CLINICAL TRIAL PROTOCOL

Protocol Title: A randomised, open study of aminosalicylate withdrawal in patients with ulcerative colitis in established remission on combination treatment of azathioprine (or 6-mercaptopurine) and an aminosalicylate.

Trial Identification: The CASA Trial
Controlled Assessment of Salicylates and Azathioprine

EudraCT Number: 2005-000695-40

Trial Sponsor: The University of Nottingham

Principal Investigators: Professor CJ Hawkey
Professor RFA Logan

Sponsor Approval:

Name: _____ Signature: _____

Title: _____ Date: _____

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1.0 INTRODUCTION

This study will help define the medical management for patients with difficult ulcerative colitis who have achieved remission on azathioprine (or 6-mercaptopurine) and an aminonsalicylate. It is important to define whether, after the introduction of azathioprine with remission established, there is any extra benefit in continuing the aminosalicylate.

This is a collaborative study involving the British Society of Gastroenterology (BSG) network of trialists in inflammatory bowel disease (IBD).

2.0 GENERAL INFORMATION

The study will be conducted in compliance with the protocol, GCP, Research Governance Framework for Health and Social Care and UK regulatory requirements. The study will be managed by personnel within the University of Nottingham. Study Personnel will be specified within the Trial Management Documentation.

The protocol and study procedures will be agreed with the Study Steering Committee (SSC – Appendix I) that includes representatives of the BSG – IBD network.

3.0 BACKGROUND INFORMATION

Ulcerative colitis (UC) is an idiopathic inflammatory condition of the colon that causes relapsing and remitting illness, most commonly from early adulthood onwards. It is a severe and potentially life threatening disease. Medical management of ulcerative colitis begins with reducing the symptoms and establishing a remission. Once remission is achieved, the goal is to maintain the patient in remission for as long as possible. As life long maintenance therapy is generally recommended for all patients, long term treatment should be based on simple effective regimens that promote patient compliance.

The first drug established for the maintenance of remission was sulphasalazine. More recently mesalazine was developed to avoid side-effects associated with the sulfa moiety of sulphasalazine, and subsequently the related compounds olsalazine and balsalazide. Maintenance with these agents (subsequently referred to as 5-ASA compounds) is often not completely effective[1] leading to a number of studies that have demonstrated the effectiveness of the addition of the immunosuppressant, azathioprine or its active metabolite 6-mercaptopurine (thiopurines), in the maintenance of patients with previously difficult to control colitis. The thiopurines are added in for those patients who are not maintained on aminosalicylates alone and who require treatment with corticosteroids at relatively frequent intervals. A key finding was the observation that for patients who had achieved remission while taking azathioprine, continued treatment for at least two years was beneficial[2]. This has revolutionised the management of ulcerative colitis to the extent that approximately 30% of patients are now maintained on azathioprine[3]. What is not known is whether azathioprine alone is sufficient, or whether its combination with an aminosalicylate is significantly more

effective. As there is a potentially harmful interaction between aminosalicylates and azathioprine when co-administered[4-7] and because azathioprine is so effective, this is an important question to answer.

This study will therefore investigate azathioprine mono therapy compared with azathioprine plus an aminosalicylate in the continuation of remission in ulcerative colitis patients already taking both drugs. Disease activity will be measured objectively using the Simple Clinical Colitis Activity Index[8] as recommended by the BSG-IBD guidelines[9] with relapse confirmed by sigmoidoscopy and mucosal biopsy. Previous studies have usually been small single centre trials, this study will involve a collaborative approach from many centres to provide larger patient numbers.

4.0 STUDY OBJECTIVES

To investigate whether azathioprine alone is as effective as azathioprine and a 5-ASA compound in maintaining recently established remission in patients on both drugs. Efficacy will primarily be assessed by the comparison of relapse rates over 1 year.

