DR. RICARDO J. O. FERREIRA (Orcid ID : 0000-0002-2517-0247)

DR. PEDRO DAVID CARVALHO (Orcid ID : 0000-0001-8255-4274)

Article type : Original Article

Impact of patient global assessment on achieving remission in patients with rheumatoid arthritis: a multinational study using the METEOR database.

Short title: Impact of PGA on remission rates

Ricardo J. O. Ferreira, RN, MSc[1,2], Pedro David Carvalho, MD[3], Mwidimi Ndosi, RN, PhD[4,5], Cátia Duarte, MD[1,6], Arvind Chopra, MD PhD[7], Elizabeth Murphy, MD[8], Désirée van der Heijde, MD PhD[9], Pedro M. Machado, MD PhD*[10,11], José A. P. da Silva, MD PhD *[1,6,12]

* José A. P. da Silva and Pedro M. Machado are joint last authors

Affiliations: 1 - Rheumatology Department, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal; 2 - Health Sciences Research Unit: Nursing, Nursing School of Coimbra, Coimbra, Portugal; 3 - Rheumatology Department, Centro Hospitalar e Universitário do Algarve, Faro, Portugal; 4 - Department of Nursing and Midwifery, University of the West of England, Bristol, UK; 5 - Academic Rheumatology Unit, University Hospitals Bristol, Bristol, UK; 6- Coimbra Institute for Clinical and Biomedical Research (iCBR), Faculty of Medicine, University of Coimbra, Coimbra, Portugal; 7 - Rheumatology Department, Centre for Rheumatic Diseases, Pune, India; 8 - Rheumatology Department, University Hospital Wishaw, Wishaw, Scotland; 9 - Rheumatology department, Leiden University Medical Centre, Leiden, The Netherlands; 10 - Centre for Rheumatology & MRC Centre for Neuromuscular Diseases, University College London, London, UK; 11 - Rheumatology Department, Northwick Park Hospital, London North West University Healthcare NHS Trust, London, UK; 12 - Coimbra Institute for Clinical and Biomedical Research (iCBR), Faculty of Medicine, University of Coimbra, Coimbra, Portugal.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/acr.23866

Corresponding author: Ricardo J. O. Ferreira
Serviço de Reumatologia, Centro Hospitalar Universitário de Coimbra, EPE.
3000-075 Coimbra. Portugal
phone number: 00351 965791542 fax 00351239400587 e-mail: rferreira@reumahuc.org

Competing Interests: The authors have declared no conflicts of interest.

Funding: Ricardo J. O. Ferreira was supported by an unrestricted grant from the Merit Foundation [RP 2015-01] for this study. Pedro M. Machado was supported by the National Institute for Health Research (NIHR) University College London Hospitals (UCL) Biomedical Research Centre (BRC). The views expressed are those of the authors and not necessarily those of the (UK) National Health Service (NHS), the NIHR, or the (UK) Department of Health.

ABSTRACT

Objectives: There is an on-going debate about excluding patient global assessment (PGA) from composite and Boolean-based definitions of rheumatoid arthritis (RA) remission. This study aimed at i) determining the influence of PGA on RA disease states, exploring differences across countries, and ii) understanding the association between PGA, measures of disease impact (symptoms) and markers of disease activity (inflammation).

Methods: Cross-sectional data from the METEOR international database were used. We calculated the proportion of patients failing ACR/EULAR Boolean-based remission (4v-remission) solely due to PGA (PGA-near-remission) in the overall sample and in the most representative countries (i.e. with over 3,000 patients in the database). Multivariable linear regression models were used to identify the main determinants of PGA, grouped in (predominantly) inflammatory (28-tender and 28-swollen joint counts and C-reactive protein) and disease impact factors (pain and function).

Results: This study included 27,768 patients. Excluding PGA from the Boolean-based definition (3v-remission) increased remission rate from 5.8% to 15.8%. The rate of PGA-

near-remission varied considerably between countries, from 1.7% in India to 17.9% in Portugal. One third of patients in PGA-near-remission scored PGA>4/10. Pain and function were the main correlates of PGA, with inflammation-related variables contributing less to the model (R^2=0.57).

Conclusions: PGA is moderately related to joint inflammation overall, but only weekly so in low levels of disease activity. A considerable proportion of patients otherwise in biological remission still perceive high PGA, putting them at risk of excessive immunosuppressive treatment.

Keywords: Arthritis, Rheumatoid; Patient Global Assessment; Patient reported outcomes; Disease activity; Remission

Significance and Innovation

- ✓ Among 27,799 patients with rheumatoid arthritis from a large number of countries, 10% failed to reach ACR/EULAR Boolean-based remission only due to a PGA>1 and among these, around 1/3 scored PGA>4 (0-10 scale).
- ✓ PGA showed a moderate to poor relationship with disease activity, especially at levels close to define treatment targets.
- ✓ The inclusion of PGA in definitions of remission may lead to overtreatment with immunosuppressive drugs.
- ✓ The patient's perspective remains essential to patient care. However, a separation between "inflammatory" and disease impact targets will probably improve safety and outcomes from the patients' perspective.

Remission is now the target of treatment in rheumatoid arthritis (RA) (1, 2). However, the percentage of patients achieving remission is strongly influenced by the remission definition used (3), and there is currently no consensus on which definition is the most appropriate to support a Treat-to-Target (T2T) approach (4). The most authoritative definition, adopted conjunctly by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR)(5), provides two alternative definitions: (i) either a Boolean-based definition [28-swollen joint count (SJC28), 28-tender joint count (TJC28), C-reactive protein (CRP, mg/dl), and patient global assessment (PGA, 0-10cm scale) all ≤1], or (ii) a Simplified Disease Activity Index (SDAI) ≤3.3. The SDAI results from the simple sum of the four Boolean components and the Physician Global Assessment (PhGA, 0-10cm scale). Two other commonly used definitions are based on 28-joint count Disease Activity Score (DAS28), either with 4 or 3 variables (i.e. with or without PGA), (6) or the Clinical Disease Activity Index (CDAI, same formula as SDAI, but without CRP) (7, 8).

