Analysis Plan for the uptake, safety, and effectiveness of monoclonal antibody therapy for COVID-19

Full Project Title	EAVE II
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Previous Versions	V2.4
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Version History		
Version	**Date**	**Notes**
V1	12/01/2022	• N/A
V2.0	20/01/2022	• The initial SAP was presented for both MAb and antiviral therapies. Henceforth these analyses have been split into separate SAPs. • References to UKHSA data have been removed, as this data does not apply to Scotland. • ICU and serology data have been added to the specification. Additionally, the statistical analyses have been refined.
V2.1	24/01/2022	• 'Community-based' removed from title, to prevent future restrictions if prescribing processes change. The treatment pathway has also been added to the list of potential confounders. • Added further variables to the SICSAG data linkage list, for further ICU-based outcomes. • The study design for the safety analyses was changed to a self-controlled case series analysis. • Cancer registry linkage with SMR06
V2.2	27/01/2022	• Data period for hospital admissions and prescriptions extended back from December to September, 2021, to allow for a control period in the new SCCS analysis. • Analysis Plan revised.
V2.3	02/02/2022	• Exposure status in light of treatment discontinuation was defined (intent-to-treat analysis) • Controls are defined • vaccination status was redefine to include the unvaccinated and those with three primary vaccinations (for the severely immunocompromised)
V2.4	07/02/2022	• The period in which the cases are identified (COVID-19 tests) was brought back to September 2021 to increase the time in which non-treated individuals can be identified, and have events.

		• Investigations of possible increase in safety event risk prior to infections also described.
V2.5	14/02/2022	• Added to uptake section a weekly summary of the uptake by demographics: age groups, sex, and ethnicity • Non-COVID-19 specific effectiveness outcomes added • The absolute risk rate and the mortality risk of each safety event will be reported. • E-value analysis removed

Introduction

The UK is experiencing a new wave of COVID-19 infections with the Omicron variant at the same time as high circulating levels of Delta. There is evidence that the Omicron variant is more transmissible and concerns that existing interventions (e.g., COVID-19 Vaccines) may be less effective and some monoclonal antibodies (mAbs) may become ineffective due to mutations.

Novel mAbs are limited resources and need to be targeted to those at highest risk of poor COVID-19 outcomes who are most likely to benefit [1, 2]. Interim guidance has been produced for both mAbs [3] and there is an urgent need to determine the numbers/proportion of the population likely to be eligible for these treatments based on existing guidance to inform planning/ordering. It is also necessary to determine the uptake of treatments as they start to be used to ensure they are being used in line with guidance. We also need rapid real-world evidence of the likely effectiveness of treatments alone and in combination to identify those patients who remain at risk despite treatments [4].

This research will address a number of key questions, using existing research-ready datasets. The overall aim of this study is to investigate the uptake, safety, and effectiveness of mAb therapy for COVID-19. We will use a data platform containing pseudonymised, linked data from vaccination records, virological testing and sequencing, clinical, and mortality records with coverage for the whole Scottish population. All data and analyses will be hosted within Public Health Scotland (PHS) and in due course in the Scottish national Trusted Research Environment.

Aims and objectives

Aims

To investigate the uptake, safety, and effectiveness of mAb therapy for COVID-19.

Objectives

We seek to:

1. estimate the uptake of mAbs by demographics and risk group,
2. investigate the effectiveness of these treatments (alone and in combination) in real world settings, stratified by viral strain,
3. identify factors associated with severe outcomes in those treated with mAbs,
4. determine the safety profile of mAb therapies.

Methods

Study cohort

The study cohort will be all individuals registered with a GP in Scotland, aged 18 or over, that tested positive for COVID-19 after December 1st, 2021.

Study design

We will use a cohort study design comparing effectiveness related events in those treated with and without mAb medications, from the cohort of test-positive individuals.

Secondly, we will use a self-controlled case series (SCCS) for those treated with mAbs after a positive test or clinically confirmed diagnosis for COVID-19, to establish the risk of safety outcomes.

Data

The table below lists the datasets, their source location, and the earliest date for which data will be extracted.

