PTC-1: Measurement of biopharmaceutical blood concentrations should be performed in a validated laboratory.

Study	Study design	Population	Scope/Intervention	Study population	Results	Tool used for RoB assessment	Risk of Bias
Bodio C. et al, 2020	Observational cross-sectional study.	RA patients treated with Ifx, Ada or Etn	Bridging ELISA vs. RGA Serum samples	163 samples	Agreement between methods: k=0.57 [0.42-0.71]	Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2)	MODERATE (3x low, 1x high)
Clarke WT. et al, 2019	Observational prospective and cross-sectional study	IBD patients treated with IFX or ADA	Direct ELISA (non-specific detection) vs. HMSA (specific detection) Serum samples	IFX: 45 samples ADA: 30 samples	- Measured concentrations were higher by HMSA: IFX: HMSA>ELISA (12.6 [10-17.3] vs 5.7 [4.8-9] µg/mL) p<0.001 ADA: HMSA>ELISA (19.9 [15.6-26] vs 10.3[8.5-14] µg/mL) p<0.001 - Good correlations: IFX: r=0.861; p<0.001 ADA: r=0.935; p<0.001 - Weak Intraclass correlations: IFX (ICC): 0.356 (95% CI=-0.069 to 0.720) ADA (ICC): 0.395 (95% CI=-0.073 to 0.759) - Qualitative agreement: IFX: concentration>5 µg/mL (k=0.106; p=0.113) concentration>7 µg/mL (k=0.050; p=0.283) concentration>10 µg/mL (k=0.095; p=0.134) ADA: concentration>5 µg/mL (k=0.651; p<0.001) concentration>7 µg/mL (k=0.651; p<0.001) concentration>10 µg/mL (k=0.133; p=0.143)	Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2)	LOW (3x low, 1x unclear)
Hock BD. et al, 2019	Observational study	IBD patients treated with ADA	Direct ELISA (non-specific detection) vs. HMSA (specific detection) Serum samples	82 random samples	Pearson's correlation: r=0.91 ICC: 0.88 (95% CI=0.80-0.93)	Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2)	LOW (4x low)
Laserna-Mendieta et al, 2019	Observational study	IBD patients treated with ADA	- Direct ELISA (non-specific detection) vs. QB Sandwich ELISA (specific detection) vs. QB -Direct ELISA (non-specific detection) vs sandwich ELISA (specific detection)	50 samples	**ELISA vs. POC** <u>Quantitative analyses (Bland-Altman limits of agreement)</u>: -Direct ELISA vs QB: 3.1 (-6.6 to 12.8), p<0.001 -Sandwich ELISA vs QB: 3.9 (-5.4 to 13.2), p<0.001 <u>Qualitative analyses</u> Subtherapeutic levels=5µg/mL -Direct ELISA vs QB: 80% agreement; kappa (95%IC): 0.688 (0.515-0.860) -Sandwich ELISA vs QB: 68% agreement; kappa (95%IC): 0.531 (0.351-0.710) Subtherapeutic levels=7.5µg/mL -Direct ELISA vs QB: 78% agreement; kappa (95%IC): 0.660 (0.489-0.832) -Sandwich ELISA vs QB: 62% agreement; kappa (95%IC): 0.454 (0.278-0.630) **ELISA vs. ELISA** Bland-Altman limits of agreement: 0.8 (-3.9 to 5.4), p>0.05	Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2)	LOW (4x low)

Novakovic et al, 2019	Observational study	IBD patients treated with IFX	Sandwich ELISA (specific detection) vs. QB	30 samples	Correlation: r=0.92, p<0.001 The Bland-Altman plot: the mean difference between Promonitor IFX and QB was −0.57 µg/mL (p=0.2)	Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2)	LOW (4x low)
Van den Bossche et al, 2019	Observational study	IBD patients treated with IFX	Sandwich ELISA (specific detection) vs. QB Sandwich ELISA (specific detection) vs. LFA	150 samples	Spearman's correlation: -Sandwich ELISA (specific detection) vs QB: r=0.888 (0.849–0.918) -Sandwich ELISA (specific detection) vs LFA: r=0.962 (0.948–0.973) Clinical agreement: -Sandwich ELISA (specific detection) vs QB: Cohen's κ score (95% CI)= 0.782 (0.715–0.849) -Sandwich ELISA (specific detection) vs LFA: Cohen's κ score (95% CI)= 0.852 (0.795–0.910) Therapeutic ranges (3-7mg/L): - Agreement (ELISA vs QB)=74.7% - Agreement (ELISA vs LFA)=84.7%	Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2)	LOW (3x low, 1x unclear)
Nasser et al, 2018	Observational study	CD patients treated with IFX	- Direct ELISA (non-specific detection) vs. QB Direct ELISA (non-specific detection) vs. LFA Direct ELISA (specific detection) vs. QB Direct ELISA (specific detection) vs. LFA Sandwich ELISA (specific detection) vs. QB - QB vs. LFA Sandwich ELISA (specific detection) vs. LFA - Direct ELISA (non-specific detection) vs direct ELISA (specific detection) vs sandwich ELISA (specific detection)	85 patients	**ELISA vs. POC** Spearman's correlation: -Direct ELISA (non-specific detection) vs LFA: r=0.97 -Direct ELISA (non-specific detection) vs QB: r=0.96 -Direct ELISA (specific detection) vs LFA: r=0.99 -Direct ELISA (specific detection) vs QB: r=0.98 -Sandwich ELISA (specific detection, Sanquin) vs LFA: r=0.95 -Sandwich ELISA (specific detection, Sanquin) vs QB: r=0.95 -Sandwich ELISA (specific detection, Grifols) vs LFA: r=0.97 -Sandwich ELISA (specific detection, Grifols) vs QB: r=0.97 **POC vs. POC** Spearman's correlation: r=0.98 **ELISA vs. ELISA** Spearman's correlation: -Direct ELISA (non-specific detection) vs direct ELISA (specific detection): r=0.97 -Direct ELISA (non-specific detection) vs sandwich ELISA (specific detection, Sanquin): r=0.93 -Direct ELISA (non-specific detection) vs sandwich ELISA (specific detection, Grifols): r=0.95 -Direct ELISA (specific detection) vs sandwich ELISA (specific detection, Sanquin): r=0.94 -Direct ELISA (specific detection) vs sandwich ELISA (specific detection, Grifols): r=0.97 -Sandwich ELISA (specific detection, Sanquin) vs Sandwich ELISA (specific detection, Grifols): r=0.94	Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2)	LOW (3x low, 1x unclear)
Teixeira et al, 2018	Observational cross-sectional multicentric study.	IBD patients in remission treated with IFX	Direct ELISA (specific detection) vs. QB	49 samples	ELISA: AUC: 0.966±0.02 (95% CI: 0.87-0.99). QB: AUC: 0.827±0.06 (95% CI: 0.69-0.92). Difference between AUC (p=0.03).	Quality Assessment of Diagnostic	MODERATE (3x low, 1x high)

						Accuracy Studies (QUADAS-2)	
Verstockt et al, 2018	Observational retrospective study	CD pts treated with ADA	Direct ELISA (specific detection) vs. LFA Serum samples	116 samples	ICC (after 4 weeks of treatment): 0.92, p<0.001 ICC (after 12 weeks of treatment): 0.97, p<0.001	Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2)	LOW (3x low, 1x unclear)
Yang et al, 2018	Observational study	Patients treated with ADA (different diseases)	RGA vs. LC–MS/MS	43 samples	Passing-Bablok regression slope is r=0.866. 12% positive bias for LC-MS/MS	Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2)	MODERATE (2x low, 2x high)
Bader et al, 2017	Observational cross-sectional study	107 pts treated with IFX (78 rheumatology & 29 dermatology)	- Sandwich ELISA (specific detection) vs. IFMA (specific detection) -Sandwich ELISA (specific detection) vs. RGA - RGA vs. IFMA (specific detection) Serum samples	107 samples	**ELISA vs. IFMA** Bland-Altman plots: Therapeutic ranges - 3-8mg/L: agreement=80% - 1.5-12mg/L: agreement=84% **ELISA vs. RGA** Bland-Altman plots: Therapeutic ranges - 3-8mg/L: agreement=64% - 1.5-12mg/L: agreement=65% **RGA vs. IFMA** Bland-Altman plots: Therapeutic ranges - 3-8mg/L: agreement=50% - 1.5-12mg/L: agreement=56%	Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2)	LOW (4x low)
Afonso J et al, 2016	Observational study	IBD patients treated with IFX	- Sandwich ELISA (specific detection) vs. QB Direct ELISA (non-specific detection) vs. QB - Sandwich ELISA (specific detection) vs. direct ELISA (non-specific detection) Serum samples	299 patients	**ELISA vs. POC** - ICC (sandwich ELISA vs QB)=0.939 (0.924-0.952) - ICC (direct ELISA vs QB)=0.889 (0.861-0.911) **ELISA vs. ELISA** Spearman's correlation: r=0.919, p<0.001	Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2)	LOW (4x low)

van Bezooijen et al, 2016	Observational study	IFX: 40 pts with sarcoidosis, uveitis or Behcet's disease ADA: 40 pts with psoriasis ETN: 40 pts with psoriasis	- Sandwich ELISA (specific detection) vs. RGA Direct ELISA (non-specific detection) vs. RGA - Sandwich ELISA (specific detection) vs. direct ELISA (non-specific detection) Serum samples	120 samples: -40 pts with IFX -40 pts with ADA -40 pts with ETN	**ELISA vs. RGA** IFX (Pearson's Correlation): - Sandwich ELISA vs. RGA: r^2=0.99, p=0.0001 - Direct ELISA vs. RGA: r^2=0.92, p=0.0001 ADA (Pearson's Correlation): - Sandwich ELISA vs. RGA: r^2=0.86, p=0.002 - Direct ELISA vs. RGA: r^2=0.78, p=0.0007 ETN (Pearson's Correlation): - Sandwich ELISA vs. RGA: r^2=0.85, p=0.0002 - Direct ELISA vs. RGA: r^2=0.86, p=0.0004 **ELISA vs. ELISA** Pearson's correlations: IFX: r^2=0.77, p=0.0001 ADA: r^2=0.88, p=0.0001 ETN: r^2=0.82, p=0.0001	Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2)	MODERATE (2x low, 2x high)
Bodini G. et al, 2015	Observational study	CD patients treated with ADA	Sandwich ELISA vs. HMSA (specific detection) Serum samples	23 patients	Correlation after 48 weeks of treatment: r=0.691, p=0.0003 Correlation after 96 weeks of treatment: r=0.822, p=0.0001	Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2)	LOW (4x low)
Martin et al, 2015	Observational retrospective study	Patients with rheumatic diseases treated with golimumab	Sandwich ELISA (specific detection in 2 steps) vs sandwich ELISA (specific detection in 1 step) Serum samples	48 patients (102 samples)	Spearman's correlation: r=0.98, p<0.0001	Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2)	MODERATE (3x low, 1x high)
Steenholdt et al, 2015	post hoc analysis of a RCT	42 CD pts treated with Ifx	RGA vs. HMSA Serum samples	41 samples	Pearson's correlation: r=0.96 [0.93-0.97], p<0.0001	Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2)	LOW (3x low, 1x unclear)
Willrich et al, 2015	Observational study	Rheumatology and gastroenterology patients treated with IFX	LC–MS/MS vs ECLIA	51 patients	Passing-Bablok regression slope is r=0.967 (95% CI: 0.894 to 1.034)	Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2)	MODERATE (3x low, 1x high)

Steenholdt C et al, 2014	Post hoc analysis of RCT	CD patients treated with IFX	- Direct ELISA (non-specific detection) vs. HMSA (specific detection) -Direct ELISA (no specific detection) vs. RGA Serum samples	66 patients	**ELISA vs. HMSA** Different IFX detection: 76% by ELISA and 88% by HMSA ICC: 0.96 (0.94-0.98), p<0.0001 **ELISA vs. RGA** Different IFX detection: 76% by ELISA and 74% by RGA ICC: 0.72 (0.23-0.88), p<0.0001	Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2)	LOW (3x low, 1x unclear)
Corstjens et al, 2013	Observational cross-sectional study	CD pts in maintenance and treated with IFX	Sandwich ELISA (specific detection) vs. LFA Serum samples	84 samples	Spearman's correlation: r^2=0.85	Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2)	LOW (4x low)
Steenholdt et al, 2013	Observational cross-sectional study	13 CD pts treated with IFX	- Direct ELISA (non-specific detection) vs. RIA (non-specific detection) - RGA vs. RIA (non-specific detection) Serum samples	13 samples	**ELISA vs. RIA** Pearson's correlation: r^2=0.98 (0.73-1.00), p=0.001 **RGA vs. RIA** Pearson's correlation: r^2=0.97 (0.62-1.00), p=0.002	Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2)	LOW (3x low, 1x unclear)

PTC-2: Measurement of ADAb should be performed in a validated laboratory, preferably using a consistent assay over time. Measurement should be performed and interpreted alongside contemporaneous biopharmaceutical blood concentrations

Study	Study design	Population	Scope/Intervention	Study population	Results	Tool used for RoB assessment	Risk of Bias
Bodio C. et al, 2020	Observational cross-sectional study.	RA patients treated with IFX, ADA or ETN	Bridging ELISA vs. RGA Serum samples	163 samples	Agreement between methods: k=0.58 [0.39-0.76]	Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2)	MODERATE (3x low, 1x high)
Ogric et al, 2019	Observational cross-sectional study	patients with chronic rheumatic diseases or IBD treated with IFX or ADA	- cELISA (direct) vs. RGA - cELISA (direct) vs. bELISA Serum samples	77 patients: -46 pts treated with IFX -31 pts treated with ADA	**cELISA vs. RGA** Spearman's correlations: - IFX ADAb: r^2=0.932, p<0.0001; kappa=1.0; 100% agreement - ADA ADAb: r^2=0.947, p<0.0001; kappa=1.0; 100% agreement **cELISA vs. bELISA** Spearman's correlations: - IFX ADAb: r^2=0.493, p=0.0375; kappa=0.517; 78% agreement - ADA ADAb: r^2=0.952, p=0.0001; kappa=0.627; 81% agreement	Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2)	LOW (3x low, 1x unclear)
Real-Fernández et al, 2019	Observational study	RA patients treated with ADA	- bELISA vs. RGA - bELISA vs. SPR - RGA vs. SPR Serum samples	50 patients	**bELISA vs. RGA** Spearman's correlations: r=0.800; p=0.022 **bELISA vs. SPR** Spearman's correlations: r=-0.241; p=0.582 **RGA vs. SPR** Spearman's correlations: r=0.108; p=0.793	Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2)	LOW (4x low)
Steenholdt C et al, 2014	Post hoc analysis of RCT	CD patients treated with IFX	bELISA vs. RGA Serum samples	66 patients	Pearson's correlation: r=0.96; p<0.0001 Spearman's correlation: r=0.78; p<0.0001	Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2)	LOW (3x low, 1x unclear)
Steenholdt et al, 2013	Observational cross-sectional study	CD pts treated with IFX	- bELISA vs RGA - bELISA vs EIA Serum samples	12 samples	**bELISA vs. RGA** Spearman's correlation: r=0.93, p=0.02 **bELISA vs. RGA** Spearman's correlation: r=0.89, p=0.03	Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2)	LOW (3x low, 1x unclear)

PTC-3: Biopharmaceutical blood concentrations are dependent on the dose, administration interval, and date of last dose. When interpreting biopharmaceutical blood concentrations, also patient-specific factors that influence PK should be considered, which include body weight, methotrexate co-prescription, disease activity, and adherence to therapy.