PGA is included in all these definitions, except in DAS28(3v), but there is an on-going debate regarding whether it should remain in the definition. Its inclusion has been justified because PGA tends to accompany disease activity (inflammation control) in clinical trials of RA (5) and because it conveys the patient perspective, which is obviously core to the objectives of treatment (9). However, a growing concern has emerged as to whether PGA reflects disease activity at the biological inflammatory process close enough to make it an appropriate instrument to define target for immunosuppressive therapies (10-12), namely in long-term follow-up and in low-disease activity populations followed in clinic al practice. Support for this has been demonstrated by low correlation of PGA with joint counts and acute phase reactants (10, 13, 14), and PGA being unrelated to structural damage or other important outcomes (15, 16) that treat to target aims to prevent. PGA is highly affected by comorbidities and by other musculoskeletal and psychological conditions (e.g. osteoarthritis, fibromyalgia, depression) that cannot be improved by therapies targeting the inflammatory process, which makes it inappropriate to guide the readjustment of such therapies (11, 17,

18). Additionally, concerns have been raised regarding the variety of formulations used to ask this question (18), which have been shown to influence remission rates by 4.7% to 6.3% (19). Patient's health literacy also affects the validity and reliability of PGA: about 40% of patients find the concept of PGA confusing and difficult to mark (20).

The importance of understanding how PGA influences disease activity classification became especially important with the new ACR/EULAR remission criteria, given that a PGA score >1 excludes remission, even if all the other three criteria are ≤1 (a condition referred to as PGA-near-remission state). Several independent studies have shown that 14% to 38% patients with RA, in different settings, are in PGA-near-remission (10, 21-25), although these proportions need to be confirmed in larger international samples. The main issue is that following current treatment recommendations (1, 2) this state of PGA-near-remission would justify intensification of immunosuppressive treatment, after considering "other patient factors, such as progression of structural damage, comorbidities and safety issues"(1), or "patient's individual circumstances"(2). It has been argued that treatment decisions are more nuanced and most rheumatologists would be unlikely to base a treatment escalation decision on the value of the PGA alone (26). The question remains: if it is acceptable that rheumatologists ignore PGA for treatment decisions, why should it be kept in target definitions? Other researchers have proposed the increase of the cut-off point of PGA to around 2.5 or 3 cm (27, 28), but this does not solve the problems of validity and reliability mentioned above.

Members of our group (10, 29) have proposed the dual-target concept involving concomitant and obligatory use of two different targets: a measure of inflammatory disease activity (biological remission or 3v-remission) and a measure of patient-reported impact of the disease (symptom remission). The latter should be based on patient reported outcomes (PROs) that are better than PGA at discriminating disease impact, thus help to guide adjunctive therapy (10, 29). This has ignited controversy (12, 26). The concepts being addressed are of crucial importance in defining management strategies, justifying the need

of further studies to enlighten the on-going debate (30). METEOR, a large international longitudinal database, reflecting current clinical practice, provides a valuable opportunity to take into account the variability of clinical settings of care provision, including differences in cultural background, as well as treatment accessibility and standards.

The objectives of the present study were (i) to determine the influence of PGA on the classification of patients according to disease activity states, particularly remission, and explore differences across countries (ii) to explore the range of PGA values among patients in remission by DAS28 and in PGA-near-remission, and (iii) to determine the associations of PGA with markers of inflammation and of impact of disease.

PATIENTS AND METHODS

Patients and study design

This study used data from the "Measurement of Efficacy of Treatment in the Era of Outcome in Rheumatology" (METEOR) database, an on-going prospective international register of patients with RA founded in 2006 (31, 32). The METEOR is a free web-based tool available worldwide, with >33 countries, >45.000 patients, and >270.000 visits, corresponding to a mean (SD) of 3.1 (3.1) person-years of follow-up. Data regarding patient's socio-demographics, diagnosis, treatment and follow-up, according to usual care, are collected anonymously in a central database. Data can also be uploaded from local electronic health record systems or registries, which is the case in, among others, the Netherlands, Portugal and India (31, 32). All data in METEOR are fully anonymised and all follow-up visits, measurements and medication were based on daily clinical practice, therefore, medical ethics approval was not required.

For this study, the patients' first visit registered in METEOR, from adult patients, with no missing data in the variables used to determine ACR/EULAR Boolean-based remission status were selected. The database included visits from June 1985 till December 2017.

Assessments

PGA of "the current activity of the disease" was measured on 0-10 cm visual analogue scale (VAS), with 0 (not active at all) and 10 (extremely active) as anchors. Although the meaning of the question was the same, the exact formulation of the question varied across countries.

Other PROs assessed were pain (VAS, 0-10cm) and physical function, measured by the Health Assessment Questionnaire Disability Index (HAQ-DI)(33). The following clinical and demographic parameters were also considered for sample characterization: gender, age at visit, disease duration since diagnosis, Gross Domestic Product per capita (GDP) of the Country, presence of erosions, and current treatment with biological (bDMARDs) or targeted synthetic (tsDMARDs).

Definitions of remission

The ACR/EULAR Boolean-based definition (5) was adapted to classify patients in three main remission states: i) Boolean-based remission (TJC28, SJC28, CRP mg/dl, and PGA, all ≤1), also designated in this study as 4v-remission, ii) PGA-near-remission (TJC28, SJC28, CRP mg/dl all ≤1 and only PGA>1) (10), and iii) Non-remission (if two or more criteria are >1). The proposed binary definition of "3v-remission" (same criteria as 4v-remission but excluding PGA) (10, 16) was also tested. Naturally, 3v-remission = 4v-remission + 4v-PGA-near-remission. The proportions of patients that failed Boolean remission due to a single criterion, other than PGA, were also calculated (21).

An even stricter 3v-Boolean-based criteria, defined by the authors as SJC28=0, TJC28=0, and CRP (mg/dl) ≤0.5 ("Strict 3v-remission") was used, in exploratory analyses, to asses the percentage of patients scoring PGA≤1 under these circumstances. The SDAI (≤3.3) and the CDAI (≤2.8) (7, 8) remission definitions were also used to establish their prevalence among patients in PGA-near-remission state.

Regarding DAS28, remission states were assessed with the DAS28-CRP (34), because it was available in more patients than DAS28-ESR and because the other definitions of remission also include CRP. We used the most recently proposed cut-offs (35).

Statistical analyses

Data were analysed using IBM® SPSS® Statistics, version 20.0 software (IBM, Armonk, NY, USA). Quantitative data were expressed as means (standard deviation, SD) and categorical data as frequencies and percentages. The influence of PGA in the rates of remission according to the various definitions was assessed in two ways: (i) comparing the remission rates according to DAS28-CRP(4v) versus DAS28-CRP(3v), and (ii) determining the proportion of patients in PGA-near-remission (Boolean definition). Secondary analyses included determining: (i) the distribution of PGA values from patients fulfilling DAS28-CRP remission, PGA-near-remission, and "Strict 3v-remission", and (ii) the proportion of patients in PGA-near-remission that are also in SDAI and CDAI remission states.

