

# PROTOCOL

## Version 3.1 10<sup>th</sup> February 2011

### **PREDICTING 5-AMINOSALICYLATE NEPHROTOXICITY IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE.**

#### **Personnel**

**Dr Tariq Ahmad**, Consultant Gastroenterologist Royal Devon & Exeter Hospital.  
**Dr Charlie Lees**, Consultant Gastroenterologist Western General hospital, Edinburgh.  
**Dr Frank Muller**, Consultant Gastroenterologist Kent and Canterbury Hospital.  
**Dr William Newman**, Consultant Medical Geneticist, University of Manchester  
**Dr Jeff Barrett**, Statistical genetics group leader WTSI, Cambridge.  
Dr Michael Delaney, Consultant Nephrologist, Kent and Canterbury Hospital.  
**Dr Ailsa Hart**, Consultant Gastroenterologist St Marks Hospital, London  
**Dr Carl Anderson**, Statistical genetics group leader WTSI, Cambridge.  
**Dr John Mansfield**, Consultant Gastroenterologist, Royal Victoria Infirmary, Newcastle.  
**Dr Dermot McGovern**, Cedars-Sinai Medical Center, Los Angeles, USA.  
**Dr Rinse Weersma**, University Medical Center Groningen, The Netherlands.  
**Professor Tim Frayling**, Professor of Human Genetics, Peninsula Medical School.  
**Dr Miles Parkes**, Consultant Gastroenterologist Addenbrooke's hospital, Cambridge.  
**Professor Jack Satsangi**, Professor of Gastroenterology University of Edinburgh.

**Research Ethics Number: South West 1 REC 10/H0203/76**

**Sponsor: Royal Devon and Exeter NHS Foundation Trust, Exeter, UK**

#### **Correspondence details:**

Dr Tariq Ahmad

Royal Devon and Exeter NHS Foundation Trust and Peninsula Medical School, Barrack Road,  
Exeter, EX2 5DW, UK

Tel +44 1392 406218

[Tariq.ahmad@rdeft.nhs.uk](mailto:Tariq.ahmad@rdeft.nhs.uk)

## Contents

Personnel .....	1
Contents .....	2
1. Background .....	3
5-aminosalicylate induced nephrotoxicity.....	3
IBD genetics at the forefront of complex disease genetics .....	4
Genetic contribution to adverse drug reactions .....	4
2. Study Aims .....	5
3. Study Plan .....	6
3. 1 Nephrotoxicity Case definitions.....	6
3. 2 Control group definitions.....	7
3.3 Participant Selection .....	7
3. 4 Defining UK research sites .....	8
3.5 Participant Recruitment in the UK.....	8
3.6 International Participant Recruitment.....	11
3.7 Consent to research .....	11
3.8 Withdrawl of participants .....	12
3.9 Clinical data collection .....	12
3.10 Sample collection .....	14
3.11 Storage and testing of DNA .....	15
3.12 Statistical analyses .....	15
4 Quality Assurance, Data Handling, Publication Policy and Finance .....	17
5. Study management structure .....	18
6. Appendices.....	19
Appendix 1 Flow chart for patient recruitment at research site.....	19
Appendix 2 Flow chart for patient recruitment at PIC .....	20
Appendix 3 Flow chart for direct patient recruitment via advertisement .....	21
Appendix 4 Recruitment of patients via the Yellow Card System .....	22
Appendix 5 Patient Information Sheet .....	23
Appendix 6 Patient Questionnaire.....	26
Appendix 7 Study Advertisement .....	29
Appendix 8 Case report form (CRF) .....	31
7. References .....	32

## 1. Background

Crohn's disease (CD) and ulcerative colitis (UC) are chronic relapsing and remitting inflammatory diseases of the gastrointestinal tract, affecting 400 patients per 100,000 population in Europe and North America. Collectively the Inflammatory bowel diseases (IBD) represent an important cause of morbidity in young people, and a significant burden to healthcare resources. In the UK direct annual healthcare costs associated with the care of patients with IBD total £720 million<sup>1</sup>.

### ***5-aminosalicylate induced nephrotoxicity***

5-aminosalicylate drugs (5-ASA) are the most frequently prescribed class of drug to induce and maintain remission in patients with mild-to-moderately active IBD. The use of these drugs as long-term maintenance therapy inevitably leads to prolonged drug exposure and therefore toxicity is an important consideration.

Nephrotoxicity is a serious but rare idiosyncratic complication of 5-ASA therapy<sup>2</sup>. Whilst the incidence is low, the morbidity and costs to the health economy are high with a significant proportion of patients developing end stage renal failure. Nephrotoxicity most frequently takes the form of a severe progressive interstitial nephritis. Whilst the precise underlying pathogenic mechanisms are yet to be elucidated, a delayed cell-mediated response, resembling that described for non-steroidal anti-inflammatory drugs seems likely<sup>3</sup>.

The precise incidence of 5-ASA induced nephrotoxicity is uncertain as cases are rare and confounding factors common. Such factors include the concomitant use of other nephrotoxic drugs (e.g. NSAIDs to manage associated joint disease), and the occurrence of other, rare IBD associated renal manifestations, which cannot always be readily distinguished. These include tubular proteinuria related to IBD inflammatory activity<sup>4</sup>, renal stone disease, amyloidosis, membranous glomerulonephritis, rapidly progressive glomerulonephritis and IgA nephropathy<sup>5</sup>. Data from clinical trials of 5-ASA drugs, in which serum creatinine has been regularly monitored, suggest a mean annual nephrotoxicity risk of 0.26% (0.13% – 0.5%)<sup>2</sup>. In

contrast data from a detailed postal questionnaire sent to all UK gastroenterologists and renal physicians estimates an incidence of 1/4000 patient years<sup>6</sup>.

Nephrotoxicity is reported most often within the first 12 months of drug exposure, but may be delayed for many years. Symptoms and signs may be mild and non-specific which may delay detection for many months. For these reasons regular monitoring of renal function for the duration of therapy is recommended, although it is not known if the serum creatinine gives sufficient warning of developing nephrotoxicity. Furthermore the benefit and cost-effectiveness of this approach has not been demonstrated. Timely recognition of renal impairment and prompt withdrawal of 5-ASA treatment is crucial to maximize chances of renal recovery. Failure to detect 5-aminosalicylate nephrotoxicity early is an increasing cause of medical litigation.

### ***IBD genetics at the forefront of complex disease genetics***

The last 4 years have seen tremendous progress in the identification of Inflammatory bowel disease susceptibility genes. Using genome wide association scans (GWAS) more than 90 IBD risk loci have been identified including at least 28 association signals shared between Crohn's disease and ulcerative colitis. The UK and international IBD Genetics consortia have been central to these discovery efforts<sup>7-11</sup>. This exciting progress has provided major pathogenic insights but has not yet translated to the clinic for patient benefit. With the exception of TPMT genotyping to identify patients at risk of myelosuppression with thiopurines, no loci are used in IBD clinical practice<sup>12</sup>.