Study	Study design	Population	Scope/Intervention	Study population	Follow-up	Outcome measures	Results	Tool used for RoB assessment	Risk of Bias
Wolbink G. et al, 2005[1]	Prospective observational	RA pts starting IFX	Measurements of IFX trough DL 2, 6 and 14 weeks after treatment initiation	105 pts Mean age: 56 y % male: 18	14 weeks	IFX DL	Median (IQR) IFX DL at various time points after treatment initiation: W2 IFX DL: 22.3 (15.3–29.4) mg/l, W6 IFX DL: 14.6 (7.3–22) mg/l, W14 IFX DL: 2.8 (0.6–6.8) mg/l. -Reviewer conclusion: Trough IFX DL were higher in induction phase vs. start of maintenance phase (W14).	Newcastle-Ottawa for cohort studies	Sum score: ***,*,* Selection: *** Comparability: * Outcome: *
Jurado T. et al, 2017[2] No 197	Restrospective observational	RA pts treated with IFX	Measurements of IFX trough DL at W2, W6, W14 and W22 after treatment initiation	66 pts Mean age: 56 % male: 14	52 weeks	IFX DL	IFX DL at various time points, stratified by W54 undetectable vs. detectable IFX DL (mean or median not specified): W2 IFX DL: 20.0 ±12.7 µg/mL vs 29.7±14.5 µg/mL W6 IFX DL: 4.2±5.9 µg/mL vs 15.7±11.1 µg/mL W14 IFX DL: 0.1±0.2 µg/mL vs 4.1±5.3 µg/mL W22 IFX DL: 0.01±0.04 µg/mL vs 2.8±3.3 µg/mL -Reviewer conclusion: Trough IFX DL were higher in induction phase vs. manitenance phase.	Quality in Prognosis Studies Tool	1.Study participation: Moderate 2.Attrition: Moderate 3.Prognostic factor: Moderate 4.Outcome: Low 5.Confounding: Low 6.Statistics: Low
Van den Bemt B. et al, 2013[3] no 206	Prospective observational	RA pts starting IFX	IFX trough DL measured at W2, W6 and W26 after treatment initiation	57 pts Mean age; 57y % male: 37	6 months	IFX DL	IFX DL in 6 months EULAR-responders (mean or median not specified): W2: 23.4 mg/L (±20.8), W6: 12.3 mg/L (±6.1) IFX DL in 6 months EULAR non- or partial responders: W2: 16.0 mg/L (±10.4), W6: 9.0 mg/L (±6.8) IFX DL (median (IQR)) at W14: EULAR responders: 0.9 (0.05–2.6) mg/L non-responders: 2.0 (0.7–5.4) mg/L. -Reviewer conclusion: Trough IFX DL were higher in induction phase vs. manitenance phase.	Quality in Prognosis Studies Tool	1.Study participation: Moderate 2.Attrition: Moderate 3.Prognostic factor: Low 4.Outcome: Low 5.Confounding: High 6.Statistics: Low

Weight / Body Mass Index (BMI)

Study	Study design	Population	Scope/Intervention	Study population	Follow-up	Outcome measures	Results	Tool used for RoB assessment	Risk of Bias

TOCILIZUMAB									
Arad 2019	Israeli cohort of TOZURA, multinational phase IV, single arm open label	RA tocilizumab 162 mg sc weekly	To determine whether trough levels are associated with disease activity / response	100 pts, 54 years, 80% female, DAS28 5.0, CDAI 31.9	24 weeks	Trough level, BMI	in a linear model, every increase of 1 BMI unit was associated with a decrease of 1.5 µg/ml in the serum TCZ concentrations ($p < 0.0001$). The TCZ concentrations were significantly lower in the > 100 kg weight group compared to the < 60 kg and the 60–100 kg weight groups ($p<0.05$)	Quality in Prognosis Studies Tool	1.Study participation: low 2.Attrition: high 3.Prognostic factor: high 4.Outcome: Low 5.Confounding: moderate 6.Statistics: moderate
Bastida 2018	Population pharmacokinetic analysis, data from prospective observational cohort, monocentric, Spain	RA, tocilizumab iv, 4, 6 and 8 mg/kg every 4 weeks	Provide scientific rationale for body weighted dosing	35 patients, 88% female, age 54 years, weight 63.5 kg, height 161 cm, disease duration 11 years, 75% cotreatment MTX, DAS28 2,2	N/A	Area under the curve concentration, weight	19 patients on 8 mg/kg every 4 weeks, 8 each on 4 and 6 mg/kg/4wks, respectively. Usual 8mg/kg/4w reached target (defined as a cAUC (area under the curve concentration) at 24 weeks of treatment >100 × 103 µg/ml) in 99,8%. Patients with extremely low weight (<50 kg) were at risk of underdosing. (mean cAUC ± SD: 142.6 ± 23.0). Patients from weights 60-120 kg are far above the threshold (cAUC). With reduced dosing (6 mg/kg), lower percentage (90.5%) achieves the target, with risk of underdosing for <60 kg For 4 mg/kg, > 30% of 40-90 kg patients would be underdosed.	Quality in Prognosis Studies Tool	1.Study participation: moderate 2.Attrition: high 3.Prognostic factor: low 4.Outcome: Low 5.Confounding: moderate 6.Statistics: low
Abdallah 2017	Pooled data RCTs (SUMMACTA and BREVACTA), population pharmacokinetic model	RA, tocilizumab after inadequate DMARD response	PK/PD sc tocilizumab	N/A (supp tab S1)	24 weeks	Drug level, body weight	Increase in body weight associated with lower trough levels. Observed trough levels for sc weekly dosing were 21.6 ± 14.5 ug/ml for > 100 kg, 41.5 ± 24.7 ug/ml for 60-100 kg and 62.1 ± 30.5 ug/ml for < 60 kg. For iv dosing levels were 20.8 ± 13 ug/ml, 19.8 ± 14.5 ug/ml and 15.2 ± 11.4 ug/ml for > 100 kg, 60-100 kg and <6k kg, respectively.	Cochrane RoB2 for RCT	Overall: low Randomisation: Low Intervention: low Missing outcome data: low Outcome measurement: low Selective reporting: Low
ABATACEPT									
D'Agostino 2017	Post hoc analysis RCT (ACQUIRE)	RA, abatacept 125 mg sc weekly and ~10mg/kg 4	Explore the effect of baseline BMI on PK and clinical response	1456 pts, age 47-51 years, female 79-85%, disease duration 6.9-8.3	6 months	Drug level and BMI: <25, 25-30 and >30	BMI: 36% normal, 34% overweight, 30% obese. Steady state trough levels were higher for sc than for body weight tiered iv administration.	Quality in Prognosis Studies Tool	1.Study participation: low 2.Attrition: high 3.Prognostic factor: ? 4.Outcome: Low 5.Confounding: high 6.Statistics: low

		weekly iv according to body weight (< 60, 60-100 and> 100 kg)		years, DAS28CRP 6.2			Median trough levels were numerically higher in the sc than in the IV group at 3 months: 33.4, 29.1 and 24.1 ug/ml vs. 19.6, 21.3 and19.7 ug/ml for normal, overweight and obese, respectively, and at 6 months: 35.1, 29.0 and 24.1 ug/ml vs. 19.1, 20.0 and 19.8 ug/ml, for normal, overweight and obese, respectively (no statistical analysis).		
TNF-INHIBITORS									
Goss 2018	RCT, CONCERTO trial, multinational	RA, ADA, 4 different dosages of MTX (2,5 ; 5 ; 10 ; 20mg/wk)	Effect of MTX on adalimumab pharmacokinetics	395 patients, 52 years, 75% female	26 weeks	adalimumab levels, body weight	For adalimumab concentration, body weight was a statistically significant explanatory variable (P = 0.0001), with a negative estimate of the regression coefficient.	Cochrane RoB2 for RCT	Overall: low Randomisation: Low Intervention: low Missing outcome data: low Outcome measurement: low Selective reporting: Low
Jani 2015	Prospective observational cohort (BRAGGSS) multicentric, UK	RA ADA, ETN	Random drug levels, clinical response and adherence to therapy	ADA 160 pts, age 56.2 years, 70% female, disease duration 8.6 years, DAS28 5.7, MTX 55%. ETN 171 pts, 57 years, 80% female, disease duration 7,8 years, DAS28 5.9, MTX 46%	12 months	Random (!) drug levels, BMI	In analysis for predictors of low drug levels, for adalimumab, BMI (regression coefficient (rc) 0.055 95%CI 0.017-0.094, p=0.005) was one of the significant predictors. In a model including both adalimumab and etanercept a BMI of ≥ 30 was associated with low drug levels (rc 0.78 95%CI 0.37-1.18 p<0.0001)	Quality in Prognosis Studies Tool	1.Study participation: moderate 2.Attrition: moderate 3.Prognostic factor: moderate 4.Outcome: moderate 5.Confounding: moderate 6.Statistics: low
Dong 2019	Prospective observational cohort, monocentric, China	AS etanercept	To investigate the effective serum level of etanercept in patients with AS	60 pts, 54/60 male, age 29 years, disease duration 4 years	24 weeks	drug levels, BMI	Cut-off drug level values of effective (ASDAS-CRP < 2.1) etanercept treatment based on results of ROC curves at weeks 4, 12, and 24 were 2.32, 2.12, and 2.36 μg/mL, respectively. Patients with etanercept levels below these cut-off values had higher body mass index (BMI) values than those above the cut-off value (23.85 ±4.14 vs 21.79 ± 3.35 kg/m2, p = 0.042) at treatment week 4 while there was no significant difference in BMI between the two groups at week 12 and 24.	Quality in Prognosis Studies Tool	1.Study participation: moderate 2.Attrition: high 3.Prognostic factor: moderate 4.Outcome: Low 5.Confounding: high 6.Statistics: moderate

Rosas 2017	Cross-sectional study, monocentric, Spain	AS adalimumab	To determine whether obesity affects serum levels of adalimumab	57 pts, male 65%, age 47 years, BMI 27.6, disease duration 9.8 years, HLAB27 77%, treatment duration 1.44 years, BASDAI4.05, ASDAS(ESR) 2.36	N/A	BMI, adalimumab level	Patients with BMI > 30 (n=15, 26%) had lower drug levels then patients with normal BMI < 25 (n=17, 30%): 5.0 (5.5) vs. 9.14 (4.3) mg/l, respectively, p=0.032. also, patients with BMI 25-30 (n=25, 44%) had higher trough levels than obese (BMI >30): 10.09 (5.9) p<0.01.	Quality in Prognosis Studies Tool	1.Study participation: low 2.Attrition: high 3.Prognostic factor: moderate 4.Outcome: Low 5.Confounding: high 6.Statistics: moderate

Methotrexate and other co-medication / DMARDs

Study	**Study design**	**Population**	**Scope/Intervention**	**Study population**	**Follow-up**	**Outcome measures**	**Results**	**Tool used for RoB assessment**	**Risk of Bias**
				ADALIMUMAB					
Burmester 2015	RCT, double blinded, parallel arm study, multinational (CONCERTO)	RA, ADA + 2.5, 5, 10 or 20 mg MTX	Clinical response and trough levels between different treatment groups	395 pts, age 49-54 years, female 71-78%, disease duration 4 months, DAS28(CRP) 5.8-6.2	26 weeks	MTX dose and ADA trough level	Mean trough concentration at week 26 were 4.4, 5.7, 6.5 and 6.9 mg/l with MTX doses of 2.5, 5, 10 and 20 mg, respectively. (no statistical analysis)	Cochrane RoB2 for RCT	Overall: low Randomisation: Low Intervention: low Missing outcome data: low Outcome measurement: low Selective reporting: Low
Goss 2018	RCT, CONCERTO trial, multinational	RA, ADA, 4 different dosages of MTX (2,5 ; 5 ; 10 ; 20mg/wk)	Effect of MTX on adalimumab pharmacokinetics	395 patients, 52 years, 75% female	26 weeks	adalimumab levels, MTX dose	After week 4, mean adalimumab concentrations were higher in the 20 mg MTX dose group compared with the 2.5 mg MTX dose group (p= 0.001). However, there were no statistically significant differences between the 2 highest MTX dose levels.	Cochrane RoB2 for RCT	Overall: low Randomisation: Low Intervention: low Missing outcome data: low Outcome measurement: low Selective reporting: Low
Pouw 2015	Prospective observational cohort, monocentric, the	RA ADA	Determine the concentration-effect relationship of adalimumab in RA	221 pts, 54 years, 80% female, disease duration 8	28 weeks	MTX dose and adalimumab level	Patients on adalimumab monotherapy had a median concentration of 4.1 ug/ml (IQR 1.3 – 7.7). Patients with concomitant MTX treatment had a median level of 7.4 ug/ml (IQR 5.3 – 10.6), p<0.001	Quality in Prognosis Studies Tool	1.Study participation: moderate 2.Attrition: high 3.Prognostic factor: low 4.Outcome: Low

	Netherlands			years, DAS28 5.3, MTX 77%			there was no significantly difference in trough levels between different methotrexate dose groups.		5.Confounding: high 6.Statistics: low
Vogelzang 2014	Prospective observational cohort, monocentric, the Netherlands	PsA, adalimumab	Association between adalimumab drug levels and disease activity	103 pts, male 53%, age 50 years, MTX 78%, disease duration 6 years, DAS28 4.0, PASI 0.6	52 weeks	Drug level, MTX use	The median adalimumab concentration at 28 weeks for patients on monotherapy was significantly lower compared with patients using adalimumab and concomitant MTX (respectively, 0.7 mg/L, IQR 0.0–3.3 vs 8.4 mg/L, IQR 4.9–11.0), p<0.001. At 52 weeks, patients on monotherapy had a median adalimumab concentration of 1.8 mg/L, IQR 0.0–3.5 compared with 8.8 mg/L, IQR 4.9–11.9 in patients treated with adalimumab and concomitant MTX (p<0.001).	Quality in Prognosis Studies Tool	1.Study participation: high 2.Attrition: high 3.Prognostic factor: low 4.Outcome: Low 5.Confounding: moderate 6.Statistics: low
Vogelzang 2015	Prospective observational cohort, monocentric, the Netherlands	RA, PsA, adalimumab	Effect of concomitant DMARD treatment on adalimumab trough levels	375 pts (272 RA, Bartelds 2011, 103 PsA, Vogelzang 2014)	28 weeks	Concomitant DMARD therapy, trough level adalimumab	Four groups of adalimumab-treated patients were compared: monotherapy (n=67); concomitant MTX (n=224); concomitant other DMARDs (leflunomide, hydroxychloroquine, sulfasalazine or a combination of these, n=26) and MTX+other DMARDs (n=58). Concentrations were significantly higher in patients with concomitant DMARD treatment compared with monotherapy: monotherapy versus other DMARDs, p=0.011; monotherapy versus MTX, p<0.001; and monotherapy versus MTX+other DMARDs, p<0.001. There was no statistical difference between both MTX groups and the other DMARDs group (p=0.579 (MTX vs other DMARDs) and p=0.352 (MTX +other DMARDs vs other DMARDs)). Trough levels at week 4, 16 and 28: MTX 3.9, 7.1 and 7.4 mg/l; MTX + other DMARDs: 4.1, 7.4 and 6.8 mg/l; other DMARDs: 4.1, 5.4 and 4.9 mg/l; monotherapy: 2.4, 2.5 and 22 mg/l; respectively.	Quality in Prognosis Studies Tool	1.Study participation: high 2.Attrition: high 3.Prognostic factor: low 4.Outcome: Low 5.Confounding: high 6.Statistics: low
INFLIXIMAB									
Mulleman 2011	RCT, bicentric, France	AS IFX	The influence of MTX on infliximab exposure	26 pts (12 vs. 14), 75-79% men, age 43-46 years, disease duration 4-4.5 years, HLAB27 71-75%, BASDAI 5.8-7.0	18 weeks	infliximab cumulative area under the concentration vs time curves between baseline and 18 weeks, MTX use	Two treatment groups, IFX+ MTX and IFX – MTX, did not differ in terms of AUC0-18, BASDAI or inflammation markers. The median AUC0-18 value was 165,502 mg/hour/L [50,569 to 203,782] for the infliximab-only group and 164,222 mg/hour/L [102,165 to 295,858] for the infliximab + MTX group.	Quality in Prognosis Studies Tool	1.Study participation: moderate 2.Attrition: high 3.Prognostic factor: moderate 4.Outcome: Low 5.Confounding: high 6.Statistics: low

