PoPSTER: Patient preferences and current Practice for adults with STEROid resistant ulcerative colitis – A mixed methods study

Short Study Title/ Acronym
PoPSTER

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Key Study Contacts

Chief Investigator	Professor Alan Lobo Tel: 0114 271 2353, Email: alan.lobo@sth.nhs.uk
Research Fellow	Dr Lizzie Coates Tel: 0114 222 0886 , Email: e.coates@sheffield.ac.uk
Sponsor	Sheffield Teaching Hospitals NHS Foundation Trust D Floor, Clinical Research Office, Royal Hallamshire Hospital, Glossop Road, Sheffield, S10 2JF Tel: 0114 226 5943 , Fax: 0114 226 5937
Funder	National Institute of Health Research Health Technology Assessment Tel: 0208 842 8044, Email: dawn.kean@nihr.ac.uk
Key Protocol Contributors	Professor Alan Lobo Dr Lizzie Coates
Committees	**Study Management Group** Sheffield Teaching Hospitals NHS Foundation Trust Professor Alan Lobo, Consultant Gastroenterologist Mr Matthew Lee, Clinical Research Fellow University of Sheffield Dr Phil Shackley, Reader in Health Economics Ms Nikki Totton, Statistician Dr Daniel Hind, Senior Research Fellow and Assistant Director Dr Lizzie Coates, Research Fellow Ms Amy Barr, Research Assistant Zoe Furniss, Trial Support Officer Professor Christopher Probert, Professor of Gastroenterology, University of Liverpool Professor Shaji Sebastian, Consultant Gastroenterologist and IBD Service Lead, Hull and East Yorkshire Hospitals NHS Trust Sue Blackwell, Patient Representative Nicola Dames, Patient Representative Hugh Bedford, Patient Representative **Independent Study Steering Committee** Chair — Professor Tariq Igbal, University of Birmingham Member — Ms Catherine Stansfield, Salford Royal Hospitals NHS Foundation Trust Member — Dr Gabrielle Thorpe, University of East Anglia Member — Dr Laura Ternent, Newcastle University PPI Member — Mrs Jayne Kranat

Study Summary

Study Title	PoPSTER: Patient preferences and current Practice for adults with STERoid resistant ulcerative colitis – a mixed methods study
Short Title	PoPSTER
Study Design	Mixed methods study design
Study Participants	Work package 1: Online survey of IBD Healthcare Professionals Work package 2: Interviews with IBD Healthcare Professionals Work package 3: Interviews with patients with ulcerative colitis Work package 4: Discrete Choice Experiment of IBD Healthcare Professionals and patients with UC Work package 5: Multi-stakeholder workshop with IBD Healthcare Professionals and patients with UC
Planned Size of Sample	Total: n=1150 Work package 1: Online survey of approximately 700 IBD Healthcare Professionals Work package 2: 20-25 interviews with IBD Healthcare Professionals Work package 3: 30-35 interviews with patients with UC Work package 4: Discrete Choice Experiment of 180 patients with UC, and up to 200 IBD Healthcare Professionals Work package 5: Multi-stakeholder workshop of up to 20 patients with UC and IBD Healthcare Professionals
Planned Study Period	November 2018 – October 2020
Research Aims	The overall aim of this research is to understand how adults with steroid resistant ulcerative colitis are being managed in secondary care, and how current practice compares with patient and clinician preferences.

Funding

FUNDER	FINANCIAL AND NON FINANCIAL SUPPORT GIVEN
National Institute of Health Research through their Health Technology Assessment programme (HTA) Tel: 020 8842 8044, Email: dawn.kean@nihr.ac.uk	Funders of the research programme

Role of Study Sponsor and Funder
Neither the funder nor the Sponsor have had any role in study design, data collection and analysis, decision to publish, or preparation of manuscripts.

Role and responsibilities of Study Management Group and Steering Committees
The overall responsibility for the study will be with Sheffield Teaching Hospitals NHS Trust who will act as sponsors for the study. The study will be conducted in accordance with the protocol, GCP and Sheffield CTRU Standard Operating Procedures. The two committees which will govern the conduct of the study are:

1. **Study Steering Committee (SSC)**

The SSC will be responsible for the overall conduct of the PoPSTER study and consists of an independent chair and four other independent members including a statistician and PPI representative. The committee will meet approximately every 6 months to monitor the study.

