RCH HREC 62586	Statistical Analysis Plan
Protocol Version 12.0 17May2022	

RCH HREC/protocol no: 62586
NCT04327206

BCG vaccination to Reduce the impact of COVID-19 in healthcare workers (BRACE) Trial

Statistical Analysis Plan

Document Version History

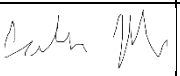
Version Date	Version	Author	Signature	Change Description	Reason/Comment
18-May-2022	1	Francesca Orsini		Initial release.	Not applicable.
10-Aug-2022	2	Cecilia Moore		Second release	a) Error in protocol version number and date corrected b) Errors in section 4.3 and 7.4 corrected. The description of outcome derivation and estimands of secondary outcome 7a.1/7b.1 are now aligned with intended analysis of outcomes detailed in 7.4.1 c) revisions to analysis of non-COVID-19 related outcomes – i) treatment policy approach for intercurrent event of COVID-19 vaccination revised to be primary analysis, ii) model for outcome 19 (episodes of fever or respiratory illness) revised to ZNIB model and censoring rules corrected to align with analysis description of outcome 17 (section 8.1), iii) revisions made to analyses of outcome 29a and 29b (unplanned absenteeism) due to the anticipated nature of the data being zero-inflated and skewed count data

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE	Adverse Event
App	Smartphone Application
AR	Adverse Reaction
BCG	Bacille Calmette-Guérin
BMI	Body Mass Index
BRACE	BCG vaccination to Reduce the impAct of COVID-19 in hEalthcare workers
CI	Confidence Interval
COVID-19	Coronavirus Disease of 2019
DSMB	Data Safety Monitoring Board
GST	Group Sequential Test
ICU	Intensive Care Unit
ITT	Intent-To-Treat
LOCF	Last Observation Carry Forward
PCR	Polymerase Chain Reaction
RAT	Rapid Antigen Test
SAE	Serious Adverse Event
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SD	Standard Deviation
SE	Standard Error
TSC	Trial Steering Committee
MedDRA	Medical Dictionary for Regulatory Activities
WHO DD	World Health Organization Drug Dictionary

1. STUDY OBJECTIVES

1.1. PRIMARY OBJECTIVE

1. To determine if BCG vaccination (Intervention) compared with placebo (Comparator) reduces the incidence of 'symptomatic COVID-19' (Outcome) measured over the 6 months following randomisation (Time) in healthcare workers (Participants).
2. To determine if BCG vaccination (Intervention) compared with placebo (Comparator) reduces the incidence of 'severe COVID-19' (COVID-19-related death, hospitalisation, or non-hospitalised severe disease, defined as 'non-ambulant'[1] for ≥ 3 consecutive days OR Unable to work[2] for ≥ 3 consecutive days) (Outcome) measured over the 6 months following randomisation (Time) in healthcare workers (Participants).

[1] "pretty much confined to bed (meaning finding it very difficult to do any normal daily activities)"

[2]"I do not feel physically well enough to go to work"

Two primary outcomes have been chosen for this study: occurrence of COVID-19 and occurrence of severe COVID-19. Considering the number of unknown factors and the little knowledge of this new virus, we deemed it of clinical importance to have sufficient power to detect the potential effect of BCG vaccine compared to control for both outcomes. Our hypothesis is that, compared to control, the BCG vaccine will reduce both the number of cases of COVID-19 (increase the number of asymptomatic SARS-CoV-2 infections) and the number of cases of severe COVID-19. In other words, we hypothesise that BCG vaccine will shift the "severity of COVID-19" curve down, i.e., generally reduce the severity of the symptoms. The method used to control type I error is explained in the sample size section (11.1).

1.2. SECONDARY OBJECTIVES

3. To determine if BCG vaccination (Intervention) compared with placebo (Comparator) reduces the incidence of symptomatic COVID-19 (Outcome) measured over the 12 months following randomisation (Time) in healthcare workers (Participants).
4. To determine if BCG vaccination (Intervention) compared with placebo (Comparator) reduces the incidence of severe COVID-19 (non-hospitalised severe disease, hospitalisation or death) (Outcome) measured over the 12 months following randomisation (Time) in healthcare workers (Participants).
5. To determine if BCG vaccination (Intervention) compared with placebo (Comparator) prolongs the time to first COVID-19 episode (Outcome) measured over 6 and 12 months following randomisation (Time) in healthcare (Participants).
6. To determine if BCG vaccination (Intervention) compared with placebo (Comparator) reduces the severity of COVID-19 (Outcome) measured over 6 and 12 months following randomisation (Time) in healthcare workers (Participants).
7. To determine if BCG vaccination (Intervention) compared with placebo (Comparator) reduces the rate and severity of illness (fever or at least one sign or symptom of respiratory disease) measured over 12 months following randomisation (Time) in healthcare workers (Participants).
8. To determine if BCG vaccination (Intervention) compared with placebo (Comparator) reduces absenteeism (days off work) measured over 6 and 12 months following randomisation (Time) in healthcare workers (Participants).
9. To evaluate the safety of BCG vaccination in healthcare workers.

1.3. PLANNED EXPLORATORY OBJECTIVES

10. To determine in a subgroup of adults with recurrent cold sores whether BCG vaccination compared with placebo reduces herpes simplex recurrences (such as cold sores).
11. To determine the BCG vaccination induces changes in the immune system that are associated with protection against non-tuberculous infectious diseases including COVID-19.
12. To determine and compare changes in the immune system induced by vaccination.
13. To identify factors (e.g. age, sex, chronic conditions such as diabetes and cardiovascular disease, smoking, asthma, prior BCG vaccination, genetics, other vaccinations including COVID-19-specific vaccines, latent TB, immunological/molecular factors) that influence immune responses, infection and COVID-19 risk.
14. (Brazil specific) To identify biomarkers for diagnosing TB infection.

2. BACKGROUND/INTRODUCTION

2.1. STUDY DESIGN

BRACE is a phase III, two arms, multicentre, randomised placebo-controlled trial in healthcare workers to determine if BCG vaccine reduces the incidence and the severity of COVID-19 during the SARS-CoV-2 pandemic. At trial design, we planned to randomise 7,244 healthcare workers 1:1 to receive BCG or placebo.

Initially the trial was designed to compare primary and secondary outcomes between BCG and no BCG which was given concurrently with the influenza vaccination (Stage 1). The trial was then expanded to international sites and the design was revised to compare primary and secondary outcomes between BCG and a placebo (Stage 2). The comparison of BCG vs placebo in Stage 2 is the primary analysis of interest, however it is planned to combine the data from the two stages of the trial in a meta-analysis for secondary analyses of the non-COVID-19 outcomes. The analysis plan for this pre-planned meta-analysis is specified in section 9.

The two stages of the study are detailed below:

Dates	Stage	Planned Sample Size	Intervention	Control	Blinding
30th Mar 2020 to 13th May 2020	Stage 1	2,834	BCG+ Influenza	Influenza	Unblinded
14th May 2020 to 1st April 2021	Stage 2	7,244	BCG	Placebo	Blinded

As part of the monitoring, there was a formal interim analysis of the efficacy data. The details of this interim analysis are in a separate SAP [https://doi.org/10.25374/MCRI.14721309.v1]. This analysis compared the number of cases of severe COVID-19 (primary outcome 2) between the BGG group and the control group for those recruited after the introduction of the placebo (Stage 2 of the study).

2.2. INTERVENTION GROUPS

Participants were randomly allocated in a 1:1 ratio to the BCG vaccine group or to the control group in both Stage 1 and 2 of the study. Randomisation was stratified by:

- stage of the study (prior to or post the addition of the placebo vaccination);
- study site;
- age (<40 years; 40 to 59 years; ≥60 years); and
- presence of comorbidity (any of diabetes, chronic respiratory disease, cardiac condition, hypertension).

The BCG vaccine group received an adult dose of 0.1 mL of BCG vaccine SSI injected intradermally over the distal insertion of the deltoid muscle onto the humerus (approximately one third down the upper arm).

The control group in Stage 2 of the trial received 0.1 mL of 0.9% NaCl (placebo) injected intradermal over the distal insertion of the deltoid muscle onto the humerus. The control group in Stage 1 of the trial received the influenza vaccine on the day of randomisation. In Stage 2 of the trial, the control group received a placebo in an effort to blind participants to their treatment group allocation (although the subsequent local reaction at the injection site with BCG vaccination prevents total blinding).

Members of the trial team, except immunisers, are also blinded to the group allocation in Stage 2, achieved by hiding or removing the treatment group variable and all other variables related to BCG from the dataset, and will remain blinded until the database is locked for analysis.

2.3. STUDY POPULATION

Participants are adult (≥18 years) healthcare workers from Europe (the Netherlands, Spain and the United Kingdom), South America (Brazil) and Australia.

INCLUSION CRITERIA

- ≥ 18 years of age
- Healthcare worker
    - defined as anyone who works in a healthcare setting or has face-to-face contact with patients.
- Provide a signed and dated informed consent form
- Pre-randomisation blood collected
- Australian sites only: If annual influenza vaccination is available, receiving the influenza vaccine is an eligibility requirement. The influenza vaccine will be required a minimum of 3 days in advance of randomisation in the BRACE trial.

EXCLUSION CRITERIA

- Has any contraindication to BCG vaccine:
    - Fever or generalised skin infection (where feasible, randomisation can be delayed until cleared)
    - Weakened resistance toward infections due to a disease in/of the immune system
    - Receiving medical treatment that affects the immune response or other immunosuppressive therapy in the last year.
        - These therapies include systemic corticosteroids (≥20 mg for ≥2 weeks), non-biological immunosuppressant (also known as 'DMARDS'), biological agents (such as monoclonal antibodies against tumour necrosis factor (TNF)-alpha).
    - Congenital cellular immunodeficiencies, including specific deficiencies of the interferon-gamma pathway
    - Malignancies involving bone marrow or lymphoid systems
    - Any serious underlying illness (such as malignancy)
        - NB: People with cardiovascular disease, hypertension, diabetes, and/or chronic respiratory disease are eligible if not immunocompromised, and if they meet other eligibility criteria
    - Known or suspected HIV infection, even if they are asymptomatic or have normal immune function.
        - This is because of the risk of disseminated BCG infection
    - Active skin disease such as eczema, dermatitis or psoriasis at or near the site of vaccination
        - A different adjacent site on the upper arm can be chosen if necessary
    - Pregnant
        - Although there is no evidence that BCG vaccination is harmful during pregnancy, it is a contra-indication to BCG vaccination. Therefore, we will exclude women who think they could be pregnant or are planning to become pregnant within the next month.

        - UK specific: Although there is no evidence that BCG vaccination is harmful during pregnancy, it is a contra-indication to BCG vaccination. Therefore, we will exclude women of childbearing potential (WOCBP) who think they could be pregnant.
        - Spain specific: If the patient is female, and of childbearing potential, she must have a negative pregnancy test (provided by Sponsor) at the time of inclusion and practice a reliable method of birth control for 30 days after receiving the BCG vaccination.
    - Another live vaccine administered in the month prior to randomisation
    - Require another live vaccine to be administered within the month following BCG randomisation
        - If the other live vaccine can be given on the same day, this exclusion criteria does not apply
    - Known anaphylactic reaction to any of the ingredients present in the BCG vaccine
    - Previous active TB disease
- Currently receiving long term (more than 1 month) treatment with isoniazid, rifampicin or quinolone as these antibiotics have activity against *Mycobacterium bovis*
- Previous adverse reaction to BCG vaccine (significant local reaction (abscess) or suppurative lymphadenitis)
- BCG vaccine given within the last year
- Previous positive SARS-CoV-2 test result (PCR on a respiratory sample or SARS-CoV-2 antigen test approved by the local jurisdiction's public health policy)
- Already part of this trial, recruited at a different site/hospital.
- Participation in another COVID-19 prevention trial
- Previously received a COVID-19-specific vaccine

2.4. SAMPLE SIZE

ORIGINAL SAMPLE SIZE

The original sample size was calculated based on the two primary outcomes of: (1) the proportion of participants with COVID-19; and (2) the proportion of participants with severe COVID-19, by 6 months following randomisation. Since the trial aims to assess two primary outcomes, an adjustment for multiplicity was applied to maintain a global Type I error rate of 5% by splitting of this alpha.

The original sample size was based on the following:

i) 7244 healthcare workers recruited in Stage 2 would provide 80% power to detect a risk ratio of 0.67 (equivalent to a 1.3% absolute difference) in the BCG group compared to the control group for severe COVID-19 at 6 months (primary outcome 2), assuming 4% of subjects will have severe COVID-19 by 6 months in the control group and allowing for 16% lost to follow-up by 6 months (2-sided alpha = 0.04).

ii) 2016 healthcare workers would provide 95% power to detect an absolute difference of 10% in incidence of COVID-19 (primary outcome 1), assuming 55% of subjects will have COVID-19 in the control group (2-sided alpha = 0.005).

iii) In the pre-planned meta-analysis, 10,078 healthcare workers recruited in Stages 1 and 2 would provide 90% power to detect a risk ratio of 0.67 (equivalent to an absolute risk difference of 1.3%) in the BCG group compared to the control group for severe COVID-19 at 6 months (primary outcome 2), assuming 4% of subjects will have severe COVID-19 by 6 months in the control group and allowing for 20% lost to follow-up by 6 months (2-sided alpha = 0.04).

iv) We originally allocated alpha=0.005 to an efficacy interim analysis using the conservative approach of splitting the alpha allocated to primary outcome (2) between the interim and final analysis. Under the original sample size calculation in Stage 1 of the trial we planned to recruit 1,668 participants per group which gave us 72% power to identify a reduction from an incidence of 4% in severe COVID-19 at 6 months

in the control group to 2% in the intervention group. If the assumptions were correct, this would equate to 100 cases in total. We therefore planned a formal interim analysis of severe COVID-19 once there had been 100 cases of severe COVID-19. For full details, refer to section 11.4 of the trial protocol.

For full details refer to section 11.1 of the trial protocol. The analysis plan for the pre-planned meta-analysis is detailed in section 9.

CEASATION OF ENROLMENT AND SUBSEQUENT EFFICACY INTERIM ANALYSIS

Recruitment into the BRACE trial was stopped prematurely on 1st April 2021, after 3,988 participants had been recruited into Stage 2, 6,285 overall (including 2,840 recruited in Stage 1). **The main reason for stopping before reaching the calculated sample of 10,078 (2,834 planned for Stage 1 + 7,244 planned for Stage 2) was the rollout of COVID-19-specific vaccines in healthcare workers around the world, which started in December 2020. The availability of COVID-19-specific vaccines decreased the interest for potential participants to be recruited into the study, and the receipt of COVID-19 specific vaccines by participants affects the ability of the trial to determine the effectiveness of BCG vaccination in protecting against COVID-19.** With 3,988 participants randomised into Stage 2 of the trial, there would be 63.3% power to identify an absolute reduction of 1.30% (relative reduction of 1/3, the effect size used to power Stage 2 of the trial) in the incidence of severe COVID-19 at the end of the trial, from an incidence of 4% at 6 months in the control group to 2.67% in the intervention group (the assumptions used in the sample size calculation for Stage 2) based on a two-sided test with alpha = 0.045, if no interim analysis were planned.

At the time recruitment was stopped, we were monitoring the occurrence of severe COVID-19 cases in preparation for the interim analysis which was scheduled to occur once 100 severe cases was reached (refer to section 11.4 of the protocol). For reasons described in detail in the Interim analysis SAP (https://doi.org/10.25374/MCRI.14721309.v1), we decided to revise the stopping rule to be used in the interim analysis of severe COVID-19 to an alpha spending function, where the threshold to identify efficacy is based on the amount of data available at the time of the interim analysis.

The interim analysis included only exposure time before any dose of any COVID-19-specific vaccine. Given that it is unknown what effect a COVID-19-specific vaccine will have on the effectiveness of the BCG vaccination (or vice versa), participants were censored at the time of their first COVID-19-specific vaccine.

The database lock for the interim analysis happened on the 30th April 2021 (30 days after recruitment was ceased). Up to the this date, 82.3% of participants had received a COVID-19-specific vaccine, or had reported an episode of severe COVID-19, and/or had been followed for at least 6 months from randomisation. Using an alpha-spending function based on the Pocock stopping rule[1], an interim analysis conducted on 82.3% of the available information on 3988 participants, and an overall alpha of 0.045 for this outcome, results in a nominal alpha of 0.04 at the interim analysis, and 0.021 at the end of the study (calculated using a Group Sequential Test (GST) of Two Proportions in NQuery (PTT12-1)). Thus, the threshold of 0.04 was used as the stopping rule for the interim analysis. At the interim time point we had 52.9% power to detect a risk ratio of 0.67 in the incidence of severe COVID-19 at 6 months. Under this spending function we will have 0.021 alpha left for the final analysis given that the treatment comparison did not reach the threshold at the interim analysis.

The details of how the interim analysis was conducted and presented are provided in the Interim analysis SAP (https://doi.org/10.25374/MCRI.14721309.v1).

2.5. STUDY PROCEDURE

Figure 1 and Table 1 provide a summary of the study procedures for the BRACE trial.

Figure 1. Trial timeline

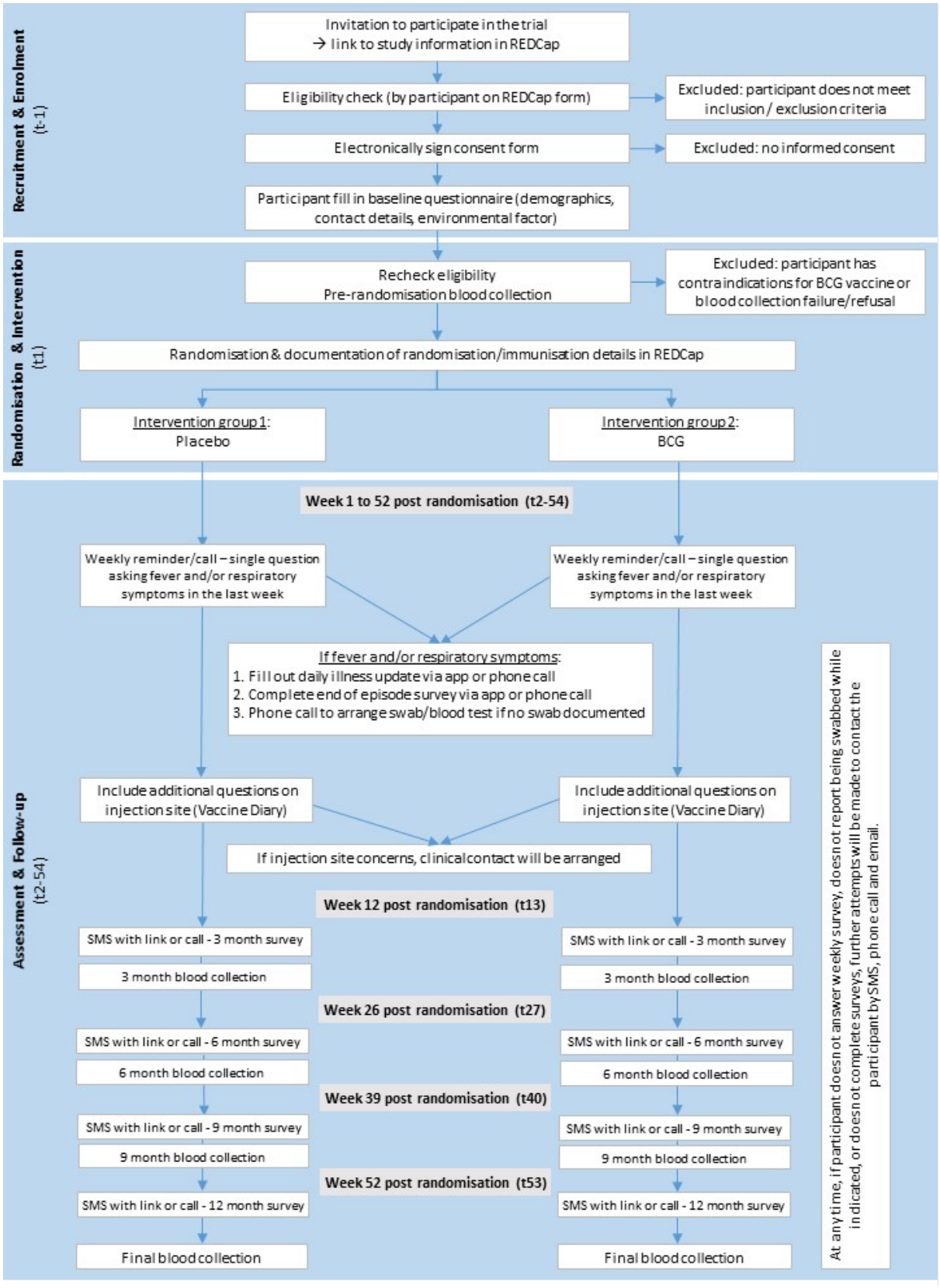


Table 1. Trial timeline

	TRIAL PERIOD									
	Pre-study	Inclusion & randomisation	Post-randomisation							
TIME POINT	t_{-1}	t_0	t_{1-12}	t_{13}	t_{14-25}	t_{26}	t_{27-38}	t_{39}	t_{40-51}	t_{52}
RECRUITMENT:										
Eligibility screen	X									
Informed consent	X									
Contact details	X									
Allocation to intervention		X								
INTERVENTIONS:										
BCG vaccine		X (BCG group)								
Saline injection		X (Placebo group)								
ASSESSMENTS:										
Baseline questionnaire	X	X								
Weekly survey			X	X	X	X	X	X	X	X
Instruction for swab testing *(if indicated by weekly survey)*			(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
3-month survey				X						
6-month survey						X				
9-month survey								X		
12-month survey										X
Clinical advice on injection site *			X	X						
*Blood collection***		X		X		X		X#		X#
*Baseline SARS-CoV-2 Test ****		X								

T=week (e.g. t1=first week). A 42day window period is accepted for the periodic survey and the blood collection timepoints

* In indicated Infectious Diseases clinician, or state-based organisation, as appropriate

** Optional consent for additional biological sample including blood sample when illness reported

*** Brazil only as outlined in Appendix 4

Sub-set of participants

3. POPULATIONS OF ANALYSIS

Intention-To-Treat Population

The intention-to-treat (ITT) population will be used for the secondary analysis of efficacy outcomes, with all participants analysed according to the study group to which they were randomly allocated, regardless of the intervention they received. The only participants excluded from this population will be participants who were randomised in error, i.e., assigned by mistake to one of the two allocations even though they were not eligible for the study.