### ***Genetic contribution to adverse drug reactions***

Recent studies have demonstrated that the same unbiased GWAS technology can be successfully employed to identify genetic factors that determine adverse drug reactions, promising a safe individualized therapeutic strategy for patients. Importantly these studies have confirmed that rare side effects may be determined by large effect variants and can be

identified using a relatively small number of rigorously characterized cases. Thus the HLA class II allele HLA-B\*5701 genotype has been shown to be a major determinant of flucloxacillin-induced cholestatic hepatitis with an odds ratio of 80 using a cohort of only 51 patients<sup>13</sup>. This same HLA allele was earlier found to associate with Abacavir hypersensitivity<sup>14</sup>, a finding that has translated into clinical practice to reduce the burden of this serious adverse reaction in a cost effective manner<sup>15</sup> - in Europe HLA-B\*5701 testing is now mandatory before prescribing Abacavir.

## 2. Study Aims

The main aim of this study is to identify clinically useful genetic markers that predict 5-ASA nephrotoxicity, so that these drugs can be avoided, or renal monitoring intensified, in genetically high risk patients. A simple, cheap, diagnostic test will be developed using these data which can be rapidly adopted into medium and large sized hospitals.

The secondary objectives are:

- (a) to understand the mechanisms underlying 5-ASA induced nephrotoxicity
- (b) through a knowledge of the mechanisms, to learn about particular functional chemical groups which predispose to toxicity, and thereby facilitate more rational drug design.
- (c) to establish a network of interested gastroenterologists for further pharmacogenetic research projects.

### 3. Study Plan

This is a case control study involving patients with documented nephrotoxicity to 5-aminosalicylate drugs including Mesalazine (Asacol<sup>®</sup>, Pentasa<sup>®</sup>, Mesren<sup>®</sup>, Salofalk<sup>®</sup>, Mezavant<sup>®</sup>, Ipocol<sup>®</sup>), Balsalazide (Colazide<sup>®</sup>), Olsalazine (Dipentum<sup>®</sup>), Sulphasalazine (Salazopyrin<sup>®</sup>)

#### 3. 1 Nephrotoxicity Case definitions

In the absence of a diagnostic test for 5-ASA induced nephrotoxicity, definitions are clinical and detailed below. The presence or absence of other risk factors for renal disease distinguishes category B from category A patients. For study inclusion participants must meet **all** the required major criteria features and any number of the additional 4 minor criteria. Patients will be classified A0-4 or B0-4 depending upon the number of minor criteria met. Thus the diagnosis of 5-ASA induced nephrotoxicity will be most confident in patients designated A4 and least confident in those designated B0.

#### Major criteria (all required):

- Normal creatinine or eGFR at baseline
- $\geq 50\%$  rise in serum creatinine, (with corresponding fall in eGFR), any time after introduction of 5-ASA
- Expert renal opinion implicates 5-ASA
  
- Other risk factors for renal disease? No – Category A; Yes – Category B

#### Minor criteria (sum number of criteria met):

- Rise in serum creatinine within 12 months of introduction of 5-ASA
- Renal biopsy demonstrates interstitial nephritis
- Fall in serum creatinine  $\geq 20\%$  from peak (with corresponding rise in eGFR), on withdrawal of 5-ASA *with or without* use of steroids

- Recurrence with rechallenge,  $\geq 20\%$  rise in serum creatinine, (with corresponding fall in eGFR), any time after introduction

### 3.2 Control group definitions

4 controls will be recruited to each case. Controls will meet the following criteria:

- (a) History of ulcerative colitis or Crohn's disease
- (b) History of exposure to 5-ASA for at least 12 months without developing nephrotoxicity
- (c) Ethnically matched to the cases

### 3.3 Participant Selection

#### Inclusion Criteria

##### **Case:**

- Patient willing to take part.
- 18 years of age or over.
- Diagnosed with 5-ASA induced nephrotoxicity (as defined in section 3.1).
- Written informed consent obtained.

##### **Control:**

- Patient willing to take part.
- History of 5-ASA usage without occurrence of nephrotoxicity (as defined in section 3.1).
- (b) Ethnically matched to the index patient.
- (c) Has the same underlying disease as the index patient.
- (d) Recruited from the same practice/specialist clinical area as the index patient.
- Written informed consent obtained.

### **Exclusion Criteria**

- Patient unwilling to take part.
- Patient is, in the opinion of the investigator, not suitable to participate in the study.
- Unable to obtain written informed consent.

### ***3.4 Defining UK research sites***

Clinicians in all UK hospitals will be invited to participate in this study. Interested clinicians will be asked whether they wish to be considered as a research site or Patient identification centre (PIC). For a site to be classed as a PIC, their only function is to identify potential participants who are subsequently recruited by the principal research site. Importantly PIC designation is a shorter simple process which does not require the appointment of a Principal Investigator.

To facilitate recruitment this study has been adopted by the National Institute for Health Research (NIHR) Comprehensive Clinical Research Network (CCRN) Portfolio.

### ***3.5 Participant Recruitment in the UK***

We will aim to recruit 300 patients with a history of 5-aminosalicylate nephrotoxicity over 2 years. In the first year we will recruit 100 patients from the UK. Patients will be identified in the following ways:

UK patients will be identified and approached in the following ways which are further illustrated in the Appendices.

- (i) Direct referrals from health care professionals within any NHS Hospital Trust. We will write to all UK consultant gastroenterologists and consultant nephrologists asking for assistance identifying patients. Consultants at designated research sites will recruit patients directly to the study. Consultants at PICs (patient identification



centres) will seek permission from their patients to pass on their names and contact details to the central research office in Exeter. A researcher from the central office will send out a patient information pack and make arrangements to recruit the patient.

- (ii) Patients will be identified from the Muller database. In 2005 Muller et al reported the UK experience of 5-aminosalicylate nephrotoxicity. The authors wrote to 1298 consultant gastroenterologists and 290 consultant nephrologists inviting case submissions. Clinical details were provided for 289 patients and are stored on a pseudo-anonymised database (referring hospital number). We have ethical approval to approach these patients through their physicians who originally submitted their details to the 2005 study.
- (iii) Engagement with the UK IBD patient group, (NACC) and their 30,000 members. Following review of the advertisement by the medical advisory group we will advertise this study directly to patients using the patient's newsletter and website.
- (iv) The Yellow Card Reporting System. Following approval of this method of recruitment by the MHRA, we will utilise the yellow card database to identify potential patients.

**Patients recruited from research sites (see appendix 1)**

Patients whose routine clinical care is carried out at an institution designated as a research site may be recruited by members of the local research team. The study information, including invitation letter and Patient information sheet will be sent to the patient by members of the local research team. An appointment with a research nurse will be made for patients interested in participating. Consent, completion of the case report form (CRF), assistance with the patient questionnaire and venepuncture will be carried out by the research nurse. When possible this

will be carried out at the same time as a patient's routine clinical blood test (this avoids more than one skin puncture). Venepuncture will only be carried out by doctors and nurses who have received appropriate training.

