International Journal of Clinical Trials
Usuf E et al. Int J Clin Trials. 2023 Feb;10(1):26-33
http://www.ijclinicaltrials.com
pISSN 2349-3240 | eISSN 2349-3259

DOI: https://dx.doi.org/10.18203/2349-3259.ijct20230048

Protocol

Prevention and treatment for COVID-19 associated severe pneumonia in the Gambia (PaTS-COVID-19), a single-blinded randomized clinical trial: study protocol

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Received: 18 July 2022
Revised: 21 November 2022
Accepted: 29 November 2022

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ABSTRACT

Background: The coronavirus disease (COVID-19) pandemic resulted in an unprecedent global response for the development of COVID-19 vaccines. However, as viral mutations continue to occur, potentially decreasing the efficacy of currently available vaccines, and inequity of vaccine access continues, identifying safe and effective drugs to minimise severity of COVID-19 disease remains a priority.
Methods: We designed an adaptive individually randomized single blinded non identical placebo-controlled trial to evaluate the safety and efficacy of repurposing licenced treatments for COVID-19 patients in an African setting. The trial has two cohorts: Cohort 1 recruits mild and moderate COVID-19 cases and their household contacts. Cases are actively followed up for 14 days, with a final visit at day 28. There are two co-primary endpoints: clinical progression to severe-pneumonia and persistence of the virus at day 14. The primary endpoint for household contacts is infection during a 14-day follow-up period. Cohort 2 recruits hospitalized patients with severe COVID-19 associated pneumonia followed up actively until discharge or death, and passively until day 90, with a final visit. The primary endpoint is clinical progression or death.
Conclusions: This randomized trial will contribute African-specific data to the global response to COVID-19. Besides the efficacy of drugs on clinical progression, the trial will provide information on the dynamics of intra-household transmission.
Trial registration: This study is registered with Clinical Trials.gov with registration number NCT04703608 and with Pan African clinical trials registry with registration number PACTR202101544570971.

Keywords: COVID-19, Mild- moderate- severe- pneumonia, Africa, Gambia, Ivermectin, Aspirin, Transmission

INTRODUCTION

The coronavirus disease (COVID-19), quickly spread to all continents with over 600 million cases and over 6.5 million deaths reported globally by October 2022.[1] The WHO African Region remains one of the least affected regions in the world, accounting for 2.5% of global cases and 3.0% of global deaths by mid-2021.[2] Half of the reported cases in Africa are from South Africa. In sub-Saharan Africa (SSA), the pandemic started later and, though robust data are lacking, some evidence suggest that the pandemic has progressed differently compared to rest of the world.[3,4] However, if transmission has been as intense as sero-prevalence surveys indicate, disease severity in SSA may indeed be lower than in other continents.[5] A younger population (6% of the population aged 60 years or more in SSA compared to 30% in Europe) may explain, only in part, the apparent lower mortality toll.[6] There has been a coordinated global effort to curtail the devastating impact of the COVID-19 pandemic by promoting research for interventions, including vaccines. This resulted in the licensure of several vaccines within just 18 months from the start of the pandemic. Although many countries have reached >80% coverage among the adult population, coverage in SSA has been disappointingly low. Beside vaccination, numerous drug trials are being carried out with the aim of providing therapeutic tools to minimize the COVID-19 burden on health systems and to reduce case fatality rates.[7] The RECOVERY trial, an adaptative trial implemented in the UK, showed lower mortality in hospitalized patients receiving low dose steroids. The intervention was quickly rolled out across the globe, despite the little information available on how this intervention would perform in Low- and Middle-Income Countries.[8,9] Countries in SSA would greatly benefit from context-specific effective treatments to manage the epidemic and care for severe cases. Most of these countries have health systems unable to cope with the increase in hospitalization demand. Therefore, we designed a single-blinded randomized drug trial aiming to address the different needs of the pandemic in the region: decrease the overall burden on health systems by decreasing transmission, decrease the mortality burden by decreasing progression towards severe disease and decrease mortality and utilisation of scarce resources (respiratory support) in severely ill patients.