Modified Intention-To-Treat Population (mITT)

The primary population for all efficacy analyses will be the modified intention-to-treat population (mITT) which will only include participants who had a negative SARS-CoV-2 test result at time of randomisation. The mITT population is the same as the ITT population but will also EXCLUDE:

- participants with positive or missing or indeterminant serology at the time of randomisation
- (Applicable only to participants at the Brazilian sites) participant with positive/missing/indeterminant PCR on a respiratory sample or a positive/missing/indeterminant SARS-CoV-2 diagnostic antigen test approved by the local jurisdiction's public health policy at the time of randomisation

Safety Population

The primary population for all safety analyses will be the safety population, which will include all randomised participants who received the vaccine (either BCG or placebo), with all participants analysed according to the intervention they received, irrespective of which group they were randomised to.

4. OUTCOME VARIABLES

4.1. DATA COLLECTION

Participants are asked weekly to report whether they have had any of the following:

1. **"Trigger symptoms"**, namely:
   - fever (self-reported, defined as temperature > 38 degrees centigrade)
   - intermittent cough
   - persistence cough
   - shortness of breath or difficulty breathing
   - sore throat

2. **"Other symptoms"**, namely:
   - runny/blocked nose
   - headache
   - muscle and/or joint ache
   - fatigue
   - nausea, vomiting and/or diarrhea
   - loss of taste and/or smell

These weekly reports are collected via a smartphone app (or in the case of Brazil via a weekly phone call) and are collected daily when they are ill (or in the case of Brazil via a phone call every 3 days) (see below). The information collected via the app/phone calls is subsequently confirmed through quarterly questionnaires, at 3, 6, 9 and 12 months post randomisation.

As soon as a participant reports:

- a **"trigger symptom"**

or

- being non-ambulant for ≥ 3 consecutive days or unable to work for ≥ 3 consecutive days irrespective of symptoms (any episode of illness characterised by ≥ 3 consecutive days or unable to work for ≥ 3 consecutive days is defined a **severe episode of illness**)

the participant is prompted to have a SARS-CoV-2 test and continues reporting their symptoms on a daily basis until resolution.

Once recovered from the illness, i.e., on the first day with no symptoms, the participant is required to complete an illness resolution form, documenting whether the SARS-CoV-2 test(s) was positive or negative. In circumstances where the participant does not recover from the illness this is entered by the study site coordinator or MCRI data team.

SARS-CoV-2 tests (date, type and results), as well as COVID-19-specific vaccination (date and brand), are also collected via the smartphone app, phone calls, and the quarterly questionnaires.

Quarterly questionnaires at 3, 6, 9 and 12 months from randomisation collect data on hospitalisations and absenteeism. When a participant is hospitalised due to a respiratory or febrile illness, the site coordinator or safety medical doctor complete a hospitalisation form collecting data on diagnosis, treatment and outcome of the hospitalisation. Information on the need for oxygen, mechanical ventilation, admission to critical care/ICU are also collected. Medical records are used by the local teams to complete the hospitalisation forms. Quarterly questionnaires also summarise all the episodes of illness that the participant has entered in the smartphone app

in the prior quarter and ask the participant to confirm those listed, edit them if needed, and retrospectively add episodes of illness that participant may have forgotten to enter into the smartphone app.

Blood samples are collected at baseline, 3-months, 6-months, 9-months and 12 months from randomisation, to assess SARS-CoV-2 serology.

4.2. PRIMARY OUTCOMES

1	**Symptomatic COVID-19 by 6 months** following randomisation defined as: - positive SARS-CoV-2 test (PCR, antigen or serology), PLUS - [fever (using self-reported questionnaire), OR - at least one 'trigger' symptom of respiratory disease including cough, sore throat, shortness of breath, respiratory distress/failure (using self-reported questionnaire)]
2	**Severe COVID-19 by 6 months** following randomisation defined as: - positive SARS-CoV-2 test (PCR, antigen or serology), PLUS - [Death as a consequence of COVID-19, OR - Hospitalised as a consequence of COVID-19, OR - Non-hospitalised severe disease as a consequence of COVID-19, defined as non-ambulant[1] for ≥ 3 consecutive days or unable to work[2] for ≥ 3 consecutive days] [1] *"pretty much confined to bed (meaning finding it very difficult to do any normal daily activities"* [2] *"I do not feel physically well enough to go to work"*

The date of occurrence for either a symptomatic COVID-19 episode (primary outcome 1) or a severe COVID-19 episode (primary outcome 2) will be defined as the first date of any symptom onset for the episode ('trigger' or 'other' symptom, as listed in section 4.1). This is to account for any potential difference between groups in time to SARS-CoV-2 testing from symptom onset.

Excluded episodes

An episode of illness with trigger symptom(s) for which a SARS-CoV-2 testing was not medically indicated (e.g. sore throat due to a known allergy), will not be considered as an episode of illness in the interest of the calculation of primary outcome 1. A severe episode of illness for which a SARS-CoV-2 testing was not medically indicated (e.g. unable to work for ≥ 3 consecutive days due to sprained ankle), will not be considered as an episode of illness in the interest of the calculation of primary outcome 2.

DEFINITION OF SARS-COV-2 TEST

SARS-CoV-2 tests comprise:

- **A PCR test,** and/or
- **A rapid antigen test (RAT),** and/or
- **Seroconversion** determined using the serology results prior to and after the onset of symptoms for an episode of illness (see Figure 3).

DEFINITION OF COVID-19 EPISODES

An episode of illness (either with trigger symptoms or severe episode) will be considered to have an associated COVID-19 test if the episode has a RAT or PCR test or serology data as follows:

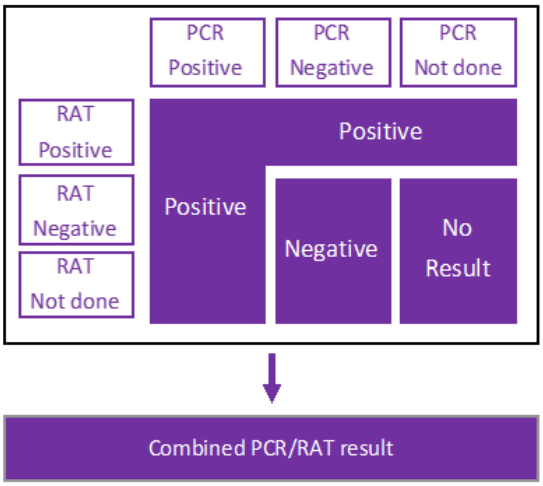
PCR/RAT tests – The results of PCR and/or RAT tests will be used for the determination of the COVID-19 episode (either symptomatic or severe) as detailed in Figure 2 using the following **testing windows**:

PCR: ≤ 3 days prior to onset of symptoms to ≤ 21 days after the onset of symptoms, *or*
≤ 7 days from the last day of symptoms

RAT: ≤ 3 days prior to onset of symptoms to ≤ 10 days after the onset of symptoms

Figure 2 details how results of the RAT/PCT tests will be interpreted.

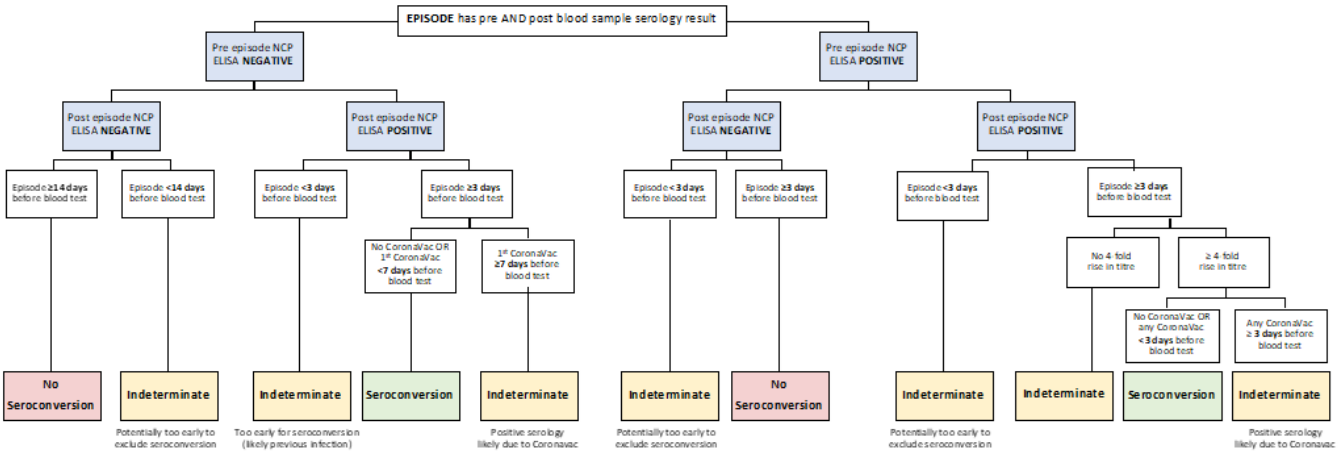
Figure 2. RAT/PCR testing interpretation



PCR/RAT taken within their testing window

Serology - The results of a serology will also be used for the determination of the COVID-19 episode if both pre-episode and post-episode blood samples results are available. The algorithm in Figure 3 details how serology results will be interpreted.

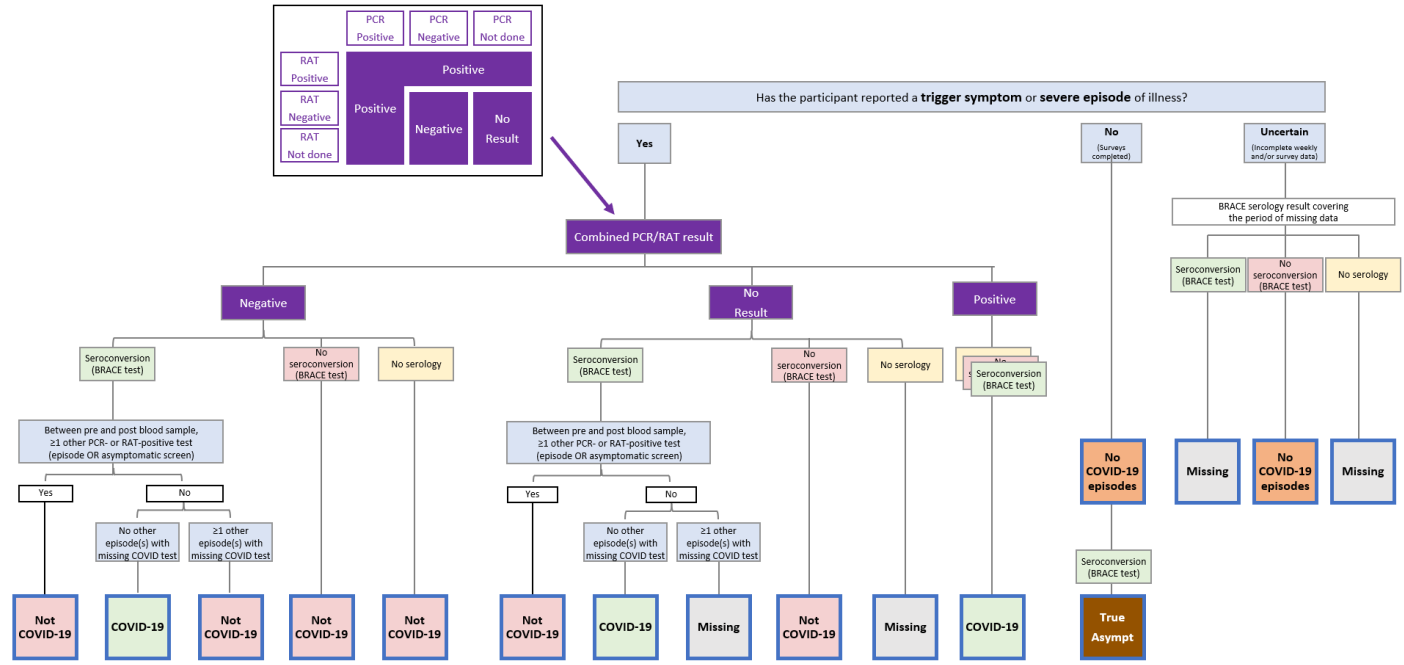
Figure 3. SARS-CoV-2 Serology Interpretation



Source: SARS-CoV-2 serology interpretation, version 20-Apr-2022
NCP=nucleocapsid protein

The combination of the results from RAT/PCR tests and/or serology will be interpreted using the algorithm in Figure 4 to categorise episode with trigger symptoms/severe episodes to: COVID-19 episodes (either symptomatic or severe), non-COVID-19 episodes, or episodes with missing information.

Figure 4. COVID-19 episode interpretation



Source: SARS-CoV-2 serology interpretation, version 20-Apr-2022
Asympt COVID-19 = Asymptomatic SARS-CoV-2 infection, as per definition provided in section 4.3, outcome 7a and 7b.

Additionally, each episode of illness (either with trigger symptoms or severe episode) will be categorised as COVID-19 episodes (either symptomatic or severe), non-COVID-19 episodes, or episodes with missing information ignoring serology, i.e. only using data from RAT and PCR tests (Figure 2). This will be used as part of a sensitivity analysis (see session "Sensitivity Analysis 2").

4.3. SECONDARY OUTCOMES

#	COVID-19 Related Outcomes
3	**Symptomatic COVID-19** by **12 months** following randomisation as defined for primary outcome 1. CALCULATION As per primary outcome 1 but over 12 months.
4	**Severe COVID-19** by **12 months** following randomisation as defined for primary outcome 2. CALCULATION As per primary outcome 1 but over 12 months.
5a	**Time to first symptom of COVID-19** over the **6 months** following randomisation. CALCULATION Participants who had either a symptomatic or severe COVID-19 episode will have time to first symptom of COVID-19 calculated as: *date of any symptom onset for the first symptomatic or severe COVID-19 episode – date of randomisation* Participants who have not had a symptomatic or severe COVID-19 episode will have time calculated as: *Earliest censoring date*– date of randomisation*

#	COVID-19 Related Outcomes
	For participants who experience more than one COVID-19 episode, the time to the first of these episodes will be used for the analysis. **as defined in section 6.2.3*
5b	**Time to first symptom of COVID-19** over the **12 months** following randomisation. **CALCULATION** As per 5a but over 12 months.
6a	**Number of episodes of COVID-19** by **6 months**. **CALCULATION** The total number of symptomatic or severe COVID-19 episodes (refer to section 4.2 for their definition) by 6 months will be calculated for each participant. Participants who have had neither a symptomatic nor a severe COVID-19 episode by 6 months will be considered to have had 0 (zero) episodes of COVID-19. Two COVID-19 episodes of illness are considered distinct if they are >10 days apart.
6b	**Number of episodes of COVID-19** by **12 months**. **CALCULATION** As 6a but over 12 months.
7a	**Asymptomatic SARS-CoV-2 infection** by **6 months** Asymptomatic SARS-CoV-2 infection will be defined as - Evidence of SARS-CoV-2 infection (by seroconversion) and - Absence of any episodes of illness (defined by trigger or non-trigger symptoms) (using self-reported questionnaire) and - No evidence of exposure prior to randomisation **CALCULATION** Participants will be considered to have met this outcome if by 6 months: - they seroconverted to SARS-CoV-2, **AND** - they have complete diary data or survey data up to the earlier of 6 months or the date of the blood draw at which they became seropositive which confirm they did not have any episodes of illness Participants will be considered to NOT have met this outcome if they: - have complete diary data or survey data up to 6 months **AND** do not show evidence of seroconversion to SARS-CoV-2 at 6 months (i.e., serology result at 3 months is not positive and at 6 months is negative) **OR** - have complete diary data or survey data up to 6 months **AND** - show evidence of seroconversion to SARS-CoV-2 at 6 months (i.e., serology result at 3 or 6 months is positive) **AND** - reported any episode of illness that could have accounted for the seroconversion (experienced either an episode which tested positive to PCR/RAT tests or an episode that was not tested for COVID-19)
7b	**Asymptomatic SARS-CoV-2 infection** over **12 months.** **CALCULATION** As per 7a but over 12 months.
8a	**Number of days unable to work** due to COVID-19 within **6 months** following randomisation (excludes quarantine/workplace restrictions)

#	COVID-19 Related Outcomes
	CALCULATION This is a count of the days marked "unable to work" across all COVID-19 episodes (either symptomatic or severe, as defined in section 4.2) by 6 months post randomisation. Participants who have not had a symptomatic or severe COVID-19 episode during this period will be regarded as having had 0 (zero) days unable to work due to COVID-19.
8b	**Number of days unable to work** due to COVID-19 within **12 months** following randomisation (excludes quarantine/workplace restrictions) CALCULATION As for outcome 8a but over 12 months.
9a	**Number of days confined to bed** due to COVID-19 within **6 months** following randomisation. CALCULATION This is a count of the days marked "confined to bed" across all COVID-19 episodes (either symptomatic or severe, as defined in section 4.2) by 6 months post randomisation. Participants who have not had a symptomatic or severe COVID-19 episode during this period will be regarded as having had 0 (zero) days confined to bed due to COVID-19.
9b	**Number of days confined to bed due to COVID-19** within **12 months** following randomisation. CALCULATION As for outcome 9a but over 12 months.
10a	**Number of days with symptoms due to COVID-19** within **6 months** following randomisation. CALCULATION The number of days with symptoms for a given COVID-19 episode is the number of days from the start to the end of the COVID-19 episode (either symptomatic or severe, as defined in section 4.2) using this formula: *Episode duration = Episode end date* – episode start date* ** defined as first day with no symptoms* For participants who die as a consequence of COVID-19, the end date will be the date of death. For participants who had multiple COVID-19 episodes within 6 months, the number of days with symptoms due to COVID-19 will be the sum of durations across all the COVID-19 episodes within the 6 months following randomisation. Participants who have not had a symptomatic or severe COVID-19 episode within 6 months of randomisation will be regarded as having had 0 (zero) days with symptoms due to COVID-19.
10b	**Number of days with symptoms due to COVID-19** within **12 months** following randomisation. CALCULATION As for outcome 10a but over 12 months.
11a	**Pneumonia due to COVID-19** by **6 months.** CALCULATION The derivation of this outcome will use data from the self-reported questionnaire and/or hospitalisation forms. Participants will be coded as having had the outcome if: - They developed pneumonia during a symptomatic or a severe COVID-19 episode within 6 months of randomisation Participants will be coded as not having had this outcome if: - They did not develop pneumonia during a symptomatic or a severe COVID-19 episode **or**

#	COVID-19 Related Outcomes
	- They did not have a symptomatic or a severe COVID-19 episode within 6 months of randomisation.
11b	**Pneumonia due to COVID-19** by **12 months.** **CALCULATION** As for outcome 11a but over 12 months.
12a	**Need for oxygen therapy due to COVID-19** by **6 months**. **CALCULATION** The derivation of this outcome will use data from the self-reported questionnaire and/or hospitalisation forms. Participants will be coded having had the outcome if: - They needed oxygen therapy during a severe COVID-19 episode within 6 months of randomisation Participants will be coded not having had the outcome if: - They did not need oxygen therapy during a severe COVID-19 episode **or** - They did not have a severe COVID-19 episode within 6 months of randomisation
12b	**Need for oxygen therapy due to COVID-19** by **12 months**. **CALCULATION** As for outcome 12a but over a 12 month period.
13a	**Admission to critical care** and **duration of stay due to COVID-19** by **6 months**. **CALCULATION** The derivation of both outcomes will use data from the self-reported questionnaire and/or hospitalisation forms. **– Admission to critical care (including ICU)** Participants will be coded as having had at least one admission to critical care/ICU due to COVID-19 if: - They were admitted to critical care/ICU during a severe COVID-19 episode within 6 months of randomisation Participants will be coded as not having had this outcome if: - They were NOT hospitalised during a severe COVID-19 episode **or** - They were NOT admitted to critical care/ICU during a hospitalisation for a severe COVID-19 episode **or** - They did not have a severe COVID-19 episode within 6 months of randomisation **– Duration of stay** For participants who were admitted to critical care/ICU during a severe COVID-19 episode within 6 months of randomisation, we will also calculate the duration of stay as the difference between the date of admission and date of discharge. For participants who had multiple COVID-19 episodes with admission to critical care within 6 months of randomisation, this number will be the sum of durations across all critical care stays.
13b	**Admission to critical care** and **duration of stay due to COVID-19** by **12 months**. **CALCULATION** As for outcome 13a but over 12 months.
14a	**Need of mechanical ventilation** (MV) and **duration of MV due to COVID-19** by **6 months**. **CALCULATION** The derivation of both outcomes will use data from the self-reported questionnaire and/or hospitalisation forms. **– Need of MV**