Martinez-Feito FRI0399 (2019)	Abstract EULAR 2019, observational study	IFX axSpA	To identify clinical and serological variables that can predict clinical response	81 pts	24 weeks	drug levels, MTX use	Patients with concomitant MTX had higher serum IFX trough levels (median and IQR) than patients without MTX and these differences were significant at W6: 26.37 (16-41.4) vs. 16.9(11.4-26.9); p=0.008; at W14: 8.4(5.4-13.9) versus 4.1(1.8-7.8); p=0.003 and at W22: 5.1(2.2-8.3) versus 3.1(0.6-5.4); p=0.006 and; respectively).	Quality in Prognosis Studies Tool	1.Study participation: high 2.Attrition: high 3.Prognostic factor: high 4.Outcome: Low 5.Confounding: moderate 6.Statistics: moderate
GOLIMUMAB									
Zhuang 2012	Open label, randomised phase 1 study, multicentric, USA	RA golimumab	Evaluating the effect of concomitant methotrexate use on golimumab pharmacokinetics	49 pts, 33 sc, 16 iv. age 55.8 years, female 76%, disease duration 9.4 years	30 weeks for SC group (20 weeks of treatment & 10 of follow up) 24 weeks for IV groups	PK parameters (maximal concentration (Cmax) and area under the concentration time curve 0-28 days (AUC0-28d), MTX	For patients treated with golimumab sc: Mean serum golimumab concentrations appeared to be higher in patients treated with concomitant MTX. The mean Cmax and AUC0–28d at steady state were 24% and 37% higher, respectively, in patients who received concomitant MTX than in patients who did not receive MTX. (no statistics)	Cochrane RoB2 for RCT	Overall: some concerns Randomisation: Low Intervention: some concerns Missing outcome data: low Outcome measurement: some concerns Selective reporting: Low
RHEUMATOID ARTHRITIS AND TNF-INHIBITORS (ADA, IFX)									
Martinez-feito 2019	Observational cohort, monocentric, spain	RA ADA or IFX	Association between drug level and concomitant use of MTX or other DMARDs	25 ADA, 67 IFX, monotherapy n=12, MTX n=59, other DMARD n=21 Age 52-64, female 58-88%, disease duration 8-10 years, DAS28 5-5.3	1 year	Detectable drug level at 1 year, monotherapy, combination with MTX or other DMARD	Proportion of patients with detectable drug at 1 year: monotherapy: 9%; +MTX: 71%; + other DMARD: 20%. This was mainly true for patients with MTX >15 mg/wk (54%) vs. MTX<15mg/wk (17%) The OR for maintaining drug levels with vs. without MTX was 2.3, p=0.06. The OR for maintaining drug level with MTX>15mg/wk vs. monotherapy was 4.9, p=0.02.	Quality in Prognosis Studies Tool	1.Study participation: loe 2.Attrition: high 3.Prognostic factor: low 4.Outcome: Low 5.Confounding: high 6.Statistics: low
Eng 2016	Observational cohort, Japan	RA ADA, IFX	To explore the impact of treatment with TNF inhibitors on levels of soluble biomarkers in RA and to identify predictors of impaired drug levels	ADA: 15 pts, 27% male, age 53 years, MTX 47%, disease duration 5 years, DAS28(CRP) 5.0, CRP 6 IFX: 11 pts, 36% male, age 54 years, MTX 72%,	6 months	Detectable or undetectable drug level with detection limit of 0.7 ug/ml for both drugs	Patients with detectable drug at 6 months of treatment numerically less often used concomitant MTX (50 vs. 83%, p=0.197), however the median dose of methotrexate was numerically higher in the group of patients with detectable drug levels (18.75 mg/week vs. 10 mg/wk, p=0.214)	Quality in Prognosis Studies Tool	1.Study participation: low 2.Attrition: high 3.Prognostic factor: moderate 4.Outcome: Low 5.Confounding: high 6.Statistics: moderate

				disease duration 6 years, DAS28(CRP) 5.3, CRP 4					

Route of administration

Study	Study design	Population	Scope/Intervention	Study population	Follow-up	Outcome measures	Results	Tool used for RoB assessment	Risk of Bias
Abdallah 2017	Pooled data RCTs (SUMMACTA and BREVACTA), population pharmacokinetic model	RA, tocilizumab after inadequate DMARD response	PK/PD sc tocilizumab	N/A (supp tab S1)	24 weeks	Drug level, iv and sc administration	Mean steady state TCZ iv 8 mg/kg every 4 weeks at 24 weeks was 18 ug/ml. For sc dosing 162 mg weekly: 40 ug/ml. (no statistics)	Cochrane RoB2 for RCT	Overall: low Randomisation: Low Intervention: low Missing outcome data: low Outcome measurement: low Selective reporting: Low
Burmester 2014	Randomised controlled trial, double blind, multicenter, (SUMMACTA)	RA, tocilizumab sc 162mg/week or iv 8mg/kg/4 weeks	To compare the efficacy and safety of sc vs. iv tocilizumab in RA	1095 pts (558 sc, 537 iv), female 82%, age 52 years, disease duration 8.7 years, DAS28 6.6-6.7, MTX 80-82%	24 weeks	Trough level, route of administration	The observed steady-state Ctrough (±SD) at week 24 was 42 (±27.4) µg/mL, following tocilizumab-SC dosing and 18 (±14.2) µg/mL following, tocilizumab-IV dosing. (no statistics)	Cochrane RoB2 for RCT	Overall: low Randomisation: Low Intervention: low Missing outcome data: low Outcome measurement: low Selective reporting: Low
Ogata 2014	Subanalyses of double-blind, parallel-group, comparative phase III study	RA pts treated with TCZ	Patients randomized 1:1 into 2 groups: 162 mg of TCZ-SC monotherapy every 2 weeks plus placebo TCZ-IV every 4 weeks or 8 mg/kg of TCZ-IV monotherapy every 4 weeks plus placebo TCZ-SC every 2 weeks	346 pts Mean age: 52 % male: 16	24 weeks	Serum TCZ concentrations	Mean trough TCZ concentrations were similar between the groups over time and proportion with TCZ ≥1 µg/mL were similar. Mean ± SD TCZ trough levels: TCZ-SC mono: 10.6 ± 7.8 µg/ml TCZ-IV mono: 12.4 ± 7.9 µg/ml.	Cochrane RoB2 for RCT	Overall: low Randomisation: Low Intervention: low Missing outcome data: low Outcome measurement: low Selective reporting: Low

Iwahashi 2014	Subanalyses of phase II/III, randomized, double blind study	RA pts treated with ABT	ABT IV 10 mg/kg every four weeks or SC 162 mg weekly.	118 pts Mean age: 55.6 % male: 27	6 months	Serum ABT (Cmax and Cmin)	Geometric means for Cmax and Cmin (d 169): SC: 42.6 µg/mL and 36.0 µg/mL IV: 277.4 µg/mL and 16.7 µg/mL. Large variation in intra-individual serum ABT levels within the 4 week interval for iv. administration. Small variation for sc (7 days interval).	Cochrane RoB2 for RCT	Overall: some concerns Randomisation: some concerns Intervention: low Missing outcome data: low Outcome measurement: low Selective reporting: Low

Dosing – interval

Study	Study design	Population	Scope/Intervention	Study population	Follow-up	Outcome measures	Results	Tool used for RoB assessment	Risk of Bias
l'Ami 2018	Randomised controled trial, parallel group, non-inferiority, monocenter, the Netherlands	RA ADA	Non-inferiority of lowering adalimumab dose to 40 mg every 3 weeks vs. remaining on 40 mg every 2 weeks	54 pts, age 58-60 years, female 93-96%, treatment duration 5.5-6 years, MTX use 93-96%, disease duration 11 years, DAS28 1.6-2.0	6 months	Drug level and dose interval	Disease activity remained stable in both groups, ADA levels decrease from 10.6±2.5 ug/ml to 6.6±2.2 ug/ml after dose interval prolongation. ADA level remained stable in the continuous group: 10.4±2.4 ug/ml and 9.3±3.0 ug/ml, p=0.001.	Cochrane RoB2 for RCT	Overall: some concerns Randomisation: Low Intervention: some concerns Missing outcome data: low Outcome measurement: some concerns Selective reporting: Low
Bartelds 2007	Prospective observational cohort, monocentric, the Netherlands	RA ADA	Association antibodies with drug level and clinical response	121 pts, 79% female, age 53, baseline DAS28 5.3, diseases duration 12 years, MTX use 79%	28 weeks	Drug levels, drug dose	Adalimumab concentrations significantly increased after dose increase to 40 mg weekly (p=0.043). Mean concentration before: 2.0 mg/l Mean concentration after: 15.0 mg/l	Quality in Prognosis Studies Tool	1.Study participation: moderate 2.Attrition: moderate 3.Prognostic factor: high 4.Outcome: Low 5.Confounding: high 6.Statistics: low
Siljehult 2018	Prospective observational cohort, multicentral, Sweden	RA infliximab	Correlation between drug levels and clinical response	94 pts, female 83%, age disease onset 42 years, disease duration 14 years, DAS28 5.6, MTX 77%, IFX	52 weeks	Dose, infliximab levels	There was no correlation between the dose in mg/kg and the measured concentration of IFX at either 14 or 52 weeks. The dose of infliximab only increased modestly from 3.24 to 3.54 mg/kg.	Quality in Prognosis Studies Tool	1.Study participation: modrate 2.Attrition: high 3.Prognostic factor: moderate 4.Outcome: moderate 5.Confounding: high 6.Statistics: moderate

				dose 3.3 (±0.6) mg/kg					
Takeuchi 2017	Randomized controlled trial, RISING study, Japan	RA infliximab (week 0 - 14: 3 mg/kg, week 14-46: 3, 6 or 10 mg/kg)	Correlation between baseline anti-ccp and RF and drug levels	307 pts, age 49-50, disease duration 7.2-8.4 years, female 79-86%,DAS28crp 5.38-5.59	54 weeks	Infliximab trough levels, dose	The median (interquartile range, IQR) trough serum levels at week 54 in the 3, 6, and 10 mg/kg groups were 0.4 (<0.1, 1.5), 2.3 (0.3, 4.7), and 5.5 (1.5, 9.0) ug/ml, respectively, showing dose dependency. (no statistics)	Quality in Prognosis Studies Tool	1.Study participation: high 2.Attrition: high 3.Prognostic factor: high 4.Outcome: Low 5.Confounding: high 6.Statistics: moderate
St Clair 2002 -.	Subanalyses of RCT	RA pts with active disease treated with IFX	PK-model for a 70-kg individual receiving 3 mg/kg IFX every 8 weeks. Preinfusion measurements at weeks 2, 6, 14, 22, 30, 38, 46, and 54	428 pts	54 weeks	Serum infliximab	PK-model : 1. 100-mg increase in IFX dose would raise the trough level from 0.8 µg/ml to 1.8 µg/ml. 2. Change in interval from 8 weeks to 6 weeks while maintaining a 3 mg/kg dose would increase the trough level from 0.8 µg/ml to 2.8 µg/ml. Observed median trough serum IFX in the group receiving 3 mg/kg every 4 weeks; range from 7.6 µg/ml to 8.8 µg/ml, a 3-fold increment in trough levels compared with the 6-week interval.	Cochrane RoB2 for RCT	Overall: some concerns Randomisation: Low Intervention: some concerns Missing outcome data: low Outcome measurement: some concerns Selective reporting: Low
Westhovens 2015	Randomised controled trial, multicenter, double blind (follow-up study of 2-year AGREE study)	RA abatacept iv 10 mg/kg or 5 mg/kg	Impact on disease activity of reduced dose of abatacept	108 pts, age 50-51 years, female 76-82%, disease duration 2.2-2.4 years, DAS28crp 2.1	12 months	Drug dose and drug level (trough, Cmin)	In the reduced abatacept dose group (~5 mg/kg), consistent Cmin was achieved between month 3 and month 6, with geometric mean Cmin ranging from 8.8 mg/mL to 12.0 mg/mL; the range was 20.3 mg/mL to 24.1 mg/mL during follow-up in the ~10 mg/kg abatacept group. (no statistics)	Cochrane RoB2 for RCT	Overall: low Randomisation: Low Intervention: low Missing outcome data: low Outcome measurement: low Selective reporting: Low
Bastida 2018	Population pharmacokinetic analysis, data from prospective	RA, tocilizumab iv, 4, 6 and 8 mg/kg every 4 weeks	Provide scientific rationale for body weighted dosing	35 patients, 88% female, age 54 years, weight 63.5 kg, height 161 cm, disease duration 11 years, 75%	N/A	Area under the curve concentration, fixed vs. weight based dosing	19 patients on 8 mg/kg every 4 weeks, 8 each on 4 and 6 mg/kg/4wks, respectively.	Quality in Prognosis Studies Tool	1.Study participation: moderate 2.Attrition: high 3.Prognostic factor: low 4.Outcome: Low 5.Confounding: moderate 6.Statistics: low

	observational cohort, monocentric, Spain			cotreatment MTX, DAS28 2,2			Usual 8mg/kg/4w reached target (defined as a cAUC (area under the curve concentration) at 24 weeks of treatment >100 × 103 µg/ml) in 99,8%. With reduced dosing (6 mg/kg), lower percentage (90.5%) achieves the target.		
l'Ami OP0209 (2020)	EULAR abstract, randomized controlled trial, single center	ETN RA, PsA, SpA	Comparing the rate of maintenance of Minimal Disease Activity of standard dosing vs. doubled dosing interval	160 pts	18 months	Dosing interval, drug levels	Median etanercept concentrations decreased from 1.50 µg/mL (25-75 th percentile 1.06-2.65) to 0.46 µg/mL (0.28-0.92) after 6 months of interval prolongation (ETN 50 mg every two weeks).	Cochrane RoB2 for RCT	Overall: high Randomisation: some concerns Intervention: high Missing outcome data: high Outcome measurement: some concerns Selective reporting: Low