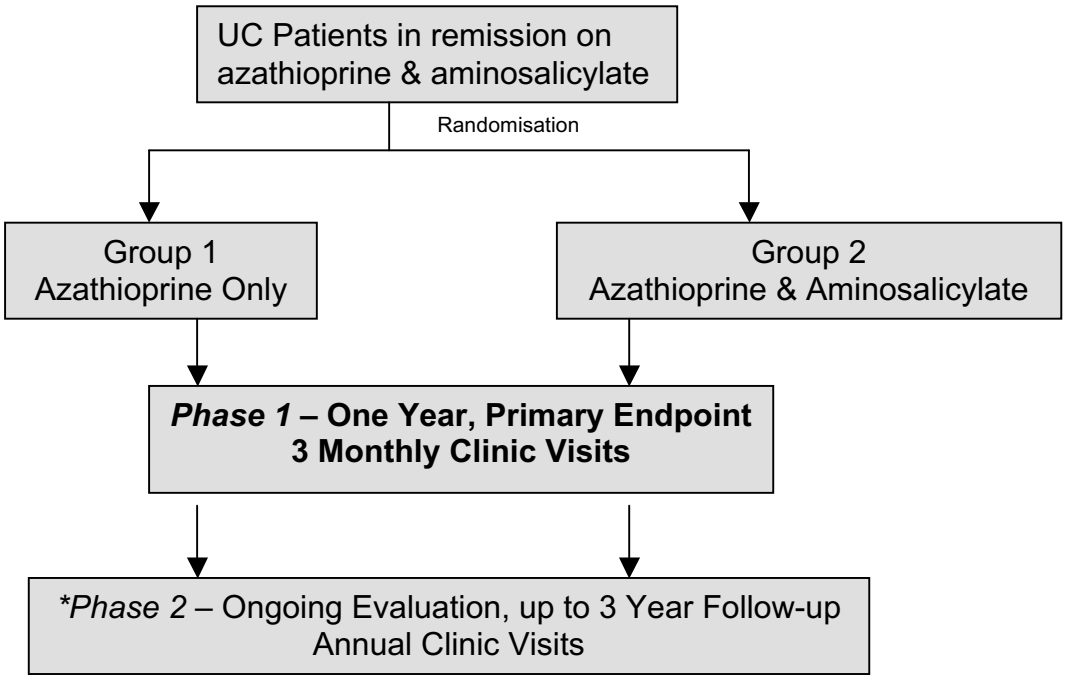
To identify factors predictive of the success of the different treatment regimens. It is anticipated that the following may have a bearing on treatment outcomes:

- Age at diagnosis of Ulcerative Colitis
- Frequency of relapse before azathioprine introduction
- Extent of the disease
- Time from last relapse at time of study entry
- Duration of azathioprine treatment
- Duration of 5-ASA treatment
- Dose of azathioprine
- Dose of a 5-ASA compound

5.0 STUDY DESIGN

This will be a randomised, open, multi-centre, withdrawal study conducted by the British Society of Gastroenterology Inflammatory Bowel Disease (BSG-IBD) network. There will be two phases, Phase 1, the primary outcome measure over one year, and Phase 2, ongoing follow-up out to 3 years. Patients will be identified from IBD databases. Following randomisation, patients will be required to attend the clinic routinely every 3 months for the first year and immediately on the sign of any relapse. After 12 months

patients will be followed up and medically assessed annually for a further 2 years.



*It is anticipated to take approximately 18 – 24 months to complete the first phase of the study to study report, depending upon the results of Phase 1, Phase 2 may be stopped prematurely by the SSC if a clear benefit is demonstrated of one group over the other.

6.0 PATIENT SELECTION

As this is a withdrawal study patients will be required to enter the study in a stable condition.