#	COVID-19 Related Outcomes
	Participants will be coded as having been in need of MV due to SARS-CoV-2 if: - They needed MV during a severe COVID-19 episode within 6 months of randomisation Participants will be coded as not having had this outcome if: - They were NOT hospitalised during a severe COVID-19 episode **or** - They did NOT need MV during a hospitalisation for a severe COVID-19 episode **or** - They did not have a severe COVID-19 episode within 6 months of randomisation **– Duration of MV** For participants who needed mechanical ventilation within 6 months of randomisation, we will also calculate the duration of MV as the difference between the date/time MV was started and the date/time MV was stopped. For participants who had multiple COVID-19 episodes requiring MV within 6 months of randomisation V, this number will be the sum of durations across all COVID-19 episodes requiring MV.
14b	**Need of mechanical ventilation** and **duration of MV** due to COVID-19 by 12 **months**. **CALCULATION** As for outcome 14a but over 12 months.
15a	**Hospitalisation due to COVID-19** (using self-reported questionnaire and/or medical/hospital records) and **duration of hospitalisation** by **6 months.** **CALCULATION** **– Hospitalisation due to COVID-19** Participants will be coded as having been hospitalised due to COVID-19 if: - They had severe COVID-19 (primary outcome 2) and were hospitalised as a consequence of COVID-19 within 6 months of randomisation Participants will be coded as not having had the outcome if: - They had severe COVID-19 (primary outcome 2) and were NOT hospitalised as a consequence of COVID-19 - They did not have severe COVID-19 (did not meet the definition of either the primary outcome 2) within 6 months of randomisation **– Duration of hospitalisation** For participants who were hospitalised due to COVID-19 within 6 months of randomisation, the duration of their hospital stay due to COVID-19 will be calculated as the difference between date of admission and date of discharge. For participants who had multiple severe COVID-19 episodes resulting in hospitalisation within 6 months of randomisation, this number will be the sum of durations across all hospitalisations due to COVID-19.
15b	**Hospitalisation due to COVID-19** (using self-reported questionnaire and/or medical/hospital records) and **duration of hospitalisation** by **12 months.** **CALCULATION** As for outcome 15a but over 12 months.
16a	**Death due to COVID-19** by **6 months**. **CALCULATION** Participants will be coded as having had the outcome if: - They had severe COVID-19 (primary outcome 2) and died as a consequence of COVID-19 within 6 months of randomisation Participants will be coded as not having had the outcome if: - They had severe COVID-19 (primary outcome 2) and did NOT die **or** - They did not have severe COVID-19 **or** - They died for other reasons (not as a consequence of COVID-19) within 6 months of randomisation

#	COVID-19 Related Outcomes
16b	**Death due to COVID-19** by **12 months**. CALCULATION As for outcome 16a but over 12 months.

#	Other Outcomes – NON-COVID-19 Related Outcomes
17	**Fever or respiratory illness***(using self-reported questionnaire), over the 12 months following randomisation. * Respiratory illness will be defined as: at least one sign or symptom of respiratory disease including cough, sore throat, shortness of breath, respiratory distress/failure, or runny/blocked nose (in combination with another respiratory symptom or fever). Fever due to reactions to any vaccine will not be considered for this outcome. CALCULATION Participants will be coded as having had the outcome if: - They developed an episode of illness with fever (self-reported, defined as temperature > 38 degrees) or respiratory illness (including due to COVID-19) within 12 months of randomisation Participants will be coded as not having had the outcome if: - They did not have any episodes of fever or respiratory illness within 12 months of randomisation
18	**Severe fever or respiratory illness***(using self-reported questionnaire), over the 12 months following randomisation, defined as: - Death, OR - Hospitalised, OR - Non-hospitalised severe disease, defined as non-ambulant1 for ≥ 3 consecutive days or unable to work 2 for ≥ 3 consecutive days as a consequence of fever or respiratory illness, as defined above (outcome 17) [1] "pretty much confined to bed (meaning finding it very difficult to do any normal daily activities" [2] "I do not feel physically well enough to go to work" (excludes stay at home exclusively for quarantine/workplace restrictions) Fever due to reactions to any vaccine will not be considered for this outcome. CALCULATION Participants will be coded as having had the outcome if: - They developed a severe episode of illness with fever (self-reported, defined as temperature > 38 degrees) or respiratory illness (including due to COVID-19) within 12 months of randomisation Participants will be coded as not having had the outcome if: - They did not have any severe episodes of fever or respiratory illness within 12 months of randomisation
19	**Number of episodes** of fever or respiratory illness (as defined in outcome 17), over the 12 months following randomisation. CALCULATION

#	Other Outcomes – NON-COVID-19 Related Outcomes
	This will reflect the number of distinct episodes of fever or respiratory illness within 12 months of randomisation. Participants who have not experienced any episodes of fever or respiratory illness within 12 months of randomisation will be considered to have had 0 (zero) episodes.
20	Number of days **unable to work** (using self-reported questionnaire) due to fever or respiratory illness (as defined in outcome 17), over the 12 months following randomisation (excludes quarantine/workplace restrictions) CALCULATION This will be calculated as the sum of the days marked as unable to work due to fever or respiratory illness within 12 months of randomisation. Participants who have not experienced any episodes of fever or respiratory illness within 12 months of randomisation will be considered to have had 0 (zero) episodes.
21	Number of days **confined to bed** (using self-reported questionnaire) due to fever or respiratory illness, illness (as defined in outcome 17), over the 12 months following randomisation CALCULATION This will be calculated as the sum of the days marked as confined to bed to fever or respiratory illness within 12 months of randomisation. Participants who have not experienced any episodes of fever or respiratory illness will be considered to have had 0 (zero) episodes within 12 months of randomisation.
22	Number of days **with symptoms** due to fever or respiratory illness (as defined in outcome 17), over the 12 months following randomisation CALCULATION For each episode of fever or respiratory illness the number of days from the start to the end dates of the episode of fever or respiratory illness will be calculated using this formula: *Episode duration = Episode end date* – episode start date* ** defined as first day with no symptoms* For participants who are hospitalised due to fever or respiratory illness, the end date will be the date of discharge from the hospital. For participants who die as a consequence of fever or respiratory illness, the end date will be the date of death. For participants who had multiple episodes of fever or respiratory illness within 12 months of randomisation, this number will be the sum of durations across all the episodes. Participants who have not had an episode fever or respiratory illness within 12 months of randomisation will be regarded as having had 0 (zero) days with symptoms due to fever or respiratory illness.
23	**Pneumonia** within a febrile or respiratory illness over the 12 months following randomisation CALCULATION Data from the self-reported questionnaire and/or hospitalisation forms will be used to derive this outcome. Participants will be coded as having had the outcome if: - They developed pneumonia during an episode of fever or respiratory illness within 12 months of randomisation Participants will be coded as not having had the outcome if: - They did not developed pneumonia during a episode of fever or respiratory illness **or** - They did not have any episodes of fever or respiratory illness - within 12 months of randomisation
24	**Need for oxygen** therapy for a febrile or respiratory illness over the 12 months following randomisation CALCULATION The derivation of this outcome will use data from the self-reported questionnaire and/or hospitalisation forms. Participants will be coded having had the outcome if:

#	Other Outcomes – NON-COVID-19 Related Outcomes
	- They needed oxygen therapy during an episode of fever or respiratory illness within 12 months of randomisation Participants will be coded not having had the outcome if: - They did not need oxygen therapy during an episode of fever or respiratory illness - They did not have an episode of fever or respiratory illness within 12 months of randomisation
25	**Admission to critical care** for a febrile or respiratory illness (using self-reported questionnaire and/or medical/hospital records), over the 12 months following randomisation Admission to critical care following elective intervention will not be counted as part of this outcome. CALCULATION The derivation of this outcome will use data from the self-reported questionnaire and/or hospitalisation forms. Participants will be coded as having had the outcome if: - They were admitted to critical care following a febrile or respiratory illness within 12 months of randomisation Participants will be coded as not having had the outcome if: - They were NOT hospitalised during any episode of fever or respiratory illness - They were NOT admitted to critical care during any hospitalised episode of fever or respiratory illness - They did not have an episode of fever or respiratory illness within 12 months of randomisation
26	**Need for mechanical ventilation (MV)** for a febrile or respiratory illness (using self-reported questionnaire and/or medical/hospital records), over the 12 months following randomisation MV required as part of an elective intervention will not be counted as part of this outcome. CALCULATION The derivation of this outcome will use data from the self-reported questionnaire and/or hospitalisation forms. Participants will be coded as having had the outcome if: - They needed MV during an episode of fever or respiratory illness within 12 months of randomisation Participants will be coded as not having had the outcome if: - They were NOT hospitalised during any episode of fever or respiratory illness - They did NOT need MV during a hospitalisation for an episode of fever or respiratory illness - They did not have an episode of fever or respiratory illness - within 12 months of randomisation
27	**Deaths** as a consequence of an episode of fever or respiratory illness over the 12 months following randomisation CALCULATION Participants will be coded as having had the outcome if: - They died as a consequence of an episode of fever or respiratory illness within 12 months of randomisation Participants will be coded as not having had the outcome if: - They had an episode of fever or respiratory illness and did NOT die - They did not have an episode of fever or respiratory illness - They died for other reasons (not as a consequence of an episode of fever or respiratory illness) - within 12 months of randomisation
28	**Hospitalisation** for a febrile or respiratory illness and **duration** of **hospitalisation** over the 12 months following randomisation. CALCULATION

#	Other Outcomes – NON-COVID-19 Related Outcomes
	The derivation of this outcome will use data from the self-reported questionnaire and/or hospitalisation forms. On participants who were hospitalised due to an episode of fever or respiratory illness, the duration of their hospital stay will be calculated as the difference between date of admission and date of discharge. If a participant experienced >1 episodes of fever or respiratory illness which resulted in hospitalisation within 12 months of randomisation, all the episodes will be included in this analysis, and the overall duration of hospitalisation will be the sum of the duration of each hospitalisation. Participants were hospitalised as a consequence of an episode of fever or respiratory illness within 12 months of randomisation will have their duration of hospitalisation equal to zero
29a	Number of days of **unplanned absenteeism** for an acute illness or hospitalisation over the 6 months following randomisation. CALCULATION The number of days the participant reported unplanned absenteeism (using self-reported questionnaire) for an acute illness or hospitalisation within **6 months** of randomisation will be calculated. This will exclude absenteeism for other reason such as elective hospitalisation, issues with vaccination site, mandatory quarantine while not ill, carer leave, annual leave/holidays/planned absence, or pregnancy-related absence. The number of days of unplanned absenteeism for an acute illness or hospitalisation within 6 months of randomisation will be set to missing for participants who don't complete the 6-month self-reported questionnaire.
29b	Number of days of unplanned absenteeism for any reason (using self-reported questionnaire) over the 12 months following randomisation. CALCULATION As 28a.
30	**Adverse events** (AEs) experienced by the participant over the **3 months** following randomisation, by type, severity (graded using toxicity grading scale), relationship to intervention of adverse events (AEs) of interest*. * AEs of interest are defined as: - Reaction at injection site (pain, tenderness, redness, swelling) of grade 3 (severe) or 4 (potentially life threatening) - Abscess at injection site - Large ulcer (>1.5 cm diameter) at injection site - Keloid scar at injection site - Lymphadenopathy (in region of injection site) - BCG osteitis/osteomyelitis - Disseminated BCG infection (BCG-osis) - Allergic reaction due to IP - Fainting episode, seizures and convulsions following IP administration (recorded on the day of IP administration only)
31	**Serious Adverse Events** (SAEs) experienced by the participant over the **3 months** following randomisation.

4.4. OTHER VARIABLES

DEMOGRAPHY AND BASELINE

Baseline characteristics that will be presented include:

- Sex – Male/Female/Other/Declined/ Missing
- Age*, years
- Body Mass Index (BMI), kg/m^2 – < 18.5 / 18.5 to 24.9/ 25 to 29.9 / >30 / Missing

- Department – Emergency / Intensive Care Unit or High Dependency Unit / Operating Theatre / General Ward / Pharmacy / Practice outside of hospital setting/ Other / Missing
- Role – Administrative-clerical staff / Allied Health / Dentist-dental therapy / Doctor / Nurse-Midwife / Patient Services Assistant-hospital maintenance / Scientist (medical research) / Other / Missing
- Contact with patients, hours - <10 / 10-20 / >20 / Missing
- Confirmed cases of COVID-19 within department – Yes / No / Missing
- Smoking – Yes / No / Missing
- Previous BCG vaccination -No / last BCG dose <1 year ago / 1-5 years ago / >5 years ago / Missing
- Evidence of BCG scar at randomisation – Yes / No / Unsure / Missing
- Positive (>5mm) Tuberculin Skin Test or positive Mantoux test in the past? Yes / No / Unsure
- Previous tuberculosis (TB) exposure – Yes / No / Missing
- Positive PCR or SARS-CoV-2 diagnostic antigen test or serology at randomisation– Yes / No / Missing
- Comorbidities
    - Diabetes – Yes / No / Missing
        - Type 1 diabetes
        - Type 2 diabetes
        - Type 1 and type 2 diabetes
        - Other diabetes
        - Missing
    - Cardiovascular disease– Yes / No / Missing
        - Ischaemic heart disease
        - Congestive heart disease
        - Other cardiovascular disease
        - Hypertension– Yes / No / Missing
        - Missing
    - Chronic respiratory disease– Yes / No / Missing
    - Number of co-morbidities
        - 1
        - 2
        - 3 or more
        - Missing

* Since year of birth rather than DOB is collected for EU participants, age will be calculated using "1-July" in their year of birth as their DOB.

COVID-19-SPECIFIC VACCINES

- Time between randomisation and first COVID-19-specific vaccine dose
- Brand of the first dose of COVID-19-specific vaccine received
    - First and second doses of the same brand
- Number of doses received

OTHER VACCINES

- Time between randomisation and first other vaccine dose
- Type of the first dose of vaccine received
- Number of doses received
- Number of types of vaccine received

PARTICIPANT FOLLOW-UP

- Withdrawal after randomisation
- Reasons for withdrawal.

PROTOCOL DEVIATIONS

- Whether there was a protocol deviation
- Reasons for protocol deviation - Received the opposite intervention/ Did not receive any intervention / Participant randomised twice/ Did not receive the questionnaire in time/ Not able to use the app/ Did not have a swab while indicated / Did not have the blood sample taken / Blood/vaccination not performed on day of randomisation, but later/ Randomised in the wrong strata / Blood sample (3m) taken and re-consent form incomplete / Blood sample taken without correct consent / Blood taken outside window / Blood collection: did not collect the right tube/ Improper preparation of BCG/ Participant received triple the dose of BCG / Problem during blood processing / Delay in delivery of bloods / BCG within 12 months of randomisation / Pregnancy at randomisation / Other
- Whether there was a protocol violation
- Reasons for protocol violations - Participant received twice the dose of BCG / Intravenous injection of BCG / Other

5. STATISTICAL METHODOLOGY

5.1. GENERAL PRINCIPLES

The details of the randomisation groups will be unblinded only once the database has been locked and the SAP has been finalised, approved by the TSC and made publicly available.

Multiple outcomes will be considered in evaluating the effectiveness of the trial intervention. The magnitude of the treatment effect, with 95% confidence interval and p-value, will be estimated for each outcome. Findings will be interpreted based on the magnitude of the treatment effect and in context of one another rather than in isolation considering the patterns and consistency in the findings across outcomes.

The comparison of BCG vs placebo in Stage 2 participants is the primary analysis of interest. It is planned to combine data from the two stages of the trial (Stage 1 + Stage 2) in a meta-analysis for the secondary analysis of the non-COVID19 outcomes only (see Section 9 for details).

5.2. DEFINITION OF BASELINE

Baseline is defined as time of enrolment, captured by date of randomisation (day 0).

5.3. DEFINITION OF THE 6- and 12-MONTH CUT-OFFS

The 6-month period from randomisation will be defined as the date of randomisation date plus 182 days following randomisation.
The 12-month period from randomisation will be defined as the date of randomisation date plus 365 days following randomisation

5.4. DESCRIPTIVE STATISTICS

5.4.1. PARTICIPANT DISPOSITION

All participants who were invited to participate in the BRACE trial will be accounted for as part of the CONSORT flow diagram. The number of participants that were screened but not randomised will be presented and the reasons for their non-participation will be listed. The number of participants who fulfilled eligibility criteria and were recruited will be presented overall and by study centre. The number and proportion of participants who discontinue the study prematurely and/or withdraw during the study will be presented, and the reasons for early withdrawal will be presented by intervention group (BCG or Placebo).
The number of participants with at least one protocol deviation, the number of protocol deviations per participant and the reasons for protocol deviation will be summarised by intervention group (BCG or Placebo).

5.4.2. PARTICIPANT CHARACTERISTICS

The demographic characteristics at randomisation of the participants in the mITT as well in the ITT and safety populations will be presented for each intervention group (BCG or Placebo) using the mean and standard deviation (SD) or median and interquartile range (IQR) for continuous data and using numbers and proportions for categorical data.

5.5. THE ESTIMAND FRAMEWORK

The estimand is the precise description of the intervention effect of interest for a given objective. The estimand is described by the following attributes:

- Population
- Outcome
- Interventions
- Handling of intercurrent events
- Summary measure

An intercurrent event is one that occurs after randomisation and prior to observation of the trial endpoint (primary or secondary). There are two important intercurrent events within this trial:

- the administration of COVID-19-specific vaccine
- the administration of any vaccine (including influenza vaccine and COVID-19-specific vaccine)

Within the analysis of this trial, we will adopt three strategies to handle the intercurrent events:

- Hypothetical Strategy: the aim of this strategy is to estimate the intervention effect of being offered the intervention in the absence of intercurrent events. This strategy involves considering what would have happened if the participant had not had the intercurrent event.
- Treatment Policy Strategy: the aim of this strategy is to assess the effect of being offered the intervention irrespective of any intercurrent events. In this strategy intercurrent events are ignored and all outcome data are used regardless of occurrence of the intercurrent event.
- Principal stratum strategy: this strategy considers measurements in a subgroup of participants where the intercurrent event(s) is not likely or less likely to occur. This strategy classifies participants according to their potential occurrence of an intercurrent event in both study groups.

The estimands of interest in this trial are outlined in section 6.

5.6. ANALYSIS SOFTWARE

All analyses will be performed using Stata Release 16.1 or later.

6. PRIMARY OUTCOMES

6.1. ESTIMANDS

Objective	Estimand
To determine if BCG vaccination compared with placebo reduces the incidence of symptomatic COVID-19 in the absence of a COVID-19 specific vaccine, over the 6 months following randomisation, in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 1.1 [Primary analysis]** Population: mITT population Outcome: **symptomatic COVID-19 by 6 months** Interventions: BCG vs Placebo Handling of Intercurrent events: - COVID-19 specific vaccine (Hypothetical Strategy) - any other vaccine (Treatment Policy strategy) Summary Measure: Adjusted* difference in proportion of participants
To determine if BCG vaccination compared with placebo reduces the incidence of severe COVID-19 in the absence of a COVID-19 specific vaccine, over the 6 months following randomisation, in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 2.1 [Primary analysis]** Population: mITT population Outcome: **severe COVID-19 by 6 months** Interventions: BCG vs Placebo Handling of Intercurrent events: - COVID-19 specific vaccine (Hypothetical Strategy) - any other vaccine (Treatment Policy strategy) Summary Measure: Adjusted* difference in proportion of participants
** 1) adjusted for stratification factors used at randomisation (age group, presence of comorbidity, and geographical location); 2) adjusted for stratification factors used at randomisation + sex, BMI at baseline, BCG vaccine before randomisation;*	

Analytical approach for the primary estimands

For the primary analysis of each of the primary outcomes, receiving a COVID-19 vaccine will be handled using a hypothetical strategy; participants who receive a COVID-19-specific vaccine will have their data used up to the date of their first dose of COVID-19-specific vaccine (data collected after the COVID-19-specific vaccine will be ignored). These primary analyses will be conducted on the mITT population including only Stage 2 participants.

