In Vitro Diagnostic Product Evaluation Protocol

Title of Project: Evaluation of the diagnostic performance of the Rapid SARS-CoV-2 Antigen Test Card for Covid-19

Product Name: Rapid SARS-CoV-2 Antigen Test Card
Manufacturer: MP Biomedicals Germany GmbH
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37269 Eschwege
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BACKGROUND

The current global Covid-19 pandemic has reached 276 million cumulative cases with over 5.3 million cumulative deaths on 23 December 2021 (WHO, 2021). The disease is caused by SARS-CoV-2, a member of the beta coronaviruses which are large (≈125nm), spherical, enveloped, single-stranded RNA viruses. Covid-19 manifests predominantly as an acute respiratory illness (cough, shortness of breath, runny nose, headache, myalgia, fever), with some progressing to acute respiratory distress syndrome (ARDS). Vascular presentations are increasingly being recognized, with vascular pathology such as microangiopathy and thromboembolism reported in almost all major organ systems of the body (ICM, 2021).

Until November 2021, the global pandemic was dominated by the Delta variant. With the emergence of the Omicron variant in December 2021, countries such as the United Kingdom have seen sharp rises in its prevalence; it is now the predominant variant in all regions of the United Kingdom (UKHSA, 2021). Early data suggests that Omicron is more infectious, with secondary attack rates in households of 13.6% and non-households of 7.6%, higher than those of Delta (10.1% And 2.8%, respectively) (UKHSA Technical Briefing 33, 23 December 2021). Approximately 1 in 3 people with Covid-19 do not have symptoms but may still infect others (NHS, 2021). Re-infections are also higher, with 9.5% of Omicron infections identified to have had previous confirmed infections (UKHSA Technical Briefing 33, 23 December 2021).

High scale testing for the virus in the population and tracing the contacts of people who have tested positive to advise them to self-isolate have been paramount in slowing the epidemic spread of the virus in the United Kingdom (DHSC, 2021). Rapid lateral flow tests provide quick and reliable results and do not require sending to a laboratory (NHS, 2021). Current UKHSA strategy recommends performing a rapid lateral flow test on occasions where a person is more likely to be infected (such as mixing in crowded indoor places) or to spread Covid-19 (such as visiting someone who is clinically vulnerable) (NHS, 2021).

Most lateral flow tests have been historically validated for Alpha and Delta variants. With the worldwide emergence of the Omicron variant in December 2021, there is a need to validate lateral flow kits to ensure that they retain high diagnostic performance to the Omicron variant, just as they do for the Delta variant. The UKHSA has, to date, validated only a very small number of lateral flow kits to the Omicron variant (UKHSA Technical Briefing 32, 2021; Table 2, page 16). This, along with the high demand for use of lateral flow test kits nationally, has prompted the need to do this study. The Rapid SARS-CoV-2 Antigen Test Card is a lateral flow test kit that is manufactured by MP Biomedicals Germany GmbH and has obtained CE marking (see Appendix 1 Instructions for Use).

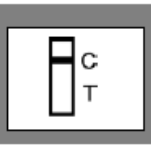
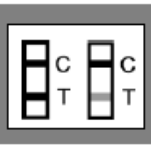
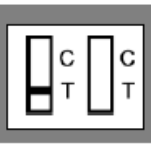
Manufacturers are responsible for the safety and performance of their assays whilst they are available on the UK market (NICE, 2021). To help fulfil this responsibility, MHRA have reminded manufacturers to have a Post Market Surveillance plan (PMSP) in place to continuously monitor, investigate and assess the influence of newly emerging variants of SARS-CoV-2 on assay performance (MHRA, 2021). As this product is registered with the MHRA, the manufacturer is seeking to assess the influence of the new variants on performance in clinical samples.

In addition, the UK Health Security Agency (UKHSA) has introduced new criteria for manufacturers seeking to place their tests on the market in the UK, known as COVID Testing Devices Authorisation. Manufacturers or distributors supplying COVID-19 tests must apply to the Department of Health and Social Care (DHSC) for approval. Their product must meet the Medical Devices (Coronavirus Test Device Approvals) Regulations 2021 (UK Statutory Instruments No 910, 2021). The data collected will support an application for authorization to maintain the products ongoing availability in the UK market under the new regulations.