Dataset	Source	Start Date
Primary care data	GP records	January 2015
the Scottish Cancer Registry, SMR06	Public Health Scotland (PHS)	January 2015
Community prescribing data	Prescribing Information System (PIS)	January 2015
SARS-CoV-2 test data	Electronic Communication of Surveillance in Scotland (ECOSS)	March 2020
COVID-19 Vaccination data	GP records and Turas Vaccination Management Tool (TVMT)	December 2020
SARS-CoV-2 sequencing data	PHS SARS-CoV-2 sequencing Database	September 2021
Hospital prescribing data	Hospital Electronic Prescribing and Medicines Administration system (HEPMA)	September 2021
Hospital admissions	Scottish Morbidity Record (SMR) 01 and Rapid Preliminary Inpatient Data (RAPID)	September 2021
mAb prescribing	Scottish Monoclonal Antibody for COVID-19 (MAC) dataset	December 2021
Mortality data	National Records of Scotland (NRS)	December 2021
Serology	Public Health Scotland (PHS)	December 2021

Intensive Care	SICSAG Episodes and Daily datasets from the Scottish Intensive Care Audit Group	December 2021

Appendix A lists the groupings of variables available for this study by data source. Amendments related to additional variables will be added as and when there is need for further analysis of emerging associations.

Statistical analyses

Exposures of interest

Treatment with mAb therapies (initially sotrovimab) for the treatment of symptomatic COVID-19. We will consider exposure to commence from the day of dispensing of treatment, and to be censored upon change in treatment (including adding a (further) mAb), death, or the end of the study period.

Exposure will be grouped by mAb therapy received, including therapy *cocktails*.

Any treatment discontinuations (in which the dose is only partially administered) due to, for example, hypersensitivity reactions will be reported; however these individuals will still be considered 'exposed' for subsequent analyses regardless of the dose they received.

Outcomes of interest

The outcomes related to treatment effectiveness are time to COVID-19 death, time to COVID-19 hospital admission, time to COVID-19 ICU admission, duration of hospital admission, and duration of ICU admission. The primary safety outcome is any hypersensitivity reaction (treatment group only), however the cause of any subsequent hospitalisation will be reported (and analysed if incidence is sufficient).

Potential confounders

We have identified variables that we believe are likely to affect receipt of MAb therapy and the risk of adverse events. We will therefore include:

- age,
- sex,
- socio-economic status (SES) measured by quintiles of the Scottish Index of Multiple Deprivation (SIMD) (1 refers to most deprived and 5 refers to least deprived),
- residential settlement measured by the urban/rural 6-fold classification (1 refers to large urban areas and 6 refers to small remote rural areas),

- vaccination status: unvaccinated, single vaccine, double vaccination, triple vaccination (for those with severely compromised immune systems), double plus booster, triple plus booster.
- smoking status,
- body mass index (BMI),
- prior SARS-CoV-2 infection,
- serology test results,
- comorbidities and concurrent therapies.

While mAb therapy is currently prescribed through outpatient care, if the prescribing pathways changed in the future, then the route to treatment will also be evaluated as a confounder.

Analytical techniques

Treatment Uptake

The number of individuals treated per day will be reported, so that we are able to estimate current uptake, and recent changes in trajectory. The number of individuals treated by week will also be reported, stratified by age group, sex, and ethnicity.

Identifying Untreated Controls

All analyses will use those who tested positive for SARS-CoV-2 between December, 2021, and the end of the study follow-up and were not treated with mAbs, but were eligible for treatment, as controls. As a precise marker of individual eligibility is not available, criteria will be estimated by a process of reverse-engineering based on the characteristics of those who were treated.

We will investigate whether it is possible, based on the sample size, to assign propensity score matched [5] controls that should have been offered mAb therapy, but did not receive it. If more than 80% of those treated can be matched, this approach will be used, with controls matched to (treated) cases based on sex, 10-year age bands, serology results, vaccination status, smoking status, BMI category (underweight, normal, overweight, or obese), prior COVID-19 infection, and comorbidities.

