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Letter to the Editor

## Lack of compliance with mandatory clinical trial registration

Dear Professor Petersen,

We have recently conducted a systematic review (Prospective register of systematic reviews [PROSPERO] registration number - CRD42022304703) of randomised controlled trials (RCTs) assessing the efficacy of melatonin as an adjunct treatment for SARS-CoV-2 infection (COVID-19). Our search strategy identified a trial by Hasan, Atrakji, and Mehuaiden, published in your journal earlier this year (Hasan et al., 2022).

The trial by Hasan *et al.* provided evidence that the use of melatonin as an adjunct treatment for COVID-19 infection significantly reduced mortality, sepsis, and thrombosis incidence in patients with COVID-19 compared with patients receiving standard care alone (Hasan et al., 2022). The results of this study show a greater effect than any of the other trials of melatonin in treating COVID-19 infections that we identified. Prospective trial registration in a publicly accessible database became mandatory in 1997 under the Food and Drug Administration Modernization Act of 1997 (FDAMA) (National Institutes of Health, 2021) and is included in the International Committee of Medical Journal Editors' (ICMJE) recommendations (International Journal of Infectious Diseases, 2018). Such registration ensures scientific integrity is upheld by mitigating publication bias in clinical trials (Simes, 1986). Other types of bias in unregistered trials were also apparent in a recent study assessing the risk of bias between prospectively registered and unregistered clinical trials. It was found that trials with prospectively registered trials had a lower risk of detection bias, performance bias, allocation concealment, and reporting bias than unregistered trials (Lindsley et al., 2022). In addition, the prospective registration of RCTs has been recommended by Cochrane since as early as 2004 (Cochrane Community, 2004).

We could not find evidence that the trial by Hasan *et al.* had been registered, and after contact with the publisher, yourself as Editor-in-Chief, and the authors, it was confirmed that indeed it had not been registered. The reviewers and editor apparently did not ascertain whether this was the case when the paper was submitted. Other disciplines have also reported poor adherence to the ICMJE guidelines. A recent assessment of trial registration across psychiatry journals found that less than 60% of trials were prospectively registered. Of these prospectively registered trials, 10% had unclear primary outcomes (Turner et al., 2021). Furthermore, a 2018 cross-sectional analysis of prospective registration of trials from high-impact journals found that 10% of trials were unregistered. Interestingly, these unregistered trials were significantly more likely to report favourable findings than registered trials ($P = 0.004$) (Gopal et al., 2018). As previously mentioned, the Hasan et al. trial also reported favourable findings regarding the use of melatonin for COVID-19 infection compared with the other trials included in our systematic review.

Failure to prospectively register trials creates difficulties when executing a systematic review. The primary outcome measure upon which the success of the Hasan et al. trial was based was not clearly defined in their published article, and we could not refer to the registration details to confirm this. We could not compare the published results with the trial protocol, so we could not assess reporting bias and any deviation from the original protocol. As a result, this casts doubt on the quality of evidence and certainty of the effect measure of melatonin as an adjunct treatment for COVID-19 infection.

In summary, although the paper by Hasan *et al.* (Hasan et al., 2022) provided evidence of significant reductions in mortality, sepsis, and thrombosis incidence in COVID-19 infected participants treated with melatonin, the trial was not prospectively registered and should not have been published. Prospective clinical trial registration is mandatory, yet a substantial proportion of trials across many disciplines are published without such registration. This leads to reporting bias and doubts about trial efficacy and integrity. It is unclear why some researchers do not register their trials; it could be an oversight, failure of leadership and supervision of junior researchers, or simply lack of knowledge of the requirements. Editors, reviewers, and publishers of journals also need to take some responsibility. There seems little point in having mandatory requirements and then failing to follow through. It could be argued that failing to comply could be considered research misconduct. Until journals enforce the provision of evidence of trial registration in accepted papers, authors will continue to try and avoid doing so with the ensuing impact on research integrity.

Yours sincerely

Mr Ronan Docherty and Professor Helen F Galley

### Declaration of Competing Interest

The authors have no competing interests to declare.

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