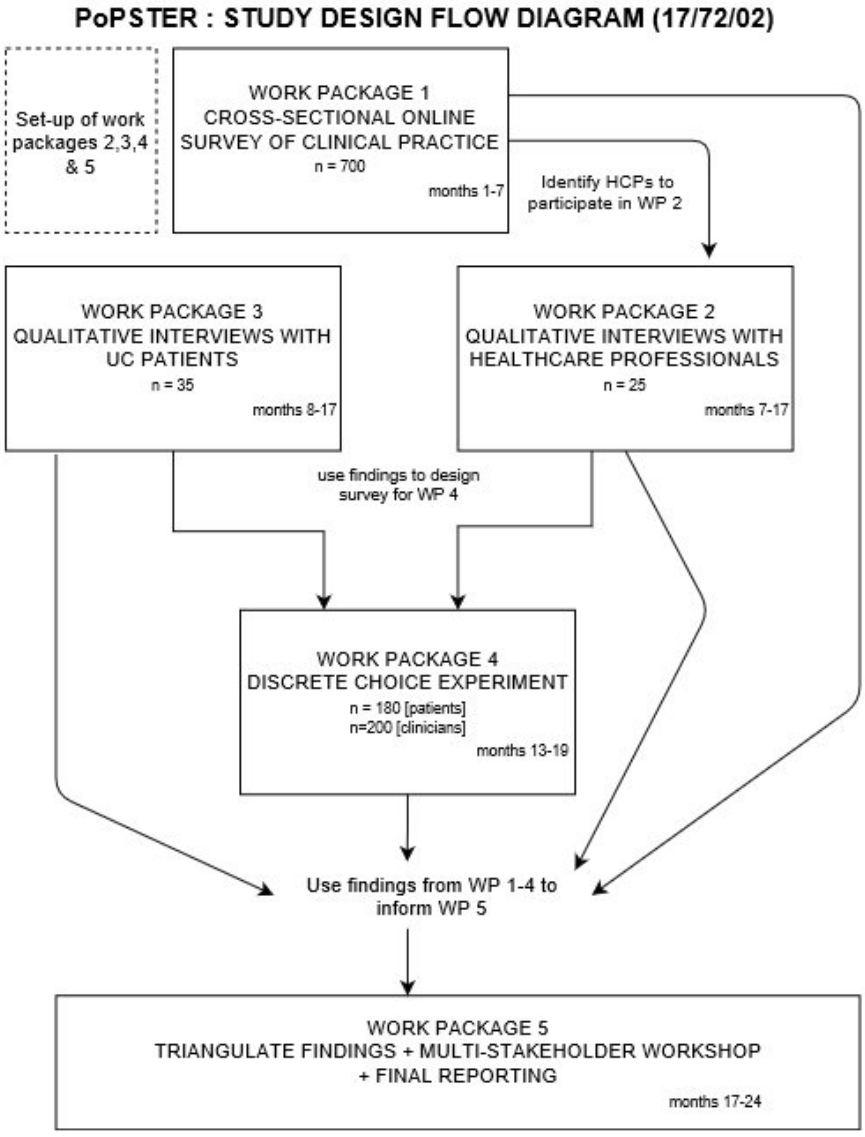
2. **Study Management Group (SMG)**

The role of the SMG is to monitor all aspects of the conduct and progress of the research, ensure that the protocol is adhered to, and take appropriate action to safeguard participants and the quality of the research itself. The SMG will comprise of the Chief Investigator and all co-investigators. The PMG will meet on a regular basis (quarterly) to monitor the day-to-day running of the study.

Protocol Contributors
All co-investigators contributed to the development of the protocol. The protocol was reviewed and the final version approved by Professor Alan Lobo.

KEY WORDS:	Inflammatory Bowel Disease Ulcerative Colitis Preferences Qualitative Research Discrete Choice Experiment

Study Flow Chart



1. Rationale

Ulcerative colitis (UC) runs a relapsing/remitting course, with debilitating symptoms, impaired quality of life and severe attacks requiring hospitalisation. For active UC not requiring hospitalisation, oral corticosteroids may induce remission in those refractory to aminosalicylate therapy [1]. Corticosteroids are recommended first line therapy for a severe relapse of UC [2].

Just under 50% of patients do not respond fully [3,4] and relapse on steroid dose reduction, leading to prolonged steroid use and debilitating side-effects. Many subsequent treatment options in the NICE treatment pathway [1] have been the subject of randomised controlled trials (RCTs), comparing individual agents with placebo or steroid comparators; direct 'head to head' comparisons are not available. NICE have recommended that the risks/benefits of methotrexate, ciclosporin, tacrolimus, adalimumab and infliximab should be assessed for the induction of remission in steroid-refractory UC [1]. Subsequently, vedolizumab has also been recommended for use in this population [5] and newer agents, ozanimod and tofacitinib, have demonstrated efficacy in RCTs [6]. Other options, including surgery, have not been the subject of RCTs. These options vary in cost, availability, mode of administration, patient acceptability, and use of healthcare facilities as well as clinician experience in their use, especially for newer agents.

There is no universally adopted definition of steroid resistant UC, which might include clinical, endoscopic and quality of life dimensions. There is also an overlap between those with ongoing symptoms or endoscopic inflammation despite corticosteroids ('steroid resistant') and those who initially respond and then relapse on reducing the steroid dose – 'steroid-dependent'. Both groups have been included in clinical trials of agents used for steroid resistant disease. Many of the pivotal trials – particularly of biologic agents – have included both groups and results of treatment in each group have frequently not been reported separately. In addition, these patients may also be on immunomodulator drugs.

Therefore, although national and international guidance [1,6,7] reflect this range of options, there remains a lack of clarity about:

a) The definition of steroid resistance (dose and duration of therapy);
b) The specific applicability of current evidence to a population of patients with UC resistant to corticosteroids; and
c) The optimum choice of treatment for this group and the importance of factors including patient and clinician preferences, concomitant immunosuppression and prior biological therapy.

2. Background

Ulcerative Colitis is associated with significant disability, psychological morbidity and distress [8–10]. It has significant socioeconomic impact arising from disrupted education and employment [8], with 20 days of household and recreational activities per year typically lost to illness [11]. In 2000, before the widespread use of biological agents, treatment costs for UC colitis were estimated at £3021 per patient per year in the UK [12], and in the EC-inception cohort at €1524 per patient year [13]; substantial costs relate to hospitalization and surgery, which are higher in those under 40 years of age [14] and with drug- refractory cases associated with high costs [15]. This may be reduced by more effective treatment but it is unclear whether newer agents are cost-effective in this population [14].

Oral corticosteroids are associated with significant side effects, which preclude long-term treatment. Long-term use of steroids is regarded as a marker of a poor IBD service [16]. There is insufficient information to inform patients with steroid-resistant UC on the choice of agent, concomitant immunosuppression and the timing of surgery. Although qualitative research highlights the divergent perspectives of medical and nursing staff [17], there are limited published patient perspectives, which are needed to inform the design of future clinical trials. Survey data suggests that patients' ideal therapy would be an effective, oral formulation with fewer tablets, less frequent dosing, and minimal side effects [18].

