IMPACT OF BIOLOGIC AND IMMUNOMODULATORY THERAPY ON SARS-COV-2 INFECTION AND IMMUNITY IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE.

SHORT STUDY TITLE / ACRONYM	**impaCt of bioLogic therApy on saRs-cov-2 Infection and immuniTY CLARITY**
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Table of Contents

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publicly available, through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature: Date:
..... 09-06-2020
Helen Quinn, Director Joint Research Office
University of Exeter & the Royal Devon and Exeter NHS Foundation Trust

Chief Investigators:

Dr Tariq Ahmad
Date: 09-06-2020

Dr Nick Powell
Date: 09-06-2020

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STUDY SUMMARY

Inflammatory bowel disease (IBD) affects about 1% of the UK population and is usually treated with immunosuppressive drugs. Side effects include an increased risk of serious infection, most notably pneumonia. Vaccination studies also show these drugs impair protective antibody responses. The impact of immunosuppressive treatment on SARS-CoV-2 infection and disease severity is unknown but is a major concern for patients and clinicians. As a precaution, the UK Government advised prolonged shielding for many patients treated with these drugs.

Using the Roche Elecsys immunoassay to test serum samples from >7500 IBD patients stored since the start of the pandemic, we will report the SARS-CoV-2 emerging seroprevalence. We will simultaneously conduct a 40-week prospective study of an additional 6970 patients treated with infliximab (anti-TNF) versus vedolizumab (anti-integrin) using our established clinical network of UK IBD centres. Data from both cohorts will be used to define the impact of immunosuppressive drug therapy and physical distancing strategies on SARS-CoV-2 seroprevalence. Serial testing in the prospective cohort will define the durability and magnitude of protective immune responses.

This study will provide an evidence base for safer prescribing of immunomodulator and biologic drugs in the COVID-19 era and inform public health policy regarding physical distancing measures, and future vaccination strategies. Although this study will define risk in IBD patients, there are potentially important lessons to be learned for millions of patients across the UK with other immune mediated diseases treated with similar therapies.

FUNDING AND SUPPORT IN KIND

FUNDER(S)	FINANCIAL AND NON FINANCIALSUPPORT GIVEN
F. Hoffmann-La Roche AG	Provision of test kits and reagents to assess SARS-CoV-2 antibodies AND £200,000 to support investigator-initiated study
Takeda UK Ltd	£50,000 to support investigator-initiated study
Royal Devon and Exeter NHS Foundation Trust	£36,000
Hull University Teaching Hospital NHS Trust	£30,000

ROLE OF STUDY SPONSOR

The study Sponsor is the Royal Devon and Exeter NHS Foundation Trust (RD&E). The Sponsor has no direct role in trial design, data analysis and interpretation, manuscript writing or dissemination of results. In terms of study conduct, the RD&E will fulfil its role of research sponsor as set out in the UK Policy Framework for Health and Social Care Research. Any delegation of duties will be formally documented but the Sponsor retains overall responsibility. A Sponsor representative will be invited to study management group meetings as an observer. The Sponsor will be responsible for financial oversight of the study.

ROLES AND RESPONSIBILITIES OF STUDY GROUPS

Study Management Group (SMG)

The overall role of the SMG is to assist the study investigators in protecting the interests of study participants and preserving the study's integrity, credibility and direction. The SMG will comprise a chair, a member of the public advisory group, a representative of the sponsor from the department of R&D at the Royal Devon and Exeter Hospital, a gastroenterologist, chief investigators, trial manager, a senior NHS research nurse and the study statistician.

Specific roles will include:

- Reviewing the protocol to ensure the study will address the project's specific aims
- Recommending and reviewing proposed protocol changes.
- Monitoring performance, including recruitment, retention, overall study progress, and adherence to study protocol.
- Evaluating patient safety. Determining when patients and local PIs should be notified about positive or abnormal findings.
- Assessing data quality and quality control procedures.
- Evaluating the data analytical plan.
- Evaluating the publication plan, including topics and preparation schedule.
- Reviewing performance of individual research sites and, if necessary, recommending actions to improve performance or to terminate participation of specific research sites.
- Reviewing and providing recommendations prior to submission of any manuscript

Public Advisory Group (PAG)