DIAGNOSTIC PRODUCT TESTING PRINCIPLE

The Rapid SARS-CoV-2 Antigen Test Card is an immunochromatographic lateral flow device that employs the principle of double antibody sandwich method. Colloidal gold conjugated anti-SARS-CoV-2 antibodies are dry-immobilized on the test device. When the specimen is added, it migrates by capillary diffusion through the strip to re-hydrate the gold conjugate complexes. If present at or above the limit of detection, SARS-CoV-2 viral antigens will react with the gold conjugate complexes to form particles, which will continue to migrate along the strip until the Test Zone (T) where they are captured by the immobilized anti-SARS-CoV-2 antibodies to form a visible red line. If there are no SARSCoV-2 viral antigens in the specimen, no red line will appear in the Test Zone (T). The gold conjugate complexes will continue to migrate alone until being captured by immobilized antibody in the Control Zone (C) to form a red line, which indicates the validity of the test.

INTERPRETATION OF RESULTS

NEGATIVE		If one colored band appears in the Control Zone (C) and no colored band appears in the Test Zone (T) within 15-20 minutes, the test result is negative and valid. A negative result does not exclude a viral infection with SARS-CoV-2 and should be confirmed by molecular diagnostic methods if COVID-19 is suspected.
POSITIVE		If two colored bands appear, with one colored band in the Control Zone (C) and another in the Test Zone (T) within 15-20 minutes, the test result is positive and valid. The result should be considered as positive no matter how faint the colored band is in the Test Zone (T). A positive result does not rule out an additional infection with other disease-causing agents.
INVALID		If no colored band appears in the control area (C) within 15-20 minutes, the test is invalid. Repeat the test with a new test card.

QUALITY CONTROL

THE CONTROL LINE IS AN INTEGRATED REAGENT AND IS USED TO CONTROL THE PROCEDURE. THE CONTROL LINE APPEARS WHEN THE TEST HAS BEEN PERFORMED CORRECTLY AND THE REAGENTS ARE REACTIVE.

INTENDED USE

Rapid SARS-CoV-2 Antigen Test Card is an immunochromatography based one step in vitro test. It is designed for the rapid qualitative determination of SARS-CoV-2 virus antigen in nasal swabs, nasopharyngeal swabs or oropharyngeal swabs from individuals suspected of Covid-19 by their healthcare provider within the first seven days of onset.

PURPOSE

The purpose of this evaluation is to determine the diagnostic performance of the Product Under Evaluation (Rapid SARS-CoV-2 Antigen Test Card) compared with RT-PCR (Cepheid GeneXpert Xpert® Xpress SARS-CoV-2) for detection of the presence SARS-CoV-2.

QUALITY CONTROL

1. This evaluation is performed using a blinded controlled trial design. After sample collection from the participant, the testing personnel are blinded to all samples. This can reduce the bias of test results and ensure quality of the trial.

2. The acquisition, preservation, and test operation of samples shall be carried out in strict accordance with the program and the principal investigator, Dr Marco Lee, is assigned to supervise the implementation of the clinical trial.

3. All RT-PCR analyses are undertaken in a UKAS accredited laboratory. The verification study will be conducted in accordance with relevant regulations and procedures that fulfil UKAS requirements.

4. The testing shall be carried out in strict accordance with standard operating procedures specified by the manufacturers.

5. Quality control DNA products are set to ensure the reliable quality of diagnostic results. Positive DNA control is ZeptoMetrix® NATtrol™ SARS-Cov-2 External Run Control NATSARS(CoV2)-ERC which is formulated with purified, intact SARS-CoV-2 viral particles at 50,000 copies/mL. Negative DNA control is ZeptoMetrix® NATtrol™ SARS-Cov-2 External Run Control NATSARS(CoV2)-NEG which contains human A549 cells at 50,000 cells/mL.