Evidence to inform the choice between anti-TNF agents, vedolizumab, tacrolimus, methotrexate, in- patient intravenous steroids, tofacitinib, ozanimod, and surgery [1,6,7,19,20] in steroid-resistant UC is limited for a number of reasons. No RCTs compare these treatments head-to-head in terms of clinical or cost-effectiveness and safety nor establish the ideal position of surgery in the treatment pathway.

There is also a lack of a widely adopted definition of steroid resistance. It has been defined as active disease despite prednisolone up to 0.75 mg/kg/day over a period of 4 weeks [6] but this is not reflected in the RCTs from which guidance is drawn. Not all patients included in these RCTs are steroid resistant and frequently results for steroid resistant and steroid dependent disease are not separately reported. For example, a minority of patients included in the pivotal trials of infliximab (IFX) in active ulcerative colitis were taking ≥ 20 mg/day prednisolone at trial entry [21], and in trials of adalimumab and vedolizumab, remission rates were not significantly different from placebo in those on corticosteroids [22] or failing corticosteroids alone [23].

The position of surgery also needs evaluation. The optimum timing of surgery is unclear and is likely to differ between patients. In a recently published qualitative study, from our group, we demonstrated that patients wished to undergo surgery when faced with severe restrictions on quality of life [24].

In a health economic assessment [25] from our group, (multi-technology appraisal TA329 [19] of anti-TNF agents) for patients in whom surgery is an option, colectomy was expected to dominate all medical treatment options. For patients in whom colectomy is not an option, infliximab and golimumab were ruled out due to dominance, with the incremental cost-effectiveness ratio (ICER) for adalimumab versus conventional treatment expected to be approximately £50,278 per quality-adjusted life-year (QALY) gained. However, there remains debate about whether surgery should be considered a comparator or an end-point and about when surgery would not be an option. Indeed, in TA342 [5], surgery and tacrolimus were not thought to be suitable comparators for vedolizumab.

These issues illustrate the pressing need for a trial with a clearly defined population of steroid resistant patients to evaluate clinical and cost-effectiveness. In order to develop such a trial, detailed understanding of how best to describe steroid resistance, and of patients and clinicians' views of treatment options and treatment objectives is required. This will allow appropriate identification of equipoise and acceptable invention and comparator arms in a trial.

3. Aims and objectives

The overarching research question for this study is:

> How are adults with steroid resistant ulcerative colitis (UC) being managed in secondary care, and how does current practice compare with patient and clinician preferences?

To answer the research question, this mixed methods study has the following objectives:

1. Describe current practice in the management of adults with steroid resistant UC and how medical resistance is defined.
2. Understand how treatment pathways and definitions of steroid resistance are operationalized in practice.
3. Understand patient experiences of different treatment options and approaches to decision making.
4. Estimate the relative utility of different treatment options; elicit patient and clinician preferences for these and their willingness to trade between them.
5. Make recommendations about future research and treatment options.

This mixed methods study includes survey of clinical practice and qualitative interviews with adults with steroid-resistant UC to understand how they are managed and their treatment preferences. In the survey and interviews with a purposive sample of healthcare professionals, we will explore how they define and treat steroid resistant UC. A discrete choice experiment with patients and clinicians will quantify their preferences and estimate relative utility and willingness to trade between different treatment options. Finally, through a multi-disciplinary stakeholder workshop with patients and healthcare professionals, we will present and discuss the findings from this study to generate recommendations about the future optimum treatment and future research.

4. Study Design and Data Collection, Analysis and Storage

This is a mixed methods study composed of five work packages (WP) using a combination of quantitative and qualitative research methods to help achieve each of the five corresponding objectives: (WP1) cross sectional online survey of healthcare professionals (HCPs), (WP2) qualitative interviews with HCPs, (WP3) qualitative interviews with patients with UC, (WP4) discrete choice experiment and (WP5) multi-stakeholder workshop. The details of the sampling, recruitment, data collection and analysis processes for each of the work packages are now described in sub-sections 4.1-4.5. Details of data storage procedures are detailed in section 4.6. Please refer to appendix 1 for the Gantt chart.

4.1 Work Package 1: Cross-sectional online survey of healthcare professionals

4.1.1 Overview

We will conduct a cross-sectional survey of IBD healthcare professionals in the UK to describe the current management of patients with steroid resistant UC. The survey will also allow us to explore how UK clinicians define steroid resistance, their preferences for different treatments and the factors influencing treatment offers.

4.1.2 Sampling

A survey of approximately 1180 healthcare professionals will be conducted online using the Qualtrics platform. This will include the 950 members of the IBD section of the British Society of Gastroenterology and the 230 members of the Royal College of Nursing IBD Nurses Network. We anticipate a 60% response, based on previous surveys of IBD HCPs [26–28] and therefore our sample size is expected to be 700.

4.1.3 Eligibility and recruitment

Healthcare professionals will be eligible to participate in this survey if they are a member of a medical, nursing or Allied Health Professional staff with a specialist interest or expertise in providing care to patients with IBD (particularly ulcerative colitis) within an NHS Trust in the UK. The membership to the IBD section of the BSG and RCN IBD Nurses Network indicates their interest in this clinical area.

Email invitations will be sent to all current members of these two groups and interested parties will be asked to provide informed consent online before completing the survey. The current section chairs of both groups have confirmed their support for distributing the survey. We will issue the survey with a detailed invitation email explaining the purpose of the study and provide a link to the online questionnaire.

We will also use the survey as an opportunity to identify and recruit healthcare professionals for WP2 by adding a section at the end of the questionnaire to ascertain their willingness to be contacted about an in-depth qualitative interview at a later stage in the project.