Objectives

This trial has two categories of COVID-19 patients and four co-primary objectives: Cohort 1: Patients with COVID-19 associated mild disease/moderate pneumonia and their household (HH) contacts Index cases: To evaluate the efficacy of the investigation product (IP) in preventing, clinical progression and viral persistence by day 14. HH contacts: to evaluate the efficacy of the IP in preventing COVID-19 infection. Cohort 2: Patients with COVID-19 associated severe-pneumonia; to evaluate the efficacy of the IP in preventing clinical progression and death. Secondary objectives of current study were; Cohort 1: to evaluate the efficacy of the IP on viral persistence at day 4, time to clinical recovery, IgG titres at day 14 and day 28 and self-reported health and breathlessness at 28 days; to evaluate the efficacy of the IP among HH contacts on; prevalence of COVID-19 symptomatic disease (see definitions below) and viral persistence at day 14 among those infected. Cohort 2: to evaluate the efficacy of the IP on days of hospital admission, days of oxygen supplementation, mortality during hospitalization, and at 28 and 90 days, change in CRP and D-Dimer between baseline and day 3-5, occurrence of clinical thrombotic and embolic events, incidence of clinical episodes of gastrointestinal bleeding, persisting breathlessness at 28 and 90 days and self-reported health at 28 and 90 days. Additional observational exploratory objectives are the following: to determine prevalence of intestinal helminths (including *Strongyloides stercoralis*) among patients with mild/moderate or severe COVID-19 pneumonia, to assess the effect of ivermectin (IVM) on intestinal helminths (including *Strongyloides stercoralis*) and to evaluate intestinal helminth infections (including *Strongyloides stercoralis*) as a potential risk factor for COVID-19 severity.

METHODS

Trial design

This is an adaptative Phase 3, individually randomized single-blinded non-identical placebo-controlled trial with two cohorts. Cohort 1: Individuals with COVID-19 associated mild disease or moderate pneumonia. Cohort 2: Individuals with COVID-19 associated severe pneumonia. The design of the cohorts will be dynamic, meaning that the specific IP will be determined by the information available before or during the trial. All trial changes will receive ethical approval before implementation. For Cohort 1, patients will be randomly allocated to one of the three arms (ratio 1:1:1). HH contacts will be included in the study and treated according to the randomization of the index case (day of randomization is day 0), Arm 1: standard care (SC); HH contacts preventive package (PP), Arm 2: SC plus IP HH contacts-PP, Arm 3: SC plus IP HH contacts-IP. Before recruitment and randomization, study subjects and HH contacts will be asked to provide a written informed consent.

The IP in Cohort 1 is Ivermectin. If HH contacts progress to mild disease/moderate pneumonia during the follow-up period, they will be recruited into the Cohort 1 and included in the same arm of their index case. If Cohort 1 index cases are hospitalized or isolated outside of their HH, the HH members may not be included into the study. Individuals meeting criteria for COVID-19 associated severe pneumonia will be recruited into Cohort 2. They can be newly recruited participants or patients from Cohort 1. HH from Cohort 1 can also be recruited into

Cohort 2. Cohort 2 will have 2 arms (ratio 1:1): Arm 1: SC and Arm 2: SC + IP.

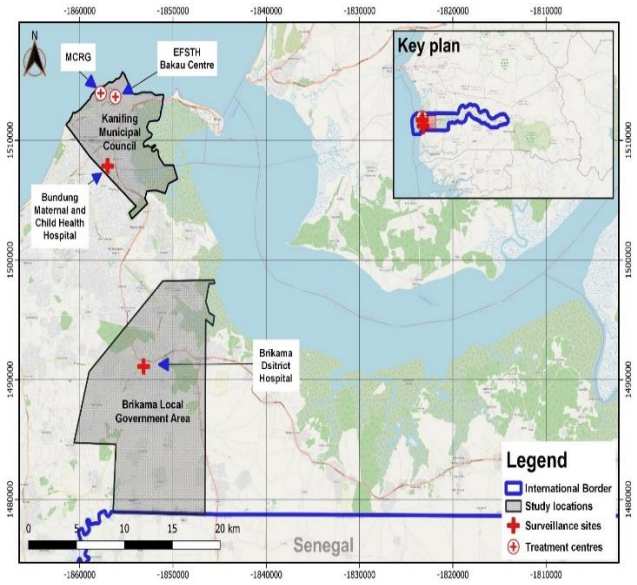

Figure 1: PaTS COVID-19 Study sites.