Trough vs. non-trough

Study	Study design	Population	Scope/Intervention	Study population	Follow-up	Outcome measures	Results	Tool used for RoB assessment	Risk of Bias
Bouman 2017	Combined study: Patients from the intervention arm of an open RCT investigating non-inferiority of a dose reduction strategy (ADA / ETN) and patients from an	ADA ETN IFX RA	Association between drug level and successful dose reduction (increase interval for ADA & ETN, dose reduction for IFX) and discontinuation of the drug	ADA 42 pts ETN 76 pts IFX 51 pts. Age 58-61 years, 57-64% female, disease duration 7.5 – 13 years, DAS28 2.4-2.6, duration current treatment: 2.9-5.6 years, MTX 45-68%	18 months	Mean drug level and timing of sampling	ADA: Peak (n=11) 8.5 ug/ml; intermediate (n=22) 7.7 ug/ml; trough (n=9) 6.7 ug/ml. All ns. ETN: peak (n=25) 2.4 ug/ml; intermediate (n=28) 2.5 ug/ml; trough (23) 1.7 ug/ml. trough levels were significantly lower than intermediate and peak levels.	Quality in Prognosis Studies Tool	1.Study participation: moderate 2.Attrition: moderate 3.Prognostic factor: moderate 4.Outcome: Low 5.Confounding: high 6.Statistics:low

	observational down titration study of IFX, the Netherlands								
Hooijberg AB0382 (2019)	Abstract EULAR 2019, observational cohort	RA ADA	To assess the effect of non-trough measurements, compared to trough measurements, on serum drug level.	121 pts (310 measurements)	Median 156 weeks	Drug level and timing of sampling between injections	The median drug level during adalimumab treatment was 6.6 (IQR 4.2-9.8) µg/ml, and the median number of days between the previous injection of adalimumab and serum sampling was 8 (5-13). The first quartile (median 2 (IQR 1-3) days) had a median drug level of 8.0 (4.7-11.0) µg/ml, the second quartile (7 (6-8) days) of 6.9 (5.4-10.0) µg/ml, the third quartile (11 (10-12) days) of 6.1 (3.4-9.5) µg/ml, and the fourth quartile (14 (13-14) days) of 5.7 (3.1-8.5) µg/ml. A weak association was found between the number of days between the previous injection of adalimumab and serum sampling and adalimumab drug level (Spearman's ρ: -0.182, p=0.001).	Quality in Prognosis Studies Tool	1.Study participation: high 2.Attrition: high 3.Prognostic factor: ? 4.Outcome: Low 5.Confounding: high 6.Statistics: moderate

CRP – ESR – Calprotectin

Study	Study design	Population	Scope/Intervention	Study population	Follow-up	Outcome measures	Results	Tool used for RoB assessment	Risk of Bias
Daien 2012	Prospective observational cohort (pilot), monocentric, France	RA ETN	Explore predictive value of etanercept levels for response to treatment	19 pts, all female, age 56 years, disease duration 5 years, DAS28 4.85, MTX 12 pts, LEF 5 pts	6 months	drug level, CRP	CRP changes between baseline and 3 months tended to correlate negatively with ETN concentrations at 3 months (r-0.46, p=0.08), and correlated significantly with change between baseline and 6 months (r-0.73, p=0.004)	Quality in Prognosis Studies Tool	1.Study participation: high 2.Attrition: low 3.Prognostic factor: low 4.Outcome: Low 5.Confounding: high 6.Statistics: low
Kneepkens 2014	Observational cohort, multicentric, the Netherlands, Spain	RA GLM	Association between drug level and clinical response	37 pts, 52 years, 84% female, disease duration 12 years, DAS28 4.4 MTX 65%	1 year	CRP, ESR and drug levels	After adjustment for baseline values, a statistically significant inverse association between golimumab level and CRP and ESR was observed. rc -.046 (-0.60 to -0.28) and rc -9.03 (-14.2 to -3.9), respectively.	Quality in Prognosis Studies Tool	1.Study participation: moderate 2.Attrition: moderate 3.Prognostic factor: moderate 4.Outcome: moderate 5.Confounding: moderate 6.Statistics: low

Zhuang 2012	Open label, randomised phase 1 study, multicentric, USA	RA golimumab	Evaluating the effect of concomitant methotrexate use on golimumab pharmacokinetics	49 pts, 33 sc, 16 IV. AGE 55.8 years, female 76%, disease duration 9.4 years	30 weeks for SC group (20weeks of treatment & 10 of follow up) 24 weeks for IV groups	PK parameters (area under the concentration time curve 0-28 days (AUC0-28d), maximal concentration Cmax), CRP	Serum golimumab concentrations in patients with elevated CRP (≥10 mg/L) were generally lower than in patients with normal CRP (<10 mg/L). Mean (SD) Cmax and AUC0–28d values after the first dose were 3.1 (1.9) ug/mL and 34.8 (17.5) ug·day/mL, respectively, in patients with baseline CRP levels ≥10 mg/L and 6.2 (3.4) ug/mL and 92.9 (42.7) ug·day/mL, respectively, in patients with baseline CRP levels <10 mg/L	Cochrane RoB2 for RCT	Overall: some concerns Randomisation: Low Intervention: some concerns Missing outcome data: low Outcome measurement: some concerns Selective reporting: Low
Wolbink 2005	Prospective observational cohort, monocentric, the Netherlands	RA infliximab	Relationship between serum trough infliximab, clinical response and CRP	105 pts, female 83%, age 56 years, disease duration 12 years, MTX 86/105, DAS28 6.1	14 weeks	drug level. CRP	Pretreatment CRP levels negatively correlated with serum infliximab levels at 2 weeks (r=-0.34, p<0.001), 6 weeks (r=-0.46, p<0.001), and 14 weeks (r=-0.43, p<0.001)	Quality in Prognosis Studies Tool	1.Study participation: low 2.Attrition: high 3.Prognostic factor: moderate 4.Outcome: low 5.Confounding: moderate 6.Statistics: low
Marsman 2016	Observational cohort, multicentric, the Netherlands and Taiwan	AS ADA	To determine the concentration-effect relationship of ADA in AS	102 pts, 42 years, 67% male, disease duration 7 years, HLAB27 83%, ASDAScrp 3.4, BASDAI 6.2	6 months	CRP, drug level	Median drug level in patients with low (< 10mg/l) baseline CRP was higher (10.6 (3.9-16.2)) than for patients with high (≥10mg/l) baseline CRP (6.9 (1.0-12.6)) p=0.019.	Quality in Prognosis Studies Tool	1.Study participation: moderate 2.Attrition: high 3.Prognostic factor: moderate 4.Outcome: moderate 5.Confounding: high 6.Statistics: low
Thurlings 2010	Porspective observational cohort, bicentric (AMC and LUMC), the Netherlands	RA, rituximab (2x 1000 mg)	Whether persistence of synovial B lineage cells and lack of clinical response are associated with low rituximab serum levels	58pts, female71-80%, DAS28 6.0-6.5, MTX 75-100%	24 weeks	Levels at week 4, 12/16 and 24, ESR	Baseline erythrocyte sedimentation rate negatively predicted rituximab levels at week 4 (AMC cohort, n=30: r2=20.17, p=0.018; LUMC cohort, n=28: r2=20.23, p=0.007).	Quality in Prognosis Studies Tool	1.Study participation: high 2.Attrition: high 3.Prognostic factor: high 4.Outcome: high 5.Confounding: high 6.Statistics: moderate

Inciarte-Mundo 2016	Cross-sectional study, monocentric, Spain	RA, PsA, infliximab, etanercept, adalimumab	To analyze the accuracy of calprotectin and TNF1 trough serum levels in detecting PDUS synovitis	RA: 42 pts, 81% female, age 64 years, disease duration 16 years, treatment duration83 months, DAS28 2.31 PsA: 50 pts, female 50%, age 55 years, disease duration 15 years, treatment duration 58 months, DAS28 1.82	N/A	Trough levels, calprotectin	Calprotectin inversely correlated with ADA (ρ = −0.461, p =0.008) and ETN (ρ = −0.436, p =0.005) trough serum levels, although non-significant correlations were found for IFX.	Newcastle-Ottawa for cohort studies	Sum score: *,-,* Selection: * Comparability: - Outcome: *

Multivariable analyses – multiple variables

Study	Study design	Population	Scope/Intervention	Study population	Follow-up	Outcome measures	Results	Tool used for RoB assessment	Risk of Bias
Dervieux 2012	Cross-sectional study	RA IFX (median 6 mg/kg/8 wks	Correlation between drug level, MTX polyglutamates (PG) and disease activity	61 pts, 64 years, 77% female, disease duration 11 years, MTX dose 15 (10-20) mg, treatment duration 70 months, CDAI 8	N/A	Drug level, MTX PG, disease activity, MTX therapy	In a multivariate linear regression analysis, lower IFX levels associated with lower infliximab doses (p<0.001), lower MTX PG levels (p=0.032), presence of ADAb (p=0.029) and shorter duration of MTX therapy (p=1.0). Nearly 50% of the variance in IFX trough levels could be explained by these 4 independent variables.	Quality in Prognosis Studies Tool	1.Study participation: moderate 2.Attrition: ? 3.Prognostic factor: ? 4.Outcome: low 5.Confounding: high 6.Statistics: low
Jani 2020	Prospective observational cohort study, multicenter (UK), OUTPASS	PsA, ETN, ADA	1- whether the presence of ADAb/drug levels predicts treatment response 2- identify a drug level threshold for optimal therapeuticresponse 3- factors	ADA 97 pts, ETN 56 pts, age 51 yrs, BMI 28.9, female gender 46%, disease duration 5 yrs, DAS28: 4.9, CRP 7.5, MTX use 25%	12 months	Adalimumab concentrations, disease activity (DAS28 (crp))	Factors that were inversely associated with ADA drug levels were ADAb level (β = –0.0073, 95% CI –0.0014 to 0.18; p < 0.0001) and BMI (β –0.15, 95% CI –0.29 to –0.00450; p = 0.043) in the final GEE model (adjusting for age, sex, adherence, BMI)	Quality in Prognosis Studies Tool	1.Study participation: moderate 2.Attrition: high 3.Prognostic factor: high 4.Outcome: low 5.Confounding: high 6.Statistics: low

			associated with drug levels						
Jamnitski 2012	Observational cohort, monocentric, the Netherlands	RA ETN	Investigate the relationship between serum etanercept levels and clinical response	292 pts, 53 years, 82% female, MTX use 76%, disease duration 8 years, DAS28 5.2	6 months	Drug level and demographic parameters	Patients with drug levels in the lowest quartile (<2.1mg/l) were more often women 89 vs. 68% (p=0.002) when compared to the highest quartile (>4.7mg/l), used lower dosages of MTX (12.6 vs. 16.9) (p=0.01) had a higher body mass index (27.5 vs. 24.9) (p=0.007); had a higher glomerular filtration rate (130.0±46.6 vs 107.8±29.4, p=0.001)	Quality in Prognosis Studies Tool	1.Study participation: high 2.Attrition: high 3.Prognostic factor: low 4.Outcome: low 5.Confounding: low 6.Statistics: low
Jani 2015	Prospective observational cohort (BRAGGSS) multicentric, UK	RA ADA, ETN	Random drug levels, clinical response and adherence to therapy	ADA 160 pts, age 56.2 years, 70% female, disease duration 8.6 years, DAS28 5.7, MTX 55%. ETN 171 pts, 57 years, 80% female, disease duration 7,8 years, DAS28 5.9, MTX 46%	12 months	Random drug levels, demographic parameters	In analysis for predictors of low drug levels, for adalimumab, anti-drug antibodies was the strongest predictor (rc 1.27 95%CI 0.44-2.09 p=0.003). Adherence (self-reported) (rc -0.68 95%CI -1.29- -0.07, p=0.028) and BMI (rc 0.055 95%CI 0.017-0.094, p=0.005) were also significant predictors.	Quality in Prognosis Studies Tool	1.Study participation: moderate 2.Attrition: moderate 3.Prognostic factor: moderate 4.Outcome: moderate 5.Confounding: moderate 6.Statistics: low
Plasencia 2015	Retrospective observational cohort, monocentric, Spain	RA IFX	The effect of dose increase on trough levels and clinical response in patients with DAS28>3.2	42 pts, 88% female, 57 years, disease duration 19 years, treatment duration 6.2 years, MTX 86%, DAS28 4.55	12 months	Infliximab levels, patient characteristics	Patients were divided into three groups based on trough levels: no drug detectable, < 1.1 ug/ml and ≥ 1.1 ug/ml. Age of disease onset was lower in patients with no detectable drug levels (49.6 years vs. 61.6 and 67.4 years for low and higher IFX levels, respectively) and duration of treatment was longer for patients with high levels (28.3 years vs. 16.3 and 17.9 years for no and low IFX levels, respectively). (no statistics). After dose increase (or shortening of the interval) drug levels in the no (p=1.0) and low (p=0.97) levels group did not increase significantly, as it did in the high levels group (p=0.017).	Quality in Prognosis Studies Tool	1.Study participation: high 2.Attrition: moderate 3.Prognostic factor: moderate 4.Outcome: low 5.Confounding: moderate 6.Statistics: moderate
Kneepkens 2015	Prospective observational cohort, monocentric, the	AS ETN	association between drug levels and clinical response	162 pts, age 43 years, men 71%, disease duration 8 years, HLAB27	24 weeks	drug levels, BMI, disease activity	Patients of the highest quartile (>4.6 ug/ml) had a statistically significantly lower BASDAI (5.4 (4-6.6)) and BMI (24.5 (22.4-26.1)) at baseline, compared to patients in the lowest quartile	Quality in Prognosis Studies Tool	1.Study participation: moderate 2.Attrition: moderate 3.Prognostic factor: low 4.Outcome: low 5.Confounding: low

	Netherlands			73%, ASDAScrp 3.6, NSAID 70%			(<1.8ug/ml): 6.4 (5.6-7.6) and 26.2 (23.6-30). P=0.03 and 0.02, respectively.		6.Statistics: low
Sigaux 2017	Observational cohort study, bicentric, France	RA TCZ (iv)	To assess tocilizumab drug levels in RA patients	40 pts, age 56 years, female 32/8, disease duration 16 months	21 pts month 0 to 6, 19 patients during follow-up, mean treatment time 21 months	Serum levels, gender, BMI, MTX	Gender had no effect on TCZ trough levels (p = 0.54), and trough levels did not differ by BMI category (BMI < 25,25–30, > 30 kg/m2, p= 0.84). Patients with and without MTX co-treatment did not differ in serum TCZ trough levels (p= 0.37).	Quality in Prognosis Studies Tool	1.Study participation: moderate 2.Attrition: high 3.Prognostic factor: high 4.Outcome: moderate 5.Confounding: high 6.Statistics: moderate
Stamp, 1440 ACR 2019	Abstract ACR 2019, cross-sectional	RA ADA	To determine the influence from variables on adalimumab concentrations and to assess the relationships between adalimumab concentrations, the presence of anti-drug antibodies and disease activity in RA.	156 pts	at least 4 months of treatment	adalimumab concentrations, demographics	Multivariate analysis, which included the presence of ADAb, revealed CRP (p< 0.001), weight (p< 0.004) and ethnicity (p< 0.001) were all independently negatively associated with adalimumab concentrations. There was a negative correlation between IL-6 and adalimumab concentrations (r=-0.038; p< 0.01).	Quality in Prognosis Studies Tool	1.Study participation: high 2.Attrition: high 3.Prognostic factor: ? 4.Outcome: low 5.Confounding: ? 6.Statistics: moderate

PTC-4: There is an association between biopharmaceutical blood concentrations and clinical response, but more data are required to recommend an optimal range for most biopharmaceuticals in most indications.

