

Supplement Table S1

PICOs

Population	Patients suffering from RA
Intervention	Management and therapy of RA with targeted levels of disease outcome
Control	Routine Management
Outcome	O1 = Target definition & rates of reaching specific targets O2 = Clinical: SJC, TJC, APR, DAS, DAS28, SDAI, CDAI / ACR- or EULAR response O3 = Functional: HAQ O4 = Radiographic: Erosion Score, Total Sharp Score, Sharp van der Heijde Score

Legend Table S1

Table S1: **APR**, acute phase reactant; **ACR**, American college of rheumatology; **CDAI**, clinical disease activity index; **DAS**, disease activity score; **DAS28**, disease activity score in 28 joints; **EULAR**, European league against rheumatism; **HAQ**, health assessment questionnaire; **SDAI**, simplified disease activity index; **SJC**, swollen joint count; **TJC**, tender joint count.

Supplement Table S2

SLR Update 2012 – Medline

Category	Terms/ MeSH
TX	1 (strateg\$ or aim\$ or goal\$ or target\$ or tight\$ or aggressiv\$ or intens\$ or control\$ or optim\$ or adapt\$ or switch\$ or add\$ or chang\$ or expand\$ or step\$ or combin\$ or intensif\$ or escalat\$).ti. (1351419) 2 ((strateg\$ or aim\$ or goal\$ or target\$ or tight\$ or aggressiv\$ or control\$) adj2 (treat\$ or therap\$)).mp. (232331) 3 (titrat\$ or adjust\$ or adapt\$ or response-based).mp. (733531) 4 ((remission or activ\$) adj3 (strateg\$ or optimi\$ or adapt\$ or control\$ or frequency or dose\$ or dosing)).mp. (68749) 5 *Remission Induction/ (268) 6 (treat\$ and target\$).m_titl. (4705) 7 remove duplicates from 5 (259) 8 remove duplicates from 6 (4494) 9 *Disease Management/ (3736) 10 remove duplicates from 9 (3685) 11 1 or 2 or 3 or 4 or 7 or 8 or 10 (2188096)
DX	12 *Arthritis, Rheumatoid/ (61427)
limits	humans 2008-current

Supplement Table S3

SLR Update 2014 - Medline

Category	Terms/ MeSH
TX	1 (strateg\$ or aim\$ or goal\$ or target\$ or tight\$ or aggressiv\$ or intens\$ or control\$ or optim\$ or adapt\$ or switch\$ or add\$ or chang\$ or expand\$ or step\$ or combin\$ or intensif\$ or escalat\$).ti. (1366688) 2 ((strateg\$ or aim\$ or goal\$ or target\$ or tight\$ or aggressiv\$ or control\$) adj2 (treat\$ or therap\$)).mp. (252474) 3 (titrat\$ or adjust\$ or adapt\$ or response-based).mp. (774681) 4 ((remission or activ\$) adj3 (strateg\$ or optimi\$ or adapt\$ or control\$ or frequency or dose\$ or dosing)).mp. (71226) 5 *Remission Induction/ (319) 6 (treat\$ and target\$).m_titl. (5198) 7 remove duplicates from 5 (310) 8 remove duplicates from 6 (4993) 9 *Disease Management/ (4689) 10 remove duplicates from 9 (4601) 11 1 or 2 or 3 or 4 or 7 or 8 or 10 (2255469)
DX	12 *Arthritis, Rheumatoid/ (64580)
limits	humans (7769) 2012 – current (1080)

Supplement S4

Randomized Comparisons T2T vs. RC. In the STREAM [1] trial, a T2T arm aimed at REM (DAS<1.6), with consecutive step-up therapy including MTX and ADA, and the control arm consisted of traditional DMARDs (no prednisone or biologics were allowed). After a follow-up of 24 months, DAS, DAS remission and HAQ change showed no significant differences between the groups, and also median SHS increase did not differ between the treatment arms (T2T 0 (IQR 0-1.1] and RC: 0.5 (IQR 0-2.5)).

The “Twin target” steered arm of a Japanese trial [2] aimed at reaching DAS28<2.6 as well as normalization of serum matrix metalloproteinase 3 (MMP3). This strategy was compared with two other treatment-targeted arms, one steering at DAS28< 2.6, the other at MMP3 normalization alone. The fourth arm consisted of a routine therapy control group. After a follow-up of 56 weeks, significantly more patients in the Twin group had attained the treatment target (56%) than in the routine control group or in the MMP3 group.

