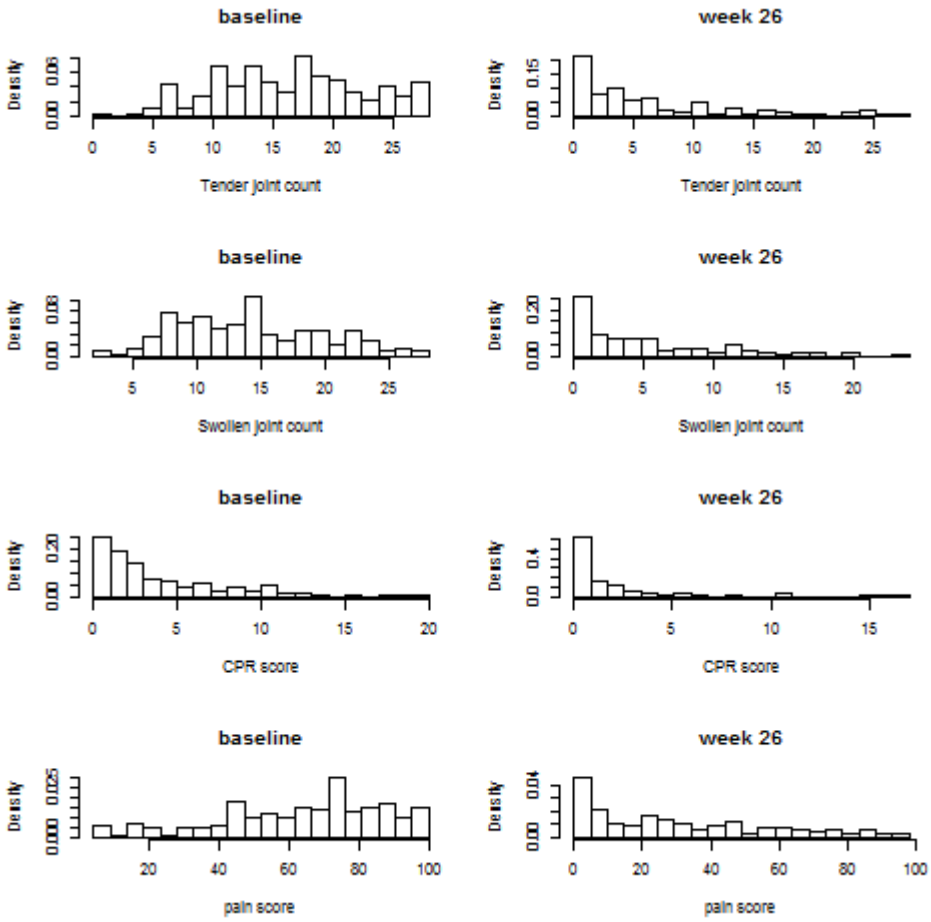
APPENDIX

Effect of treatment on disease activity

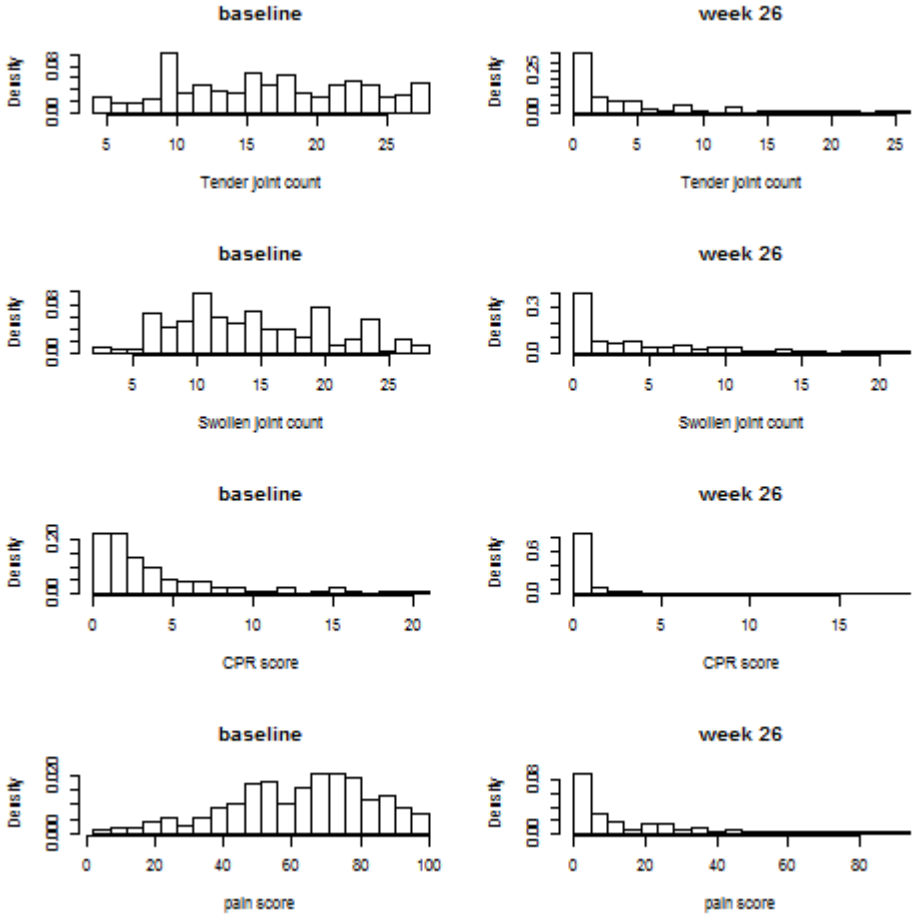
Figure S1 presents the distributions of the 28-joint Disease Activity Score (DAS28) variables at baseline and at 26 weeks after therapy for the methotrexate (MTX) arm in PREMIER.

