Project Brief: CROWN CORONATION (**C**OVID-19 **R**esearch **O**utcomes **W**orldwide **N**etwork for **CORONA**virus preven**tion**)

Full Title of Study/Programme	An international, Bayesian platform adaptive, randomized, placebo-controlled trial assessing the effectiveness of candidate interventions in preventing COVID-19 disease in adults
Technical Focus Area/Key Words	COVID-19, Infectious Diseases, Public Health
Rationale	A safe and effective vaccine against SARS-CoV-2 would be the ideal and hoped for solution to the COVID-19 pandemic. As such, vaccine development and testing are a top priority for stakeholders. However, despite all the resources and expertise invested in this effort, success is not guaranteed. Even if an effective SARS-CoV-2 is developed, it will still take many months to ramp up production to the extent that it can be rolled out across the globe. Furthermore, a vaccine might only have partial effectiveness and the immunity conferred might be short-lived. This proposal presents an alternative approach to boost the immune response to SARS-CoV-2 using the readily available, safe and well-established Measles, [Mumps] and Rubella (MR or MMR) vaccine. Administering the MR (or MMR) vaccine to those at risk for COVID-19 might boost immune response to SARS-CoV-2 in several ways, including by boosting the innate immune response.
Primary Objectives	To determine the effectiveness of MR (or MMR) vaccine in preventing symptomatic (i.e. any of the following: cough, shortness of breath or difficulty breathing, fever, chills, muscle pain, sore throat, new loss of taste or smell, nausea, vomiting, or diarrhoea), laboratory test-confirmed COVID-19 in adults with repeated exposures to SARS-CoV-2 by day 60 after receiving the trial intervention.
Secondary Objectives	1. To determine the effectiveness of MR (or MMR) vaccine in mitigating the severity of COVID-19 in adults who become infected with SARS-CoV-2 by day 60 after receiving the trial intervention. Severity will be graded on a simplified version of the ordinal WHO COVID-19 severity scale. 2. To determine the effectiveness of MR (or MMR) vaccine in preventing/reducing the incidence of SARS-CoV-2 infection (by serology) over up to 150 days of follow-up
Primary Endpoint/Outcome	Symptomatic COVID-19: Clinical diagnosis of COVID-19 with laboratory confirmation (i.e. based on viral PCR), and symptoms of COVID-19 (cough, shortness of breath or difficulty breathing, fever, chills, muscle pain, sore throat, new loss of taste or smell, nausea, vomiting, or diarrhoea) by day 60 after receiving trial intervention.
Secondary Endpoint/Outcome	The following secondary outcome is of special interest: Severity of COVID-19 over the study period i) Uninfected – no clinical or virologic evidence of infection (Score = 0) ii) Ambulatory – no limitation of activities (score=1) or with limitation (Score=2)

	iii) Hospitalized – mild no oxygen (Score=3) or with oxygen (Score=4), hospitalized severe – Score=5-7*, dead (Score=8) *Score 5 is non-invasive ventilation or high flow oxygen; Score 6 is intubation with mechanical ventilation; Score 7 is intubation with additional organ support (e.g. vasopressors, renal replacement therapy (RRT), extra corporeal membrane oxygenation [ECMO]). These outcome definitions are based on WHO R&D Blueprint consensus definitions for COVID-19. The study period refers to the 60 days following commencement of trial intervention and an additional 3 months of observation period of participants i.e. 150 days in total. The secondary clinical outcomes consist of: ● Primary endpoint, but instead of the 60-day time-window, over the course of the first 30 days of treatment; ● Symptomatic COVID-19 (with subsequent virological confirmation) during the 150-day study period; ● Incident COVID-19 during the 60-day study period, which includes asymptomatic infections identified by serology samples taken at the time-point of study exit.
Study Design	An international, multi-site, randomized, placebo-controlled, Bayesian platform clinical trial. Frequent interim analyses will be performed in a Bayesian manner to modify the trial early for overwhelming evidence of efficacy, futility or harm, using pre-specified thresholds.
Study arms	Currently 2 arms: MMR vaccine or placebo
Study population	Participants will include adults (18 years or older) who are at risk for contracting SARS-CoV-2 based on their work in hospitals or in the community.
Study sample size	The target sample size for the study in South Africa is 2500, of which 250 is targeted for Wits RHI Clinical Site.
Follow up/duration	● for 150 days from IMP administration; or ● until discontinuation of the participant's treatment arm. Participants who complete 60 days of follow up (primary outcome ascertainment) will be followed up for a further 3 months i.e. a total of 150 days (5 months) of participant follow-up.
Study/Programme sites	Ward 21 CRS, Johannesburg, South Africa and multiple other sites in South Africa and worldwide
Study/Programme duration	Estimated 1 year
Intervention	MR (or MMR) vaccine one 0.5 ml dose deep subcutaneous injection Placebo consists of 0.5 ml deep subcutaneous injection of sterile water or saline
Investigators	IOR: Prof Sinead Delany-Moretlwe Sub Investigators: Dr Darshnika Lakhoo, Dr Kim Comline
Other Partners & Collaborators	COVID-19 Therapeutics Accelerator Desmond Tutu HIV Foundation University of Cape Town

	University College London Comprehensive Clinician Trials Unit
Sponsors/Donors	Washington University School of Medicine in St Louis, United States of America Wits Reproductive Health & HIV Institute, a Division of WITS HEALTH CONSORTIUM (PTY) LTD
Linked Sub-studies	In planning phase
Publications/key presentations to date	None
Progress Update as at 09 March 2021	Screened: 106 Enrolled: 68
Overall Study/Project Contact	Prof Sinead Delany-Moretlwe (sdelany@wrhi.ac.za)
Briefing owner and date	Dr Darshnika Pemi Lakhoo (dlakhoo@wrhi.ac.za) 09 March 2021