Association between biopharmaceutical blood concentrations and clinical response:

Rheumatoid arthritis + TNF-inhibitors

Study	Study design	Population	Scope/Intervention	Study population	Follow-up	Outcome measures	Results	Tool used for RoB assessment	Risk of Bias
				ADALIMUMAB					
Goss 2018	RCT, CONCERTO trial, multinational, multicenter	RA, ADA, 4 different dosages of MTX (2.5, 5, 10 and 20 mg/wk)	Effect of MTX on adalimumab pharmacokinetics	395 patients, 52 years, 75% female	26 weeks	Response rates (DAS28crp <2.6 and < 3.2) and adalimumab levels	Adalimumab range and % DAS28 < 2.6 and< 3.2, respectively: 0-1.845 ug/ml, 24.7 and 40.4%, 1.845-5.83 ug/ml, 34.8 and 49.4% 5.83-8.935 ug/ml, 48.9 and 65.9% >8.935 ug/ml, 48.3 and 68.5% Higher percentages of response up to 8,935 ug/ml, no additional benefit above On the basis of logistic regression analyses, the likelihood of a patient achieving DAS28(CRP) <3.2 was statistically significantly related to the concentration of adalimumab (P < 0.001)	Cochrane RoB2 for RCT	Overall: low Randomisation: Low Intervention: low Missing outcome data: low Outcome measurement: low Selective reporting: Low
Chen 2016	Longitudinal observational cohort (dose-halving common practice in Taiwan)	RA ADA with remission (DAS28< 2.6) or low disease activity (DAS28 <3.2)	Correlation between ADA levels, and (persistent) clinical response after dose-halving	64 pts, 39% remission, 61% LDA. 86-92% female, disease duration 9 years, DAS28 2.2-3.15, MTX 86-91%	24 weeks	Baseline and week 24 drug levels and disease activity: persistent remission or LDA or flare	Persistent remission: 23 pts, persistent LDA: 24 pts, flare: 15 pts (23.5%) ADA levels 10.5, 4.5 and 0.9 mg/l at baseline for patients with persistent remission, persistent LDA or flare, respectively (p<0.001) ADA levels at week 24 after dose reduction: 5.2, 2.0, 0.1 mg/l for patients with persistent remission, persistent LDA or flare, respectively (p<0.001)	Quality in Prognosis Studies Tool	1.Study participation: high 2.Attrition: high 3.Prognostic factor: low 4.Outcome: low 5.Confounding: moderate 6.Statistics: high
Rosas 2014	Cross-sectional study, multicentric, Spain	RA, adalimumab	To assess the usefulness of measuring serum adalimumab levels after at least 3 months of treatment	57 pts, female 79%, age 63 years, disease duration 14 years, concomitant DMARD 100%, DAS28 2.7, SDAI	N/A	DAS28(ESR): remission<2.6, low activity 2.6–3.1, moderate3.2–5.1, severe >5.1	There was a negative correlation (univariate analysis) between adalimumab levels and DAS28: r=-0.43. Patients with DAS28 ≤3.2 had higher adalimumab levels: 9.3 (4.1) mg/l, vs 4.4 (4.0) mg/l for patients with DAS28>3.2, p<0.001 When divided into tertiles: <5.5mg/l (mean 2.5 mg/l) corresponded with DAS28 of 3.34 (1.22), 5.5-11.3 mg/l (mean	Newcastle-Ottawa for cohort studies	Sum score: **, -, * Selection: ** Comparability: - Outcome: *

				6.4, treatment duration 2.7 years		Drug level	7.9 mg/l) corresponded with DAS28 of 3.04 (1.22) and >11.3 mg/l (mean 13.1 mg/l) corresponded with DAS28 2.23 (0.72).		
Bartelds 2007	Prospective observational cohort, monocentric, Amsterdam, the Netherlands	RA ADA	Association antibodies with drug level and clinical response	121 pts, 79% female, age 53, baseline DAS28 5.3, diseases duration 12 years, MTX use 80%	28 weeks	Clinical response: EULAR response, drug levels and antibodies	EULAR non-responders had significantly lower serum adalimumab concentrations than good responders, median 5.4 (0.0 – 21.2) ml/l vs 9.8 (0.0 -33) ml/l (p=0.001)	Quality in Prognosis Studies Tool	1.Study participation: moderate 2.Attrition: moderate 3.Prognostic factor: high 4.Outcome: low 5.Confounding: high 6.Statistics: low
Stamp, 1440 ACR 2019	Abstract ACR 2019, cross-sectional	RA ADA	To determine the influence from variables on adalimumab concentrations and to assess the relationships between adalimumab concentrations, the presence of anti-drug antibodies and disease activity in RA.	156 pts No further information available	at least 4 months of treatment	DAS28, DAS28≤3.2, adalimumab concentrations	There was a negative correlation between adalimumab concentration and DAS28 (r=-0.37; p< 0.0001). Adalimumab concentrations were higher in those with DAS28 ≤3.2 compared to those with DAS28 >3.2 (median (IQR) 10.8 (6.4-20.8) mg/l vs.7.1 (1.5-12.6) mg/l; p < 0.001).	Quality in Prognosis Studies Tool	1.Study participation: high 2.Attrition: high 3.Prognostic factor: ? 4.Outcome: low 5.Confounding: ? 6.Statistics: moderate
ETANERCEPT									
Daien 2012	Prospective observational cohort, monocentric, France	RA ETN	Explore predictive value of etanercept levels for response to treatment	19 pts, all female, age 56 years, disease duration 5 years, DAS28 4.85, MTX 12 pts, LEF 5 pts	6 months	DAS28, EULAR response, remission (DAS28<2.6) LDA (DAS28 2.6-3.2) drug level	At 3 and 6 months, median concentrations were higher (ns) for responders than for nonresponders. 3.6 vs.2.1 ug/ml at 3 months and 3.6 vs. 2.4 ug/ml at 6 months. ETN concentration at 3 months was inversely correlated with change in DAS28 at 3 months (r-0.50, p=0.03) but not at 6 months (r-0.48, p=0.06). At 3 months the median ETN concentration was significantly lower for 6 month nonresponders than for responders, 1.75 vs. 3.7 ug/ml, p=0.03. The 3 month ETN concentration was significantly correlated with the change in DAS28 between baseline and 6 months (r-0.62, p=0.006)	Quality in Prognosis Studies Tool	1.Study participation: high 2.Attrition: low 3.Prognostic factor: low 4.Outcome: low 5.Confounding: high 6.Statistics: low

Jamnitski 2012	Longitudinal observational cohort, monocentric, the Netherlands	RA ETN	Investigate the relationship between serum etanercept levels and clinical response	292 pts, 53 years, 82% female, MTX use 76%, disease duration 8 years, DAS28 5.2	6 months	Drug level and EULAR response	Drug levels were higher for EULAR good responders (n=103 at M6) as compared to moderate (n=115 at M6) and non-responders (n=74 at M6), there were no differences between moderate and non-responders. Levels at 1, 4 and 6 months: Good: 3.4 (2.22-4.62), 3.98 (2.72-5.35) and 3.78 (2.53-5.17) (p<0,05 for all vs. moderate and poor response) Moderate: 2.52 (1.26-4.11), 3.08 (2.03-4.52) and 3.1 (2.12-4.47) (ns with poor response) Non: 2.64 (1.20-3.89), 2.54 (1.12-3.94) and 2.80 (1.27-3.93) There was a significant correlation between the height of the level and EULAR response (OR 2.51 95%CI 1.58-3.98 p<0.001)	Quality in Prognosis Studies Tool	1.Study participation: high 2.Attrition: high 3.Prognostic factor: low 4.Outcome: low 5.Confounding: low 6.Statistics: low
INFLIXIMAB									
Siljehult 2018	Prospective observational cohort, multicentric, Sweden	RA infliximab	Correlation between drug levels and clinical response	94 pts, female 83%, age disease onset 42 years, disease duration 14 years, DAS28 5.6, MTX 77%, IFX dose 3.3 (±0.6) mg/kg	52 weeks	DAS28, EULAR response, ESR, CRP, infliximab levels	Good responders had significantly higher concentrations of IFX, e.g. at 52 weeks good responders had an IFX concentration of 6.6 ± 1.4 µg/mL, compared with 3.6 ± 1.3 µg/mL in patients with a moderate response and 2.6 ± 1.6 µg/mL in those with a poor response (p < 0.001). Patients with a good response at 14 weeks and an IFX concentration > 0.5 µg/mL were still good to moderate responders after 52 weeks (16/18; 88.9%). The concentration of IFX was inversely correlated with DAS28, and with levels of ESR and CRP at 14 weeks (p < 0.01, p < 0.05, and p < 0.001, respectively) and 52 weeks (p < 0.001 for all three analyses)	Quality in Prognosis Studies Tool	1.Study participation: moderate 2.Attrition: high 3.Prognostic factor: moderate 4.Outcome: moderate 5.Confounding: high 6.Statistics: moderate
Van der Maas 2012	Cross-sectional with observation period, monocentric, the Netherlands	RA infliximab	To get insight in serum trough levels of infliximab in patient with RA	147 pts, age 58 years, female 69%, disease duration 11 years, DMARDs 78%, DAS28 3.5, treatment duration 2.5 years	1,5 years	Infliximab level, DAS28	4 trough level groups were identified, 0, <1, 1-5 and >5 mg/l. For patients with DAS28<2.6 (n=40), 13 (2-23), 23 (10-35), 48 (32-63) and 18 (6-29)% (95%CI) of patients were in the representative trough level groups, respectively. For patients with DAS28≤ 3.2 (n=65), 13 (4-20), 18 (9-28), 55 (43-67) and 14 (5-22)% (95%CI) of patients were in the representative trough level groups. For patients with DAS28>3.2 (n=82), 29 (19-39), 18 (10-27), 32 (22-42) and 21 (12-30)% (95%CI) of patients were in the representative trough level groups.	Newcastle-Ottawa for cohort studies	Sum score: **, -, ** Selection: ** Comparability: - Outcome: **

Pascual-Salcedo 2011	Longitudinal observational, retrospective cohort study, monocentric, Spain	RA infliximab	Influence of immunogenicity on long term treatment	85 pts, age 54 years, female 81%, MTX 81%, mean treatment duration 4.24 years, DAS28 5.49	> 4 years	Infliximab levels, EULAR response	Serum trough infliximab levels (Median, IQR) were higher in EULAR responders (good and moderate) than in EULAR non-responder patients at 6 months (992, 46-2960 vs 0, 0-60 ng/ml, P = 0.005), 1 year (1792, 384-3904 vs 0, 0-555 ng/ml, P = 0.021) and >4 years (1536, 220-3456 vs 0, 0-2672 ng/ml, P = 0.101), respectively	Newcastle-Ottawa for cohort studies	Sum score: ***, -, ** Selection: *** Comparability: - Outcome: **
Finckh 2010	Nested case control cohort study, multicentric, Switzerland	RA IFX	Correlation between antibodies and drug levels and acquired drug resistance (defined by increased DAS28 or increased dose of IFX or DMARDs)	64 pts, 24 acquired drug resistance/ 40 ongoing good response. Age 58/60 years, female 79/74%, disease duration 14 years, MTX 85/79%, treatment duration 3/2.3 years, IFX dose 5,4/4,3mg/kg (p=0,02) ; interval 7,1/8,7 weeks (p=0,01)	N/A	Drug levels in patients with continuous good clinical response and acquired drug resistance	Median IFX concentration with acquired therapeutic resistance 3 382 ng/L [IQR: 122–26 201] compared to 17 248 ng/L [IQR: 372–28 176] in patients with ongoing good responses, no statistically significant difference. Of note: patients with acquired drug resistance had significantly higher dosages of IFX (5.4 mg/kg vs. 4.3, p= 0.02) and shorter infusion intervals (7.1 vs. 8.7 weeks, p=0.01)	Newcastle-Ottawa for cohort studies	Sum score: ***, *, * Selection: *** Comparability: * Outcome: *
Mulleman 2010	Cross-sectional cohort, followed up for 42 weeks, monocentric, France	RA IFX	Predictive value of trough levels for sustainable clinical response	28 pts, 20 female, age 59 years, treatment duration 45 months, IFX dose: 4.1 (2.7-5.9) mg/kg / 8.1 (5.0-12.4) weeks, DAS28 3.0 (0.8-7.6)	42 weeks	Infliximab concentration, DAS28 ≤ or > 3.2, treatment maintenance	Patients with low disease activity (DAS28<3.2) had higher median drug level values (3.26 mg/l) than those with persistent disease (0.16 mg/l), (p<0.01). Patients with high baseline infliximab exposure, above the median of 2.27 mg/l, had better treatment maintenance (p<0.01).	Newcastle-Ottawa for cohort studies	Sum score: **, -, * Selection: ** Comparability: - Outcome: *
Takeuchi 2009	Randomized controlled	RA infliximab (week 0 -	Impact of trough level on radiographic and	334 pts, age 49-50, disease duration 7-8	54 weeks	Trough level, EULAR response, TSS (total sharp	A significant association was observed between clinical response and trough serum infliximab levels at week 54. Better EULAR response was obtained in patients with higher	Cochrane RoB2 for RCT	Overall: low Randomisation: Low Intervention: low

	trial, RISING multicentric, Japan	14: 3 mg/kg, week 14-46: 3, 6 or 10 mg/kg)	clinical response to IFX + MTX	years, DAS28 6.2, Sharp score (median) 28-38		score) change, DAS28 remission	trough serum infliximab levels (p<0.0001). no: <0.1 ug/ml, moderate: 11 ug/ml and good 3.0 ug/ml. Furthermore, patients achieving remission also had significantly higher trough serum levels than patients without remission (p<0.0001). remission: 3.1 ug/ml, no remission 1.0 ug/ml. Significant differences were observed among trough serum infliximab levels at week 54 in patients classified as progressed (0.5 ug/ml), no change (2.0 ug/ml) or improved (3.8 ug/ml) in joint damage (p = 0.0022). Progression of joint damage was most frequently observed in patients with <0.1 ug/ml trough serum level, and none of these patients showed improvement. In contrast, there was no case with progression of joint damage in patients with >10.0 ug/ml trough serum level.		Missing outcome data: low Outcome measurement: low Selective reporting: Low
Wolbink 2005	Prospective observational cohort, monocentric, the Netherlands	RA infliximab	Relationship between serum trough infliximab, clinical response and CRP	105 pts, female 83%, age 56 years, disease duration 12 years, MTX 86/105, DAS28 6.1	14 weeks	EULAR response, drug level	After 14 weeks of treatment responders had significantly (p<0.01) higher median serum trough infliximab concentrations than non-responders (3.6 (1.4–8.2) v 0.5 (0.2–2.2) mg/l. % EULAR responders per IFX concentration group at week 14: 0-1.2 mg/l: 50%; 1.3-4.7 mg/l: 90%; 5-25.8 mg/l: 88%	Quality in Prognosis Studies Tool	1.Study participation: low 2.Attrition: high 3.Prognostic factor: moderate 4.Outcome: low 5.Confounding: moderate 6.Statistics: low
GOLIMUMAB									
Kneepkens 2014	Longitudinal observational cohort, multicentric, the Netherlands and Spain	RA GLM	Association between drug level and clinical response	37 pts, 52 years, 84% female, disease duration 12 years, DAS28 4.4 MTX 65%	1 year	Clinical response (DAS28 < or ≥ 3,2) and drug levels	Golimumab levels were higher for 52 week responders (DAS28<3.2) (1.36 (0.5-1.82) ug/ml), compared with nonresponders (DAS28≥3.2) (0.43 (0.23-0.84) ug/ml) (p= 0,023) The lowest golimumab level quartile (<0.25 ug/ml) comprised 32% of all nonresponding patients, while the highest quartile (>1.4ug/ml) comprised 47% of all responding patients.	Quality in Prognosis Studies Tool	1.Study participation: moderate 2.Attrition: moderate 3.Prognostic factor: moderate 4.Outcome: moderate 5.Confounding: moderate 6.Statistics: low
COMBINATION OF TNF INHIBITORS (adalimumab, etanercept, infliximab)									
Moots 2017	Cross-sectional study, multinational	RA adalimumab, etanercept	Relationship of anti-drug antibodies and efficacy and patient reported outcome with drug levels	ETN n=200, age 57 years, female 78%, treatment duration 14.6	N/A	CDAI, SDAI, DAS28 ESR/CRP, TJC, HAQ, SF-36, EQ-5D	In patients treated with etanercept, there were no significant correlations between drug trough level and efficacy endpoints or inflammation markers. In patients treated with adalimumab, there were negative correlations between serum trough level and DAS28(ESR) (r=-0.172, p=0.0155), DAS28(CRP) (r=-0.154, p=0.0297), TJC (r=-	Quality in Prognosis Studies Tool	1.Study participation: moderate 2.Attrition: high 3.Prognostic factor: ? 4.Outcome: moderate 5.Confounding: high 6.Statistics: low