Study setting and context

The Gambia is surrounded by Senegal except for its coast on the Atlantic Ocean. Besides the designated official points of entry, borders are porous and difficult to monitor. The population is estimated at ˜2.4 million. There are 0.1 doctors per 1,000 population and 0.4 intensive care unit (ICU) beds per 100,000 population.[10] In 2020, the gross domestic product (GDP), following containment measures to limit COVID-19, contracted by 2.4% after growing 6.2% in 2019.[11]

Recruitment sites

Pre-COVID-19 test sites

We set up active surveillance at two public hospitals, i.e., Brikama District Hospital and Bundung maternity and child health hospital (Figure 1). At presentation, patients are screened for mild COVID-19 disease, moderate or severe pneumonia and invited to participate in the trial if they meet clinical criteria. For mild/moderate cases, consented individuals confirmed to be positive for COVID-19 by RT-PCR are recruited into Cohort 1, with follow-up at home or a treatment centre. Individuals with severe pneumonia at screening are tested after consent and if positive transferred to one of the two treatment centres for severe COVID-19 (Figure 1).

Post-COVID-19 test sites

Confirmed COVID-19 cases tested outside of the surveillance sites through the national testing services or MRCG are approached by the study team and, if consent is provided, recruited into Cohort 1 or Cohort 2 as applicable. Mild/moderate cases recruited from these sites are followed up either at the treatment centre or home, depending on national guidelines at time of recruitment. Severe cases recruited into Cohort 2 are managed at one of the two COVID-19 treatment centres.

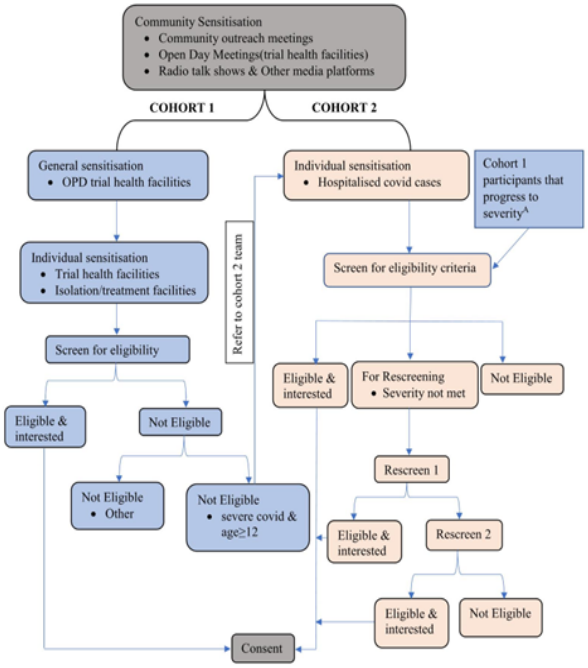

Figure 2: PaTS COVID-19 Screening and recruitment process.

Inclusion criteria

Cohort 1: Individuals ≥5 years of age with confirmed COVID-19 mild disease or moderate pneumonia defined as follows: Mild disease; Influenza-like-illness with any of the following symptoms: cough, fever, headache, sore throat, nasal congestion/runny nose, body pains (myalgia), fatigue (malaise), diarrhoea, abdominal pain, anorexia, nausea or vomiting without evidence of pneumonia or hypoxia. Moderate pneumonia; clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing) with no need for supplemental oxygen (oxygen saturation ≥90%% on room air or respiratory rate (RR) between 20 and 30 breaths/minute). HH contacts: Individuals ≥5 years of age living in the same HH with the index cases, defined as those individuals eating from same cooking pot or sleeping in the HH during the following 2 weeks. HH contacts are recruited into the study only if the index case remains at home. Cohort 2: Individuals ≥12 years of age with suspected or confirmed COVID-19 associated severe pneumonia (fever, cough, dyspnoea or fast breathing) plus either oxygen saturation (SpO2) <90% on room air or respiratory rate > 30breaths/minute. Suspected COVID-19 disease is defined according to the following clinical or radiological criteria: Clinically suspected; Signs and symptoms of pneumonia (as defined above) and no

alternative diagnosis to explain the clinical presentation or radiologically suspected: typical radiological signs of COVID-19 on chest X-ray or lung ultrasound.

