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Letter to the Editor *A reply to addressing research priorities in pneumonia in LMIC*

Conducting research in Africa: Lessons from the COAST trial

Marco Zampoli[1,2], Diane Gray[1,2], Cornelius Sendagire[3], Diana Mwendwa Marangu[4]

[1]Division of Paediatric Pulmonology, Red Cross War Memorial Children's Hospital, [2]Department of Paediatrics and Child Health, University of Cape Town, Cape Town, South Africa, [3]Department of Anaesthesia/Critical care, Uganda Heart Institute, Kampala, Uganda, [4]Department of Paediatrics and Child Health, Kenyatta National Hospital, University of Nairobi, Nairobi, Kenya.

***Corresponding author:**
Marco Zampoli,
Division of Paediatric Pulmonology, Red Cross War Memorial Children's Hospital, University of Cape Town, Cape Town, South Africa.

m.zampoli@uct.ac.za

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Dear Editor,

We thank *Bush* and *Masekela* for the recent editorial: *Addressing research priorities in community-acquired pneumonia in children: A case of a missed opportunity*,[1] highlighting the importance and challenges of African led research that addresses priority health issues and how we ensure this is done effectively, safely, and ethically. This is particularly relevant in the context of recent critiques of global health research, where multi-national funders and research groups from high resource settings collaborate with researchers in resource poorer settings.[2,3] This has led to a heightened awareness of the need for fairness, respect, care, and honesty in conducting research in lower resource settings, but also the complexities of achieving this within systems that perpetuate the status quo of power imbalances and the historical disadvantages that continue to drive disease and poor health outcomes globally.[4]

The authors highlight the COAST trial of oxygen therapy in African children with pneumonia and the circumstances surrounding the early trial termination as an example of the challenges researchers face when conducting interventional trials in African countries.[5] We share their concern about the worrying trend in tensions between science and social media. However, one of the challenges they have not addressed in our view, and the likely source of tension between science and community, is the ethical dilemma that arises due to the vulnerability of research participants and local scientists/clinicians due to extreme poverty and limited healthcare resources that are present throughout many parts of Africa. The authors propose that an organization such as the Pan African Thoracic Society (PATS) could have an oversight role to scrutinize and endorse appropriate research in the respiratory field in Africa, hence ensuring that priority research is completed safely. We believe this would be widely supported and positively contribute to providing scientific and contextual oversight.

The commentary raises several valid and important points, yet the community could not accept the study as safe and justified despite scientific and ethical rigor and extensive ongoing engagement with professional and academic stakeholders. There was, in fact, broader regional reservation than a single lay-campaign, and the endorsement from local pediatric associations was not unanimous. At the heart of this unease, was the critical issue of whether the trial was indeed ethically justified. This perception may be why it was unacceptable to the community and society it targeted. Given this prevailing perception, the controversial termination of this trial is perhaps not unexpected. Identifying ways in which the anticipated ethical dilemmas of

the protocol could have been more rigorously examined and debated before its adoption and implementation is crucial to avoid this happening in the future. Here, the leadership and guidance from PATS may have been appropriate and helpful.

The first ethical dilemma relates to the local 'standard of care' as justification for the study in a lower resource setting, which, in this case, is oxygen to treat severe community-acquired pneumonia (CAP) in children. We agree that there is no clear pre-existing evidence demonstrating a safe hypoxic threshold in severe CAP. In mild to moderate hypoxia, the long-held dogma of oxygen needs to be reviewed, particularly as there is emerging evidence that excess oxygen may cause harm. Identifying a safe limit of hypoxia would further offer the benefit of preventing unnecessary use of oxygen in both high- and low-income settings, which may be relevant in times of high demand, such as the current COVID-19 pandemic or settings where oxygen is a scarce resource. But is it acceptable to conduct experimental research in the most vulnerable populations – those that do not have access to the global standard of care and have higher mortality than communities that do? The question that should always be asked is - would this same trial have been approved in a high-income country? If yes, then it would be respectful first to answer this question in these settings where children are less vulnerable. If the answer is no, then it should not happen in a lower resource setting unless explicitly and transparently justified. In this case, the justification was challenged by the community. It is unlikely that this study would be easily undertaken in a high-income setting (despite the importance of the research question), so why should research subjects, research staff, and communities in Africa accept different standards of ethical research and care compared to higher-income countries? The Global Ethics Code for research in resource-poor settings, adopted by several prominent universities and international organizations, has coined this phenomenon as 'Ethics dumping.'[4] There are times when such research is permissible and desirable to facilitate research that is responsive to the health needs of a community, but this needs to be clearly justified and acceptable to all stakeholders. One, for example, cannot argue that childhood pneumonia or hypoxemia in Africa is pathophysiologically different from childhood pneumonia or hypoxemia elsewhere in the world as justification for why this research could only be done in Africa. The Pneumonia Etiology Research for Child Health study, which included sites in Kenya and Zambia, found viruses caused most severe CAP cases (61%) and respiratory syncytial virus (RSV) the leading pathogen at all sites.[6] RSV is the leading cause of lower respiratory tract infections in high-income countries too, so it would have been prudent and more acceptable if researchers piloted their hypothesis of permissive hypoxemia in children with severe CAP or bronchiolitis in a high-income setting where the standard of care for hypoxemia is oxygen.[7] If anything, CAP in African children is associated with more severe disease and co-morbidity such as malnutrition, anemia, and malaria, which adds a further layer of vulnerability to these participants enrolled in experimental research that withholds oxygen when the harm of doing so was unknown. The lower-than-expected mortality in all arms (observed 1.6% vs. an estimated 9%) is interesting and raises questions about the suitability of the data used to estimate expected mortality and threshold level for safe permissive hypoxemia in the study design.[5] Perhaps the lower-than-expected mortality observed in all arms of the COAST trial simply reflects the benefits of access to essential health care by mere recruitment into the trial. Important too in examining the ethical framework is the vulnerability of both local researchers and participants to undue influence and exploitation in global health research, due to the associated advantages in terms of access to financial compensation, capacitating other research, health resources, and basic healthcare (e.g., oxygen). A proof-of-concept study from a high-income setting or adopting a stepwise approach to a lower threshold for safe hypoxemia (i.e., not starting at SpO_2 80%) would have been preferable alternatives and more acceptable to front-line staff caring for patients. This may have then ensured that this important experimental research could have been completed unhindered.