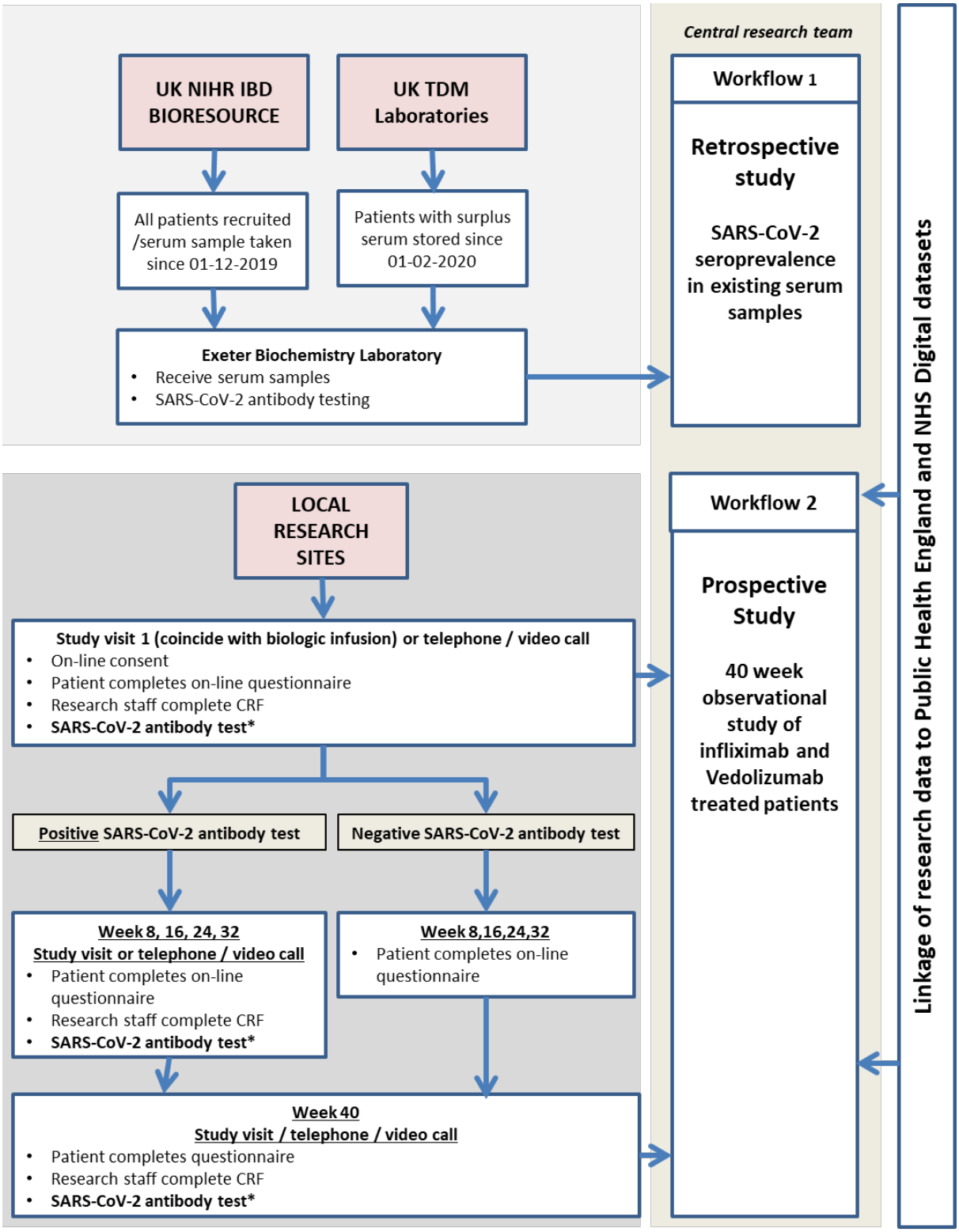
The PAG will comprise 5 people with lived experience of IBD who will collaborate with researchers throughout this project.

Specific roles will include:

- Review of study documents including patient information sheets and consent forms
- Advising on barriers to recruitment.
- Production of a bimonthly newsletter to disseminate study progress to participants and PIs, supported by the study manage.
- Dissemination of study findings

KEY WORDS: SARS-CoV-2, Immune-mediated inflammatory diseases, Inflammatory bowel disease, anti-TNF therapy, vedolizumab, immunosuppressant, vulnerable patient groups.

STUDY FLOW CHART



*standard venepuncture or home finger-prick

STUDY PROTOCOL

IMPACT OF BIOLOGIC AND IMMUNOMODULATORY THERAPY ON SARS-COV-2 INFECTION AND IMMUNITY IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE.

