, hepatitis B or C, human immunodeficiency virus (HIV)
- Moderate to severe heart failure (New York Heart Association class III/IV)
- Oral anticoagulant therapy, anti-malarial therapy
- Live vaccine exposure (including yellow fever) less than 3 weeks prior to inclusion

Screening Visit (Visit 0)

The screening visit allows for assessment of eligibility for inclusion in the study, evaluation of the patient's response to induction therapy if already commenced,

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3 commencement of induction therapy where not commenced, and acquisition of
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5 consent and assent.
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11 *Induction Therapy*

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15 All enrolled patients receive either corticosteroids or exclusive enteral nutrition (EEN)
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17 as induction as determined by the clinical team and the patient/caregiver. For EEN
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19 any balanced formula (polymeric or elemental) administered orally or via nasogastric
20
21 tube is permitted and should be prescribed for 6-8 weeks. Tapering of steroids is at
22
23 the discretion of the prescribing clinician. Adaptation of induction therapy (e.g. dose
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25 increase of steroids or return to EEN) or crossover from one induction therapy to the
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27 other is permitted in order to achieve remission, however patients must have
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29 discontinued their induction therapy by week 12. If induction therapy is not
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31 discontinued by week 12 the patient is considered a treatment failure, with the
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33 protocol for this detailed below.
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45 Inclusion Visit and Risk Group Allocation (week 5 +/- 3 weeks; visit 1)

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49 In order to incorporate response to initial induction therapy within the risk
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51 stratification criteria, inclusion and risk group allocation is performed at week 5 +/- 3
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53 weeks of induction therapy. Data from the screening visit is reviewed with ineligible
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55 patients excluded and patients are then stratified into the high or low risk group
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57 (Table 1) based upon the ECCO/ESPGHAN consensus guidelines¹. Patients with
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perianal fistulising disease at diagnosis are auto-allocated to the high-risk group regardless of other factors at inclusion visit. All other patients are allocated to the low risk group. Patients with low thiopurine methyltransferase (TPMT) activity or homozygous mutations are excluded should they be categorised as low risk.

DEFINING HIGH RISK CROHN'S DISEASE PATIENTS	
ECCO/ESPGHAN CONSENSUS GUIDELINES	MODIFIED STUDY CRITERIA
Severe perianal disease	Complex perianal fistulising disease phenotype
Extensive (pan-enteric) disease; deep colonic ulcers on endoscopy	Panenteric disease phenotype (defined as L3 with L4b as per Paris classification ²³ or L3 with deep ulcers in the duodenum, stomach or oesophagus not related to non-steroidal anti-inflammatory medications or <i>Helicobacter pylori</i>)
	Overall cumulative disease extent of ≥ 60 cm
Strictureing and penetrating disease at onset	B2, B3 or B2B3 disease behaviour ²⁰
Marked growth retardation > -2.5 height Z scores	Severe growth impairment (height z-score < -2 or crossing ≥ 2 centiles) likely related to Crohn's disease
Persistent severe disease despite adequate induction therapy	Hypoalbuminemia (< 30 g/L), elevated CRP (at least 2 times upper limit of normal range), or wPCDAI > 12.5 despite at least 3 weeks of optimized induction therapy with steroids or EEN
Severe osteoporosis	Not included

Table 1 – Definition of high-risk patients based upon ECCO/ESPGHAN consensus guidelines (ECCO – European Crohn's and Colitis Organisation; ESPGHAN – European Society for Paediatric Gastroenterology, Hepatology and Nutrition; CRP – C-reactive protein; wPCDAI – weighted Paediatric Crohn's Disease Activity Index; EEN – exclusive enteral nutrition)

Randomisation and Treatment Allocation

Randomisation is undertaken following allocation to high or low risk group at week 5 +/- 3 weeks. This process utilises an integrated module within the electronic case report form (CRF) system. Within both the high and low risk groups patients are 1:1 randomised to MTX versus ADA or AZA/6MP respectively in blocks of four stratified by EEN or steroid induction therapy. Code for randomisation is prepared and held by the central coordinating site and site co-ordinators are then informed of the results. Immunomodulator or biologic therapy should be commenced within 2 weeks of randomisation as per the protocol outlined in Table 2.

AZA/6MP and MTX are prescribed and dispensed according to local guidelines. ADA (Humira ®) is provided by AbbVie. Co-interventions are prohibited.

	Therapy	Route	Dose	Notes
LOW RISK PROTOCOL	Methotrexate	SC	15mg/m ² body surface area weekly (max dose 25mg)	Ondansetron 4-8mg orally 1 hour pre injection and folic acid 15mg (5mg in patients <20kg) 3 days post injection are recommended for all patients
	VERSUS			
	Azathioprine	PO	2.5mg/kg (rounded down to nearest 12.5mg)	Half calculated dose for TPMT heterozygotes/activity 6-9nmol/h/ml
HIGH RISK PROTOCOL	OR			
	6-Mercaptopurine	PO	1.5mg/kg (rounded down to nearest 12.5mg)	Half calculated dose for TPMT heterozygotes/activity 6-9nmol/h/ml
	Methotrexate	SC	15mg/m ² body surface area weekly (max dose 25mg)	Ondansetron 4-8mg orally 1 hour pre injection and folic acid 15mg (5mg in patients <20kg) 3 days post injection are recommended for all patients
HIGH RISK PROTOCOL	VERSUS			
	Adalimumab (Humira ®)	SC	160mg then 80mg after 2 weeks then 40mg every 2 weeks thereafter (patients >35kg) 120mg then 80mg after 2 weeks then 40mg every 2 weeks thereafter (patients 25-35kg) 80mg then 40mg after 2 weeks and 20mg every 2 weeks thereafter (patients <25kg)	

Table 2: Medication protocol for low and high-risk patients following randomisation (TPMT – thiopurine methyltransferase)

Follow Up Visits (Visit 2, 3, 4, 5 and 6)

Patients are followed up at pre-specified intervals (Figure 1) with a window of +/- 2 weeks. A telephone call is undertaken at week 4 following initiation of induction in order to support patient compliance with induction regime and advise weaning where appropriate. Data as described in Box 3 are collected at each consultation. Patients' compliance with therapy is determined at each face-to-face follow up visit by pill and vial counts plus by patients' reporting.

Box 3: Standard requirements for each study visit

- An explicit history of illness since last visit, including review of symptoms, medications (including compliance check) and adverse events.
- Physical examination
- wPCDAI, PGA and PCDAI scoring
- Anthropometrics (height measured using a calibrated wall mounted stadiometer)
- Blood tests
 - White blood cells
 - Absolute neutrophil count
 - Haemoglobin
 - Haematocrit
 - Platelet count
 - Erythrocyte sedimentation rate (ESR)
 - C-reactive protein (CRP)
 - Amylase
 - Albumin
 - Aspartate transaminase (AST)
 - Alanine transaminase (ALT)
 - Conjugated bilirubin
 - Gamma glutamyl transferase (GGT)
- Stool samples for faecal calprotectin and microbiome analysis
- Health economic parameters (EQ-5D-Y proxy 1; EQ-5D-Y; EQ-5D-5L; WPAI:CD; school attendance questionnaire)
- Quality of life evaluation (IMPACT 3)
- Urine human chorionic gonadotropin (hCG) in all female patients of child-bearing potential
- Confirmation of contraception use or of absolute abstinence in all patients

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7 Remission is defined as wPCDAI \leq 12.5, normal CRP (\leq 1.5 times upper normal
8 range) and being free of steroids or EEN. Once remission is achieved and induction
9 therapy is discontinued, a patient is considered to be failing treatment or
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14 experiencing a relapse in the following circumstances:

- 15
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17 • wPCDAI $>$ 40
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19 • CRP $>$ 2 times upper normal limit in the absence of any clear infectious
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21 process
- 22
23 • wPCDAI $>$ 12.5 but $<$ 40 and/or CRP $>$ 1.5 times but $<$ 2 times over upper
24
25 normal limit at 2 consecutive visits within 2-8 weeks
- 26
27 • Development of CD related complications e.g. fistulisation
- 28
29 • Requirement for additional CD-specific medication/surgery since last study
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32
33 visit

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37 A patient will also be considered a treatment failure should induction therapy be
38 continued at week 12. In addition, the treating clinician may escalate treatment at
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40 any time point independent of wPCDAI score if it is felt that the patient is
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42
43
44 experiencing a relapse.

