

**SCIENTIFIC PROTOCOL FORM 4B**

**For studies not classified as Clinical Trials**

*Studies not classified as Clinical Trials may include recruitment and procedures conducted on human participants, but will generally not involve assessments of the efficacy/safety of drugs or other therapeutic or investigational products (including medical devices)*

**Investigators who choose to submit a full scientific protocol may do so BUT MUST ENSURE that the protocol includes all the information requested in FORM 4A or FORM 4B. Investigators who choose to submit a protocol can also complete the (appropriate) form and insert a reference to the relevant section of the Scientific Protocol, *e.g.* Background information Form 4B Section 2.1*****Provide a summary of findings from previous studies, relevant to this proposed study***

***Answer: “Refer to section xxx### of attached Clinical Study Protocol.”***

**1. GENERAL INFORMATION**

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| --- |
| *1.1 Name, title, address, telephone numbers/email addresses of the* ***Chief Investigator*** *- the person responsible for overseeing the conduct of the study on PMH sit****e*** |
| **1**. Surname: | GROVER | Given Name | ZUBIN | Title | DR |
| Qualifications relevant to the study | MBBS MD FRACPConsultant in Paediatric Gastroenterology and Clinical Lead in Inflammatory Bowel disease |
| Role in this study | Study Design , Data Collection, Coordination of the project, Data Analysis and writing up the Project |
| Mailing Address: | Gastroenterology Department , PMH Subiaco |
| Telephone | 93408882 | Email Address | zubin.grover@health.wa.gov.au |

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| *1.2 Name, title, address, telephone numbers/email addresses of the*  ***Contact Person on the PMH site*** *- the person to whom correspondence about this application should be directed (if different from above)* |
| **2**. Surname: |  | Given Name |  | Title |  |
| Qualifications relevant to the study |  |
| Role in this study |  |
| Mailing Address: |  |
| Telephone |  | Email Address |  |

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| --- |
| *1.3 Name, title, address, telephone numbers/email addresses of all* ***other investigators*** *involved with this trial* |
| **3**. Surname: | Ravikumara | Given Name | Madhur | Title | Dr |
| Qualifications relevant to the study | MBBS MRCP FRACP |
| Role in this study | Reviewing Study design , Data Collection, and assistance in writing up the Project |
| Mailing Address: | Gastroenterology Department , PMH Subiaco |
| Telephone | 93402228 | Email Address | Madhur.Ravikumara@health.wa.gov.au |

|  |  |  |  |  |  |
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| **4**. Surname: | Mews | Given Name | Cathy | Title | Dr |
| Qualifications relevant to the study | MBBS FRACP |
| Role in this study | Data Collection, |
| Mailing Address: | Gastroenterology Department , PMH Subiaco |
| Telephone | 93402228 | Email Address | catherine.mews@health.wa.gov.au |

**2. BACKGROUND INFORMATION**

***2.1 Provide a summary of findings from previous studies, relevant to this proposed study***

Crohn’s disease (CD) is a chronic relapsing inflammatory bowel disease (IBD) frequently resulting in progressive damage to the gastrointestinal tract. (1) Cohort studies comparing the natural history of paediatric vs. adult onset CD confirms it’s more aggressive nature with extensive intestinal involvement, rapid progression and increased disease activity index, year by year, despite use of more immunosuppression (1-3). These observations demand the need for both better treatment endpoints and interventions in the paediatric population.

The conventional therapeutic end points for Crohns disease (CD) have relied on patient reported symptoms. Paediatric Crohns disease activity index (PCDAI) is the most widely used clinical tool that relies heavily on self-reported symptoms including abdominal pain, diarrhoea and wellbeing. Escalating or de-escalating immunosuppressive treatments according to symptom based indices leads to significant risk of both over-treating patients for symptoms that are non-inflammatory (no ulcers on endoscopy) in origin (irritable bowel syndrome) and undertreating patients with minimal symptoms but significant intestinal inflammation. Adult studies report up to 70% of CD patients with significant ulceration on endoscopy report no symptoms, yet these patients remain at high risk of progressive intestinal damage (4, 5). In addition treatment of patients with high risk, high cost drugs based on symptoms and without good supporting evidence of inflammation is futile, leading to unacceptable benefit: risk ratio. Ultimately, current treatment targets are to avoid disease relapse, hospitalisation and progressive intestinal damage leading to surgical resection.