BACKGROUND

Inflammatory bowel disease (IBD), comprising Crohn's disease (CD) and ulcerative colitis (UC), is a chronic immune-mediated inflammatory disease (IMID) that affects approximately 1% of the UK population[1–4]. Like other IMIDs, IBD treatment typically requires immunosuppression with immunomodulators (e.g. azathioprine), and/or monoclonal antibodies, that selectively target disease relevant cytokines, such as tumour necrosis factor (TNF) or interleukin (IL)12p40, or the immune cells that produce them (anti-integrin). The efficacy of IBD therapies depends on effective modulation of mucosal immune responses. However, these drugs also suppress immune responses required for protective host immunity, thereby leaving patients susceptible to infection. Large prospective registries of IBD patients have consistently shown a significant increased risk of all types of opportunistic infection associated with anti-TNF drugs with pneumonia by far the most frequent complication[5,6]. In contrast, vedolizumab, a gut selective anti-integrin α4β7 monoclonal antibody, blocks lymphocyte trafficking to the gut and does not increase susceptibility to systemic opportunistic infections.

Insights into how different IBD therapies impact host immunity can also be inferred from serological responses to vaccination. Infliximab monotherapy is linked to impaired induction of protective immunity following hepatitis B[7], hepatitis A[8], pneumococcal[9,10] or influenza vaccination[11,12], and some studies have found that impaired seropositivity is especially pronounced when anti-TNF therapy is combined with immunomodulators[13,14]. Vedolizumab, however, which has a gut specific mechanism of action, does not hinder hepatitis B or influenza vaccination, but is associated with impaired antibody responses to cholera toxin, administered orally[15].

The coronavirus (COVID-19) pandemic is a global crisis caused by SARS-CoV-2, a novel coronavirus not previously known to infect humans[16,17]. In severe cases, SARS-CoV-2 causes life-threatening pneumonia, acute respiratory distress syndrome and multi-organ failure. The impact of immunosuppressive and biologic drugs on SARS-CoV-2 acquisition, illness and immunity are currently unknown[18]. However, public health measures, such as enhanced social distancing and shielding, have been advocated for most patients with IBD treated with immunosuppressant medicines.

This study investigates the impact of biologic and immunomodulatory therapy on SARS-CoV-2 infection and immunity in patients with inflammatory bowel disease.

The study will utilise:

1. **Existing stored serum samples** collected by therapeutic drug monitoring laboratories across the UK and the UK NIHR IBD Bioresource project.
2. The established **UK IBD clinical research network** of 145 research sites to deliver an appropriately powered prospective study in 40 weeks. This network has successfully recruited to the UK NIHR IBD BioResource (https://www.ibdbioresource.nihr.ac.uk) and the pharmacogenetic studies, PRED4 and PANTS (https://www.ibdresearch.co.uk, IRAS 86045 and 115956)[19–23].

3. The PHE approved **Elecsys SARS-CoV-2 serology assay** as part of a collaboration with F. Hoffmann-La Roche AG
4. The **sample reception, storage and serology testing facilities** of the Academic Department of Blood Sciences at the Royal Devon and Exeter NHS Foundation Exeter who have more than 20 years' experience supporting investigator led and commercial multi-site research projects

RATIONALE

This proposal will define COVID-19 risk in an important vulnerable patient group and how commonly used immunosuppressive and biologic drugs impact this risk. The results of this study will have major implications for healthcare policy of vulnerable patients with IMIDs in the UK. The study will also inform the strategy of forthcoming vaccination in this population.

AIMS

The aims of this study are to define the impact of biologic class, concomitant use of an immunomodulator and physical distancing strategies on SARS-CoV-2 infection and immunity

OBJECTIVES

In patients with IBD does biologic class, concomitant use of an immunomodulator and/or physical distancing strategies impact:

1. Emergence of seroprevalence of anti-SARS-CoV-2 antibodies?
2. Titres of anti-SARS-CoV-2 antibodies?
3. Risk of seropositive symptomatic COVID-19?
4. Severity of COVID-19?
5. Durability of detectable anti-SARS-CoV-2 antibodies and their titre over time?
6. Immunity for coronavirus disease following seroconversion?

OUTCOMES

Workflow 1

Primary outcome measure

Cumulative seropositivity of anti-SARS-CoV-2 antibodies, using the Roche Elecsys assay.

Secondary outcome measure

In patients with more than one test, change in anti-SARS-CoV-2 antibody positivity and cut-off index (COI).

Workflow 2

Primary outcome measure

Positive anti-SARS-CoV-2 antibody test, using the Roche Elecsys assay, at week 0 or week 40.