Dose Optimisation and Therapeutic Drug Monitoring

Drug monitoring is undertaken as detailed below. In addition to this, samples for drug monitoring should be collected at the time of medication cessation in the event of drug discontinuance due to adverse effect or loss of response. Potential adaptations to therapies which may be made at specific follow up visits are detailed in Box 4.

Box 4 – Potential adaptations to therapies at follow up visits

Month 2 (Visit 2)

- Failure to discontinue induction therapy by week 12
 - Offer switch to the ancillary study (ADA STEP-up) to those prescribed MTX or AZA/6MP, or an increase in dose frequency to weekly in those prescribed ADA
 - Alternatively, the patient may leave the study and receive therapies as per the discretion of the treating clinician.

Months 4, 6, 9 and 12 (Visits 3, 4, 5 and 6)

- Thiopurine non response
 - Protocol as per metabolite levels (detailed in Table 3)
- Thiopurine intolerance (except pancreatitis)
 - Switch to alternate thiopurine (AZA to 6MP or vice versa) or split dose to provide twice daily (BD) dosing
- Thiopurine failure (any exacerbation despite dose optimisation/pancreatitis/cytopaenia)
 - Offer switch to ancillary study (ADA STEP-up) or exit study
- MTX intolerance or failure (any exacerbation or elevation of liver enzymes as detailed below)
 - Offer switch to ancillary study (ADA STEP-up) or exit study
- ADA failure (any exacerbation)
 - Increase frequency to weekly dosing

Azathioprine

RESULT	ACTION
6-TG <150	Consider non-compliance; repeat sample at subsequent visit and increase dose if low 6-TG confirmed (+25mg or +12.5mg if dose <50mg)
6-TG 150-800	No adaptation
6-TG >800	Decrease dose if repeat sample at subsequent visit confirms high 6-TG (-25mg or -12.5mg if dose <50mg)
6-MMP >8000 or signs of hepatotoxicity	Stop medication – switch to ancillary study Erythrocyte lysate sample frozen at -80C and shipped to central lab at end of study for thiopurine nucleotides

Table 3 – Azathioprine dose adjustments based upon metabolite levels

TPMT genotype or phenotype at screening determines the initial dose of AZA/6MP; and measurement of thiopurine metabolites (6-thioguanine (6-TG) and 6-methylmercaptopurine (6-MMP)) at visit 2 determines requirement for subsequent dose adjustment performed according to the recommendations in Table 3. Where possible thiopurine metabolites are measured locally; central lab measurements are provided for centres where this is unavailable.

At visit 2 a urine sample for TPMT metabolite determination and an erythrocyte lysate sample for quantification of Thiopurine Nucleotides by Liquid Chromatography-Tandem Mass Spectrometry should be frozen at -80°C and shipped on dried ice to the central lab at the end of the study. At each visit from visit

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3 2 to 6, an additional EDTA blood sample will be collected for further 6-TG and 6-
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5 MMP testing and frozen at -80C.
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11 12 *Methotrexate*

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16 Washed erythrocyte for MTX levels will be obtained at visits 2, 4 and 6 and stored
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18 frozen at local centres. These samples will be sent on dry ice for central analysis to
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20 evaluate response to therapy and adverse effects in relation to drug levels.
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27 28 *Adalimumab*

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31 Adalimumab trough levels are measured after 3 injections of maintenance therapy
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33 (e.g. at visit 2) within the local laboratory (central lab testing available if local lab
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35 testing is unavailable). Dosing interval may be shortened to weekly in the event of
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37 low ADA levels (<8 mcg/ml) and negative ADA antibodies. Further samples should
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39 be obtained at visits 3, 4, 5 and 6 and should be frozen for later analysis within the
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41 central lab.
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49 50 *Pharmacogenetics*

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53 DNA for pharmacogenetics should be taken from patients randomised to MTX or
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55 AZA/6MP for multiplex genotyping of polymorphism related to drug metabolism to
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57 evaluate safety and response to therapy. Analysis will be performed at the end of the
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59 study, or earlier in those patients showing toxicity.
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Ancillary Study

Patients unable to discontinue induction therapy or those randomised to thiopurine or MTX therapy who experience treatment failure may be invited to participate in the ancillary study (STEP-up ADA) until visit 5. Any initial maintenance therapy will be stopped and induction and maintenance regime for ADA as previously described will be commenced. Up to 3 additional study visits at 3-month intervals will be offered to these patients in order to obtain 12 months of follow up. A maximum of 68 patients can participate in this ancillary study allowing a 1:1 comparison of TOP-down ADA to STEP-up ADA therapy.

Unscheduled Visits

Unscheduled visits may be arranged based upon clinical requirements. As for scheduled visits per protocol treatment adaptations are possible if intolerance or failure of the study drug is detected. Subsequent scheduled visits will not be changed after an unscheduled visit.

Treatment Discontinuation

Patients who discontinue treatment before completing 12 months of study drug within either the main study or the ancillary study will receive a single follow-up visit. This will be either 12 months after the commencement of study treatment or at the point of inclusion in the ancillary study.

Modifications to the protocol while the study is being conducted will be relayed to all site staff by email and then onto their relevant ethical and regulatory boards. The current manuscript is based on protocol 5.1 last modified 28th May 2019.

Allocation Concealment and Blinding

For ethical reasons we decided against a double dummy design for blinding the patient, parents and care givers. Due to the differences in medication administration route and the significant nausea commonly associated with MTX blinding of the allocation to the patients, their families or their physicians is not possible. Where possible however, blinding of an alternative clinician to score the wPCDAI, PCDAI and PGA at each study visit should occur (prospective randomized open blind end-point (PROBE) evaluation).

Safety

The external and independent Advisory Board of PIBDSETQuality serves as an independent Data and Safety Monitoring Board which meets at pre-specified intervals with access to all data within the study. The principal investigator at each site is responsible for reporting any safety issues (adverse events, serious adverse events (SAEs), suspected unexpected serious adverse reactions), drop-outs, or any new information which may impact the study in any way. The principal investigator shall report to the sponsor all SAEs experienced by a study subject receiving an Adalimumab (Humira) within 24 hours of learning of the event regardless of the relationship of the event to the product. All SAEs are immediately sent to AbbVie pharmacovigilance by the sponsor. SAEs will be followed from the date of patient's signature of informed consent, until complete resolution or 30 days after the end of the study/patient's final study visit.