Another aspect of this trial that may have caused unease with front-line staff and the *community* is the inclusion of High Flow Nasal Therapy (HFNT) as an interventional arm, especially in the permissive hypoxemia stratum. In addition to the cost of entrained oxygen, Fisher-Paykel commercial devices and their *single-use* consumables of circuits and patient interfaces cost significantly more (estimated 200 USD per single-use) than oxygen. They would hardly be affordable in many African countries if proven beneficial when the trial is over. It is commendable that the equipment was donated, but it is unclear what agreements were in place to support post-trial access to the consumables. There is a contradiction to ethically justify a permissive hypoxemia arm because oxygen is a scarce resource but then include a high-tech expensive HFNT arm in the trial. In addition, the scientific rationale for including an arm with HFNT in a trial where the investigational drug is oxygen is not clear, as HFNT and oxygen are not the same nor comparable. HFNT has several beneficial physiological mechanisms of actions that standard oxygen therapy does not and include: delivery of heated humidified gas into the airways, washout of the upper airways and reduction of dead space, reduction in upper airway resistance, modest positive airway distending pressure, and reduction of ambient air entrainment which delivers higher inspired FiO_2.[8] Moreover, there is evidence and less uncertainty that HFNT is superior to standard oxygen therapy for bronchiolitis in terms of treatment failure and rescue therapy.[9] Randomizing a child with SpO_2 of 80% (with a high probability of having RSV-associated bronchiolitis) to HFNT using a Fisher-Paykel AirVo device (even without

supplemental O_2) or nothing, is asking for *extreme* individual equipoise that would sit very uncomfortable with many front-line staff in both rich and poor resource settings. The finding of a trend toward improved survival in the HFNT arms should have been anticipated and is therefore not surprising.[5]

In their editorial commentary about this trial, Peters *et al*., independent members of the trial Steering Committee, offer a balanced view of the debate and correctly highlight the challenge of personal versus collective equipoise in clinical trials.[10] They conclude that clinical trials are not 'just science, they include public relations.' We agree with this statement and put forward a few suggestions for consideration by researchers to avert similar dilemmas:

1. As already suggested, PATS plays a role in stakeholder engagement and oversight. PATS is well placed to play this leadership role. But given the considerable imbalances of power and resources that persist in global health research, this needs to be governed by an ethical code that ensures fairness, respect, care, and honesty in any research undertaken
2. African Institutions and professional bodies strengthen leadership in upholding the Global Code of Conduct for Research Ethics in resource-poor settings,[4] or similar framework. Institutions in lower-resourced settings need to lead in taking responsibility for the type of research undertaken and how this is done
3. Create an environment that embeds an ethical approach into ongoing research conduct to manage ethical dilemmas faced by front-line research staff. Such a model has been recently proposed by Molyneux *et al.*[11] In this model, research team members learn how to address ethical dilemmas as they arise. Regular meetings to share and discuss are undertaken and actioned by addressing the urgency/seriousness of issues arising and their relatedness to the research
4. Development a priori of robust assessment tools of acceptability of research and healthcare interventions from the perspective of recipients and deliverers such as front-line research staff proposed by Sekhon *et al.*[12] Acceptability may be prospective/anticipated (before participating in the intervention), concurrent (while participating in the intervention), or retrospective/experienced (after participating in the intervention). For example, in the case of the COAST trial, a broader assessment of anticipated acceptability before the start of the study could have highlighted the aspects of the intervention that could be modified to increase acceptability, and thus participation. Likewise, a retrospective inquiry into what was deemed unacceptable with the COAST trial would be a helpful exercise.

Hopefully, such an approach would empower large-scale African-led research to answer priority health issues while ensuring that participants, researchers, and frontline staff are safe and respected; and that research funding is used maximally and effectively towards real health improvements for African people. Undoubtedly, the highly experienced and skilled research team of the COAST study endeavored to follow the best of good clinical practice and earnestly sort stakeholder engagement and support but was thwarted. Perhaps, for research where controversy is anticipated, or broader input thought relevant, similar situations could be mitigated if a pan African scientific authority such as PATS engaged with its members and provided feedback on study design and implementation aspects that would be both scientifically rigorous and acceptable to the broader communities. African institutions and professional organizations have an opportunity to support this process actively. This too, may reassure funders that African institutions are taking responsibility for effective research that is responsive and contextual to the needs of the African continent. A model of ongoing review and assessment of ethical dilemmas that arise needs to be embedded in research practice as we move forward and learn how to maximize the impact of clinical research safely.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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