Challenges and strategies for conducting clinical research during COVID-19: Experiences from resource-limited settings

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Introduction

- The ability to conduct research during pandemics is particularly important, especially where pathogens are novel, the corresponding therapeutics are non-existent or in need of validation and epidemiological profiles are unknown.

- Pandemic containment and mitigation strategies which have caused widespread social and economic disruptions, have also had a major impact on research activities.

- This presents challenges for research — especially in resource-limited settings — that could be significant and negatively impact the essential contribution of these settings to important SARS-CoV-2 research.

Case study: SARS-CoV-2 and malaria interactions

- **Study design:** prospective cohort study conducted 15th April – 30th October 2020
- **Study sites:** COVID-19 treatment centres in Uganda
- **Sample size:** 600 patients with polymerase chain reaction (PCR) confirmed COVID-19
- **Malaria diagnosis:** rapid diagnostic tests, microcopy and molecular analysis
- **Clinical labs:** Complete Blood Count , liver and renal function tests and HIV

Case study: SARS-CoV-2 and malaria interactions

- **Immunology:** Previous individual *P. falciparum* exposure was measured using serologic responses to a panel of six antigens
- **Markers of inflammation:** C-reactive protein (CRP), Interleukin (IL)-2, IL-6, IL-7, IL-8, IL-10, transforming growth factor beta (TGF-β) and tumor necrosis factor (TNF-α)
- **Laboratory personnel:** unaware of patients' clinical status to avoid any potential bias
- **Clinical management:** done according to Ministry of Health (MoH)/World Health Organization guidelines.

Ethical approvals

- Whereas the need to learn as much as possible as quickly as possible is of utmost importance, the relationship between response and research gives rise to several ethical and regulatory challenges.

- As ethical review is required before the launch of any research study, this pandemic presents exceptional circumstances for which special considerations for modifying the ethics review process are warranted.

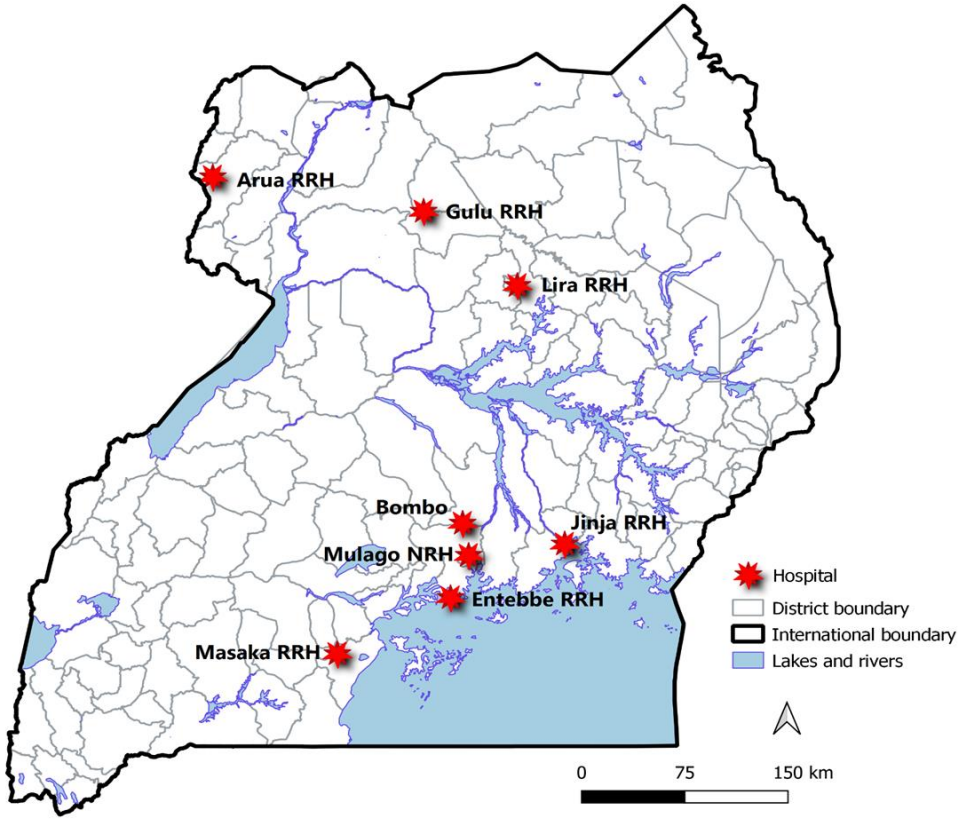
- Expedited approaches to ethical review and approval are required to facilitate timely initiation of research activities
  - These need to be supported by existing national or international regulations and guidelines.