6. Before any diagnostic testing is carried out, the department undertaking the diagnostic tests shall check and confirm that the test kits are within the effective period and the storage conditions meet the requirements of the kits.

EXPERIMENTAL DESIGN

1. METHODS

The performance of the Rapid SARS-CoV-2 Antigen Test Card is compared to RT-PCR method on the Cepheid analyzer, which provides a Ct value.

Three groups of participants will be recruited.

Group A

This group consists of Covid-19 suspected NHS staff members who either have symptoms compatible with Covid-19 *or* have been in recent contact with someone who has Covid-19

Inclusion criteria:

a. This group consists of Covid-19 suspected NHS staff members who:
   i) Have symptoms compatible with Covid-19 *or*
   ii) Have been in recent contact with someone who has Covid-19

b. Age ≥ 18 years
c. Within 10 days of onset of symptoms *or* within 10 days of contact with a confirmed Covid-19 case
d. Voluntarily presents to the Airedale swabbing centre for RT-PCR swabbing

Exclusion criteria:

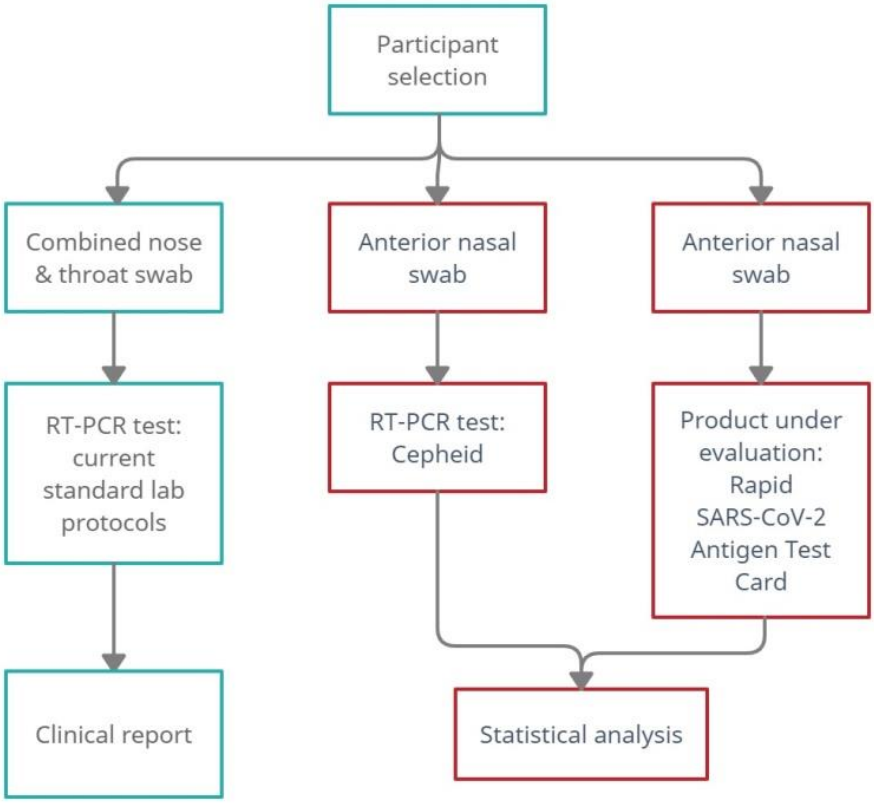
a. Demographic data not available or not provided

Sample rejection criteria:

a. Samples received without the corresponding pair
b. Anterior nasal swabs received >8 hours from time of collection
c. Improperly stored swabs

Verbal consent will be sought from all eligible participants by the Airedale swabbing team.

