UK Health Security Agency

Protocol: Surveillance of patients with COVID-19 who are treated with neutralising monoclonal antibodies or antivirals

Contents

1. Amendment history

Protocol Version	Date	Author of Changes	Details
2.0	25 April 2022	UKHSA COVID-19 Therapeutics Group	Second issue – details of changes outlined below

This protocol updates the interim genomic surveillance protocol which outlined the sampling process for genomic surveillance within inpatient settings. This protocol has been updated in line with the changing clinical policy and to encompass community settings, where coronavirus (COVID-19) therapeutics are now widely used. The key updates within this version are:

- all patients treated with neutralising monoclonal antibodies (nMABs) and directly acting antivirals (AVs) are included for surveillance including community settings and patients of all ages
- patients in hospital should have samples sequenced pre-treatment, at day 5 after start of treatment or discharge, and at day 14 if in a high-risk group as directed by NHS England/Improvement (NHSE/I) clinical policies
- patients in the community should have samples sequenced pre-treatment, and at approximately day 5 after the start of treatment
- experimental pathogen genomic analyses for new variants
- equitable use analyses to support national antimicrobial stewardship

2. Background and aims

Therapeutics including neutralising monoclonal antibodies (nMABs) and directly acting antivirals (AVs) are a core public health mitigation measure for the next phase of the SARS-CoV-2 (COVID-19) pandemic. nMABs and AVs are currently recommended as directed by the National Health Service England and Improvement (NHSE/I) clinical commissioning policies for non-hospitalised patients and hospitalised patients.

Both nMABs and AVs suppress or inhibit the replication of SARS-CoV-2, the virus causing COVID-19, by targeting key stages in the virus' life cycle to reduce the likelihood of hospitalisation, severe disease and death. Mutations may arise conferring reduced susceptibility to therapies, but in order to pose a risk to public health, drug-resistant variants must not only emerge but must also be fit enough to be able to transmit and compete with other circulating viruses. New variants with a growth advantage can change the circulating viral population rapidly.

The UK Health Security Agency (UKHSA) has initiated a programme of work that aims to support rapid deployment of specific COVID-19 therapeutics in England by undertaking genomic, virological, and epidemiologic surveillance, through both national surveillance systems and academic collaboration. This surveillance programme aims to:

- monitor for the development of SARS-CoV-2 mutations and variants in patients treated with nMABs and AVs and to describe which mutations emerge and at what frequency, through the comparison of pre- and post-treatment genomes
- determine and describe the biological characteristics of mutations which develop post-treatment, by undertaking laboratory assessments in collaboration with academic partners
- monitor for the transmission of mutations associated with resistance in the UK population
- monitor for the development of SARS-CoV-2 mutations and variants in patients who are highly immunosuppressed, and to describe which mutations emerge and at what frequency, through describing the intra-host SARS-CoV-2 evolution in patients with evidence of persistent SARS-CoV-2 infection
- monitor the outcomes of patients with COVID-19 who have received nMABs or AVs, through linkage of treatment data with hospital episode and mortality databases
- monitor for the equitable use of therapies to support antimicrobial stewardship nationally

This protocol describes the planned surveillance programme for the second 6 months of community and hospital use of COVID-19 therapeutics. The protocol will be regularly reviewed and updated as the delivery and uptake of therapeutics occurs.

3. Eligibility and sampling

This protocol applies to individuals in primary or secondary care at the time of COVID-19 diagnosis, that is all individuals within the community or hospitalised or under a secondary care clinical service.

The following patients are eligible for surveillance in England:

All individuals who receive nMABs or AVs for the treatment of COVID-19

3.1 Patients in hospital

Patients in hospital should have positive samples pre-treatment, at day 5 after start of treatment or discharge, and at day 14 if in a high-risk group as directed by NHSE/I clinical policies sent for whole genome sequencing.

Pre-treatment sample (day 0): Send the original diagnostic SARS-CoV-2 reverse-transcriptase polymerase chain reaction (RT-PCR) sample for sequencing where possible. If this is no longer available, a further pre-treatment sample may be taken for surveillance purposes and sent for sequencing.