Secondary outcome measures

1. Proportion of patients with symptomatic COVID-19 disease and a positive PCR test, prior to week 0 and prior to week 40

2. Proportion of patients with symptomatic COVID-19 disease and a positive anti-SARS-CoV-2 antibody test, prior to week 0 and prior to week 40

3. Anti-SARS-CoV-2 antibody COI, at week 0 and 40

4. Proportion of patients with symptomatic COVID-19 disease, a positive PCR test, and hospitalisation or death, prior to week 0 and prior to week 40

5. In patients with detectable anti-SARS-CoV-2 antibodies at week 0, time in days to a reduction in antibody COI by at least 50% or negative COI of detectable anti-SARS-CoV-2 antibodies

6. In patients with detectable anti-SARS-CoV-2 antibodies at week 0, time in days to a reduction in antibody COI by at least 75% or negative COI of detectable anti-SARS-CoV-2 antibodies

7. Proportion of patients with detectable anti-SARS-CoV-2 antibodies at week 0 who acquire PCR positive COVID-19 disease between week 0 and week 40

STUDY DESIGN

Workflow 1: Retrospective study of SARS-CoV-2 seroprevalence across the UK using surplus serum samples.

Using the Roche Elecsys assay we will test >7500 serum samples from IBD patients for SARS-CoV-2 antibodies. These include i) surplus serum samples from UK therapeutic drug monitoring laboratories retained since 09-02-2020 and ii) serum samples from patients recruited to the UK NIHR IBD Bioresource project from 01-12-2019 to 30-03-2020. For each sample the supplier of the sample (the therapeutic drug monitoring laboratory or the UK NIHR IBD Bioresource) will provide the age and sex of the patient, the date of the serum sample, the drug tested and the name of the referring hospital. No other patient identifiers will be provided to ensure these samples will be anonymous to the research team. Patient consent for SARS-CoV-2 antibody testing will not be sought and no study visits are required.

Workflow 2: 40-week prospective observational UK-wide study of SARS-CoV-2 seroprevalence in IBD patients receiving infliximab or vedolizumab.

In parallel we will conduct a prospective observational study of 6970 patients receiving infliximab or vedolizumab in UK infusion units. This study is specifically designed to determine whether anti-TNF therapy (with or without an immunomodulator) impacts SARS-CoV2 seroprevalence, the magnitude/durability of serological responses and the proportion of patients who acquire PCR positive COVID-19 after seroconversion. A comparator group will comprise patients receiving vedolizumab. Current data suggests that vedolizumab, a gut selective anti-integrin α4β7 monoclonal antibody, is not associated with an increased risk of systemic infection or pneumonia. Furthermore, it is administered in hospital at the same 8 weekly intervals as infliximab.

Study visits will occur at the same time as scheduled infusions/injections of infliximab or vedolizumab.

At visit 1 the study will be discussed, and electronic informed consent obtained. Patients will complete an electronic questionnaire which will capture symptoms (aligned to the COVID symptoms study, Menni Nature Medicine 2020) tests and hospitalisations related to suspected, or confirmed, COVID-19 illness and details of isolating strategies adopted (see patient questionnaire). The research teams will complete an electronic case report form detailing IBD treatment at the time of the visit and confirm details of prior SARS-CoV-2 testing and/or hospitalisations. A blood sample will be collected immediately prior to biologic infusion or injection and sent to the central laboratory in Exeter for SARS-Cov-2 antibody testing. This result will be returned to the local research team.

Subsequent visits will depend on the SARS-CoV-2 antibody test result from study visit 1. These visits will continue even if the patient stops the biologic drug taken at visit 1.

Patients with positive SARS-CoV-2 antibody test at visit 1
Visits will occur at weeks 8, 16, 24, 32 and 40 and timed to coincide with biologic infusions or injections. At each visit patients will complete an electronic questionnaire and study teams will complete a CRF. A blood sample will be collected immediately prior to biologic infusion or injection and sent to the central laboratory in Exeter for SARS-Cov-2 antibody testing.

Patients with negative SARS-CoV-2 antibody test at visit 1
Patients will be asked to complete the on-line questionnaire every 8 weeks (detailed above) and attend 1 further study visit at week 40 (as above).

Remote visits

If a patient is receiving subcutaneous infliximab or vedolizumab and it is not feasible, or appropriate for them to attend hospital then the visit may occur by telephone or video call. Blood samples may be obtained using conventional venepuncture or using the Exeter home finger prick test kit.

PROSPECTIVE STUDY SCHEDULE OF VISITS

Study Procedure	Research staff gives PIS to patients.	Patient provides (e) consent (if not done during retrospective study visit)	Research staff complete medical history	Patient completes questionnaire	Research staff confirms ongoing participation.	Research staff takes blood sample prior to infusion.	Research staff update CRF with any changes since last visit
Baseline (Visit 1)	x	x	x	x		x	
Weeks 8, 16, 24, 32				x	Antibody positive patients only	Antibody positive patients only	Antibody positive patients only
Week 40				x		x	x

DATA COLLECTION

All clinical data will be entered onto a purpose designed electronic database designed using REDCap [24] software. Authorised users will have access, via high-grade-security acceptable passwords. All access to and modifications of the database are logged, so user errors can be easily tracked if needed. Whenever possible study data will be collected on an electronic device to reduce the handling of paper. When completing the case record form, local investigators will be prompted for any missing data items. Data submitted will be reviewed and if ambiguous or incomplete data clarification forms will be issued.