		and infliximab		months, MTX 61.5% ADA n=199, age 54 years, female 81%, treatment duration 13.5 months, MTX 70% IFX n=196, age 61 years, female 80%, treatment duration 13.1 months, MTX 64%			0.167, p=0.0187), ESR (r=-0.290, p<0.0001) and CRP (r=-0.440, p<0.0001). In patients treated with infliximab, negative correlations were observed between serum levels and ESR (r=-0.261, p=0.0003) and CRP (r=-0.399, p<0.0001) In patients treated with etanercept or infliximab, no statistically significant correlations were observed between drug levels and patient-reported outcomes. In patients with adalimumab, a negative correlation was observed between levels an HAQ-DI (r=-0.225, p=0.0014). Positive correlations were found with: EQ-5D utility score (r = 0.177, p = 0.0126), EQ-5D visual analog scale (VAS) score (r = 0.224, p=0.0014), SF-36 mental component score (r = 0.141, p= 0.0475), SF-36 Role Physical (r = 0.154, p = 0.0297), SF-36 General Health (r = 0.200, p = 0.0047), and SF-36 Role Emotional (r = 0.160, p= 0.0238)		
Bouman 2017	Combined data: Patients from the interventio n arm of an open RCT investigatin g non-inferiority of a dose reduction strategy (ADA / ETN) and patients from an longitudinal observation al down titration study of IFX ,the	ADA ETN IFX RA	Association between drug level and successful dose reduction (increase interval for ADA and ETN, dose reduction for IFX) and discontinuation of the drug	ADA 42 pts ETN 76 pts IFX 51 pts. Age 58-61 years, 57-64% female, disease duration 7.5 – 13 years, DAS28 2.4-2.6, duration current treatment: 2.9-5.6 years, MTX 45-68%	18 months	Predictive value of random drug levels for successful dose reduction and discontinuation of TNFi	Mean drug levels were not significantly different between patients continuing without dose reduction, with dose reduction or discontinuing treatment ADA: 6.8, 8.1 and 8.5 ug/ml, resp. ETN: 2.4, 2.0 and 2.7 ug/ml, resp. IFX: 0.55, 1.7 and 1.0 ug/ml, resp. Using ROC analysis, no significant predictive value of serum levels for successful dose reduction of discontinuation could be provided, except for a significant but small inverse association between lower etanercept levels and higher chance for successful dose reduction (AUC 0.36, optimal cut off <2.6 ug/ml) For ADA, high trough levels were associated with successful dose reduction (AUC 0.86) with trough levels > 7.8 ug/ml showing a sensitivity of 100% and a specificity of 86%	Quality in Prognosis Studies Tool	1.Study participation: moderate 2.Attrition: moderate 3.Prognostic factor: moderate 4.Outcome: low 5.Confounding: high 6.Statistics: low

	Netherlands								
Chen 2015	Longitudinal observational cohort, Taiwan	RA ADA and ETN	Association between drug levels and therapeutic response	ADA 36 pts, 53 years, 89% female, disease duration 5.4 years, DAS28 6.1, MTX 89% ETN 34 pts, 58 years, 88% female, disease duration 5.4 years, DAS28 5.95 MTX 88%	12 months	EULAR response and drug level	There was a significantly higher ADA level in EULAR responders at 6 and 12 months compared to both moderate and poor responders. at 6 months: 6.5, 1.0 and 0.4 mg/l, resp. (p<0.001 for both) at 12 months: 5.9, 0.5 and 0.3 mg/l, resp. (p<0.01 for both) For ETN 6 month good responders had higher drug levels than moderate responders and nonresponders. 12 month good responders had higher drug levels than moderate and non- responders. at 6 months: 2.3, 1.0, 0.2 mg/l, resp. (p<0.05 (vs. moderate) ; p<0.001 (vs. poor)) at 12 months: 1.3, 0.5, 0.1 mg/l, resp. ns (vs moderate) ; p<0.01 (vs poor))	Quality in Prognosis Studies Tool	1.Study participation: high 2.Attrition: ? 3.Prognostic factor: moderate 4.Outcome: low 5.Confounding: high 6.Statistics: moderate
Sanmarti 2015	Cross-sectional study	RA etanercept, adalimumab	Confirmation of the study results by Chen et al 2015, optimal cut-offs for adalimumab and etanercept	127 patients in total, 54 adalimumab, 73 etanercept. 82% female, age 61 years, disease duration 13 years, treatment duration 60 months	N/A	DAS28≤2.6, etanercept and adalimumab trough level cut-offs	Serum levels of adalimumab and etanercept were significantly higher in patients in remission (DAS28≤2.6) than in those who were not (median (P25–P75) adalimumab 6.9 µg/mL (2.7–12) vs 0.5 (0.1–1), p<0.001, etanercept 2.3 µg/mL (1.5–3.1) vs 0.8 (0.4–1.8), p<0.001)	Newcastle-Ottawa for cohort studies	Sum score: ***, -, ** Selection: *** Comparability: - Outcome: **
Jani 2015	Prospective observational cohort (BRAGGSS), multicenter, UK	RA ADA, ETN	Random drug levels, clinical response and adherence to therapy	ADA 160 pts, age 56.2 years, 70% female, disease duration 8.6 years, DAS28 5.7, MTX 55%. ETN 171 pts, 57 years, 80% female, disease duration 7,8	12 months	Random drug levels, EULAR response, change in DAS28crp, adherence to treatment	In a multivariable GEE model, after adjusting for confounders BMI, disease duration, age, sex and adherence, there was a relationship between adalimumab level and change in DAS-28 (regression coefficient (rc) 0.060 95% CI 0.015, 0.10, p=0.009), also in a subgroup analysis in MTX treated patients (adjusted for dose) (rc 0.076 95%CI 0.028, 0.12 p=0.002) Drug levels < 1.0 ug/ml was associated with no response (rc 2.29 95% CI 1.13-3.44 p<0.0001)	Quality in Prognosis Studies Tool	1.Study participation: moderate 2.Attrition: moderate 3.Prognostic factor: moderate 4.Outcome: moderate 5.Confounding: moderate 6.Statistics: low

				years, DAS28 5.9, MTX 46%			Etanercept non trough levels (cut off <3.23ug/mL) at 3 months had a poor value for prediction EULAR no response at 12 months (AUC 0.58 95%CI 0.46-0.70)		
Radstake 2009	Prospective observational cohort study, monocentric, the Netherlands	RA ADA IFX	Exploring clinical response, antibody formation and drug levels of ADA and IFX	IFX: 35 pts, age 57 years, 86% female, MTX 100%, DAS28 5.6 ADA: 34 pts, age 56 years, 79 female, MTX 41%, DAS28 5.7	6 months	ADA and IFX levels at 3 and 6 months and EULAR response	IFX: correlation between drug level and good response was r=0.54, p=0.03 serum infliximab levels for good, moderate and non-responders at 3 and 6 months, respectively: 3.1 (0.8-17), 1.9 (0-5), 0.2 (0-14) and 2.7 (0.9-10), 0.8 (0-9), 0 (0-0) ADA: correlation between drug level and good response was r=0.64, p=0.01 serum adalimumab levels for good, moderate and non-responders at 3 and 6 months, respectively: 31 (3-151), 12 (1-138), 2 (0-7) and 32 (3-150), 14 (2-41), 1 (0-0)	Newcastle-Ottawa for cohort studies	Sum score: ***, -, ** Selection: *** Comparability: - Outcome: **

Rheumatoid arthritis + other biologics

Study	Study design	Population	Scope/Intervention	Study population	Follow-up	Outcome measures	Results	Tool used for RoB assessment	Risk of Bias
TOCILIZUMAB									
Arad 2019	Israeli cohort of the TOZURA study (multinational, stage IV, single arm, open label)	RA tocilizumab 162 mg sc weekly	To determine whether trough levels are associated with disease activity / response	100 pts, 54 years, 80% female, DAS28 5.0, CDAI 31.9	24 weeks	CDAI, Trough level	At week 12, in multivariate analysis, for every increase of 10 µg/ml in the serum concentration of TCZ there was a corresponding improvement of 2.22 units in the CDAI score (p = 0.002). In a multivariate binary GEE model, every increase of 10 µg/ml in the serum concentration of TCZ was associated with an OR of 1.41 of being in a state of CDAI remission or LDA versus moderate/high disease activity state (p = 0.001)	Quality in Prognosis Studies Tool	1.Study participation: low 2.Attrition: high 3.Prognostic factor: high 4.Outcome: Low 5.Confounding: moderate 6.Statistics: moderate
Sigaux 2017	Longitudinal observational cohort study,	RA TCZ (iv)	To assess tocilizumab drug levels in RA patients	40 pts, age 56 years, female 32/8, disease duration 16 months, 24 pts	21 pts month 0 to 6, 19 patients during follow-up,	Serum levels, delta DAS28crp 0-3 months,	No significant correlation was found between TCZ level and change in DAS28-CRP within the first 3 months (p= 0.29)	Quality in Prognosis Studies Tool	1.Study participation: moderate 2.Attrition: high 3.Prognostic factor: high 4.Outcome: moderate 5.Confounding: high 6.Statistics: moderate

	bicentric, France			with DMARD therapy	mean treatment time 21 months				
Benucci 2016	Retrospective longitudinal observational cohort, Italy	RA TCZ	Association between drug level and disease activity	126 pts (110 female), 59 years, disease duration 11 years, 107 pts + MTX, 6 pts + LEF, 13 pts TCZ mono. All used prednisolone	6 months	Trough level and disease activity (DAS28, CRP, ESR)	Patients with TCZ trough levels below 10 ug/ml (n=84), as compared to patients with TCZ levels >10 ug/ml, had after 6 months of treatment a higher DAS-28 (3.09 vs. 2.78, p=0.0005), ESR (27 vs. 14, p=0.0001) and CRP (1.47 vs. 0.65 mg/dl, p=0.0086). There were no statistically significant differences at baseline between these parameters	Newcastle-Ottawa for cohort studies	Sum score: ***, -, *** Selection: *** Comparability: - Outcome: ***
RITUXIMAB									
Boumans 2013	Combined data of 3 monocenter prospective observational cohorts, the Netherlands	RA RTX (2x 1000mg)	Association between drug level and structural damage	62 pts, 69-75% female, age 51-58 years, DAS28 6.0-6.6, disease duration 12-14 years, MTX 46-100%	1 year	Drug levels at 4, 12-16 and 24 weeks of treatment and radiographic progression between baseline and 1 year after treatment	There were no differences in drug level between radiological progressors (increase Sharp van der Heijde Score≥3) and non-progressors: 126 vs 128 ug/ml (p=0.74) and 6.0 vs. 8.2 ug/ml (p=0.68), at week 4 and 12-16, respectively	Newcastle-Ottawa for cohort studies	Sum score: **, -, * Selection: ** Comparability: - Outcome: *

Axial spondyloarthritis + TNF inhibitors

Study	Study design	Population	Scope/Intervention	Study population	Follow-up	Outcome measures	Results	Tool used for risk of bias assessment	Risk of bias
ADALIMUMAB									
Ducourau 2020	Prospective, randomised, open label multi-	AxSpA, adalimumab	to evaluate the ability of methotrexate (MTX) to decrease adalimumab immunisation	MTX+ 52 pts, MTX- 55pts, male 42-51%, HLAB27 58-60%, age 43-41 years, disease duration 3-2 yerars, ASDAS 3.0	Median 88 weeks	Drug concentration, drug survival	Maintenance of adalimumab in patients within the first quartile of adalimumab concentrations (<4 µg/mL) at W8 was poorer than in others (median survival of 68.6 weeks vs 92.7 weeks, respectively, p=0.09). Adalimumab concentrations measured at W12 and 26 were not statistically associated with adalimumab long-term maintenance.	Cochrane RoB2 for RCT	Overall: high Randomisation: Low Intervention: some concerns Missing outcome data: low Outcome measurement: high Selective reporting: Low

	center study (2013-2014)			– 3.2, CRP (mg/L) 2.5 - 4					
Ding 2020	Observational cohort study, monocentric, China	AS adalimumab	To determine a concentration-effect curve for adalimumab in patients with AS	31 pts, age 31 yrs, male 94%, disease duration 7 yrs, CRP 16 mg/l, ASDAScrp 4.06, BASDAI 6.1, NSAIDs 15%	12 weeks	ADA concentrations, ASDAS	Week 12 adalimumab levels were significantly associated with primary response at 12 weeks of treatment (median 4.28, IQR 0.34−9.24 vs. 13.26 µg/mL, IQR 10.15−16.63 µg/mL among primary nonresponders vs. primary responders, p=0.0008) response was defined as either a decrease in ASDAS from baseline (ΔASDAS) ≥ 2.0 or a moderate disease activity achievement (ASDAS < 2.1) with ΔASDAS ≥ 1.1	Quality in Prognosis Studies Tool	1.Study participation: moderate 2.Attrition: high 3.Prognostic factor: ? 4.Outcome: low 5.Confounding: high 6.Statistics: low
Senabre 2019	Cross-sectional, monocentric, Spain	AS adalimumab	To assess the prevalence of anti-drug antibodies in patients with axSpA, to investigate their relationship with serum levels of adalimumab and disease activity	51 pts, 535 male, age 47 years, disease duration 71 months, DMARDs 21.6%, HLAB27 82%, BASDAI 4.2, ASDAScrp 2.0, ASDASesr 2.3, adalimumab treatment 9.8 months	N/A	BASDAI, ASDAS (CRP/ESR), trough levels	Patients classified as inactive disease/low activity (ASDAS-CRP < 2.1, ASDAS-ESR < 2.1 and BASDAI < 4) had higher median adalimumab levels (mg/l) compared to those with moderate/ high activity: 9.3 vs 0.3, 9.9 vs 3.0 and 9.5 vs 2.6, respectively. (p<0.001 for ASDAS-CRP & ESR ; p<0.01 for BASDAI)	Newcastle-Ottawa for cohort studies	Sum score: **, **, * Selection: ** Comparability: ** Outcome: *
Kneepkens 2015 (2)	Prospective observational cohort, multicentric, the Netherlands and Taiwan	AS ADA	Association between drug level and clinical response	115 pts, 42 years, 68% male, disease duration 8 years, HLAB27 83%, ASDAS 3.5, BASDAI 6.4, NSAIDs 65%	24 weeks	BASDAI, BASDAI50 response, ASDAScrp, ESR, drug levels, antibodies	There was no statistically significant difference in adalimumab levels between BASDAI50 responders and nonresponders: 12.0 (3.2-16) vs. 7.4 (4.1-15.5), p=0.3. GEE analysis showed a significant association between adalimumab level and disease activity, both ASDAS (p=0.02) and BASDAI (p=0.02), and ESR (p<0.001)	Quality in Prognosis Studies Tool	1.Study participation: moderate 2.Attrition: moderate 3.Prognostic factor: moderate 4.Outcome: moderate 5.Confounding: moderate 6.Statistics: low
ETANERCEPT									
Dong 2019	Prospective observational cohort, monocentric, China	AS etanercept	To investigate the effective serum level of etanercept in patients with AS	60 pts, 54/60 male, age 29 years, disease duration 4 years	24 weeks	BASDAI, ASDAS CRP/ESR, drug levels	Levels were significantly higher in patients with ASDAS-CRP < 2.1 (2.56 ± 1.31, 2.43 ± 1.17, and 2.64 ± 1.22 µg/mL at week 4, 12, 24, respectively) than in patients with ASDAS–CRP ≥ 2.1 (1.51 ± 0.63, 1.61 ± 0.26, and 1.66 ± 1.05 µg/mL at weeks 4,	Quality in Prognosis Studies Tool	1.Study participation: moderate 2.Attrition: high 3.Prognostic factor: moderate 4.Outcome: low