Pearson's correlation coefficients between PGA, and SJC28, TJC28, CRP, DAS28-CRP3v, pain scores and function (HAQ-DI) were calculated, and categorized as high, $r \geq 0.60$; moderate, $r=0.40$-$.59$ and low $r<0.40$ (36). Correlations with DAS28-CRP(3v) were separately assessed for patients in remission/low disease activity, as this is the subgroup where the use of PGA in managing treatment according to current recommendations has the greatest impact. Differences between the most represented countries (n>3000 patients) in the database were explored. Multivariable linear regression models ("Enter" Method, with all variables) with PGA as dependent variable were used to analyse its main determinants from two main domains: (predominantly) inflammatory (SJC28, TJC28, CRP) and patient-reported impact measures (Pain and Function).

RESULTS

Patient characteristics

Among the 43,341 patients (264,920 visits) available in the database, only 27,768 patients/visits were included (i.e. the first among 109,556 recorded visits without missing data in the four Boolean criteria). Table 1 presents the patient characteristics, representing 32 countries (Supplementary Table S1). Mean (SD) disease duration since diagnosis was 4.3 (7.3) years, 83.4% diagnosed from the year 2000 onwards and 23.2% of the patients were currently on bDMARDS. The mean DAS28-CRP(3v) was 4.2 (2.6) and the mean PGA was 4.9 (2.6).

Influence of PGA in remission states

The overall remission rate according to the ACR/EULAR Boolean-based definition was 5.8%. An additional 10.0% of patients failed to achieve remission solely because of PGA ("PGA-near-remission" patients). The rate of PGA-near-remission across countries was 1.7% in India, 7.1% in Italy, 13.7% in the Netherlands, 15.6% in other countries, and 17.9% in Portugal (Table 2).

Altogether, the remission rate would increase from 5.8 to 15.8% if the Boolean 3v-remission was used instead of the 4v, i.e., if PGA was excluded from the definition. The maximum difference was observed in Portugal: from 9.0 to 26.9% (Table 2). PGA was clearly the major obstacle to 4v-remission, justifying 79.7% of all the cases of near-remission in the overall sample.

The inclusion of PGA in the DAS28-CRP formula led to a drop of 1.8% in the remission rate in the overall sample (16.7 versus 14.9%) (Table 2), a difference that varied from 0.5% in India to 3.2% in Portugal. If the low disease activity state was considered the target, the decrease in rate imposed by PGA was 2.9% in the overall sample (24.8 versus 21.9%), reaching a maximum difference of 4.3% in Portugal.

PGA values among patients in (near-)remission and "strict 3v-remission"

Figure 1 presents the distribution of PGA in these patients with low or null signs of inflammation. It shows that a considerable proportion report a high PGA: 37.4% of patients in ACR/EULAR Boolean PGA-near-remission had a PGA >4/10. The mean (SD) PGA in these patients was 3.9 (2.0) for the overall sample, with similar values in the different countries (Table 3). Among patients in PGA-near-remission, 13.1% and 9.8% were in SDAI and CDAI remission states, respectively (data not shown).

Considering only the patients with SJC28=0, TCJ28=0, and CRP (mg/dl) ≤0.5, herein defined as in “strict 3v-remission” (n=2395), only 43.5% had a PGA≤1 and 20.0% had a PGA>4.

The mean (SD) PGA among patients in DAS28CRP3v remission was 2.5cm (2.3), while for patients in low disease activity state was 3.7cm (2.4) (Table 3).

PGA associations with inflammation-related variables and with disease impact measures

In the overall sample, the correlation of PGA was strong with Pain (r_p=0.75), moderate with function (r_p=0.52) and DAS28-CRP(3v) (r_p=0.51), and weak with the individual components of DAS28-CRP(3v) (all p<0.001) (Table 4). The correlation between DAS28-CRP(3v) and PGA in patients in remission and in low disease activity was 0.25. These correlations varied considerably across countries, with patients from the Netherlands and India presenting the lowest correlations between PGA and inflammatory and patient-reported measures. There was a clear relationship between DAS28 and PGA: the mean value of PGA in patients with high disease activity, as defined by DAS28, was 6.2 as compared to 2.5 for patients in remission (Table 3).

In multivariable analysis, pain ($\beta_{standardized}$=0.591) and function ($\beta_{standardized}$=0.156) were the main explanatory factors of PGA. To a smaller extent, TJC28 ($\beta_{standardized}$=0.111), CRP

($\beta_{standardized}$=0.034), and SJC28 ($\beta_{standardized}$=0.030) were also statistically significant in the model, which explains 57.3% of PGA's variance (p<0.001) (Table 5).

DISCUSSION

This study assessed the influence of PGA on the classification of patients' remission status according to two definitions, using a large international clinical practice cohort, and tested its associations with factors predominantly associated with "inflammatory activity" or with impact of disease.

Overall, the ACR/EULAR Boolean-based (4v-) remission was achieved by 5.8% of the patients but another 10% failed to meet criteria for this status solely because of PGA>1. This difference varies across countries: from 1.7% in India to 17.9% in Portugal. Previous studies (10, 21-25) have reported PGA-near-remission rates between 14% (n=236, European patients) (25) and 38% (n=309, patients from Coimbra, Portugal) (10). Obviously, dropping a factor from an equation, especially if Boolean, will lead to an increase in the proportion of observations being determined/filtered. However, PGA stands out from the other factors used to define remission because it: i) is much more subjective than other factors, and conveys information that is unrelated to inflammation, ii) cannot be expected to improve with immunosuppressive therapy in patients who are otherwise in remission, and iii) is responsible for 10 fold more cases of near-remission in the Boolean-based definition than each of the others factors (10.0%, versus 1.0, 0.9, and 0.7% for CRP, TJC28, SJC28 respectively – Table 2).

These results demonstrate a remarkable impact of PGA on the rate of patients achieving treatment target and suggest that 10% of RA patients overall and up to 38% of all RA patients in certain settings (10) may be exposed to an overtreatment risk, if rheumatologists adhere strictly to the current Boolean definition of target (29).