6.1 Inclusion Criteria

Patients who meet the following criteria will be eligible for study entry:

i. Male and female patients aged between 18 and 75 years with ulcerative colitis.
ii. Patients whose ulcerative colitis has been in clinical remission, defined as, being off steroids for 3 months or longer.
iii. Patients taking both azathioprine (or 6 mercaptopurine) and an aminosalicylate.
iv. Patients taking azathioprine (≥50mg/day) OR 6-mercaptopurine (≥25mg/day) at a stable dose for at least 8 weeks.
v. Patients taking an aminosalicylate at a stable dose (specified below) for at least 4 weeks:
    sulphasalazine ≥1.5g/day
    Pentasa (slow release mesalazine) ≥750mg/day
    Asacol (mesalazine)or generic equivalents ≥800mg/day
    Colazide (balsalazide) ≥2.25g/day

Dipentum (olsalazine) ≥750mg/day

vi. Patients on combined treatment with azathioprine (or 6-MP) and an aminosalicylate for a minimum of 6 months but no more than 4 years. Patients may enter if they have briefly been off either treatment during this time (eg because of abnormal blood test results) but prescription of each drug should cover at least 85% of the period of time for continuous drug treatment to be declared. NB Duration of aminosalicylate may be longer.

vii. Patients who have given written informed consent.

6.2 Exclusion Criteria

The following patients will be excluded from the study:

i. Patients with Crohn's disease.
ii. Patients with a baseline Walmsley Simple Activity Index >2.
iii. Patients with a baseline sigmoidoscopy grade of ≥2 (Baron Scale).
iv. Patients requiring long term treatment with oral steroids for any medical condition.
v. Women who are pregnant or lactating.
vi. Patients with known HIV infection.
vii. Other serious medical or psychiatric illness currently ongoing, or experienced within the past three months, that in the opinion of the investigator would compromise the study.
viii. Patients unable to comply with the protocol requirements, including severe alcohol and drug use.

7.0 STUDY PROCEDURES

An overview of the study procedures is provided in Table 1.

Table 1: Overview of Study Procedures

Procedure	Phase 1						Phase 2	
	BSL	3 months	6 months	9 months	12 months	Unscheduled Visit	2 year	3 year
Consent	x							
Selection Criteria	x							
Randomisation	x							
Demographics	x							
Disease History	x							
Disease Assessment[1]	x	x	x	x	x	x	x	x
Other Medical History	x							
Concomitant Medication	x	x	x	x	x	x	x	x
Blood Monitoring FBC CRP Albumin LFT BUN Creatinine	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]
Adverse Events		x	x	x	x	x	x	x
Sigmoidoscopy[2]	x		As required on sign of relapse					
Biopsy	x		Taken if sigmoidoscopy required for confirmation of relapse					

[1] Walmsley Simple Activity Index[8] (see Appendix IV)

[2] Sigmoidoscopy, graded according to Baron Scale

[3] Blood monitoring to continue outside routine study visits as required.

7.1 Baseline

Suitable patients will be identified from the investigators IBD database and asked to attend a clinic for study entry. The following procedures will be completed:

- Confirmation of eligibility
- Written Informed Consent
- Randomisation, randomisation will be minimised according to age (≥40 <40) gender and duration of remission (≥1yr <1yr)
  After patient characteristics are entered on the website, the investigator is asked to click the randomisation button which links to the external database. This will return immediately a message to the investigator to inform them to which group their patient has been randomised. In case there are any problems the investigator will contact the Trial Co-ordinator.
- Demographics (DoB, sex, ethnicity, smoking status, weight & height)
- Detailed disease history to include:
  - Age on diagnosis of ulcerative colitis
  - Extent of current disease
  - Date started on azathioprine
  - Dose of azathioprine
  - Date started on aminosalicylate
  - Dose of aminosalicylate
  - Frequency of relapse before azathioprine
  - Last relapse date

    - Extra-intestinal complications (current or previous)
    - Previous ulcerative colitis medication
- Walmsley Simple Activity Index[8] (see Appendix IV) for assessment of disease activity.
- Baseline Assessment of Functioning

None	Patient can perform all usual activities including working/studying (if applicable)
Mild	Some activities avoided but continuing to maintain usual routine including working/studying (if applicable).
Moderate	Working/Studying/Daily activities restricted until daily bowel habit completed
Severe	Not working, house bound or restricted to close proximity of a toilet.

