

**REPLY**

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**Reply***To the Editor:*

We read with interest the communication by Ferreira et al on our editorial about the measurement of remission in rheumatoid arthritis. They agree with large parts of our editorial, particularly the importance of including patient-reported outcomes (PROs) in the evaluation of RA disease activity. Their main argument is that a PRO such as the PGA does not capture active RA when the 28-joint counts suggest quiescent disease. For example in one article, they suggested that the main predictors of PGA in patients with a small number of swollen and tender joints in the 28-joint count are pain and fatigue (1).


The 28-joint count was adopted as an RA outcome measure based on data that suggested this reduced count (ignoring feet, ankles, hips, and neck) could adequately capture response to treatment. It was never intended to comprehensively assess all active joints. The pain experienced by patients with persistently elevated PGA scores who have low 28-joint count levels may well be due to RA disease activity affecting joints not counted, which are often affected by RA. In fact, one of Ferreira's coauthors championed the assessment of structural disease in the feet, showing that including this site enhanced our ability to comprehensively assess structural damage in RA (2). We believe that PGA gives us a window into overall disease activity, including disease in these other joints. We further note that one active joint among the 28 joints counted can cause patients considerable suffering and can serve as the basis for elevated PGA scores. In psoriatic arthritis, investigators recently agreed to readopt a 66/68-joint count to evaluate outcomes, including remission, for the reasons outlined above (3).

Ferreira et al argue that they are "concerned" about overtreatment that may lead to unnecessary exposure to potentially harmful medicines. They assert that there is a sizable group of patients in "near-remission" (4,5) because they fail to reach the PGA cut point of less than or equal to 1 and that additional treatment of these patients would constitute overtreatment. However, we disagree with the concern about overtreatment; no single study has to date shown that overtreatment is a problem. In a recent publication using a disease activity score in 44 joints (DAS44) of less than 1.6 as the treat-to-target goal, 38% of patients with RA not on target were found to not have treatments increased (ie, were undertreated), whereas only 9% of those with treatment increased were actually at the DAS44 target of less than 1.6. So, although the concern of our colleagues for patients is appreciated, evidence suggests that the main

problem is undertreatment and not overtreatment in patients in RA. With all the therapies available to patients with RA, all efforts by the scientific community should be taken to achieve remission for at least the majority of our patients in the third decade of the 21st century.

Our colleagues argue in favor of using C-reactive protein (CRP) as a main outcome because it reflects the inflammatory response. However, as noted in our editorial, effective RA treatments have variable effects on CRP, with some, such as anti-interleukin-6 agents and Janus kinase inhibitors, causing a drop in CRP levels, whereas others do not affect CRP. Considering also the possibility that CRP may reflect infection and not inflammation, an exclusion of CRP from composite instruments would therefore follow an analogous logic as PGA exclusion. All this would be a dramatic step back in time, before composite measures had been introduced to cover the activity of a complex systemic disease such as RA.

Lastly, we are concerned that a dual target, as proposed by Ferreira et al, will make it easier for sponsors of new treatments to focus on the easier-to-achieve target for approval (as has already occurred with DAS28 remission thresholds). If so, the dual target approach would lead to ignoring patient assessments entirely. Although the authors argue that separating PROs from objective markers will serve patient interests, the reality will likely be the opposite, with the separation leading to PROs being measured on the side as a secondary outcome. So in our view, the only guarantee that PROs will not be put aside is if they continue to remain an integral, and thus required, part of disease activity instruments.

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