This is certainly worrying, unless PGA is shown to represent disease dimensions that are amenable to improvement by the therapies being considered, typically immunosuppressive agents. This is not supported by our data.

If we consider only the patients whose treatment is recommended to increase based solely on PGA (PGA-near-remission), PGA shows no relationship with disease activity (Table 5), nor should it be expected to, given that SJC28, TJC28 and CRP (mg/dl) are all ≤1. The observation that 20% of the 2395 patients in "strict 3v-remission" scored PGA >4, underlines this interpretation and questions the possibility that high PGA values in such patients may be a reflection of subclinical inflammation (37, 38). Although PGA has been previously attributed high face validity in overall samples of RA patients (18), this becomes obviously questionable in patients with low or absent signs of active inflammation. Confounding factors, namely the different interpretation of non-standardized questions (20, 39), and the impact of unrelated factors, such as comorbidities or psychological distress, become of paramount importance (10, 18, 40).

Our data also demonstrate, as expected, that PGA has a positive correlation with disease activity. Considering the overall sample, PGA was associated with pain and function (HAQ-DI) and also, although to a lesser extent, with objective measures of disease activity (SJC28, CRP). Explaining the discrepancy observed between countries regarding the correlation between PGA and parameters of disease activity is beyond the scope of this paper. A multitude of factors, including patient education on PROs, and patient expectations are probably involved (41, 42).

Overall, mean values of PGA were lower in patient groups with lower indices of disease activity. This is true at the group level (40). However, if we adopt the treat-to-target strategy, classification becomes individual and dichotomised (remission versus non-remission) – correlations are no longer relevant as even factors with a good correlation may become inadequate for classification. This is critical when classification has important treatment implications.

The present study has some strengths and limitations**.** METEOR also incorporates data imported from other registries and the formulation of the PGA question presented to patients is not exactly the same. Our previous research (19) suggests that PGA score varies by different formulations of the question. There was a significant amount of missing data (e.g. BMI, smoking status, erosions) that could introduce some selection bias. A sizeable proportion of PGA's variance was not explained by our models, in part because other variables that have been shown to impact upon PGA, such as fatigue and stiffness, are not available in METEOR. As health related quality of life measures are not included in the METEOR, we were unable to assess the correlation between PGA and quality of life. However, other studies have demonstrated that PGA correlates better with quality of life measures than with these predominantly inflammatory measures (43). There may also exist a selection bias derived from the fact that countries/centres that adopt a more regular metrology, and thus contribute to cooperative databases, are the ones with better adherence to therapeutic guidelines. In our analyses we have compared results across countries with quite different levels of income and cultural background. As main strengths, this study used a large database, from clinical practice and from rich and poor countries, with a diversity of cultural backgrounds. In addition, we used both simple and powerful statistical analyses allowing easier interpretation and implementation of the results in clinical practice, while providing strong evidence for practice and further research.

Taken together, the current results and published evidence described above suggest that PGA has a general correlation with disease activity level, which makes it an appropriate component of indices used for a semi-quantitative evaluation of disease status, in a strategy aimed at making the patient better. They also demonstrate, however, that PGA lacks specificity and biological support around the cut-off points used to define treatment target and make therapeutic decisions, as demonstrated by a correlation of just 0.25 with DAS28CRP(3v) in patients in low-disease activity and remission states. A target should, by definition, be sharp and meaningful, especially when we are dealing with targeted

immunosuppressive agents. The mean value of PGA for patients otherwise in remission (3.9 cm) and its distribution (37% have a PGA>4) suggest that this cannot be properly resolved by simply increasing the maximum acceptable value of PGA to 2 or 3, as previously suggested (27, 28).

This evidence supports our proposal for a dual-target strategy to manage RA (10, 29): (i) a biological remission target, aiming at the control of inflammation, defined by the 3v-remission concept and used to guide immunosuppressive therapy, and (ii) a symptom-remission target, defined by a well-validated and discriminative PRO, such as the Rheumatoid Arthritis Impact of Disease (RAID) score, to guide adjuvant therapy for the control of the disease impact factors (symptom remission). Achieving inflammatory remission should be seen as a strong contribution towards remission of disease impact, but not a guarantee. Both targets should be considered independent but obligatory and complementary, requiring equal attention from rheumatologists and the caring team (12). The full resolution of the impact of disease on patients' lives (the ultimate objective of treatment) will certainly require a multidisciplinary approach involving nurses, physiotherapists, occupational therapists, psychologists and other health care professionals. This dual target strategy and separation of measures would ensure that remission is more meaningful to patients, while it is likely to reduce the risk of overtreatment with immunosuppressants (10, 12, 29). A study protocol within the scope of this proposal was recently published by a Danish research group (44), reinforcing its current scientific and clinical relevance.

Nevertheless, with or without PGA, physicians should always be aware of the limitations of disease activity indices (such as non-inclusion of the feet, size and relevance of involved joints to the individual patients, active swollen joints versus cold chronic scarring) and holistically consider patient's symptoms, needs, and individual circumstances (1, 2, 45).

Further investigation will be required to verify whether the exclusion of PGA from the definition of remission negatively affects its long-term predictive value of important outcomes such as radiographic damage and physical function. This work is currently underway (46). A

detailed examination of the potential association of PGA with subclinical inflammation in patients otherwise in remission is also warranted.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. RJOF had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design: RJOF, CD, MN, DvdH, PMM, JAPS.

Cleaning database: RJOF and PDC.

Statistical Analysis: RJOF and PMM.

Interpretation of data: All authors

ACKNOWLEDGMENTS:

We would like to thank the Merit Board for all of their support and to all METEOR investigators. Thank you also to Ms Manjit Saluja who contributed substantially to the Indian data collection. We would like to acknowledge Sytske-Anne Bergstra (Leiden, Netherlands) and Rosaline van den Berg (Rotterdam, Netherlands) for their support in database management and characterization. We would like to specially acknowledge Laure Gossec (Paris, France), Maarten de Wit (Amsterdam, Netherlands), Johannes W. G. Jacobs (Utrecht, Netherlands), and Eduardo Santos (Coimbra, Portugal) for their support in developing the concept of dual-target.