Multiple studies have confirmed benefits of achieving mucosal healing (MH), and the finding of MH on serial endoscopy is associated with reduction in CD related surgery and hospitalisations (6-8).

US FDA now demands repeat endoscopy to establish the therapeutic efficacy of any new CD related treatments as a best measure to document reduction in inflammation in conjunction with symptom control (9).

Panel of international Paediatric IBD experts have also endorsed this approach and recommend post intervention endoscopies to measure outcomes in CD drug trials (10) .This treatment strategy is integrating into routine clinical care and is referred as a “treat-to-target” approach. This approach recommends a follow up Ileo-colonoscopy before and/or after making a change in treatment to ensure improvement or resolution of inflammation (mucosal healing) in addition to control of symptoms (11-12)

Prospective paediatric studies are few but accumulating evidence suggest that early repeat endoscopy to confirm mucosal healing is feasible and leads to better patient outcomes in CD at 1, 2 and 3 years in those achieving healing of the intestinal mucosa. (13-15)

Treat to target is integrating into routine clinical management of CD but repeat endoscopy is invasive, particularly in children and requires detailed validation of surrogate biomarkers with endoscopic measures of mucosal inflammation. Serum CRP and Faecal Calprotectin (FC), singly and more so in combination have emerged as the two most reliable surrogate biomarkers of mucosal inflammation. Adult endoscopic studies report poor correlation of endoscopic disease activity (SES-CD) with symptom based score (CDAI). Serum CRP (r=0.53) and stool calprotectin (r=0.75) were more reliable in predicting mucosal inflammation (16). Similar, detailed quantitative analysis of paediatric symptom based scores (PCDAI) and established proxies like CRP and FC following interventions is limited to our small study including 24 children with a new diagnosis CD (17). We demonstrated individual reliability of symptom based scores (PCDAI), serum CRP and stool calprotectin in predicting mucosal healing

Patient reported symptom score (PCDAI) were, as predicted, the least reliable, serum CRP had moderate utility and FC had the best individual utility predicting mucosal inflammation. Despite limitations of small size, we confirmed that of 13/24(54%) children with active ulcers on follow up endoscopy; 80% reported minimal or no symptoms; 40% had no symptoms and with normal bloods but only 10% had normal faecal calprotectin (FC) showing the superior sensitivity of FC. In addition, a composite score combining all three proxies (PCDAI, CRP, FC) significantly improved reliability in predicting mucosal healing.

These results need to be replicated in larger studies and in more clinical scenarios than just after initial induction therapy for new patients, in particular in patients with established CD at varying stages of clinical decision making.

Therefore the aims of our proposed multicentre study is to systematically compare individual and composite reliability of PCDAI, CRP and FC in predicting endoscopic disease activity in a large sample of children undergoing clinically indicated endoscopy, at different stages of CD activity both after initial induction therapies and at other stages of clinical decision making.

***2.2 If applicable, provide a summary of known and potential risks and benefits, if any, to human subjects.***

Repeat endoscopy to measure reduction or resolution of inflammatory load in children with Crohns disease is gradually integrating into our routine clinical practise. The clinical scenarios where repeat endoscopy is generally performed at our institute include confirmation of early MH (week 8-12) after commencement of induction therapies, prior to significant changes in treatment strategies such as escalation of immunosuppression (in particular commencement of long term biologic therapies) in those with suspected relapse and de-escalation of immunosuppressive therapies in those thought to be in deep remission (absence of symptoms and absence of intestinal inflammation).

Potential benefits of repeat endoscopy in CD are obvious with accurate measurement of intensity of inflammation before escalating immunosuppression and avoiding overtreatment in those with abdominal symptoms which are non-inflammatory in nature. In addition, emerging evidence suggest that treatment adjustments made following early repeat endoscopic assessments is associated with superior clinical outcomes. (12)

In contrast, there are potential risks for repeating endoscopy. Risks of serious complication from paediatric colonoscopy performed under intravenous sedation and general anaesthesia are although rare. The common adverse events include transient hypoxia in 0.28%, bleeding 0.4% and perforation 0.01%. All endoscopies at our institute are performed under general anaesthesia further minimising risk of transient hypoxia which is 8 times more common in those undergoing these procedures under IV sedation (18).

