SMART Release & Return Study
Statistical Analysis Plan
(IRAS ID 311842)

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1 Change control

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3 Background and rationale

Close contact with those infected with SARS-CoV-2 and high numbers of infections can cause essential services dangerous workforce shortages if large proportions of staff are quarantined or isolating at the same time. The UK introduced daily contact testing to ease such pressures regarding quarantine, and this study extends the daily testing principle to return to work from isolation after serial negative lateral flow test results. At the time this study was conceived there was a requirement for NHS and social care workers in the UK have a negative PCR test before they could be released from quarantine after 10 days from exposure following daily negative lateral flow tests (LFTs)[1]. PCR testing can be difficult to organise and slow to return results (up to 48 hours to receive results at times) adding further workforce pressures.

Christmas 2021 saw quarter of NHS staff in Cheshire and Merseyside being absent from work, with workforce pressures greater than those in the Alpha wave of the prior winter. This occurred at the same time as surging non-Covid pressure on acute NHS trusts from winter and from a backlog of care displaced by Covid-19 measures. The Liverpool population had the world's longest running cohort of SARS-CoV-2 rapid antigen community testing so was well placed to host this study.[2]

Omicron cases surged in Winter 2021 and continued to exert pressures through Spring 2022. NHS staff also faced pressures from burnout after two years of responding to urgent Covid-19 demands. Some cases of Covid testing regimes proved unpopular with hospital staff such as the twice weekly LAMP resulting in low compliance of around 25%. Since staff are already on site if then notified as positive, then onward transmission is possible. An alternative solution using LFTs at home could avoid onward transmission as the staff member is still at home when notified as positive.

Some reports have occurred which suggest that nasal-only swabbing for LFTs may delay the detection of Omicron cases.[3] Social media and Covid monitoring apps have also indicated that substantial numbers of people are testing positive for Omicron for longer than 5 days, with some even reportedly positive for 10 or more days post-exposure. Reporting bias is possible here though. Those NHS staff testing positive between 10-14 days post-exposure were subject to additional guidance updated on 7/1/22.[1]

4 Objectives

The research questions to be answered are:

1. Does the addition of dual swabbing and use of two different manufacturer's devices at the same time add substantial value (in timely case detection) over a single device?
2. Does nose only swabbing detect Omicron infection as early as nose plus throat swabbing for LFT?
3. Is two consecutive days of negative (dual) LFT results a reliable indicator that an Omicron case will not subsequently revert to (validated) LFT positive/shedding within the same course of infection?
4. Can Omicron be cultured from cases after two consecutive days of negative LFTs by Day 7/8 when they are eligible to return to work from isolation?
5. Will NHS staff cases take up the offer of accelerated return to work given serial negative LFTs when their employer strongly encourages/organises participation?
6. Is there an association between discordance (Y/N) of the dual LFT tests and the LFT test type which is positive (Innova/Orient Gene)?
7. Is there an association between discordance (Y/N) of the dual LFT tests and the LFT test type which is positive (Innova/Orient Gene) given the LFT test type which is recorded first (Innova/Orient Gene)?
8. Is there an association between discordance (Y/N) of the dual LFT tests and the LFT test type which is positive (Innova/Orient Gene) depending upon the time from the first recorded positive result?
9. Do hospital staff find dual LFT testing acceptable?
10. Do hospital staff have more confidence in dual or single testing?

This document describes the statistical analyses addressing points 1-3 and 6-8 on the objectives list.

5 Study design and participants

This is an urgent pilot service evaluation with the order of swabbing randomised as directed by an instructional leaflet. This will give a series of dual LFT results over 10 days with PCR results on days 1 and 5. This will be a quantitative and qualitative (participant and employer survey) observational study of uptake and staffing impacts. Operational evidence will be gathered via a survey of participants.

All participants will be fully vaccinated. Participants will be asked to test with dual LFTs for 10 days post-consent and will be asked to complete a postal PCR test on days 1 and 5. Pathways for uninfected contact participants, asymptomatic infected contact participants and new cases referred to the study can be seen in the study protocol.

A sample of at least 30 participants who have either of their two daily lateral flow tests positive on each day from Day 5 to Day 7 will be invited to have another swab for viral culture on Day 7, or on Day 8, 9 or 10 if they are serially lateral flow positive until then. In addition, a sample of at least 30 participants who have either of their two daily lateral flow tests negative on each of Days 5 and 6, or 6 and 7, after having at least two consecutive days of either lateral flow test positive between days 1 and 4, will be invited to have another swab for viral culture on Day 7 or Day 8. From each of the viral culture's RNA sequencing will be attempted in order to confirm that the virus cultured from the swabs provided is SARs-CoV-2 and will also confirm which variant is present.