Exclusion criteria

Exclusion criteria for current study were pregnant (confirmed) or lactating women, known contra-indication or allergy to IP, already on IP or need to start taking the IP (or in the case of aspirin already taking other non-steroidal anti-inflammatory drugs) and known bleeding disorder.

Sensitisation and community engagement

Community sensitisation: We provided general information on COVID-19 and created awareness about the trial at the surveillance sites and surrounding communities. An ancillary qualitative study was conducted prior to the trial and the findings informed our implementation strategy including community engagement, and radio/TV talk shows.[12] Individual sensitisation and consenting: Informed consent is obtained from each patient before enrolment. When the patient is critically ill consent may be obtained from a relative acting as the patient's legally designated representative and further consent is sought when the patient has sufficiently recovered. Parents give consent for their children (<18 years old) and children 12-17 years old provide assent. Impartial witness: For illiterate participants, an impartial witness (a literate community member), is present during the sensitisation and consenting process.

Randomization allocation and blinding

Once laboratory results are available, consenting individuals fulfilling entry criteria for Cohort 1 are recruited and randomly allocated to one of the three study arms. Each cohort have its own randomization list, prepared by the trial statistician before any recruitment. Access to randomization lists is restricted for investigators and trial staff with the tablet/computer showing the allocation of a new participant once the eligibility CRF has been completed. The allocation is in six blocks from A to F.

Interventions

The trial drugs being tested are: Cohort 1 Ivermectin (IVM) is an antiparasitic drug used for mass drug administration for the control of scabies and other parasitic infections. Ivermectin is also an endectocide and is being investigated as a vector control intervention against malaria.[13] It also has reported anti-inflammatory activity and in vitro activity against SARS-Co-V2 at high doses. Available data on IVM for COVID-19 treatment, at the time of selecting it as IP, were from non-peer reviewed, non-randomized studies, with high risk of bias and small sample size.[14] In this trial, all participants are given 0.3-0.4mg/kg of oral IVM once daily for 3 days. Cohort 2 Aspirin has anti-viral, anti-inflammatory and anti-thrombotic activity. It is licensed for the secondary prevention of cardiovascular diseases and the management of ischaemic heart disease. Moreover, it is used as an acute antithrombotic treatment for ischaemic strokes and, at higher doses as an analgesic and anti-inflammatory. It is hypothesised to have a mitigating role through multiple mechanisms in the pathogenesis of severe COVID-19. At the time of selecting it as IP, there were ongoing studies worldwide, including a planned RCT in Nigeria and Pakistan (CRASH-19).[15] We administer 150 mg Aspirin once daily for 28 days, or until hospital discharge or death.

Day	Index case Enrolment sites	Place	Index case procedures	Sample/s HH contacts procedures
Day 0	Surveillance	Health facility	Consenting Sampling NPS/OPS Randomisation[A] Oxygen saturation[A] General clinical assessment[A] IVM/placebo[A]	Not applicable
	Others	Isolation unit/Home	Consenting Sampling[B] Randomisation Oxygen saturation General clinical assessment IVM/placebo	Consenting Sampling IVM/placebo Passive case detection
Day 1	Surveillance	Home	Randomisation[C] Oxygen saturation AE & general clinical assessment (including progress to cohort 2) IVM/placebo	Consenting[C] Sampling[C] IVM/placebo Passive case detection
	Others	Isolation unit/Home		
Day 2-3	Surveillance	Home	Oxygen saturation AE & general clinical assessment(including progress to cohort 2) IVM/placebo[D]	IVM/placebo[D] Passive case detection
	Others	Isolation unit/Home		
Day 4	Surveillance	Home	Oxygen Saturation NPS/OPS Sampling Stool sampling(+2 days window period) AE & general clinical assessment(including progress to cohort 2)	Passive case detection
	Others	Isolation unit/Home		
Day 5-13	Surveillance	Home	Oxygen saturation AE & general clinical assessment(including progress to cohort 2)	Passive case detection
	Others	Isolation unit/Home		
Day 14	Surveillance	Home	Oxygen saturation Sampling AE & general clinical assessment(including progress to cohort 2)	Passive case detection Sampling Study exit
	Others	Isolation unit/Home		
Day 28(±4 days)	Surveillance	Health facility/Home	Oxygen saturation AE & general clinical assessment(including progress to cohort 2) Sampling Long covid questionnaire(EQ-5D score) & Study exit	Not applicable
	Others			