Follow up sample: A sample should be sent for sequencing at day 5 after the start of treatment. Use an existing clinical sample if available (for example, if in Intensive Care Unit (ICU), use routinely taken respiratory material) or take a nose and throat swab for surveillance use only if no prior sample is available on day 5. If the patient is planned for discharge before their day 5 sample date, take a SARS-CoV-2 RT-PCR sample at discharge.

Individuals in the high-risk groups described in NHSE/I clinical policies should have a further sample on day 14, if they remain an inpatient, or where possible if they attend an outpatient appointment. If patients with evidence of persistent infection have follow up samples for clinical purposes, residual material should also be sent for sequencing (including from non-respiratory sites). Where individuals remain persistently positive (for example, positive sample results at or after day 14), further clinical advice may be sought from local infection specialist services (for example, infection prevention and control, virology, infectious diseases or microbiology).

Samples may be sent for genome sequencing at the discretion of the clinician in hospitalised individuals in the high-risk groups described in NHSE/I clinical policies who are eligible for treatment, but do not receive it (for example, due to patient choice), where there is evidence of a persistent infection. This will enable an improved understanding of within host adaptation of the virus.

All samples taken from individuals treated with COVID-19 therapeutics or in patients with evidence of persistent infection for surveillance should be clearly labelled as such, to support local laboratory staff to identify and prioritise sending these samples for sequencing.

3.2 Patients in the community

Patients in the community should have sequenced samples pre-treatment, and at approximately day 5 after the start of treatment.

Individuals eligible for treatment in the community may access treatment with a positive SARS-CoV-2 lateral flow test, reported on the gov.uk portal. These individuals will also have been sent a priority SARS-CoV-2 RT-PCR kit to be used for surveillance, following instruction from the COVID-19 Medicine Delivery Unit (CMDU). These SARS-CoV-2 RT-PCR kits will be directed automatically for sequencing when they are returned.

Where individuals do not have a SARS-CoV-2 RT-PCR kit and are unable to undertake a surveillance sample prior to treatment (for example, the only pre-treatment test available is a lateral flow test), where possible, a pre-treatment SARS-CoV-2 RT-PCR should be undertaken at the CMDU. These SARS-CoV-2 RT-PCR kits are not to be used to access treatment as, if a negative sample is sent, a replenishment kit will not be automatically sent to the individual.

All patients treated with nMABs and AVs in the community should undertake a repeat SARS-CoV-2 RT-PCR swab 5 days after the start of treatment using the replacement home test kit. If a kit is not available, individuals can request a SARS-CoV-2 RT-PCR kit when advised by the CMDU, by calling 119. If they attend a follow up clinic, a repeat SARS-CoV-2 RT-PCR swab may be taken and sent.

4. Testing processes

4.1 For patients in hospital

SARS-CoV-2 RT-PCR testing for hospital inpatients should be undertaken using the normal hospital testing and sequencing pathway – samples should be sent to UKHSA laboratories or collaborating laboratories, highlighting that these samples are from individuals prioritised for treatment.

If the local laboratory performs sequencing, please submit sequence data to CLIMB within 2 days of sequencing with patient metadata submitted to UKHSA via existing protocols. Contact the Covid19.genomicsurveillance@phe.gov.uk mailbox if access is required.

If sequencing is sent to UKHSA, the data will be uploaded to CLIMB from UKHSA, and a summary report will be issued to the sending laboratory.

Original sample material should be stored for 14 days at -80°C in the local laboratory if possible; where new mutations are identified on sequencing, UKHSA may request the original specimen to attempt viral culture for further characterisation.

4.2 For patients in the community

The overall testing process is outlined in Figure 1.

Eligible individuals will use lateral flow tests to access treatment. Individuals will have received priority RT-PCR test kits which are to be used for surveillance only and will have their samples processed in UKHSA-commissioned laboratories; these samples are prioritised for sequencing Only positive samples from individuals undertaking treatment will be replenished automatically.