The positive implications of this project are providing clinicians managing children with paediatric CD, a detailed validation of non-invasive proxies (CRP, FC, and PCDAI) in a large sample size with potential of mitigating the need for repeated endoscopic monitoring. The potential benefits to patients are closed direct determination of inflammatory disease activity before introducing high risk, high cost immunosuppressive drugs.

***2.3 Description of, and justification for investigational interventions or evaluations on human subjects, if any:***

All children with suspected CD routinely undergo clinical, laboratory and endoscopic assessment at diagnosis. Follow up clinical and laboratory tests (both blood and faecal markers) are also part of routine clinical service delivery. Confirmation of mucosal healing with repeat endoscopy is already integrated into our clinical practice and remains the commonest indication (~35%) for colonoscopy in children attending PMH. Therefore, the only investigational intervention of our proposed study is to ensure symptoms based score; stool and serum biomarkers are performed opportunistically within two weeks of clinically indicated endoscopy and an independent, central, blinded review of endoscopy images.

***2.4 Statement that the study will be conducted in compliance with the protocol, GCP and the application regulatory requirements.***

Endoscopic reassessment of mucosal inflammation will be at the discretion of the treating gastroenterologist and some patients may decline a follow up endoscopy or may be unable to perform routine clinical laboratory test within time expected time frame. However, it will be made clear to all subjects and their families that medical care will not be contingent on recruitment into the study and that they are free to withdraw from the study at any time without effect on their ongoing medical care. As a part of good clinical practice, children and families willing to participate in the study will be asked to repeat, back to the researchers, their understanding of participation in the study.

*2.5 If applicable, describe the population to be studied*

We expect to prospectively enrol 90 children with either new diagnosis or established CD (≤16 years), from two participating Children’s Hospital (Princess Margaret Hospital for children and Lady Cilento Children’s Hospital, Brisbane).

Treatment at diagnosis or during maintenance therapy will not be dictated by protocol and will be at the discretion of the treating specialist.

Enrolled patients will be asked to provide routine blood and faecal samples for assessment of biomarkers (CRP, FC) to assess treatment response within two weeks of the scheduled colonoscopy. Endoscopic disease activity will be scored using a validated simple endoscopic score for Crohns disease at the time of procedure and de-identified images will be evaluated by an independent, central, blinded review process.

*2.6 Reference to literature and data that are relevant to the study, and that provide*