Figure 3: Procedures for cohort 1 participants and HH contacts.

Trial procedures

Cohort 1 procedures: During the screening visit (Day 0), demographical, epidemiological, and clinical data are collected. A detailed history of co-morbidities and other potential risk factors is also taken. When COVID-19 disease is confirmed, consented individuals are enrolled. First, a nurse/field worker prepares the treatment doses for days 1 to 3. The follow up consists of daily visits by a field worker/nurse for 2 weeks (day 1-14) and a last visit at day 28 for index cases only. The IP is given by study personnel on days 1 to 3 with daily assessment of signs/symptoms to determine the progression to severe pneumonia. Information on HH members beyond day 1 is

collected by passive case detection. Study samples for index cases and HH contacts are collected as outlined in (Figure 3). Index cases and HH contacts progressing into severe COVID-19 pneumonia during follow up (thus meeting the clinical primary endpoint of Cohort 1) are screened for Cohort 2 and, if meeting criteria, enrolled in Cohort 2.

Cohort 2 procedures: Baseline data, including detailed history of co-morbidities and risk factors, symptom onset date, vital signs, level of respiratory support and level on the ordinal scale are collected. Following randomization, research nurses administer and document the IP. To ensure the assessment of the outcome is blinded (as both IP do not look identical), this is performed by staff not involved in the administration of the IP. Patients are reviewed daily by research nurses until hospital discharge or death to identify any deterioration/serious adverse events (SAE) and to collect outcome data. Study samples are collected as outlined in (Figure 4). All patients are managed by hospital staff. Research staff provide clinical advice as needed.

Other laboratory procedures

D-dimer and CRP analysis**:** Blood for D-dimer and CRP measurement is collected for Cohort 2 patients (Figure 4) at 2 timepoints and analysed in parallel later. Results are not available for patient care as their use in clinical management is not validated.[16] Intestinal helminths: stool samples are collected from both Cohort 1 and 2 patients (Figure 3-4) and samples are processed by Kato Katz and agar culture.[17]

Outcome measures

The primary endpoints are defined as follows: Cohort 1 Index cases: treatment failure: patients with COVID-19 associated mild disease/moderate pneumonia progressing within 14 days after recruitment into moderate or severe pneumonia, defined according to the most recent WHO guidelines as follows.[16] Clinical signs of pneumonia plus: Severe pneumonia, oxygen saturation (SpO_2) <90% on room air or respiratory rate >30 breaths/min, moderate pneumonia, oxygen saturation (SpO_2) ≥90% on room air and respiratory rate between 20-30 breaths/min. Laboratory endpoint-positive SARS-CoV2 virus RT-PCRs at day 14. Cohort 1 HH contacts: percentage of HH members infected with COVID-19 during the 14 days following recruitment (defined as those RT-PCR and IgM/IgG negative at day 1 who become positive either by RT-PCR or IgM/IgG positive by day 14). Cohort 2: Treatment failure: worsening clinical condition from admission for a period of at least 24 hours on the following scale (moving from any point to the following one or more): Not requiring supplemental oxygen to maintain SpO_2 within target range. Requiring supplemental oxygen given by nasal cannula or face mask to maintain SpO_2 within target range. Requiring non-invasive (e.g., CPAP or BiPAP) or invasive ventilatory support to maintain SpO_2 within target range (or not maintaining SpO_2 within target range with supplemental oxygen given by nasal cannula or face mask). Death during hospitalization.