Treatment Effectiveness

For the primary treatment effectiveness analyses, we first report the number of individuals in both the treated and untreated cohort subgroups who, within 28 days of the positive COVID-19 test, were admitted to hospital, admitted to ICU, or died. The proportions will also be reported specifically for COVID-19 admissions/deaths. In those admitted to ICU, we will report on the percentage that required ventilation or oxygen, and that died. In those admitted to hospital, the proportion that required each level of critical care will be reported. A sample table is shown below.

The 28-day endpoint was selected to align with the COVID-19 clinical trial, reported by Gupta *et al.* [6]. An additional sensitivity analysis will be conducted looking at events occurring within 14 days of positive SARS-CoV-2 test. Subgroup analyses by age group, sex, smoking status, obesity, vaccination status, serology test results, and prior COVID-19 status will be considered.

COVID-19 Outcome within 28 Days of Treatment	Treated with mAb after positive COVID-19 test N (%)	Not treated with mAb after positive COVID-19 test N (%)	p-value for difference in proportions
Hospital Admission			
All-cause Hospital Admission			
COVID-19 Hospital Admission			
ICU Admission			
All-cause ICU Admission			
COVID-19 ICU Admission			
Oxygen in (COVID-19) ICU			
Ventilation in (COVID-19) ICU			
Death			
All-cause Death			
COVID-19 Death			
COVID-19 Death in ICU			
Critical Care Level			
1			
2			
3			

Adjusted survival analysis will be used to model time to COVID-19 hospital admission and time to COVID-19 ICU admission. To account for the competing risk of death, the analyses will be conducted a) in survivors only, b) with each outcome combined with death, and c) with censoring at death. Additionally, the time to COVID-19 death will be independently assessed. Each analysis will be censored at change in treatment, or the study end date. A sample table is shown below.

COVID-19 Outcome	**Adjusted Hazard Ratio (95% CI)**	**p-value**
Time to COVID-19 Admission (survivors only)		
Time to COVID-19 Admission or Death		
Time to COVID-19 Admission		
Time to COVID-19 ICU Admission (survivors only)		
Time to COVID-19 ICU Admission or Death		
Time to COVID-19 ICU Admission		
Time to COVID-19 Death		

In those who survived their admission, we will report the median and interquartile range of the duration of both hospital and ICU admissions, and the number of days requiring oxygen or ventilation, stratified by mAb therapy.

Duration of COVID-19 Outcome (days) in survivors	**Treated with mAb after positive COVID-19 test Median (IQR)**	**Not treated with mAb after positive COVID-19 test Median (IQR)**
COVID-19 Admission		
COVID-19 ICU Admission		
Oxygen in ICU		
Ventilation in ICU		

Treatment Safety

For safety analyses, descriptive analyses will be carried out to visually inspect trends in the numbers of adverse events by treatment category. Where there are not enough events for statistical analysis, we will not analyse specific potential outcomes of interest. Additionally, if incidence is under 5 events, the exact number will be masked for confidentiality protection.

The absolute risk rate and the mortality risk of each event will be reported.

A Self-Controlled Case Series (SCCS) study design will be used to analyse the association between mAb therapy and safety outcomes. As such, for each of these analyses, the population was all individuals who had both a positive COVID test and had experienced the safety outcome, at *any* point in the analysis period: September 2021 until the data extraction date.