6 Sample Size

The number of positive cases required with 80% power at 5% significance to detect a significant difference between the two approaches in the proportion of cases missed is ~164 positive cases.[4] Raised to 200 to account for loss to follow-up. Using only a contact cohort with ~10% case rate this would require a sample of 2000, but more as case rates fall. More detailed information about the sample size calculation can be found in the study protocol.

7 Randomisation

Each participant has a randomised testing schedule generated by the research team that will be used by the packing company to generate and individualised day-by-day instruction sheet in the pack they receive. The order in which lateral flow and (on days 1 and 5) PCR tests are instructed to be taken are detailed on the sheet and the participant is asked to upload the results via NHS Test & Trace systems in that order. The enhanced NHS Test & Trace lateral flow reporting link that uses AI reading of photographs of test kits will be provided.

8 Tables and confidence intervals

Tables will provide descriptive analysis results (to 1 decimal place) and any appropriate statistical tests (to 3 decimal places). Ninety-five percent confidence intervals will be provided where appropriate.

9 Data checks

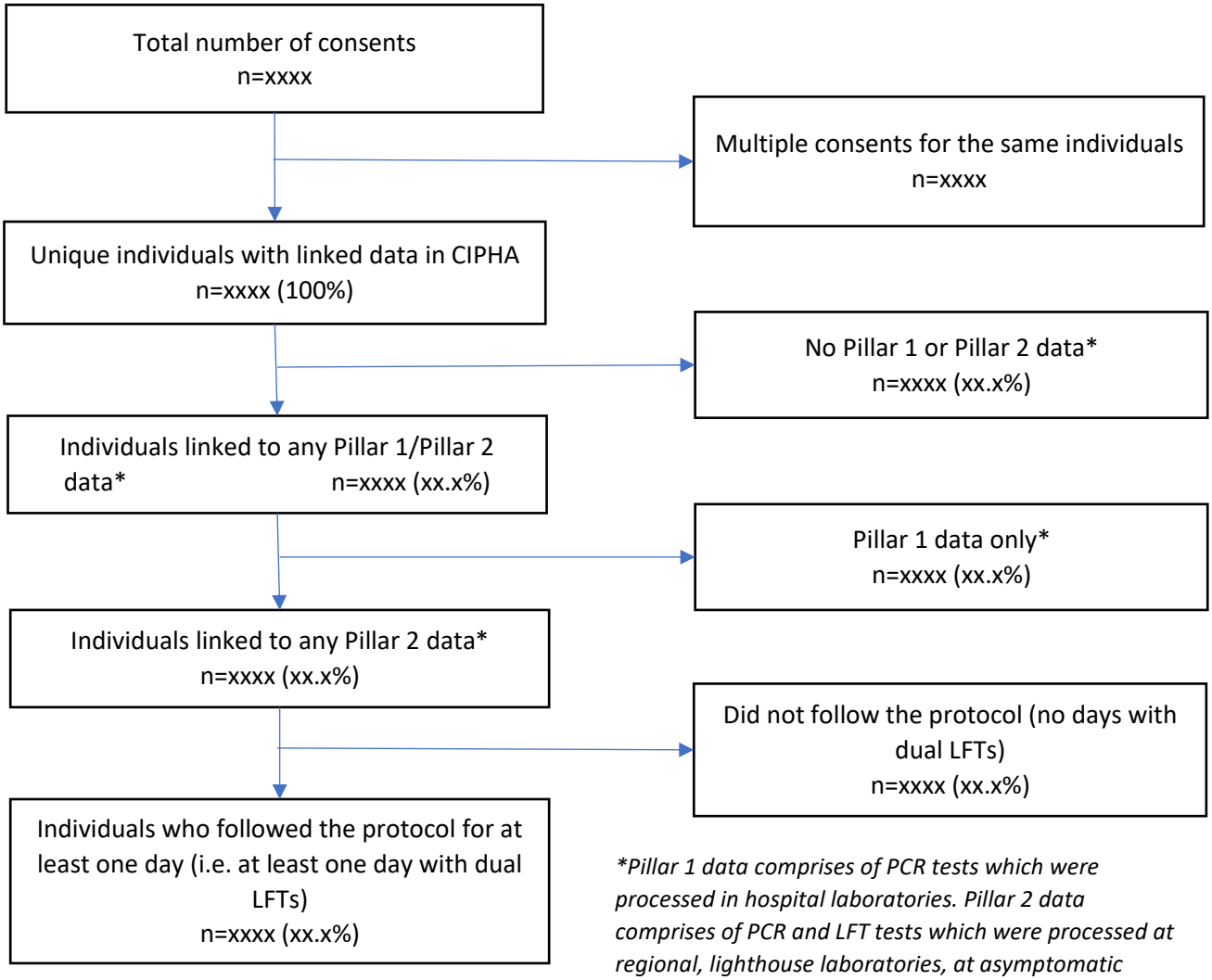
The following data checks will be carried out on the SMART_RR data set prior to analysis. Any discrepancies will be queried with Graphnet Health (Sarah Adams):

1. The only categories within PCR results are 'Positive', 'Negative' and 'Equivocal'.
2. The only categories within LFT results are 'Positive', 'Negative' and 'Equivocal'.