Box 5 – Criteria for premature termination of study treatment or participation

- Pregnancy at any stage
- Treatment failure as per protocol
- Failure to tolerate allocated treatment or alternatives as listed within the protocol
- Significant drug related side effects manifesting as significantly abnormal bloods results or adverse effects based upon the clinical judgement of the treating physician
- Request of participant to be withdrawn from treatment
- The judgement of the treating physician being that it is in the best interests of the participant to withdraw from study treatment
- Loss of participant to follow up
- Patient death

Participants may withdraw consent for further participation or data collection at any time without giving reason and without prejudicing further care or treatment. Patients will be permanently withdrawn from study treatment in the event of any of the situations outlined in Box 5. Patients should be provided with a study alert card for use in the event of an emergency.

Biochemical markers are monitored with a clearly defined protocol for adjustments to therapy based on abnormal results (e.g. neutropenia, pancreatitis, elevated liver enzymes).

Data Collection, Management and Monitoring

Patient CRFs are completed in a prospective manner using an electronic web-based system designed specifically by PIBDnet for this trial. In order to maintain data

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3 security and integrity, the web-based data entry will be linked to a password secured
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5 Microsoft Access database, where data will be stored until time of analysis. Files will
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7 be saved on a code secured net-drive and backed-up following each data entry on a
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9 disk locked in a cabinet. Patients will be identified only by a study code assigned at
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11 the point of enrolment. Code of patient identifiers will be kept at each participating
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13 site. Handling of patient-identifiable is compliant with the legislation of each
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15 participating centre and the European General Data Protection Regulation (GDPR).
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17 Investigators will be invited to fax or email the paper source document to the
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19 coordinating site on a random basis to allow appropriate monitoring. Access to data
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21 with detailed information on study outcomes will be made available to other research
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23 groups on request and at the discretion of the principal investigators.
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30 Monitoring arrangements are in place for all sites after initial site initiation. The
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32 monitoring visits will occur regularly partly dependant on recruitment rate at
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34 individual sites. The monitoring is performed usually by someone external to the
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36 clinical team.
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40 **Analysis and Statistical Methods**

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43 Descriptive statistics (mean, median, standard deviation, standard error, quartiles,
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45 minimum, maximum, and two-sided 95% confidence limits of mean and median) will
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47 be presented for each treatment of the low and high risk paediatric CD groups and
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49 where applicable, for the paired difference of each patient. Frequency tables will be
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51 presented where applicable.
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60 **Primary Analysis**

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Difference in the 12-month steroid/EEN free sustained remission rates between the treatment groups will be undertaken using Chi square test. Mantel Haenzel test will be used to combine data from all participating sites.

Secondary Analyses

Chi-square tests or Fisher's exact tests will be used to compare rates of remission, steroid intake, dropout and serious adverse events between the two arms of each risk group and between the low and high risk MTX groups. Logistic regression analyses may be performed to adjust for any imbalances in baseline covariates. To compare time to disease flare between the arms of each risk group and between high and low risk MTX groups, a Kaplan–Meier survival estimate will be used and the log-rank test of equality over strata. A Cox proportional hazard model will be constructed to obtain a hazard ratio after validation of the proportionality assumption and adjusting for possible confounding variables (including age and disease duration). Student's t tests or Wilcoxon rank sum tests will be used to compare growth, steroid dose, adverse events, changes in quality of life and patient reported outcomes between the two arms of each risk group and between the high and low risk MTX groups. The predictive value of faecal calprotectin levels, CRP, serum tests or other clinical predictors for response (including genomic and serological markers) will be assessed for each arm of the study using sensitivity, specificity, negative and positive predictive values or area under the ROC curve. Multivariate logistic regression analyses will then be performed.

Analyses will be performed using the R software (<http://cran.r-project.org>). All comparisons will be made using a 2-sided significance level of 0.05.

Sample Size Considerations

Estimated remission rates are based on recent analysis from the RISK study¹⁸, indicating an advantage of early anti-TNF introduction over immunomodulator therapy. For the low risk group, it was hypothesized that 48% of children will be in remission at 12 months for the AZA/6MP arm versus 70% for the MTX arm. On the basis of this data with an alpha risk of 5% and a power of 80% a sample requirement of 88 patients per arm was calculated assuming a 10% loss of follow up. For the high-risk group, it was hypothesised that 40% of children will be in remission at 12 months for the MTX arm versus 65% for the adalimumab arm. To detect this difference with an alpha risk of 5% and a power of 80%, a sample size of 68 participants is necessary, again assuming a 10% loss of follow-up. In total 312 participants will be included in the study (176 low-risk group; 136 high risk group).

Patient and Public Involvement

Patients were not involved in the development of this study; however, the French patient charity AFA Crohn, RCH, France was involved in study design and critically reviewed and commented upon all aspects of the trial.

Discussion

REDUCE-RISK in CD is the first multicentre international RCT aiming to compare three different medication strategies for maintenance of remission in newly diagnosed CD based upon a risk stratification protocol. During the 12-month follow up period the effects of the differing management strategies will be assessed via data collected and outcome measures as defined above in order to analyse the efficacy and safety of each medication and better define the most appropriate first-line maintenance immunomodulators to be used in specific subsets of CD patients. As a group we speculatively hypothesise that MTX will be superior to thiopurines for maintaining remission in CD in the low risk group although in the absence of head to head studies prior to this one this study will provide randomised data to address this. Additionally, from our own work and others we know response to induction therapy is an important prognostic marker and we wanted to allow the induction treatment to have a chance to work before we assigned high or low risk status.^{24,25} Thus it was a pragmatic compromise with the timing of introduction of the maintenance treatment to give the induction treatment long enough to show its effect while recognising both treatments have a “lag period” of a few weeks before they become fully effective.

We also hypothesise that ADA will be superior to MTX in the high-risk group based upon the results from the RISK study.¹⁸ Of note Adalimumab (Humira) was chosen to allow delivery of the study out of hospital, to reduce drug costs and it allowed single therapies to be compared with each other. Practically if we had used

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3 Infliximab (Remicade) then we would have needed to use combination therapy which
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5 we did do not want to do as it would have further complicated the trial design.

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8 In addition to this, the ancillary study will compare outcomes in ADA treated patients
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10 from inclusion (Top-down) versus patients switched to ADA due to failure of
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12 immunomodulators (Step-up), with the potential to stratify which patients might
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14 benefit from such a top-down treatment strategy. We acknowledge that comparison
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16 of the ancillary group with the group randomised from baseline to ADA is not
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18 randomised and may be subject to selection bias noting the ancillary group have
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20 failed or been intolerant to initial therapy. However we feel it is important to include
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22 this to allow us to compare the trial with studies which have allocated patients
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24 directly to anti-tnf (RISK, TISKids) and to see how many patients benefit from
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26 “rescue therapy” after failure of their initial allocation.
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33 The design and completion of interventional studies in PIBD is a recognised
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35 challenge between rigorous study design methodology and pragmatic considerations
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37 around feasibility and completion within a paediatric dataset.²³ This particular study
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39 is limited by the inability to blind the treatment allocation to the patients, their families
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41 or their treating physician due to the differences in medication administration route
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43 and the side effects commonly associated with the study medication. Although the
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45 protocol advises that where possible blinding of an alternative clinician to score
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47 disease assessment at each study visit should occur in order to obtain prospective
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49 randomized open blind end-point (PROBE) evaluation this may be practically difficult
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51 in smaller centres where staff are familiar with the majority of their patient cohort.
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ETHICS AND DISSEMINATION

The study is being conducted according to the principles of the Declarations of Helsinki and to date has been approved by all participating sites as listed within supplementary Table 1. Clinical trials authorisation and ethics approval has been obtained from the local ethics review committees of these participating nations and centres. The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines²⁶ were adhered to in the production of the protocol for this trial (see uploaded material for details).