If a SARS-CoV-2 RT-PCR kit is not available, individuals can request a SARS-CoV-2 RT-PCR kit when advised by the CMDU, by calling 119.

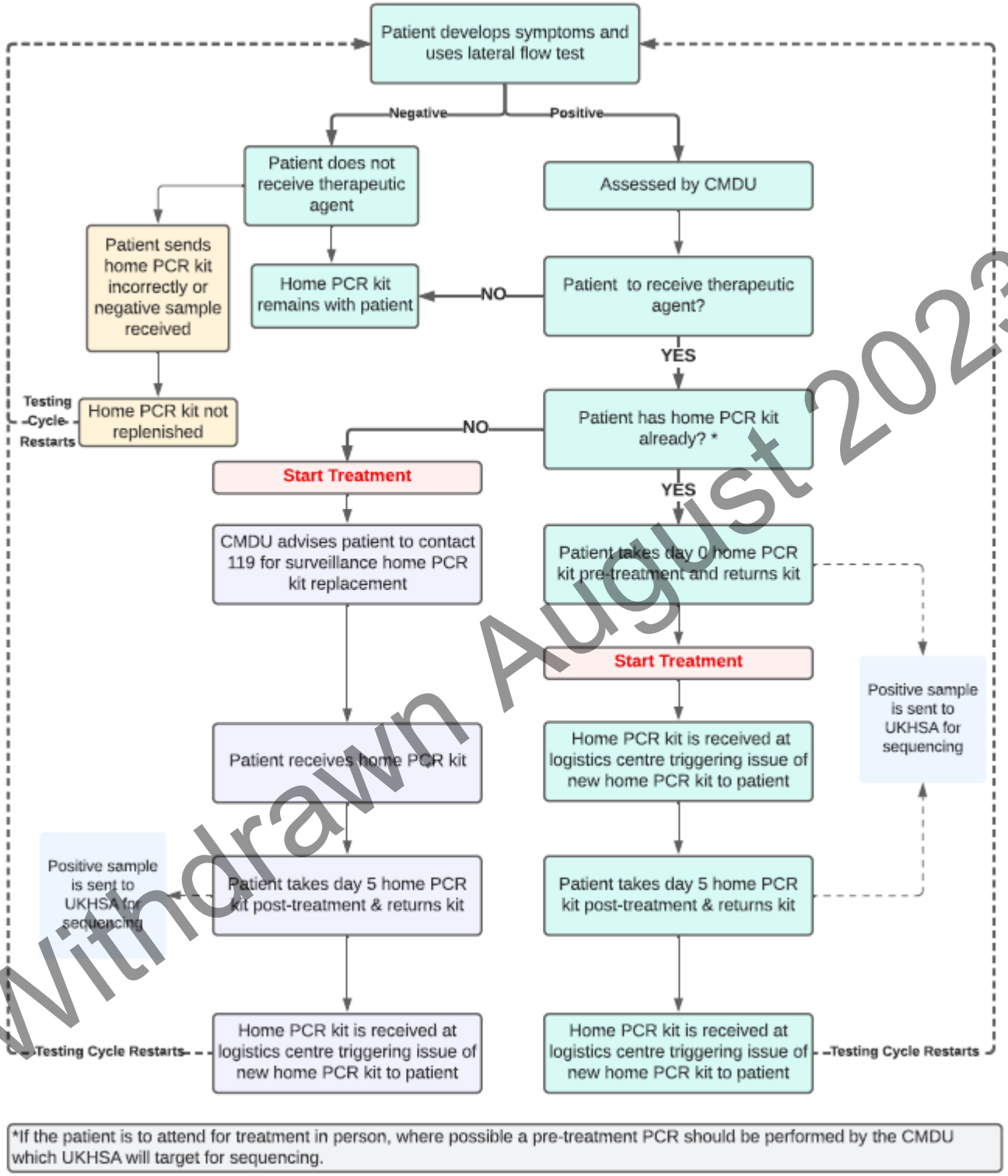
The NHSE/I COVID-19 treatment pathway outlines how CMDUs support individuals in the community to access treatment.