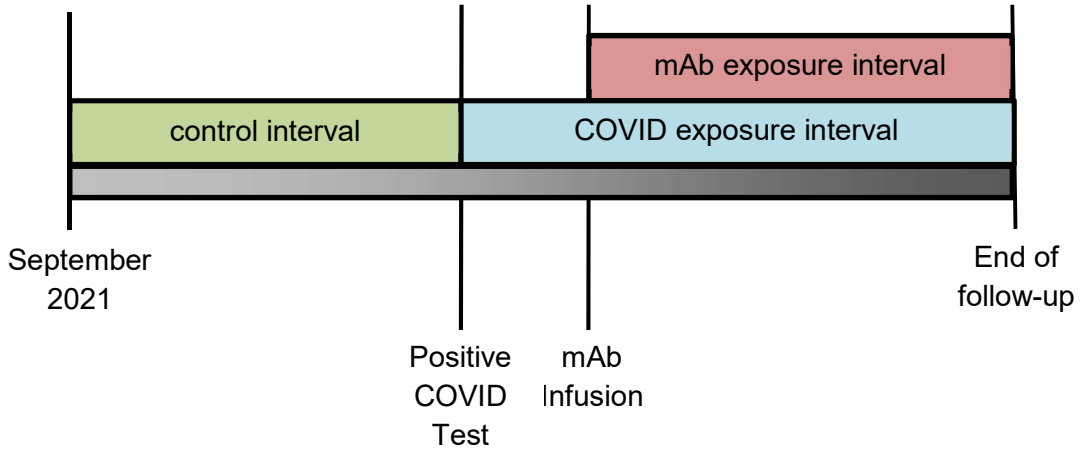
The standard SCCS is modelled on the assumption that the follow-up time is independent of the incidence (and event time) of the (safety) event. Therefore, we will conduct a sensitivity analysis excluding any individuals who died as a result of the event. If the results suggest that this change increased the estimated risk of the event in the sotrovimab-treated group, and the sample size is sufficiently large, we will conduct a sensitivity analysis using the extension of the SCCS which uses event-dependent observation periods weighted based on the time between the event and the subsequent death [7,8].

The incidence rate ratio (IRR) of each safety outcome will be derived from the ratio of incidence rates in time intervals of control (pre-infection), and in two different exposed periods: post COVID infection, and post-mAb treatment (where applicable). Conditional Poisson regression will be used adjusting for only time-varying confounders, as time-invariant confounders are not required in an SCCS. These confounders are month of event (for possible seasonality) and vaccination status. Age on September 1st 2021 will be used instead of a time-varying confounder, as the follow-up for each individual is relatively short.

The incidence of each event relative to the date of the SARS-CoV-2 will be inspected to determine whether the day of the SARS-CoV-2 itself should be included in the control time (i.e., there is evidence of reverse causality such that hospitalisation for the event is the reason for the COVID test [7]) or in the post-COVID exposure time. Additionally, if there is incidence of an increased risk of events shortly prior to COVID-19 infection, a pre-COVID risk window will be included (up to 28 days, depending on the observed risk profile).

In the subset of those tested in the community, we will conduct a sensitivity analysis in which the five days prior to testing were also included as COVID-exposed time, to account for the lag between SARS-CoV-2 infection and symptom development.

Subgroup analyses (without formal testing, where numbers are not sufficient) will be conducted by sex, age quintiles, vaccination status, previous SARS-CoV-2 infections, serology test results, smoking status, and comorbidities. An overview of the SCCS study design and a sample table for a single safety outcome are shown below.



Exposure	**IRR (95% CI)**	**p-value**
Covid		

mAb therapy		

Reporting Guidelines and Conventions

Analyses will be carried out by one statistician and independently checked by additional statisticians. All analyses will be carried out using R/RStudio, version 3.6.1.

Results will be reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) [9] and REporting of studies Conducted using Observational Routinely-collected Data (RECORD) (via the COVID-19 extension) [10] guidelines and included in supplementary material. Due to data disclosure control requirements, we will not report results based on fewer than five events.

Dissemination

The analysis will be written in a manuscript and submitted to a peer-reviewed journal. We will also seek to provide near real-time reports on treatment safety and effectiveness to regulators and government COVID-19 advisory bodies, as appropriate. All code will be made publicly available via the EAVE II GitHub repository.