- Concomitant Medications and current ulcerative colitis medication
- Blood taken for full blood monitoring
    - FBC, CRP, albumin values to be recorded in the CRF, LFT, BUN/Creatinine to be measured and only recorded if abnormal.
- Sigmoidoscopy graded according to the Baron Scale

  Baron Scale
  Grade 0 normal mucosa with visible vessels
  Grade 1 loss of vascular pattern
  Grade 2 contact bleeding
  Grade 3 spontaneous mucosal bleeding
- Biopsy samples will be taken for histological examination and confirmation of remission.

Patients meeting the selection criteria will be randomised to continue or stop their aminosalicylate. A letter will be sent to the patient's General Practitioner (GP) informing them of the patient's participation in the study.

7.2 Routine visits – Phase 1: 3 monthly. Phase 2: annually

On routine attendance at the investigators clinic the following will be completed:

- Full blood monitoring (FBC, CRP, albumin values to be recorded in the CRF, LFT, BUN/Creatinine to be measured and only recorded if abnormal).
- Walmsley Simple Activity Index[8] (see Appendix IV)
- Collection of any adverse events
- Information on any concomitant medication

7.3 Unscheduled Visits

On entering the study patients will be given a rapid reaction telephone number and instructed to contact that number immediately and arrange a clinic visit with 3 days at the sign of any relapse.

Sign of relapse is defined as:

- Bloody diarrhoea lasting 3 days or more

- Non-bloody diarrhoea lasting 10 days or more.
- Rectal bleeding lasting 3 days or more
- Symptoms the patient associates with relapse of their ulcerative colitis.

During any unscheduled visit the following will be completed:

- Full blood monitoring (FBC, CRP, albumin values to be recorded in the CRF, LFT, BUN/Creatinine to be measured and only recorded if abnormal).
- Walmsley Simple Activity Index[8] (see Appendix IV)
- Collection of any adverse events
- Sigmoidoscopy graded according to the Baron Scale

  Baron Scale

  Grade 0 normal mucosa with visible vessels
  Grade 1 loss of vascular pattern
  Grade 2 contact bleeding
  Grade 3 spontaneous mucosal bleeding
- Biopsy samples will be taken for histological examination and confirmation of relapse.

7.4 Patient Withdrawal

Patients may be withdrawn from the study at anytime. Withdrawals will not be replaced as the sample size calculation has made allowances for a 5% dropout.

Reasons for patient withdrawal include:

- Poor compliance with the study requirements (protocol violation).
- Adverse event that in the judgement of the Investigator requires study withdrawal.
- Patient wishes to withdraw from the study.
- Patient is lost to follow-up.

All withdrawals will be assessed by the SSC whilst blind to randomisation status, who will evaluate the patient outcomes – whether they can be defined as having relapsed or whether statistical censoring is required. Details will be provided to the SSC by the Data Management Team, all decisions will be documented and ratified prior to the statistical analysis being performed.

7.5 Concomitant Medication

The investigator will record any medication taken by the patient during the course of the study. Any changes during the study will be documented. In addition any medications given to treat an adverse event will also be recorded.

7.6 End of Study

The end of the study is defined as the last visit of the last patient ongoing in the study. The MHRA and Ethics Committees will be notified within 90 days of the end of the study.

The study may be terminated prematurely by the SSC due to information that becomes available during the course of the study. In this case the MHRA and

Ethics Committees will be notified within 15 days of the premature end of the study.

8.0 ASSESSMENT OF EFFICACY

The objective is the continuation of remission, efficacy will be assessed by the comparison of the clinical relapse rates on azathioprine alone, compared with the combination treatment of azathioprine and an aminosalicylate.
Relapse will be defined as:

- Appropriate symptoms with incidence of Grade 2 or 3 sigmoidoscopic findings (confirmed by histology).

Any introduction of oral steroids for the treatment of ulcerative colitis will be defined as a relapse.

9.0 ASSESSMENT OF SAFETY

Safety will be assessed by the collection of all adverse events and adverse reactions. This will include those events considered related to the drug treatments and the deterioration of UC or UC-related symptoms. Clinical significant laboratory abnormalities will be recorded as adverse events. Information that needs to be collected on each event is provided in Appendix V.