10 Data Flow

A flow diagram will be constructed in the format of Figure 10-1.

Figure 10-1: *Flow diagram for SMART_RR study*



**Pillar 1 data comprises of PCR tests which were processed in hospital laboratories. Pillar 2 data comprises of PCR and LFT tests which were processed at regional, lighthouse laboratories, at asymptomatic testing centres or by individuals at home.*

11 Number of Participants by Consent Date

A histogram of the number of participant consents by consent date will be plotted. Additionally, a second histogram of the number of participant consents by consent date, for individuals who had at least one day with dual LFT tests recorded (one Innova, one Orient Gene) will be plotted.

12 Definitions and Logic Rules

COVID status at baseline

COVID status at baseline (*day0status*) is defined as the result of the Pillar 1 PCR test on day 0 or day 1. The Pillar 1 PCR test is a more reliable, independent indicator of COVID status (being processed by the hospital laboratory) than the LFT tests which can be assessed by the individual taking the test. However, a number of individuals did not have a linked Pillar 1 test on days 0 or 1 of the study period. Therefore, an additional logic rule for COVID status at baseline is required. The rule followed is as follows:

- IF a participant has a Pillar 1 PCR test recorded on day 0 or day 1 AND it gives a positive or negative result (i.e. not equivocal) then *day0status* = Pillar 1 (day 0/1) test result.
- ELSE IF a participant does not have a Pillar 1 test recoded on day 0 or day 1 as either positive or negative, AND the participant has two positive or two negative LFT tests recorded on day 1 (i.e. consistently either positive or negative) THEN *day0status* = dual LFT test result from day 1.
- ELSE *day0status* = unknown.

Participants who consent multiple times

For those individuals who consent multiple times, only one consent for each participant is to be kept. For each participant with multiple consent dates, we consider each separately, constructing the 10-day study window associated with each consent date. The rule we follow is:

- KEEP that consent date associated with the study window which contains the most days with dual LFT tests recorded AND DROP all others for that participant.
- IF there is more than 1 consent date associated with study windows which jointly contain the most days with dual LFT tests recorded THEN KEEP the consent date which is associated with a known COVID status at baseline (i.e. *day0status* = positive OR negative) AND DROP all other consents for that participant.

Note that further logic rules may be needed if there are any participants with multiple study windows where more than 1 window had a known COVID status at baseline.

Study day at which those who were negative at baseline became positive during the study

The study day at which those individuals who were negative at baseline became positive during the study (*neg2posday*) is defined as:

- IF a participant has negative COVID status at baseline (*day0status* = NEGATIVE) AND there is at least one study day (1-10) at which there are dual LFT tests which are both positive, THEN *neg2posday* is the minimum study day on which these dual positive LFT tests occur.
- ELSE *neg2posday* = NA.

13 Analysis

Statistical tests and confidence intervals (where appropriate) will be generated. Analyses will be carried out in R (version 3.6.1 or later). The analyses will be quality checked by a second statistician using R (version 3.6.1 or later).

13.1 Does the addition of dual swabbing and use of two different manufacturer's devices at the same time add substantial value (in timely case detection) over a single device?

The number of participants who tested positive at any point in the study will be calculated. Out of these the number and proportion of participants who had concordant and discordant LFT tests on their 1st day with dual tests recorded. Of those with a discordant result, the number of participants, proportion and 95% Clopper-Pearson CI where the 1st recorded test was positive and those where the 2nd recorded test was positive will be calculated.

13.2 Does nose only swabbing detect suspected Omicron infection as early as nose plus throat swabbing for LFT?

Out of the participants who tested positive at any point in the study, the number and proportion of participants who tested positive with both tests, tested positive with the Innova test only, and tested positive with the Orient Gene test only on the first day on which dual tests were recorded. The total number of omicron cases that would have been detected (including proportion and 95% Clopper-Pearson CIs) by the Innova test only, or the Orient Gene test only will be calculated.

13.3 Is two consecutive days of negative (dual) LFT results a reliable indicator that an Omicron case will not subsequently revert to (validated) LFT positive/shedding within the same course of infection?

Out of the participants who tested positive at any point in the study, the number and proportion of participants who subsequently had two or more consecutive days of dual negative LFT tests will be calculated. Of those the number, proportion and 95% Clopper-Pearson CI of those who had a subsequent positive LFT test result will be calculated.

13.4 Is there an association between discordance (Y/N) of the dual LFT tests and the LFT test type which is positive (Innova/Orient Gene)?