4.1.4 Data collection

The data for the survey will be collected online using Qualtrics. Qualtrics is a secure online survey platform, enabling participants to complete the survey via an iPad, tablet, or computer. Where participants request a paper-based questionnaire, this will be returned via freepost to the study team, who will enter the data directly into the online survey. We anticipate that the survey will take approximately 15 minutes to complete.

The aim of the survey is to describe:

- Current management pathways for patients with steroid resistant UC;
- How healthcare professionals define steroid resistance
- Preferences for different treatment options, e.g. vedolizumab, tacrolimus, methotrexate, anti-TNF agents (infliximab, adalimumab, golimumab), surgery
- Factors influencing the offer of treatments, e.g. local protocols, individual clinical preference, supporting research evidence, costs of treatment, perceived patient preference; stage of the disease; side effects

We will also collect demographic information about participants (role, clinical specialty, year of registration etc.) and their department and hospital to help understand how practice varies between regions and hospital types. The collection of this information will also feed in to the purposive sampling strategy for WP2. The survey will include a combination of question types: binary response (yes/no); frequency response (always, sometimes, occasionally, never) or options to be selected from a menu. The content of the survey will be developed by study team, and piloted with local clinicians from the collaborating clinical centres prior to distribution [29].

In order to maximize response rates, we will undertake the following activities:

- The survey will be open for approximately 8 weeks, and up to four reminders will be sent to non-responders encouraging them to complete this.
- Incentive prize draw for participation.
- Advertise the survey on social media via our dedicated study Twitter account and Facebook networks.
- Whilst we anticipate that most potential participants will be able to complete the online questionnaire successfully, they will also be able to request a paper-based version of this.

4.1.5 Data analysis

Quantitative results from the survey will be mostly presented using descriptive statistics. Continuous outcomes will be presented using means and standard deviations or medians and interquartile ranges as appropriate to the data. Categorical data will be presented using frequencies and percentages per category. These results will be presented for all respondents and then further split by variables of interest e.g. centre, job role, geographic location etc. to identify any potential differences in disease management or clinical preference depending on these factors. All results will be extracted using suitable statistical programs such as R or Stata [30,31]. Qualitative results from open-ended questions will be summarised thematically.

4.2 Work Package 2: Qualitative interviews with HCPs

4.2.1 Overview

We will carry out qualitative interviews with a sample of healthcare professionals with expertise in IBD to understand in more depth how patients with steroid resistance are currently managed. Whilst the survey in WP1 will provide us with a national picture of current service provision, the completion of in-depth interviews with staff will allow us to understand how this is operationalized in clinical practice, and the barriers and facilitators to provision of different treatments.

4.2.2 Sampling

Approximately 20-25 healthcare professionals (HCPs), sampled purposively based on job role (medical, nursing), centre size, teaching hospital status, location (and other factors identified by study team as influencing practice), will be recruited from across the United Kingdom.

4.2.3 Eligibility and recruitment

We will recruit 20-25 HCPs over a two-month period, drawn from the sub-sample of participants in the WP1 survey who consent to being approached about a qualitative interview. HCPs will be eligible to participate in these qualitative interviews if they are a member of medical or nursing staff with a specialist interest or expertise in working with patients with Inflammatory Bowel Disease, particularly ulcerative colitis. The research team will develop a purposive sampling strategy, and then contact potential participants by email, letter or telephone to invite them to take part in a telephone interview.

Where the initial contact is by letter or email, this will give a short summary reminder of the study and a copy of the participant information sheet. In these cases, the researcher will follow up with a telephone call (or email) to discuss the study with the potential participant, and where they are interested, organize a mutually convenient time at which to complete the interview. Where the initial contact is by telephone, the researcher will provide a verbal explanation of the

study, provide the HCP with an opportunity to ask questions and where they are still interested, the researcher will provide a copy of the participant information sheet by email/post prior to the agreed interview date. Reasons for non-participation will be recorded.

Due to the nature of the telephone interviews, verbal consent to participate in the interview and to this being audio recorded for the purposes of analysis, will be taken from all participants before data collection commences. Separate, anonymous recordings of participants providing consent will be stored securely for audit purposes. All participants will be assigned a unique anonymous study ID.

4.2.4 Data collection

Individual semi-structured interviews (up to a maximum of 60 minutes duration) will be conducted with healthcare professionals by telephone. We will use semi-structured interview topic guides to explore how they operationalize definitions of steroid resistance, their current practice and preferences for treatment options for patients with steroid resistant UC (which will also be used to inform the design of DCE outlined in section 4.4). In line with PPI group feedback, the interviews will also include questions on the types of information that HCPs need to make decisions about the treatments that they offer. The interviews will incorporate case vignettes of hypothetical patients with steroid resistant UC. These vignettes will be developed by the clinical members of the research team, and will be used to facilitate critical distance for the interview participant and a mechanism to encourage them to think about different strategies for treating this patient group, to help them to explain their clinical practice. The qualitative interviews with healthcare professionals will also provide us with an opportunity to explore any emerging issues from WP1 in more depth.

4.2.5 Data analysis

All interviews will be transcribed verbatim for the purposes of analysis. Key themes arising from the data will be summarized based on thematic analysis of transcriptions [32]. We will carry out a deductive thematic analysis, structured around the findings from WP1, and in accordance with the six recommended stages of thematic analysis [28]: (1) familiarisation with the data; (2) generation of initial codes; (3) searching for themes; (4) reviewing themes; (5) defining and naming themes and (6) producing the report. NVivo software (QSR International) will be used to help structure the analysis.