**Patients recruited from PICs (see appendix 2)**

Patients meeting the inclusion criteria will be approached by a health care professional directly involved in their care. Potential participants will be given an invitation letter and patient information sheet. The contact details of patients interested in participating will be passed to the central research office in Exeter by the PIC site. Arrangements will be made for a member of the Exeter research team to visit the patient at home to discuss the study, take face to face informed consent, assist with the patient questionnaire and carry out venepuncture. As an alternative to venepuncture participants may be asked to donate a saliva sample, using an oragene kit, from which DNA will be extracted. In these circumstances consent and sample collection will be carried out by post. The act of completion and return implies that they have consented to participate in the research (as they will have been provided with and received adequate information to enable them to give informed consent).

**Patients recruited directly from study advert (see appendix 3)**

Patients contacting the research office will be sent a study information pack comprising patient invitation letter, participant information sheet and participant questionnaire. Patient's willing to take part will be asked to complete and return a reply slip and questionnaire. If the patient's routine clinical care is carried out at an institution designated as a research site then they will be directed to the local PI for recruitment. Otherwise arrangements will be made for a member of the Exeter research team to visit the patient at home to discuss the study, take face to face informed consent, assist with the patient questionnaire and carry out venepuncture, having confirmed eligibility with the patient's own clinical team. As an alternative to venepuncture participants may be asked to donate a saliva sample, using an oragene kit, from which DNA will be extracted. In these circumstances consent and sample collection will be carried out by post.

The act of completion and return implies that they have consented to participate in the research (as they will have been provided with and received adequate information to enable them to give informed consent).

### **Control Group**

The control group will comprise patients with IBD who have a history of exposure to 5-ASA for at least 12 months without developing nephrotoxicity. The DNA for these control IBD patients has already been collected, and the genotyping carried out, as part of earlier genetic projects carried out by members of the UK IBD Genetics Consortium. These data are available to us in an anonymised form. Control subjects have previously given broad consent for future studies investigating the genetics of IBD.

### **3.6 International Participant Recruitment**

To ensure we recruit adequate numbers of participants and / or to replicate our findings in a second stage experiment we will engage with other IBD genetics consortia (including Alberta, US NIDDK, US Pediatric, Belgian and German consortia), many of whom we are currently collaborating with, as part of the work of the international IBD genetics consortium. Patients will be identified from existing international IBD DNA banks. Eligible patients will have previously given broad informed consent for use of their DNA for IBD genetic studies.

### **3.7 Consent to research**

All patients recruited to the study will be required to give written informed consent. This will be carried out in person or by post, but all subjects will be given the opportunity to contact a member of the research team to discuss the project in more detail if desired. All subjects will be informed of the nature and purpose of the study, its requirements and possible hazards, and their rights to withdraw at any time from the study without prejudice and without jeopardy to

any future medical care at the study site. They will have adequate opportunity to ask the Investigator or nominated designee about any aspect of the study.

Three consent Forms will be signed, one for the researcher, one for the hospital casenotes and the other for the participant. Signed Consent Forms will remain in the study file and be available for monitoring purposes at any time.

### **3.8 Withdrawal of participants**

Subjects will be informed that they are free to withdraw from the study at any time up to the time the samples and data are coded but not anonymised. When the sample is fully anonymised, this will not be possible. The Investigator may remove a subject if, in his / her opinion, it is in the best interests of the subject. If a patient permanently withdraws from the study, or is lost to follow-up, the reason will be recorded.

### **3.9 Clinical data collection**

Detailed clinical data for each participant will be collected by rigorous case-note review, using the case record form (CRF) which will be supplied by the investigator. This will be carried out by local clinicians, local research nurses (if available) or by clinical members of the research team, once appropriate permission has been granted by the relevant hospital trust.

All CRFs are to be completed in a clear, legible manner. Black ink must be used to ensure accurate interpretation of data. Any changes or corrections made by drawing a line through the data to be changed, entering corrected information, and signing (or initialing) and dating the change.

Once the CRF is returned to the research office and entered onto a specially designed database, the CRF will then be classed as the source documentation. Data collected into the CRF's and

subsequently entered onto the database will be reviewed for discrepancies, missing data and queries. Research nurses and data managers will liaise with the relevant clinicians regarding data corrections. The Chief Investigator will be updated on a regular basis and will review the reports produced by the statistician in order to ensure consistency and accuracy of the data. Once CRF's and corresponding queries and reports are reviewed, the CRF will be signed off by the Chief Investigator or designated person.

The database especially designed for this project will be held at the Royal Devon and Exeter Hospital in the Department of Gastroenterology Research Office. It will be password protected and undergoes back up on a daily basis.

Patient confidentiality will be maintained at all times and will be protected in accordance with the Royal Devon and Exeter NHS Foundation trust data protection policy. Data will be pseudo-anonymised. A unique study ID will be given to each participant and the associated personal details will be removed from the research database. Access to the secure file linking study ID with personal details will be held on a separately protected computer.

The following abbreviations are for use when values or answers cannot be provided: NA = Not Applicable, NK = Not Known, ND = Not Done, NR= Not Retrievable or Not Available.

Every effort should be made to have the CRFs completed and as soon as possible following recruitment of a participant.

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties other than those noted below is prohibited. Records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations will not be made publicly available. All study centre personnel will comply with the privacy rules of their institutions and/or professional groups and with the ICH Guideline for Good Clinical Practice.

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited, except for trial-related inspection on request by one or more of the following:

- The Research Ethics Committee, and
- Auditors (including those instructed by regulatory bodies).

Documents relating to the trial that contain personal data that may disclose the identity of the subject will remain with the Investigator in a locked filing cabinet. The Investigator will not provide any personal data that may identify the subject to any third party at any time during or after the study. Subject confidentiality will be further assured by utilising unique subject identification code number.

The Investigator will maintain adequate records for the study including completed CRFs, volunteer medical records, laboratory reports, worksheets, nursing notes, signed Consent Form/Subject Information Sheet, drug disposition records, adverse experience reports, information regarding subjects who discontinued, all correspondence with the Research Ethics Committee and other pertinent data.

### **3.10 Sample collection**

When possible we will obtain 10mls venous blood from participants. This will be sent to the Peninsula genetics laboratory in Exeter using appropriate transport pack. We will also use a saliva based DNA kit (Oragene) which will permit patient consent and sample collection through the post. The UK IBD genetics consortium has already demonstrated that recruitment of samples using this method is entirely feasible. DNA will be extracted in the clinical genetics laboratory at the Royal Devon and Exeter Hospital

### 3.11 Storage and testing of DNA

All DNA samples collected will be stored at the Peninsula Medical School in locked, alarmed -80C freezers. Designated members of the research team will have access to the samples. Dr Tariq Ahmad will act as custodian.

All DNA samples will be pseudo-anonymised as we may wish to recruit patients to future studies investigating 5-aminosalicylate nephrotoxicity based upon their genotype. This is explained to the patients on the patient information sheet. The file linking the sample code to personal identifiable information will be kept on a separate secure computer and access limited to the chief investigator.

Coded DNA samples will be sent to other centres in the UK and USA for genetic analyses but all samples will be anonymised and personal details will be removed and remain confidential.

We will use the latest GWAS genotyping platform (e.g. Illumina 1M chip) and additionally carry out high resolution class I and II HLA typing, taking advantage of any facilities made available by the SAEC. We will draw on publicly available Wellcome Trust Case Control Consortium (WTCCC) data for country and sex-matched population controls.