In this group, the experimental design is as follows:



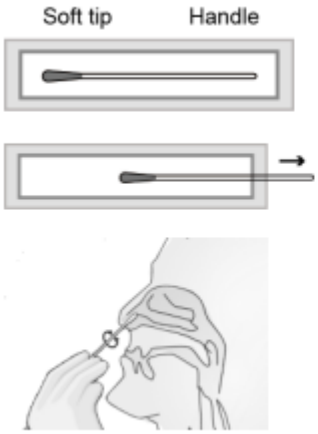
Three swabs will be provided by the Airedale swabbing team to the participant, who will perform self-swabbing:

1. a combined nose & throat swab for RT-PCR (standard-of-care sample)
2. an anterior nasal swab for RT-PCR (on Cepheid GeneXpert Xpert® Xpress SARS-CoV-2)
3. an anterior nasal swab for lateral flow test (the Rapid SARS-CoV-2 antigen test card, the Product under Evaluation)

The participant will be asked to first perform a combined nose & throat swab for RT-PCR (see Appendix 4 for instructions for nose & throat swab). This swab will be processed by current standard laboratory methods, and the result will be reported to the participant and appear in the participant's medical record. This is the current standard-of-care test and will remain unchanged in this study.

The participant will then be asked to perform two anterior nasal swabs, in any order.

The procedure for anterior nasal swabbing is summarized in the steps below:



Find the swab in the sealed wrapper. Identify the soft, fabric tip on the swab.

Peel open the wrapper of the swab and carefully pull out the swab.
CAUTION: Do not touch the soft, fabric tip of the swab with your hands.

Carefully insert the swab into one nostril. The swab tip should be inserted no less than 2.5 cm from the edge of the nostril. Roll the swab 3-4 times along the mucosa inside the nostril to ensure that both mucus and cells are collected. Leave swab in the nostril for several seconds. Using the same swab, repeat this process for the other nostril.
CAUTION: This may feel uncomfortable. Do not insert the swab any deeper if you feel strong resistance or pain.

One anterior nasal swab will be analysed by PCR on the Cepheid GeneXpert Xpert® Xpress SARS-CoV-2, which provides a cycle threshold (CT) value depicting the strength of the PCR-positive signal from the analyser. Trained personnel from the laboratory will undertake the Cepheid RT-PCR test in the laboratory.

Another anterior nasal swab will be collected using a dry cotton swab according to the self-test instructions stated in the manufacturer's Information For Use (IFU) in Appendix 1. The lateral flow test will be performed at the point of collection according to the manufacturer's protocol shown Appendix 1.

Both anterior nasal swabs will have the participant barcodes and labels removed on receipt by the laboratory personnel and will be re-labelled with fresh barcoded study numbers to achieve anonymization. The laboratory personnel performing each of the three diagnostic tests will be blinded to the results of the other tests.

The results from the Cepheid analyser and from the antigen test card are *not* reported to the participant and will not appear in the participant's medical record; they will be used solely for evaluation of the diagnostic performance of the antigen test card.

Group B

This group consists of patients who have confirmed Covid-19 infection (with a positive PCR test result)

Inclusion criteria:

a. This group consists of patients in hospital who:
   have confirmed Covid-19 infection (with a positive PCR test result) *and*
   - admitted to hospital for >24 hours *and*
   - the medical team feels that patient can give valid consent *and*
   - does not require respiratory support other than supplementary nasal oxygen (i.e., participants on non-invasive ventilation such as CPAP, and intubated patients are excluded)
b. Age ≥ 18 years
c. Within 10 days of onset of symptoms, *or* if asymptomatic, within 10 days of date of PCR test

Exclusion criteria:

a. Demographic data not available or not provided

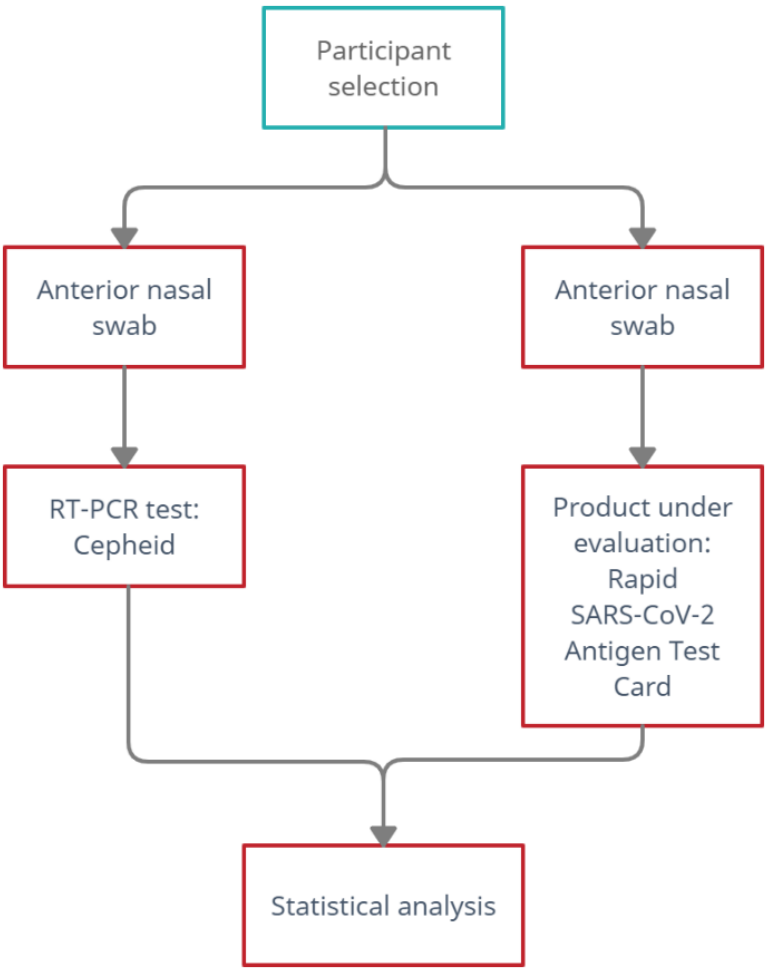
Sample rejection criteria:

d. Samples received without the corresponding pair
e. Anterior nasal swabs received >8 hours from time of collection
f. Improperly stored swabs

Participants in this group will be identified as follows:
Patients meeting the inclusion/exclusion criteria above will be identified through review of patient admissions on the Red Wards (which has only Covid-19 patients) by:
Dr Marco Lee (chief investigator, consultant microbiologist) at Airedale General Hospital
Dr Nuthar Jassam (co-investigator, consultant biochemist) at Harrogate District Hospital
Dr Sulman Hasnie (consultant microbiologist) at Bradford Royal Infirmary

Patients who have been admitted for >24 hours will be identified on the electronic bed management systems. The reviewers will assess the medical notes of the patient to ensure that the patient does not require respiratory support other than supplementary nasal oxygen and does not have any other medical condition that will affect capacity to consent (such as acute delirium or reduced consciousness). The reviewers will confirm with a member of the patient's medical team that the patient can give valid consent. The reviewers or the research nurses at the respective Trusts will then approach the patient to obtain verbal consent for the study.

In this group, the experimental design is as follows:



Two swabs will be provided to the participant, who will perform self-swabbing:

1. an anterior nasal swab for RT-PCR (on Cepheid GeneXpert Xpert® Xpress SARS-CoV-2)
2. an anterior nasal swab for lateral flow test (the Rapid SARS-CoV-2 antigen test card, the Product under Evaluation)

The participant will then be asked to perform two anterior nasal swabs, in any order.

Both anterior nasal swabs will be labelled with barcoded study numbers to achieve anonymization. The laboratory personnel performing each of the two diagnostic tests will be blinded to the results of the other test.

The results from the Cepheid analyser and from the antigen test card are *not* reported to the participant and will not appear in the participant's medical record; they will be used solely for evaluation of the diagnostic performance of the antigen test card.