4.3 Work Package 3: Qualitative interviews with patients with UC

4.3.1 Overview

We will also carry out qualitative interviews with people living with UC to explore their experiences of different treatments and decision making about different treatments, as well as their treatment preferences. Adjustment to life with UC is a complex process and patients' responses vary, so it's important to conduct in-depth qualitative work that allows a detailed exploration of individual experience.

4.3.2 Sampling

Approximately 30-35 patients with UC, purposively sampled (based on age, gender, ethnicity, duration of disease and previous treatment, including response to steroids) will be recruited from the three collaborating NHS centres (Sheffield, Hull and Liverpool).

4.3.3 Eligibility and recruitment

We will recruit 30-35 patients over a two-month period (i.e. 5 patients per centre, per month). Patients with ulcerative colitis extending beyond the rectum and who have active disease at the time of participation or have previously had active disease successfully treated with steroids are eligible for this work package. In addition, patients who may have been considered to have had steroid resistant disease and already made a decision to have surgery are also eligible as they are able to reflect on the decision making processes for each stage of treatment, albeit through retrospective accounts.

Individual patients will be invited to participate in the qualitative interview study by letter or email, or given verbal explanations of the study during clinical appointments at the local Gastroenterology departments of participating centres, or over the telephone. The letters will provide a short summary of the proposed study and a copy of the participant information sheet will be provided. Potentially interested participants will be required to opt-in to the study by contacting the research team (by telephone or email). Those patients who are approached during face-to-face appointments and express an interest in finding out more about the research will be provided with a copy of the participant information sheet to review, and if they are interested advised to contact the research team (as above) or give verbal consent to their healthcare professional to pass on their contact details directly to the research team to follow-up. The study will also be advertised in local Gastroenterology departments using posters and leaflets, and via social media outlets.

To inform the purposive sampling strategy, during the initial contact with interested patients, the research team will collate summary clinical and demographic information about each patient. This initial contact will also allow the potential participant to ask any questions about the research before they agree to participate. Where the patient is still interested in taking part in an interview, a mutually convenient time for this will then be organised. Reasons for non-participation will be recorded.

Due to the nature of the telephone interviews, verbal consent to participate in the interview and to this being audio recorded for the purposes of analysis, will be taken from all participants before data collection commences. Separate, anonymous recordings of participants providing consent will be stored securely for audit purposes. All participants will be assigned a unique anonymous study ID.

4.3.4 Data collection

Individual semi-structured interviews (up to a maximum of 60 minutes duration) will be conducted with patients by telephone. Alternative interview modes (face-to-face or online) will be offered to patients to help maximize recruitment. We will also make it clear to potential participants in recruitment materials that 60 minutes is the likely maximum interview duration, and that they will be able to take breaks as they see fit, in recognition of the issues faced by patients during an UC flare. We will use semi-structured interview topic guides to explore the lived experience of UC, and approaches to treatment decision-making, using the Coping in Deliberation (CODE) framework [33].

The CODE framework is a multi-level, theoretically informed framework which promotes an exploration of the complexity of decision making by patients in preference-sensitive healthcare settings, such as steroid UC [33]. Within CODE, deliberation is classed as a six-stage process: (1) presentation of health threat; (2) choice; (3) options; (4) preference construction; (5) the decision itself and (6) consolidation; and coping is presented in three stages: (1) threat; (2) primary and secondary appraisal; and leading to (3) a coping effort. Breaking down the

processes down into categories provides a helpful structure through which to explore the divergent experiences and preferences of patients at different stages in the treatment pathway.

The interviews will be tailored to patient's experiences in relation to steroid resistance. For example, for responders we will ask: what would you have regarded as a failure of steroid therapy (which on-going symptoms, side-effects, need for endoscopy); and what would you have done if the steroids had not worked? In non-responders, which of these features were important in deciding non-response?

As part of the interviews, patients will be asked about their preferences for future treatment options, which will also help to identify key attributes and levels for the design of the choice questionnaire [34] (see 4.4.3 below).

4.3.5 Data analysis

All interviews will be transcribed verbatim for the purposes of analysis. Key themes arising from the data will be summarized based on thematic analysis of transcriptions [32]. We will carry out a deductive thematic analysis, structured around the CODE framework to allow us to explain patient preferences, via the six recommended stages of thematic analysis as described in 4.2.5 above. NVivo software (QSR International) will be used to help structure the analysis.

4.4 Work Package 4: Discrete choice experiment

4.4.1 Overview

Discrete choice experiments (DCEs) are an attribute-based measure of benefit, based on the assumption that health-care interventions, services or policies can be described by their attributes [35]. In DCEs, respondents make decisions about quantity or quality differentiated versions of a good or service that requires them to make trade-offs. The resulting choices are analysed to estimate the overall utility (value) and willingness to trade between services. In the last decade, DCEs have been increasingly used to identify patient preferences in health and healthcare [34,36–39]. While some studies have applied the DCE method to Ulcerative Colitis [40,41]. Evidence on preferences for the steroid resistant population is currently non-existent in the research literature. This study will use a discrete choice experiment to elicit patient and healthcare professional (HCP) preferences for the treatment of ulcerative colitis in the UK.

4.4.2 Sampling

Clear guidelines are lacking in the literature on methods to calculate sample sizes, which vary substantially from 100 to 600 [42]. A number greater than 100 is recommended as it ensures a basis for modelling preference data [43]. We will undertake an online DCE with up to 180 patients with ulcerative colitis, and up to 200 HCPs.

4.4.3 Development and design of the choice questionnaire

During the first stage of the qualitative study with HCPs and patients (work packages 2 and 3) we will conduct in-depth semi-structured interviews to identify key attributes such as drug treatment and levels (e.g., risk reduction, symptom control) important to both clinicians and patients [44,45]. Should the preferences of the HCPs and patients overlap significantly, then we will conduct a single choice experiment with both. Patient co-applicants will review the findings and they will be asked to comment on its comprehensiveness, treatment preferences, and to check that attributes have not been omitted. Data will be analysed using CODE framework analysis [33] in the latest version of NVivo (QSR International).