6.2. PRIMARY ANALYSIS

6.2.1.SUMMARY STATISTICS

The outcomes of symptomatic COVID-19 and severe COVID-19 prior to 6 months will be described by intervention group as the absolute number of participants with the event. The primary outcome of severe COVID-19 by 6 months will also be presented as the number of participants within 5 categories, according to the most severe event they encountered over the 6-month period, by intervention group:

- Severe COVID-19 which resulted in death
- Severe COVID-19 which resulted in hospitalisation
- Non-hospitalised severe COVID-19
  This category will be further broken down as:
  - Non-hospitalised severe COVID-19 who were confined to bed for 3 consecutive days or more
  - Non-hospitalised severe COVID-19 who were too sick to go to work for 3 consecutive days or more

The numbers of participants whose follow-up data is censored due to:

- missing PCR, RAT or serology test result,
- incomplete data entry,
- drop-out from the study, and
- intercurrent event (COVID-19 specific vaccine / Any other vaccine)

will also be reported separately by intervention group.

6.2.2.ANALYSIS

The outcomes of symptomatic COVID-19 and severe COVID-19 prior to 6 months will be compared between the BCG group and the placebo group recruited in Stage 2 using a difference in proportions. This will be estimated using a time-to-event analysis. The first analysis will be adjusted for stratification factors used in randomisation, namely age group (<40 years; 40 to 59 years; >=60 years), presence of comorbidity (any of diabetes, chronic respiratory disease, cardiovascular disease, hypertension), and geographical location (Europe/Australia/South America). Although randomisation was stratification was by participating hospitals and clinics, for the analysis it was decided to group the sites into the 3 regions due to the high number of randomising sites which could lead to computational problems. For participants who were randomised in the incorrect stratum, the correct stratum will be used as covariate in the model. To do this analysis, the survival curve for each combination of strata and randomised group will be calculated using a flexible parametric survival model (Royston-Parmar model[2]). This will be done using the *stpm2* command in Stata, with the *meansurv* and *timevar* options specified. The average survival curve for each randomised group will be estimated as a weighted average of the corresponding stratum-specific survival curves, with weights proportional to the number of individuals in each stratum in the randomised group at baseline. The parameter of interest will be the (adjusted) point estimate for the difference in proportion with the event at 6 months between BCG and control group. A two-sided bias-corrected 95% CI for the difference in proportion (BCG – Control) will be calculated with bootstrap standard errors using the Stata bootstrap command. A bootstrap p-value will also be calculated. The bootstrapping will sample 1000 times (with replacement) and be stratified by the stratification factors. Note because modelling will be used to estimate the difference in proportion, the results from this analysis will not correspond directly to the raw summaries that will be presented.

A Kaplan-Meier survival curve will also be presented by treatment arm.

The proportional hazards assumption will be checked when running these analyses.

The analysis of both primary outcomes (for all estimands 1.1-6 and 2.1-6) will then be repeated including adjustment for the following baseline covariates which are expected to be associated with COVID-19:

1. Sex (Female / Male)
2. BMI at baseline (< 30 / ≥ 30 kg/m2)
3. BCG vaccination before enrolling into the trial (Yes / No)

Should the fully adjusted models not run when all the all the covariates listed above are included in the model, the covariates will be removed starting from the bottom of the list to the top, until the adjusted model runs.

Handling of missing data

Protocol version 12 stated that, for the primary analysis, multiple imputation (MI) would be used to handle missing data if >10% of the primary outcome data were missing. During the trial it became apparent that a number of participants would have partial data on the primary outcomes due to the expansion of COVID-19 vaccination programs. Therefore, survival analysis will be used to estimate the proportion with symptomatic COVID-19 or severe COVID-19, which enables this partial follow-up data to be included in the analysis. Strategies to handle missingness due to non-testing within trigger and severe episodes is also described in section 6.2.3. Given the survival analysis strategy enables all participants with at least some follow-up data to be included in the analysis, the analysis will be conducted using the available data with no MI.

6.2.3. DATES AND CENSORING FOR 6-MONTH FOLLOW-UP

Censoring dates used for the analysis of the primary outcomes are described in table 2 below.

Table 2. Dates and censoring algorithm

MAIN ANALYSIS	SENSITIVITY ANALYSIS*
Censored at the earlier of: **[A]** their first COVID-19 specific vaccine dose or **[B]** day 182 of their participation in the trial or **[C]** their last entered date prior to which there are more than 3 consecutive days of missing data which aren't ruled out by negative serology or **[D]** their first day with symptoms for their first episode of illness with trigger/severe symptoms, which the algorithm in Figure 4 cannot ascertain be a COVID-19 episode (categorised as missing in Fig.4) unless the definition of the outcome is met (as per Fig. 4) and first day with symptoms for their first symptomatic/severe COVID-19 episode precedes all the events above, [A] – [D].	Censored at the earlier of: **[A]** or **[B]** or **[E]** date of withdrawal/last contact unless the definition of the outcome is met (as per Fig. 4) and first day with symptoms for their first symptomatic/severe COVID-19 episode precedes [A], [B] and [E]. [Episodes of illness with trigger/severe symptoms which the algorithm in Figure 4 cannot ascertain be a COVID-19 episode will be ignored from the censoring algorithm.]

*See section sensitivity analysis 3

6.3. SUPPLEMENTARY ANALYSES

The following supplementary analyses will be conducted on primary outcomes 1 and 2 with the intent to provide additional insights into the treatment effect:

i. **Including follow-up after first dose of any COVID-19-specific vaccine** (ie the intercurrent event of COVID-19-specific vaccine handled using a **Treatment Policy Strategy.** This analysis is summarised in estimands 1.2 and 2.2 below.

ii. **Excluding COVID-19 episodes (either trigger or severe) starting ≤14 days from date of randomisation** (ie the **intercurrent event of symptomatic/severe COVID-19 in the first 14 days post randomisation**, handled using a **Principal Stratum Strategy**). This analysis is summarised in estimands 1.3 and 2.3 below). For this analysis, time at risk of COVID-19 will start on the 15th day post randomisation date (as opposed to date of randomisation as for the primary analysis). In line with the definition of mITT that excludes participants who were exposed to COVID-19 prior to being randomised into the study, participants who:
    - had a COVID-19 episodes (either symptomatic or severe), or
    - had a trigger symptoms/severe episode reported, which the algorithm in Figure 4 cannot ascertain be a COVID-19 episode

    starting ≤14 days from date of randomisation, will be excluded from this analysis.

iii. **Censoring participants at the time of any subsequent vaccine** (ie the **intercurrent event of any vaccine**, including influenza vaccination and COVID-19-specific vaccine, handled by the **Hypothetical Strategy**, summarised in estimands 1.4 and 2.4 below).

iv. **on the ITT population** (as summarised in estimands 1.5 and 2.5 below)

v. **Treatment Policy Strategy on the ITT population** (summarised in estimands 1.6 and 2.6 below).

The following table summarises the estimands of secondary interest around primary outcomes 1 and 2.

Objective	Estimand
To determine if BCG vaccination compared with placebo reduces the incidence of symptomatic COVID-19 **irrespective of receiving a COVID-19-specific vaccine or any other vaccine**, over the 6 months following randomisation, in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 1.2** [Supplementary analysis i.] Population: as for estimand 1.1 Outcome: as for estimand 1.1 Interventions: as for estimand 1.1 Handling of Intercurrent events: - COVID-19 specific vaccine (**Treatment Policy strategy**) - any other vaccine (Treatment Policy strategy) Summary Measure: as for estimand 1.1
To determine if BCG vaccination compared with placebo reduces the incidence of symptomatic COVID-19 **following the 14 days after randomisation** in the absence of any COVID-19-specific vaccine, over the 6 months, in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 1.3** [Supplementary analysis ii.] Population: as for estimand 1.1 Outcome: as for estimand 1.1 Interventions: as for estimand 1.1 Handling of Intercurrent events: as for estimand 1.1 - COVID-19 specific vaccine (Hypothetical strategy) - any other vaccine (Treatment Policy strategy) - COVID-19 in the 14 days post randomisation (**Principal Stratum Strategy**) Summary Measure: as for estimand 1.1
To determine if BCG vaccination compared with placebo reduces the incidence of symptomatic COVID-19 **in the absence of any vaccine** (including COVID-19-specific vaccine), over the 6 months following randomisation, in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 1.4** [Supplementary analysis iii.] Population: as for estimand 1.1 Outcome: as for estimand 1.1 Interventions: as for estimand 1.1 Handling of Intercurrent events: - COVID-19 specific vaccine (Hypothetical Strategy) - any other vaccine (**Hypothetical strategy**) Summary Measure: as for estimand 1.1
To determine if BCG vaccination compared with placebo reduces the incidence of symptomatic COVID-19 in the absence of a COVID-19-specific vaccine, over the 6 months following randomisation, in healthcare workers exposed to SARS-CoV-2.	**Estimand 1.5** [Supplementary analysis iv.] Population: **ITT population** Outcome: as for estimand 1.1 Interventions: as for estimand 1.1 Handling of Intercurrent events: as for estimand 1.1 Summary Measure: as for estimand 1.1
To determine if BCG vaccination compared with placebo reduces the incidence of symptomatic COVID-19 **irrespective of receiving a COVID-19-specific vaccine or any other vaccine**, over the 6 months following randomisation, in healthcare workers.	**Estimand 1.6** [Supplementary analysis v.] Population: **ITT population** Outcome: as for estimand 1.1 Interventions: as for estimand 1.1 Handling of Intercurrent events: **as for estimand 1.2** Summary Measure: as for estimand 1.1
To determine if BCG vaccination compared with placebo reduces the incidence of severe COVID-19 **irrespective of receiving a COVID-19 specific vaccine or any other vaccine**, over the 6 months following randomisation, in healthcare workers who did not have a previous SARS-	**Estimand 2.2** [Supplementary analysis i.] Population: as for estimand 2.1 Outcome: as for estimand 2.1 Interventions: as for estimand 2.1 Handling of Intercurrent events:

Objective	Estimand
CoV-2 positive test result when assessed at time of randomisation.	- COVID-19 specific vaccine (**Treatment Policy strategy**) - any other vaccine (Treatment Policy strategy) Summary Measure: as for estimand 2.1
To determine if BCG vaccination compared with placebo reduces the incidence of severe COVID-19 **following the 14 days after randomisation** in the absence of any COVID-19 specific vaccine, over the 6 months, in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 2.3** [Supplementary analysis ii.] Population: as for estimand 2.1 Outcome: as for estimand 2.1 Interventions: as for estimand 2.1 Handling of Intercurrent events: as for estimand 2.1 - COVID-19 specific vaccine (Hypothetical strategy) - any other vaccine (Treatment Policy strategy) - COVID-19 in the 14 days post randomisation (**Principal Stratum Strategy**) Summary Measure: as for estimand 2.1
To determine if BCG vaccination compared with placebo reduces the incidence of severe COVID-19 **in the absence of any vaccine** (including a COVID-19 specific vaccine), over the 6 months following randomisation, in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 2.4** [Supplementary analysis iii.] Population: as for estimand 2.1 Outcome: as for estimand 2.1 Interventions: as for estimand 2.1 Handling of Intercurrent events: - COVID-19 specific vaccine (Hypothetical Strategy) - any other vaccine (**Hypothetical strategy**) Summary Measure: as for estimand 2.1
To determine if BCG vaccination compared with placebo reduces the incidence of severe COVID-19 in the absence of a COVID-19 specific vaccine, over the 6 months following randomisation, in healthcare workers exposed to SARS-CoV-2.	**Estimand 2.5** [Supplementary analysis iii.] Population: **ITT population** Outcome: as for estimand 2.1 Interventions: as for estimand 2.1 Handling of Intercurrent events: as for estimand 2.1 Summary Measure: as for estimand 2.1
To determine if BCG vaccination compared with placebo reduces the incidence of severe COVID-19 **irrespective of receiving a COVID-19-specific vaccine or any other vaccine**, over the 6 months following randomisation, in healthcare workers.	**Estimand 2.6** [Supplementary analysis v.] Population: **ITT population** Outcome: as for estimand 2.1 Interventions: as for estimand 2.1 Handling of Intercurrent events: **as for estimand 2.2** Summary Measure: as for estimand 2.1
** 1) adjusted for stratification factors used at randomisation (age group, presence of comorbidity, and geographical location); 2) adjusted for stratification factors used at randomisation + sex, BMI at baseline, BCG vaccine before randomisation;*	

The analyses for estimands 1.2-1.6 and 2.2-2.6 will be conducted using the same methodology as for the primary analysis (estimand 1.1 and 2.1, as specified in section 6.2.2).

6.4. SUBGROUP ANALYSES

The following sub-group analyses will be performed (only for estimands 1.1 and 2.1, unless otherwise indicated), but since we have not powered the trial to consider sub-groups, the results will be considered exploratory only. These sub-group analyses will examine the evidence for differences in the effect of the intervention between the sub-groups. The intervention effect in each sub-group and their 95% confidence intervals will be presented, together with the p-value for the intervention-by-subgroup interaction, as a guide to the strength of the evidence for an interaction.

1 – By age group (stratification factor at randomisation)

Subgroups will be defined by age at randomisation, as follows:

- <40 years vs.
- 40 to 59 years vs.
- >=60 years

2 – By presence of comorbidities

Subgroups will be:

- Presence of comorbidity at randomisation (any of diabetes, chronic respiratory disease, cardiovascular disease -including hypertension/high blood pressure, and obesity defined as BMI >= 30 kg/m^2) vs.
- Absence of comorbidity

2a – By presence of diabetes

Subgroups will be:

- Presence of diabetes at randomisation vs.
- Absence of diabetes at randomisation

2b – By presence of chronic respiratory disease

Subgroups will be:

- Presence of chronic respiratory disease at randomisation vs.
- Absence of chronic respiratory disease at randomisation

2c – By presence of ANY cardiovascular disease

Subgroups will be:

- Presence of cardiovascular disease at randomisation vs.
- Absence of cardiovascular disease at randomisation

2d – By presence of hypertension/high blood pressure

Subgroups will be:

- Presence of hypertension at randomisation vs.
- Absence of hypertension at randomisation

2e – By presence of obesity (BMI>=30 kg/m2)

Subgroups will be:

- Presence of obesity at randomisation vs
- Absence of obesity at randomisation

3 – By geographical Location

Sub-groups will be:

- Australia vs
- Europe vs
- South America

4 – By sex

Sub-groups will be:

- Females vs
- Males

5 – By BCG in the past or not

Sub-groups will be:

- Participants who received BCG vaccine before participating in the trial vs

- Participants who never received BCG vaccine before participating in the trial

Prior BCG vaccination status will be ascertained by self-reported answer to the question "Have you been vaccinated with BCG in the past?".

6 – By baseline serology results to SARS-CoV-2 (negative or non-negative) *[ITT population only]*
Sub-groups will be:

- Participants with negative serology to SARS-CoV-2 when enrolling into the trial (participants at the Brazilian sites will also need to show negative PCR on a respiratory sample or a negative SARS-CoV-2 diagnostic antigen test approved by the local jurisdiction's public health policy at the time of randomisation) **vs**
- Participants with non-negative (ie positive/missing/indeterminant) serology to SARS-CoV-2 when enrolling into the trial (Applicable only to participants at the Brazilian sites: positive/missing/indeterminant PCR on a respiratory sample or a positive/missing/indeterminant SARS-CoV-2 diagnostic antigen test approved by the local jurisdiction's public health policy at the time of randomisation)

This subgroup analysis will only be run on the ITT population (estimand 1.5 and 2.5).

6.5. SENSITIVITY ANALYSES

Sensitivity analysis 1 – BCG/Placebo vaccination date (as opposed to their randomisation date)
The primary analysis includes follow up data from the randomisation date (day 0), which is also when most participants received their trial BCG/placebo injection. However, a small number of participants received the intervention several days or weeks following randomisation. A sensitivity analysis on estimands 1.1 and 2.1 will be run, to have these participants follow up data start on the actual vaccination date (as opposed to their randomisation date).

Objective	Estimand
To determine if BCG vaccination compared with placebo reduces the incidence of symptomatic COVID-19 in the absence of a COVID-19 specific vaccine, over the 6 months **following vaccination**, in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 1.1_s1 [Sensitivity analysis 1]** Population: as for estimand 1.1 Outcome: **symptomatic COVID-19 by 6 months following vaccination** Interventions: as for estimand 1.1 Handling of Intercurrent events: as for estimand 1.1 Summary Measure: as for estimand 1.1
To determine if BCG vaccination compared with placebo reduces the incidence of severe COVID-19 in the absence of a COVID-19 specific vaccine, over the 6 months **following vaccination**, in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 2.1_s1 [Sensitivity analysis 1]** Population: as for estimand 2.1 Outcome: **severe COVID-19 by 6 months following vaccination** Interventions: as for estimand 2.1 Handling of Intercurrent events: as for estimand 2.1 Summary Measure: as for estimand 2.1
** 1) adjusted for stratification factors used at randomisation (age group, presence of comorbidity, and geographical location); 2) adjusted for stratification factors used at randomisation + sex, BMI at baseline, BCG vaccine before randomisation;*	

Sensitivity analysis 2 – Clinical algorithm based only on combined PCR/RAT result (Fig. 2) using the ITT population (i.e. disregarding all serology testing and baseline PCR in Brazil)
As a second sensitivity analysis on estimands 1.1 and 2.1, for the derivation of the primary outcomes, episodes of illness will be re-categorised as COVID-19 episodes (either symptomatic or severe), non-COVID-19 episodes, episodes with missing information using only the combination of the results from RAT and PCR tests (as in Figure 2).

Objective	Estimand
To determine if BCG vaccination compared with placebo reduces the incidence of symptomatic COVID-19 (**determined using PCR/RAT tests only**) in the absence of a COVID-19 specific vaccine, over the 6 months following randomisation, in healthcare workers.	**Estimand 1.1_s2 [Sensitivity analysis 2]** Population: **ITT population** Outcome: **symptomatic COVID-19 by 6 months determined using PCR/RAT tests only** Interventions: as for estimand 1.1 Handling of Intercurrent events: as for estimand 1.1 Summary Measure: as for estimand 1.1
To determine if BCG vaccination compared with placebo reduces the incidence of severe COVID-19 (**determined using PCR/RAT tests only**) in the absence of a COVID-19 specific vaccine, over the 6 months following randomisation, in healthcare workers.	**Estimand 2.1_s2 [Sensitivity analysis 2]** Population: **ITT population** Outcome: **severe COVID-19 by 6 months determined using PCR/RAT tests only** Interventions: as for estimand 2.1 Handling of Intercurrent events: as for estimand 2.1 Summary Measure: as for estimand 2.1
** 1) adjusted for stratification factors used at randomisation (age group, presence of comorbidity, and geographical location); 2) adjusted for stratification factors used at randomisation + sex, BMI at baseline, BCG vaccine before randomisation;*	

Sensitivity analysis 3

A third sensitivity analysis on estimands 1.1-1.6 and 2.1-2.6 will adopt a modified version of the censoring rule section as presented in table 2, in the column "SENSITIVITY ANALYSIS" (section 6.2.3).

7. SECONDARY COVID-19 RELATED OUTCOMES

Similarly to the analyses of the primary outcomes, the analyses of the COVID-19 related secondary outcomes will be conducted following three different approaches, specifically:

1. Censoring participants at the time of their COVID-19 specific vaccine (ie **the intercurrent event of COVID-19-specific vaccine**, will be handled using a **Hypothetical Strategy**)
2. Including follow-up after first dose of any COVID-19-specific vaccine (ie **the intercurrent event of COVID-19-specific vaccine**, will be handled using a **Treatment Policy Strategy**)
3. Censoring participants at the time of any vaccine (ie the i**ntercurrent event of any vaccine**, including influenza vaccination and COVID-19-specific vaccine, will be handled using a **Hypothetical Strategy**)

The analyses will be conducted on the mITT population, unless otherwise indicated, and including only Stage 2 participants.