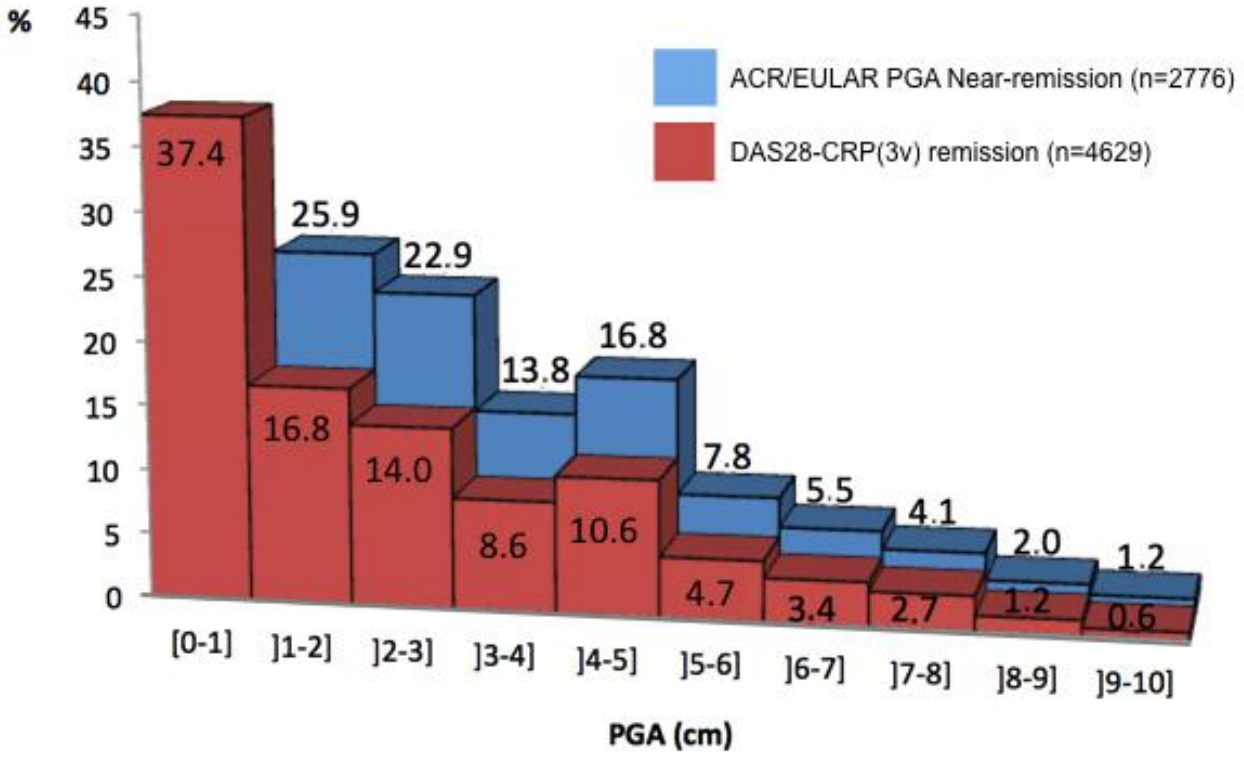
REFERENCES

1. Smolen JS, Landewe R, Bijlsma J, Burmester G, Chatzidionysiou K, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis;76:960-77.
2. Singh JA, Saag KG, Bridges SL, Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Care Res 2016;68:1-25.
3. Martins FM, da Silva JA, Santos MJ, Vieira-Sousa E, Duarte C, Santos H, et al. DAS28, CDAI and SDAI cut-offs do not translate the same information: results from the Rheumatic Diseases Portuguese Register Reuma.pt. Rheumatology (Oxford) 2015;54:286-91.
4. Boers M. Let's stop fooling ourselves. In RA, only ACR/EULAR criteria define remission and equate with absence of disease! Ann Rheum Dis 2016;75:e68.
5. Felson DT, Smolen JS, Wells G, Zhang B, van Tuyl LH, Funovits J, et al. American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Arthritis Rheum 2011;63:573-86.
6. Fransen J, van Riel PL. The Disease Activity Score and the EULAR response criteria. Rheum Dis Clin North Am 2009;35:745-57, vii-viii.
7. Aletaha D, Smolen J. The Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI): a review of their usefulness and validity in rheumatoid arthritis. Clin Exp Rheumatol 2005;23:S100-8.
8. Aletaha D, Nell VP, Stamm T, Uffmann M, Pflugbeil S, Machold K, et al. Acute phase reactants add little to composite disease activity indices for rheumatoid arthritis: validation of a clinical activity score. Arthritis Res Ther 2005;7:R796-806.
9. van Tuyl LH, Sadlonova M, Davis B, Flurey C, Goel N, Hewlett SE, et al. Remission in Rheumatoid Arthritis: Working Toward Incorporation of the Patient Perspective at OMERACT 12. J Rheumatol 2016;43:203-7.
10. Ferreira RJO, Duarte C, Ndosi M, de Wit M, Gossec L, da Silva JAP. Suppressing Inflammation in Rheumatoid Arthritis: Does Patient Global Assessment Blur the Target? A Practice-Based Call for a Paradigm Change. Arthritis Care Res (Hoboken) 2018;70:369-78.
11. Bykerk VP, Massarotti EM. The new ACR/EULAR remission criteria: rationale for developing new criteria for remission. Rheumatology (Oxford) 2012;51(Suppl 6):vi16-20.
12. Ferreira RJO, Duarte C, Ndosi M, de Wit M, Gossec L, da Silva JAP. The controversy of including PGA to define remission in RA. Nat Rev Rheumatol 2018;14:245.
13. Studenic P, Radner H, Smolen JS, Aletaha D. Discrepancies between patients and physicians in their perceptions of rheumatoid arthritis disease activity. Arthritis Rheum 2012;64:2814-23.
14. Khan NA, Spencer HJ, Abda EA, Alten R, Pohl C, Ancuta C, et al. Patient's global assessment of disease activity and patient's assessment of general health for rheumatoid arthritis activity assessment: are they equivalent? Ann Rheum Dis 2012;71:1942-9.
15. Navarro-Compan V, Gherghe AM, Smolen JS, Aletaha D, Landewe R, van der Heijde D. Relationship between disease activity indices and their individual components and radiographic progression in RA: a systematic literature review. Rheumatology (Oxford) 2015;54:994-1007.
16. Svensson B, Andersson ML, Bala SV, Forslind K, Hafstrom I. Long-term sustained remission in a cohort study of patients with rheumatoid arthritis: choice of remission criteria. BMJ open 2013;3:e003554.
17. Gul HL, Ferreira JF, Emery P. Remission in rheumatoid arthritis: is it all the same? Expert Rev Clin Pharmacol 2015;8:575-86.
18. Nikiphorou E, Radner H, Chatzidionysiou K, Desthieux C, Zabalan C, van Eijk-Hustings Y, et al. Patient global assessment in measuring disease activity in rheumatoid arthritis: a review of the literature. Arthritis Res Ther 2016;18:251.