	PRE-INTERVENTION	INTERVENTION	POST INTERVENTION								
		Day 1		Day 2	Day 3	Day 4	Day 5	Day 6-27	Day 28 (±4)	Discharge /death	Day 90 (±7)
PROCEDURES											
ENROLMENT											
Eligibility screening	x										
Informed consent	x										
Randomisation/Allocation	x										
ASSESSMENTS											
Sociodemographic, clinical risk factors	x										
Examination, vital signs & baseline ECG	x										
Blood sampling(D-dimer and CRP)	x					x					
Stool sample				x							
IP administration		x		x	x	x	x	x	x[a]		
END POINTS											
Deterioration			x	x	x	x	x	x	x[a]		
Duration of hospital admission										x	
Duration on oxygen therapy										x	
In hospital mortality										x	
MRC dyspnoea score									x	x	x
EQ-5D score									x		x
SAFETY											
SAE(s)			x	x	x	x	x	x	x	x	x
Drug specific reaction			x	x	x	x	x	x	x[a]	x	

Figure 4: Overview of cohort 2 enrolment, intervention, and assessment procedures.

The trial secondary endpoints definitions are outlined below: Cohort 1; Index-cases: Positive SARS-CoV2 virus RT-PCRs at 4 days from recruitment until clinical recovery defined as two consecutive days of no fever (T ≤37.5^{0}C) and normal respiratory rate (RR≤20 breaths per minute) (only once if day 28 as end of follow-up). IgG geometric mean titer (GMT) at day 14 and 28 after recruitment. Poor self-reported health at day 28 (assessed by a linear self-reported health scale from the EQ-5D questionnaire in person or by telephone at 28±4 days after enrolment). Breathlessness at day 28 (assessed by the MRC Dyspnoea score administered in person or by telephone at 28±4 days after enrolment).[18] HH contacts: Percentage of HH members infected that develop COVID-19 symptoms over the 14 days following recruitment (defined as those asymptomatic at day 1 that become symptomatic by day 14 (COVID-19 positive either by RT-PCR or IgM/IgG and meet criteria for Cohort 1 index case or Cohort 2). IgG GMT at day 14 after recruitment. Cohort 2; duration of hospital admission in days, duration on oxygen supplementation in days, death ratio during hospitalization, at 28 (±4) days and 90 (±7) days after enrolment, occurrence of clinical thrombotic and embolic events (myocardial infarction, pulmonary embolus, deep venous thrombosis, cerebrovascular accidents), occurrence of clinical episodes of gastrointestinal bleeding, change in CRP and D-Dimer levels between baseline (enrolment) and day 3-5, persisting breathlessness at 28 and 90 days assessed by the MRCG Dyspnoea score at 28±4 days and 90±7 days

after enrolment.[18] Poor self-reported health at 28 and 90 days assessed by a linear self-reported health scale from the EQ-5D questionnaire at 28±4 days and 90±7 days after enrolment. The trial exploratory endpoints include: Proportion of patients in cohorts 1 (index cases) and 2 with intestinal helminth infections (and *Strongyloides stercoralis* specifically).

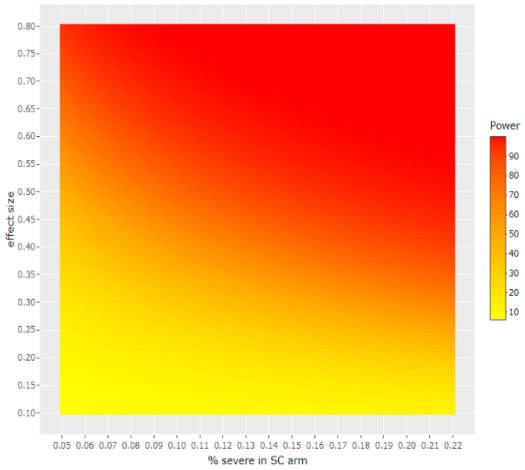

Figure 5: Power for cohort 1 with a sample size of 350 index cases.