Discussions with clinical and patient experts will confirm the list of attributes and levels. We will design choice profiles and pilot the choice experiment questionnaire with a random selection of PPI members. They will be invited to participate in a pilot exercise to provide feedback on comprehension of the choice questionnaire and to confirm plausibility of attribute combinations and levels.

Following validation of the attributes and levels chosen, we will construct a choice experiment using NGene software (ChoiceMetrics, Australia). A main effects fractional factorial design will be used to avoid presenting too many alternatives to participants [36,37]. We will present forced unlabelled choices 'option 1' or 'option 2' to respondents avoiding the use of an 'opt out' alternative for the purposes of realism.

4.4.4 Eligibility and recruitment

We will recruit 180 patients from three NHS centres (Sheffield, Hull and Liverpool) over a three-month period (i.e. 20 patients per centre, per month) [42]. All patients who have a diagnosis of ulcerative colitis extending beyond the rectum will be eligible to participate in this work package. We will recruit up to 200 healthcare professionals from the IBD section of BSG and RCN (as with WP1).

Individual patients will be invited to participate in the DCE by letter or email, or given verbal explanations of the study during clinical appointments at the local Gastroenterology departments of participating centres. The letters / emails will provide a short summary of the proposed study and a link to the online survey, to enable interested patients to easily access this. Those patients who are approached during face-to-face appointments and express an interest in finding out more about the research will be provided with a copy of the recruitment letter or where they agree, sent a follow-up email containing a direct link to the survey to facilitate easy access to this. The study will also be advertised in local Gastroenterology departments using posters and leaflets and via social media outlets.

As with WP1, HCPs will be invited to participate by email. The cover email will include a link to the online survey. Paper based questionnaires will be available on request (as with WP1).

Consent to participate will be taken online, via the Qualtrics platform where the survey will be hosted. Participants will first be presented with the electronic participant information sheet, which will provide a detailed explanation of the study, simple instructions and contact details (email address and telephone number) for the research team in the event of any queries or questions. After reading the PIS, participants will need to tick a box to confirm they have read and understood this before they move on to complete the questionnaire.

4.4.5 Data collection

The survey will be administered via Qualtrics, which is a secure online survey platform, enabling participants to complete the survey via a computer, iPad or tablet. Qualtrics saves responses automatically at the end of each completed screen, and allows the researchers to download all responses into software for data cleaning and statistical analysis.

The questionnaire will contain hypothetical choice scenarios (typically range from 8-12 choice sets to avoid cognitive burden) and will ask patients and clinicians to make choices between two sets of treatments (e.g. immunosuppressive agents (methotrexate, tacrolimus), biologic agents (anti-TNF and anti-integrin), new oral agents, in-patient intravenous steroids or

surgery), with varying levels e.g. symptom control, on-going burden of treatment, frequency of treatment, side-effects. For patients, demographic data, duration of disease and previous treatments, current disease activity via the IBD-Control questionnaire [46], health related quality of life via the EQ-5D-5L [47] and medication use will be gathered after the completion of the choice set. Gathering data on patients' clinical status will allow us to model the differences in preferences based on their clinical background. For healthcare professionals, demographic information about participants (including role, grade, clinical specialty, year of registration, degree of sub-specialisation in IBD) and their department and hospital will be collected. The questionnaire should take no more than 25 minutes to complete.

4.4.6 Data analysis

Responses from the choice questionnaires will be modelled using a conditional logit model which is commonly used for the analysis of choice data [36] using the latest version of Stata [31]. Regression coefficients will be used to estimate the relative importance of attributes and the marginal rates of substitution will be calculated (i.e. trade off preferences for treatments). Furthermore, latent class models will be used to analyse individual heterogeneity and to identify subsets of patients and clinicians with varying preferences [48].

4.5 Work Package 5: Multi-stakeholder workshop

4.5.1 Overview

We will triangulate the findings from WP1-4 to generate summary findings from the research for consideration by a multi-disciplinary group at a whole-day workshop to be held towards the end of the study. The workshop represents a key stage in our dissemination strategy and will involve direct knowledge mobilization, using the findings to help generate the recommendations from PoPSTER. Bringing together patients and clinicians to review our findings provides an excellent opportunity to ensure that our study makes realistic and meaningful recommendations to the NIHR.

4.5.2 Triangulation of research findings

Given the different methodological approaches, varied datasets to be generated and the involvement of multiple researchers in data collection and analysis we will develop a triangulation protocol to manage the analysis and interpretation of the data from WP1-4, as part of the preparation for the multi-stakeholder workshop. We will adapt the approach recommended by Farmer et al [49]. Subsequent to the initial analysis stages for each WP, and subject to decision rules underpinning the analyses of these data, we will complete the following steps:

1. Data sorting: to identify areas where the content overlaps or deviates.
2. Convergence coding: develop a convergence coding matrix to compare findings in terms of (a) meaning and interpretation and (b) frequency and prominence between datasets against the following criteria – agreement; partial agreement; silence or dissonance.
3. Convergence assessment: we will review all compared data segments to provide an overall assessment of convergence.
4. Completeness assessment: we will compare the unique topic areas for each data source to document the key differences in scope or coverage.
5. Researcher comparison: we will compare assessments by different researchers and a plan for handling of disagreement and how final decisions on interpretations will be reached.

6. Feedback: the findings from this stage of the process will be shared with the multidisciplinary members of the SMG and PPI groups for review and clarification.