19. Ferreira RJO, Eugenio G, Ndosi M, Silva C, Medeiros C, Duarte C, et al. Influence of the different "patient global assessment" formulations on disease activity score by different indices in rheumatoid arthritis. Clin Rheumatol 2018;37:1963-1969. doi: 10.1007/s10067-018-4063-9.
20. Hirsh J, Wood P, Keniston A, Peng M, Ramaswami S, Caplan L, et al. Limited health literacy predicts patient confusion about patient global assessments of disease activity and rheumatoid arthritis model disease states. Arthritis Care Res (Hoboken) 2018 Published Online First: 2018/06/29. doi: 10.1002/acr.23692.
21. Studenic P, Smolen JS, Aletaha D. Near misses of ACR/EULAR criteria for remission: effects of patient global assessment in Boolean and index-based definitions. Ann Rheum Dis 2012;71:1702-5.
22. Vermeer M, Kuper HH, van der Bijl AE, Baan H, Posthumus MD, Brus HL, et al. The provisional ACR/EULAR definition of remission in RA: a comment on the patient global assessment criterion. Rheumatology (Oxford) 2012;51:1076-80.
23. Balogh E, Dias JM, Orr C, Mullan R, Harty L, FitzGerald O, et al. Comparison of remission criteria in a tumour necrosis factor inhibitor treated rheumatoid arthritis longitudinal cohort: patient global health is a confounder. Arthritis Res Ther 2013;15:R221.
24. Ferreira RJO, Dougados M, Kirwan J, Duarte C, de Wit M, Soubrier M, et al. Drivers of patient global assessment in patients with rheumatoid arthritis who are close to remission: an analysis of 1588 patients. Rheumatology (Oxford) 2017;56:1573-8.
25. Gossec L, Kirwan JR, de Wit M, Balanescu A, Gaujoux-Viala C, Guillemin F, et al. Phrasing of the patient global assessment in the rheumatoid arthritis ACR/EULAR remission criteria: an analysis of 967 patients from two databases of early and established rheumatoid arthritis patients. Clin Rheumatol 2018;37:1503-10.
26. van Tuyl LHD, Boers M. Rheumatoid arthritis: Remission - keeping the patient experience front and centre. Nat Rev Rheumatol 2017;13:573-4.
27. Masri KR, Shaver TS, Shahouri SH, Wang S, Anderson JD, Busch RE, et al. Validity and reliability problems with patient global as a component of the ACR/EULAR remission criteria as used in clinical practice. J Rheumatol 2012;39:1139-45.
28. Wells GA, Boers M, Shea B, Brooks PM, Simon LS, Strand CV, et al. Minimal disease activity for rheumatoid arthritis: a preliminary definition. J Rheumatol 2005;32:2016-24.
29. Ferreira RJO, Ndosi M, de Wit M, Santos EJF, Duarte C, Jacobs JWG, et al. Dual target strategy: a proposal to mitigate the risk of overtreatment and enhance patient satisfaction in rheumatoid arthritis. Ann Rheum Dis 2018 Published Online First: 2018/08/22. doi: 10.1136/annrheumdis-2018-214199.
30. Acebes C, Andreu JL, Balsa A, Batlle E, de Toro-Santos J, Garcia Llorente F, et al. Exploring the remission concept in rheumatoid arthritis with patients and rheumatologists: time for a new approach? Clin Exp Rheumatol 2017;35:816-22.
31. Lukas C, Huizinga T, van der Heijde D. METEOR as an information technology tool to assess rheumatoid arthritis disease activity in clinical practice and improve patient outcome via tailor-made treatment. Int J Adv Rheumatol 2009;7:44-50.
32. Bergstra SA, Machado PM, van den Berg R, Landewe RB, Huizinga TW. Ten years of METEOR (an international rheumatoid arthritis registry): development, research opportunities and future perspectives. Clin Exp Rheumatol 2016;34:S87-s90.
33. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum 1980;23:137-45.
34. van der Heijde DM, van't Hof MA, van Riel PL, van Leeuwen MA, van Rijswijk MH, van de Putte LB. Validity of single variables and composite indices for measuring disease activity in rheumatoid arthritis. Ann Rheum Dis 1992;51:177-81.
35. Fleischmann RM, van der Heijde D, Gardiner PV, Szumski A, Marshall L, Bananis E. DAS28-CRP and DAS28-ESR cut-offs for high disease activity in rheumatoid arthritis are not interchangeable. RMD open 2017;3:e000382.

36. Sharma AK. Textbook of correlations and regression. New Delhi: Discovery Publishing House; 2005.
37. Saleem B, Brown AK, Keen H, Nizam S, Freeston J, Wakefield R, et al. Should imaging be a component of rheumatoid arthritis remission criteria? A comparison between traditional and modified composite remission scores and imaging assessments. Ann Rheum Dis 2011;70:792-8.
38. Nguyen H, Ruyssen-Witrand A, Gandjbakhch F, Constantin A, Foltz V, Cantagrel A. Prevalence of ultrasound-detected residual synovitis and risk of relapse and structural progression in rheumatoid arthritis patients in clinical remission: a systematic review and meta-analysis. Rheumatology (Oxford) 2014;53:2110-8.
39. Henriques M, Duarte C, Ndosi M, Marques A, Silva JAP, Ferreira RJO. “It can't be zero”: a qualitative study of patients' perspective on patient global assessment in rheumatoid arthritis [abstract]. Ann Rheum Dis 2017;76(Suppl 2):112.
40. Jacobs JW, Ten Cate DF, van Laar JM. Monitoring of rheumatoid arthritis disease activity in individual patients: still a hurdle when implementing the treat-to-target principle in daily clinical practice. Rheumatology (Oxford) 2015;54:959-61.
41. Hifinger M, Putrik P, Ramiro S, Keszei AP, Hmamouchi I, Dougados M, et al. In rheumatoid arthritis, country of residence has an important influence on fatigue: results from the multinational COMORA study. Rheumatology (Oxford) 2016;55:735-44.
42. Putrik P, Ramiro S, Hifinger M, Keszei AP, Hmamouchi I, Dougados M, et al. In wealthier countries, patients perceive worse impact of the disease although they have lower objectively assessed disease activity: results from the cross-sectional COMORA study. Ann Rheum Dis 2016;75:715-20.
43. Harrison MJ, Boonen A, Tugwell P, Symmons DP. Same question, different answers: a comparison of global health assessments using visual analogue scales. Qual Life Res 2009;18:1285-92.
44. Jørgensen TS, Lykkegaard JJ, Hansen A, Schrøder HM, Stampe B, Sweeney A-MT, et al. Protocol for evaluating and implementing a pragmatic value-based healthcare management model for patients with inflammatory arthritis: a Danish population-based regional cohort and qualitative implementation study. BMJ open 2018;8.
45. Nikiphorou E, Aletaha D, Bukhari M. Are we failing patients in our assessment of treatment failure? Rheumatology (Oxford) 2018 Published Online First: 2018/06/14. doi: 10.1093/rheumatology/key107.
46. Ferreira RJO, Welsing PMJ, Gossec L, Jacobs JWG, Machado PM, van der Heijde DM, et al. The impact of patient global assessment in the definition of remission as a predictor of long-term radiographic damage in patients with rheumatoid arthritis: protocol for an individual patient data meta-analysis. Acta Reumatol Port 2018;43:52-60.