9.1 Adverse Event Definitions

European Directive 2001/20/EC defines the following:

Adverse Event: any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a casual relationship with this treatment.

Adverse Reaction: all untoward and unintended responses to an investigational medicinal product related to any dose administered.

Serious Adverse Event or Serious Adverse Reaction: any untoward medical occurrence or effect that at any dose:

- results in death,
- is life-threatening,
- requires hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly or birth defect.

Unexpected Adverse Reaction: an adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg investigator's brochure for an unauthorised investigational product or summary of product characteristics for an authorised product.

9.2 Procedure for Reporting Adverse Events

All adverse events reported spontaneously be the patients or in response to observation by the Investigator will be recorded in the patient's electronic case report form.

At baseline the investigator will ask the patient "Are you experiencing any symptoms?" During the study at each visit, the Investigator will inquire "Have you had any symptoms since the last time you were asked?"

9.3 Procedure for Reporting Serious Adverse Events

In the event of a serious adverse event the Investigator should inform the Study Co-ordinator at The University of Nottingham within 24 hours of knowledge of the event. The name and contact details of the key Study Management Personnel will be provided to each site as part of the Clinical Study Site File.

Potential adverse reactions that can be expected with azathioprine (and 6-mercaptopurine), and aminosalicylates, are given in Appendices VI & VII respectively. These reflect the information provided in the Summary of Product Characteristics (SmPCs).

Suspected Unexpected Serious Adverse Reactions (SUSARs) that are fatal or life-threatening will be reported by the Investigator to their local ethics committee (LREC) within 7 days, all other SUSARs to be reported as soon as possible but within a maximum of 15 days. SUSARs will also be reported by The University of Nottingham to the MHRA and MREC according to the same requirements.

9.4 Ongoing Safety Monitoring

Throughout the study serious adverse event details will be reviewed by the SSC to assess the ongoing safety of the two treatment arms.
In accordance with regulatory requirements an annual safety report will be prepared and sent to the MHRA and MREC.

10.0 STATISTICAL ANALYSES

A full analysis strategy will be developed independently of the trial database, before undertaking any analysis, after the start of randomisation. This will be presented to, and agreed by, the Study Steering Committee (SSC) at their first meeting (i.e. before any analyses are performed). Analyses will be performed while blind to randomisation status.

Results will be summarised as point estimates (e.g. differences between percentages, or time to an event) together with their associated interval estimates (e.g. 95% confidence limits for analyses relating to the primary outcome variable and 99% confidence limits for analyses relating to the secondary outcome variables). The significance level for all analyses of the primary outcome variable will be P=0.05 (two-sided); for secondary outcome variables, P=0.01 (two-sided).

Interim analyses of the data are planned and stopping rules for the trial have been formulated and are to be approved by the SSC.

Data files will be transferred into and analysed using STATA version 8.

10.1 Sample Size

Current available evidence suggests that the relapse rate in patients with ulcerative colitis who have been in symptomatic remission on the combined treatment of azathioprine and 5-amino salicyclic acid for less than 4 years is in the order of 20% or less[10,11] over a one year period. Assuming a significance level of 5% and power of 80%, 198 patients per group are required to establish that mono-treatment with azathioprine is equivalent to treatment on both drugs (non inferiority being defined as no more than 10% increase in relapse rates.) Allowing for a 5% drop out rate 210 patients will be recruited to each arm of the trial.

10.2 Brief Analysis Plan

10.2.1 Primary and Supportive Analyses

The primary outcome is relapse (binary) between randomisation and one year follow-up. For a participant to be classed as relapsed there must be incident grade 2 or 3 changes on sigmoidoscopy (confirmed by histology) between randomisation and one year follow-up.

The primary analysis will be pragmatic, based on intention to treat, and will utilise all available follow-up data from all randomised participants. Relapse will be analysed by logistic regression with a contrast for combination treatment of azathioprine and 5-amino salicyclic acid versus mono-treatment of azathioprine adjusted for factors included in the minimisation randomisation and for age and extent of the disease by including them as covariates.