Ethical Approvals

- Submission to Ethics Committee (EC) at a time when the EC could not meet physically.
- Given the need to answer these scientific questions in the context of the pandemic, review was expedited and approval provided within 48 hours
  - Guided by existing national guidelines, with all expedited review decisions presented at the next full EC meeting for ratification and final approval
  - Approach allowed for timely study recruitment, which facilitated optimal accrual.
- National level: the Uganda National Council for Science and Technology (UNCST) was responsive; provided timely guidelines for researchers on the management of research activities.
- The UNCST also had an online electronic platform for submission of research applications that ensured safe, ongoing paperless research review.

Operational challenges of scale-up

Originally planned for two sites in central Uganda – scaled up to a total of eight sites



Operational scope and issues

1. Eight health facilities – wide geographical scope
2. Four different laboratories – molecular, clinical, immunological (x2)
3. Issues with coordination at field sites
    - introductory letter from MoH
    - clearance from health facility leadership
    - clearance from district leaders for overnight stays
    - supporting clinical sites with personal protective equipment (PPE) supplies.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Consent procedures

- Voluntary informed consent is a prerequisite for research participation and an ethical and legal requirement
  - In this study, written informed consent was obtained from all patients (signature/thumb-print).
- Treatment centres set up to ensure strict infection prevention and control (IPC), which presented unique challenges to the consent process
  - Designated areas: red zone (admission area) and green zone (administrative area); access to red zone by health facility staff only.
- Concerns about the potential for fomite transmission from consent documents
  - Limited data on the duration that droplets on paper could remain infectious, and what risk this imposed
- Considerations about how best to handle consent forms that had been handled by patients inside the red zone to ensure staff were not exposed to infection.

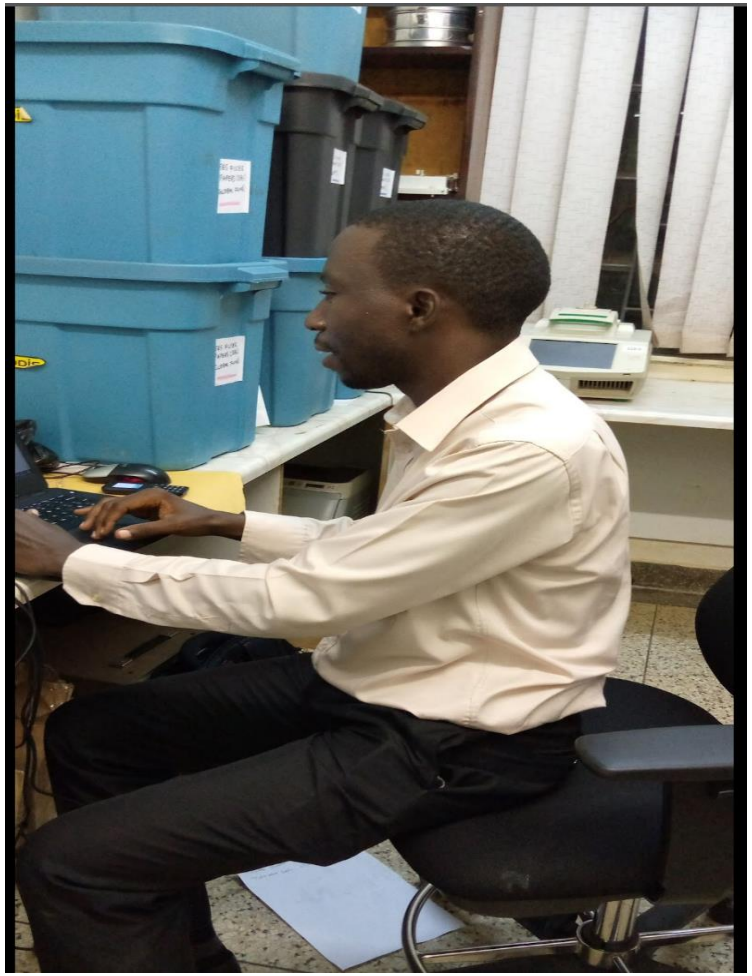
Consent procedures

- Option 1: leave all consent forms within the red zone — raised concerns about long-term safety of study documents in this public space.