*background for the study*

1. Baert F, Moortgat L, Van Assche G, et al.Mucosal healing predicts sustained clinical remission in patients with early- stage Crohn’s disease. Gastroenterology 2010; 138:463-68.
2. Schnitzler F, Fidder H, Ferrante M, et al. Mucosal healing predicts long-term outcome of maintenance therapy with infliximab in Crohn's disease. Inflamm Bowel Dis 2009; 15:1295–1301.
3. [Frøslie KF](http://www.ncbi.nlm.nih.gov/pubmed?term=Fr%C3%B8slie%20KF%5BAuthor%5D&cauthor=true&cauthor_uid=17681162), [Jahnsen J](http://www.ncbi.nlm.nih.gov/pubmed?term=Jahnsen%20J%5BAuthor%5D&cauthor=true&cauthor_uid=17681162), [Moum BA](http://www.ncbi.nlm.nih.gov/pubmed?term=Moum%20BA%5BAuthor%5D&cauthor=true&cauthor_uid=17681162), etal. Mucosal healing in inflammatory bowel disease: results from a Norwegian population-based cohort. [Gastroenterology.](http://www.ncbi.nlm.nih.gov/pubmed/17681162)2007; 133:412-22.
4. [Modigliani R](http://www.ncbi.nlm.nih.gov/pubmed?term=%22Modigliani%20R%22%5BAuthor%5D), [Mary JY](http://www.ncbi.nlm.nih.gov/pubmed?term=%22Mary%20JY%22%5BAuthor%5D), [Simon JF](http://www.ncbi.nlm.nih.gov/pubmed?term=%22Simon%20JF%22%5BAuthor%5D), et al. Clinical, biological, and endoscopic picture of attacks of Crohn's disease. Evolution on prednisolone. Grouped'EtudeThérapeutique des Affections Inflammatoires Digestives. Gastroenetrology 1990; 98:811-818.
5. [Bhattacharya A](https://www.ncbi.nlm.nih.gov/pubmed/?term=Bhattacharya%20A%5BAuthor%5D&cauthor=true&cauthor_uid=27753691)1, [Rao BB](https://www.ncbi.nlm.nih.gov/pubmed/?term=Rao%20BB%5BAuthor%5D&cauthor=true&cauthor_uid=27753691), [Koutroubakis IE](https://www.ncbi.nlm.nih.gov/pubmed/?term=Koutroubakis%20IE%5BAuthor%5D&cauthor=true&cauthor_uid=27753691), et al. Silent Crohn's Disease Predicts Increased Bowel Damage During Multiyear Follow-up: The Consequences of Under-reporting Active Inflammation. [Inflamm Bowel Dis.](https://www.ncbi.nlm.nih.gov/pubmed/27753691) 2016 Nov;22(11):2665-2671.
6. Baert F, Moortgat L, Van Assche G, et al. Mucosal healing predicts sustained clinical remission in patients with early- stage Crohn’s disease. Gastroenterology 2010; 138:463-68.
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8. Frøslie KF, Jahnsen J, Moum BA, et al. Mucosal healing in inflammatory bowel disease: results from a Norwegian population-based cohort. Gastroenterology. 2007; 133:412-22.
9. William Sandborn, The Present and Future of Inflammatory Bowel Disease Treatment, [Gastroenterol Hepatol (N Y)](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4969780/). 2016 Jul; 12(7): 438–441.
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15. [Kang B](https://www.ncbi.nlm.nih.gov/pubmed/?term=Kang%20B%5BAuthor%5D&cauthor=true&cauthor_uid=27095752)1, [Choi SY](https://www.ncbi.nlm.nih.gov/pubmed/?term=Choi%20SY%5BAuthor%5D&cauthor=true&cauthor_uid=27095752)1, [Kim HS](https://www.ncbi.nlm.nih.gov/pubmed/?term=Kim%20HS%5BAuthor%5D&cauthor=true&cauthor_uid=27095752)2, et al. Mucosal Healing in Paediatric Patients with Moderate-to-Severe Luminal Crohn's Disease Under Combined Immunosuppression: Escalation versus Early Treatment. [J Crohns Colitis.](https://www.ncbi.nlm.nih.gov/pubmed/27095752) 2016 Nov;10(11):1279-1286. Epub 2016 Apr 19.
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**3. study Objectives and Purpose**

*3.1 Provide a detailed description of the objectives and the purpose of the study.*

The objective of our study is to assess the reliability of non-invasive proxies; Symptom based Score (PCDAI), C reactive Protein (CRP) and stool biomarker Faecal Calprotectin (FC) for predicting endoscopic inflammatory disease activity for children undergoing clinically indicated Ileocolonoscopy.

The purpose of this research is to enhance patient monitoring and care by validating a composite score utilising both subjective and objective markers to measure treatment success and mitigate need for repeated endoscopic monitoring.

**4. STUDY DESIGN**

**The scientific integrity of the study and the credibility of the data depend substantially on the study design. A description of the study design, should include:**

*4.1**A specific statement of the primary outcomes and the secondary outcomes, if any, to be measured during the study.*

The primary and secondary outcomes of our study are:

1. To compare individual performance of PCDAI, CRP and FC with simple endoscopic disease score (SES-CD) in children with CD undergoing elective endoscopy at diagnosis and during maintenance therapy.

 b) To prospectively validate the reliability of a composite score (PCDAI ≤10, CRP < 5mg/dl and FC <500 μgram/gm or ≥ 50% drop from baseline FC whichever is less) in predicting mucosal healing, defined as simple endoscopic score for CD (SES-CD =0-2) in children undergoing repeat endoscopy.