Genotypic data will be kept by the Department of Gastroenterology at the Royal Devon and Exeter Hospital under secure conditions. Participants and/or their GP's will not be told of the genotypes identified from the studies at any stage during the study.

### 3.12 Statistical analyses

Statistical methodology for genetic association studies is a rapidly developing field, and the most up to date methods will be applied to bring the most powerful statistical methods to bear on the data analysis, and thus extract the maximum information possible from the genotype data. A detailed statistical analysis plan will be prepared prior to starting the analysis by Dr Jeff Barrett,

Dr Carl Anderson and Professor Tim Frayling with additional support from Dr Roy Powell (Research and Development Department, Royal Devon & Exeter NHS Foundation Trust).

Prior to the association analyses, a test for Hardy Weinberg equilibrium will be undertaken at each SNP, using Fisher's exact test. Any marker found to deviate significantly ( $p < 0.001$ ) will be flagged and the reasons for deviation explored. Population substructure will also be tested for, and adjusted for in the analysis if any is detected. The extent of missing genotype data per SNP and per patient will be examined and the reasons for this explored. Tests to ensure that any missing genotype data is at random will also be conducted. Multiple imputation methods will be used should missing genotypes be extensive.

For assessing association between a SNP and the risk of an ADR, two tests for association will be undertaken to compare genotype frequencies between cases and controls. The first will be a Chi-squared test, which makes no assumption regarding the underlying mode of inheritance, and the second will be a Cochran-Armitage test for trend, which assumes an additive mode of inheritance. In the event that it is necessary to adjust for the effect of potential confounding factors, two logistic regression models will be fitted – the first including covariates to represent the confounding factors only and the second including covariates to represent both the confounding factors and the SNP – and a likelihood ratio test used to assess for association. The regression analysis will be conducted twice under the two different assumptions regarding mode of inheritance. In addition to the p-value, the false discovery rate will be calculated to assess for statistical significance whilst accounting for the multitude of tests undertaken.

In the event that copy-number variants (CNVs) are investigated in addition to SNPs, the most up to date methods to assess for association with CNVs will be applied.

### ***Sample size calculation***

A sample size of 300 cases and 1200 controls provides greater than 95% power to identify an association at “beyond doubt” p values of  $1 \times 10^{-12}$  at odds ratios of at least 5.0 with an allele frequency of greater than 2%



MAF	Sample size	Power
0.05	100	0.26
	200	0.98
	300	0.99
0.1	100	0.85
	200	0.99
	300	0.99
0.2	100	0.99
	200	0.99
	300	0.99

#### 4 Quality Assurance, Data Handling, Publication Policy and Finance

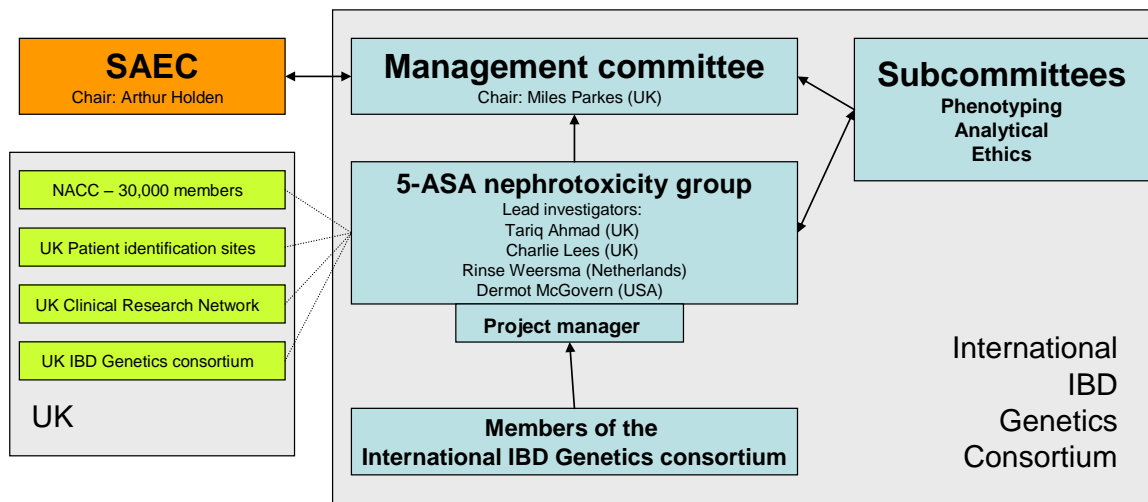
The Chief Investigator will take overall responsibility for the internal monitoring of all CRFs, taking care to ensure that entries are complete and legible and to otherwise ensure compliance to the protocol, and to ICH GCP. The Investigator will permit representatives of the regulatory authorities to inspect facilities and records relevant to this study.

The Investigator will be responsible for preparing the final study report. All results generated in this study may be submitted for publication or presentation.

The study has been funded by the Serious Adverse Event Consortium.

The study will be sponsored by the Royal Devon and Exeter NHS Foundation Trust.