- Option 2: remove completed consent forms from red zone after each enrolment by
  - taking them out in biohazard plastic bags, disinfecting outside red zone and subsequently transferring and keeping in a second safely sealed biohazard plastic bag
  - storing in safe location until removal and disinfection.

- Other challenges
  - Disinfection of consent documents — ultraviolet (UV) light automated disinfection system used
  - Consent for severely ill patients, especially when next of kin unavailable
    - active efforts to locate the next of kin
    - Patients with no designated next of kin were also not enrolled.

Consent document handling



Research staff and clinical care team interactions

- Treatment centre heads were hesitant to have multiple research groups entering the centres.

- Primary clinical care teams at treatment centres performed all study procedures (e.g. obtaining consent, sample collection and data collection).

- Staff training ensured consistency in study procedures across sites
  - Ideal approach to ensure optimal adherence to IPC procedures and minimise exposure risk to multiple individuals from different research groups.

- Clinical care staff were fully supportive and facilitated scheduling of different research activities to ensure compliance was maintained and work overload minimised.

Participant compensation

- National guidelines require research participants to be compensated for time spent participating in studies.
- Direct cash payments generally discouraged while research participants were still hospitalized, given potential transmission risks.
- Mobile money (digital) platform
  - Ideal for participants/next of kin if registered for this service, and compensation at time of discharge for those with no mobile money accounts
  - generally worked well, though those compensated at discharge complained, perceiving payment as delayed.
- Given the stigma associated with COVID-19 in these settings, important to keep patients' personal registration details on electronic payment platforms confidential
  - Compensation only managed by the research coordinator and not administrative staff.

Psychosocial needs of patients

- Though not a primary study objective, the research team encountered several issues relating to psychosocial needs of study participants and healthcare workers.

- Telephone contacts provided on consent forms became an unintended helpline used to address patient concerns about several issues that were mostly outside the scope of the study
  - Long duration of hospitalisation, especially for asymptomatic patients
  - Requests for improvement in aspects of their welfare and care
  - Delays in return of COVID-19 PCR test results during follow-up
  - Queries about study compensation
  - Reports of significant levels of stress relating to confinement within treatment centres, away from family and economic activities
  - Fear of stigmatisation in the community following discharge.

- Study team responded to issues that could be addressed and provided feedback to clinical care teams for follow-up and appropriate management.

Psychosocial needs of facility and study staff

- Healthcare worker concerns
  - Limitations in PPE supplies — research team supplemented these as needed
  - Stigmatisation by the communities they work in
  - Challenge of staying away from the family for prolonged periods while on duty.

- Study staff reported anxiety related to the fear of contracting COVID-19. This was addressed through
  - optimal IPC training and PPE supplies
  - frequent testing for SARS-CoV-2 infection
  - psychosocial support
  - flexible working schedules.

Multiple research groups/activities on the same patients

- Several research groups worked at the same treatment centres, resulting in overlapping research activities.

- Patients underwent multiple assessments, with numerous samples collected for different tests
  - routine clinical labs
  - study-specific sample collections
  - COVID-19 follow-up diagnostic testing.

- Challenges
  - Patients expected formal feedback on laboratory results for all different samples collected
  - Some studies unable to return results before patient discharge for tests not done real-time
  - Subsequent refusals to participate in later studies, especially when patients felt no benefit from prior participation.

Feedback on laboratory results

- All results needed for clinical care were available immediately.
- Research-specific specialised assays were often unavailable during period of hospitalisation — this should have been better communicated to patients.
- At times, the different research groups did not provide patients with adequate explanations for various assays and the possible turnaround times.
- Better coordination between the research groups could have streamlined such operational aspects
    - In one treatment centre, three research groups had a collaborative agreement in place that streamlined communication and research procedures.

Conclusions

- While conducting research during global health emergencies is challenging, the COVID-19 pandemic should compel the scientific community to innovate solutions to standard research practices that are difficult to implement

- Ethics committees and investigators should respond to challenges by updating policies and procedures around research review and approvals, consent, assessments, compensation and modifications in research methods.

- We demonstrate herein that more adaptable and innovative approaches may be needed to support the implementation of research activities during global health emergencies.

Conclusions

- Overall, these approaches can be generalisable to similar settings to support timely implementation of clinical research in complex emergencies.

- The necessary changes in policies and procedures highlighted during this pandemic should have a positive and lasting impact on clinical research in similar situations.

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