**Hypothesis**

In a previous small single centre study of 24 children with new diagnosis CD, we confirmed symptoms based score alone (PCDAI) was unreliable, blood test (CRP) had moderate utility and stool biomarkers (FC) had the best individual utility in predicting endoscopic mucosal healing. We also demonstrated that combination of PCDAI ≤10, CRP < 5mg/dl and FC <500 μgram/gm has greater accuracy identifying mucosal healing (SES-CD 0-2) following standard EEN or Steroid induction therapy with specificity of 85% and positive like hood ratio 5.3. The reliability of this composite score (PCDAI ≤10, CRP < 5mg/dl and FC <500 μgram/gm) in this small pilot study needs further validation in a larger prospective multicentre cohort study. To overcome limitations of this pilot study, we also want to extend this study to include; children with established CD experiencing clinical relapse, those in clinical remission with raised surrogate biomarkers (CRP>5mg/L and/or FC > 250 μgram /gm of stool) and confirming mucosal healing in those with normal surrogate markers (CRP<5mg/L and FC < 250 μgram /gm of stool and no symptoms. Our hypothesis is that establishing reliability of this composite index in predicting endoscopic healing in this mixed sample population will be useful both as a discriminative tool (for distinguishing active (SES-CD≥3) vs. inactive inflammation (SES-CD= 0-2) and evaluative tool (for defining treatment success).

**Study Definitions, Protocol and Analysis**

**Study definition:**

Clinical remission will be defined as Paediatric Crohns Disease Activity Index (PCDAI) ≤10; Biochemical remission, CRP<5mg/dl. PCDAI >30 moderate to severe Paediatric CD. (13)

Endoscopic disease activity will be determined by the endoscopist at time of procedure using the validated Simple Endoscopic Scoring for CD (SES-CD). Endoscopic disease activity will be defined as inactive (0-2), mild (3-6) moderate (7-15) and severe (>15). To minimize inter-observer variability, endoscopic images and detailed patient report will be collected systematically and stored and read by independent central readers blinded to clinical and biochemical results. To minimise variability, the first morning stool sample will be used to determine level of FC. In order to minimise bias, endoscopic scores will be scored by the investigator blinded to the results of other objective and subjective variables. Performance of paired PCDAI, CRP, and FC will be evaluated against SES-CD using ROC curve analysis. Faecal Calprotectin (FC) will be measured by a quantitative enzyme immunoassay. It is unclear if a change from baseline or a standard cutoff value FC best reflects treatment response , but available data suggest cutoff values > 250 μgram /gm is strongly associated with mucosal inflammation and can be used as a guide to consider serial colonoscopy.

Performance of Composite score PCDAI<10, CRP<5mg/L, FC<500 µgram/gm in confirming endoscopically inactive disease (0-2) will be further reviewed in this large cohort.

*4.2 A description of the type/design of study to be conducted and if applicable, a schematic diagram of study design, procedures and stages.*

Design:

In this prospective cohort study, enrolled patients will be asked to provide routine blood and faecal samples for assessment of biomarkers (CRP, FC) within two weeks of the clinically indicated Ileocolonoscopy. Endoscopic disease activity will be scored using a validated simple endoscopic score for Crohns disease at the time of procedure and de-identified images will be stored for later evaluation by an independent, central, blinded review process.

In this study, we investigate the individual and combined reliability of symptoms, biomarkers (CRP, FC) with a validated endoscopic inflammatory index at three common clinical scenarios.

a) Children undergoing elective endoscopy for confirmation of early MH after commencement of induction therapies (Usually EEN or steroids).

b) Prior to significant changes in treatment strategies such as escalation of immunosuppression therapies (in particular commencement of long term biologic therapies) in children with suspected disease relapse.

c) De-escalation of immunosuppressive therapies in those thought to be in deep remission (absence of symptoms and absence of intestinal inflammation).

Therefore the only investigational intervention of our proposed study is to ensure symptoms based score, stool and serum biomarkers are performed concurrently (within two weeks) of elective scheduled endoscopy done for above indications.

Schematic diagram:

**Study Protocol version 2 June 2017:**

**1. New Diagnosis CD**

**Post induction endoscopy for confirmation of MH**

**Baseline**

* PCDAI
* CRP
* FC (Calprotectin)
* Endoscopy(SES-CD)
* Mini- index

**At 12 weeks**

* PCDAI
* CRP
* FC
* Repeat Endoscopy
* Mini-index

Choice of therapy based on physician & patient discretion

**Induction:**

EEN/Steroids 8 weeks **+/-**

**Maintenance:**

Azathioprine or Methotrexate

**2. Established Paediatric CD undergoing clinically indicated Ileocolonoscopy**

Record indication for Colonoscopy

* Suspected relapse
* Establishing mucosal healing
* De-escalation of therapy
* **PCDAI**
* **CRP**
* **FC (Calprotectin)**
* **Endoscopy (SES-CD)**
* **Mini-index**
* **TDM of Biologics**

*4.3* *A description of the measures taken to minimize/avoid bias, including:*

*(a) randomisation*

*(b) Blinding*

*This is an open label study and a*ll the principal investigators and research assistant will have access to the clinical information. To minimize inter-observer variability, endoscopic images and detailed patient report will be collected systematically and stored and read by at least two separate investigators. In order to minimise bias, endoscopic scores will be scored by the investigator blinded to the results of other objective and subjective variables.