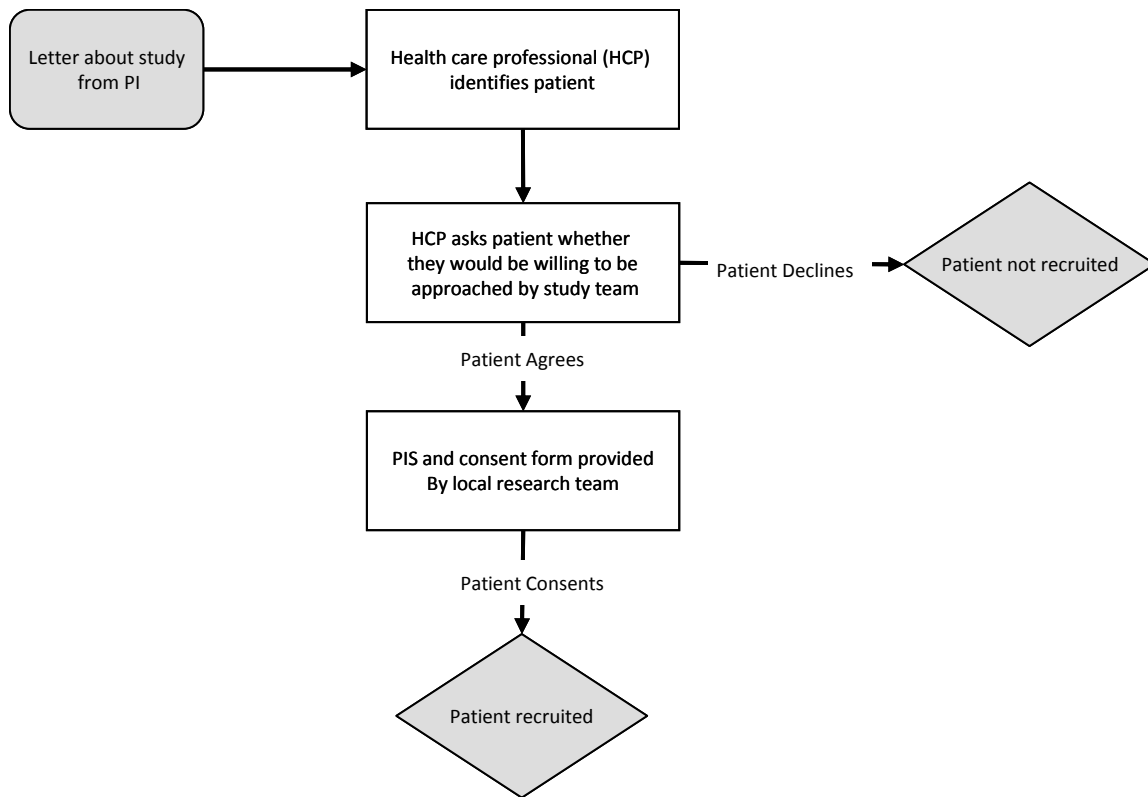
## 5. Study management structure



## 6. Appendices

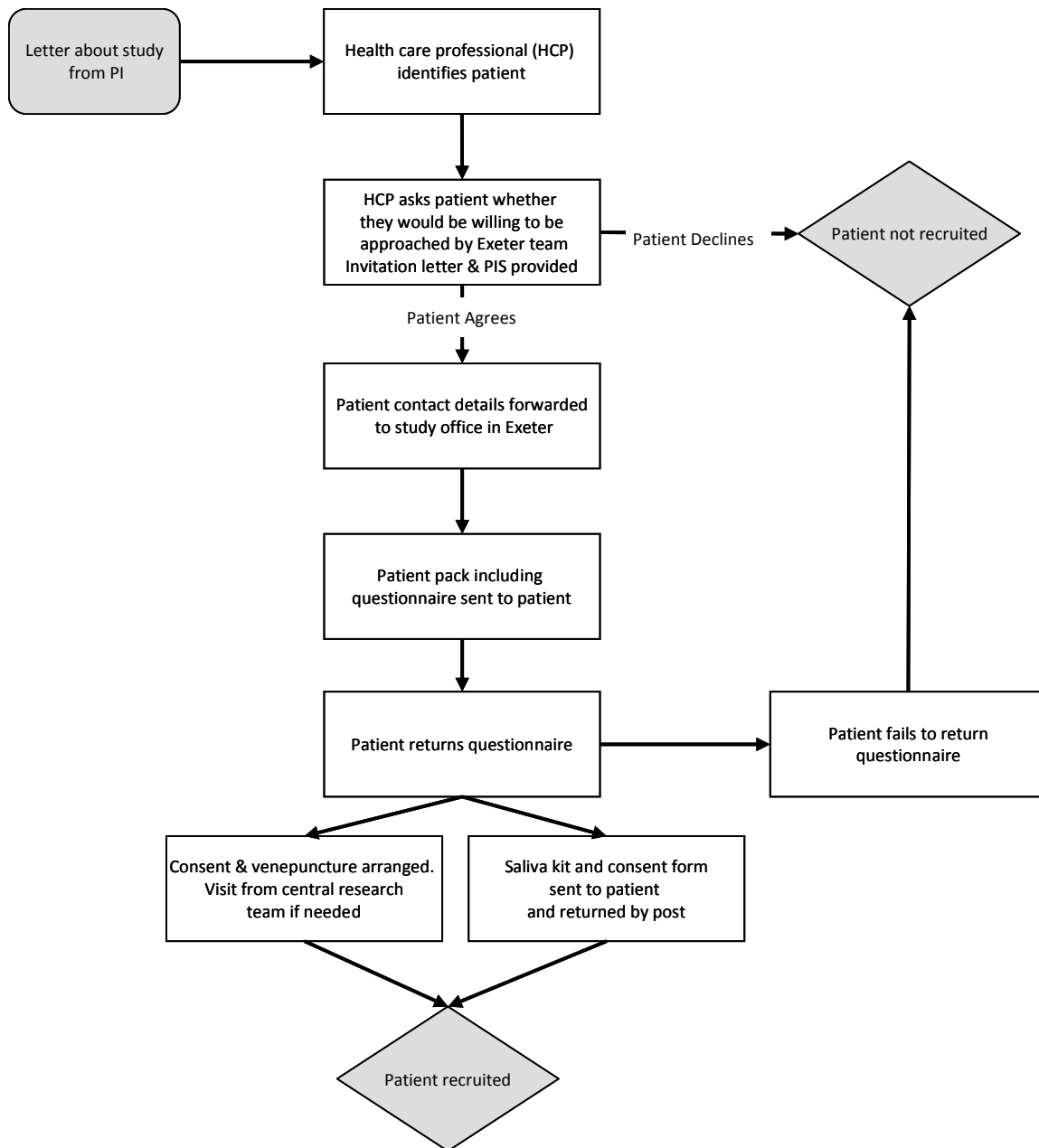
### Appendix 1 Flow chart for patient recruitment at research site