Furthermore, the T2T concept was confirmed in the IDEA study, a double-blind randomized controlled trial with 112 treatment-naïve RA patients comparing the efficacy of methotrexate and infliximab with methotrexate and intravenous corticosteroid for remission induction [3].

Non-randomized studies. In a non-controlled prospective cohort study (DREAM [4]), T2T proved successful: patients with very early RA received target-oriented treatment aiming at remission (DAS28<2.6). After 6 months, 47% achieved the target, 58% good EULAR response and the median time to first DAS28<2.6 was 25.3 weeks (IQR13.0-52.0). After 12 months, 58% achieved the treatment target, 68% good EULAR response, and there was no clinically relevant radiographic progression in a majority of patients.

Comparing the DREAM cohort with a RC cohort of 2 early RA inception cohorts,[5] the authors found that after 1 year, 55% (T2T) versus 30% (RC) of the patients were at DAS28<2.6, and median time to its first achievement was 25 weeks (T2T) vs. >52 weeks (RC) ($p<0.0001$). Furthermore, there was a significant difference in DAS28 change -2.5 (T2T) vs. -1.5 (RC) ($p<0.0001$).

Similarly,[6] comparing the DMARD arms of the BeSt study (N=234) to routine treatment in 2 ERA clinics (N=201) showed significantly better outcomes after 1 year in patients receiving T2T. HAQ improvement was 0.7 vs. 0.5 ($p = 0.029$), 31% vs. 18% of patients had DAS28 <2.6 ($p<0.005$) and median SHS progression was 2.0 (with an expected progression of 7.0) vs. 1.0 (expected progression 4.4); however, as the authors state, the BeSt cohort had longer median disease duration (0.5 vs 0.4 years, $p = 0.016$), higher mean DAS28 (6.1 vs 5.7, $p<0.001$), more rheumatoid factor-positive patients (66% vs 42%, $p<0.001$), and more patients with pre-existing erosions (71% vs 53%, $p<0.001$).

In a comparison of early RA patients included in the GUEPARD trial, a T2T-trial aiming at low disease activity (DAS28ESR<3.2), with routine care patients of the ESPOIR cohort,[7] T2T led to higher percentages of patients characterised as “remission including functional remission (HAQ <0.5) and absence of radiological progression” (32.3% vs 10.2%, $p=0.011$). Also, more patients in the T2T regime were classified as having “low DAS and HAQ <0.5 and absence of radiological progression” (36.1% vs 18.9%, $p=0.045$), and more T2T patients had HAQ<0.5 (70.2% vs 45.2%, $p=0.005$). There was no difference in DAS decrease and EULAR,

ACR responses, and the mean SHS progression was similar in the two groups as was the percentage of patients without progression.

Supplement Table S5

Additional references presented to the task force

Presented to the task force in the year	Author	Domain
2012	Moreland et al, 2012 [8]	Supportive Evidence
2012	Vermeer et al, 2011 [4]	Supportive Evidence
2012	Emery et al, 2011 [9]	Supportive Evidence
2012	Gullick et al, 2012 [10]	Supportive Evidence
2012	Smolen et al, 2009 [11]	Supportive Evidence
2012	Aletaha et al 2009 [12]	Supportive Evidence
2012	Ma et al, 2010 [13]	Supportive Evidence
2012	Brown et al, 2008 [14]	Supportive Evidence
2012	Van der Heijde et al, 2005 [15]	Supportive Evidence
2012	Aletaha et al, 2011 [16]	Supportive Evidence
2012	Dougados et al, 2013 [17]	Supportive Evidence
2012	Hama et al, 2012 [18]	Supportive Evidence
2012	Fukae et al, 2011 [19]	Supportive Evidence
2012	Fukae et al, 2010 [20]	Supportive Evidence
2012	Naredo et al, 2008 [21]	Supportive Evidence
2012	Pascual-Ramos et al, 2009 [22]	Supportive Evidence
2012	Foltz et al, 2012 [23]	Supportive Evidence
2012	Bugatti et al, 2012 [24]	Supportive Evidence
2012	Suter et al, 2011 [25]	Supportive Evidence
2012	Gandjbakhch et al, 2011 [26]	Supportive Evidence
2012	Boyesen et al, 2011 [27]	Supportive Evidence
2012	Dohn et al, 2011 [28]	Supportive Evidence
2012	Haavardsholm et al, 2008 [29]	Supportive Evidence
2012	Provan et al, 2011 [30]	Supportive Evidence
2012	Solomon et al, 2010 [31]	Supportive Evidence
2012	Scire et al, 2013 [32]	Supportive Evidence