*4.4 A description of methods to be used for the study.*

**Methodology**

We expect to prospectively enrol at least 90 children with CD (≤16 years), from two participating Children’s Hospital (Princess Margaret Hospital for children and Lady Cilento Children’s Hospital, Brisbane).

In an open label design children with new diagnosis CD will be offered standard induction therapy with either Exclusive Enteral Nutrition (EEN) or Steroids (CS). All enrolled patients will be recommended comprehensive assessment using PCDAI, CRP, Faecal Calprotectin and Pan Endoscopy (SES-CD) at diagnosis and at 12 weeks as part of treat to target approach to ensure improvement of inflammation in addition to control of symptoms.

In addition, children with established CD undergoing scheduled Ileocolonoscopy for clinical reasons, including significant change in immunosuppression for suspected relapse or de-escalation of therapies in those with deep remission (no symptoms and mucosal healing) will also be invited to participate in the study. Enrolled patients will be asked to provide blood and faecal samples for assessment of biomarkers (CRP, FC) within two weeks of the scheduled colonoscopy.

Exclusion:

Children younger than 2 years (Very early onset IBD), patients with incomplete colonoscopy, inability to deliver the blood and stool sample within 2 weeks of colonoscopy and proven infectious ileocolitis (positive stool culture for salmonella/shigella etc) will be excluded from the study.

**Timelines**

**June 2017 June 2018**

 **RECRUITMENT ANALYSIS Presentation PMH Research**

Approximately 35% of paediatric colonoscopies at Princess Margaret Hospital (approximately 45/year) and 40% at Lady Cilento children’s hospital (65/year) are performed for diagnosis, suspected relapse and to confirm mucosal healing in children with CD. As treat to target (control of symptoms and mucosal healing) strategy is integrated into routine clinical management, we expect less than 10% drop out rates and expect to enrol more than 90 children over a year.

Therefore the only investigational intervention of our proposed study is to ensure symptoms based score, routine stool and serum biomarkers are performed concurrently (within two weeks) of elective scheduled endoscopy and independent, central, blinded review of endoscopy images

*4.6 Maintenance of any blinding records or randomisation codes and procedures for breaking codes.*

All clinical data will remain in the medical notes. All de-identified clinical data with associated research data will be stored in a password protected computer environment. If the PI ceases to be engaged at the current organisation the source data will remain in the password protected environment of the Princess Margaret Hospital for Children.

**5. SELECTION AND WITHDRAWAL OF SUBJECTS, IF APPLICABLE**

*5.1 Subject Inclusion criteria*

*New or established diagnosis of Crohns Disease based on standard clinical, endoscopic and histological criteria.*

*5.2 Subject Exclusion criteria*

*Very early onset IBD (< 2 years) , inability to complete full ileocolonoscopy, collect or deposit routine blood and faecal samples within two weeks of scheduled endoscopy and proven infectious colitis.*

*5.3 Subject withdrawal criteria and procedures specifying:*

 *(a) When and how to withdraw subjects from the study*

 *(b) the type and timing of the data to be collected for withdrawn subject/s.*

 *(c) Whether and how subjects are to be replaced.*

 *(d)The follow-up for subjects withdrawn from the study*

As this clinical research involves performing routine laboratory tests as a part of good clinical practise and ongoing monitoring withdrawal from the study and loss to follow up is less likely. The patients in this study will be patients who require ongoing medical care through the gastroenterology departments, however it will be made clear to all subjects and their families that their medical care will not be contingent on recruitment into the study and that they are free to withdraw from the study at any time without effect on their ongoing medical care.