Consent

Patients and their caregivers are provided with study-specific information including an explicit description of the study outline and alternatives for participation. It is made clear to all patients approached that declining to participate in the study will not jeopardize the quality of subsequent care received. After a period of consideration, if agreeable, the patient's parent or caregiver is asked to sign consent forms with age-appropriate assent obtained from the child where relevant (see appendix 1 for model consent forms). The signed forms are filed within the patient's medical record with a copy provided to the participant and their caregiver. Consent will be obtained by site staff with the relevant training and who are identified as assigned on the delegation log. Participants taking part in the ancillary study will not be re-consented.

Dissemination

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3 Results of the study will be submitted for publication within a peer-reviewed journal.

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5 In accordance with the H2020 general grant agreement, the dissemination process
6
7 will ensure open access to the scientific publications resulting from this project.

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10 Journal authorship guidelines will be adhered to and there are no plans to use
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12 professional writers.
13

14 15 16 17 **AUTHOR CONTRIBUTIONS**

18
19 RH prepared the draft manuscript with comments and review from all authors.

20
21 RKR, MA, LR, NC, SK, AL, DT, GV, MN and LB and FMR were involved in the
22
23 conception, design, planning and then drafting of the original research protocol and
24
25 RKR, RH, MA, LR, NC, SK, AL, DT, GV, MN and LB and FMR provided critical
26
27 review of the manuscript and approved the final uploaded draft.
28
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31 As sponsor PIBDnet has full responsibility and control for the original study design,
32
33 collection, management, analysis, and interpretation of data, including writing of the
34
35 report and the decision where to submit the report for publication.
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37

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54
55 entérologie, Hôpital Necker Enfants Malades, 149 rue de Sèvres, 75015 Paris,
56
57 France).
58
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60

COMPETING INTERESTS

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Remaining authors: nil competing interests declared.

FIGURE LEGENDS

Figure 1 – Study Design of the REDUCE-RISK in CD trial

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M2 = Month 2, V2 = visit 2.

For peer review only

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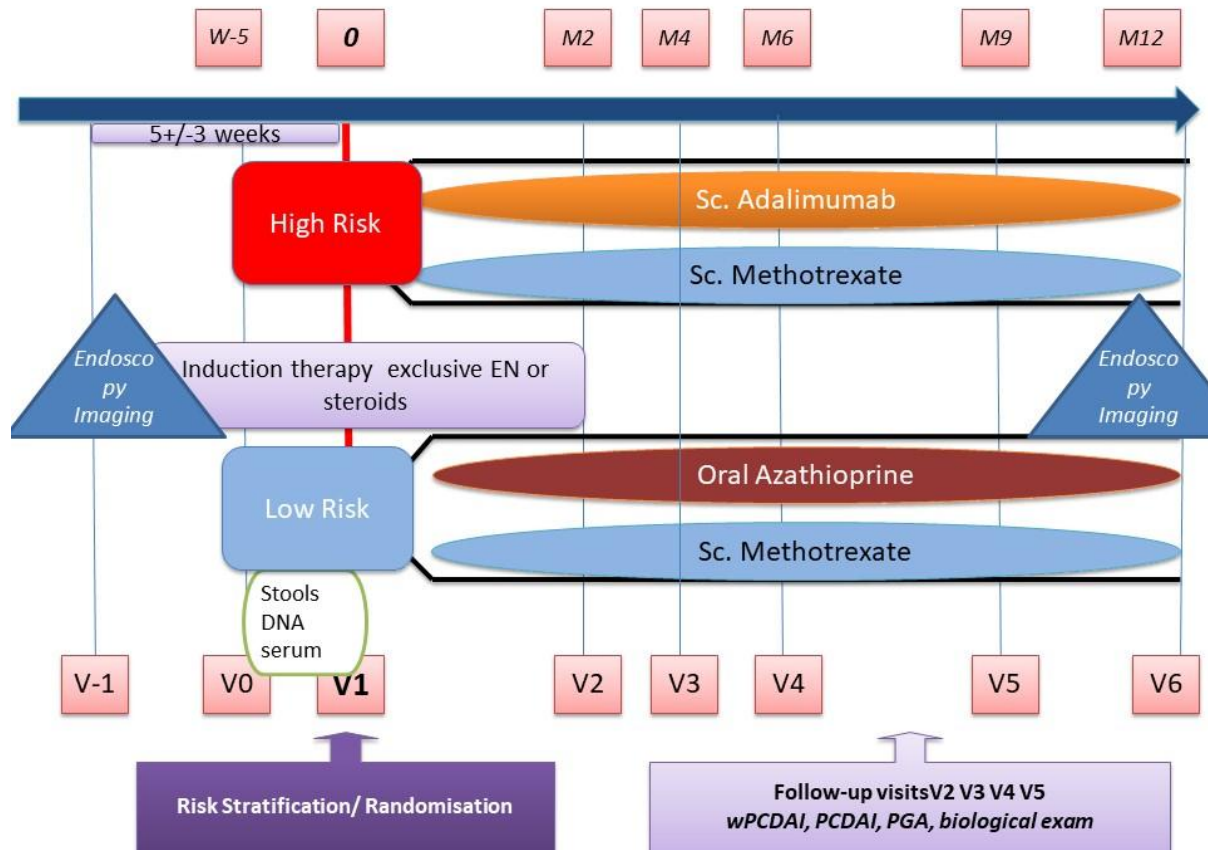


Figure 1 – Study Design of the REDUCE-RISK in CD trial

Participating Sites – REDUCE-RISK in CD Study			
Country	City	Site	Ethics committee
Belgium	Brussels	Universitair Ziekenhuis	Commissie Ethiek, UZ Brussel
	Brussels	Clinique Saint Luc UCL	
	Liège	Clinique de l'Espérance	
	Brussels	HUDERF	
Canada	Toronto	SickKids	SickKids Research Ethics Board, Toronto
Czech Republic	Prague	FN Motol	Eticka Komise, Plzen Eticka Komise, VFN Praha Eticka Komise, FN Motol Praha
	Plzeň	FN Plzeň	
	Prague	First Medical Faculty	
France	Paris	Hôpital Necker Enfants Malades	CPP Hôpital Necker, Paris
	Paris	Hôpital Robert Debré	
	Paris	Hôpital Armand Trousseau	
	Le Havre	Hôpital Jacques Monod	
	Nancy	Hôpitaux de Brabois	
	Toulouse	Hôpital des Enfants	
	Tours	Hôpital Clocheville	
	Caen	CHU Caen Côte de Nacre	
	Marseille	Hôpital de la Timone	
Germany	Munich	Childrens Hospital	Ethikkommission LMU, München
	Ulm	Universitätsklinikum	
	Hannover	MHH Kinderklinik	
	Giessen	UKGM	
	Berlin	Charite Hospital	
Greece	Athens	Children's Hospital "AGIA SOFIA"	Ethics Committee, Athens
Israel	Jerusalem	Shaare Zedek Medical Center	Helsinki Committee, Schneider Medical Center, Petah Tikva Ethics and Research Committee, Wolfson Medical Center, Tel Aviv Institutional Review Board, SZMC, Jerusalem
	Tel Aviv	Wolfson Medical Center	
	Petah Tikva	Schneider Children's Medical Center	
	Ramat Gan	Sheba Medical Center	
	Haifa	Rambam Medical Center	
Italy	Rome	Università degli Studi di Roma La Sapienza	Comitato Etico dell'Universita' "SAPIENZA", Roma Comitato Etico Regionale per la Sperimentazione Clinica della Regione Toscana Sezione, Firenze Comitato Etico, Servizio Sainuario Regionale, Bologna
	Bologna	Maggiore Hospital	
	Florence	Azienda Ospedaliero Universitaria	
	Parma	Azienda Ospedaliero	
	Rome	Opsedale Pediatrico Bambino Gesù	
Netherlands	Rotterdam	Erasmus Medical Center	Medische Etische Toetsings Commissie, Erasmus MC,