SAMPLE COLLECTION

All consumables required for the research visits will be supplied by the Exeter central research team. All blood samples will be labelled with the patient's unique study number assigned to the patient at the point of recruitment. The sample will be packaged under UN3373 and sent via first class post to the Royal Devon and Exeter Hospital.

DATA LINKAGE

Participants of the prospective study will consent to linkage of their research data to datasets held by Public Health England and NHS Digital. We have already had initial discussions with Public Health England regarding access to SARS-CoV-2 testing data and mortality. This will help understand the context of positive serology assays and will also facilitate identification of infection and possible re-infection during follow-up. The NHS number will be held in the database to allow this data linkage. However, the central research team will use a study ID number and not have access to the NHS number.

LABORATORY PROCEDURES

We will use the Roche Elecsys Anti-SARS-CoV-2 immunoassay to detect antibodies to SARS-CoV-2 in serum samples. The assay uses a recombinant protein representing the nucleocapsid (N) antigen for the determination of antibodies against SARS-CoV-2. Roche report that the assay has 100% clinical sensitivity for samples collected >14 days after PCR confirmation and based on testing of 5272 samples 99.81% specificity with no cross-reactivity with the common cold coronaviruses.

Testing will be conducted at the Department of blood sciences at the Royal Devon and Exeter NHS FT using the Roche Diagnostics Cobas 8000 Analyzer Series.

Pseudonymized serum samples from workflow 2 will be stored in the Peninsula Tissue Bank for future research (see consent section)

RETURNING ANTIBODY TESTS TO PATIENTS

Knowledge of test results may lead patients to change their physical distancing behaviour even though it is currently unknown whether, or for how long, a test confers immunity. However, our patient survey has clearly demonstrated that even when patients are made aware of these limitations, they still wish to have results returned to them. Therefore, we will notify patients via email when their antibody test result is available, and they will retrieve this following authentication with REDCap. Research teams at study sites will also have access to results through REDCap. When returning results, we will emphasise the uncertainty regarding what a positive test means for an individual in terms of immunity. We will encourage the patients to continue to follow appropriate physical distancing measures.

STUDY SETTING

NHS Hospital Study sites

Patient identification and recruitment and data collection with take place in hospital clinics and infusion units based at NHS hospitals across the UK.

Exeter Biochemistry department

The Exeter biochemistry team (who are not members of the central research team) will receive and process samples and conduct SARS-CoV-2 antibody testing.

SAMPLE AND RECRUITMENT

Summary of Eligibility Criteria

Inclusion criteria

- Age **5** years and over.
- Diagnosis of inflammatory bowel disease
- Current treatment with infliximab or vedolizumab for 6 weeks or more
- Written informed consent obtained from patient or parent / guardian.

Exclusion criteria

- Patients participating in vaccine trial

Case identification

Workflow 1

The study will use surplus serum samples from UK clinical laboratories saved following therapeutic drug monitoring tests. Additional serum samples will be obtained from the UK NIHR IBD Bioresource.

Workflow 2

Research nurses at each site will invite all patients scheduled to attend an infusion unit for infliximab or vedolizumab to participate by email, telephone, text or in person at, or before, their next biologic infusion.

CONSENT

Workflow 2

The local research teams will send out participant information sheets and links to further study information. Invitations will be sent out electronically, either through an email or a text message. For patients who do not have access to electronic devices the information will be sent via Royal Mail. Patients will be given sufficient time to decide whether they would like to take part and given the opportunity to ask questions either via telephone or when they come to their infusion appointments. Patients who lack capacity to consent will not be recruited.

Patients 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 at the time of consent.

The researcher will enter the patient's email address and confirm they want to initiate the e-consent process. This will trigger an email going to the patient with a personalised link. The patient will then have to enter their surname and date of birth to confirm they are the correct patient before being able to proceed with completing the e-consent form. Patients will be asked to give consent electronically by confirming statements.

Children

The study will invite children aged 5 and over to participate. Study information has been devised for patients aged 5-10 years old and 11-15 years. Parental consent will be obtained for all children under the age of 16. Additionally, assent will be sought from children over the age of 11. In Scotland, children who are deem capable of understand the study and therefore giving consent, will be given the opportunity to use the young person consent form and decide themselves if they would like to take part. Once a child who has given assent reaches 16 years old, they will be given the opportunity to consent using the young person's consent form.