7.1. SYMPTOMATIC COVID-19 AND SEVERE COVID-19 BY 12MONTHS (#3 and #4)

7.1.1. ESTIMANDS

Objective	Estimand
To determine if BCG vaccination compared with placebo reduces the incidence of symptomatic COVID-19 in the absence of a COVID-19 specific vaccine, over the 12 months following randomisation, in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 3.1** Population: mITT population Outcome: symptomatic COVID-19 by 12 months Interventions: BCG vs Placebo Handling of Intercurrent events: - COVID-19 specific vaccine (Hypothetical Strategy) - any other vaccine (Treatment Policy strategy) Summary Measure: Adjusted* difference in proportion of participants

Objective	Estimand
To determine if BCG vaccination compared with placebo reduces the incidence of symptomatic COVID-19 irrespective of receiving a COVID-19 specific vaccine or any other vaccine, over the 12 months following randomisation, in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 3.2** Population: as for estimand 3.1 Outcome: as for estimand 3.1 Interventions: as for estimand 3.1 Handling of Intercurrent events: - COVID-19 specific vaccine (**Treatment Policy strategy**) - any other vaccine (Treatment Policy strategy) Summary Measure: as for estimand 3.1
To determine if BCG vaccination compared with placebo reduces the incidence of symptomatic COVID-19 in the absence of a COVID-19 specific vaccine, over the 12 months following the 14 days after randomisation, in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 3.3** Population: as for estimand 3.1 Outcome: **symptomatic COVID-19, but excluding COVID-19 episodes that started in the 14 days window after randomisation** Interventions: as for estimand 3.1 Handling of Intercurrent events: as for estimand 3.1 Summary Measure: as for estimand 3.1
To determine if BCG vaccination compared with placebo reduces the incidence of symptomatic COVID-19 in the absence of any other vaccine (including COVID-19 specific vaccine), over the 12 months following randomisation, in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 3.4** Population: as for estimand 3.1 Outcome: as for estimand 3.1 Interventions: as for estimand 3.1 Handling of Intercurrent events: - COVID-19 specific vaccine (Hypothetical Strategy) - any other vaccine (**Hypothetical strategy**) Summary Measure: as for estimand 3.1
To determine if BCG vaccination compared with placebo reduces the incidence of symptomatic COVID-19 in the absence of a COVID-19 specific vaccine, over the 12 months following randomisation, in healthcare workers exposed to SARS-CoV-2.	**Estimand 3.5** Population: **ITT population** Outcome: as for estimand 3.1 Interventions: as for estimand 3.1 Handling of Intercurrent events: as for estimand 3.1 Summary Measure: as for estimand 3.1
To determine if BCG vaccination compared with placebo reduces the incidence of symptomatic COVID-19 irrespective of receiving a COVID-19 specific vaccine or any other vaccine, over the 12 months following randomisation, in healthcare workers.	**Estimand 3.6** Population: **ITT population** Outcome: as for estimand 3.1 Interventions: as for estimand 3.1 Handling of Intercurrent events: as for estimand 3.2 Summary Measure: as for estimand 3.1
To determine if BCG vaccination compared with placebo reduces the incidence of severe COVID-19 in the absence of a COVID-19 specific vaccine, over the 12 months following randomisation, in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 4.1** Population: mITT population Outcome: **severe COVID-19 by 12 months** Interventions: BCG vs Placebo Handling of Intercurrent events: - COVID-19 specific vaccine (Hypothetical Strategy) - any other vaccine (Treatment Policy strategy) Summary Measure: Adjusted* difference in proportion of participants
To determine if BCG vaccination compared with placebo reduces the incidence of severe COVID-19 irrespective of receiving a COVID-19 specific vaccine or any other vaccine, over the 12 months following	**Estimand 4.2** Population: as for estimand 4.1 Outcome: as for estimand 4.1

Objective	Estimand
randomisation, in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	Interventions: as for estimand 4.1 Handling of Intercurrent events: - COVID-19 specific vaccine (**Treatment Policy strategy**) - any other vaccine (Treatment Policy strategy) Summary Measure: as for estimand 4.1
To determine if BCG vaccination compared with placebo reduces the incidence of severe COVID-19 in the absence of a COVID-19 specific vaccine, over the 12 months following the 14 days after randomisation, in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 4.3** Population: as for estimand 4.1 Outcome: **severe COVID-19, but excluding severe COVID-19 episodes that started in the 14 days window after randomisation** Interventions: as for estimand 4.1 Handling of Intercurrent events: as for estimand 4.1 Summary Measure: as for estimand 4.1
To determine if BCG vaccination compared with placebo reduces the incidence of severe COVID-19 in the absence of any vaccine (including COVID-19 specific vaccine), over the 12 months following randomisation, in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 4.4** Population: as for estimand 4.1 Outcome: as for estimand 4.1 Interventions: as for estimand 4.1 Handling of Intercurrent events: - COVID-19 specific vaccine (Hypothetical Strategy) - any other vaccine (**Hypothetical strategy**) Summary Measure: as for estimand 4.1
To determine if BCG vaccination compared with placebo reduces the incidence of severe COVID-19 in the absence of a COVID-19 specific vaccine, over the 12 months following randomisation, in healthcare workers.	**Estimand 4.5** Population: **ITT population** Outcome: as for estimand 4.1 Interventions: as for estimand 4.1 Handling of Intercurrent events: as for estimand 4.1 Summary Measure: as for estimand 4.1
To determine if BCG vaccination compared with placebo reduces the incidence of severe COVID-19 irrespective of receiving a COVID-19 specific vaccine or any other vaccine, over the 12 months following randomisation, in healthcare workers.	**Estimand 4.6** Population: **ITT population** Outcome: as for estimand 4.1 Interventions: as for estimand 4.1 Handling of Intercurrent events: **as for estimand 4.2** Summary Measure: as for estimand 4.1
** 1) adjusted for stratification factors used at randomisation (age group, presence of comorbidity, and geographical location); 2) adjusted for stratification factors used at randomisation + sex, BMI at baseline, BCG vaccine before randomisation;*	

7.1.2. ANALYSIS

Since outcomes 3 and 4 are the equivalent of the primary outcomes 1 and 2 over 12 months post randomisation, the same analyses that are presented in section 6.2 will be applied on these outcomes (summarised in estimands 3.1 to 3.6 for symptomatic COVID-19 by 12 months and in estimands 4.1 to 4.6 for severe COVID -19 outcome)

7.1.3.ADDITIONAL ANALYSIS

Additional outcomes 3 and 4 will be compared between the following groups:

- Participants who received BCG vaccine at recruitment AND who show evidence of the scar left by this vaccine 12 months post randomisation

- Participants who received placebo AND participants who received BCG vaccine at recruitment but don't show evidence of the scar left by this vaccine 12 months post randomisation

The same analyses that are presented in section 6.2 will be run.

7.1.4. SUBGROUP ANALYSIS

The following subgroup analyses (described in detail in section 6.4) will be conducted for estimands 3.1 and 4.1:

- Sub-Group analysis 1 – Age group (stratification factor at randomisation)
- Sub-Group analyses 2, 2a, 2b, 2c, 2d, 2e – Presence of comorbidities
- Sub-Group analysis 3 – Geographical Location
- Sub-Group analysis 4 – Sex
- Sub-Group analysis 5 – BCG in the past or not
- Sub-Group analysis 6 – Serology results to SARS-CoV-2 at enrolment (ITT pop only, estimand 3.5 and 4.5)

Additionally, a second categorisation of subgroup analysis 5 will be done to include evidence of a scar due to BCG vaccine in the past, as assessed by the immuniser and the photo of the scar review by clinical BRACE team unblinded to the treatment allocation. The will be conducted as follows:

- **Sub-Group analysis 5a – By BCG in the past or not (as confirmed by scar evidence)**
  - Participants who received BCG vaccine before participating in the trial and show evidence of a scar vs
  - Participants who never received BCG vaccine before participating in the trial and show no evidence of a scar

This subgroup analysis will exclude those participants who reported prior BCG vaccine but have no evidence of a scar, and those who did not report prior BCG vaccine but have evidence of a scar.

7.2. TIME TO FIRST SYMPTOM OF COVID-19 (#5a and #5b)

7.2.1.ESTIMANDS

Objective	Estimand
To determine if BCG vaccination compared with placebo prolongs the time to first SARS-CoV-2-proven respiratory illness in the absence of a COVID-19 specific vaccine, measured over 6 months following randomisation in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 5a.1** Population: mITT population Outcome: **time to COVID-19 by 6 months** Interventions: BCG vs Placebo Handling of Intercurrent events: - COVID-19 specific vaccine (Hypothetical Strategy) - any other vaccine (Treatment Policy strategy) Summary Measure: Adjusted* hazard ratios
To determine if BCG vaccination compared with placebo prolongs the time to first SARS-CoV-2-proven respiratory illness in the absence of a COVID-19 specific vaccine, measured over 12 months following randomisation in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 5b.1** Population: mITT population Outcome: **time to COVID-19 by 12 months** Interventions: BCG vs Placebo Handling of Intercurrent events: - COVID-19 specific vaccine (Hypothetical Strategy) - any other vaccine (Treatment Policy strategy) Summary Measure: Adjusted* hazard ratios
To determine if BCG vaccination compared with placebo prolongs the time to first SARS-CoV-2-	**Estimand 5a.2**

Objective	Estimand
proven respiratory illness irrespective of receiving a COVID-19 specific vaccine or any other vaccine, measured over 6 months following randomisation in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	Population: as 5a.1 Outcome: as 5a.1 Interventions: as 5a.1 Handling of Intercurrent events: - COVID-19 specific vaccine (**Treatment Policy strategy**) - any other vaccine (Treatment Policy strategy) Summary Measure: as 5a.1
To determine if BCG vaccination compared with placebo prolongs the time to first SARS-CoV-2-proven respiratory illness irrespective of receiving a COVID-19 specific vaccine or any other vaccine, measured over 12 months following randomisation in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 5b.2** Population: as 5b.1 Outcome: as 5b.1 Interventions: as 5b.1 Handling of Intercurrent events: - COVID-19 specific vaccine (**Treatment Policy strategy**) - any other vaccine (Treatment Policy strategy) Summary Measure: as 5b.1
To determine if BCG vaccination compared with placebo prolongs the time to first SARS-CoV-2-proven respiratory illness following the 14 days after randomisation irrespective of receiving a COVID-19 specific vaccine or any other vaccine, measured over the 6 months in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 5a.3** Population: as 5a.1 Outcome: **time to COVID-19 by 6 months, but excluding COVID-19 episodes that started in the 14 days window after randomisation** Interventions: as 5a.1 Handling of Intercurrent events: as 5a.1 Summary Measure: as 5a.1
To determine if BCG vaccination compared with placebo prolongs the time to first SARS-CoV-2-proven respiratory illness following the 14 days after randomisation irrespective of receiving a COVID-19 specific vaccine or any other vaccine, measured over the 12 months in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 5b.3** Population: as 5b.1 Outcome: **time to COVID-19 by 12 months, but excluding COVID-19 episodes that started in the 14 days window after randomisation** Interventions: as 5b.1 Handling of Intercurrent events: as 5a.1 Summary Measure: as 5b.1
To determine if BCG vaccination compared with placebo prolongs the time to first SARS-CoV-2-proven respiratory illness in the absence of any vaccine, measured over 6 months following randomisation in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 5a.4** Population: as 5a.1 Outcome: as 5a.1 Interventions: as 5a.1 Handling of Intercurrent events: - COVID-19 specific vaccine (Hypothetical Strategy) - any other vaccine (**Hypothetical Strategy**) Summary Measure: as 5a.1
To determine if BCG vaccination compared with placebo prolongs the time to first SARS-CoV-2-proven respiratory illness in the absence of any vaccine, measured over 12 months following randomisation in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 5b.4** Population: as for estimand 5b.1 Outcome: as for estimand 5b.1 Interventions: as for estimand 5b.1 Handling of Intercurrent events: - COVID-19 specific vaccine (Hypothetical Strategy) - any other vaccine (**Hypothetical Strategy**) Summary Measure: as for estimand 5b.1

Objective	Estimand
To determine if BCG vaccination compared with placebo prolongs the time to first SARS-CoV-2-proven respiratory illness in the absence of a COVID-19 specific vaccine, measured over 6 months following randomisation in healthcare.	**Estimand 5a.5** Population: **ITT population** Outcome: as for estimand 5a.1 Interventions: as for estimand 5a.1 Handling of Intercurrent events: as for estimand 5a.1 Summary Measure: as for estimand 5a.1
To determine if BCG vaccination compared with placebo prolongs the time to first SARS-CoV-2-proven respiratory illness in the absence of a COVID-19 specific vaccine, measured over 12 months following randomisation in healthcare.	**Estimand 5b.5** Population: **ITT population** Outcome: as for estimand 5b.1 Interventions: as for estimand 5b.1 Handling of Intercurrent events: as for estimand 5b.1 Summary Measure: as for estimand 5b.1
To determine if BCG vaccination compared with placebo prolongs the time to first SARS-CoV-2-proven respiratory illness irrespective of receiving a COVID-19 specific vaccine or any other vaccine, measured over 6 months following randomisation in healthcare.	**Estimand 5a.6** Population: **ITT population** Outcome: as for estimand 5a.1 Interventions: as for estimand 5a.1 Handling of Intercurrent events: **as for estimand 5a.2** Summary Measure: as for estimand 5a.1
To determine if BCG vaccination compared with placebo prolongs the time to first SARS-CoV-2-proven respiratory illness rrespective of receiving a COVID-19 specific vaccine or any other vaccine, measured over 12 months following r39andomization in healthcare.	**Estimand 5b.6** Population: **ITT population** Outcome: as for estimand 5b.1 Interventions: as for estimand 5b.1 Handling of Intercurrent events: **as for estimand 5b.2** Summary Measure: as for estimand 5b.1
** 1) adjusted for stratification factors used at randomisation (age group, presence of comorbidity, and geographical location); 2) adjusted for stratification factors used at randomisation + sex, BMI at baseline, BCG vaccine before randomisation;*	

7.2.1.ANALYSIS

The time to COVID-19 (either symptomatic or severe COVID-19) will be calculated and presented in the two intervention groups.
Survival curves for the time to COVID-19 episode will be constructed for each intervention group using the Kaplan-Meier product limit method.

Adjusted analyses will be used to compare the time to event distributions between groups by means of Cox's proportional hazards model. Initially the model will be adjusted for the stratification factors used during randomisation (age group, presence of comorbidity, geographical location -Europe/Australia/South America). Additional analyses will be conducted using the same Cox's proportional hazards but also adjusted for the following baseline covariates (as described in section 6.2.2): sex, BMI, BCG prior to study enrolment. The proportional hazards assumption will be checked when running these analyses. Assuming the proportional hazards assumption is found to be reasonable, results from the proportional hazards regression will be presented as the hazard ratios and their corresponding 95% confidence intervals.

7.2.2.SUBGROUP ANALYSIS

The following subgroup analyses (described in details in section 6.4) will be conducted for estimands 5a.1 and 5b.1:

- Sub-Group analysis 1 – Age group (stratification factor at randomisation)
- Sub-Group analyses 2, 2a, 2b, 2c, 2d, 2e – Presence of comorbidities
- Sub-Group analysis 3 – Geographical Location
- Sub-Group analysis 4 – Sex
- Sub-Group analysis 5 – BCG in the past or not
- Sub-Group analysis 6 – serology results to SARS-CoV-2 at enrolment (ITT pop only, estimands 5a.5 and 5b.5)

7.3. NUMBER OF EPISODES OF COVID-19 (#6a and #6b)

7.3.1.ESTIMANDS

Objective	Estimand
To determine if BCG vaccination compared with placebo reduces the number of COVID-19 episodes in the absence of a COVID-19 specific vaccine, measured over 6 months following randomisation in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 6a.1** Population: mITT population Outcome: **number of COVID-19 episodes by 6 months** Interventions: BCG vs Placebo Handling of Intercurrent events: - COVID-19 specific vaccine (Hypothetical Strategy) - any other vaccine (Treatment Policy strategy) Summary Measure: Adjusted* difference in the expected counts
To determine if BCG vaccination compared with placebo reduces the number of COVID-19 episodes in the absence of a COVID-19 specific vaccine, measured over 12 months following randomisation in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 6b.1** Population: mITT population Outcome: **number of COVID-19 episodes by 12 months** Interventions: BCG vs Placebo Handling of Intercurrent events: - COVID-19 specific vaccine (Hypothetical Strategy) - any other vaccine (Treatment Policy strategy) Summary Measure: Adjusted* difference in the expected counts
To determine if BCG vaccination compared with placebo reduces the number of COVID-19 episodes irrespective of receiving a COVID-19 specific vaccine or any other vaccine, measured over 6 months following randomisation in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 6a.2** Population: as 6a.1 Outcome: as 6a.1 Interventions: as 6a.1 Handling of Intercurrent events: - COVID-19 specific vaccine (**Treatment Policy strategy**) - any other vaccine (Treatment Policy strategy) Summary Measure: as 6a.1
To determine if BCG vaccination compared with placebo reduces the number of COVID-19 episodes irrespective of receiving a COVID-19 specific vaccine or any other vaccine, measured over 12 months following randomisation in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 6b.2** Population: as 6b.1 Outcome: as 6b.1 Interventions: as 6b.1 Handling of Intercurrent events: - COVID-19 specific vaccine (**Treatment Policy strategy**) - any other vaccine (Treatment Policy strategy) Summary Measure: as 6b.1
To determine if BCG vaccination compared with placebo reduces the number of COVID-19 episodes illness in the absence of any vaccine, measured over 6 months following randomisation in healthcare	**Estimand 6a.3** Population: as 6a.1 Outcome: as 6a.1

Objective	Estimand
workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	Interventions: as 6a.1 Handling of Intercurrent events: - COVID-19 specific vaccine (Hypothetical Strategy) - any other vaccine (**Hypothetical Strategy**) Summary Measure: as 6a.1
To determine if BCG vaccination compared with placebo reduces the number of COVID-19 episodes in the absence of any vaccine, measured over 12 months following randomisation in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 6b.3** Population: as 6b.1 Outcome: as 6b.1 Interventions: as 6b.1 Handling of Intercurrent events: - COVID-19 specific vaccine (Hypothetical Strategy) - any other vaccine (**Hypothetical Strategy**) Summary Measure: as 6b.1
** 1) adjusted for stratification factors used at randomisation (age group, presence of comorbidity, and geographical location)*	

7.3.2.ANALYSIS

The median and IQR for the number of episodes will be presented by intervention group.

The difference between BCG and placebo groups will be summarised as difference in the logs of expected number of episodes and its 95%CI estimated using a Zero-Inflated Negative Binomial (ZINB) model. Since this secondary outcome will be analysed mainly for descriptive purposes, the model will only be adjusted for the stratification factors used at randomisation (Geographical Location (Australia/Europe/South America, age group and presence of comorbidity).

The analysis will be done using the *zinb* command in Stata, with the *inflate()* and *exposure()* options. The *inflate()* option will be used to indicate whether the participant had the COVID-19 event, while the *exposure()* option will be used to indicate the amount of exposure over which the number of episodes of COVID-19 were observed for each participant (refer to section 6.2.3).

7.3.3.ADDITIONAL ANALYSIS

Additionally, the median and IQR of the number of episodes will be calculated and presented by intervention group in the subgroups of participants who:

- had COVID-19 (either symptomatic or severe)
- had symptomatic COVID-19
- had severe COVID-19

7.3.4.SUBGROUP ANALYSIS

None

7.4. ASYMPTOMATIC SARS-COV-2 INFECTION (#7)

7.4.1.ESTIMANDS

Objective	Estimand
To determine if BCG vaccination compared with placebo reduces the incidence of asymptomatic COVID-19 irrespective of receiving a non-CoronaVac COVID-19 specific vaccine or any other vaccine, over the 6 months following randomisation, in healthcare workers who did not receive CoronaVac during the study or have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 7a.1** Population: mITT population Outcome: **asymptomatic SARS-COV-2 infection by 6 months** Interventions: BCG vs Placebo Handling of Intercurrent events: - non-CoronaVac COVID-19 specific vaccine (**Treatment Policy strategy**) - CoronaVac vaccine (**Principal Stratum strategy**) - any other other vaccine (Treatment Policy strategy) Summary Measure: Adjusted* difference in proportion of participants
To determine if BCG vaccination compared with placebo reduces the incidence of asymptomatic COVID-19 irrespective of receiving a non-CoronaVac COVID-19 specific vaccine or any other vaccine, over the 12 months following randomisation, in healthcare workers who did not receive CoronaVac during the study or have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 7b.1** Population: mITT population Outcome: **asymptomatic SARS-COV-2 infection by 12 months** Interventions: BCG vs Placebo Handling of Intercurrent events: - non-CoronaVac COVID-19 specific vaccine (**Treatment Policy strategy**) - CoronaVac vaccine (**Principal Stratum strategy**) - any other other vaccine (Treatment Policy strategy) Summary Measure: Adjusted* difference in proportion of participants
** 1) adjusted for stratification factors used at randomisation (age group, presence of comorbidity, and geographical location); 2) adjusted for stratification factors used at randomisation + sex, BMI at baseline, BCG vaccine before randomisation*	

7.4.2.ANALYSIS

The outcome of asymptomatic COVID-19, determined by seroconversion at 3 or 6 months not associated with any episode of illness will be described by intervention group as the absolute number of participants with the outcome.

The treatment effect for this outcome will be the difference in proportion (BCG - Control) estimated using a binomial regression model, adjusted for stratification factors used at randomisation (age group, presence of comorbidity, and geographical location). An additional analysis will be conducted using the same binomial regression model but also adjusted for the following baseline covariates (as described in section 6.2.2): sex, BMI, and BCG prior to study enrolment. Should the binomial regression model have convergence difficulties (due to low prevalence outcome), generalised liner model (GLM) approach with Gaussian error distribution and identity link function will be adopted.

Since the administration of CoronaVac (which is a post randomisation intercurrent event) more than 7 days prior to the blood collection makes the results of serology indeterminant, CoronaVac will be handled the Principal Stratum strategy i.e. estimating the treatment effect in participants who would not have received CoronaVac in either treatment arm. For the main analysis we will assume that the occurrence of this intercurrent event is not related to the study intervention (BCG/Placebo), and we will restrict the analysis to participants who did not receive CoronaVac (all participants who received CoronaVac will be excluded from the analysis).