**6. TREATMENT OF SUBJECTS, IF APPLICABLE**

*6.1 The treatment(s), interventions or methods to be utilised, including the name(s) of any the product(s), the dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow-up period(s) for subjects for each treatment group/arm of the study.*

**None**

*6.2 Medications/treatment(s) permitted (including rescue medication) and not permitted before and/or during the study.*

*None*

 *6.3 Procedures for monitoring subject compliance.*

*NA*

**7. ASSESSMENT OF EFFICACY**

*7.1 Specification of the efficacy parameters*

*NA*

*7.2 Methods and timing for assessing, recording, and analysing of efficacy parameters.*

*As outlined in methods, individual and composite reliability of non-invasive proxies in predicting endoscopic Crohns disease activity will be performed at the conclusion of the study.*

**8. Assessment of safety**

*8.1 Specification of safety parameters*

*NA*

*8.2 The methods and timing for assessing, recording, and analysing safety parameters.*

*NA*

*8.3 Procedures for eliciting reports of and for recording and reporting adverse event and inter-current illnesses.*

All practices and procedures are subject to monthly review of adverse outcomes within the department of Gastroenterology. All patients will remain under their primary gastroenterologist who will advocate for patient best interests as part of their commitment to the Doctor - patient relationship. All patients admitted with Crohn's disease are admitted under the Gastroenterology team and seen by Nurses, Dieticians and the on-call team who will also monitor patients for best outcomes. We also nominated Dr.Andre Schultz as DMSC although this is not a clinical intervention trial but a prospective review of a good clinical practise.

*8.4 The type and duration of the follow-up of subjects after adverse events.*

Risks of serious complication from paediatric colonoscopy performed under intravenous sedation and general anaesthesia are rare with transient hypoxia in 0.28%, bleeding 0.4% and perforation 0.01%. All endoscopies at our institute are performed under general anaesthesia further minimising risk of transient hypoxia which is 8 times more common in those undergoing these procedures under IV sedation In addition complications prior to and following endoscopy are recorded as part of GCP and will be subjected to morbidity review and clinical incident reporting.

**9. STATISTICS**

*9.1 A description of the statistical methods to be employed, including timing of any planned interim analysis(ses)*

It is estimated, from anecdotal clinical evidence, that approximately 70% of CD patients undergoing an endoscopy will be determined to have active CD – meaning 30% of CD patients will have inactive CD and thus will have undergone an endoscopy that was presumably unnecessary. Assuming a null hypothesis that the area under the curve (AUC) will be 0.65, a sample of 120 participants will provide over 85% power to detect an alternative AUC of 0.8 or more, assuming alpha of 0.05. Within the active CD group, it is estimated that 42% of participants will be classified as mild (an SES-CD score of 3-10) and 58% will be classified as moderate or severe (an SES-CD score of >=11). Again, assuming a null hypothesis that the area AUC for classifying the active group into mild vs ‘moderate or severe’ will be 0.65, a sample of 84 participants (within this subgroup) will provide over 75% power to detect an alternative AUC of 0.8 or more, assuming alpha of 0.05.

ROC curve analysis will be performed to, in turn, assess the discriminative ability of the continuous measures FC, CRP, and PCDAI, with sensitivity, specificity, positive predictive value, and negative predictive value calculated for the optimal diagnostic cut points (determined by examining the output from the ROC analysis).

As additional exploratory research, both logistic regression and ordinal logistic regression will be used to examine the combined ability of FC, CRP and PCDAI to predict IBS status (inactive/active) and classification (inactive/mild/moderate/severe) respectively.

 In addition to presenting odds ratios and 95% confidence intervals, the individual predictions from each model will be compared with the gold standard endoscopy assessment, across a range of probability thresholds, to calculate sensitivity and specificity as a means to determine model efficacy. Variables considered for inclusion in the modelling, in addition to study site, include sex, age of CD diagnosis, disease location, and disease behaviour / duration.

*9.2 If applicable, the number of subjects planned to be enrolled. In multicentre studys, the numbers of enrolled subjects projected for each study site should be specified. Reason for choice of sample size, including reflections on (or calculations of) the power of the study and clinical justification.*

Approximately 35% of paediatric colonoscopies at Princess Margaret Hospital (approximately 45/year) and 40% at Lady Cilento children’s hospital (60/year) are performed for diagnosis, suspected relapse and to confirm mucosal healing in children with CD. As treat to target (control of symptoms and mucosal healing) strategy is integrated into routine clinical management, we expect less than 10% drop out rates and expect to enrol more than 90 children over a year.