Working through these steps will promote transparency and increase the robustness of the analysis process, and will also allow us to identify how the data converge or diverge in order to generate meta-themes that intersect different study findings. The output from step 6 will form the basis of the material to be presented at the multi-stakeholder workshop.

4.5.3 Eligibility and recruitment

Patients with UC and IBD healthcare professionals will be invited to attend a whole day workshop for PoPSTER. We will include a statement on the consent forms for WP1-4 to ascertain whether participants are interested in attending this workshop. We will then sample purposively based on the findings of WP1-4, to achieve representation across relevant patient and professional groupings. Where necessary, we will advertise the workshop via wider patient and clinical forums, such as the BSG.

We will send letters and emails to all potential participants, reminding them about the research and the purpose of the workshop, providing details of the date, time and location of the event. People who are interested in attending the workshop will be asked to register with the research team. Informed consent to participate in the workshop and to have their contributions audio recorded and used for research purposes will be sought from all attendees at the start of the day.

4.5.4 Data collection

To encourage reflection, provide a focus for discussion and promote clear decision making, the workshop will be structured around Borton's reflective prompt questions: 'What?', 'So What?', 'Now what?' [50]. This will enable the workshop attendees to consider the research findings and generate recommendations for future research and management strategies for steroid resistant UC:

What? - Discussion about what the research has found across WP1-4
So what? - Discussion around the implications of the findings for future treatment options and research priorities.
Now what? - Agreement about what needs to happen next and the key recommendations to be made to the NIHR.

We will summarise the triangulated research findings from WP1-4 (what?) in terms of key themes, and we will use rounds of small group discussion (each group will include representatives from the patient community, medics and nurses and at least one researcher from the PoPSTER team) about each of the key themes, and plenary feedback sessions to generate the recommendations. A member of the research team will facilitate each small group, and they will summarise the details of the discussions (so what?) and agreed recommendations (now what?).

This approach will allow us to make clear recommendations on the optimum treatments for steroid resistant UC from the patient and clinician perspective. We can then use the findings to inform the design of a randomised controlled trial to evaluate clinical and cost-effectiveness of recommended treatment options.

As above, we will seek written informed consent from all workshop participants to use the notes of the discussions in the reporting from this study, and to have the plenary discussion sessions recorded.

4.5.5 Data analysis

A report of the workshop group discussions and decision points will be generated, using the what/so what/now what framework. The structure of this approach lends itself well to clear post-meeting reporting [51].

4.6 Data storage

Physical data

Completed paper consent forms and questionnaires will be stored in the investigator site file in a locked office at the University of Sheffield, as will any notes taken during the interviews by the researchers. The notes will be written up into electronic format and anonymised, and the originals subsequently destroyed as soon as possible. Access to this data will be limited to appropriate members of the research team only.

Electronic data

Interviews and the workshop will be audio recorded using an encrypted recorder and then transcribed and anonymised, with the original files subsequently being destroyed as soon as possible. Access to electronic data will be limited to appropriate members of the research team only.

Archiving

Study data will be retained for a period of 5 years after the end of the study, and will be archived in line with Sheffield CTRU Standard Operating Procedures. Documentation stored at site will be sent to the Sheffield CTRU for archiving.

5 Ethics

5.1 Assessment and management of risk

Information may be received during the course of the interviews in WP2 and WP3 which have safeguarding implications, either for the participant, or individuals in the care of healthcare professionals involved. A risk management plan will be put in place to detail the processes to be followed in the event of such situations arising - information will be reported and shared in line with local Trust policies, and provided on a need to know basis. Issues identified and decisions made will be recorded and stored by the central study team.

Aside from such issues, there is also a chance that participants may become distressed during discussions, given the sensitivity of IBD. They will be encouraged to a break in such situations, and also have the option of leaving entirely if necessary.

5.2 Research Ethics Committee (REC) and other regulatory review

REC and HRA approvals

The study will not be initiated before the protocol, informed consent forms and participant information sheets have received approval from the Research Ethics Committee (REC), the Health Research Authority (HRA) and local Capacity and Capability is confirmed by the

respective National Health Service (NHS) Research & Development (R&D) departments. MHRA approval is not required for this study. The application will be submitted through the IRAS central allocation system.

Regulatory review and compliance
This study will be conducted in accordance with Good Clinical Practice Guidelines and CTRU standard operating procedures. The study will be conducted subject to Research Ethics Committee favourable opinion including any provisions for site specific assessment. Local research governance approvals will be sought from all participating research sites. The approval letter from the ethics committee and copy of approved patient information leaflets, consent forms and any ethically approved data collection tools will be present in the site files before initiation of the study and patient recruitment.

Amendments
Should a protocol amendment be made that requires REC approval, the changes in the protocol will not be instituted until the amendment and revised informed consent forms and participant information sheets (if appropriate) have been reviewed and received approval / favourable opinion from the REC and/or HRA. Minor protocol amendments only for logistical or administrative changes may be implemented immediately; and the REC will be informed.

5.3 Peer review

This study has undergone extensive peer review as part of the Health Technology Assessment (NIHR) application process. Key collaborators have been involved in developing the research proposal with specialist expertise in IBD and research methods. The protocol and associated documentation for this study was peer reviewed within the study team prior to submission.

5.4 Patient and Public Involvement (PPI)

There are three patient co-applicants on this grant who will be integral members of the study management group and as such, will steer the delivery of the research, develop study documents and interpretation of the results.

In parallel to this, we will establish a wider patient network using existing local links in the collaborating centres and online patient networks, and this group of patients will provide input to the study design and implementation. We will convene two dedicated PPI meetings of this group per project year, timed to coincide with key stages of the project, such as development of study materials for each work package; pilot testing of interview topic guides or questionnaires; interpretation of qualitative research findings and so on.