Sample size and power determination

Our power calculation was based on the feasibility of the required follow-up as well as hospital bed capacity as it was not possible to accurately anticipate the number of COVID-19 patients in The Gambia. At the time of the first DSMB report, we re-estimated the sample size based on initial data from the trial. Cohort 1 index cases: Considering that 65% and 30% of the index cases in the placebo arm meet the clinical and laboratory primary endpoint, 350 patients would provide 80% power for an efficacy of 30% and 20%, for the clinical and laboratory co-primary endpoints, respectively (Figure 5). HH contacts: HH contacts are recruited from approximately one third of index cases (N=115 index cases), with a median of 5 contacts per case (115x5=575 household contacts). Assuming 35% of HH contacts in the control arm become infected during follow-up, the trial would have 80% power to detect a 30% decrease of infection for the intervention arm (or Arm 3; IP for both index cases and HH contacts) compared to Arm 1 (placebo and placebo). Power will be slightly lower considering the clustering effect. Cohort 2: Assuming the trial will be able to recruit 150 patients per arm, it will have 80% power only if at least half of patients reach the primary endpoint, as we do not expect an effect size higher than 35% (Figure 6). Because it was difficult to anticipate the effect of the intervention in Cohort 2, we assumed that we would have >80% power for the secondary endpoints (i.e., duration of admission and duration of oxygen supplement) if the hazard ratio is at least 0.66.

Statistical analysis

A detailed statistical analysis plan will be made available at the trial registry before the database is locked. Analysis of Cohort 1 will be independent from that of Cohort 2 and recruitment can finish at different points in time. Analysis of all outcomes will be primarily on an intention-to-treat basis for patients who had at least one dose of IP.

Comparability of participants between arms

Baseline characteristics will be presented by study arm using descriptive statistics. Main risk factors for disease progression will be compared between arms at recruitment and adjustments will be done if imbalances are detected.

Flow of participants

For each cohort, the number and flow of subjects through screening, randomisation, allocation, follow-up and analysis will be documented, as per CONSORT 2010 guidelines.[19]

Primary and secondary outcome analysis

For each cohort, the number of subjects meeting the primary outcome will be calculated for each arm and generalised estimating equations used to calculate risk ratios with confidence intervals. Analysis of secondary outcomes will be performed according to the type of data. Continuous variables will be compared between arms using random effects models, and categorical data with generalised estimating equations. Survival analysis of the time to "failure" will be performed using Cox regression with frailty.

Data collection, management and security

A data management plan was developed and approved before starting participant recruitment. Data are collected by electronic data capture using encrypted and reliable mobile devices. The trial data are stored in a research electronic data capture (REDCap) database.

Study withdrawal

Participants are free to withdraw from the study at any time. If they agree safety visits will continue and previously collected information and samples will be analysed.

Concomitant drug therapies allowed and disallowed during active follow ups

Participants at home are encouraged to call the study team if they feel unwell and are discouraged from self-medicating. Hospitalized participants receive concomitant therapies as determined by the clinical

management teams at each site, in consultation with the trial research clinician/s and in accordance with local and national guidelines. Cohort 2 patients are not allowed to receive other NSAID drugs (E.g., ibuprofen, diclofenac) while Aspirin is the IP.

Safety and adverse event monitoring

Any participant who receives at least 1 tablet of IP is included in the evaluation for safety.

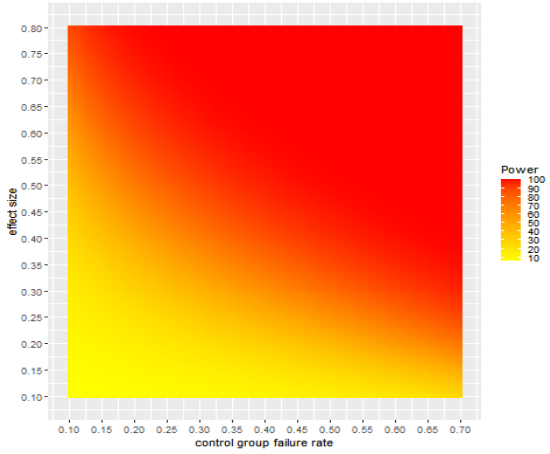

Figure 6: Power for cohort 2 with a sample size of 150 individuals per arm.