Presented to the task force in the year	Author	Domain
2014	Dirven et al, 2012 [33]	Follow Up of previously found studies
2014	Van den Broek et al, 2013 [34]	Follow Up of previously found studies
2014	Radner et al, 2012 [35]	Patient Self Assessment
2014	Cheung et al, 2013 [36]	Patient Self Assessment
2014	Dougados et al, 2013 [37]	Patient Self Assessment
2014	Van der Goes et al, 2013 [38]	Comorbidities
2014	Dirven et al, 2012 [39]	Comorbidities
2014	Krishnan et al, 2012 [40]	Comorbidities

References Supplementary File

1. van Eijk IC, Nielen MM, van der Horst-Bruinsma I, Tjhuis GJ, Boers M, Dijkmans BA, et al. Aggressive therapy in patients with early arthritis results in similar outcome compared with conventional care: the STREAM randomized trial. *Rheumatology*. 2012 Apr; 51(4):686-694.
2. Urata Y, Uesato R, Tanaka D, Nakamura Y, Motomura S. Treating to target matrix metalloproteinase 3 normalisation together with disease activity score below 2.6 yields better effects than each alone in rheumatoid arthritis patients: T-4 Study. *Annals of the rheumatic diseases*. 2012 Apr; 71(4):534-540.
3. Nam JL, Villeneuve E, Hensor EM, Conaghan PG, Keen HI, Buch MH, et al. Remission induction comparing infliximab and high-dose intravenous steroid, followed by treat-to-target: a double-blind, randomised, controlled trial in new-onset, treatment-naive, rheumatoid arthritis (the IDEA study). *Annals of the rheumatic diseases*. 2014 Jan; 73(1):75-85.
4. Vermeer M, Kuper HH, Hoekstra M, Haagsma CJ, Posthumus MD, Brus HL, et al. Implementation of a treat-to-target strategy in very early rheumatoid arthritis: results of the Dutch Rheumatoid Arthritis Monitoring remission induction cohort study. *Arthritis and rheumatism*. 2011 Oct; 63(10):2865-2872.
5. Schipper LG, Vermeer M, Kuper HH, Hoekstra MO, Haagsma CJ, Den Broeder AA, et al. A tight control treatment strategy aiming for remission in early rheumatoid arthritis is more effective than usual care treatment in daily clinical practice: a study of two cohorts in the Dutch Rheumatoid Arthritis Monitoring registry. *Annals of the rheumatic diseases*. 2012 Jun; 71(6):845-850.
6. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Kerstens PJ, Nielen MM, Vos K, van Schaardenburg D, et al. DAS-driven therapy versus routine care in patients with recent-onset active rheumatoid arthritis. *Annals of the rheumatic diseases*. 2010 Jan; 69(1):65-69.
7. Soubrier M, Lukas C, Sibilia J, Fautrel B, Roux F, Gossec L, et al. Disease activity score-driven therapy versus routine care in patients with recent-onset active rheumatoid arthritis: data from the GUEPARD trial and ESPOIR cohort. *Annals of the rheumatic diseases*. 2011 Apr; 70(4):611-615.
8. Moreland LW, O'Dell JR, Paulus HE, Curtis JR, Bathon JM, St Clair EW, et al. A randomized comparative effectiveness study of oral triple therapy versus etanercept plus methotrexate in early aggressive rheumatoid arthritis: the treatment of Early Aggressive Rheumatoid Arthritis Trial. *Arthritis and rheumatism*. 2012 Sep; 64(9):2824-2835.
9. Emery P, Mease PJ, Rubbert-Roth A, Curtis JR, Muller-Ladner U, Gaylis NB, et al. Retreatment with rituximab based on a treatment-to-target approach provides better disease control than treatment as needed in patients with rheumatoid arthritis: a retrospective pooled analysis. *Rheumatology*. 2011 Dec; 50(12):2223-2232.
10. Gullick NJ, Oakley SP, Zain A, Gibson T, Jones T, Mistlin A, et al. Goal-directed therapy for RA in routine practice is associated with improved function in patients with disease duration up to 15 years. *Rheumatology*. 2012 Apr; 51(4):759-761.
11. Smolen JS, Han C, van der Heijde DM, Emery P, Bathon JM, Keystone E, et al. Radiographic changes in rheumatoid arthritis patients attaining different disease activity states with methotrexate monotherapy and infliximab plus methotrexate: the impacts of remission and tumour necrosis factor blockade. *Annals of the rheumatic diseases*. 2009 Jun; 68(6):823-827.