Figure S1 Short-term effects: MTX.



When using combination therapy with adalimumab + MTX, similarly shaped distributions were observed, but movements between baseline and week 26 were slightly larger compared with MTX alone (ie, from 16.6 to 4.09 for number of tender joints, from 14.3 to 3.88 for number of swollen joints, from 3.84 to 0.89 for C-reactive protein [CRP] concentration, from 62.48 to 15.9 for pain score) (Figure S2).

Figure S2 Short-term effects: adalimumab + MTX.



The number of tender and/or swollen joints (0–28) can be assumed to follow a binomial distribution, of which the mean (denoted as p) differs per patient as a function of the underlying disease activity (act). With a mean between zero and one, we used a logistic function such that:

$$n = bin(p, 28)$$

$$\mathrm{p} = \frac{1}{1 + \exp(\mathrm{C} + \beta.\,\mathrm{act})}$$

When considering the linear part of this probability and by looking at ln(p/(1-p)), we again compared the distributions before and after treatment. Figure S3 shows results for the MTX arm. Given that we have integer values (with the minimum and maximum leading to ±infinity), we set the maximum and minimum of the distribution at slightly lower and higher numbers (±6).

Figure S3 Short-term variables transformed: MTX.

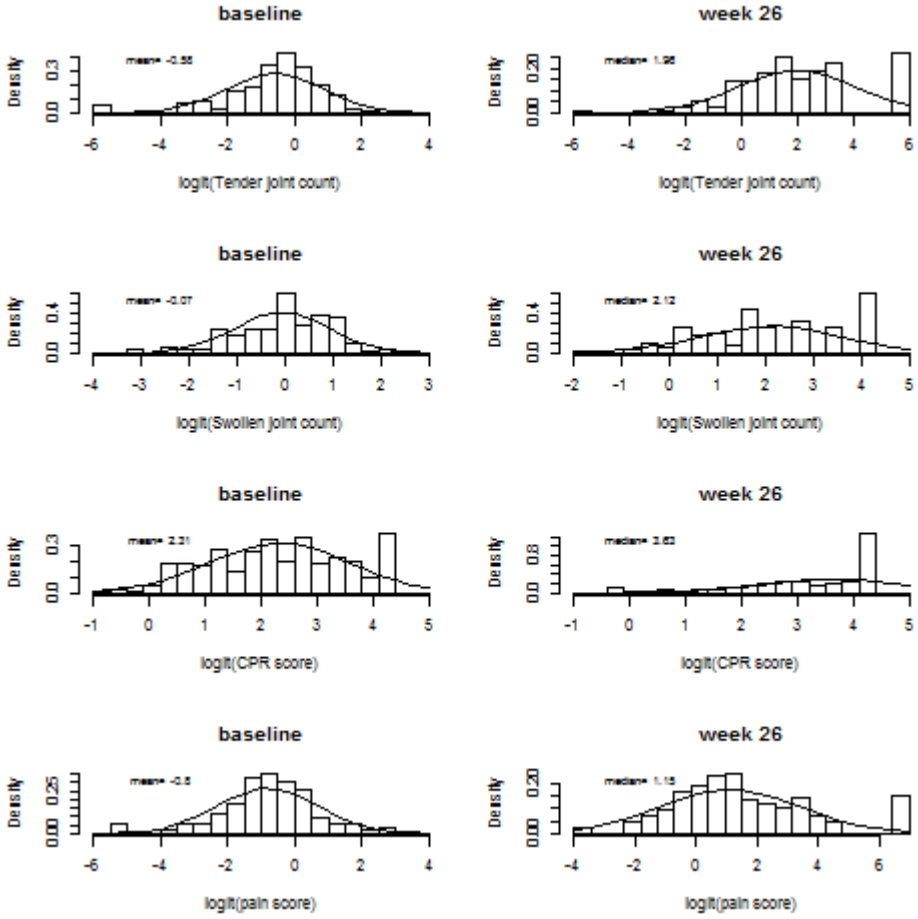
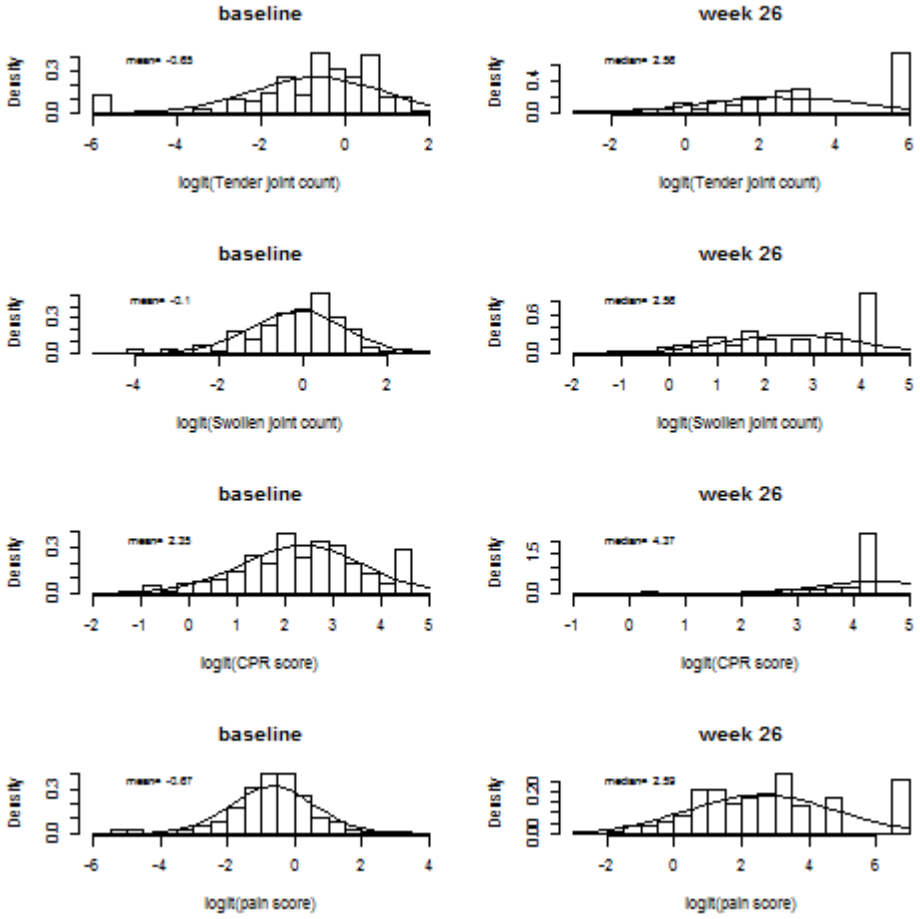


Figure S4 Short-term variables transformed: adalimumab + MTX.



It was found that the logit of the variables followed normal distributions and the patient's base-case score on these 4 domains was randomly taken from a multivariate normal distribution which was estimated on the observed base-case distribution of these variables in the PREMIER trial. The effect of therapy on each of these 4 domains at week 26 was modelled by assigning shifts to the right in the (logit) distribution means, reflecting the improvement in score, estimated again on data observed in PREMIER (Figure S3 and Figure S4). Given the censoring at the right, we used the sample median as the estimator of the new mean. As expected, greater shifts were observed for combination therapy than for monotherapy (figure S4).The shifts follow a multivariate normal distribution and the covariance matrices in both the distribution of the baseline value as well as the shifts capture the positive correlation between the 4 variables.

The fact that the correlation is not perfect implies that, for instance, a treatment that affects pain in a patient may not necessarily improve the number of tender joints in that same patient. After mathematical transformations, the individual components of disease activity were captured using a multivariate normal distribution with shifted means.