# PATIENT IDENTIFICATION AT RESEARCH SITE

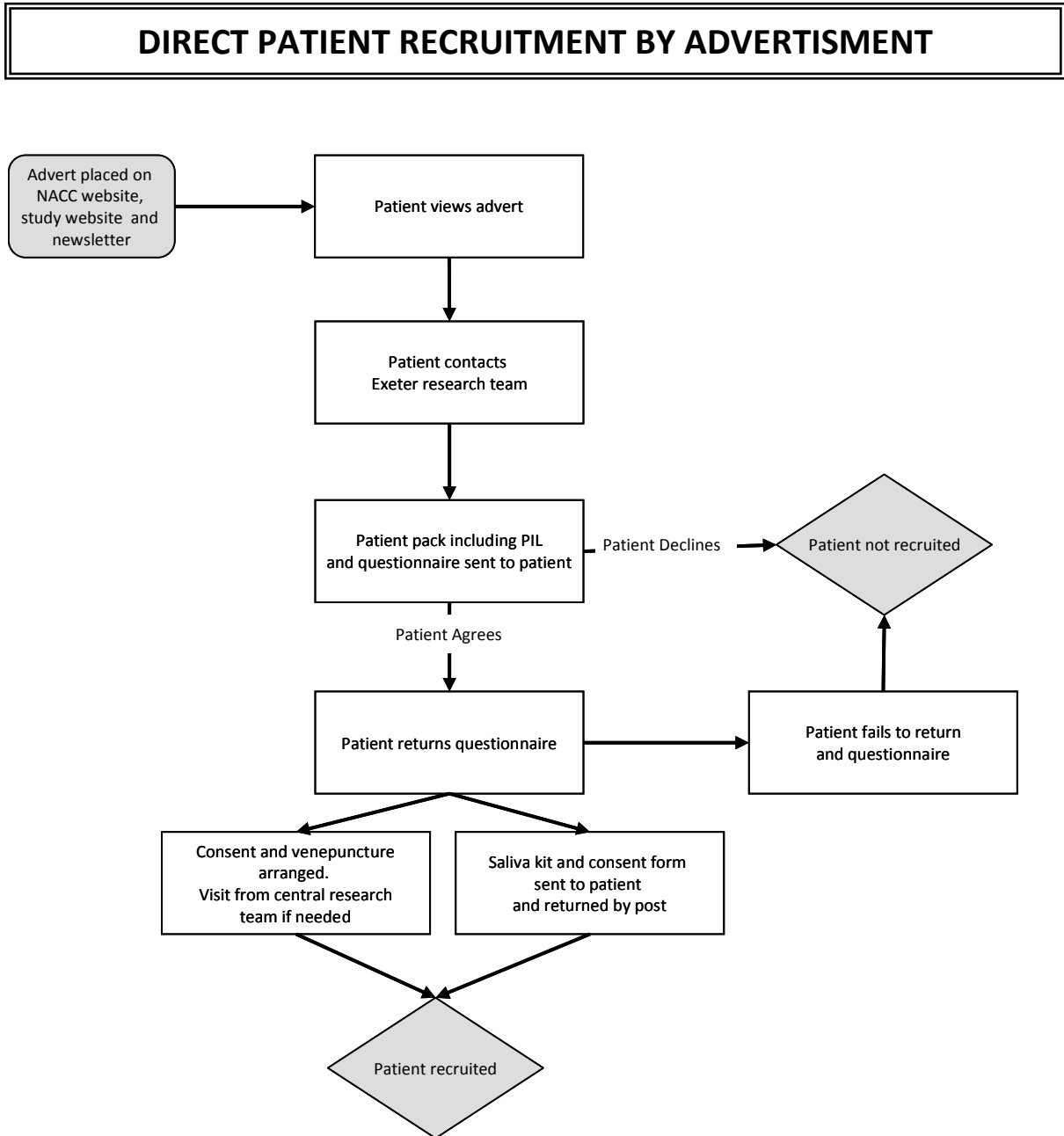


Appendix 2 Flow chart for patient recruitment at PIC

**PATIENT IDENTIFICATION AT PIC SITE**

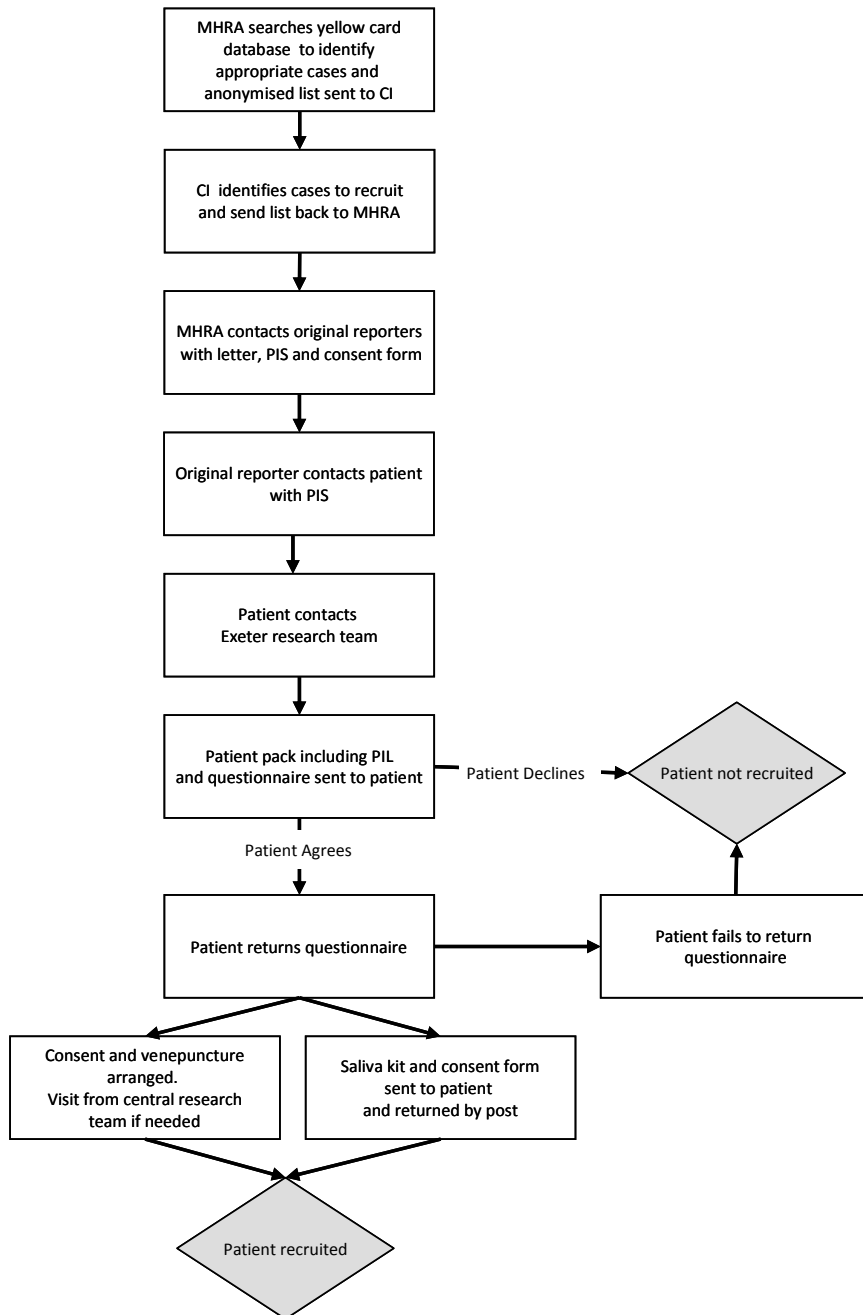


Appendix 3 Flow chart for direct patient recruitment via advertisement



Appendix 4 Recruitment of patients via the Yellow Card System

**RECRUITMENT OF PATIENTS VIA THE YELLOW CARD SYSTEM**



Appendix 5 Patient Information Sheet

**Participant information sheet**

**Predicting 5-aminosalicylate induced nephrotoxicity in patients with inflammatory bowel disease.**

You are being invited to take part in a research study. Before you decide, it is important that you understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. Ask us if there is anything that is not clear, or if you would like more information. Take time to decide whether or not you wish to take part.

**What is the purpose of the study?**

5-aminosalicylate drugs are frequently prescribed to treat patients with ulcerative colitis and Crohn's disease. For the majority of patients these drugs are effective at controlling symptoms, and side effects are rare and usually mild. Unfortunately a tiny minority of patients (like you) develop more serious side effects. These include kidney damage, a rare unpredictable side effect of treatment with 5-aminosalicylate drugs. At present we do not know why this happens.

Recent evidence suggests that side effects to some drugs may be determined by our genes (the basic building blocks of life). The purpose of this study is to identify the genes which determine kidney damage caused by 5-aminosalicylate drugs. It is hoped that we might then be able to develop a test to predict which patients will develop these serious side effect before patients are treated. We require your permission to include you in this study.

**Why have I been asked to participate?**

You have been asked to participate because we believe you have Crohn's disease or ulcerative colitis and have experienced kidney damage whilst taking a 5-aminosalicylate drug.

5-aminosalicylate drugs include Mesalazine (Asacol®, Pentasa®, Mesren®, Salofalk®, Mezavant®, Ipocol®), Balsalazide (Colazide®), Olsalazine (Dipentum®), Sulphasalazine (Salazopyrin®)

***Do I have to take part?***

It is up to you to decide whether or not to take part. If you do decide to take part you would be given this information sheet to keep, and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. This would not affect the standard of care you receive.

