A COASTal view: Where prior beliefs and uncertainty collide.

Mark J. Peters[1,2] William Macharia[3] and Elizabeth Molyneux[4]

[1]Paediatric Intensive Care Unit, Great Ormond Street Hospital for Children NHS Trust and

[2]Respiratory Critical Care and Anaesthesia Unit, University College London, Great Ormond Street Hospital Institute of Child Health, NIHR Biomedical Research Centre, London. UK WC1N 1EH

[3] Department of Paediatric and Child Health, Aga Khan University, 3rd Parklands Avenue, Box 30270, GPO 00100, Nairobi

[4] Department of Paediatric and Child Health, College of Medicine, Box 360 Blantyre Malawi

Corresponding author

Mark J Peters

Professor of Paediatric Intensive Care

Respiratory Critical Care and Anaesthesia Unit, University College London, Great Ormond Street Hospital Institute of Child Health, NIHR Biomedical Research Centre, London. WC1N 1EH

mark.peters@ucl.ac.uk

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Declarations

All authors were independent members (Chaired by EM) of the COAST Trial Steering Committee.

MJP is Chief Investigator on the UK National Institute of Health Research Heath Technology Assessment programme trial of Conservative vs Liberal Oxygenation in Critically Ill children.

Tweet: (140 characters): Any individual's lack of equipoise should not undermine a well-designed trial that aims to resolve clinical uncertainty.

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The Children's Oxygen Administration Strategies Trial (COAST) trial was an ambitious project based in Uganda and Kenya. The target population was children with severe pneumonia as assessed by presentation peripheral oxygen saturation into two strata (hypoxaemia SpO_2 80-92% and severe hypoxaemia <80%). The comparisons were between high flow humidified nasal therapy (HFNT) and standard low-flow nasal oxygen in the severe hypoxaemia stratum, but also – in a fractional factorial design - of more liberal oxygen use vs permissive hypoxaemia in the less severe stratum. The primary outcome measure was mortality at 48-hours. It was conducted by a team with an outstanding track record of delivering large pragmatic and practice-changing trials in low-income settings. We had the privilege of being independent members of the Trial Steering Committee (TSC).

Unfortunately, and unusually for this team, the trial was unable to recruit to the prespecified target of 4200 acutely ill children. However,the 1842 children enrolled however do provide important data. A pneumonia diagnosis was supported by x-ray changes in 1111/1842 = 60.3% of children. Crucially, the observed deaths in the less severe stratum of the trial (SpO_2 80-92%) were <u>much</u> lower than the investigators had anticipated (observed mortality 23/1454 =1.6% vs. expected 9%). Perhaps the most striking result in this stratum was that mortality amongst the permissive hypoxaemia group was the same as for those given low-flow oxygen. Given the recent results of the Higher or Lower Oxygenation Targets for Acute Hypoxaemia Respiratory Failure (HOT-ICU), [1] Conservative Oxygen Therapy during Mechanical Ventilation in the ICU (ICU-ROx) [2] and Conservative versus liberal oxygenation targets pilot trial in critically ill children (Oxy-PICU)[3], this is perhaps the result we would now expect, but this was far from certain when the trial was first planned. This finding has important implications for oxygen use which is a scarce resource in this setting. Only 15% of the less severe stratum assigned to permissive hypoxaemia required any supplemental oxygen. Non-significant differences in point estimates hinted that HFNC might be superior to low-flow oxygen but the reduced study power from lower death rates and incomplete recruitment have left this question open. Interestingly, HFNC in air alone is raised as a possible strategy which may have value where oxygen supply is scare. These important findings should generate new investigations to prioritise limited resources in low- and middle-income countries.

Perhaps the most interesting learning from COAST is to consider why this trial was not completed as planned. The investigators are a highly respected team with international and local expertise with an extraordinary record of delivering pragmatic trials in this setting. Their landmark Fluid Expansion in Severely Ill Children[4] and Transfusion in African Children (TRACT) trials[5, 6] illustrate this.

So how did such an experienced team, with us on the TSC, miss the target of 4200 patients by so far? The late British prime minister Harold Macmillan described unpredictability as arising from "*Events, dear boy, events*". COAST indeed suffered from '*events*'. One being a doctors' strike in Kenya which significantly delayed opening for recruitment in 2017.

The other 'event' was more complex. It involved vocal opposition to the trial by staff involved in research governance processes in Uganda. Despite all relevant advance approvals, trial recruitment was stopped in Uganda three times. In contrast the Kenya Paediatric Association provided professional education and strong support for the study. Following supportive external reviews of the science, including three independent data monitoring committee reviews (indicating no safety concerns) and robust trial governance, recruitment was restarted twice in Uganda. The delays resulting from these pauses eventually rendered the recruitment target unfeasible during the existing funding envelope. We wonder if there is a possibility of an aligned ethics governance process across East Africa? This might catalyse the much-needed growth for multiple-centre research in the region.