As a sensitivity analysis, we will repeat the analysis under the assumption of conditional independence of the treatment and the intercurrent event (known as principal ignorability). For this analysis, separate models will be specified for the outcome and the intercurrent event itself, assuming that conditional on baseline covariates the outcome in the control group and the occurrence of the intercurrent event in the intervention group are independent. In order to conduct this analysis, we will first model the probability of the occurrence of the intercurrent event on the intervention group as well study site, sex, presence of comorbidities, and age (variables that could potentially confound the outcome and the intercurrent event),

using logistic regression. Then, we will use the predicted probabilities as weights for participants on the control group in the analysis model for the outcome.
As a second, and very conservative, sensitivity analysis, participants in study sites where CoronaVac was available (Mato Grosso do Sul, Rio de Janeiro, and Amazonas -BRA), will be excluded from the analysis of this outcome so that this intercurrent event is no longer relevant.
Participants with unavailable/indeterminant serology data, and participants on whom the absence of episodes of illness over 6 months cannot be ascertained (due to incomplete data entry) will be coded as missing the outcome.

7.4.3.ADDITIONAL ANALYSIS

Since a SARS-CoV-2 infection could also be detected by a positive PCR/RAT not associated with a severe episode of illness or an episode with "trigger" symptoms" (e.g., SARS-CoV-2 infection detected via a screening test), and since seroconversion could also be explained by not severe SARS-CoV-2 infection not characterised by trigger symptoms, we will calculate and report by intervention group the number of participants who:

- Show evidence of COVID-19 determined by a positive PCR or positive RAT (and not serology) not related any episode of illness OR
- Show evidence of COVID-19 determined by a positive PCR or positive RAT (and not serology) related to a non-trigger non-severe episode of illness
- Show evidence of COVID-19 determined by seroconversion at 3 or 6 months associated with an episode of illness which is not trigger AND not severe (as defined in section 4.1)

Moreover, in those participants who meet the asymptomatic outcome the following information will be described and reported by intervention group as mean, standard deviation (or median and IQR if distribution is skewed) or absolute and relative frequencies, according to the nature of the variable:

- Sex – Male/Female/Other/Declined/Missing
- Age, years
- Body Mass Index (BMI), kg/m^2 – < 18.5 / 18.5 to 24.9/ 25 to 29.9 / >30 / Missing
- Role – Administrative-clerical staff / Allied Health / Dentist-dental therapy / Doctor / Nurse-Midwife / Patient Services Assistant-hospital maintenance / Scientist (medical research) / Other / Missing
- Contact with patients, hours - <10 / 10-20 / >20 / Missing
- Confirmed cases of COVID-19 within department – Yes / No / Missing
- Smoking – Yes / No / Missing
- Previous BCG vaccination -No / last BCG dose <1 year ago / 1-5 years ago / >5 years ago / Missing

7.4.4.SUBGROUP ANALYSIS

The following subgroup analyses (described in detail in section 6.4) will be conducted for estimands 7a.1 and 7b.1:

- Sub-Group analysis 1 – Age group (stratification factor at randomisation)
- Sub-Group analyses 2, 2a, 2b, 2c, 2d, 2e – Presence of comorbidities
- Sub-Group analysis 3 – Geographical Location
- Sub-Group analysis 4 – Sex
- Sub-Group analysis 5 – BCG in the past or not

7.5. NUMBER OF DAYS UNABLE TO WORK DUE TO COVID-19 (#8a and #8b)

7.5.1.ESTIMANDS

Objective	Estimand
To determine if BCG vaccination compared with placebo reduces the number of days unable to work due to COVID-19 in the absence of a COVID-19 specific vaccine, measured over 6 months following randomisation in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 8a.1** Population: mITT population Outcome: **number of days unable to work due to COVID-19 by 6 months** Interventions: BCG vs Placebo Handling of Intercurrent events: - COVID-19 specific vaccine (Hypothetical Strategy) - any other vaccine (Treatment Policy strategy) Summary Measure: adjusted* difference in the expected counts
To determine if BCG vaccination compared with placebo reduces the number of days unable to work due to COVID-19 in the absence of a COVID-19 specific vaccine, measured over 12 months following randomisation in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 8b.1** Population: mITT population Outcome: **number of days unable to work due to COVID-19 by 12 months** Interventions: BCG vs Placebo Handling of Intercurrent events: - COVID-19 specific vaccine (Hypothetical Strategy) - any other vaccine (Treatment Policy strategy) Summary Measure: adjusted* difference in the expected counts
To determine if BCG vaccination compared with placebo reduces the number of days unable to work due to COVID-19 irrespective of receiving a COVID-19 specific vaccine or any other vaccine, measured over 6 months following randomisation in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 8a.2** Population: as 8a.1 Outcome: as 8a.1 Interventions: as 8a.1 Handling of Intercurrent events: - COVID-19 specific vaccine (**Treatment Policy strategy**) - any other vaccine (Treatment Policy strategy) Summary Measure: as 8a.1
To determine if BCG vaccination compared with placebo reduces the number of days unable to work due to COVID-19 irrespective of receiving a COVID-19 specific vaccine or any other vaccine, measured over 12 months following randomisation in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 8b.2** Population: as 8b.1 Outcome: as 8b.1 Interventions: as 8b.1 Handling of Intercurrent events: - COVID-19 specific vaccine (**Treatment Policy strategy**) - any other vaccine (Treatment Policy strategy) Summary Measure: as 8b.1
To determine if BCG vaccination compared with placebo reduces the number of days unable to work due to COVID-19 illness in the absence of any vaccine, measured over 6 months following randomisation in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 8a.3** Population: as 8a.1 Outcome: as 8a.1 Interventions: as 8a.1 Handling of Intercurrent events: - COVID-19 specific vaccine (Hypothetical Strategy) - any other vaccine (**Hypothetical Strategy**) Summary Measure: as 8a.1
To determine if BCG vaccination compared with placebo reduces the number of days unable to work due to COVID-19 in the absence of any vaccine, measured over 12 months following randomisation	**Estimand 8b.3** Population: as 8b.1 Outcome: as 8b.1

Objective	Estimand
in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	Interventions: as 8b.1 Handling of Intercurrent events: - COVID-19 specific vaccine (Hypothetical Strategy) - any other vaccine (**Hypothetical Strategy**) Summary Measure: as 8b.1
** 1) adjusted for stratification factors used at randomisation (age group, presence of comorbidity, and geographical location)*	

7.5.2.ANALYSIS

As per section 7.3.2.

7.5.3.ADDITIONAL ANALYSIS

As per section 7.3.3.

7.5.4.SUBGROUP ANALYSIS

None.

7.6. NUMBER OF DAYS CONFINED TO BED DUE TO COVID-19 (#9a and #9b)

7.6.1.ESTIMANDS

Objective	Estimand
To determine if BCG vaccination compared with placebo reduces the number of days confined to bed due to COVID-19 in the absence of a COVID-19 specific vaccine, measured over 6 months following randomisation in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 9a.1** Population: mITT population Outcome: **number of days confined to bed due to COVID-19 by 6 months** Interventions: BCG vs Placebo Handling of Intercurrent events: - COVID-19 specific vaccine (Hypothetical Strategy) - any other vaccine (Treatment Policy strategy) Summary Measure: adjusted* difference in the expected counts
To determine if BCG vaccination compared with placebo reduces the number of days confined to bed due to COVID-19 in the absence of a COVID-19 specific vaccine, measured over 12 months following randomisation in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 9b.1** Population: mITT population Outcome: **number of days confined to bed due to COVID-19 by 12 months** Interventions: BCG vs Placebo Handling of Intercurrent events: - COVID-19 specific vaccine (Hypothetical Strategy) - any other vaccine (Treatment Policy strategy) Summary Measure: adjusted* difference in the expected counts
To determine if BCG vaccination compared with placebo reduces the number of days confined to bed due to COVID-19 irrespective of receiving a COVID-19 specific vaccine or any other vaccine, measured over 6 months following randomisation in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 9a.2** Population: as 9a.1 Outcome: as 9a.1 Interventions: as 9a.1 Handling of Intercurrent events: - COVID-19 specific vaccine (**Treatment Policy strategy**) - any other vaccine (Treatment Policy strategy) Summary Measure: as 9a.1
To determine if BCG vaccination compared with placebo reduces the number of days confined to bed due to COVID-19 irrespective of receiving a COVID-19 specific vaccine or any other vaccine,	**Estimand 9b.2** Population: as 9b.1 Outcome: as 9b.1

Objective	Estimand
measured over 12 months following randomisation in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	Interventions: as 9b.1 Handling of Intercurrent events: - COVID-19 specific vaccine (**Treatment Policy strategy**) - any other vaccine (Treatment Policy strategy) Summary Measure: as 9b.1
To determine if BCG vaccination compared with placebo reduces the number of days confined to bed due to COVID-19 illness in the absence of any vaccine, measured over 6 months following randomisation in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 9a.3** Population: as 9a.1 Outcome: as 9a.1 Interventions: as 9a.1 Handling of Intercurrent events: - COVID-19 specific vaccine (Hypothetical Strategy) - any other vaccine (**Hypothetical Strategy**) Summary Measure: as 9a.1
To determine if BCG vaccination compared with placebo reduces the number of days confined to bed due to COVID-19 in the absence of any vaccine, measured over 12 months following randomisation in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 9b.3** Population: as 9b.1 Outcome: as 9b.1 Interventions: as 9b.1 Handling of Intercurrent events: - COVID-19 specific vaccine (Hypothetical Strategy) - any other vaccine (**Hypothetical Strategy**) Summary Measure: as 9b.1
** 1) adjusted for stratification factors used at randomisation (age group, presence of comorbidity, and geographical location)*	

7.6.1.ANALYSIS

As per section 7.3.2.

7.6.2.ADDITIONAL ANALYSIS

As per section 7.3.3.

7.6.3.SUBGROUP ANALYSIS

None.

7.7. NUMBER OF DAYS WITH SYMPTOMS DUE TO COVID-19 (#10a and #10b)

7.7.1.ESTIMANDS

Objective	Estimand
To determine if BCG vaccination compared with placebo reduces the number of days with symptoms due to COVID-19 in the absence of a COVID-19 specific vaccine, measured over 6 months following randomisation in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 10a.1** Population: mITT population Outcome: **number of days with symptoms due to COVID-19 by 6 months** Interventions: BCG vs Placebo Handling of Intercurrent events: - COVID-19 specific vaccine (Hypothetical Strategy) - any other vaccine (Treatment Policy strategy) Summary Measure: adjusted* difference in the expected counts

Objective	Estimand
To determine if BCG vaccination compared with placebo reduces the number of days with symptoms due to COVID-19 in the absence of a COVID-19 specific vaccine, measured over 12 months following randomisation in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 10b.1** Population: mITT population Outcome: **number of days with symptoms due to COVID-19 by 12 months** Interventions: BCG vs Placebo Handling of Intercurrent events: - COVID-19 specific vaccine (Hypothetical Strategy) - any other vaccine (Treatment Policy strategy) Summary Measure: adjusted difference in the expected counts
To determine if BCG vaccination compared with placebo reduces the number of days with symptoms due to COVID-19 irrespective of receiving a COVID-19 specific vaccine or any other vaccine, measured over 6 months following randomisation in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 10a.2** Population: as 10a.1 Outcome: as 10a.1 Interventions: as 10a.1 Handling of Intercurrent events: - COVID-19 specific vaccine (**Treatment Policy strategy**) - any other vaccine (Treatment Policy strategy) Summary Measure: as 10a.1
To determine if BCG vaccination compared with placebo reduces the number of days with symptoms due to COVID-19 irrespective of receiving a COVID-19 specific vaccine or any other vaccine, measured over 12 months following randomisation in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 10b.2** Population: as 10b.1 Outcome: as 10b.1 Interventions: as 10b.1 Handling of Intercurrent events: - COVID-19 specific vaccine (**Treatment Policy strategy**) - any other vaccine (Treatment Policy strategy) Summary Measure: as 10b.1
To determine if BCG vaccination compared with placebo reduces the number of days with symptoms due to COVID-19 illness in the absence of any vaccine, measured over 6 months following randomisation in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 10a.3** Population: as 10a.1 Outcome: as 10a.1 Interventions: as 10a.1 Handling of Intercurrent events: - COVID-19 specific vaccine (Hypothetical Strategy) - any other vaccine (**Hypothetical Strategy**) Summary Measure: as 10a.1
To determine if BCG vaccination compared with placebo reduces the number of days with symptoms due to COVID-19 in the absence of any vaccine, measured over 12 months following randomisation in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 10b.3** Population: as 10b.1 Outcome: as 10b.1 Interventions: as 10b.1 Handling of Intercurrent events: - COVID-19 specific vaccine (Hypothetical Strategy) - any other vaccine (**Hypothetical Strategy**) Summary Measure: as 10b.1
** 1) adjusted for stratification factors used at randomisation (age group, presence of comorbidity, and geographical location)*	

7.7.2.ANALYSIS

As per section 7.3.2.

7.7.3.ADDITIONAL ANALYSIS

As per section 7.3.3.

7.7.4.SUBGROUP ANALYSIS

None.

7.8. PNEUMONIA DUE TO COVID-19 (#11a and #11b)

7.8.1.ESTIMANDS

Objective	Estimand
To determine if BCG vaccination compared with placebo reduces the incidence of pneumonia due to COVID-19 in the absence of a COVID vaccine, measured over 6 months following randomisation in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 11a.1** Population: mITT population Outcome: **pneumonia due to COVID-19 by 6 months** Interventions: BCG vs Placebo Handling of Intercurrent events: - COVID-19 specific vaccine (Hypothetical Strategy) - any other vaccine (Treatment Policy strategy) Summary Measure: Adjusted* difference in proportion of participants
To determine if BCG vaccination compared with placebo reduces the incidence of pneumonia due to COVID-19 in the absence of a COVID vaccine, measured over 12 months following randomisation in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 11b.1** Population: mITT population Outcome: **pneumonia due to COVID-19 by 6 months by 12 months** Interventions: BCG vs Placebo Handling of Intercurrent events: - COVID-19 specific vaccine (Hypothetical Strategy) - any other vaccine (Treatment Policy strategy) Summary Measure: Adjusted* difference in proportion of participants
To determine if BCG vaccination compared with placebo reduces the incidence of pneumonia due to COVID-19 irrespective of receiving a COVID-19 specific vaccine or any other vaccine, measured over 6 months following randomisation in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 11a.2** Population: as 11a.1 Outcome: as 11a.1 Interventions: as 11a.1 Handling of Intercurrent events: - COVID-19 specific vaccine (**Treatment Policy strategy**) - any other vaccine (Treatment Policy strategy) Summary Measure: as 11a.1
To determine if BCG vaccination compared with placebo reduces the incidence of pneumonia due to COVID-19 irrespective of receiving a COVID-19 specific vaccine or any other vaccine, measured over 12 months following randomisation in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 11b.2** Population: as 11b.1 Outcome: as 11b.1 Interventions: as 11b.1 Handling of Intercurrent events: - COVID-19 specific vaccine (**Treatment Policy strategy**) - any other vaccine (Treatment Policy strategy) Summary Measure: as 11b.1
To determine if BCG vaccination compared with placebo reduces the incidence of pneumonia due to COVID-19 illness in the absence of any vaccine, measured over 6 months following randomisation in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 11a.3** Population: as 11a.1 Outcome: as 11a.1 Interventions: as 11a.1 Handling of Intercurrent events: - COVID-19 specific vaccine (Hypothetical Strategy) - any other vaccine (**Hypothetical Strategy**) Summary Measure: as 11a.1

Objective	Estimand
To determine if BCG vaccination compared with placebo reduces the incidence of pneumonia due to COVID-19 in the absence of any vaccine, measured over 12 months following randomisation in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 11b.3** Population: as 11b.1 Outcome: as 11b.1 Interventions: as 11b.1 Handling of Intercurrent events: - COVID-19 specific vaccine (Hypothetical Strategy) - any other vaccine (**Hypothetical Strategy**) Summary Measure: as 11b.1
** 1) adjusted for stratification factors used at randomisation (age group, presence of comorbidity, and geographical location)*	

7.8.2.ANALYSIS

Absolute and relative frequencies of pneumonia prior to 6/12 months will be presented by intervention group. The outcome will be compared between the BCG group and the placebo group using a difference in proportions estimated using the same time-to-event analysis approach adopted for primary outcomes 1 and 2 (flexible parametric survival model), adjusted by the stratification factors used at randomisation. A two-sided bias-corrected 95% CI for the difference in proportion (BCG – Control) and a bootstrap p-value will be calculated with bootstrap standard errors. A Kaplan-Meier survival curve will also be presented by treatment arm for descriptive purposes.
For participants that meet the outcome the date of the first day with symptoms associated to a symptomatic/severe COVID-19 event will be taken as the outcome. Participants who did not have COVID-19 within the first 6/12 months on the study will be censored according to the same rules used for the censoring of primary outcomes 1 and 2 (section 6.2.3).

Should the overall number of pneumonia events be so small that the analysis model described has computational difficulties, the outcome will be analysed using the Cox's proportional hazards model, adjusted for the stratification factors used during randomisation (age group, presence of comorbidity, geographical location -Europe/Australia/South America), and presented as the hazard ratio rather than the difference in proportion.

The analysis will be adjusted for the stratification factors only if a minimum number of events is observed, namely 1 event per strata per intervention group.

7.8.3.ADDITIONAL ANALYSIS

None.

7.8.4.SUBGROUP ANALYSIS

None.

7.9. NEED OF OXYGEN DUE TO COVID-19 (#12a and #12b)

7.9.1.ESTIMANDS

Objective	Estimand
To determine if BCG vaccination compared with placebo reduces the need for oxygen therapy due to COVID-19 in the absence of a COVID vaccine, measured over 6 months following randomisation in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 12a.1** Population: mITT population Outcome: **need of oxygen therapy due to COVID-19 by 6 months** Interventions: BCG vs Placebo Handling of Intercurrent events: - COVID-19 specific vaccine (Hypothetical Strategy) - any other vaccine (Treatment Policy strategy) Summary Measure: Adjusted* difference in proportion of participants

Objective	Estimand
To determine if BCG vaccination compared with placebo reduces the need for oxygen therapy due to COVID-19 in the absence of a COVID vaccine, measured over 12 months following randomisation in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 12b.1** Population: mITT population Outcome: **need of oxygen therapy due to COVID-19 by 12 months** Interventions: BCG vs Placebo Handling of Intercurrent events: - COVID-19 specific vaccine (Hypothetical Strategy) - any other vaccine (Treatment Policy strategy) Summary Measure: Adjusted* difference in proportion of participants
To determine if BCG vaccination compared with placebo reduces the need for oxygen therapy due to COVID-19 irrespective of receiving a COVID-19 specific vaccine or any other vaccine, measured over 6 months following randomisation in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 12a.2** Population: as 12a.1 Outcome: as 12a.1 Interventions: as 12a.1 Handling of Intercurrent events: - COVID-19 specific vaccine (**Treatment Policy strategy**) - any other vaccine (Treatment Policy strategy) Summary Measure: as 12a.1
To determine if BCG vaccination compared with placebo reduces the need for oxygen therapy due to COVID-19 irrespective of receiving a COVID-19 specific vaccine or any other vaccine, measured over 12 months following randomisation in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 12b.2** Population: as 12b.1 Outcome: as 12b.1 Interventions: as 12b.1 Handling of Intercurrent events: - COVID-19 specific vaccine (**Treatment Policy strategy**) - any other vaccine (Treatment Policy strategy) Summary Measure: as 12b.1
To determine if BCG vaccination compared with placebo reduces the need for oxygen therapy due to COVID-19 illness in the absence of any vaccine, measured over 6 months following randomisation in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 12a.3** Population: as 12a.1 Outcome: as 12a.1 Interventions: as 12a.1 Handling of Intercurrent events: - COVID-19 specific vaccine (Hypothetical Strategy) - any other vaccine (**Hypothetical Strategy**) Summary Measure: as 12a.1
To determine if BCG vaccination compared with placebo reduces the need for oxygen therapy due to COVID-19 in the absence of any vaccine, measured over 12 months following randomisation in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 12b.3** Population: as 12b.1 Outcome: as 12b.1 Interventions: as 12b.1 Handling of Intercurrent events: - COVID-19 specific vaccine (Hypothetical Strategy) - any other vaccine (**Hypothetical Strategy**) Summary Measure: as 12b.1
** 1) adjust by stratification factors used at randomisation;*	

7.9.2.ANALYSIS

As per section 7.8.2.

7.9.3.ADDITIONAL ANALYSIS

On the subset of participants who needed oxygen due to severe COVID-19, the mean and standard deviation (or median and IQR if not normally distributed) of the duration of oxygen therapy will be calculated and presented by intervention group.

7.9.4.SUBGROUP ANALYSIS

None.