Figure 1 - PGA distribution in patients with RA in remission by DAS28-CRP(3v) and in PGA-Near-remission.



ACR: American College of Rheumatology; CRP: C-reactive protein; DAS28CRP3v: disease activity score with 28-joint counts using C-reactive protein and 3 variables; EULAR: European League Against Rheumatology; PGA: Patient Global Assessment.

Figure 1 footnote: PGA-Near-remission patients are defined as having Tender 28-Joint Counts ≤1, Swollen 28-Joint Counts ≤1, CRP (mg/dl) ≤1 and PGA >1/10; thus, in the graph there are no patients within the [0- 1] interval (those were classified in ACR/EULAR Boolean-based remission).

Table 1 - Summary of the clinical and demographic characteristics of the study population (n=27768[a]).

Variable	Observed Values [b]	Missing %
Female, n (%)	21976 (79.7)	0.7
Age at visit (years)	52.6 (14.1)	1.8
Country with GDP >20.000 int. Dol., n (%)	16319 (59.7)	1.5
Disease duration, since diagnosis [c] (years)	4.3 (7.3)	7.6
Year of Diagnosis ≥2000, n (%)	21430 (83.4)	7.6
Rheumatoid factor positive, n (%)	17076 (74.7)	17.7
ACPA positive, n (%)	11533 (71.5)	58.1
Erosions, n (%)	7359 (54.6)	51.4
Treatment with steroids, n (%)	10407 (37.5)	0.0
Treatment with csDMARDs, n (%)	19556 (70.4)	0.0
Treatment with bDMARDs, n (%)	6449 (23.2)	0.0
Treatment with tsDMARDs, n (%)	2 (<0.1)	0.0
TJC28	9.1 (9.0)	0.0
SJC28	4.6 (5.3)	0.0
CRP mg/dl	2.2 (3.0)	0.0
PGA (0-10)	4.9 (2.6)	0.0
DAS28-CRP(3v)	4.2 (2.6)	0.0
SDAI remission (≤3.3), n (%)	1419 (6.4)	20.8
CDAI remission (≤2.8), n (%)	1418 (6.4)	20.8
Pain (0-10)	4.9 (2.6)	9.3
HAQ-DI (0-3)	1.1 (0.7)	20.0

ACPA: anti-citrullinated antibody; bDMARDs: Biological Disease-Modifying Antirheumatic Drugs; CDAI: Clinical Disease Activity Index; CRP: C-reactive protein; csDMARDs: Conventional Synthetic Disease-Modifying Antirheumatic Drugs; DAS28CRP: disease activity score with 28-joint counts using C-reactive protein; GDP: Gross Domestic Product; HAQ-DI: health assessment questionnaire disability index; PGA: Patient Global Assessment; SDAI: Simplified Disease Activity Index; SJC28: swollen 28-joint count; TJC28: tender 28-joint count; tsDMARDs: Target Synthetic Disease-Modifying Antirheumatic Drugs; VAS: visual analogue scale.
a. One visit only per patient (the first visit providing all Boolean criteria)
b. Values are mean (SD) unless stated.
dc This definition was chosen instead of time since the date of the onset of symptoms because the latter had significantly more missing data (28.2%; mean (SD) = 6.9 (8.1) years).

Table 2 - Impact of PGA in the various remission criteria, in the overall sample and by country

Disease activity status	Overall sample n=27768	The Netherlands n=3296	Italy n=4156	Portugal n=4373	India n=8936	Other countries n=7007
ACR/EULAR Boolean-based, n (%)						
4v-Remission [a]	1605 (5.8)	202 (6.1)	243 (5.8)	395 (9.0)	5 (0.1)	760 (10.8)
PGA-near-remission [b]	2776 (10.0)	453 (13.7)	293 (7.1)	784 (17.9)	151 (1.7)	1095 (15.6)
Non-remission [c]	23387 (84.2)	2641 (80.2)	3620 (87.1)	3194 (73.1)	8780 (98.2)	5152 (73.6)
(Proposed) 3v-Remission [d]	*4381 (15.8)*	*655 (19.8)*	*536 (12.9)*	*1179 (26.9)*	*156 (1.8)*	*1855 (26.4)*
Near-Remission [e] only, n (%)						
due to PGA	2776 (79.7)	453 (74.1)	293 (78.3)	784 (82.4)	151 (91.5)	1095 (79.4)
due to CRP	271 (7.8)	57 (9.3)	31 (8.3)	82 (8.6)	5 (3.0)	96 (7.0)
due to TJC28	249 (7.2)	63 (10.3)	32 (8.6)	47 (4.9)	8 (4.8)	99 (7.2)
due to SJC28	185 (5.3)	38 (6.2)	18 (4.8)	39 (4.1)	1 (0.6)	89 (6.5)
DAS28CRP3v [f], n (%)						
Remission (<2.4)	4629 (16.7)	601 (18.2)	561 (13.5)	1269 (29.0)	142 (1.6)	2056 (29.3)
Low (≥2.4 ≤2.9)	2258 (8.1)	434 (13.2)	313 (7.5)	514 (11.8)	210 (2.4)	787 (11.3)
DAS28CRP4v [f], n (%)						
Remission (<2.4)	4131 (14.9)	551 (16.7)	503 (12.1)	1130 (25.8)	96 (1.1)	1851 (26.4)
Low (≥2.4 ≤2.9)	1957 (7.0)	395 (12.0)	236 (5.7)	468 (10.7)	150 (1.7)	708 (10.1)
Differences between 3v and 4v definitions, %						
for DAS28CRP remission / low	1.8% / 2.9%	1.5% / 2.7%	1.4% / 3.2%	3.2% / 4.3%	0.5% / 1.2%	2.9% / 4.1%
for ACR/EULAR Boolean remission	10.0%	13.7%	7.1%	17.9%	1.7%	15.6%