CMDU staff should provide individuals with the patient information leaflet (Annexe A) which should include a date for when a follow up nose and throat swab should be carried out. If the treatment is couriered to the individual, the patient information leaflet (Annexe A) should be posted with the treatment package.

Individuals will swab themselves at day 5 post start of treatment, by using the replenished postal RT-PCR priority kit. This can be sent at any time up to 7 days.

All priority RT-PCR swab-kits will be prioritised for sequencing through UKHSA commissioned laboratories.

Figure 1. COVID-19 community surveillance testing overview



COVID-19 community surveillance testing overview – text version

Patient develops symptoms and uses lateral flow test:

- positive – assessed by CMDU
- negative – patient does not receive therapeutic agent

If negative:

- patient sends home PCR kit incorrectly or negative sample received
- home PCR kit not replenished
    - testing cycle restarts

or

- home PCR kit remains with patient

If positive, patient to receive therapeutic agent?

- yes – go to next question
- no – home PCR kit remains with patient

If yes, patient has home PCR kit already? *

- yes – patient takes day 0 home PCR kit pre-treatment and returns kit
- no – start treatment

If yes:

- positive sample is sent to UKHSA for sequencing

and

- start treatment
- home PCR kit is received at logistics centre triggering issue of new home PCR kit to patient
- patient takes day 5 home PCR kit post-treatment and returns kit
    - positive sample is sent to UKHSA for sequencing
    - home PCR kit is received at logistics centre triggering issue of new home PCR kit to patient
        - testing cycle restarts

If no:

- CMDU advises patient to contact 119 for surveillance home PCR kit replacement
- patient receives home PCR kit
- patient takes day 5 home PCR kit post-treatment and returns kit
    - positive sample is sent to UKHSA for sequencing
    - home PCR kit is received at logistics centre triggering issue of new home PCR kit to patient
        - testing cycle restarts

* if the patient is to attend for treatment in person, where possible a pre-treatment PCR should be performed by the CMDU which UKSHA will target for sequencing

4.3 Sample reports

For NHS samples sent to UKHSA, a sample report will be issued to the Trust with the variant nomenclature and Pango lineage. This is not a clinical service but is provided for information. These samples will be prioritised for sequencing if information on their antiviral treatment is included.

Appropriate further virological investigations on an original sample such as further viral genomic sequencing, culture of the virus, and phenotypic assessment may be undertaken.

No human genomic sequence data will be analysed.

5. Analysis

5.1 Genomic surveillance of patients on treatment

Use of nMABs or AVs will result in a treatment record in Blueteq. UKHSA will receive the Blueteq dataset under a data-sharing agreement with NHSE/I. This dataset will be ingested weekly to a restricted area in the COVID-19 Datastore which can be accessed only by UKHSA. The data items transferred will be:

- NHS number
- patient name
- date of birth
- drug name
- form ID
- form name
- indication drug is used within
- date of application to use drug
- estimated treatment start date
- treating Trust

The Blueteq dataset will be linked to the national COVID-19 line list and the SARS-CoV-2 genome dataset using the available identifiers. A pseudonymised dataset of genomes from treated individuals will be entered into standard variant horizon scanning analyses (for example, mutation scanning). Individual cases with mutations may be analysed longitudinally. No individual-case data will leave UKHSA and any horizon scanning results will be presented in aggregate only. Further detailed description on surveillance analyses are provided within the SARS-CoV-2 Therapeutics technical briefing.

5.2 Genomic surveillance of highly immunosuppressed patients who do not receive treatment

The national genomic dataset will be routinely scanned for individuals who have serial genomic data available but do not link to Blueteq. This dataset will be pseudonymised and used for variant horizon scanning (for example, mutation detection). NHS Trusts' Infection, Microbiology or Virology departments who would like to report or discuss specific individuals with persistent SARS-CoV-2 RT-PCR positivity following treatment, may do so by emailing COVID19.genomicsurveillance@phe.gov.uk from a nhs.net or secure nhs.uk email address only. This is not a mandated requirement; however, it can be used if you would like to highlight

specific patients or if you would like to contact UKHSA to discuss longitudinal genomic data for specific patients. This is not an accredited clinical service and analyses are experimental.