7.10. ADMISSION TO CRITICAL CARE DUE TO COVID-19 (#13a and #13b)

7.10.1. ESTIMANDS

Objective	Estimand
To determine if BCG vaccination compared with placebo reduces admission to critical care DUE TO COVID-19 in the absence of a COVID vaccine, measured over 6 months following randomisation in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 13a.1** Population: mITT population Outcome: **admission to critical care due to COVID-19 by 6 months** Interventions: BCG vs Placebo Handling of Intercurrent events: - COVID-19 specific vaccine (Hypothetical Strategy) - any other vaccine (Treatment Policy strategy) Summary Measure: Adjusted* difference in proportion of participants
To determine if BCG vaccination compared with placebo reduces admission to critical care DUE TO COVID-19 in the absence of a COVID vaccine, measured over 12 months following randomisation in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 13b.1** Population: mITT population Outcome: **admission to critical care due to COVID-19 by 12 months** Interventions: BCG vs Placebo Handling of Intercurrent events: - COVID-19 specific vaccine (Hypothetical Strategy) - any other vaccine (Treatment Policy strategy) Summary Measure: Adjusted* difference in proportion of participants
To determine if BCG vaccination compared with placebo reduces admission to critical care due to COVID-19 irrespective of receiving a COVID-19 specific vaccine or any other vaccine, measured over 6 months following randomisation in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 13a.2** Population: as 13a.1 Outcome: as 13a.1 Interventions: as 13a.1 Handling of Intercurrent events: - COVID-19 specific vaccine (**Treatment Policy strategy**) - any other vaccine (Treatment Policy strategy) Summary Measure: as 13a.1
To determine if BCG vaccination compared with placebo reduces admission to critical care due to COVID-19 irrespective of receiving a COVID-19 specific vaccine or any other vaccine, measured over 12 months following randomisation in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 13b.2** Population: as 13b.1 Outcome: as 13b.1 Interventions: as 13b.1 Handling of Intercurrent events: - COVID-19 specific vaccine (**Treatment Policy strategy**) - any other vaccine (Treatment Policy strategy) Summary Measure: as 13b.1
To determine if BCG vaccination compared with placebo reduces admission to critical care due to COVID-19 illness in the absence of any vaccine, measured over 6 months following randomisation in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 13a.3** Population: as 13a.1 Outcome: as 13a.1 Interventions: as 13a.1 Handling of Intercurrent events: - COVID-19 specific vaccine (Hypothetical Strategy)

Objective	Estimand
	- any other vaccine (**Hypothetical Strategy**) Summary Measure: as 13a.1
To determine if BCG vaccination compared with placebo reduces admission to critical care due to COVID-19 in the absence of any vaccine, measured over 12 months following randomisation in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 13b.3** Population: as 13b.1 Outcome: as 13b.1 Interventions: as 13b.1 Handling of Intercurrent events: - COVID-19 specific vaccine (Hypothetical Strategy) - any other vaccine (**Hypothetical Strategy**) Summary Measure: as 13b.1
** 1) adjust by stratification factors used at randomisation;*	

7.10.2. PRIMARY ANALYSIS

As per section 7.8.2.

7.10.3. ADDITIONAL ANALYSIS

In the those of participants who were admitted to critical care due to severe COVID-19, the mean and standard deviation (or median and IQR if distribution is skewed) of the duration of critical care will be calculated and presented by intervention group.

7.10.4. SUBGROUP ANALYSIS

None.

7.11. NEED OF MECHANICAL VENTILATION DUE TO COVID-19 (#14a and #14b)

7.11.1. ESTIMANDS

Objective	Estimand
To determine if BCG vaccination compared with placebo reduces the need of mechanical ventilation due to COVID-19 in the absence of a COVID vaccine, measured over 6 months following randomisation in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 14a.1** Population: mITT population Outcome: **need of mechanical ventilation due to COVID-19 by 6 months** Interventions: BCG vs Placebo Handling of Intercurrent events: - COVID-19 specific vaccine (Hypothetical Strategy) - any other vaccine (Treatment Policy strategy) Summary Measure: Adjusted* difference in proportion of participants
To determine if BCG vaccination compared with placebo reduces the need of mechanical ventilation DUE TO COVID-19 in the absence of a COVID vaccine, measured over 12 months following randomisation in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 14b.1** Population: mITT population Outcome: **need of mechanical ventilation due to COVID-19 by 12 months** Interventions: BCG vs Placebo Handling of Intercurrent events: - COVID-19 specific vaccine (Hypothetical Strategy) - any other vaccine (Treatment Policy strategy) Summary Measure: Adjusted* difference in proportion of participants
To determine if BCG vaccination compared with placebo reduces the need of mechanical ventilation due to COVID-19 irrespective of receiving a COVID-19 specific vaccine or any other vaccine, measured over 6 months following randomisation in healthcare workers who did not have a previous	**Estimand 14a.2** Population: as 14a.1 Outcome: as 14a.1 Interventions: as 14a.1 Handling of Intercurrent events: - COVID-19 specific vaccine (**Treatment Policy strategy**)

Objective	Estimand
SARS-CoV-2 positive test result when assessed at time of randomisation.	- any other vaccine (Treatment Policy strategy) Summary Measure: as 14a.1
To determine if BCG vaccination compared with placebo reduces the need of mechanical ventilation due to COVID-19 irrespective of receiving a COVID-19 specific vaccine or any other vaccine, measured over 12 months following randomisation in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 14b.2** Population: as 14b.1 Outcome: as 14b.1 Interventions: as 14b.1 Handling of Intercurrent events: - COVID-19 specific vaccine (**Treatment Policy strategy**) - any other vaccine (Treatment Policy strategy) Summary Measure: as 14b.1
To determine if BCG vaccination compared with placebo reduces the need of mechanical ventilation due to COVID-19 illness in the absence of any vaccine, measured over 6 months following randomisation in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 14a.3** Population: as 14a.1 Outcome: as 14a.1 Interventions: as 14a.1 Handling of Intercurrent events: - COVID-19 specific vaccine (Hypothetical Strategy) - any other vaccine (**Hypothetical Strategy**) Summary Measure: as 14a.1
To determine if BCG vaccination compared with placebo reduces the need of mechanical ventilation due to COVID-19 in the absence of any vaccine, measured over 12 months following randomisation in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 14b.3** Population: as 14b.1 Outcome: as 14b.1 Interventions: as 14b.1 Handling of Intercurrent events: - COVID-19 specific vaccine (Hypothetical Strategy) - any other vaccine (**Hypothetical Strategy**) Summary Measure: as 14b.1
** 1) adjust by stratification factors used at randomisation;*	

7.11.2. ANALYSIS

As per section 7.8.2.

7.11.3. ADDITIONAL ANALYSIS

In participants who needed MV due to severe COVID-19, the mean and standard deviation (or median and IQR if distribution is skewed) of the duration of critical care will be calculated and presented by intervention group.

7.11.4. SUBGROUP ANALYSIS

None.

7.12. HOSPITALISATION DUE TO COVID-19 (#15a and #15b)

7.12.1. ESTIMANDS

Objective	Estimand
To determine if BCG vaccination compared with placebo reduces the incidence of hospitalisation due to COVID-19 in the absence of a COVID vaccine, measured over 6 months following randomisation in	**Estimand 15a.1** Population: mITT population Outcome: **hospitalisation due to COVID-19 by 6 months**

Objective	Estimand
healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	Interventions: BCG vs Placebo Handling of Intercurrent events: - COVID-19 specific vaccine (Hypothetical Strategy) - any other vaccine (Treatment Policy strategy) Summary Measure: Adjusted* difference in proportion of participants
To determine if BCG vaccination compared with placebo reduces the incidence of hospitalisation due to COVID-19 in the absence of a COVID vaccine, measured over 12 months following randomisation in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 15b.1** Population: mITT population Outcome: **hospitalisation due to COVID-19 by 12 months** Interventions: BCG vs Placebo Handling of Intercurrent events: - COVID-19 specific vaccine (Hypothetical Strategy) - any other vaccine (Treatment Policy strategy) Summary Measure: Adjusted* difference in proportion of participants
To determine if BCG vaccination compared with placebo reduces the incidence of hospitalisation due to COVID-19irrespective of receiving a COVID-19 specific vaccine or any other vaccine, measured over 6 months following randomisation in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 15a.2** Population: as 15a.1 Outcome: as 15a.1 Interventions: as 15a.1 Handling of Intercurrent events: - COVID-19 specific vaccine (**Treatment Policy strategy**) - any other vaccine (Treatment Policy strategy) Summary Measure: as 15a.1
To determine if BCG vaccination compared with placebo reduces the incidence of hospitalisation due to COVID-19 irrespective of receiving a COVID-19 specific vaccine or any other vaccine, measured over 12 months following randomisation in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 15b.2** Population: as 15b.1 Outcome: as 15b.1 Interventions: as 15b.1 Handling of Intercurrent events: - COVID-19 specific vaccine (**Treatment Policy strategy**) - any other vaccine (Treatment Policy strategy) Summary Measure: as 15b.1
To determine if BCG vaccination compared with placebo reduces the incidence of hospitalisation due to COVID-19 illness in the absence of any vaccine, measured over 6 months following randomisation in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 15a.3** Population: as 15a.1 Outcome: as 15a.1 Interventions: as 15a.1 Handling of Intercurrent events: - COVID-19 specific vaccine (Hypothetical Strategy) - any other vaccine (**Hypothetical Strategy**) Summary Measure: as 15a.1
To determine if BCG vaccination compared with placebo reduces the incidence of hospitalisation due to COVID-19 in the absence of any vaccine, measured over 12 months following randomisation in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 15b.3** Population: as 15b.1 Outcome: as 15b.1 Interventions: as 15b.1 Handling of Intercurrent events: - COVID-19 specific vaccine (Hypothetical Strategy) - any other vaccine (**Hypothetical Strategy**) Summary Measure: as 15b.1
** 1) adjust by stratification factors used at randomisation;*	

7.12.2. ANALYSIS

As per section 7.8.2.

7.12.3. ADDITIONAL ANALYSIS

In participants who were admitted to hospital due to COVID-19, the mean and standard deviation (or median and IQR if not normally distributed) of the hospital stay will be calculated and presented by intervention group.

7.12.4. SUBGROUP ANALYSIS

None.

7.13. DEATH DUE TO COVID-19 (#16a and #16b)

7.13.1. ESTIMANDS

Objective	Estimand
To determine if BCG vaccination compared with placebo reduces the incidence of death due to COVID-19 in the absence of a COVID vaccine, measured over 6 months following randomisation in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 16a.1** Population: mITT population Outcome: **death due to COVID-19 by 6 months** Interventions: BCG vs Placebo Handling of Intercurrent events: - COVID-19 specific vaccine (Hypothetical Strategy) - any other vaccine (Treatment Policy strategy) Summary Measure: Adjusted* difference in proportion of participants
To determine if BCG vaccination compared with placebo reduces the incidence of death due to COVID-19 in the absence of a COVID vaccine, measured over 12 months following randomisation in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 16b.1** Population: mITT population Outcome: **death due to COVID-19 by 12 months** Interventions: BCG vs Placebo Handling of Intercurrent events: - COVID-19 specific vaccine (Hypothetical Strategy) - any other vaccine (Treatment Policy strategy) Summary Measure: Adjusted* difference in proportion of participants
To determine if BCG vaccination compared with placebo reduces the incidence of death due to COVID-19irrespective of receiving a COVID-19 specific vaccine or any other vaccine, measured over 6 months following randomisation in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 16a.2** Population: as 16a.1 Outcome: as 16a.1 Interventions: as 16a.1 Handling of Intercurrent events: - COVID-19 specific vaccine (**Treatment Policy strategy**) - any other vaccine (Treatment Policy strategy) Summary Measure: as 16a.1
To determine if BCG vaccination compared with placebo reduces the incidence of death due to COVID-19 irrespective of receiving a COVID-19 specific vaccine or any other vaccine, measured over 12 months following randomisation in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 16b.2** Population: as 16b.1 Outcome: as 16b.1 Interventions: as 16b.1 Handling of Intercurrent events: - COVID-19 specific vaccine (**Treatment Policy strategy**) - any other vaccine (Treatment Policy strategy) Summary Measure: as 16b.1

Objective	Estimand
To determine if BCG vaccination compared with placebo reduces the incidence of death due to COVID-19 illness in the absence of any vaccine, measured over 6 months following randomisation in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 16a.3** Population: as 16a.1 Outcome: as 16a.1 Interventions: as 16a.1 Handling of Intercurrent events: - COVID-19 specific vaccine (Hypothetical Strategy) - any other vaccine (**Hypothetical Strategy**) Summary Measure: as 16a.1
To determine if BCG vaccination compared with placebo reduces the incidence of death due to COVID-19 in the absence of any vaccine, measured over 12 months following randomisation in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 16b.3** Population: as 16b.1 Outcome: as 16b.1 Interventions: as 16b.1 Handling of Intercurrent events: - COVID-19 specific vaccine (Hypothetical Strategy) - any other vaccine (**Hypothetical Strategy**) Summary Measure: as 16b.1
** 1) adjust by stratification factors used at randomisation;*	

7.13.2. ANALYSIS

Same as per 7.8.2.

7.13.3. ADDITIONAL ANALYSIS

None.

7.13.4. SUBGROUP ANALYSIS

None.

8. NON-COVID19 RELATED SECONDARY OUTCOMES

For these secondary outcomes, these intercurrent events will be handled using a treatment policy strategy, and all outcome data will be used regardless of occurrence of the intercurrent event. In a secondary analysis, the intercurrent events of receiving any vaccine (including a COVID-19-specific vaccine) will be handled using a Hypothetical Strategy; participants who receive any vaccine (including a COVID-19-specific vaccine) will have their data used up to the date of their first dose of vaccine (data collected after the first dose of the vaccine will be ignored).

The analyses of these secondary outcomes will be conducted on the ITT population including only Stage 2 participants. No subgroup analyses for any of these outcomes are planned.

8.1. FEVER OR RESPIRATORY ILLNESS (#17)

8.1.1. ESTIMANDS

Objective	Estimand
To determine if BCG vaccination compared with placebo reduces the incidence of fever or respiratory illness irrespective of receiving any vaccine (including COVID-19 specific vaccine), over the 12 months following randomisation, in healthcare workers exposed to SARS-CoV-2.	**Estimand 17.1** Population: ITT population Outcome: fever or respiratory illness by 12 months Interventions: BCG vs Placebo Handling of Intercurrent events: - any vaccine, including COVID-19 specific vaccine (**Treatment Policy strategy**) Summary Measure: Adjusted difference in proportion of participants

Objective	Estimand
To determine if BCG vaccination compared with placebo reduces the incidence of fever or respiratory illness in the absence of any vaccine (including COVID-19 specific vaccine), over the 12 months following randomisation, in healthcare workers exposed to SARS-CoV-2.	**Estimand 17.2** Population: ITT population Outcome: fever or respiratory illness by 12 months Interventions: BCG vs Placebo Handling of Intercurrent events: - any vaccine, including COVID-19 specific vaccine (**Hypothetical strategy**) Summary Measure: Adjusted difference in proportion of participants

8.1.2.ANALYSIS

The outcome of respiratory or febrile illness prior to 12 months will be described by intervention group as the absolute number of participants with the event.
The numbers of participants whose follow-up data is censored due to:

- incomplete data entry,
- drop-out from the study, and
- intercurrent event (any vaccine, including COVID-19 specific vaccine) (for estimand 17.2 only)

will also be reported separately by intervention group.

Participants with complete data entry (i.e. complete APP weekly data and/or survey data) will be censored:

- (for estimand 17.1) at the 12 months follow-up or 12 months unless the definition of the outcome is met and precedes this date.
- (for estimand 17.2) at the earlier of their first dose of any vaccine given during the 12 months follow-up or 12 months unless the definition of the outcome is met and precedes both of these dates.

Participants with incomplete data entry (i.e. incomplete APP weekly data and incomplete survey data) will be censored at the earlier of:

- their first dose of any vaccine given during the 12 months follow-up (for estimand 17.2 only) or
- their last entered date prior to which there are more than 3 consecutive days of missing data following the last

unless the definition of the outcome is met and precedes both of these dates.

When the definition of the outcome is met, the first day with symptoms for the first episode of fever or respiratory illness will be used in the analysis.

The analysis of this outcome will be conducted as for the primary analysis of the primary outcome 1 and 2 (as presented in section 6.2.2). This outcome will be compared between the BCG group and the placebo group using a difference in proportions. This will be estimated using a time-to-event analysis adjusted for stratification factors used in randomisation, with the survival curve for each combination of strata and randomised group calculated using a flexible parametric survival model (Royston-Parmar model[2]).
A Kaplan-Meier survival curve will also be presented by treatment arm.

8.2. SEVERE FEVER OR RESPIRATORY ILLNESS (#18)

8.2.1. ESTIMANDS

Objective	Estimand
To determine if BCG vaccination compared with placebo reduces the incidence of severe fever or respiratory illness irrespective of receiving any vaccine (including COVID-19 specific vaccine), over	**Estimand 18.1** Population: ITT population Outcome: severe fever or respiratory illness by 12 months Interventions: BCG vs Placebo

Objective	Estimand
the 12 months following randomisation, in healthcare workers exposed to SARS-CoV-2.	Handling of Intercurrent events: - any vaccine, including COVID-19 specific vaccine (**Treatment Policy strategy**) Summary Measure: Adjusted difference in proportion of participants
To determine if BCG vaccination compared with placebo reduces the incidence of severe fever or respiratory illness in the absence of any vaccine (including COVID-19 specific vaccine), over the 12 months following randomisation, in healthcare workers exposed to SARS-CoV-2.	**Estimand 18.2** Population: ITT population Outcome: severe fever or respiratory illness by 12 months Interventions: BCG vs Placebo Handling of Intercurrent events: - any vaccine, including COVID-19 specific vaccine (**Hypothetical strategy**) Summary Measure: Adjusted difference in proportion of participants

8.2.2.ANALYSIS

As per section 8.1.2

8.3. NUMBER OF EPISODES OF FEVER OR RESPIRATORY ILLNESS (#19)

8.3.1. ESTIMANDS

Objective	Estimand
To determine if BCG vaccination compared with placebo reduces the number of fever or respiratory illness irrespective of receiving any vaccine (including COVID-19 specific vaccine), over the 12 months following randomisation, in healthcare workers exposed to SARS-CoV-2.	**Estimand 19.1** Population: ITT population Outcome: number of fever or respiratory illness by 12 months Interventions: BCG vs Placebo Handling of Intercurrent events: - any vaccine, including COVID-19 specific vaccine (**Treatment Policy strategy**) Summary Measure: difference in the expected counts
To determine if BCG vaccination compared with placebo reduces the number of fever or respiratory illness in the absence of any vaccine (including COVID-19 specific vaccine), over the 12 months following randomisation, in healthcare workers exposed to SARS-CoV-2.	**Estimand 19.2** Population: ITT population Outcome: number of fever or respiratory illness by 12 months Interventions: BCG vs Placebo Handling of Intercurrent events: - any vaccine, including COVID-19 specific vaccine (**Hypothetical strategy**) Summary Measure: difference in the expected counts

8.3.1. ANALYSIS

Median and IQR of the number of episodes will be calculated and presented by intervention group.
The difference between the BCG and Placebo groups in the number of episodes and its 95%CI will be estimated using a Zero-Inflated Negative Binomial (ZINB) model, adjusted by the stratification factors used at randomisation (Geographical Location (Australia/Europe/South America, age group and presence of comorbidity). For further details on the ZINB model refer to section 7.3.2. Particularly the *exposure()* option will be used to indicate the number of days elapsed from the date of randomisation to:

- the date of the 12 months follow-up (for estimand 19.1), or the date of 12 months follow-up or date of first dose of any vaccine, whichever is earlier, (for estimand 19.2)for those participants with complete data entry
- the date of 3 consecutive days of missing data with the participant (for estimand 19.1), or the first date of 3 consecutive days of missing data or date of first dose of any vaccine, whichever is earliest, (for estimand 19.2) for those participants with incomplete data entry

8.4. NUMBER OF DAYS UNABLE TO WORK DUE TO FEVER OR RESPIRATORY ILLNESS (#20)

8.4.1. ESTIMANDS

Objective	Estimand
To determine if BCG vaccination compared with placebo reduces the number of days unable to work due to fever or respiratory illness irrespective of receiving any vaccine (including COVID-19 specific vaccine), over the 12 months following randomisation, in healthcare workers exposed to SARS-CoV-2.	**Estimand 20.1** Population: ITT population Outcome: number days unable to work due to fever or respiratory illness by 12 months Interventions: BCG vs Placebo Handling of Intercurrent events: - any vaccine, including COVID-19 specific vaccine (**Treatment Policy strategy**) Summary Measure: as for estimand 20.1
To determine if BCG vaccination compared with placebo reduces the number of days unable to work due to fever or respiratory illness in the absence of any vaccine (including COVID-19 specific vaccine), over the 12 months following randomisation, in healthcare workers exposed to SARS-CoV-2.	**Estimand 20.1** Population: ITT population Outcome: number days unable to work due to fever or respiratory illness by 12 months Interventions: BCG vs Placebo Handling of Intercurrent events: - any vaccine, including COVID-19 specific vaccine (**Hypothetical strategy**) Summary Measure: difference in the expected counts

8.4.2. ANALYSIS

As per section 8.3.1.