ACR: America College of Rheumatology; DAS28CRP3v: disease activity score with 28-joint counts using C-reactive protein and 3 variables; DAS28CRP4v: disease activity score with 28-joint counts using C-reactive protein and 4 variables; EULAR: European League Against Rheumatology; SJC28: swollen 28-joint count; TJC28: tender 28-joint count; CRP: C-reactive protein; PGA: Patient Global Assessment

a. 4v-Remission = TJC28, SJC28, CRP mg/dl, and PGA all ≤1

b. PGA-near-remission = TJC28, SJC28, and CRP mg/dl all≤1; PGA>1

c. Non-remission = two or more out of the four criterion (TJC28, SJC28, CRP, or PGA) are >1

d. TJC28, SJC28, and CRP mg/dl all≤1; PGA not considered. It equates to merging "4v-remission" and "PGA-near-remission" disease states

e. Near-remission = only one out of the four criterion (TJC28, SJC28, CRP, or PGA) are >1

f. The cut-offs proposed by Fleischmann et al. [29] were used

Table 3 – Mean values of PGA across disease activity states

Disease activity status	Mean (SD) PGA, in cm					
	Overall sample n=27768	**The Netherlands n=3296**	**Italy n=4156**	**Portugal n=4373**	**India n=8936**	**Other countries n=7007**
ACR/EULAR Boolean-based PGA-near remission, n (%)						
Remission [a]	0.4 (0.4)	0.4 (0.4)	0.3 (0.4)	0.4 (0.4)	0.0 (0.0)	0.4 (0.4)
PG-Near-remission [b]	3.9 (2.0)	3.8 (1.9)	4.2 (2.2)	3.9 (1.9)	3.8 (1.6)	3.8 (2.0)
Non-remission [c]	5.3 (2.4)	4.1 (2.6)	6.1 (2.5)	5.1 (2.6)	5.5 (1.8)	5.2 (2.7)
DAS28CRP3v [d], n (%)						
Remission (<2.4)	2.5 (2.3)	2.6 (2.2)	2.4 (2.4)	2.7 (2.3)	3.7 (1.6)	2.4 (2.3)
Low (≤2.9)	3.7 (2.4)	3.2 (2.3)	4.0 (2.6)	3.6 (2.4)	4.2 (1.8)	3.7 (2.5)
Moderate (≤4.6)	4.9 (2.3)	4.0 (2.5)	5.7 (2.2)	4.9 (2.4)	4.9 (1.8)	4.9 (2.4)
High (>4.6)	6.2 (2.1)	4.8 (2.6)	7.2 (2.1)	6.5 (2.2)	5.9 (1.7)	6.8 (2.2)

ACR: America College of Rheumatology; DAS28CRP3v: disease activity score with 28-joint counts using C-reactive protein and 3 variables; EULAR: European League Against Rheumatology; PGA: Patient Global Assessment

a. Remission = TJC28, SJC28, CRP mg/dl, and PGA all ≤1

b. PGA-Near-remission = TJC28, SJC28, CRP mg/dl, are all ≤1, and PGA >1

c. Non-remission = TJC28 or SJC28 or CRP mg/dl >1, irrespective of PGA value

d. The cut-off proposed by Fleischmann et al. [29] were used

Table 4 - Pearson's Coefficient correlations between PGA and inflammatory and disease impact measures by country and by disease activity status.

	PGA correlation*					
	TJC28	SJC28	CRP mg/dl	DAS28-CRP3v	Pain (0-10) [a]	HAQ-DI [b]
All countries (n=27768)	0.43	0.36	0.23	**0.51**	**0.75**	**0.52**
The Netherlands (n=3296)	0.27	0.17	0.13	0.30	**0.57**	0.39
Italy (n=4156)	**0.51**	0.42	0.18	**0.58**	**0.86**	**0.57**
Portugal (n=4373)	0.48	0.40	0.21	**0.54**	**0.86**	**0.57**
India (n=8936)	0.30	0.20	0.20	0.34	**0.65**	**0.50**
Other countries (n=7007)	**0.52**	0.43	0.24	**0.59**	**0.74**	**0.56**

CRP: C-reactive protein; HAQ-DI: Health Assessment Questionnaire Disability Index; PGA: Patient Global Assessment; SJC28: swollen 28-joint count; TJC28: tender 28-joint count.

a. Percentage of missing data for Pain was 9.3% (Overall sample), 18.6% (The Netherlands), 4.3% (Italy), 21.4% (Portugal), <0.1% (India) and 12.1% (Other countries).

b. Percentage of missing data for HAQ was 19.9% (Overall sample), 49.0% (The Netherlands), 13.8% (Italy), 21.6% (Portugal), 6.9% (India) and 25.5% (Other countries).

* p-values were <0.001 in all instances

Correlations ≥0.50 are in bold.

Table 5 - Multivariable linear regression analysis to explain PGA[a] (n=20719).

variable	Unstandardized β	β	p-value	95% Confidence interval for β		Adjusted R-Square	p-value
				Lower bound	Upper bound		
Constant	1.232		**<0.001**	1.181	1.284		
TJC28	0.030	0.111	**<0.001**	0.027	0.033		
SJC28	0.014	0.030	**<0.001**	0.009	0.19		
CRP mg/dl	0.027	0.034	**<0.001**	0.019	0.035	0.573	**<0.001**
Pain	0.058	0.591	**<0.001**	0.057	0.059		
HAQ-DI	0.548	0.156	**<0.001**	0.510	0.585		

CRP: C-reactive protein; HAQ-DI: Health Assessment Questionnaire Disability Index; PGA: Patient Global Assessment; SJC28: swollen 28-joint count; TJC28: tender 28-joint count.
a. Using Enter's method and TJC28, SJC28, CRP, Pain and HAQ-DI as independent variables.