Patient involvement is also paramount to the completion of work package 5, with the focus on triangulation and dissemination of findings. As discussed above, our aim is to bring together patients and HCPs to help generate the recommendations from our study.

5.5 Protocol compliance

This study will be conducted in compliance with the protocol, GCP and regulatory requirements.

5.6 Data protection and patient confidentiality

Participant confidentiality will be respected at all times. Study documents (paper and electronic) will be retained in a secure location during and after the study has finished. All source documents will be retained for a period of 5 years following the end of the study. Where study related information is documented in the medical records – those records will be retained for 5 years after the last patient visit. Each site is responsible for ensuring that records are archived and the information about the location of this supplied to the Chief Investigator.

All electronic data will be accessed on university computers that are password protected and maintained within university servers with encrypted off/cross-site backups.

5.7 Indemnity

The study has been financed by the NIHR and details have been drawn up in a separate agreement. This is an NHS sponsored study. If there is negligent harm during the research project when the NHS body owes a duty of care to the person harmed, NHS Indemnity will cover NHS staff, medical academic staff with honorary contracts and those conducting the trial. NHS Indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Ex-gratia payments may be considered in the case of a claim. The University of Sheffield has in place insurance against liabilities for which it may be legally liable and this cover includes any such liabilities arising out of this research project.

5.8 Access to the final study dataset

Access to the study data will be granted to members of the research team to ensure that they only have access to the data required to complete their tasks. All electronic data will be accessed on university computers that are password protected and maintained within university servers with encrypted off/cross-site backups.

6 Dissemination, outputs and anticipated impact

Our dissemination strategy has clearly defined goals, target audiences, credible messengers and adequately resourced knowledge mobilization strategies to promote the uptake of the research [52].

6.1 Goals

1. Make recommendations about future research to evaluate treatments for steroid resistant UC
2. Raise awareness of patient and clinician preferences for treatments for steroid resistant UC

6.2 Passive diffusion

Conference presentations: we will present the findings at local and national meetings, including the annual meetings of the British Society of Gastroenterology, the European Crohn's and Colitis Organisation, and the Digestive Diseases Weeks of United European Gastroenterology and the American Gastroenterology Association.

Non-peer reviewed publications: We will contribute pieces to news briefs and website of the patient charity Crohn's and Colitis UK (https://www.crohnsandcolitis.org.uk) and the IA Journal (Ileostomy and Internal Pouch Support Group).

Peer-reviewed publications: We anticipate that we will publish at least one article from each of the five work packages. We will publish in relevant clinical journals (such as Gut, Journal of Crohn's and Colitis, Inflammatory Bowel Diseases, or Nature Gastroenterology and Hepatology, Gastrointestinal Nursing) and methodological journals (e.g. BMC Health Services Research, Implementation Science). Open access publication will ensure that our findings are widely available.

Web-based activities and social media: We will utilize the team's links with the BSG and CCUK to arrange postings on their webpages and Facebook pages. We will also set up a dedicated Twitter account for the study to raise awareness amongst the patient and wider clinical community throughout the conduct of the study. We will also collaborate with existing local Twitter accounts @shefgastro and @ShefIBD. We will use currently active hashtags to influence social networks, including #IBD #colorectalresearch and #UC.

7.3 Active dissemination

Sheffield Teaching Hospitals and The University of Sheffield will put out a media release to raise awareness of the study at its inception. Through the research team's links with BSG and CCUK, we will distribute directed communications about the research to their members through the completion of the study.

All study participants (healthcare professionals and patients) will receive a copy of the study findings – both from the specific work package they participate in, and an overall summary following completion of WP5. Indeed, the conduct of the multi-stakeholder workshop is predicated on a commitment to knowledge mobilization.

We will work collaboratively with people with ulcerative colitis throughout the study and develop dissemination materials that are accessible and meaningful to both patients and healthcare professionals. This will enable us to develop materials that are tailored to different stakeholder groups – shorter plain language summaries and summary briefings. We have also requested a small amount of funding to support graphic design work to facilitate the development of visually pleasing and accessible outputs.

In addition, clinical and patient members of the study team are well connected within the wider IBD community and are well positioned to transfer the knowledge generated via the research.

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Appendix 1 – Gantt chart

This is a 24-month project with concurrent work packages, which commenced in November 2018.

	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12	M13	M14	M15	M16	M17	M18	M19	M20	M21	M22	M23	M24
	Nov-18	Dec-18	Jan-19	Feb-19	Mar-19	Apr-19	May-19	Jun-19	Jul-19	Aug-19	Sep-19	Oct-19	Nov-19	Dec-19	Jan-20	Feb-20	Mar-20	Apr-20	May-20	Jun-20	Jul-20	Aug-20	Sep-20	Oct-20
Study Wide Tasks																								
Study Steering Committee meetings																								
Study Management Group meetings																								
Patient and Public Involvement Panel meetings																								
REC/HRA application and approvals																								
Local governance approvals (WP3-4)																								
WP1: Online Survey																								
Survey design and piloting																								
Survey recruitment and data collection																								
Survey data analysis																								
WP2: HCP Interviews																								
Qualitative study design and set up																								
Recruitment of HCPs																								
Data collection																								
HCP qualitative data analysis																								
WP3: Patient Interviews																								
Qualitative study design and set up																								
Recruitment of patients																								
Data collection																								
Patient qualitative data analysis																								
WP4: Discrete Choice Experiment																								
DCE design and set up																								
DCE questionnaire development and piloting																								
Recruitment of patients																								
Data collection																								
DCE data analysis																								
WP5: Multi-stakeholder Workshop																								
Workshop design																								
Recruitment to workshop																								
Triangulation of findings from WP1-4																								
Multi-stakeholder workshop																								
Reporting and wider dissemination activity																								