Oversight and monitoring

Trial study team: The trial has a chief investigator (CI) who is responsible for the overall supervision. Each cohort has a lead principal investigator giving oversight to the cohorts. Trial steering committee (TSC): The TSC has five independent members, the CI and Co-investigators, supervising the progress of the trial towards its objectives. The data safety monitoring board (DSMB): The DSMB comprises three individuals with wide expertise in research, including specific background in Clinical trials, management of COVID-19 and statistics and provides overall supervision for the trial.

Sponsor monitoring and audit visits

The Sponsor, LSHTM conducts monitoring visits in accordance with the approved study monitoring plan. All SAEs that culminate in the death of participants are reviewed by the Medicines Control Agency (MCA) and the local ECs. Planned routine quality assurance visits to ensure compliance of the trial with study protocol and other relevant documents such as ICH GCP are conducted.

Dissemination plans

The results of the trial will be published in *peer review* journals, uploaded on the ClinicalTrials.gov and Pan African trial registers and shared with the Gambian ministry of health.

DISCUSSION

This trial will provide data to evaluate prevention and treatment at different stages of COVID-19 clinical spectrum in an African setting. Besides the primary endpoints of efficacy on clinical progression, we will have data to understand the dynamics of transmission in a low resource African setting. The public health benefits will include an understanding of the burden of disease, hospitalisation, and deaths and the need for oxygen which is crucial in the management of severe COVID-19. The trial design has been adaptive from inception, with allowance for changing the IP as needed. This has, in theory, an added advantage, making the trial relevant to global efforts to control the pandemic. There was a need to change dexamethasone to aspirin before starting the trial as dexamethasone became international treatment guidelines.[8]

In addition to the primary endpoints, our trial secondary and exploratory endpoints are relevant to address several open questions on the continent, including the proportion of patients that may develop long term post-COVID-19 sequelae, the role of D-Dimer and CRP as biomarkers in the management of severe COVID-19 patients and the prevalence and importance of helminthiasis in COVID-19 patients. High CRP has been shown to be associated with increased mortality in a UK population, though this has not been shown in any African population.[20] Setting a randomized control trial in The Gambia within the context of a new disease came with a number of challenges. The dynamic nature and the restrictions on travel and movements meant that sourcing materials were slower than usual. Training staff took long due to restrictions with physical distancing and limited capacity in rooms. Some households were reluctant for staff dressed in PPEs to access their premises. Our community engagement conducted before the trial started helped us strategize our approach to communities to reduce the stigma and misinformation.[12]

Trial status

Recruitment began on 22nd February 2021 for Cohort 1 and is going. For Cohort 2, recruitment started on 18th March 2021 and ended on 28th February 2022 and the follow up of patients has completed and data analysis is ongoing.

CONCLUSION

In conclusion, this study will contribute data to understand COVID-19 in SSA specifically focusing on the effect of drugs for both mild and severe cases and additionally give insight on transmission in this setting.

ACKNOWLEDGEMENTS

Authors would like to thank study team including the nurse coordinators, the MRCG CSD and molecular laboratory and data management departments, our Ministry of Health collaborators at the treatment centre, epidemiology and disease control unit and the National public health laboratory. Authors would also like to thank Dr. Brahima Diallo who led the community engagement study and developed the map for the study sites. Omar Ceesay supported community engagement initiatives and Asheme Mahmoud is the Project manager. Authors would also like to thank clinical trials unit led by Dr Armel Zemsi and supported by Gibbi Sey and Daisy Clara H. Williams.

Funding: Study was funded by UK research and innovation as part of the COVID-19 strategic priorities supplementary funding for the medical research council unit the Gambia at the London school of hygiene & tropical medicine.
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Usuf E, Brotherton H, Nadjm B, Mohammed N, Gai A, Sillah F, et al. Prevention and treatment for COVID-19 associated severe pneumonia in the Gambia (PaTS-COVID-19), a single-blinded randomized clinical trial: study protocol. Int J Clin Trials 2023;10(1):26-33.