Group C

This group consists of NHS staff members who are asymptomatic for Covid-19, have no known Covid-19 contact in the past 10 days, and volunteering for the study

Inclusion criteria:

a. This group consists of NHS staff members who:
    - are asymptomatic for Covid-19
    - have no known Covid-19 contact in the past 10 days
b. Age ≥ 18 years
c. Voluntarily presents to the Airedale laboratory for swabbing

Exclusion criteria:

a. Demographic data not available or not provided

Sample rejection criteria:

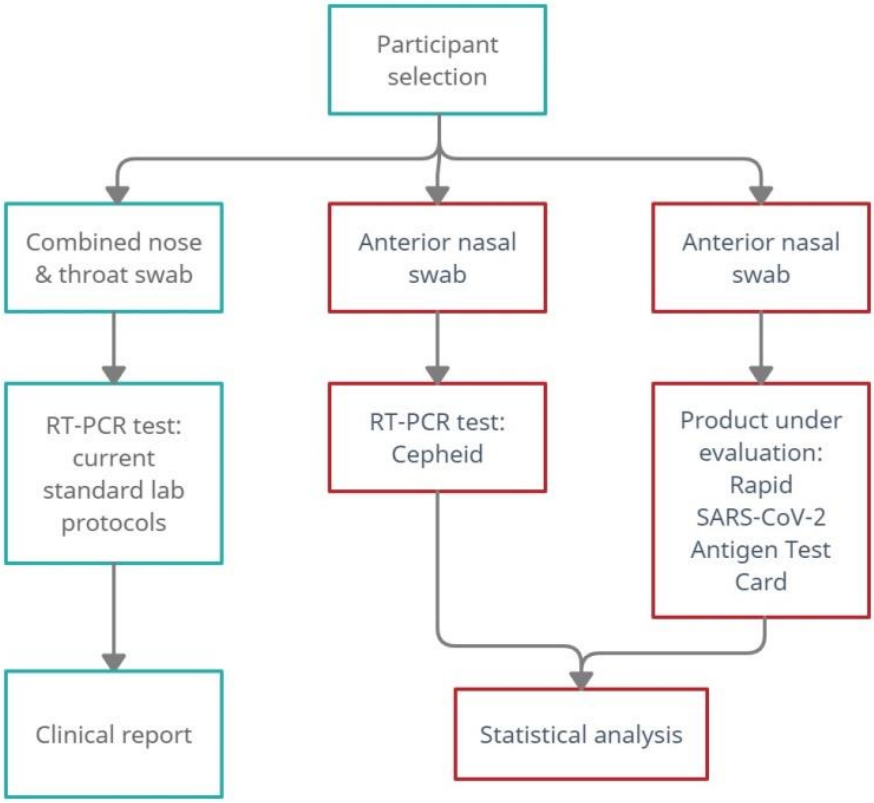
g. Samples received without the corresponding pair
h. Anterior nasal swabs received >8 hours from time of collection
i. Improperly stored swabs

Participants in this group will be identified as follows:
The study team will send out an email via Trust Communications Team to all Airedale NHS staff members requesting volunteers for the study. The email will state:
"Research is essential to generate new knowledge for the benefit of patients and services in the NHS. As part of the Government's response to the Covid-19 pandemic, Airedale has prioritised Covid-19 research and has been actively recruiting participants to Covid-19 studies. Airedale's research team is undertaking a study evaluating the diagnostic performance of a new lateral flow test kit called the Rapid SARS-CoV-2 Antigen Test Card (MP Biomedicals) and is asking for Airedale staff volunteers to take two nose swabs and a combined nose & throat swab to help evaluate its performance. If you are interested, you can come to Airedale laboratory reception (location C46) on XX/XX/XXXX (date) between YY:YY and ZZ:ZZ (time) to participate in the study. Alternatively, you can email ips.microbiology@nhs.net or telephone ext. 3489 to discuss with a study personnel."

This email will be sent out weekly until recruitment is complete. The dates and times stated in the email will be flexible depending on availability of the study team. In addition, an identical message will appear in the Newsletter section on the Trust Intranet homepage.

NHS staff members will have their eligibility criteria checked by a member of the study team and be sign-posted to a room in the laboratory that has been set up for study participants to be consented and the swabs to be collected. Verbal consent will be sought from all eligible participants by the Airedale study team.