Withdrawal of Participants

Participants may choose to withdraw from the study at any time but their anonymised biological samples will be retained. The reason for withdrawal must be documented in the electronic CRF and a withdrawal log should be completed.

Use of Tissue Samples in Future Research

Consent will be sought in line with the Human Tissue Act (2004) from the patients to use their serum samples in future work. Pseudonymisation of the data will allow us to go back to individual patients via the local principal investigators. We will submit a new ethics application for any future studies using these samples.

Patients will be informed that their serum sample:

• Will be considered a gift to the Exeter Clinical Research Facility and will be transferred to the Peninsula Research Bank. A steering committee may approve the use of these samples for future research.

• May be used as part of collaborations in the UK or overseas including collaborations with companies.

• Will only be made available to researchers in an anonymised form after careful consideration of their study protocol and approval by the relevant REC.

• Will not be used for profit.

• Will not be used in animal research.

STATISTICS AND ANALYSES

Pseudonymised data will be managed using REDCap electronic data capture tools hosted at the Royal Devon and Exeter NHS Trust and statistical analyses will be undertaken in R (R Foundation for Statistical Computing, Vienna, Austria).

All hypotheses will include two-sided alternatives and p-values <0.05 considered significant. We will include patients with missing clinical data in analyses for which they had data and specify the denominator for each variable. Descriptive statistics will be reported as median and interquartile range for continuous variables and as number and proportions for categorical variables unless otherwise stated.

Anti-SARS-CoV-2 antibody tests are reported as numeric values in the form of a cut-off index (COI) derived from the electrochemiluminescence signal of the sample divided by the cut-off signal. Binary qualitative results are reported as non-reactive (COI < 1.0; negative) and reactive (COI ≥ 1.0; positive). Both binary and continuous SARS-CoV-2 antibody COIs will be analysed.

In workflow 1, cumulative seropositivity rates of anti-SARS-CoV-2 antibodies will be estimated using the Kaplan-Meier method. Stratified log-rank tests will be used to compare seropositivity rates between drugs (infliximab vs vedolizumab), adjusted for baseline demographic factors (age, sex, region). Patients who had more than one test, chi-squared analyses will be used to test differences in the proportions of patients whose antibody status changed, stratified by drug.

In workflow 2, multinominal regression and multivariable linear regression will be undertaken to identify independent factors at baseline that predict primary and secondary categorical outcomes and

anti-SARS-CoV-2 COIs at week 40, respectively. Univariable analyses using Fisher's exact and Mann-Whitney U tests will be used to identify baseline characteristics associated with our predefined categorical outcomes. Variables with $p<0.05$ in the model will be included. In addition, the following factors that affect SARS-CoV-2 acquisition and COVID-19 outcomes will be included in our model: age, sex, ethnicity, region, comorbidity, body mass index, and physical distancing behaviour.

We will use a propensity score approach to combine the entire group of measured covariates, explore the extent of covariate balance, and then compare seropositivity rates across treatment groups, adjusted for the propensity score using regression and matching methods.

Time to reduction or loss of anti-SARS-CoV-2 antibody COI will be estimated using the Kaplan-Meier method. Stratified log-rank tests will be used to compare time to reduction or loss of anti-SARS-CoV-2 antibody COI between drugs (infliximab vs vedolizumab), adjusted for baseline demographic factors.

We will build risk prediction models, including all measured patient variables individually. This will be done using forward and backward stepwise variable selection with appropriate model penalisation methods, such as Akaike Information Criterion and Bayesian Information Criterion. We will use cross validation to test and refine the model, adjust for overfitting, and estimate the diagnostic accuracy of the model. Summary measures for the predictive models, including the c-index, will be calculated.

Sample size determination

Workflow 1: We have identified the following IBD patients with banked serum. Additional patients with banked serum stored at other UK laboratories will also be identified. We have not undertaken sample size calculations for workflow 1.