12. Aletaha D, Funovits J, Breedveld FC, Sharp J, Segurado O, Smolen JS. Rheumatoid arthritis joint progression in sustained remission is determined by disease activity levels preceding the period of radiographic assessment. *Arthritis and rheumatism*. 2009 May; 60(5):1242-1249.
13. Ma MH, Scott IC, Kingsley GH, Scott DL. Remission in early rheumatoid arthritis. *The Journal of rheumatology*. 2010 Jul; 37(7):1444-1453.
14. Brown AK, Conaghan PG, Karim Z, Quinn MA, Ikeda K, Peterfy CG, et al. An explanation for the apparent dissociation between clinical remission and continued structural deterioration in rheumatoid arthritis. *Arthritis and rheumatism*. 2008 Oct; 58(10):2958-2967.
15. van der Heijde D, Klareskog L, Boers M, Landewe R, Codreanu C, Bolosiu HD, et al. Comparison of different definitions to classify remission and sustained remission: 1 year TEMPO results. *Annals of the rheumatic diseases*. 2005 Nov; 64(11):1582-1587.
16. Aletaha D, Smolen JS. Joint damage in rheumatoid arthritis progresses in remission according to the Disease Activity Score in 28 joints and is driven by residual swollen joints. *Arthritis and rheumatism*. 2011 Dec; 63(12):3702-3711.
17. Dougados M, Devauchelle-Pensec V, Ferlet JF, Jousse-Joulin S, D'Agostino MA, Backhaus M, et al. The ability of synovitis to predict structural damage in rheumatoid arthritis: a comparative study between clinical examination and ultrasound. *Annals of the rheumatic diseases*. 2013 May; 72(5):665-671.
18. Hama M, Uehara T, Takase K, Ihata A, Ueda A, Takeno M, et al. Power Doppler ultrasonography is useful for assessing disease activity and predicting joint destruction in rheumatoid arthritis patients receiving tocilizumab--preliminary data. *Rheumatology international*. 2012 May; 32(5):1327-1333.
19. Fukae J, Isobe M, Kitano A, Henmi M, Sakamoto F, Narita A, et al. Radiographic prognosis of finger joint damage predicted by early alteration in synovial vascularity in patients with rheumatoid arthritis: Potential utility of power doppler sonography in clinical practice. *Arthritis care & research*. 2011 Sep; 63(9):1247-1253.
20. Fukae J, Kon Y, Henmi M, Sakamoto F, Narita A, Shimizu M, et al. Change of synovial vascularity in a single finger joint assessed by power doppler sonography correlated with radiographic change in rheumatoid arthritis: comparative study of a novel quantitative score with a semiquantitative score. *Arthritis care & research*. 2010 May; 62(5):657-663.
21. Naredo E, Moller I, Cruz A, Carmona L, Garrido J. Power Doppler ultrasonographic monitoring of response to anti-tumor necrosis factor therapy in patients with rheumatoid arthritis. *Arthritis and rheumatism*. 2008 Aug; 58(8):2248-2256.
22. Pascual-Ramos V. Hypervascular synovitis and ACR Class. Criteria as predictors of radiographic damage in early RA. *Ultrasound Quart*. 2009; 25(1):31-38.
23. Foltz V, Gandjbakhch F, Etchepare F, Rosenberg C, Tanguy ML, Rozenberg S, et al. Power Doppler ultrasound, but not low-field magnetic resonance imaging, predicts relapse and radiographic disease progression in rheumatoid arthritis patients with low levels of disease activity. *Arthritis and rheumatism*. 2012 Jan; 64(1):67-76.
24. Bugatti S, Manzo A, Caporali R, Montecucco C. Assessment of synovitis to predict bone erosions in rheumatoid arthritis. *Therapeutic advances in musculoskeletal disease*. 2012 Aug; 4(4):235-244.
25. Suter LG, Fraenkel L, Braithwaite RS. Role of magnetic resonance imaging in the diagnosis and prognosis of rheumatoid arthritis. *Arthritis care & research*. 2011 May; 63(5):675-688.
26. Gandjbakhch F, Conaghan PG, Ejbjerg B, Haavardsholm EA, Foltz V, Brown AK, et al. Synovitis and osteitis are very frequent in rheumatoid arthritis clinical remission:

results from an MRI study of 294 patients in clinical remission or low disease activity state. *The Journal of rheumatology*. 2011 Sep; 38(9):2039-2044.