In this group, the experimental design is as follows:



Three swabs will be provided by the Airedale swabbing team to the participant, who will perform self-swabbing:

1. a combined nose & throat swab for RT-PCR (standard-of-care sample)
2. an anterior nasal swab for RT-PCR (on Cepheid GeneXpert Xpert® Xpress SARS-CoV-2)
3. an anterior nasal swab for lateral flow test (the Rapid SARS-CoV-2 antigen test card, the Product under Evaluation)

For Group C (asymptomatic NHS staff volunteers), there is a chance that the lateral flow test and/or PCR test may yield a positive result because around 1 in 3 positive Covid cases are asymptomatic. The current isolation guidance for healthcare premises is to self-isolate if a lateral flow test or a PCR test is positive (https://www.gov.uk/government/publications/covid-19-management-of-exposed-healthcare-workers-and-patients-in-hospital-settings/covid-19-management-of-exposed-healthcare-workers-and-patients-in-hospital-settings). Therefore, it is our duty to ensure that the national guidance is adhered to. We therefore propose that a "standard-of-care" nose & throat swab is collected from Group C participants (with full name, date of birth, NHS number) in addition to the two research nose swabs (see Appendix 4 for instructions for nose & throat swab). This standard-of-care swab will be performed on the normal laboratory PCR workflow and reported back to participant and appear on the participant's medical record. The staff member will be consented for this and be advised to follow current Trust self-isolation guidance if the result for this swab is positive.

The participant will then be asked to perform two anterior nasal swabs, in any order.

Both anterior nasal swabs will be labelled with barcoded study numbers to achieve anonymization. The laboratory personnel performing each of the three diagnostic tests will be blinded to the results of the other test.

The results from the Cepheid analyser and from the antigen test card are *not* reported to the participant and will not appear in the participant's medical record; they will be used solely for evaluation of the diagnostic performance of the antigen test card.

2. SELECTION OF TEST INSTITUTIONS

This evaluation will be conducted at Airedale General Hospital, Harrogate District Hospital, and Bradford Royal Infirmary. Swabs will be collected by the staff swabbing centre staff at Airedale General Hospital, and research nurses at Harrogate District Hospital and Bradford Royal Infirmary. RT-PCR tests will be performed in the UKAS-accredited microbiology laboratory at Airedale General Hospital.

3. SAMPLE TYPES

For Group A, one nose & throat swab and two anterior nasal swabs from each participant. The nose & throat swab will be performed first for the standard-of-care test. The subsequent two anterior nasal swabs for Cepheid PCR and lateral flow test can be done in any order.

For Groups B and C, two anterior nasal swabs from each participant, which can be done in any order.

4. NUMBER OF SAMPLES

RT-PCR positive Delta samples: at least 100
RT-PCR positive Omicron samples: at least 100
RT-PCR negative samples: at least 250

The minimum sample size of 100 per Covid-19 variant was based on the minimum sample size to detect a sensitivity of at least 90%, based on 80% power (Bujang and Adnan, 2016).

The MHRA Guidance *Target Product Profile: Point of Care SARS-CoV-2 detection tests* outline the desired performance characteristics for the product aimed at detecting SARS-CoV-2 (MHRA, 2021). It recommends at least 150 total positive clinical samples (which should cover a clinically meaningful range of viral loads) and at least 250 negative clinical samples.

5. DEMOGRAPHIC DATA

The following data will be collected from each participant:

- Age
- Gender

- Symptomatic or Asymptomatic or Contact
- Days from symptom onset or Days from contact (if applicable)
- CT value of RT-PCR results

Age and gender data are required for two reasons:
1. A previous diagnostic performance study of the Rapid SARS-CoV-2 Antigen Test Card performed in China, Turkey, and Korea (Appendix 2) collected Age and Gender data, and we would like to compare the data across both studies to see if there is a statistical difference in baseline demographics.
2. There is a requirement for age and gender in the data collection in the NICE document: *Diagnostic tests for COVID-19 evidence framework* (NICE, 2021):
If possible, individual patient data should be made available (with information governance procedures in place), linked to the results of the index and reference tests. For example:

- *whether a person had symptoms*
- *time since symptoms or confirmed diagnosis of COVID-19 (for antibody tests)*
- *sex*
- *age*
- *comorbidities*
- *the length of time between index and reference test*

Presence of symptoms and days from onset of the disease data are required because positivity rates vary between symptomatic vs asymptomatic people (Ra et al., 2020) and respiratory viral load decreases from date of onset of disease (Biguenet et al., 2020). If there is a difference in results of the lateral flow test compared with RT-PCR, then a clinical reason can be considered to explain this difference. The CT value of the RT-PCR result is a semi-quantitative value that can broadly categorise the concentration of viral genetic material in a patient sample and may also be used to elucidate any differences in lateral flow test diagnostic performance (PHE, 2020).

A sample of the case data form is shown in the Appendix 3.

POSSIBLE ADVERSE EFFECTS

There may be irritation of the inside of the nose from the dry cotton swab. The Patient Information Sheet will clearly request the participant not to insert the swab any deeper if the participant feels strong resistance or pain.

STATISTICAL ANALYSIS

1. The sensitivity, specificity, accuracy, and confidence intervals will be calculated by comparing the results of the Product under Evaluation (Rapid SARS-CoV-2 Antigen Test Card) with the results of the comparator RT-PCR (Cepheid GeneXpert Xpert® Xpress SARS-CoV-2).

Table 1 Comparison of test results for the Product Under Evaluation and RT-PCR

	RT-PCR Results	Total

Product Under Evaluation Results	Positive (+)	Negative (-)	
Positive (+)	a	b	a+b
Negative (-)	c	d	c+d
Total	a+c	b+d	a+b+c+d

Sensitivity (PPA) = a/(a+c) * 100%
Specificity (NPA) = d/(b+d) * 100%
Accuracy (OPA) = (a+d)/(a+b+c+d) * 100%
PPV = a/(a+b) * 100%
NPV = d/(c+d) * 100%

2. Stratified statistics will be performed for positive samples to evaluate the detection rate for Delta and Omicron variants separately.

Table 2 Detection rate of Rapid SARS-CoV-2 Antigen Test Card for Delta variant

	Number of samples	Detection Rates
1-3 days		
4-7 days		
8-10 days		
TOTAL		

Table 3 Detection rate of Rapid SARS-CoV-2 Antigen Test Card for Omicron variant

	Number of samples	Detection Rates
1-3 days		
4-7 days		
8-10 days		
TOTAL		

EXPECTED TIME SCALE

We aim to complete the study within one month.

DATA ANALYSIS AND PUBLICATION

An interim data analysis will be performed after 30 positive PCR tests. Final data analysis will be performed at the end of recruitment.

The data collected will support an application for authorization to maintain the products ongoing availability in the UK market under the new regulations introduced in the Medical Devices (Coronavirus Test Device Approvals) Regulations 2021.

The results will not be published and will not be reported via the national reporting system.

APPENDIX 1

SELF-TEST INSTRUCTIONS FOR USE:

ITT-B06_MP Bio
Self-Test_Instructior

APPENDIX 2

ITT-B07_MP Bio Self-Test_Clinical Eva

APPENDIX 3

SAMPLE CASE DATA FORM

Participant number	Participant number	Gender	Age	Symptomatic (S) or Asymptomatic (A) or Contact (C)	Number of days	Product Under Evaluation result	RT-PCR result	CT value of RT-PCR	SARS-CoV-2 variant
1	A000001	M	30	S	5	+	+	25	Omicron
2	A000002	M	42	C	3	+	+	23.1	Delta
3	A000003	F	28	C	1	-	+	29	Omicron
4	A000004	F	36	C	1	-	-	>40	Omicron
5	A000005	M	40	A	N/A	-	-	>40	Omicron
……									

APPENDIX 4

INSTRUCTIONS FOR SELF-SWABBING OF NOSE & THROAT

Taking a covid swab ver 2.pptx

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