							12, and 24, respectively. p-values 0.002, <0.001 and 0.032 wat week 4, 12 and 24, respectively.		5.Confounding: high 6.Statistics: moderate
Kneepkens 2015	Prospective observational cohort, monocentric, the Netherlands	AS ETN	association between drug levels and clinical response	162 pts, age 43 years, men 71%, disease duration 8 years, HLAB27 73%, ASDAScrp 3.6, NSAID 70%	24 weeks	ASDASCRP, BASDAI, drug levels	Etanercept levels were significantly higher for patients with ASDAS<2.1 than for patients with ASDAS>2.1: 3.8 (2.5-5.2) vs.2.3 (1.2-3.4) (p<0.001) In the lowest quartile of etanercept levels, (<1.80) comprised 35% of patients with ASDAS >2.1, the highest quartile (> 4.6) comprised only 14%. The highest quartile comprised 36% of all patients with ASDAS<2.1, this was statistically significant to the number of patients with ASDAS<2.1 in the lowest quartile (15%, p=0.001	Quality in Prognosis Studies Tool	1.Study participation: moderate 2.Attrition: moderate 3.Prognostic factor: moderate 4.Outcome: moderate 5.Confounding: moderate 6.Statistics: low
de Vries 2009	Prospective observational cohort, monocentric, the Netherlands	AS ETN	Correlation between ETN level and clinical response	53 pts, 76% male, age 41 years, HLAB27 88%, BASDAI 6.4, ESR 22 CRP 17	6 months	BASDAI 50 response, drug level	48 and 41 samples were available at 3 and 6 months, respectively. Mean etanercept level for BASDAI responders at 3 months was 2.7 ug/ml, for non-responders the level was 2.8. there was no statistical difference between these levels.	Newcastle-Ottawa for cohort studies	Sum score: ***, -, *** Selection: *** Comparability: - Outcome: ***
INFLIXIMAB									
Krzysiek 2009	Randomized study, infliximab maintenance vs, on demand after induction period, multicentric, France	AS IFX, maintenance group	Association between drug level and clinical response	93 pts in continuous group with sufficient data for analysis. 74% male, age 40 years, disease duration 12 years, BASDAI 6.1	1 year	ASAS20 response, drug level	Treatment failure was not associated with low infliximab concentrations either during induction or after 1 year of treatment. 39% of 28 nonresponding patients had an infliximab concentration >10ug/ml at week 52. 14% of 65 responding patients had an concentration <1ug/ml. Median concentrations for responders (n=65) at week 6, 10, 16, 46 and 52: 24.5, 17.8, 10.1, 7.7, 7.1 ug/ml, resp. Median concentrations for nonresponders (n=28) at week 6, 10, 16, 46 and 52: 32.5, 22.4, 16.0, 8.6, 10.1 ug/ml, resp.	Cochrane RoB2 for RCT	Overall: high Randomisation: Low Intervention: some concerns Missing outcome data: high Outcome measurement: some concerns Selective reporting: Low
de Vries 2007	Prospective observational cohort, monocentric, the	AS IFX (5 mg/kg/6 wk)	Correlation between IFX level and ASAS response	38 pts (68% males, Age 40; HLA 84% : BASDAI 6,4	54 weeks	ASAS20 response criteria, drug level	At week 54, ASAS responders (n=21) had significantly higher drug levels than non-responders (n=17), 8.2 vs 6.3 ug/ml, p<0.01.	Newcastle-Ottawa for cohort studies	Sum score: ***, *, *** Selection: *** Comparability: *

	Netherlands								Outcome: ***
GOLIMUMAB									
Martinez-Feito 2018	Prospective observational cohort, multicentric, Spain, the Netherlands	axSpA, golimumab	Association between GLM levels and clinical response, determining the optimal concentration range	49 pts, 48 years, 73% men, disease duration 10.5 years, HLAB27 69%, ASDAS 3.5, monotherapy 37%	52 weeks	Clinical response: ASDAS, ΔASDAS, GLM levels	Patients with ASDAS<2.1 at week 52 (LOCF, n=33, 69%) had higher trough levels than patients with ASDAS≥2.1 (n=16): 1.07 (0.7 – 1.9) vs. 0.6 (0.1 – 1.4) p<0.01. In multivariable regression analysis, there was an association between golimumab levels and ASDAS at 24 weeks: r=-0.455, 95%CI -0.769 - -0.121, p<0.01. Among patients with levels <0.7 mg/l only one (7%) achieved major clinical improvement (ΔASAS ≥1.1). An additional 59% and 62.5% of patients in the 0.7-1.5-4 and >1.4 mg/l group, respectively, achieved this treatment goal (p>0.01). Of patients with levels <0.7mg/l (n=15), 37% had ASDAS<2.1 and 63% had ASDAS≥2.1 Of patients with levels 0.7 – 1.4 mg/l, 88% had ASDAS<2.1 and 12% had ASDAS≥2.1 Of patients with levels >1.4mg/l (n=16), 75% had ASDAS<2.1 and 25% had ASDAS≥2.1	Newcastle-Ottawa for cohort studies	Sum score: ***, **, ** Selection: *** Comparability: ** Outcome: **
COMBINATION OF TNF INHIBITORS (adalimumab, etanercept, infliximab)									
Arends 2010	Longitudinal observational cohort, monocentric, the Netherlands	AS, ADA, IFX ETN	Association drug level and disease activity	20 pts per drug (total 60 pts) age 42 63% male, disease duration 8 years, 84% HLA-B27+, DMARD 23% baseline BASDAI 5.9, CRP 17 ESR 25 ASDAS 3.8	12 months	drug level, antibodies, disease activity: BASDAI, ASDAS, CRP, ESR)	Serum levels at 3, 6 and 12 months were mean 30.6, 36.3 and 23.4 for IFX, 3.1, 2.8 and 2.9 for ETN and 5.7, 5.5 and 8.0 for ADA, respectively. No significant correlations were found between IFX levels and BASDAI, CRP, ESR or ASDAS. ETN levels were negatively correlated with CRP at 12 months and ESR after 3, 6 and 12 months (p<0.05). ADA levels were negatively correlated with BASDAI after 6 months, CRP after 12 months, ESR after 6 months and ASDAS after 3 months (p<0.05)	Quality in Prognosis Studies Tool	1.Study participation: moderate 2.Attrition: high 3.Prognostic factor: high 4.Outcome: low 5.Confounding: high 6.Statistics: moderate

Peripheral spondyloarthritis including psoriatic arthritis + TNF inhibitors

Study	**Study design**	**Population**	**Scope/Intervention**	**Study population**	**Follow-up**	**Outcome measures**	**Results**	**Tool used for RoB assessment**	**Risk of Bias**
ADALIMUMAB									

Chimenti 2016	Cross-sectional, observational, monocentric, Italy	PsA ADA	Explore correlation with drug levels and clinical response	30 pts, mean age 55 years, disease duration 12 years, treatment duration 56 (± 30) months, DAS 1.4, Serum ADA level 9.1	N/A	DAS44 < 1.6 or ≥1.6, drug level, CRP, SJC	Significant inverse correlations between serum ADA levels and CRP (r-0.43, p<0.05) SJC (r-0.4, p<0.5) and DAS44-CRP (r-0.36, p<0.05). Mean ADA concentration was significantly higher in patients with DAS <1.6 (n=18, mean 10.7 ug/ml) than in those with DAS ≥1.6 (n=12, mean 6.5 ug/ml).	Newcastle-Ottawa for cohort studies	Sum score: **, - ** Selection: ** Comparability: - Outcome: **
Paramarta 2014	Subanalysis of RCT, monocentric ,the Netherlands	Peripheral SpA, ADA (no AS or PsA)	Association with drug levels and response to treatment	26 pts, no more information available	Single measurement, 2 weeks after last injection (treatment duration 12 or 24 weeks)	ASDAS inactive disease, adalimumab trough level	Median trough level at the end of this study was 11.5 ug/ml. Levels were not different between responders (12.6 IQR 7.3-16.2 ug/ml) and nonresponders (9.3 IQR 3.1 – 14.5 ug/ml. levels did also not correlate with other end of study disease activity parameters such as global assessment, TJC, SJC, BASDAI, ASDAS, ESR or CRP.	Newcastle-Ottawa for cohort studies	Sum score: ***, -, ** Selection: *** Comparability: - Outcome: **
INFLIXIMAB									
Plasencia 2012	Observational ambispective cohort study monocentric, Spain	SpA, IFX	Influence of immunogenicity on long term treatment of IFX	94 pts, 56% men, age 50 years, HLAB27 59%, DMARD therapy 77%, ASDAS 3.08	> 4 years	ASDAS response, ifx level	Patients with inactive disease had higher IFX levels (median, IQR) than those with active disease (inactive: 4992, 2976–8768 ng/ml vs. moderate: 2048, 840–4112 ng/ml vs. high: 1104, 0–3150 ng/ml, p=0.001 at 6 months; inactive: 4128, 2768–7824 ng/ml vs. moderate: 2336, 852–3568 ng/ml vs. high: 1328, 0–3366 ng/ml, p=0.010 at 1 year; inactive: 4192, 2872–5344 ng/ml vs. moderate: 2432, 636–4288 ng/ml vs. high: 308, 0–3296 ng/ml, p=0.009 at >4 years).	Newcastle-Ottawa for cohort studies	Sum score: ***, -, ** Selection: *** Comparability: - Outcome: **
COMBINATION OF TNF INHIBITORS (adalimumab, etanercept)									
Jani 2020	Prospective observational cohort study, multicenter (UK), OUTPASS	PsA, ETN, ADA	1- whether the presence of ADAb/drug levels predicts treatment response 2- identify a drug level threshold for optimal therapeuticresponse 3- factors	ADA 97 pts, ETN 56 pts, age 51 yrs, BMI 28.9, female gender 46%, disease duration 5 yrs, DAS28: 4.9, CRP 7.5, MTX use 25%	12 months	Adalimumab and etanercept concentrations, disease activity (DAS28 (crp))	Using GEE, ADA drug levels were significantly associated with ΔDAS28 over 12 months (β 0.055, 95% CI 0.011–0.099; p = 0.014). There was no significant association between ETN drug levels and ΔDAS28 over 12 months (β –0.039, 95% CI –0.31 to 0.23; p = 0.77).	Quality in Prognosis Studies Tool	1.Study participation: moderate 2.Attrition: high 3.Prognostic factor: high 4.Outcome: low 5.Confounding: high 6.Statistics: low

			associated with drug levels						

Combination of diseases and TNF inhibitors

Study	Study design	Population	Scope/Intervention	Study population	Follow-up	Outcome measures	Results	Tool used for RoB assessment	Risk of Bias
Gehin 2019	Observational cohort (NOR-DMARD), multicentric, Norway	RA, SpA, PsA, certolizumab	Association between serum levels, antibodies and treatment response	116 SpA, 91 RA and 61 PsA. SpA: age 42 years, female 47%, disease duration 2,6 years, ASDAS crp 2.6, DMARDs 19%. RA age 54 years, female 79%, disease duration 10 years, DAS28 4.0, DMARDs 74%. PsA age 50 years, female 66%, disease duration 6.6 years, DAS28 3.9 DMARDs 67%	6 months	Clinical response (ASDAS-CRP, improvement ≥1.1, DAS28, EULAR good/moderate, improvement ≥ 0.6	In multivariate analysis, levels ≥ 20 mg/l were associated with ASDAS improvement at 3 (p=0.01) and 6 (p<0.01) months, greater improvement in DAS28 at 3 months (p=0.04) and borderline at 6 months (p=0.08) in RA, for PsA there was a trend towards greater improvement of DAS28 (p=0,14 at 3M; p=0,28 at 6months). Serum levels ≥20 mg/l were associated with response at 3 and 6 months (OR 2.3, 95% CI 1.2-4.5 p=0.01 and OR 1.9 , 95% CI 1.0-3.5, p=0.05). Certolizumab levels ≥ 40 mg/l were not associated with additional benefit. ORs for clinical response with certolizumab levels< 20 vs. ≥ 20 mg/l at 3 months were 3.4 (1.0-11.1, p<0.05), 1.5 (0.5-5.1, p=0.48) and 4.3 (1.0-17.9, p<0.05) for axSpA, RA and PsA, respectively, and at 6 months 3.3 (1.0-10.8, p<0.05), 1.1 (0.3-3.4, p=0.92), 3.3 (0.8-13.3, p=0.09) for axSpA, RA and PsA, respectively.	Quality in Prognosis Studies Tool	1.Study participation: low 2.Attrition: high 3.Prognostic factor: low 4.Outcome: low 5.Confounding: high 6.Statistics: low
Inciarte-Mundo 2016	Cross-sectional study, monocentric, Spain	RA, PsA, infliximab, etanercept, adalimumab	To analyse the accuracy of calprotectin and TNF1 trough serum levels in detecting PDUS synovitis	RA: 42 pts, 81% female, age 64 years, disease duration 16 years, treatment duration 83 months, DAS28 2.31 PsA: 50 pts, female 50%, age	N/A	Trough levels, power dopler ultrasound (PDUS)	RA patients with PDUS synovitis had significantly lower ETN (0.98 (0.7-2.3) vs. 2.54 (0.2-4.7) ug/ml), ADA (1.68 (0.6-12) vs. 8.39 (4.2-12) ug/ml) and IFX (1.68 (0.6-11) vs. 8.39 (4.2-12) ug/ml) trough serum levels. (p<0.05 for all) PsA patients with PDUS synovitis had lower trough serum levels of ETN (0.91 (0.6-1.6) vs. 1.38 (0.1-3.5) ug/ml) and ADA (0.88 (0.2-9.8) vs. 6.95 (4.1-12) ug/ml but not IFX (2.86 (0.1-6.5) vs. 3.21 (0.7-7.7) ug/ml. (p<0,05 for ADA & ETN ; not for IFX)	Newcastle-Ottawa for cohort studies	Sum score: *, -, * Selection: * Comparability: - Outcome: *