Unique patients with drug treatment at time of serum sampling

	infliximab	adalimumab	vedolizumab	ustekinumab	Other	Total
Exeter TDM service 09/02/2020 - 28/05/2020	2076	944	194	19		3233
Expected additional serum samples 30/05/20-30/07/2020	434	204	71	8		717
UK NIHR IBD Bioresource 1/12/2019 - 30/03/2020	380	296	187	76	2185	3124
Hull University Hospital	152	2	90	59		303

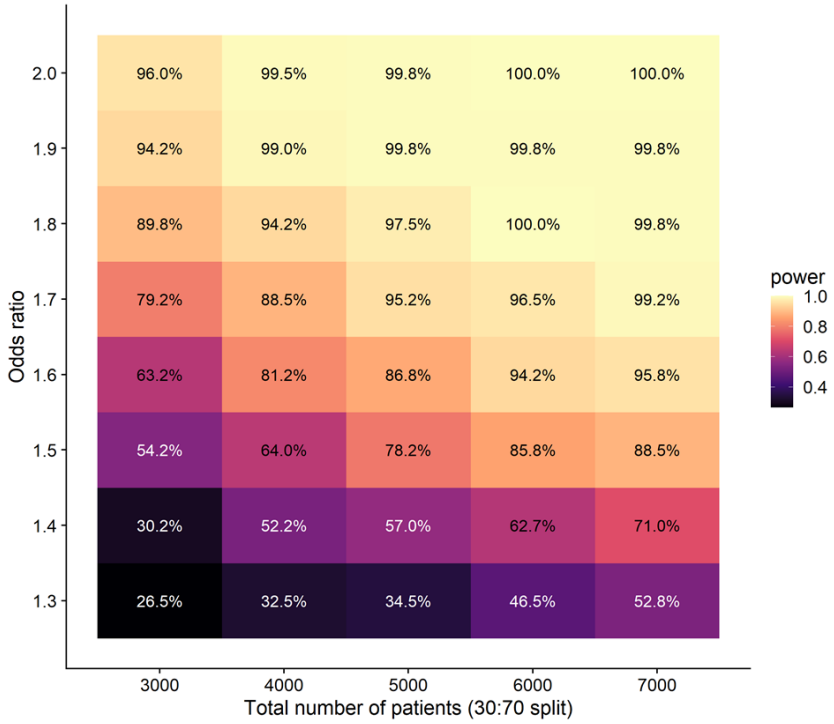
Workflow 2: Limited data are available regarding the risk of SARS-CoV-2 in patients with IBD to inform sample size calculations. For workflow 2, data from the TREAT post-marketing adverse event registry cite a relative annual risk of pneumonia in infliximab-treated patients of 1.7. Whilst the aetiology of pneumonia in this cohort is unknown, it is recognized that viruses are important co-factors or causative agents in up to 95% immunosuppressed patients presenting with hospital acquired pneumonia[25]. Furthermore, the TREAT registry data are likely to underestimate rates of anti-TNF related pneumonia because of confounding by voluntary reporting. Less long-term safety data are available for vedolizumab, however, there is no evidence that vedolizumab increases the risk of systemic infections.

The following assumptions have been made in calculating the sample size for the workflow 2:

1. Proportion of patients treated with each drug(s): vedolizumab: 30% (20% with concomitant immunomodulator), infliximab 70% (60% with concomitant immunomodulator)
2. Seroprevalence of SARS-CoV-2 in background population: 0.05

3. Odds ratio for SARS-CoV-2 seropositivity with immunosuppressant use: 1.3
4. Odds ratio SARS-CoV-2 seropositivity for infliximab versus vedolizumab: ≥1.5.
5. Drop-out rate: 20%

Using these assumptions and a multivariable logistic regression model which included adjustments for sex and ethnicity, a sample size of 6970 patients provides 80% power for the comparison of infliximab versus vedolizumab controlling for immunosuppressant status at the 0.05 significance level.



Study power. Heatmap demonstrating statistical power prediction according to different models of effect size (odds ratio of SARS-CoV-2 infection in infliximab vs vedolizumab treated patients) and study subject numbers.

Decision points

Interim analysis will be not be conducted for workflow 1 or 2. However, data generated from the retrospective study, available by December 2020, might inform analyses to be conducted on the prospective dataset. Any changes to the statistical analysis plan will be reported in the study protocol (see 1.9).

Stopping rules

Recruitment will close on Wed 23rd December 2020 or sooner if the pre-specified 6970 patients have been recruited.

Procedure for accounting for missing, unused, and spurious data

Patients who exited the study because of loss to follow-up, patient withdrawal of consent, or elective withdrawal of drug by their physician will be censored at the time of study exit.

Procedures for reporting any deviation(s) from the original statistical plan

Deviations from the original statistical plan may be made prior to data analysis. These changes will be discussed with the study management committee and described in an amended protocol. Additional

analysis conducted after the start of data analysis will be reported as exploratory analyses in the protocol.

ETHICAL AND REGULATORY CONSIDERATIONS

The study will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of Good Clinical Practice and GDPR, and in accordance with all applicable regulatory requirements including, but not limited to, the UK policy framework for health and social care research 2017

The project proposal and study protocol have been reviewed by the Sponsor, the Royal Devon and Exeter NHS Foundation Trust.