A per protocol analysis will also be performed restricted to participants who complied with the protocol. As such, participants who were found to have violated the protocol will be excluded from this analysis.

Further analyses will also be conducted to assess the robustness of the conclusions to missing primary outcome data.

10.2.2 Additional Analyses Using the Primary Outcome Measure

Baseline predictors of relapse rates will be investigated using logistic regression analyses where sample sizes permit by including pre-specified baseline participant characteristics as predictors in addition to covariates for age and extent of disease. These will include time from last relapse at time of study entry, duration of azathioprine treatment, duration of 5-amino salicyclic acid, dose of azathioprine treatment, and dose of 5-amino salicyclic acid.

A number of subgroup analyses will also be performed to investigate differential predictors of relapse. These will be based on intention to treat and will focus on differences in relapse rates.

10.2.3 Analyses of Secondary Outcomes

Secondary outcomes of interest include:

i) Time to relapse within the first year of follow-up
ii) Change in symptoms, without defined relapse, as assessed using the Walmsley Simple Activity Index

Time to relapse will be analysed using a Cox proportional hazard model with a contrast for combination treatment of azathioprine and 5-amino salicyclic acid versus mono-treatment of azathioprine adjusted for age and extent of the disease by including them as covariates.
For the change in symptoms outcome, non parametric Wilcoxon analyses will be performed to assess significance of the results between the combination treatment of azathioprine and 5-amino salicyclic acid versus mono-treatment of azathioprine.

10.3 Procedure for Reporting Deviations from Original Statistical Plan

Once the SSC have approved the Full Analysis Strategy no changes can be made to the statistical plan without first reporting them to, and having them approved by, the SSC. Minor changes may be approved by chairman's action.

11.0 DATA ACCESS AND QUALITY ASSURANCE

11.1 Monitoring

The study will be monitored by designated personnel from The University of Nottingham. Details of personnel and the monitoring plans will be specified in the Study Management File. Site visits and meetings with the investigator and co-workers will be conducted at intervals agreed with the sites.

11.2 Source Document Verification

On-site monitoring will include source data verification (SDV). SDV will compare the electronic case report form data with the primary source data (eg patient notes, laboratory results) contained in the patient records held at the study sites.

11.3 Quality Assurance Audit

In accordance will GCP this study may be subject to an independent Quality Assurance audit at the study sites.

12.0 ETHICS APPROVAL

Written approval of the study will be obtained from a Multicentre Research Ethics Committee (MREC) followed by Local Research Ethics Committees (LREC) for each participating site prior to the study starting.

Approval letters must contain the following information:

- Name and address of the ethics committee
- Date of the meeting
- Information that identifies the version of both the protocol and the subject information/informed consent
- Details of any other documents reviewed

All protocol amendments will be submitted to the Ethics Committees for approval prior to implementation. In addition the Ethics Committees will be informed of any administrative changes.

13.0 REGULATORY APPROVAL

This study will be conducted in the UK under UK regulations. The final protocol will be submitted to the Medicines and Healthcare Products Registration Agency (MHRA) for Clinical Trial Authorisation (CTA) approval.

14.0 DATA HANDLING AND RECORD KEEPING

An electronic (e)-grid system will be used for randomisation and data recording. Trial personnel will train each site on using the web based data capture.

Most centres involved with the study will have a Specialist IBD nurse whose responsibilities include database maintenance. The IBD nurses will be responsible for local coordination, registration and data recording.

15.0 FUNDING

Funding for the study comes from The Moulton CharitableTrust.

16.0 PUBLICATION POLICY

In accordance with the Research Governance Framework for Health and Social Care and GCP, results will be appropriately published and disseminated. Upon completion of the study, a report will be prepared and approved by the Principal Investigators and agreed by the SSC. The data will then be prepared for publication.

As this is a multi-centre study the results from each individual centre should not be published prior to the publication of the entire study and without prior agreement of the SSC.

17.0 REFERENCES

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