***What will happen to me if I take part?***

If you decide to take part we will ask your permission to look at your medical records, ask you to complete a short questionnaire, and ask you to provide us with a sample of your saliva (using a kit which we will provide) or blood sample (which we will arrange). We will provide a prepaid envelope to post these items back to us. We will extract DNA from your saliva or blood sample for genetic analyses. If after review of your medical notes it is felt that you do not meet the criteria for inclusion in the study we will write to you and destroy your DNA sample.

***What are the possible benefits of taking part?***

There are no direct benefits to you of taking part but it is hoped that information we get from this study may help us in the future to improve treatment for patients with ulcerative colitis and Crohn's disease.

***Are there any risks to me?***

You may experience some minor discomfort at the venepuncture site but otherwise there are no known risks from taking part in this study. Taking part in the study will not affect your current treatment, nor will it affect your ability to obtain insurance for health purposes.

***What will happen to my DNA?***

DNA will be extracted from your saliva or blood sample at the Peninsula Medical School. Your DNA sample will be given a code number so that your identity will not be revealed to laboratory staff or those performing the genetic analyses. Only the Chief Investigator will be able to link your coded DNA sample to you. All coded clinical details will be kept securely, at the Peninsula Medical School. Your coded DNA sample will be sent to other centres in the UK and USA for genetic analyses but your personal details will be removed and remain confidential.

Your saliva or blood sample will be considered to be a gift to the Peninsula Medical School, which will act as custodian of all samples obtained as part of this project. DNA may be stored indefinitely for future genetic studies in the UK and overseas aimed at understanding the genetic factors involved in Inflammatory Bowel Disease and its treatment. Genetic results may be used to identify specific patients for further studies and any future studies would require approval by an ethics committee.



***If I participate will my personal medical information be kept confidential?***

All information that is collected about you during the course of the project would be kept strictly confidential. All DNA samples received by the University will be identified by a code number only. Any information about you, which leaves the research centre, will have your name and address removed so that you cannot be recognised from it.

We will write to your GP to inform them of your participation in this study.

***What would happen to the results of the research study?***

We hope to be able to publish the results of this research and will be happy to provide you with a copy of the publication if you request it. You will not be identifiable in this publication.

Individual data will not be made available to participants unless the results could potentially impact on the individual's clinical care. Results would then be shared with the participant and their GP. This decision would be made by Dr Tariq Ahmad.

***Will I be paid for taking part in the study?***

We are unfortunately unable to pay people for taking part.

***Who has reviewed the study?***

The study has been reviewed by the South West 1 Research Ethics Committee 10/H0203/76.

***Who is organising and funding the research?***

This study is funded by the International serious adverse event consortium (SAEC) and supported by the National institute for health service research clinical research network (NIHR CRN) and the Peninsula Medical School.

***I have some further questions, who can I ask?***

If you would like any further details, or you would simply like to leave a message by telephone rather than writing, please contact:

Mrs Suzie Mariott	Research nurse	01392 XXXXXX
Dr Tariq Ahmad	Consultant Gastroenterologist	01392 406218

Appendix 6 Patient Questionnaire

**Participant Questionnaire**

**Predicting 5-aminosalicylate induced nephrotoxicity in patients  
with Inflammatory bowel disease.**

Date questionnaire completed: \_\_\_\_\_

Name: \_\_\_\_\_

Date of birth: \_\_\_\_\_

Address \_\_\_\_\_

Postcode \_\_\_\_\_

Daytime Telephone Number \_\_\_\_\_

Evening Telephone Number \_\_\_\_\_

E-mail \_\_\_\_\_

**Question 1: Your doctors**

a. Who is your current gastroenterologist? \_\_\_\_\_

b. In which hospital do you see your gastroenterologist? \_\_\_\_\_

c. Have you, or are you currently being looked after by a kidney specialist? Y/N

d. Who is your kidney specialist? \_\_\_\_\_

e. In which hospital do you see your kidney specialist? \_\_\_\_\_

f. Who is your GP? \_\_\_\_\_

g. What is the address of your GP \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

**Question 2: At what age were you diagnosed with inflammatory bowel disease? \_\_\_\_**

**Question 3: Your weight and height**

a. What is your current weight \_\_\_\_\_

b. What is your current height \_\_\_\_\_

**Question 4: Smoking**

a. Please describe your smoking status? Never / Ex / Current

b. Were you smoking at the time your bowel disease was diagnosed? Yes / No

c. At what age did you start smoking? \_\_\_\_\_

d. At what age did you stop smoking? \_\_\_\_\_

e. On average how many cigarettes do or did you smoke per day?

Less than 5 / 5-9 / 10-14 / 15-19 / 20-24 / 25-29 / >30

**Question 5: Do you suffer from any of the following disorders?**

Type I diabetes Yes / No / Unsure

Type II diabetes Yes / No / Unsure

High blood pressure Yes / No / Unsure

Angina or heart attack Yes / No / Unsure

Poor circulation to the legs Yes / No / Unsure

**Question 6: Please list your current medication prescribed by your GP**

**Question 7: Please list any other medication which you take which is not prescribed by your GP**

Appendix 7 Study Advertisement

**Study Advert**

## **Volunteers wanted for genetic study of rare drug side effects.**

Volunteers are being sought for a worldwide study investigating the genetics of a rare side effect of 5-aminosalicylate drugs.

5-aminosalicylate drugs are frequently prescribed to treat patients with ulcerative colitis and Crohn's disease. . Drugs in this group include Asacol, Pentasa, Mesren, Salofalk, Mezavant, Ipocol, Colazide, Dipentum, and Salazopyrin. For the vast majority of patients these drugs are effective at controlling symptoms, and side effects are rare and usually mild. Unfortunately a tiny minority of patients develop more serious side effects. These include kidney damage, a rare unpredictable side effect of treatment with 5-aminosalicylate drugs. At present we do not know why this happens.

Recent evidence suggests that side effects to some drugs may be determined by our genes (the basic building blocks of life). This purpose of this study is to identify the genes which determine kidney damage caused by 5-aminosalicylate drugs. It is hoped that we might then be able to develop a test to predict which patients will develop these serious side effect before patients are treated.

This study builds on the highly successful research of the UK and international IBD genetics consortia in identifying more than 90 genes for ulcerative colitis and Crohn's disease. The study is led by UK Gastroenterologists and is supported by the International serious adverse events consortium and the National Institute for health service research.

We are looking for 200 volunteers with ulcerative colitis or Crohn's disease, aged over 18, who have developed kidney damage following the use of any of these 5-aminosalicylate drugs. Volunteers will be asked to complete a short questionnaire, donate a blood or saliva sample for DNA analyses and give permission to allow review of their medical notes.