Table 13.4-1: *2x2 Contingency table for LFT test result (positive/negative) by LFT test type (Innova/Orient Gene)*

		Innova		
		Negative	Positive	TOTAL
Orient Gene	Negative	xxxx (xx.x%)	xxxx (xx.x%)	xxxx
	Positive	xxxx (xx.x%)	xxxx (xx.x%)	xxxx
TOTAL		xxxx	xxxx	xxxx (100%)

Note that pairs of tests which included at least one equivocal result were excluded.

McNemar test with Yang's adjustment will be conducted.

13.5 Is there an association between discordance (Y/N) of the dual LFT tests and the LFT test type which is positive (Innova/Orient Gene) given the LFT test type which is recorded first (Innova/Orient Gene)?

Table 13.5-1: *2x2 Contingency table for LFT test result (positive/negative) by LFT test type (Innova/Orient Gene) when Orient Gene is recorded first.*

		Innova		
		Negative	Positive	TOTAL
Orient Gene	Negative	xxxx (xx.x%)	xxxx (xx.x%)	xxxx
	Positive	xxxx (xx.x%)	xxxx (xx.x%)	xxxx
TOTAL		xxxx	xxxx	xxxx (100%)

Note that pairs of tests which included at least one equivocal result were excluded.

Table 13.5-2: *2x2 Contingency table for LFT test result (positive/negative) by LFT test type (Innova/Orient Gene) when Innova is recorded first.*

		Innova		
		Negative	Positive	TOTAL
Orient Gene	Negative	xxxx (xx.x%)	xxxx (xx.x%)	xxxx
	Positive	xxxx (xx.x%)	xxxx (xx.x%)	xxxx
TOTAL		xxxx	xxxx	xxxx (100%)

Note that pairs of tests which included at least one equivocal result were excluded.

For both cases, McNemar test with Yang's adjustment will be conducted.

13.6 Is there an association between discordance (Y/N) of the dual LFT tests and the LFT test type which is positive (Innova/Orient Gene) depending upon the time from the first recorded positive result?

Only those participants who tested positive while in the study are included here (i.e. any participant who never tested positive at any timepoint will be excluded). Also, any dual LFT test results which included an equivocal result and any dual tests prior to a participant's first recorded positive test will also be excluded.

Table 13.6-1: *Discordant (by test type positivity) and concordant results from dual LFT tests by days from first recorded positive test.*

	Day from 1st recorded positive test											**Chi-sq test for trend**
Orient Gene (Innova) Results	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	
Positive (Negative)	xxxx (xx.x%)	xxxx (xx.x%)	xxxx (xx.x%)	xxxx (xx.x%)	xxxx (xx.x%)	xxxx (xx.x%)	xxxx (xx.x%)	xxxx (xx.x%)	xxxx (xx.x%)	xxxx (xx.x%)	xxxx (xx.x%)	x.xxx (*p*=x.xx)
Negative (Positive)	xxxx (xx.x%)	xxxx (xx.x%)	xxxx (xx.x%)	xxxx (xx.x%)	xxxx (xx.x%)	xxxx (xx.x%)	xxxx (xx.x%)	xxxx (xx.x%)	xxxx (xx.x%)	xxxx (xx.x%)	xxxx (xx.x%)	x.xxx (*p*=x.xx)
Concordant	xxxx (xx.x%)	xxxx (xx.x%)	xxxx (xx.x%)	xxxx (xx.x%)	xxxx (xx.x%)	xxxx (xx.x%)	xxxx (xx.x%)	xxxx (xx.x%)	xxxx (xx.x%)	xxxx (xx.x%)	xxxx (xx.x%)	
Total	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx	

13.7 Is daily lateral flow dual self-testing acceptable to hospital staff?

An optional exit survey via an on-line questionnaire will capture participant experiences and descriptive statistics of responses will be presented alongside reflections of investigators who discussed participant feedback from the trial coordination regularly throughout the study.

13.8 Do hospital staff have more confidence in single or dual daily lateral flow self-testing?

A 10-point Likert scale from “No confidence” at all to “Full confidence” in dual testing vs single testing will capture participants’ attitudes on exit from the study via an optional on-line questionnaire. If responses are heavily skewed then preferences for the two testing regimens will be compared using a Wilcoxon signed ranks test with exact confidence interval for the medial difference, otherwise a paired t test with confidence interval for the difference in means will be used.

14 References

1. 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
2. www.liverpool.ac.uk/coronavirus/research-and-analysis/covid-smart-pilot
3. Discordant SARS-CoV-2 PCR and Rapid Antigen Test Results When Infectious: A December 2021 Occupational Case Series. www.medrxiv.org/content/10.1101/2022.01.04.22268770v1
4. Machin et al. Sample Size Tables for Clinical Studies. 2009. 3rd edition. London: Wiley-Blackwell. Table 7.1