The Exeter research team will ensure that the NHS Research Ethics Committee, Health Research Authority and NHS Trust approvals are in place prior to starting both workflow 1and 2. In addition, the Exeter research team will coordinate the distribution of the electronic site file, collating of CV's, GCP's and delegation logs. The CI will ensure that all study reporting is conducted including annual and end of study reporting to the REC.

A key ethical consideration for this study is whether serology test results generated during a research study should be communicated back to patients. To inform this decision we surveyed 250 patients from across the UK. All patients reported that they would want to be told their test results despite the fact the significance of a positive test in terms of immunity to further infection is not currently known. We have therefore decided to allow patients access to the database to retrieve their results. A copy will also be sent to the local principal investigator.

Assessment and management of risk

The study does not pose any direct risk to patients. However, in the unlikely event that the patient should experience an untoward event as a direct consequence of participation in the research study, the event will be logged on the serious adverse event form and emailed to the central research office and reported to the sponsor.

The study will be remotely monitored by the Exeter central research team and the sponsor. The Exeter Central research team will ensure that all the appropriate documentation and training is given prior to giving the 'Green Light' to recruit patients. All site initiation training will be conducted remotely via telephone or TEAMS.

Amendments

Any amendments that are required after study approval will be delegated by the CI to the Exeter Research Team. The Exeter Research Team will discuss the amendment with the Sponsor, and they will then be processed as a non-substantial or substantial amendment. The Exeter Research Team will follow the HRA guidance https://www.hra.nhs.uk/approvals-amendments/amending-approval/

PEER REVIEW

The study protocol has been independently reviewed by the IBD clinical research group of the British Society of Gastroenterology, by the sponsor's scientific committee and the external funders. We anticipate that this project will be subject to further peer review by the NIHR

PATIENT & PUBLIC INVOLVEMENT

Patient Survey

We conducted an electronic survey to gauge the opinion of patients with IBD on our planned research. 250 patients completed the questionnaire from 74 hospitals including 71 patients who regularly attend a biologic infusion unit. All of our proposed research questions were rated as important or very important by at least 83% of participants and 3 of the questions were rated as important or very important by 90% of patients. All but one patient expressed either equal or strong preference for computer-based forms including 82% of patients expressing a strong preference. Every patient surveyed wanted to be informed of the test result despite the fact we don't know if a positive test means an individual is immune from further infection.

Exeter IBD Patient Panel

The Exeter IBD Patient panel helped refine the study questions. The group have reviewed the study protocol and supported the writing of the patient information sheet and the practicalities and testing of electronic consent and patient questionnaire. A member of the Exeter IBD patient's panel sits on the Study management committee ensuring patient involvement in all aspects of study delivery, data analysis and dissemination of findings

INDEMNITY

NHS Indemnity will apply.

DATA SHARING

The CI's, SMG, Sponsor, funders and research team members are committed to ensure that the research findings and data relevant to the coronavirus pandemic are shared rapidly and openly to inform the public health response and help save lives. The data will be shared in line with the principles set out in the 2016 statements of data sharing in public health emergencies https://wellcome.ac.uk/press-release/statement-data-sharing-public-health-emergencies

DISSEMINATION POLICY

Plan for dissemination of results

Findings will be written up and submitted to a peer-reviewed scientific journal. Findings will be presented by the study team at national and international conferences including the British Society of Gastroenterology annual meeting and the European Crohn's and Colitis meeting. The study team will prepare a lay summary of the study findings for dissemination to the members of the national patient group, Crohn's and colitis UK.

BENEFIT TO THE NHS

This protocol addresses clinically relevant priority research questions relating to SARS-CoV-2 in a vulnerable patient group. Obtaining estimates of the proportion of vulnerable patients already exposed to COVID-19 helps inform our knowledge and future planning. A greater understanding of the impact of immunosuppressive and biologic drugs on SARS-CoV-2 acquisition, illness and immunity is needed

to help define at risk patient groups and to determine the impact of preventative social distancing strategies.

AUTHORSHIP ELIGIBILITY GUIDELINES

Author-contribution statements will be mandatory in all publications arising from this study. Authorship will be contingent on substantial contributions to the design, performance, analysis, intellectual content and reporting (and revising) of the work. Authors will agree to be accountable for all aspects of the work and will provide approval for the final version to be published.

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APPENDICIES

Appendix 1- Required documentation

1. CVs of the research team
2. Delegation log

Appendix 2 – Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
NSA 1	2	5/08/2020	TA/CB	Clarification of workflow in protocol