8.5. NUMBER OF DAYS CONFINED TO BED DUE TO FEVER OR RESPIRATORY ILLNESS (#21)

8.5.1. ESTIMANDS

Objective	Estimand
To determine if BCG vaccination compared with placebo reduces the number of days confined to bed due to fever or respiratory illness irrespective of receiving any vaccine (including COVID-19 specific vaccine), over the 12 months following randomisation, in healthcare workers exposed to SARS-CoV-2.	**Estimand 21.1** Population: as for estimand 21.1 Outcome: as for estimand 21.1 Interventions: as for estimand 21.1 Handling of Intercurrent events: - any vaccine, including COVID-19 specific vaccine (**Treatment Policy strategy**) Summary Measure: as for estimand 21.1
To determine if BCG vaccination compared with placebo reduces the number of days confined to bed due to fever or respiratory illness in the absence of any vaccine (including COVID-19 specific vaccine), over the 12 months following randomisation, in healthcare workers exposed to SARS-CoV-2.	**Estimand 21.2** Population: ITT population Outcome: number days confined to bed due fever or respiratory illness by 12 months Interventions: BCG vs Placebo Handling of Intercurrent events: - any vaccine, including COVID-19 specific vaccine (**Hypothetical strategy**) Summary Measure: difference in the expected counts

8.5.2. ANALYSIS

As per section 8.3.1.

8.6. NUMBER OF DAYS WITH SYMPTOMS DUE TO FEVER OR RESPIRATORY ILLNESS (#22)

8.6.1. ESTIMANDS

Objective	Estimand
To determine if BCG vaccination compared with placebo reduces the number of days with symptoms due to fever or respiratory illness irrespective of receiving any vaccine (including COVID-19 specific vaccine), over the 12 months following randomisation, in healthcare workers exposed to SARS-CoV-2.	**Estimand 22.1** Population: ITT population Outcome: number days with symptoms due fever or respiratory illness by 12 months Interventions: BCG vs Placebo Handling of Intercurrent events: - any vaccine, including COVID-19 specific vaccine (**Treatment Policy strategy**) Summary Measure: as for estimand 22.1
To determine if BCG vaccination compared with placebo reduces the number of days with symptoms due to fever or respiratory illness in the absence of any vaccine (including COVID-19 specific vaccine), over the 12 months following randomisation, in healthcare workers exposed to SARS-CoV-2.	**Estimand 22.2** Population: ITT population Outcome: number days with symptoms due fever or respiratory illness by 12 months Interventions: BCG vs Placebo Handling of Intercurrent events: - any vaccine, including COVID-19 specific vaccine (**Hypothetical strategy**) Summary Measure: difference in the expected counts

8.6.2. ANALYSIS

As per section 8.3.1.

8.7. PNEUMONIA (#23)

8.7.1.ESTIMANDS

Objective	Estimand
To determine if BCG vaccination compared with placebo reduces the incidence of pneumonia irrespective of receiving any other vaccine (including COVID-19 specific vaccine), over the 12 months following randomisation, in healthcare workers exposed to SARS-CoV-2.	**Estimand 23.1** Population: ITT population Outcome: pneumonia by 12 months Interventions: BCG vs Placebo Handling of Intercurrent events: - any vaccine, including COVID-19 specific vaccine (**Treatment policy**) Summary Measure: as for estimand 23.1
To determine if BCG vaccination compared with placebo reduces the incidence of pneumonia in the absence of any vaccine, including COVID-19 specific vaccine, measured over 12 months following randomisation in healthcare exposed to SARS-CoV-2.	**Estimand 23.2** Population: ITT population Outcome: pneumonia by 12 months Interventions: BCG vs Placebo Handling of Intercurrent events: - any vaccine, including COVID-19 specific vaccine (**Hypothetical strategy**) Summary Measure: Adjusted difference in proportion of participants

8.7.2.ANALYSIS

The absolute and relative frequencies of participants with the outcome prior to 12 months will be presented by intervention group. The outcome will be compared between the BCG group and the placebo group using a difference in proportions estimated using the same time-to-event analysis approach adopted for primary outcomes 1 and 2 (flexible parametric survival model). A two-sided bias-corrected 95% CI for the difference in proportion (BCG – Control) and a bootstrap p-value will be calculated with bootstrap standard errors. A Kaplan-Meier survival curve will also be presented by treatment arm for descriptive purposes.
For participants that meet the outcome the date of the first day with symptoms associated to a febrile or respiratory illness will be taken as the outcome. Participants who did not have pneumonia within 12 months will be censored according to the same rules used for the censoring of outcomes 17 (section 8.1.2).

Should the overall number of pneumonia events be so small that the analysis model described has computational difficulties, the outcome will be analysed using the Cox's proportional hazards model, adjusted for the stratification factors used during randomisation (age group, presence of comorbidity, geographical location -Europe/Australia/South America), and presented as the hazard ratio rather than the difference in proportion.

The analysis will be adjusted for the stratification factors only if a minimum number of events is observed, namely 1 event per strata per intervention group.

8.8. NEED OF OXYGEN (#23)

8.8.1.ESTIMANDS

Objective	Estimand
To determine if BCG vaccination compared with placebo reduces the need for oxygen therapy irrespective of receiving any other vaccine (including COVID-19 specific vaccine), over the 12 months following randomisation, in healthcare workers exposed to SARS-CoV-2.	**Estimand 24.1** Population: ITT population Outcome: need of oxygen therapy by 12 months Interventions: BCG vs Placebo Handling of Intercurrent events: - any vaccine, including COVID-19 specific vaccine (**Treatment Policy strategy**) Summary Measure: as for estimand 24.1
To determine if BCG vaccination compared with placebo reduces the need for oxygen therapy in the absence of any vaccine, measured over 12 months following randomisation in healthcare exposed to SARS-CoV-2.	**Estimand 24.2** Population: ITT population Outcome: need of oxygen therapy by 12 months Interventions: BCG vs Placebo Handling of Intercurrent events: - any vaccine, including COVID-19 specific vaccine (**Hypothetical strategy**) Summary Measure: Adjusted difference in proportion of participants

8.8.2.ANALYSIS

As per section 8.7.2.

8.9. ADMISSION TO CRITICAL CARE FOLLOWING A FEBRILE OR RESPIRATORY ILLNESS (#25)

8.9.1.ESTIMANDS

Objective	Estimand
To determine if BCG vaccination compared with placebo reduces admission to critical care following a febrile or respiratory illness irrespective of receiving any vaccine, including COVID-19 specific vaccine (including COVID-19 specific vaccine), over the 12 months following randomisation, in healthcare workers exposed to SARS-CoV-2.	**Estimand 25.1** Population: ITT population Outcome: admission to critical care following a febrile or respiratory illness by 12 months Interventions: BCG vs Placebo Handling of Intercurrent events: - any vaccine, including COVID-19 specific vaccine (**Treatment Policy strategy**) Summary Measure: as for estimand 25.1
To determine if BCG vaccination compared with placebo reduces admission to critical care following a febrile or respiratory illness in the absence of any vaccine, measured over 12 months following randomisation in healthcare exposed to SARS-CoV-2.	**Estimand 25.2** Population: ITT population Outcome: admission to critical care following a febrile or respiratory illness by 12 months Interventions: BCG vs Placebo Handling of Intercurrent events: - any vaccine, including COVID-19 specific vaccine (**Hypothetical strategy**) Summary Measure: Adjusted difference in proportion of participants

8.9.2.ANALYSIS

As per section 8.7.2.

Additionally, in the subgroups of participants who were admitted to critical care following a febrile or respiratory illness, the mean and standard deviation (or median and IQR if distribution is skewed) of the duration of critical care will be calculated and presented by intervention group.

8.10. NEED OF MV FOR A FEBRILE OR RESPIRATORY ILLNESS (#26)

8.10.1. ESTIMANDS

Objective	Estimand
To determine if BCG vaccination compared with placebo reduces Need of MV for a febrile or respiratory illness irrespective of receiving any vaccine, including COVID-19 specific vaccine , over the 12 months following randomisation, in healthcare workers exposed to SARS-CoV-2.	**Estimand 26.1** Population: ITT population Outcome: Need of MV for a febrile or respiratory illness by 12 months Interventions: BCG vs Placebo Handling of Intercurrent events: - any vaccine, including COVID-19 specific vaccine (**Treatment Policy strategy**) Summary Measure: as for estimand 26.1
To determine if BCG vaccination compared with placebo reduces the need of MV for a febrile or respiratory illness in the absence of any vaccine, measured over 12 months following randomisation in healthcare exposed to SARS-CoV-2.	**Estimand 26.2** Population: ITT population Outcome: Need of MV for a febrile or respiratory illness by 12 months Interventions: BCG vs Placebo Handling of Intercurrent events: - any vaccine, including COVID-19 specific vaccine (**Hypothetical strategy**) Summary Measure: Adjusted difference in proportion of participants

8.10.2. ANALYSIS

As per section 8.7.2.

Additionally, in the subgroup of participants who needed MV for a febrile or respiratory illness, the mean and standard deviation (or median and IQR if distribution is skewed) of the duration of MV will be calculated and presented by intervention group.

8.11. DEATH AS A CONSEQUENCE OF AN EPISODE OF FEVER OR RESPIRATORY ILLNESS (#27)

8.11.1. ESTIMANDS

Objective	Estimand
To determine if BCG vaccination compared with placebo reduces the incidence of death as a consequence of an episode of fever or respiratory illness irrespective of receiving any vaccine, including COVID-19 specific vaccine, measured over 12 months following randomisation in healthcare exposed to SARS-CoV-2.	**Estimand 27.1** Population: ITT population Outcome: death as a consequence of an episode of fever or respiratory illness by 12 months Interventions: BCG vs Placebo Handling of Intercurrent events: - any vaccine, including COVID-19 specific vaccine (**Treatment Policy strategy**) Summary Measure: as for estimand 27.1
To determine if BCG vaccination compared with placebo reduces the incidence of death as a consequence of an episode of fever or respiratory illness in the absence of receiving any vaccine, including COVID-19 specific vaccine, measured over 12 months following randomisation in healthcare exposed to SARS-CoV-2.	**Estimand 27.2** Population: ITT population Outcome: death as a consequence of an episode of fever or respiratory illness by 12 months Interventions: BCG vs Placebo Handling of Intercurrent events: - any vaccine, including COVID-19 specific vaccine (**Hypothetical strategy**) Summary Measure: Adjusted difference in proportion of participants

8.11.2. ANALYSIS

As per section 8.7.2.

8.12. HOSPITALISATION FOR AN EPISODE OF FEVER OR RESPIRATORY ILLNESS (#28)

8.12.1. ESTIMANDS

Objective	Estimand
To determine if BCG vaccination compared with placebo reduces the incidence of hospitalisation for an episode of fever or respiratory illness irrespective of receiving any vaccine, including COVID-19 specific vaccine, measured over 12 months following randomisation in healthcare exposed to SARS-CoV-2.	**Estimand 28.1** Population: ITT population Outcome: hospitalisation for an episode of fever or respiratory illness by 12 months Interventions: BCG vs Placebo Handling of Intercurrent events: - any vaccine, including COVID-19 specific vaccine (**Treatment Policy strategy**) Summary Measure: as for estimand 28.1
To determine if BCG vaccination compared with placebo reduces the incidence of hospitalisation for an episode of fever or respiratory illness in the absence of receiving any vaccine, including COVID-	**Estimand 28.2** Population: ITT population

Objective	Estimand
19 specific vaccine, measured over 12 months following randomisation in healthcare exposed to SARS-CoV-2.	Outcome: hospitalisation for an episode of fever or respiratory illness by 12 months Interventions: BCG vs Placebo Handling of Intercurrent events: - any vaccine, including COVID-19 specific vaccine (**Hypothetical strategy**) Summary Measure: Adjusted difference in proportion of participants

8.12.2. ANALYSIS

Same as per 8.7.2.

In the subset of participants who were admitted to hospital due to COVID-19, the mean and standard deviation (or median and IQR if not normally distributed) of the hospital stay will be calculated and presented by intervention group.

8.13. NUMBER OF DAYS OF UNPLANNED ABSENTEEISM FOR AN ACUTE ILLNESS OR HOSPITALISATION (#29a and #29b)

8.13.1. ESTIMANDS

Objective	Estimand
To determine if BCG vaccination compared with placebo reduces absenteeism, measured over 6 months following randomisation in healthcare workers who did not have a previous SARS-CoV-2 positive test result when assessed at time of randomisation.	**Estimand 29a.1** Population: mITT population Outcome: **Number of days of unplanned absenteeism for an acute illness or hospitalisation by 6 months** Interventions: BCG vs Placebo Handling of Intercurrent events: - any vaccine, including COVID-19 specific vaccine (Treatment Policy strategy) Summary Measure: Mean difference
To determine if BCG vaccination compared with placebo reduces absenteeism, measured over 6 months following randomisation in healthcare exposed to SARS-CoV-2.	**Estimand 29a.2** Population: **ITT population** Outcome: as for estimand 29a.1 Interventions: as for estimand 29a.1 Handling of Intercurrent events: - as for estimand 29a.1 Summary Measure: as for estimand 29a.1
To determine if BCG vaccination compared with placebo reduces absenteeism, measured over 12 months following randomisation in healthcare.	**Estimand 29b.1** Population: ITT population Outcome: **Number of days of unplanned absenteeism for an acute illness or hospitalisation by 12 months** Interventions: BCG vs Placebo Handling of Intercurrent events: - any vaccine, including COVID-19 specific vaccine (Treatment Policy strategy) Summary Measure: Mean difference

8.13.2. ANALYSIS

The median and IQR for the number of days of unplanned absenteeism for an acute illness or hospitalisation will be presented by arm.
The difference between BCG and placebo groups will be summarised as difference in the logs of expected number of days and its 95%CI estimated using a Zero-Inflated Negative Binomial (ZINB) model, adjusting for stratification factors. The analysis will be done using the zinb command in Stata, with the inflate() option. The inflate() option will be used to indicate whether the participant had one or more days of unplanned absenteeism for an acute illness or hospitalisation.

8.14. ADVERSE EVENTS and SERIOUS ADVERSE EVENTs

The number and proportion of participants with 1 or more adverse events over the 3 months following randomisation will be described overall as well as by type, severity (grade 0-4) and relationship to intervention. All results summaries will be presented by intervention group in the Safety population.

9. META-ANALYSIS

The data from the participants in the two stages of the trial will be combined in a meta-analysis for secondary analyses of all the non-COVID-19 outcomes.

The original trial plan included a meta-analysis of all the outcomes (both COVID-19- and non-COVID-19-related outcomes) combining data from Stage 1 and Stage 2 participants. However, in Stage 1 healthcare workers were recruited only in Victoria and Western Australia, both of which states had almost negligible COVID-19 exposure risk during the trial period (30th Mar 2020 to 13th May 2020). In light of this, the overwhelming majority of Stage 1 blood samples are likely to be seronegative. Moreover, with a low prevalence of COVID-19, there is a high probability that positive SARS-CoV-2 serology results are false positive. For these reasons, in December 2021 the BRACE team decided it was not justifiable to devote extra resources (time and costs) to the data cleaning of potential COVID-19 episodes and to testing SARS-CoV-2 serology for all participants in Stage 1. As a consequence, the meta-analysis will only be run on non-COVID-19 related outcomes and its main objective will be to determine if BCG vaccination compared with control reduces the rate and severity of febrile or other non-COVID-19 illness.

The analyses of these secondary non-COVID-19 outcomes will be the same as described in section 8 conducted on all Stage 1 and Stage 2 participants.

10. PLANNED ANALYSES

ANALYSIS OF THE 6 MONTHS COVID-19 OUTCOMES, Stage 2 participants

The first manuscript will include results from the analysis of the COVID-19-related outcomes collected in the first 6 months of each participant's participation in the trial and one non-COVID-19 related outcome at 6 months (29a). This analysis will include only participants recruited in Stage 2 of the trial.

ANALYSIS OF THE 12 MONTHS COVID-19 OUTCOMES, Stage 2 participants

A future manuscript will present results of the analyses of the COVID-19 related outcomes collected at 12 months. This analysis will include only participants recruited in Stage 2 of the trial.

ANALYSIS OF THE 12 MONTHS NON COVID-19 RELATED OUTCOMES (META ANALYSIS), Stages 1 and 2.

A future manuscript will present results of the analyses of all the non-COVID-19 related outcomes collected at 12 months. As addressed in section 9, this analysis will combine participants recruited in Stages 1 and 2 of the trial.

ANALYSIS OF THE EXPLORATORY OUTCOMES

A future manuscript will present results of the analyses of all the exploratory outcomes at 12 months combining participants recruited in Stages 1 and 2 of the trial.

11. REFERENCES

1. Pocock SJ. Group sequential methods in the design and analysis of clinical trials. Biometrika. 1977;64:191–199. [Google Scholar]

2. Royston P. Flexible Parametric Alternatives to the Cox Model: Update. The Stata Journal 2004; 4: 98-101. DOI:10.1177/1536867x0100400112.

3. Pittet LF, Messina NL, Gardiner K, Orsini F, Abruzzo V, Bannister S, Bonten M, Campbell JL, Croda J, Dalcolmo M, Elia S, Germano S, Goodall C, Gwee A, Jamieson T, Jardim B, Kollmann TR, Guimarães Lacerda MV, Lee KJ, Legge D, Lucas M, Lynn DJ, McDonald E, Manning L, Munns CF, Perrett KP, Prat Aymerich C, Richmond P, Shann F, Sudbury E, Villanueva P, Wood NJ, Lieschke K, Subbarao K, Davidson A, Curtis N; BRACE trial Consortium Group. BCG vaccination to reduce the impact of COVID-19 in healthcare workers: Protocol for a randomised controlled trial (BRACE trial). BMJ Open. 2021 Oct 28;11(10):e052101. doi:10.1136/bmjopen-2021-052101. PMID: 34711598; PMCID: PMC8557250.

12. SIGNATURES PAGE

Signature of Chief Principal Investigator:	Nigel Curtis Nigel Curtis (Aug 11, 2022 15:09 GMT+10)	Aug 11, 2022
Print Name	Prof. Nigel Curtis	Date
Signature of Trial Statistician:		Aug 11, 2022
Print Name	Dr Cecilia Moore	Date
Signature of Trial Statistician:	KJLee KJLee (Aug 11, 2022 16:56 GMT+10)	Aug 11, 2022
Print Name	Prof. Katherine Lee	Date

BRACE_SAP_V2.0 Date 10Aug2022 [CL]

Final Audit Report 2022-08-11

Created:	2022-08-11
By:	Thilanka Morawakage (thilanka.morawakage@mcri.edu.au)
Status:	Signed
Transaction ID:	CBJCHBCAABAAQEwaWeDJbYq-LL1p-W7nJCtPSekafM9p

"BRACE_SAP_V2.0 Date 10Aug2022 [CL]" History

Document created by Thilanka Morawakage (thilanka.morawakage@mcri.edu.au)
2022-08-11 - 4:32:47 AM GMT- IP address: 165.225.226.254

Document emailed to nigel.curtis@rch.org.au for signature
2022-08-11 - 4:34:17 AM GMT

Document emailed to cecilia.moore@mcri.edu.au for signature
2022-08-11 - 4:34:17 AM GMT

Document emailed to katherine.lee@mcri.edu.au for signature
2022-08-11 - 4:34:17 AM GMT

Email viewed by cecilia.moore@mcri.edu.au
2022-08-11 - 4:59:22 AM GMT- IP address: 89.184.212.227

Signer cecilia.moore@mcri.edu.au entered name at signing as Cecilia Moore
2022-08-11 - 5:00:49 AM GMT- IP address: 165.225.227.5

Document e-signed by Cecilia Moore (cecilia.moore@mcri.edu.au)
Signature Date: 2022-08-11 - 5:00:51 AM GMT - Time Source: server- IP address: 165.225.227.5

Email viewed by nigel.curtis@rch.org.au
2022-08-11 - 5:08:54 AM GMT- IP address: 203.16.41.5

Signer nigel.curtis@rch.org.au entered name at signing as Nigel Curtis
2022-08-11 - 5:09:08 AM GMT- IP address: 203.16.41.5

Document e-signed by Nigel Curtis (nigel.curtis@rch.org.au)
Signature Date: 2022-08-11 - 5:09:10 AM GMT - Time Source: server- IP address: 203.16.41.5

Email viewed by katherine.lee@mcri.edu.au
2022-08-11 - 6:55:31 AM GMT- IP address: 77.95.117.75

Signer katherine.lee@mcri.edu.au entered name at signing as KJLee

2022-08-11 - 6:55:59 AM GMT- IP address: 165.225.226.222

Document e-signed by KJLee (katherine.lee@mcri.edu.au)

Signature Date: 2022-08-11 - 6:56:01 AM GMT - Time Source: server- IP address: 165.225.226.222

Agreement completed.

2022-08-11 - 6:56:01 AM GMT