			Rotterdam
Poland	Warsaw	Centrum Zdrowia MDM	Bioethical Commission at the Institute of Polish Mother's Health Center, Lodz
	Białystok	Uniwersytecki Dziecięcy Szpital Kliniczny	
	Łódź	Instytut Centrum Zdrowia Matki Polki	
United Kingdom	Glasgow	The Royal Hospital for Children	North West - Liverpool East Research Ethics Committee, NHS, Manchester
	London	Royal London Children's Hospital, Barts Health NHS Trust	
	Edinburgh	Sick Children's Hospital	
	Birmingham	Children's Hospital	
	Oxford	John Radcliffe Hospital	

Supplementary Table 1 – Sites participating in REDUCE-RISK in CD



INFORMED CONSENT FORM

Parents/Guardian Informed Consent Form for Participation of a Minor in a Clinical Trial

Risk-stratified randomized controlled trial in paediatric Crohn's Disease: Methotrexate versus azathioprine or adalimumab for maintaining remission in patients at low or at high risk for aggressive disease course, respectively – a treatment strategy.

Dear parents,

Your child's doctor, Dr....., working at Hospital, propose your child to participate in a clinical trial related to its disease.

It is important to read this note carefully before taking any decision. Do not hesitate to ask the physician all the questions you may have about it.

The participation of your child is based on volunteering. Therefore, your child can refuse to participate or stop its participation in the trial at any time, all of this without prejudice to the patient's right to receive the standard treatment.

If you refuse your child to participate, he/she will still receive the best medical support.

Purpose of the research and trial's objectives

Your child has just been diagnosed with Crohn's disease. The disease is characterised by chronic inflammation of the digestive track (bowel/colon). This disease changes over between remission period and relapse period. There are efficient drugs able to prevent relapse and to maintain remission. In order to reduce the likelihood of long-term complications, induction treatment has already been prescribed to your child. This first treatment has to be followed up by a maintenance treatment that will be introduced to avoid the inflammation from returning. Consensus guidelines of ECCO / ESPGHAN (french and european IBD specialized organizations) recommend 3 efficient treatments: either immunosuppressive treatment with Thiopurines (azathioprine and 6-mercaptopurine), or Methotrexate or anti TNF (adalimumab).

So far, no clinical trial has been conducted to compare those 3 treatments in children with Crohn's disease and to answer the following question: "Which treatment is the most efficient, for which patient and/or in which situation?"

Progression of Crohn's disease is not the same for all patients. That's why this study will first classified all children in high and low risk groups based on more or less severe course of Crohn's disease. The lower risk group will be randomized (which is like tossing a coin) to receive either thiopurines or methotrexate as maintenance treatment. The high risk group will be randomized to receive either methotrexate or adalimumab. Results will show whether there is different efficiency between the 3 drugs for patients with a more or less severe disease.

Sponsor

PIBD-Net (www.pibd-net.org) is a global, international and non-profit organisation gathering physicians and researchers specialised in inflammatory bowel diseases. The acronym stands for Pediatric Inflammatory Bowel Diseases Network and it is present in 31 countries (Europe, North America, Australia and Japan). This organisation is dedicated in improving the medical care of children with inflammatory bowel disease through the establishment of clinical researches.

PIBD-Net and partners received funding from European Commission for Horizon 2020 program (project no.668023) in order to perform this research.

The approximate number of participants and duration of follow-up

A total of 312 new-onset children with Crohn's disease (136 in that high-risk group and 176 in the low risk) will be enrolled in many sites around the world. The period of recruitment is 45 months and your child will be followed up for 12 months after enrolment.



What will happen to your child during the trial?

If you agree to have your child participating in this study, your child will be first directed into one of two groups based on certain predictors of its disease (such as its location and severity). You will know which group your child is in. Next, your child will be randomized to receive maintenance treatment namely:

- **METHOTREXATE or AZATHIOPRINE for the low risk group ;**
- **METHOTREXATE or ADALIMUMAB for the high risk group ;**

You cannot choose the treatment group but you will know which drug your child will receive.

You will not be asked to come to clinic just because of this study which is designed to mirror regular follow-up in clinic. After signing the informed consent allowing your child to be part of this research, your child will have clinic visit every 2 months during the first 6 months and then every 3 months during the last 6 months. At each visit, a clinic examination is performed and blood, urine and stool samples are collected (this process follows our standard clinical practices of our patients not involved in this protocole).

Your doctor, your child and yourself will be asked to complete short questionnaires to evaluate the quality of life of your child. Most of the recorded data for this study is needed anyway as part of a regular visit but there might be a few more questions we will ask you for this study.

We will also contact you over the phone at week 4 to ask how your child feels regarding its Crohn's disease, whether your child has any bad reactions to the medications your child will receive and check your child compliance to the treatment.

To optimize the medications we prescribe, we will draw 12 ml (3-4 teaspoons) of blood at inclusion visit, 10ml at visit V2, and then 5ml at each next study visits to measure the level of the medications your child will receive. A urine sample will be collected at inclusion visit and a DNA sample (either 5ml of blood or buccal swab) will be collected at the beginning of the study, and also in case of drug intolerance.

We will also collect your child stool (poop) six times during the year to measure the amount of inflammation in its bowel as well as bacteria flora in its intestine.

We will evaluate whether the drugs work based on

- completed questionnaires
- clinic examination
- results of biological samples

Optional Ancillary study (« ADA STEP-up »)

In case of failing (intolerance or relapse) of your child immunomodulator therapy (: either azathioprine/6MP or methotrexate), your child will be invited to participate in the ancillary study. If you agree, your child will be prescribed adalimumab during 12 months.

This adalimumab treatment can increase the study duration by a maximum of 9 months, meaning a maximum of 3 additional visits. Those visits are identical to the regular follow up study visits.

The expected benefits to the participant or to others because of the trial

The medications your child will receive in this study are not experimental and thus there are no direct benefit for using these drugs that are available outside of the study. However, your child will be monitored closely to ensure optimization of the treatment by adapting drug amounts based on new analyses (urine, DNA, blood and stool samples). In addition, patients involved in this study have access to molecular analyses in order to better understand why a patient is less responsive than expected. That might result in a more tight control of the disease and better monitoring of the treatment of your child.



After study completion, we will have the required data to recommend how to use these medications in new children who develop Crohn's disease.

Risks added by the research

As previously mentioned, all medications used in this trial are not experimental and are being used very often in clinical practice in children/adolescents and adults with Crohn's disease. There is no additional risk compares to regular clinical practices. The known risks and discomfort that may be anticipated are listed below.

Known risks and discomfort that may be anticipated

The medications yourchild will receive in this study are not experimental but used in regular practices. They can also be associated with side effects (all described in the corresponding drug information sheet).

