EDITORIAL

The Clinician and the COVID -19 Pandemic – Keeping Track, Keeping Pace and Keeping the Faith

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As this editorial is being written, the highly anticipated new James Bond movie *No Time to Die*[1] has been released. Its title probably resonates with the multitude of health care workers [HCWs] who have put their lives on the line since the beginning of the pandemic and continue to do so amidst the challenge of new waves, deadlier strains, frazzled colleagues and family and beleaguered healthcare systems hoping each day for a glimmer of light at the end of a long and dark tunnel. It is useful at this point to address some key issues faced by clinicians and clinician researchers and dwell on potential solutions that may in some manner mitigate this and learnings for the future.

A critical area has been that of a mountain of evidence including studies with alternative systems of medicine. In 2010, at the rate of 75 trials and 11 systematic reviews a day, a question was asked by a few authors as to whether we could at all *keep track* of evidence.[2] Eleven years later, the COVID-19 pandemic compounded this manifold. While there are success stories of high quality studies,[3,4,5] several smaller studies with low sample sizes have led to wasteful research and wasted resources.[6] Hydroxychloroquine [HCQ] which found appeal with national guidelines and favour with regulators soon made an inglorious exit.[7] Repeated iterations continue to be made in the SOLIDARITY study.[8] How does the practising clinician *keep pace*?

A second challenge has been the infodemic associated with publications. Not just journals, but media as well reported and continues to report results from clinical research in multiple social platforms including articles in the pre print stage and often disseminates flawed research.[6] It becomes next to impossible for the clinician to appreciate the true quality and utility of media messages.[9] Not just this, the average person has stayed on top of this mounting information as television and radio channels broadcast peer reviewed [and otherwise] information into the homes of people. This has brought greater difficulty for the practicing clinician already reeling under pressure of treating COVID -19 patients not knowing how to address patient and caregiver concerns particularly with sketchy and often conflicting evidence.

A third area is doing research during the pandemic. An example would be taking written informed consent wearing personal protective equipment [PPE], explaining benefit -risk of unproven interventions as also taking consent for placebo controlled trials, retaining participants in ongoing COVID and non COVID trials, keeping abreast of COVID specific guidelines from the ethics committees and regulatory bodies and finally sustaining clinical research itself as an enterprise. All this amidst desperate participants and caregivers and the need to maintain the highest standards of science and ethics at all times and be in readiness for audits and inspections. In addition, studies with use non pharmacological interventions such as masks are not easily implementable and yet need to be done.[10]

The Emergency Use Authorization [EUA] of COVISHIELD™ and COVAXIN™ ushered in hitherto unanticipated difficulty for researchers. The first author of this editorial became the Principal Investigator for the COVISHIELD™ multi -centric clinical trial during the first wave. From trying to expedite approval from the Institutional Ethics Committee to pressure from the funding agency to dealing with participant expectations, and intense media glare, the team of the first author and possibly some PIs in the country reached breakpoint quickly. The primary challenge was really managing participant expectations in a trial with a 3:1 randomization and which was double-blind. Some questions from participants are listed here - *What are the chances I have got placebo? Why are you excluding me because I have antibodies? Is it my fault I got COVID to be excluded from your trial? Why did I get COVID-19 disease despite being vaccinated? Can you break the blind quickly as I am a COVID warrior as I have volunteered when no one else in the country came forward?* When a Serious Adverse Event [SAE] occurred in the study [shown later to be not causally related to the investigational product and at the point where due process was still being followed], participants said they felt betrayed that they were not informed about it.[11] Following study completion, as the names of these participants did not feature in the COWIN app,[12] a fresh set of issues cropped up. *"I wish I had never taken part in your clinical trial. I wish I had waited for the Emergency Use Authorization and got my vaccine from the system"*. These were among the kinder calls and comments.

A fifth and perhaps less addressed area is that of mental health. Studies on burn out among physicians conducted during the pandemic have shown high levels of emotional exhaustion, depersonalization, anxiety, and fear of risk to themselves and their families. Many HCWs hesitated to go home to their families for fear of infecting them. Several were torn between the obligation to be a caregiver to the patient and family responsibilities.[13,14]

Hindsight they say is always hundred percent. How could we have done better? Or could we have done better at all? While is it not easy to keep track and keep pace with evidence, there are a few tools that can help.

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Trials/Studies that are open label, single arm, observational in nature are extremely unlikely to prove the efficacy of a new or a repurposed intervention. Similarly, announcement or approval by the regulator of the conduct of a clinical trial may lend hope but is no guarantee of the efficacy or safety of the intervention or vaccine.[9] Also, benefit -risk is an evolving dynamic and the risk of extremely rare adverse events must still be explained to the participant and the general populace in the best way possible. The media can play a vital role here. As a country, our clinicians are hard pressed for time and this was compounded during the pandemic leading to paucity of Real World Evidence [RWE] from India. Academia -industry collaboration and investment in RWE studies would go a long way in good quality data collection, adopting Electronic Health Records [EHRs] as a matter of routine and delivering research that finally matters to the patient.[15]

As regards research, clinician researchers would do well to understand the huge effect of participants' expectations. These are beliefs about the nature and the possibility of improvement after an intervention.[16] Expectations are verbalized and can be measured and addressed. Total knee arthroplasty in osteoarthritis offers a good example here about addressing expectations. Tolk J and colleagues randomized patients scheduled to undergo total knee arthroplasty into two groups – the control which received the routine preoperative counselling and the test group that in addition received an additional module on realistic expectations. The fulfilment of expectations in the latter group was significantly higher relative to the group that did not undergo training in the additional module.[17] As a country of over a billion people, we will need more vaccines and paediatric vaccine studies are now underway. Putting in place measures to address participant expectations [including parents] early on in these trials will go a long way in ensuring completion of these studies hopefully devoid of expectation challenges seen with the early vaccine studies. In addition, agencies like the Indian Council of Medical Research [ICMR] and the pharmaceutical industry should work closely with the government machinery ensure that participants in these studies are linked on the COWIN app right from the beginning and participants [or parents tomorrow] do not run from pillar to post seeking vaccination certificates after the trial is completed. The issue of post-trial access during a pandemic is one fraught with ethical dilemmas such as how soon should the COVID -19 vaccine be given to the placebo recipient and how long do you withhold vaccination in them just to answer questions of science needs to be addressed through a pragmatic approach.[18]

Finally, a global crisis like this pandemic does beget change. Learnings have been many and even unimaginable until last year. We thought we could not practice medicine from home but we did. We thought we could not work from home but we did. The mRNA vaccines [a novel technology] reached a large population quickly and clinical trials were completed and reported in record time. Virtual clinical trials where patient visits to the trial site are partly or entirely avoided may become the new normal.[19]

So where do we go from here? As we continue navigate the thick, long tail of the pandemic, *keep the faith* we must. A test of this pandemic for many of us has been searching for some significance and meaning to our existence as our lives were upended when we lost colleagues, loved ones and family members. Perhaps the answer lies in the sixth stage of grief as described by David Kessler in his book Finding Meaning– *meaning is what you make happen*.

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