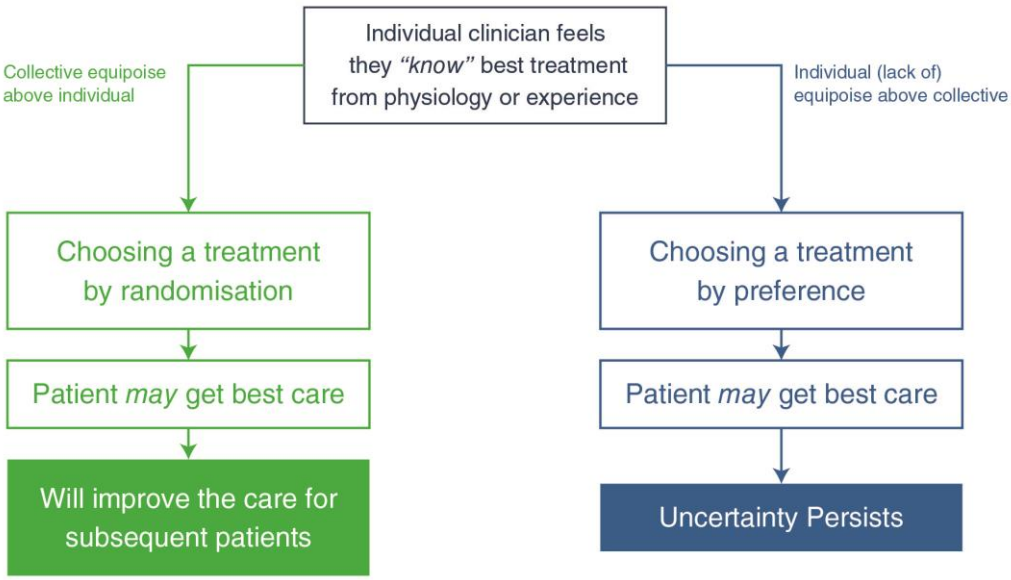
Having said that, we believe the challenges experienced by the COAST investigators overlaps with those that every important trial has to face: how do we handle individual versus general equipoise? When the data do not permit us to make an evidenced-based recommendation between two approaches, most intensivists or acute care doctors will make a decision based on experience or inferences from physiology. Often this may be rewarded by an acute physiological response (increased blood pressure with fluid administration for example) but possible later harms may not be so visible. In our example, the same fluid bolus may subsequently contribute to worsening lung injury or heart failure. In other words, our perception

of risk and benefit is subject to an availability bias as information becomes visible at different times. The observation that '*less-is-more'* in most interventions in critical care does suggest that we frequently get this wrong. [7, 8] So, when a colleague is adamant that they won't use HFNC instead of CPAP[9], or tolerate a lower haemoglobin,[10] blood pressure[11] or oxygen target[3], how should we balance doctors' individual freedom to choose, within the area of true uncertainty that a trial is trying to address? (Figure) We suspect all trialists will recognise this challenge. One approach is to engage with the doubter and encourage them to use the trial to resolve the question – which may prove them right! Another is to bemoan the lack of progress that must follow from not engaging in well-designed trials ('perpetuating ignorance'). This enthusiasm for trials does not remove the expectation that all trials are subject to rigorous peer-review and safety monitoring, and that they remain attentive to criticism and concerns as they are performed. But we have to be open to asking fundamental questions or we will only ever improve in small increments. Oxygen therapy has a peculiar place in many doctors' hearts which means they are reluctant to question its value. The more challenging the questions we ask, the more effort is needed in advance in consultation and spreading the rationale for a study. Clinical trials are not 'just science', they include public relations.

Ultimately it is up to trialists to design studies that can address clinically important questions *and* carry as much of the community with them as much as possible in addressing this. COAST took on very challenging questions. It recorded an extraordinarily low mortality compared to expectations. In the face of serious challenges, the investigators have made future studies in this area possible by undermining strongly held prior beliefs regarding the role of oxygen therapy and its delivery.

Figure. **The Challenge of Personal vs. Collective Equipoise in Clinical Trials**

Most clinicians favour specific treatment approaches based on physiology or experience. Ideally a clinical trial permits an individual to set aside their prior beliefs in order to reduce uncertainty. Trials that address long-held assumptions such as the risks and benefits of supplemental oxygen have to face this challenge.



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