- ✗ **METHOTREXATE: weekly subcutaneous (under the skin)** This drug may be associated with side effects mainly in the day of the injection including flu-like symptoms, nausea, vomiting, headache or fatigue. Your child will be asked to take a vitamin called folic acid which will reduce these non-dangerous side effects. This injection may cause slight discomfort.METHOTREXATE may cause reduced blood counts, especially white blood cells and elevated liver enzymes. Thoses parameters will be checked regularly. In this study, molecular analyses will be performed to screen patients who can't tolerate METHOTREXATE..This drug causes an unusual sensitiveness to the sun (however, there is no data stating that it increases the risk of cancer or lymphoma). METHOTREXATE can cause foetal abnormalities so pregnancy is not allowed and efficient contraceptive is essential (for both male and female).
- ✓ **AZATHIOPRINE (or 6MP): to be taken orally.** THIOPURINES may cause reduced blood counts, especially white blood cells and elevated liver enzymes. Thoses parameters will be checked regularlyIn this study, molecular analyses will be done in order to screen patients who can't tolerate those drugs. In some rare cases (<3%), the drug may cause inflammation in the pancreas which is usually mild and not dangerous. As all drugs, THIOPURINES can't be tolerated by some patients due to allergy. Approximately 10% of children will not tolerate the drug because of nausea, vomiting, tummy pain, diarrhea, headaches or fever..THIOPURINES are associated with an increased infectious risk (about 1%). Infections are likely cause.. by viruses. In rare cases, THIOPURINES may increase risk for blood cancer called lymphoma (especially for patients > 65 year old).—This drug causes an unusual sensitiveness to the sun and can be associated with skin cancer in case of significant sun exposure.

ADALIMUMAB: subcutaneous (under the skin) injections every 2 weeks Adalimumab is associated with minor pain during the injection and local reactions could appear with minimal significance..ADALIMUMAB is associated with an increased infectious risk. However, serious infections are uncommon. Before starting ADALIMUMAB treatment, tuberculosis must be excluded. With time, the effect of adalimumab may wain as a result of the development of antibodies against the drug. Skin inflammatory damages (such as « psoriasis ») were observed in some patients. Anti TNF drugs have been closely monitored since their use as standard treatment. Those drugs may be responsible of heart failure for patients with severe heart disease, hepatitis, decreasing blood cells, demyelinating neurologic disease, or lupus (without affecting main organs). In addition, some cases of cancer have been notified in patient treated by ADALIMUMAB, but risks of cancer is slightly increased only for melanoma. Number of cancer seems not to be increased compared to patients with Crohn's diseases and without being treated with those drugs.

Circumstances under which participation in the medical trial may be discontinued in accordance with the decision of the investigator or the Sponsor:

- a. The doctor has the right to take your child out of the study at any time. This will be made after clinical considerations, your child's side effects from the drugs, intolerance to the drugs or lose of response.
- b. Regulatory authorities (Ministry of Health or Ethics committee), may stop your child participating in the study.



An explanation of alternative treatments, their advantages and disadvantages, if any, for the participant:

The current standard therapy for maintenance therapy in Crohn's disease is either METHOTREXATE or thiopurines or anti-TNF biologics for the more severe Crohn diseases. This is exactly the medications given also as part of this study. The difference is that instead letting you and the doctor choose between the options, the choice is standardized based on predictive variables of your disease and randomization. If you choose not to have your child participating in the study, your child will likely receive anyway one or more of these three drugs. The only exception would be that if anti-TNF is prescribed, either adalimumab or infliximab can be given and as part of this study your child will receive adalimumab only. However, your child will not have access to molecular analyses described in this protocole with a close monitoring of drug safety. Indeed, those 'new' analyses are not done in the standardclinical practise of Crohn's disease.

If you participate in this study, what will you have to do more than usual ?

If you agree to have your child participating in this study, please make sure to follow the listed points belowPlease come at your appointments with your child. If not possible, please inform its physician as soon as possible

- Please ensure that your child takes the treatment as instructed by its doctor
- Please inform the physician involved in the study of any event happening during the research (such as hospitalization,...)
- Your child must not participate in any other clinical trial that involves the use of an investigational product throughout the course of this trial. It is to avoid accidents such as possible interactions between medicines.

Biological samples collected during this research project

If you agree to have your child participating in this research, additional blood, urine and stool samples will be collected at the same time as our standard clinic samplings. Please see below:

- ✓ 10ml of blood during inclusion visit (on randomisation day).
- ✓ 5ml of blood (PAX tube) during inclusion visit for RNA analyses
- ✓ 10ml of blood at follow up visits M2 (2 months after inclusion)
- ✓ 5 ml of blood at follow up visits M4, M6, M9 and M12 (4, 6, 9, 12 months after inclusion)
- ✓ Stool sample at inclusion visit and follow up visits M2, M4, M6, M9 and M12 (2, 4, 6, 9, 12 months after inclusion visit).
- ✓ A DNA sample will be collected at inclusion visit and in case of intolerance of one of the drugs for DNA analyses.
- ✓
- ✓ Urine sample (15ml) will be collected at M2 visit (2 months after inclusion).

Those samples will be sent to specialized laboratories in order to be used to perform specific studies such as adalimumab, methotrexate, thiopurine analyses and serology, genetic (both DNA and RA), microbiology studies. They will also be re-used for further testing on Crohn's disease, its diagnosis and its treatment as well as efficacy and tolerance by molecular ("omic") analyses.

At any time, you can request to your clinician to have those biological samples destroyed or not to be used for further researches.

Confidentiality

As part of biomedical research in which PIBD-Net sponsor proposes your child's participation, treatment of personal data will be set up to analyse results of this research based on its aim. Therefore, your child medical data and quality of life will be transferred to PIBD-Net sponsor. Those data will be anonymous and identified by a coded number and its initials. Those confidential data could be transferred to local and foreign authorities. If your child has to be withdrawn for any reasons, collected data prior its withdrawal will be used unless you do not want



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2
3 them to. Then, you will have to inform the physician accordingly.
4

5 According to the EU General Data Protection Regulation (GDPR) dated on 26May2018, you have the right to
6 access to your child and your personal data, modify them and oppose the use of your child and your data. You
7 have also the right to request that your child and your personal data are erased, are limited in use, and to ask for
8 a complete copy of all data collected from you and your child for the study. You can contact the Data Privacy
9 Officer (DPO) of the sponsor at any time at dpo@pibd-net.org for any request regarding your child and your
10 personal data.
11

12 Data collected for the study are transferred outside of the EU, as our database is based in Israel. However, we
13 guarantee that data protection will be as strict as requested by GDPR.
14

15 **Voluntary participation**

16 Your participation in this research is entirely voluntary. It is your choice whether to have your child participating or
17 not, all the services your child receives at this hospital will continue and nothing will change. If you choose not to
18 participate in this research project, your child will be offered the treatment that is routinely offered in this hospital
19 for Crohn's disease. You may change your mind later and stop participating even if you agreed earlier.
20
21

22 **Right to refuse or withdraw**

23 Your child does not have to take part in this research if you do not wish to do so and refusing to participate will not
24 affect its treatment in any way. Your child will still have all the benefits that it would otherwise have at this
25 hospital. You may stop participating in the research at any time that you wish without losing any of its rights as a
26 patient here. Its treatment at this hospital will not be affected in any way.
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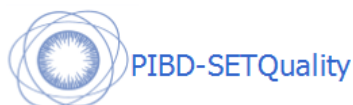
29 **Alternatives to participating**

30 If you do not wish that your child takes part in the research, your child will be provided with the established
31 standard treatment available at this hospital.
32