5.3 Genomic surveillance analyses

Amino acid residues which contact with specific sites of nMABs or AVs are provided by external academic partners based on in silico modelling to determine genomic positions and specific mutations considered to be of concern for therapeutic agents. Genomic positions and mutations of concern are scanned for, in all genomes in the UKHSA genomic dataset and within subsequent samples from the treated cohort genomic dataset. Horizon scanning processes using profiles of mutational combinations for which there are laboratory evidence for changes in nMAB or antiviral activity (for example fold reduction/binding alteration) are undertaken throughout the national genomic dataset and the treated cohort genomic dataset. This is refined using in-vitro resistance and structural modelling data.

5.4 Genomic analyses in new variants

If a new variant is identified, enhanced analysis of genomic sequences to detect early signals of treatment failure, resistance and emergence of new mutations will take place. Emergence of new mutations or variants will take place using methods described. Signals of treatment failure will be identified through inter-patient group, SARS-CoV-2 diversity in pre- and post-treatment samples, comparing diversity within variants to previous strains. Signals of resistance will be described by comparing the prevalence of distinct amino acid frequencies of contact residues in spike protein or other target areas, for example non-specific polymerase-12, for specific therapeutic agents in pre- and post-treatment samples, augmented by structural modelling data. Growth rates and minority variant increases within these residues of interest will also be described. Where possible, longitudinal genomic sequence data will be analysed within patients either identified through surveillance or highlighted by clinicians. Early signals will be provided through working group collaborations with academic partners.

6. Epidemiological surveillance, monitoring of treatment outcomes and antimicrobial stewardship

6.1 Treatment outcomes monitoring

All eligible patients will be included for an initial 6-month period of treatment outcome monitoring. Sample size calculation will be developed as Blueteq data starts to flow and linkage to immunosuppression data becomes available.

1. The index date for eligible patients will be the date of initial positive SARS-CoV-2 RT-PCR following confirmation of eligibility for surveillance. Patients will be followed up for a period of 6 months to determine epidemiological outcomes and to confirm either negative testing or the potential for reinfection. The overall study end date will be open-ended to allow for continued surveillance and monitoring.
2. The data used will be a linked dataset of Blueteq, COVID-19 national case list and demographic and address data, COVID-19 genomic and variant and mutation dataset, Emergency care dataset from Hospital Episode Statistics via NHS Digital's Secondary User Service, including Critical Care data, National Immunisation Management Service and COVID-19 deaths.
3. A set of reporting metrics will be developed for further analyses, including admission to hospital, mortality, ICU admission, length of stay and epidemiological characteristics of treated patients.
4. Comparator populations will be drawn from hospital and community cases as appropriate for the analysis. Epidemiological characteristics will be compared between the denominator and treated population to identify factors contributing to the decision to treat and potential candidates for confounding by indication.
5. A detailed comparative retrospective analysis will be undertaken at 4-month intervals:
    a. Propensity score matching based on characteristics identified during surveillance will be used to develop a synthetic control arm from the denominator population that closely resemble the characteristics of the treated cases with respect to demographic and clinical characteristics. Further adjustment with mixed effect models will be used to account for any additional confounders identified during descriptive analyses and hospital clustering effects.
    b. The primary outcome will be all-cause 28-day mortality from index specimen date. Secondary outcomes will aim to include length of stay, 60-day mortality and rate of re-admission, alongside other outcomes which are dependent on data availability Where possible, time to negative RT-PCR and viral load reduction will also be compared between groups.

6. For genomic analyses, sequencing coverage of cases and cohort size once available will be used to estimate the power with which significant changes in mutation or variant prevalence are detected.
7. Determine early signals of treatment failure by comparison of case fatality ratio between circulating strains and variants. Where possible, length of SARS-CoV-2 positivity, cycle threshold values, re-admission rates and severity indicators will be used to supplement this data.
8. Further community treatment data may be analysed by external academic providers, as commissioned by National Institute for Health Research and under appropriate research governance arrangements.