References

1. Department of Health and Social Care. *Interim Clinical Commissioning Policy: Casirivimab and imdevimab for patients hospitalised due to COVID-19*. 2021. 17/09/2021. https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=103175
2. Hippisley-Cox J, Coupland CA, Mehta N, et al. Risk prediction of covid-19 related death and hospital admission in adults after covid-19 vaccination: national prospective cohort study. *BMJ*. Sep 17 2021;374:n2244. doi:10.1136/bmj.n2244
3. Clift AK, Coupland CAC, Keogh RH, et al. Living risk prediction algorithm (QCOVID) for risk of hospital admission and mortality from coronavirus 19 in adults: national derivation and validation cohort study. *BMJ*. Oct 20 2020;371:m3731. doi:10.1136/bmj.m3731
4. Simpson CR, Robertson C, Kerr S, et al. External validation of the QCovid risk prediction algorithm for risk of COVID-19 hospitalisation and mortality in adults: national validation cohort study in Scotland. *Thorax*. 2021;doi:10.1136/thoraxjnl-2021-217580
5. Desai RJ. Alternative approaches for confounding adjustment in observational studies using weighting based on the propensity score: a primer for practitioners. *BMJ*. 2019; https://doi.org/10.1136/bmj.l5657
6. Gupta A, Gonzalez-Rojas Y, Juarez E, et al. Early Treatment for Covid-19 with SARS-CoV-2 Neutralizing Antibody Sotrovimab. *NEJM*. 2021; 385:1941-1950. doi: 10.1056/NEJMoa2107934

7. Fonseca-Rodriguez O, Fors Connolly A-M, Katsoularis I, Lindmark K, Farrington P. Avoiding bias in self-controlled case series studies of coronavirus disease 2019. Statistics in Medicine 2021; 40:6197-6208. doi:10.1002/sim.9179
8. Farrington CP, Whitaker HJ, Hocine MN. Case series analysis for censored, perturbed, or curtailed post-event exposures. Biostatistics 2009;10:3-16. doi:10.1093/biostatistics/kxn013
9. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. Int J Surg 2014;12:1495-9.
10. Benchimol EI, Smeeth L, Guttmann A, et al. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement. PLoS Med 2015;12:e100188

Appendix A

Data items/variables and data sources

Data category	Data item	Data source
Demographic	Sex	GP practice
	Age	
	Ethnicity	
Socioeconomic	Scottish Index of Multiple Deprivation (Quintiles)	GP practice
Other characteristics	Body Mass Index	GP practice
	Smoking Status	
Geographic	Urban Rural Index (UR6)	GP practice
Clinical diagnoses	Underlying conditions	GP practice
Vaccinations	Vaccine type	GP practice, TVMT
	Vaccine dose	
	Vaccination date	
Intensive Care	Admission date	SICSAG (Episode-level)
	Severe respiratory disease flag	
	Primary diagnosis {Hospital}	
	Primary diagnosis {Unit}	
	Discharge date	
	Discharge destination (e.g., death, home, community)	
	Ventilation	SICSAG (Daily-level)
	Oxygen treatment	
	Level of Critical Care	
Cancer Registry Data	Diagnosis Date	SMR06
	Diagnosis	
	Vital Status	
Serology	Date sample collected	PHS Serology
	Organism tested for	
	Qualitative Result	
Sequencing	Date sample collected	PHS Sequencing
	Qualitative Result	
Laboratory tests	RT-PCR SARS-CoV-2 test result	ECOSS
	Date of RT-PCR SARS-CoV-2 test	
Primary care	Clinical events	GP practice
Monoclonal antibody prescriptions	Medication	Scottish MAC
	Strength	
	Medication administration date	
Concurrent prescriptions	Medication	PIS, HEPMA
	Prescription issue date	
	Prescription dispensing date	
	Strength	
	Formulation	
	Route of Administration	
Hospitalisation	Admission Date	SMR01

	Diagnosis	
	Hospital admission Date	SMR01, RAPID
	Diagnosis	
	Discharge date	
	Discharge destination (e.g., death, home, community)	
Mortality	Deaths	NRS

Abbreviations: General Practitioner (GP), Turas Vaccination Management Tool (TVMT), Electronic Communication of Surveillance in Scotland (ECOSS), Reverse-transcription polymerase chain reaction (RT-PCR), Prescribing Information System (PIS), Morbidity Record (SMR), Rapid Preliminary Inpatient Data (RAPID), National Records of Scotland (NRS), Scottish Monoclonal Antibodies for COVID-19 (MAC), Hospital Electronic Prescribing and Medicines Administration system (HEPMA)