33 **Reimbursement**

34 There is no reimbursement for participating in this study. There are no special visits to the hospital excepted
35 during this study. All DNA, blood, urine and stool samples will be taken at the time of a routine clinic visit.
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40 **This proposal has been reviewed and approved by [name of the local IRB], which is a committee whose**
41 **task it is to make sure that research participants are protected from harm.**
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Informed consent form

We, the undersigned :

M, Miss, (*name, first name of parent/legal guardian*)

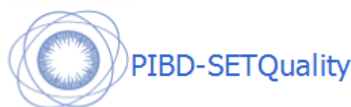
M, Miss, (*name, first name of parent/legal guardian*)

I, M, Miss,(*name, first name of parent*) hereby declare that my consent below has been given voluntarily and that I have understood all of the above. I undertake to also inform the child's father/mother (*please cross off as appropriate*) of my consent for the participation of our child in the clinical trial. If the child's father/mother (*please cross off as appropriate*) does not agree to affix his/her consent to mine, I undertake to inform the physician in-charge and to withdraw my consent for the participation of my child in the clinical trial. I have also received a lawfully and dated copy of this informed consent form

I agree that my child (*name, first name of the child*).....**takes part of the study named** "*Risk-stratified randomized controlled trial in paediatric Crohn's Disease : Methotrexate versus azathioprine or adalimumab for maintaining remission in patients at low or at high risk for aggressive disease course, respectively – a treatment strategy* ", managed by PIBD Net. It has been explained to us by (*name, first name of explaining investigator /sub investigator, phone,*).....

.....physician in this clinical trial.

- We hereby declare that we agree for our child to participate in the clinical trial as detailed in this document
- Our child has been informed and agreed to take part of this clinical trial.
- We had the opportunity to ask all the questions we had to the physician who explained potential risks and constraints linked to our child participation in this clinical trial.
- We received appropriate answers to all our questions
- We hereby declare that at the time of signing this document, our child is not participating in another clinical trial that involves the use of any investigational product, and that we undertake that our child will not participate in any other clinical that involves the use of an investigational product throughout the course of this trial.
- We declare that our child has a health insurance.
- .We hereby declare that we are free to choose that our child will not participate in the clinical trial, and that we are free to stop our child participation in the trial at any time, and all of this without prejudice to our child's right to receive the standard treatment. Then, we will inform the physician whether data collected prior our decision can be used or not.
- We have been informed that the doctor has the right to take our child out of the study at any time, if needed.
- That in case of completing a questionnaire – we are entitled not to answer all or some of the questions in the questionnaire.
- We are informed that samples collected during this clinical trial will be kept and used for further testing on Crohn's disease. We can decide at any time not to have those samples used by informing our child physician.
- That we are guaranteed confidentiality concerning the identity of the patient and that of the parents/guardians. This confidentiality will be kept by all those concerned with and involved in the clinical trial, and their identity will not be disclosed in any publication.
- That the Medical Institution has arranged for appropriate insurance coverage of the investigators, physicians and medical staff involved in the clinical trial, against claims filed by clinical trial participants and/or third party claims related to the clinical trial, either during the course of the trial or thereafter. This is



without prejudice to our rights under the law.

- That in case of pregnancy during the course of the clinical trial, the girl/woman will be counselled (by the principal investigator) concerning the possible effects on the foetus and the fate of the pregnancy, including the possibility of discontinuing the pregnancy.
- We hereby declare that our below consent has been given voluntarily and that we have understood all of the above mentioned. We also received a lawfully signed and dated copy of this informed consent.
- By signing this consent form, we authorize the sponsor of the clinical trial, the Institutional Helsinki Committee, the auditing entity at the Medical Institute and the Ministry of Health direct access to the patient's medical file, to verify the clinical trial methods and the clinical data. This access to our child medical information will be performed with confidentiality maintained, according to the laws and procedures of maintaining confidentiality.
- We declare that we are informed and give our approval to receive all information related to our child participation in this clinical trial. We know that data will only be used for treatment and follow up cares
- We hereby declare that we know and agree to have the information on our child's participation in the clinical trial provided to his/her attending physician at the HMO/Health care Services with which our child is insured, in case the clinical trial involved the provision of services : performing medical examinations or supplying devices or products or implants. We know that the HMO will not use this information for purposes other than medical treatment and follow up

I agree to have my child participating in the ancillary study (« ADA STEP-up »)

Yes

No

[please tick]

<u>Signature of parents or guardians/representatives of the patient</u>	<u>Signature of the child</u>
Name, First Name : _____	Name, First Name : _____
Date : _____	Date : _____
Signature : _____	Signature : _____
Name, First Name : _____	
Date : _____	
Signature : _____	

Declaration of the Investigator/Sub-Investigator : This consent was obtained by me after I have explained all the above mentioned to the parents (or guardians) of the clinical trial participant and ensure that all my explanations were understood by them.

Investigator/Sub-investigator' Signature :

Name, First Name: _____

Date: _____

Signature : _____



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This is a triplicate document. First / original copy to be kept by the investigator for 15 years, second copy to be given to parents or legal guardians, third copy to be kept in Investigator files (under sealed envelope).

For peer review only



Informed consent for Genetic Analyses

Hereby declare that we agree for genetic examinations of our child to study genes involved in tolerance / non tolerance of the drugs by molecular (“omic”) analyses and analyses of drug efficacy in Crohn disease’s patients.

Hereby declare that we agree that all recorded data collected during this trial including genetic data can be processed by the sponsor or acting as sponsor. I understand that, as stipulated in the General Data Protection Regulation, I can access, modify, erase or ask for a copy of my child’s personal data and my personal data at any time, by asking to the investigator who will contact the sponsor.

We can decide not to participate anymore in the genetic part of the trial by informing our doctor who will inform the sponsor.

Yes No *[please tick]*

Hereby declare that we agree that all biological samples collected during this trial can be used for future genetic research on Crohn’s disease.

Yes No *[please tick]*

Parents/guardians Signature:

Investigator Signature:

Name, First name:

Name, First name:

Date : Signature :

Date : Signature :

Name, First name:

Date : Signature :

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. *Ann Intern Med.* 2013;158(3):200-207

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	Throughout manuscript
Protocol version	#3	Date and version identifier	21
Funding	#4	Sources and types of financial, material, and other support	30
Roles and responsibilities:	#5a	Names, affiliations, and roles of protocol contributors	1,2,30

1 contributorship

2 Roles and [#5b](#) Name and contact information for the trial sponsor 29
 3 responsibilities:
 4 sponsor contact
 5 information
 6
 7

8
 9 Roles and [#5c](#) Role of study sponsor and funders, if any, in study 30
 10 responsibilities:
 11 sponsor and funder design; collection, management, analysis, and
 12 interpretation of data; writing of the report; and the
 13 decision to submit the report for publication,
 14 including whether they will have ultimate authority
 15 over any of these activities
 16
 17

18
 19 Roles and [#5d](#) Composition, roles, and responsibilities of the 23,30
 20 responsibilities:
 21 coordinating centre, steering committee, endpoint
 22 adjudication committee, data management team,
 23 and other individuals or groups overseeing the trial,
 24 if applicable (see Item 21a for data monitoring
 25 committee)
 26
 27

28 Introduction

29
 30
 31 Background and [#6a](#) Description of research question and justification for 6-8
 32 rationale undertaking the trial, including summary of relevant
 33 studies (published and unpublished) examining
 34 benefits and harms for each intervention
 35
 36
 37