***9.3 The level of significance to be used***

*<0.05*

***9.4 Criteria for the termination of the study***

*Meeting study enrolment criteria*

***9.5 Procedure for accounting for missing, unused, and spurious data***

*All the data will be collected by RA prospectively, site supervisors will cross check the randomly quality of data collection by RA as most information is available in health records including patient details, biomarkers, endoscopy reports are recorded as a part of routine clinical practise. A quarterly teleconference will be held to update on data collection, recruitment and at 12 months an interim analysis will also be performed.*

***9.6 Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in protocol and/or in the final report, as appropriate).***

*This is not a large multi-centre trial, but the Chief Investigators (Z.Grover/PJ Lewindon/Ravikumara) will report to the site specific HREC(PMH and Lady Cilento), with all relevant emerging data.*

***9.7 If applicable, the selection of subjects to be included in the analyses (e.g. all randomized subjects, all dosed subjects, all eligible subjects, evaluable subjects)***

*All children with new or established diagnosis of Crohns disease (> 2 years) undergoing Ileocolonoscopy will be eligible to participate in the study and will be included in the analysis.*

**10. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS**

*The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/ institution will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data/documents.*

All aspects of the study including data, documents and protocols will be followed in accordance with good clinical practise and ethical principle and will be available for audit by research governance committee.

**11. QUALITY CONTROL AND QUALITY ASSURANCE**

*All the data will be collected by research assistants (RA) prospectively at each site, site supervisors will cross check the randomly quality of data collection by RA as most information including patient details, biomarkers, endoscopy reports are available electronically and clinical information is recorded in, medical notes as a part of routine clinical practise. A quarterly teleconference will be held to update on data collection, recruitment and at 12 months an interim analysis will also be performed.*

**12. ETHICS**

*12.1 Description of ethical considerations relating to the study*

**Intervention**

All children with suspected CD routinely undergo clinical, laboratory and endoscopic assessment at diagnosis. Follow up clinical and laboratory tests (both blood and faecal markers) are also part of accepted current clinical service delivery. Confirmation of mucosal healing with repeat endoscopy is already integrating into our clinical practice and is the commonest indication (~35%) for repeat colonoscopy in children attending PMH. Therefore the only investigational intervention of our proposed study is to ensure symptoms based score, routine stool and serum biomarkers are performed opportunistically within two weeks of scheduled repeat endoscopy and an independent, central, blinded review of endoscopy images. By formalising this clinical approach and studying protocolised symptom and biomarker data with each endoscopy, we will demonstrate the utility and reliability of non-endoscopic surrogates of this treat to target practice.

**13. DATA HANDLING AND RECORD KEEPING**

All clinical data will remain in the medical notes. All de-identified clinical data with associated research data will be stored in a password protected computer environment. If the PI ceases to be engaged at the current organisation the source data will remain in the password protected environment of the Princess Margaret Hospital for Children. All patients have regular medical follow up and all data will be imparted during consultations. When/if medical care transfers to practitioner subsequent information will be passed on by letter. Six monthly project reports will be submitted to PMH foundation. In addition there will be no storage of biological samples for the purposes of this research; mucosal biopsies go to histopathologist for routine reporting and get paraffin embedded, routine serum and faecal samples will be analysed and reported by path west.

**14. FINANCING AND INSURANCE**

 *Financing and insurance if not addressed in a separate agreement*.

PMH hospital has granted funding of 89,102 $ for this project, the amount will be used to recruit part time research assistant (20 hrs/week /Site). Endoscopy and biomarkers are performed routinely to measure therapeutic response and are part of good clinical practise. No external agencies are involved in this research project.

**15. PUBLICATION POLICY**

*15.1 Publication policy, if not addressed in a separate agreement.*

Generous funding from PMH foundation will be acknowledged in all presentations and publication. Dr Grover will be the first author as he will be contributing to design, data collection, analysis and writing of manuscript incorporating suggestions from associate investigators. A/Prof Peter Lewindon will review the manuscript and coordinate research at LCH and assist with data collection and patient recruitment.

**16. SUPPLEMENTS**

**Note**: Since the protocol and the clinical study report are closely related, further relevant information can be found in the [ICH Guideline for Structure and Content of Clinical Study Reports](http://www.tga.gov.au/DOCS/pdf/euguide/ich/013795en.pdf).