The effect of treatment on mTSS

The effect of treatment on mTSS was modeled as a linear function of treatment (tx) and time (months). Regression coefficients for subsequent treatment strategies are assumed to be the same as those applied for MTX.

$$mTSS = Months * (0.4615_{(0.030).}tx + 0.0700_{(0.0029).} * (1 - tx))$$

tx = 1 for MTX therapy and 0 for combination therapy (adalimumab + MTX)
subscript values represent the standard errors of the co-efficients

The effect of disease activity and TSS on the Health Assessment Questionnaire

In the model, the Health Assessment Questionnaire (HAQ) score was derived from the simulated DAS variables and the TSS. The relationship was estimated using logistic regression, adjusted to allow for the fact that the HAQ variable is restricted to values between 0 and 3.

$$E(HAQ) = \frac{\exp(x'\beta)}{1+\exp(x'\beta)} * 3$$

$$x'\beta = -1.73_{(0.3131)} + 0.0031_{(0.0032)}.Sharp + 0.0205_{(0.0126)}.TJ + 0.0631_{(0.0221)}.CRP + 0.0184_{(0.0032)}.Pain$$

subscript values represent the standard errors of the coefficients

The effect relating TSS and HAQ score was nonsignificant. The estimated coefficient suggested that, at the average values of the response variables, a 20-point increase in TSS increased the HAQ score by approximately 0.05. This relationship is less pronounced than that found to be significant in the study by Aletaha et al. (3), who addressed the relationship between TSS and HAQ score concentrating on patients who are in remission. Their results suggested that an increase of 20 TSS points led to an approximate 0.2-point increase in HAQ. Given the short-term horizon of the PREMIER study and assuming that the relationship between TSS and irreversible damage was more pronounced in patients in remission versus patients with active disease, we included the latter estimate. The average HAQ score in PREMIER was approximately 1.5; thus, we estimated the coefficient at 0.02.

Utility as a function of HAQ

The relationship between HAQ and utility, as derived from the Health Utilities Index Mark 3 (HUI3), was also estimated using data from PREMIER. Logistic regression was used as follows:

$$E(utility) = \frac{\exp(x'\beta)}{1+\exp(x'\beta)}$$

$$x'\beta = 1.5213_{(0.0073)} - 0.9693_{(0.0044)} * HAQ$$

subscript values represent the standard errors of the coefficients

Hospital stay and general practitioner visits as a function of HAQ

The model included the costs of medication and general practitioner (GP) visits and hospital stays as the two other main types of direct medical costs. The more severe the effects on health-related quality of life (HRQL), the greater the costs, which was reflected by a relationship between costs and the HAQ score. To reflect that many patients may have zero hospitalizations and zero GP visits, a zero-inflated Poisson model was used.

$$P(gp-visits > 0) = \frac{\exp(x'\beta)}{1+\exp(x'\beta)}$$

$$gp-visits \,|\, (gp-visits > 0) \approx Poisson(x'\alpha)$$

$$x'\beta = 1.7789_{(0.3426)} - 0.7002_{(0.2057)}.HAQ$$

$$x'\alpha = 0.1081_{(0.2499)} + 0.0478_{(0.1355)}.HAQ$$

$$P(hosp-days>0)=\frac{\exp(x'\beta)}{1+\exp(x'\beta)}$$

$$hosp-days\,|\,(hosp-days>0)\approx Poisson(x'\alpha)$$

$$x'\beta=3.616_{(0.4144)}-0.786_{(0.2218)}.HAQ$$

$$x'\alpha=2.4898_{(0.1054)}+0.0497_{(0.0543)}.HAQ$$

Survival as a function of HAQ

The data available from PREMIER were not suitable for estimating survival rates. As such, the conditional probability of death (the hazard rate) was estimated per week (t) as a function of HAQ and age starting at the age of 51 year using the following formula (31):

$$h(t)=\exp(-10.28+0.095*(51+t/52)+\log(2.73)*haq[t]))$$

Patient response as a function of DAS28 variables

In PREMIER, patient response was measured based on the American College of Rheumatology (ACR) criteria. In the model, we included only a subset of four variables from this definition of response; therefore, a link function was needed. For this purpose, patients were categorized in four response (R) categories: R ≤ 20%, 20% < R ≤ 50%, 50% < R ≤ 70%, and R > 70%. We subsequently used ordered logistic regression linking the ACR response to two variables: 1) the relative change in the DAS28 score, calculated as $\mathrm{DAS28}=1.15+1.1.(0.56\sqrt{\mathrm{TJC28}}+0.28\sqrt{\mathrm{SJC28}}+0.36.\ln(\mathrm{CRP}))$ and 2) the difference in the pain score. The linear element and cut off points were as follows:

$$x'\beta=10.19_{\ 0.65}\Delta DAS+0.032_{0.0038}\Delta Pain$$

$$0\,|\,1\ -7.3407_{\ 0.5005}$$

$$1\,|\,2\ -5.2318_{\ 0.4405}$$

$$2\,|\,3\ -3.4187_{\ 0.4008}$$

$$3\,|\,4\ \ 1.1294_{\ 0.4246}$$

Work loss as a function of HAQ

Data on work-related activity from PREMIER were used to estimate the impact of HAQ on lost productivity. A detailed description of the analyses has been presented elsewhere (32).