38 Background and [#6b](#) Explanation for choice of comparators 6-7
 39 rationale: choice of
 40 comparators
 41
 42

43 Objectives [#7](#) Specific objectives or hypotheses 8-10
 44

45 Trial design [#8](#) Description of trial design including type of trial (eg,
 46 parallel group, crossover, factorial, single group),
 47 allocation ratio, and framework (eg, superiority,
 48 equivalence, non-inferiority, exploratory)
 49
 50
 51

52 Methods:

53 **Participants,**
 54 **interventions, and**
 55 **outcomes**
 56
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1	Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Supplemental table 1
2				
3				
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8	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	10-12
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15	Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	15-16
16				
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20	Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	18, 19,22
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27	Interventions: adherence	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	19-21
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32	Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	13,23
33				
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36	Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-10
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49	Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	See figure 1 8,12,15,16-19
50				
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55	Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions	27
56				
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supporting any sample size calculations

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2
3 Recruitment [#15](#) Strategies for achieving adequate participant enrolment to reach target sample size Not listed
4
5

6 **Methods:**

7 **Assignment of**
8 **interventions (for**
9 **controlled trials)**
10
11

12
13 Allocation: sequence [#16a](#) Method of generating the allocation sequence (eg, 15,16,22
14 generation computer-generated random numbers), and list of
15 of any factors for stratification. To reduce predictability
16 of a random sequence, details of any planned
17 restriction (eg, blocking) should be provided in a
18 separate document that is unavailable to those who
19 enrol participants or assign interventions
20
21

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23
24 Allocation [#16b](#) Mechanism of implementing the allocation 22
25 concealment sequence (eg, central telephone; sequentially
26 mechanism numbered, opaque, sealed envelopes), describing
27 any steps to conceal the sequence until
28 interventions are assigned
29
30

31
32
33 Allocation: [#16c](#) Who will generate the allocation sequence, who will 15
34 implementation enrol participants, and who will assign participants
35 to interventions
36
37

38 Blinding (masking) [#17a](#) Who will be blinded after assignment to 22
39 interventions (eg, trial participants, care providers,
40 outcome assessors, data analysts), and how
41
42

43 Blinding (masking): [#17b](#) If blinded, circumstances under which unblinding is N/A
44 emergency permissible, and procedure for revealing a
45 unblinding participant's allocated intervention during the trial
46
47

48 **Methods: Data**
49 **collection,**
50 **management, and**
51 **analysis**
52
53

54
55 Data collection plan [#18a](#) Plans for assessment and collection of outcome, 24-25
56 baseline, and other trial data, including any related
57 processes to promote data quality (eg, duplicate
58
59

1		measurements, training of assessors) and a	
2		description of study instruments (eg, questionnaires,	
3		laboratory tests) along with their reliability and	
4		validity, if known. Reference to where data	
5		collection forms can be found, if not in the protocol	
6			
7			
8			
9	Data collection plan:	#18b Plans to promote participant retention and complete	Not listed
10	retention	follow-up, including list of any outcome data to be	
11		collected for participants who discontinue or deviate	
12		from intervention protocols	
13			
14			
15	Data management	#19 Plans for data entry, coding, security, and storage,	25
16		including any related processes to promote data	
17		quality (eg, double data entry; range checks for data	
18		values). Reference to where details of data	
19		management procedures can be found, if not in the	
20		protocol	
21			
22			
23			
24			
25	Statistics: outcomes	#20a Statistical methods for analysing primary and	25-26
26		secondary outcomes. Reference to where other	
27		details of the statistical analysis plan can be found,	
28		if not in the protocol	
29			
30			
31			
32	Statistics: additional	#20b Methods for any additional analyses (eg, subgroup	26-27
33	analyses	and adjusted analyses)	
34			
35			
36	Statistics: analysis	#20c Definition of analysis population relating to protocol	26
37	population and	non-adherence (eg, as randomised analysis), and	
38	missing data	any statistical methods to handle missing data (eg,	
39		multiple imputation)	
40			
41			
42	Methods:		
43	Monitoring		
44			
45			
46	Data monitoring:	#21a Composition of data monitoring committee (DMC);	23
47	formal committee	summary of its role and reporting structure;	
48		statement of whether it is independent from the	
49		sponsor and competing interests; and reference to	
50		where further details about its charter can be found,	
51		if not in the protocol. Alternatively, an explanation of	
52		why a DMC is not needed	
53			
54			
55			
56			
57			
58	Data monitoring:	#21b Description of any interim analyses and stopping	23
59			
60			

1	interim analysis		guidelines, including who will have access to these	
2			interim results and make the final decision to	
3			terminate the trial	
4				
5	Harms	#22	Plans for collecting, assessing, reporting, and	23
6			managing solicited and spontaneously reported	
7			adverse events and other unintended effects of trial	
8			interventions or trial conduct	
9				
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11				
12	Auditing	#23	Frequency and procedures for auditing trial conduct,	24
13			if any, and whether the process will be independent	
14			from investigators and the sponsor	
15				
16				
17	Ethics and			
18	dissemination			
19				
20				
21	Research ethics	#24	Plans for seeking research ethics committee /	4
22	approval		institutional review board (REC / IRB) approval	
23				
24				
25	Protocol	#25	Plans for communicating important protocol	22
26	amendments		modifications (eg, changes to eligibility criteria,	
27			outcomes, analyses) to relevant parties (eg,	
28			investigators, REC / IRBs, trial participants, trial	
29			registries, journals, regulators)	
30				
31				
32				
33	Consent or assent	#26a	Who will obtain informed consent or assent from	29-30
34			potential trial participants or authorised surrogates,	
35			and how (see Item 32)	
36				
37				
38				
39	Consent or assent:	#26b	Additional consent provisions for collection and use	No additional
40	ancillary studies		of participant data and biological specimens in	consent see
41			ancillary studies, if applicable	page 30
42				
43				
44	Confidentiality	#27	How personal information about potential and	24
45			enrolled participants will be collected, shared, and	
46			maintained in order to protect confidentiality before,	
47			during, and after the trial	
48				
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51	Declaration of	#28	Financial and other competing interests for principal	30
52	interests		investigators for the overall trial and each study site	
53				
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55	Data access	#29	Statement of who will have access to the final trial	Not provided
56			dataset, and disclosure of contractual agreements	
57			that limit such access for investigators	
58				
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1	Ancillary and post	#30	Provisions, if any, for ancillary and post-trial care,	N/A
2	trial care		and for compensation to those who suffer harm from	
3			trial participation	
4				
5				
6	Dissemination policy:	#31a	Plans for investigators and sponsor to communicate	29
7	trial results		trial results to participants, healthcare professionals,	
8			the public, and other relevant groups (eg, via	
9			publication, reporting in results databases, or other	
10			data sharing arrangements), including any	
11			publication restrictions	
12				
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16	Dissemination policy:	#31b	Authorship eligibility guidelines and any intended	29
17	authorship		use of professional writers	
18				
19				
20	Dissemination policy:	#31c	Plans, if any, for granting public access to the full	Not planned
21	reproducible		protocol, participant-level dataset, and statistical	
22	research		code	
23				
24				
25	Appendices			
26				
27	Informed consent	#32	Model consent form and other related	Appendix 1
28	materials		documentation given to participants and authorised	
29			surrogates	
30				
31				
32				
33	Biological specimens	#33	Plans for collection, laboratory evaluation, and	Not provided
34			storage of biological specimens for genetic or	
35			molecular analysis in the current trial and for future	
36			use in ancillary studies, if applicable	
37				
38				
39				

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