Every COVID-19 patient should be able to join a randomised clinical trial

Yang Chen (UCL & LSE) *and* ***Bogdan Enache (LSE)*** *are two clinicians on the frontline of the pandemic. They explain their concern that evidence-based medicine is being jettisoned in favour of guidelines drawn up on the basis of expert opinion and case series, and make the case for every COVID-19 patient to be offered the opportunity to join a randomised clinical trial.*

As two aspiring clinical researchers who met at LSE, we feel that the school motto *Rerum cognoscere causas* – "to know the causes of things" – accurately describes the challenge of delivering a global, evidence-based response to COVID-19.

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We are clinicians by background, but during our Executive MSc in Health Economics, Outcomes and Management in Cardiovascular Sciences, we have been afforded a new vantage point and perspective on the healthcare response.

On the frontline, we have both seen a striking unity of human spirit, resilience and teamworking that is in stark contrast to the divergent clinical, research and health policy responses. We believe that the familiar concepts of evidence-based medicine (EBM) and leadership warrant greater collective and explicit emphasis so that our patients can receive the highest quality of care in these difficult times.

We have sadly observed many examples where EBM has not been followed judiciously enough. While treating COVID-19 patients, we have anecdotally seen and heard from fellow colleagues and professionals an urge to follow official guidelines or protocols to help determine which treatments to give. This is a natural instinct – in times of uncertainty, decision-making feels safer when following a document written by an authoritative and respected source. However, we are concerned in the faith being placed in guidelines currently based on evidence from cohorts, case series or expert opinion, drawn from first principles and biological plausibility.

In dealing with unpredictable workloads and stress, our contention is that no further undue burden should be placed on clinicians to decide what treatment is 'best' depending on which local, national or international guideline or expert they follow. The principles of EBM should take centre stage. To handle clinical equipoise appropriately, randomisation of treatment as part of a clinical trial should be the only way to arrive at unbiased answers, releasing precious time for doctors and nurses to concentrate on getting the fundamentals correct.

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We therefore believe that there is an urgent unmet need for each and every COVID-19 patient, regardless of their geography, to be offered enrolment into a pragmatic randomised clinical trial (RCT). Instead, as a community, we have knowingly delivered unproven treatments in a non-trial setting. Good intentions do not excuse bad science.

More worryingly, there have been anecdotes of patients who have refused to take part in a clinical trial for fear of receiving perceived inferior treatment, or even those who have taken matters into their own hands. The value of EBM needs concerted and compelling messaging from our academic and clinical communities, amplified not just in research literature but also on mainstream and social media platforms.

On a more positive note, there is no lack of will or desire to help from members of our broad community and so the challenge will be on how to harness this energy and use it to its greatest effect. However, currently the energy seems unfocused with too many individuals or small groups trying to 'be the leader.' For example, the number of systematic reviews registered on PROSPERO featuring COVID-19 stands at over 900 at the time of writing. How many of these overlap and how many will lead to informative, useful conclusions? What is the opportunity cost and research waste of unbounded efforts from enthusiastic amateurs and dedicated professionals?

This lack of coordination also seems to affect research from a basic science perspective. In the UK, a study aiming to better understand the natural history of the virus and immunity is underway, but how many laboratories have joined together to create a truly global bioresource that may arrive at critical answers faster and more accurately? As two early-career clinicians, we must ask: why is this research not on a larger scale? And what central leadership mechanism is needed, along with active followership, in order to better coordinate our response?

In a political vacuum, the World Health Organization (WHO), would appear to be perfectly positioned to take international leadership. The responsibility of ensuring patients in different healthcare systems are entered into clinical trials and/or appropriate bioresources could then rest with such a central body, thus ensuring no overlap or duplication of work from smaller centres. There is already precedence for this given in WHO's SOLIDARITY trial, an international RCT testing four different treatment regimens.

More broadly, given that countries have so far taken a heterogenous approach to policies such as social distancing and mask-wearing, could the WHO additionally coordinate randomised studies of entire healthcare policies given the apparent equipoise? In normal times, such RCTs would be prohibitive to conduct. However in the time of COVID-19, the case should be made far more strongly that currently, any intervention should only be pursued in the context of an RCT.

Lastly, how do we better coordinate messaging as a community, and calibrate writing style and tone to be commensurate with the intended impact of our message? If opinion and stories trump nuance and complex study designs – should leaders in local departments and national boards be directing more attention to identifying the most media-savvy clinicians and scientists? In both our undergraduate and postgraduate training, we have developed in an environment where the art of communication is becoming as important as the science of generating EBM. Does nominating non-traditional leaders as public advocates of EBM represent a paradigm shift that even COVID-19 cannot compel… and if so, what does this say about medical hierarchies?

Once the pandemic is over, there is an opportunity for our healthcare response to leave an indelible mark that is positive and framed around change and renewal. Our perspective is that greater leadership and use of EBM, in order to offer a coordinated response, should be the policy not just for COVID-19 but for the practise of medicine moving forward.

In an age of heightened patient, public and societal need, and a world of many heroes, we are reminded of the words of one of ours, the late Doug Altman: *We need less research, better research and research done for the right reasons*.

This post represents the views of the authors and not those of the COVID-19 blog, not LSE.

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