6.2 Usage and dispensing analyses

Alongside clinical and epidemiological data from section 6.1, further capture and analysis of prescription data will determine appropriate use of COVID-19 therapies to assess and improve stewardship. Blueteq data will be aggregated by NHS Trust level to deduce the total number of doses registered on the Blueteq platform. The number of patients receiving each therapy and relative dose will be produced. Dispensed data (provided by Rx-Info) will be used to assess the dispension and uptake of different key therapies by NHS Trusts and regionally in England and will be used to monitor equity of access to therapy.

7. Data management

7.1 Data storage

All data will be stored within UKHSA. Data collection, storage and use will be consistent with the procedures described in the NHS Information Governance Toolkit.

The datasets containing patient identifiable information will be held in the COVID-19 Datastore in a location accessible only to authorised members of UKHSA. A pseudonymised dataset (personally identifiable information removed and identified by COG-ID) will be used for genomic analysis, some of which may be conducted on the UKHSA EDGE platform through established processes. The pseudonymised dataset will be shared with specific academic partners at the request of the Department of Health and Social Care and will be governed under a data-sharing agreement. Clinical data will be retained for 10 years; genomic data will be kept indefinitely at present.

7.2 Data linkage

Most data linkages in this analysis are already undertaken as part of routine COVID-19 surveillance. The new linkages are:

- Blueteq linked to the COVID-19 line list, Blueteq linked to the genomic data second-generation surveillance system extract and Blueteq linked to Rx-Info (dispensing data)
- the linkage to the daily COVID-19 line list refers to records of treatment being matched to people testing positive for COVID-19 and reported to UKHSA
- once linked to the COVID-19 line list, further linkages will be undertaken to Emergency care dataset from Hospital Episode Statistics via NHS Digital's Secondary User Service, including Critical Care data, National Immunisation Management Service/Mortality

Sequencing data will be linked to the UKHSA national database through EDGE in accordance with all COVID-19 sequence results in the UK. All laboratory results will also be recorded in UKHSA's laboratory information management system (LIMS) system, Molis, in line with standard of care practice. If clinical advice is given to an individual, data will be recorded on HPZone as per standard of care.

Data including questions on clinical relevance from NHS Trusts, will be transferred using secure nhs.net to phe.gov email accounts and stored in the relevant HPZone record. Information from these documents may be included in the study database.

All patient samples will be stored within UKHSA in accordance with UKHSA regulations relating to samples taken as part of routine diagnostic testing (UKHSA policy on storage and retention).

8. Ethics

This is a public health surveillance protocol which is used to monitor emerging risks to public health. The protocol has been approved as surveillance by the independent UKHSA Research Ethics and Governance Group. This surveillance and data generation are approved under Regulation 3 (4) of the Health Service (Control of Patient Information) Regulations 2002, for recognising trends in COVID-19 disease outcomes, monitoring and managing the incident response to the COVID-19 pandemic and monitoring and managing adverse reactions to medicines used in the COVID-19 pandemic.

9. Project management and governance

9.1 Project management

This project will be managed by the UKHSA Therapeutics Programme Group and is accountable to the UKHSA Chief Medical Advisor.

9.2 Dissemination

Results from this surveillance programme will be published on the UKHSA webpages regularly in the form of a technical briefing and will be disseminated appropriately to inform public health guidance and risk assessment, as well as to relevant expert clinical groups. Aggregate depersonalised surveillance data may be made available to companies to support post deployment surveillance activities in collaboration with UKHSA. Data from antimicrobial stewardship analyses will be published through or by the English surveillance programme for antimicrobial utilisation and resistance programme. Any public reporting will contain aggregate data and will avoid any risk of deductive disclosure.

About the UK Health Security Agency

UKHSA is responsible for protecting every member of every community from the impact of infectious diseases, chemical, biological, radiological and nuclear incidents and other health threats. We provide intellectual, scientific and operational leadership at national and local level, as well as on the global stage, to make the nation health secure.

UKHSA is an executive agency, sponsored by the Department of Health and Social Care.

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