27. Boyesen P, Haavardsholm EA, Ostergaard M, van der Heijde D, Sesseng S, Kvien TK. MRI in early rheumatoid arthritis: synovitis and bone marrow oedema are independent predictors of subsequent radiographic progression. *Annals of the rheumatic diseases*. 2011 Mar; 70(3):428-433.

28. Dohn UM, Ejbjerg B, Boonen A, Hetland ML, Hansen MS, Knudsen LS, et al. No overall progression and occasional repair of erosions despite persistent inflammation in adalimumab-treated rheumatoid arthritis patients: results from a longitudinal comparative MRI, ultrasonography, CT and radiography study. *Annals of the rheumatic diseases*. 2011 Feb; 70(2):252-258.

29. Haavardsholm EA, Boyesen P, Ostergaard M, Schildvold A, Kvien TK. Magnetic resonance imaging findings in 84 patients with early rheumatoid arthritis: bone marrow oedema predicts erosive progression. *Annals of the rheumatic diseases*. 2008 Jun; 67(6):794-800.

30. Provan SA, Semb AG, Hisdal J, Strandén E, Agewall S, Dagfinrud H, et al. Remission is the goal for cardiovascular risk management in patients with rheumatoid arthritis: a cross-sectional comparative study. *Annals of the rheumatic diseases*. 2011 May; 70(5):812-817.

31. Solomon DH, Kremer J, Curtis JR, Hochberg MC, Reed G, Tsao P, et al. Explaining the cardiovascular risk associated with rheumatoid arthritis: traditional risk factors versus markers of rheumatoid arthritis severity. *Annals of the rheumatic diseases*. 2010 Nov; 69(11):1920-1925.

32. Scire CAL, M.; Symmons, D.P.; Verstappen, S.M. . Early and sustained remission is associated with improved survival in patients with inflammatory polyarthritis: Results from the norfolk arthritis register. *Annals of the rheumatic diseases*. 2013; 71:95-96.

33. Dirven L, van den Broek M, Kroon HM, Grillet BA, Han KH, Kerstens PJ, et al. Large-joint damage in patients with early rheumatoid arthritis and its association with treatment strategy and damage of the small joints. *Rheumatology*. 2012 Dec; 51(12):2262-2268.

34. van den Broek M, Dirven L, Kroon HM, Kloppenburg M, Roday HK, Peeters AJ, et al. Early local swelling and tenderness are associated with large-joint damage after 8 years of treatment to target in patients with recent-onset rheumatoid arthritis. *The Journal of rheumatology*. 2013 May; 40(5):624-629.

35. Radner H, Grisar J, Smolen JS, Stamm T, Aletaha D. Value of self-performed joint counts in rheumatoid arthritis patients near remission. *Arthritis research & therapy*. 2012; 14(2):R61.

36. Cheung PP, Gossec L, Ruysen-Witrand A, Le Burlout C, Mezieres M, Dougados M. The relationship of patient-reported joints with active synovitis detected by power Doppler ultrasonography in rheumatoid arthritis. *Clinical and experimental rheumatology*. 2013 Jul-Aug; 31(4):490-497.

37. Dougados M, Nataf H, Steinberg G, Rouanet S, Falissard B. Relative importance of doctor-reported outcomes vs patient-reported outcomes in DMARD intensification for rheumatoid arthritis: the DUO study. *Rheumatology*. 2013 Feb; 52(2):391-399.

38. van der Goes MC, Jacobs JW, Jurgens MS, Bakker MF, van der Veen MJ, van der Werf JH, et al. Are changes in bone mineral density different between groups of early rheumatoid arthritis patients treated according to a tight control strategy with or without prednisone if osteoporosis prophylaxis is applied? *Osteoporosis international : a journal established as result of cooperation between the European Foundation for*

Osteoporosis and the National Osteoporosis Foundation of the USA. 2013 Apr; 24(4):1429-1436.

39. Dirven L, van den Broek M, van Groenendael JH, de Beus WM, Kerstens PJ, Huizinga TW, et al. Prevalence of vertebral fractures in a disease activity steered cohort of patients with early active rheumatoid arthritis. BMC musculoskeletal disorders. 2012; 13:125.

40. Krishnan E, Lingala B, Bruce B, Fries JF. Disability in rheumatoid arthritis in the era of biological treatments. Annals of the rheumatic diseases. 2012 Feb; 71(2):213-218.