People interested in volunteering for the study should contact Dr Ahmad on 01392 XXXXXX or by email at [tariq.ahmad@rdeft.nhs.uk](mailto:tariq.ahmad@rdeft.nhs.uk)

Appendix 8 Case report form (CRF)

Attached

## 7. References

1. Bassi A, Dodd S, Williamson P, Bodger K. Cost of illness of inflammatory bowel disease in the UK: a single centre retrospective study. *Gut* 2004;53:1471-8.
2. Gisbert JP, Gonzalez-Lama Y, Mate J. 5-Aminosalicylates and renal function in inflammatory bowel disease: a systematic review. *Inflamm Bowel Dis* 2007;13:629-38.
3. Popoola J, Muller AF, Pollock L, O'Donnell P, Carmichael P, Stevens P. Late onset interstitial nephritis associated with mesalazine treatment. *BMJ* 1998;317:795-7.
4. Poulou AC, Goumas KE, Dandakis DC, Tyrmpas I, Panagiotaki M, Georgouli A, Soutos DC, Archimandritis A. Microproteinuria in patients with inflammatory bowel disease: is it associated with the disease activity or the treatment with 5-aminosalicylic acid? *World J Gastroenterol* 2006;12:739-46.
5. Corrigan G, Stevens PE. Review article: interstitial nephritis associated with the use of mesalazine in inflammatory bowel disease. *Aliment Pharmacol Ther* 2000;14:1-6.
6. Muller AF, Stevens PE, McIntyre AS, Ellison H, Logan RF. Experience of 5-aminosalicylate nephrotoxicity in the United Kingdom. *Aliment Pharmacol Ther* 2005;21:1217-24.
7. Parkes M, Barrett JC, Prescott NJ, Tremelling M, Anderson CA, Fisher SA, Roberts RG, Nimmo ER, Cummings FR, Soars D, Drummond H, Lees CW, Khawaja SA, Bagnall R, Burke DA, Todhunter CE, Ahmad T, Onnie CM, McArdle W, Strachan D, Bethel G, Bryan C, Lewis CM, Deloukas P, Forbes A, Sanderson J, Jewell DP, Satsangi J, Mansfield JC, Cardon L, Mathew CG. Sequence variants in the autophagy gene IRGM and multiple other replicating loci contribute to Crohn's disease susceptibility. *Nat Genet* 2007;39:830-2.
8. Fisher SA, Tremelling M, Anderson CA, Gwilliam R, Bumpstead S, Prescott NJ, Nimmo ER, Massey D, Berzuini C, Johnson C, Barrett JC, Cummings FR, Drummond H, Lees CW, Onnie CM, Hanson CE, Blaszczyk K, Inouye M, Ewels P, Ravindrarajah R, Keniry A, Hunt S, Carter M, Watkins N, Ouwehand W, Lewis CM, Cardon L, Lobo A, Forbes A, Sanderson J,



- Jewell DP, Mansfield JC, Deloukas P, Mathew CG, Parkes M, Satsangi J. Genetic determinants of ulcerative colitis include the ECM1 locus and five loci implicated in Crohn's disease. *Nat Genet* 2008;40:710-2.
9. Barrett JC, Hansoul S, Nicolae DL, Cho JH, Duerr RH, Rioux JD, Brant SR, Silverberg MS, Taylor KD, Barmada MM, Bitton A, Dassopoulos T, Datta LW, Green T, Griffiths AM, Kistner EO, Murtha MT, Regueiro MD, Rotter JI, Schumm LP, Steinhart AH, Targan SR, Xavier RJ, Libioulle C, Sandor C, Lathrop M, Belaiche J, Dewit O, Gut I, Heath S, Laukens D, Mni M, Rutgeerts P, Van Gossum A, Zelenika D, Franchimont D, Hugot JP, de Vos M, Vermeire S, Louis E, Cardon LR, Anderson CA, Drummond H, Nimmo E, Ahmad T, Prescott NJ, Onnie CM, Fisher SA, Marchini J, Ghorji J, Bumpstead S, Gwilliam R, Tremelling M, Deloukas P, Mansfield J, Jewell D, Satsangi J, Mathew CG, Parkes M, Georges M, Daly MJ. Genome-wide association defines more than 30 distinct susceptibility loci for Crohn's disease. *Nat Genet* 2008;40:955-62.
10. Anderson CA, Massey DC, Barrett JC, Prescott NJ, Tremelling M, Fisher SA, Gwilliam R, Jacob J, Nimmo ER, Drummond H, Lees CW, Onnie CM, Hanson C, Blaszczyk K, Ravindrarajah R, Hunt S, Varma D, Hammond N, Lewis G, Attlesey H, Watkins N, Ouwehand W, Strachan D, McArdle W, Lewis CM, Lobo A, Sanderson J, Jewell DP, Deloukas P, Mansfield JC, Mathew CG, Satsangi J, Parkes M. Investigation of Crohn's disease risk loci in ulcerative colitis further defines their molecular relationship. *Gastroenterology* 2009;136:523-9 e3.
11. Barrett JC, Lee JC, Lees CW, Prescott NJ, Anderson CA, Phillips A, Wesley E, Parnell K, Zhang H, Drummond H, Nimmo ER, Massey D, Blaszczyk K, Elliott T, Cotterill L, Dallal H, Lobo AJ, Mowat C, Sanderson JD, Jewell DP, Newman WG, Edwards C, Ahmad T, Mansfield JC, Satsangi J, Parkes M, Mathew CG, Donnelly P, Peltonen L, Blackwell JM, Bramon E, Brown MA, Casas JP, Corvin A, Craddock N, Deloukas P, Duncanson A, Jankowski J, Markus HS, McCarthy MI, Palmer CN, Plomin R, Rautanen A, Sawcer SJ, Samani N, Trembath RC, Viswanathan AC, Wood N, Spencer CC, Bellenguez C, Davison D, Freeman C, Strange A, Langford C, Hunt SE, Edkins S, Gwilliam R, Blackburn H, Bumpstead SJ, Dronov S, Gillman M, Gray E, Hammond N, Jayakumar A, McCann OT,

- Liddle J, Perez ML, Potter SC, Ravindrarajah R, Ricketts M, Waller M, Weston P, Widaa S, Whittaker P, Attwood AP, Stephens J, Sambrook J, Ouwehand WH, McArdle WL, Ring SM, Strachan DP. Genome-wide association study of ulcerative colitis identifies three new susceptibility loci, including the HNF4A region. *Nat Genet* 2009;41:1330-4.
12. Ahmad T, Tamboli CP, Jewell D, Colombel JF. Clinical relevance of advances in genetics and pharmacogenetics of IBD. *Gastroenterology* 2004;126:1533-49.
  13. Daly AK, Donaldson PT, Bhatnagar P, Shen Y, Pe'er I, Floratos A, Daly MJ, Goldstein DB, John S, Nelson MR, Graham J, Park BK, Dillon JF, Bernal W, Cordell HJ, Pirmohamed M, Aithal GP, Day CP. HLA-B\*5701 genotype is a major determinant of drug-induced liver injury due to flucloxacillin. *Nat Genet* 2009;41:816-9.
  14. Mallal S, Nolan D, Witt C, Masel G, Martin AM, Moore C, Sayer D, Castley A, Mamotte C, Maxwell D, James I, Christiansen FT. Association between presence of HLA-B\*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir. *Lancet* 2002;359:727-32.
  15. Hughes DA, Vilar FJ, Ward CC, Alfirevic A, Park BK, Pirmohamed M. Cost-effectiveness analysis of HLA B\*5701 genotyping in preventing abacavir hypersensitivity. *Pharmacogenetics* 2004;14:335-42.