				55 years, disease duration 15 years, treatment duration 58 months, DAS28 1.82			**!! values for ADA and IFX RA are the same in the table, probably incorrect for IFX!!**		
Ducourau 2011	Prospective observational cohort	RA, SpA IFX	Correlation between antibodies, infliximab concentrations and infliximab maintenance	RA 17 pts, age 47-49 years, disease duration 6-10 years, MTX 43-60%. SpA 91 pts, age 44-47 years, disease duration 5-9 years, MTX 32%	Up to 40 months (?) not completely clear	Trough level after treatment initiation and maintenance of infliximab	RA: trough concentrations at week 14 above median of >3.2 mg/l and above the first quartile (>0.05 mg/l) showed longer infliximab maintenance although not significantly (logrank 0.06 and 0.2, resp.) SpA: trough concentrations at week 12 above median >13.7 mg/l was not associated with longer infliximab maintenance (logrank 0.9) However maintenance was longer for SpA patients with concentrations above the first quartile (> 6.5 mg/l, logrank 0.05))	Quality in Prognosis Studies Tool	1.Study participation: low 2.Attrition: moderate 3.Prognostic factor: high 4.Outcome: low 5.Confounding: high 6.Statistics: low
Gehin FRI0536 (2020)	EULAR abstract 2020 Observational study as part of NOR-DMARD study	RA, axial SpA, PsA, GLM	To identify the therapeutic target concentration of GLM	91 pts (RA:20, PsA:30, AxSpA:41)	3 months	Random GLM levels, treatment response (EULAR response, ASDAS, DAPSA)	Golimumab serum concentrations varied considerably between patients on standard dose (range 0.0-8.2 mg/L) with a median of 2.2 (IQR 1.0-3.5) mg/L. The proportions of responders after 3 months among patients with golimumab concentration <1.0, 1.0-3.9 and ≥4.0 mg/L, were 19%, 49% and 74%, respectively. The proportion of responders was highest among patients with golimumab concentrations ≥4.0 mg/L, but the difference in response between patients with concentrations ≥4.0 mg/L compared to 1.0-4.0 mg/L was not statistically significant (OR 2.1 (95% CI 0.6-7.1), P=0.24).	Newcastle-Ottawa for cohort studies	Sum score: **, **, ** Selection: ** Comparability: ** Outcome: **

Optimal range:

Rheumatoid arthritis + TNF-inhibitors

Study	Study design	Population	Scope/Intervention	Study population	Follow-up	Outcome measures	Results	Tool used for RoB assessment	Risk of Bias
ADALIMUMAB									

Goss 2018	RCT, CONCERTO trial, multinational	RA, ADA, 4 different dosages of MTX (2,5 ; 5 ; 10 ; 20mg/wk)	Effect of MTX on adalimumab pharmacokinetics	395 patients, 52 years, 75% female	26 weeks	Response rates (DAS28crp <2.6 and < 3.2) and adalimumab levels	Percentage response DAS28crp <2.6 or < 3.2 per adalimumab range: 0-1.845 ug/ml: 24.7 and 40.4 %; 1.845-5.83 ug/ml: 34.8 and 49.4%; 5.83-8.935 ug/ml: 48.9 and 65.9%; >8.935 ug/ml: 48.3 and 68.5%, respectively. Higher percentages of response up to 8,935 ug/ml, no additional benefit above	Cochrane RoB2 for RCT	Overall: low Randomisation: Low Intervention: low Missing outcome data: low Outcome measurement: low Selective reporting: Low
Bouman 2017	Combined data: Patients from the intervention arm of an open RCT investigating non-inferiority of a dose reduction strategy (ADA / ETN) and patients from an observational down titration study of IFX, the Netherlands	ADA ETN IFX RA (results for ADA only)	Association between drug level and successful dose reduction and discontinuation of the drug	ADA 42 pts ETN 76 pts IFX 51 pts. Age 58-61 years, 57-64% female, disease duration 7.5 – 13 years, DAS28 2.4-2.6, duration current treatment: 2.9-5.6 years, MTX 45-68%	18 months	ADA trough level and successful dose reduction	For ADA, high trough levels were associated with successful dose reduction (AUC 0.86) with trough levels > 7.8 ug/ml showing a sensitivity of 100% and a specificity of 86%	Quality in Prognosis Studies Tool	1.Study participation: moderate 2.Attrition: moderate 3.Prognostic factor: moderate 4.Outcome: low 5.Confounding: high 6.Statistics: low
Chen 2016	Longitudinal observational cohort (dose-halving common	RA ADA Remission (DAS28< 2.6) or low disease activity (DAS28 <3.2)	Correlation between ADA levels, and (persistent) clinical response after dose-halving	64 pts, 39% remission, 61% LDA. 86-92% female, disease duration 9 years, DAS28 2.2-3.15, MTX 86-91%	24 weeks	Optimal cut off drug level for persistent remission or LDA	Optimal cut-off ADA trough level at baseline for predicting persistent remission after dose-halving was 6.4 ug/ml (AUC 0.998, p<0.001) and for predicting persistent LDA was 1.9 ug/ml (AUC 0.995, p<0.001)	Quality in Prognosis Studies Tool	1.Study participation: high 2.Attrition: high 3.Prognostic factor: low 4.Outcome: low 5.Confounding: moderate 6.Statistics: high

	practice in Taiwan)								
Pouw 2015	Prospective observational cohort	RA ADA	Determine the concentration-effect relationship of adalimumab in RA	221 pts, 54 years, 80% female, disease duration 8 years, DAS28 5.3, MTX 77%	28 weeks	ΔDAS28 and adalimumab level	To reach a DAS28 improvement of 1.2 or more, trough levels of 3 ug/ml appear to be sufficient. Serum levels up to 8 ug/ml show a positive association with ΔDAS28. However, it appears that levels above 8 µg/mL did not give further improvement of clinical efficacy A cut off value of 5 ug/ml had an AUC of 0.695 (95%CI 0.626 – 0.764, p<0.0001) with a sensitivity of 91% and specificity of 43%	Quality in Prognosis Studies Tool	1.Study participation: moderate 2.Attrition: high 3.Prognostic factor: low 4.Outcome: low 5.Confounding: high 6.Statistics: low
Rosas 2014	Cross-sectional study. Multicenter Spain	RA, adalimumab	To assess the usefulness of measuring serum adalimumab levels after at least 3 months of treatment	57 pts, female 79%, age 63 years, disease duration 14 years, concomitant DMARD 100%, DAS28 2.7, SDAI 6.4, treatment duration 2.7 years	N/A	DAS28(ESR): remission<2.6, low activity 2.6–3.1, moderate3.2–5.1, severe >5.1, drug level	A cut-off value of 4.3 mg/l was associated with low disease activity (DAS28 ≤3.2) with an AUC of 0.83 (95% CI 0.688-0.919, sensitivity 88%, specificity 60%) 88% of patients with an level> 4.3 mg/l showed a DAS28≤3.2.	Newcastle-Ottawa for cohort studies	Sum score: **, -, * Selection: ** Comparability: - Outcome: *
Ternant 2015	Prospective observational study, post hoc PK/PD modeling	RA adalimumab	PK and concentration-effect relationship of adalimumab in RA	30 pts, female 77%, age 55 years, DAS28 5.6, MTX 100%	52 weeks	IC50	IC50 11.0 mg/l	Newcastle-Ottawa for cohort studies	Sum score: **, -, ** Selection: ** Comparability: - Outcome: **
Ducourau 2014	Post hoc analysis, France	RA adalimumab	Relationship between drug level and DAS28	30 pts,	52 weeks	IC50, DAS28	With a baseline DAS28 of 5.7, the IC50 of adalimumab was 11.8 mg/l. There was a large interindividual variability in IC50	Newcastle-Ottawa for cohort studies	Sum score: **, -, ** Selection: ** Comparability: - Outcome: **
ETANERCEPT									
Breedveld 2018	Randomised, double blind, placebo controlled,	RA ETN	PK and PD assessment of etanercept in dosages ranging from 10 mg once	61 pts, (49 ETN, 12 placebo). Age 49-55 years, female 67-100%, disease duration	Intervention 4 weeks + 4 weeks of follow-up	Concentration effect curve (SJC and TJC and ESR vs drug level)	There was no increase in percentage change of TJC and SJC with etanercept levels above 2000 ng/ml, despite increased etanercept concentrations.	Cochrane RoB2 for RCT	Overall: low Randomisation: Low Intervention: low Missing outcome data: low

	parallel-dose study		weekly to 50 mg twice weekly	3.5-6.5 years, CRP 37-72 mg/L, ESR 31-64 mm/h			Percentage change in SJC from baseline per concentration range (ng/ml): 0-99 1%; 100-499 14%; 500-999 41%; 1000-1999 33%; 2000-2999 52%; 3000-6080 54% Percentage change in TJC from baseline per concentration range (ng/ml): 0-99 16%; 100-499 15%; 500-999 31%; 1000-1999 52%; 2000-2999 62%; 3000-6080 69% Percentage change in ESR from baseline per concentration range (ng/ml): 0-99 9%; 100-499 17%; 500-999 26%; 1000-1999 37%; 2000-2999 22%; 3000-6080 37%		Outcome measurement: low Selective reporting: Low
Daien 2012	Prospective observational cohort, pilot, monocentric, France	RA ETN	Explore predictive value of etanercept levels for response to treatment	19 pts, all female, age 56 years, disease duration 5 years, DAS28 4.85, MTX 12 pts, LEF 5 pts	6 months	DAS28, EULAR response, (remission DAS28<2.6, LDA DAS28 2.6-3.2) drug level	A concentration of 3.1 ug/ml at 3 months was associated with 6 months responder status (sens. 87% spec. 67%) With this threshold, the DAS28 at 6 months was significantly higher in patients with low than in those with high median 3-month ETN concentrations (4.43, IQR 2.50–5.23, vs. 2.94, IQR 1.82–4.57; p = 0.02) Therapeutic maintenance was 33 vs. 77% for patients with 3 month ETN levels of <3.1 and ≥3.1 ug/ml, respectively, p=0.11	Quality in Prognosis Studies Tool	1.Study participation: high 2.Attrition: low 3.Prognostic factor: low 4.Outcome: low 5.Confounding: high 6.Statistics: low
INFLIXIMAB									
Mulleman 2010	Cross-sectional cohort, followed up for 42 weeks, monocentric, France	RA IFX	Predictive value of trough levels for sustainable clinical response	28 pts, 20 female, age 59 years, treatment duration 45 months, IFX dose: 4.1 (2.7-5.9) mg/kg / 8.1 (5.0-12.4) weeks, DAS28 3.0 (0.8-7.6)	42 weeks	Infliximab concentration, DAS28 ≤ or > 3.2	An infliximab concentration greater than 1.037 mg/l predicted low disease activity (DAS28≤3.2) with 84% sensitivity and 78% specificity, AUC 0.83 p<0.01	Newcastle-Ottawa for cohort studies	Sum score: **, -, * Selection: ** Comparability: - Outcome: *
Siljehult 2018	Prospective observational cohort. Sweden	RA infliximab	Correlation between drug levels and clinical response	94 pts, female 83%, age disease onset 42 years, disease duration 14 years, DAS28 5.6, DMARDs	54 weeks	DAS28, infliximab levels	An IFX concentration ≥ 4.66 µg/mL at 14 weeks predicted a moderate to good response at 52 weeks, with a specificity of 91.3% and a sensitivity of 39.3% (AUC 0.689)	Quality in Prognosis Studies Tool	1.Study participation: moderate 2.Attrition: high 3.Prognostic factor: moderate 4.Outcome: moderate 5.Confounding: high

				95,7%, MTX 77%, IFX dose 3.3 (±0.6) mg/kg			Patients with a good response at 14 weeks and an IFX concentration > 0.5 µg/mL were still good to moderate responders after 52 weeks (16/18; 88.9%).		6.Statistics: moderate
Van den Bemt 2013	Prospective observational cohort. Monocenter, the Netherlands	RA infliximab	Early prediction of clinical response based on disease activity and trough level	57 pts, age 57 years, 63% female, disease duration 6.1 years, DAS28 5.0, MTX 59%	6 months	Infliximab trough level at week 2, 6, 14 EULAR response, DAS28	Patients with a good EULAR response after 6 months tended to have higher infliximab serum trough concentrations (2 weeks 23.4 mg/l (±20.8), 6 weeks 12.3 mg/l (±6.1)) compared with non- or partially responding patients (2 weeks 16.0 mg/l (±10.4),6 weeks: 9.0 mg/l (±6.8)). After 14 weeks, infliximab serum trough concentrations tended to be higher in the group of EULAR responders compared with the non-responders (median (interquartile range) 0.9 (0.05–2.6) vs. 2.0 (0.7–5.4) mg l-1, P = 0.06). After 6 weeks, all patients with infliximab serum trough concentrations <2.5 mg/l (n = 9) did not attain infliximab response, while 15 of 46 patients with infliximab serum trough concentrations >2.5 mg/l reached good EULAR response (ROC area 0.67 (95% CI 0.52, 0.82), sensitivity 100%, specificity 23%, PPV 35%, NPV 100%) the Youden index was maximized with DAS scores after 6 weeks ≥4.2 and/or infliximab serum trough concentrations ≤2.5 mg/l (sensitivity 100%, specificity: 54%, PP: 45%, NP:100%, Youden index 0.54). Consequently, none of the 21 of 54 (39%) patients with either DAS28 at 6weeks ≥4.2 and/or infliximab serum trough concentrations ≤2.5 mg/l reached EULAR response after 6 months.	Quality in Prognosis Studies Tool	1.Study participation: low 2.Attrition: high 3.Prognostic factor: ? 4.Outcome: low 5.Confounding: high 6.Statistics: low
CERTOLIZUMAB									
Jani 2017	Prospective observational cohort (BRAGGSS) multicenter UK	RA CZP	Association between random certolizumab levels, antidrug antibodies and treatment response	115 pts, age 58 years, female 70%, disease duration 7 years, DAS28 5.9 MTX use 53%	12 months	Random drug levels, EULAR response, change in DAS28crp, adherence to treatment	In a concentration effect curve, there was a trend for higher certolizumab levels (>23-24 ug/ml) to be associated with improvement in DAS28 from baseline. Patients with the highest certolizumab levels had a higher proportion of EULAR response at 12 months. (no statistics)	Quality in Prognosis Studies Tool	1.Study participation: low 2.Attrition: moderate 3.Prognostic factor: low 4.Outcome: low 5.Confounding: low 6.Statistics: low

Paul 2020	Pooled analyses of 3 RCTs (RAPID1 RAPID2 (+ open label extension) and EXXELERATE)	RA CZP	to identify plasma concentrations of CZP associated with improvement of disease activity	1935 pts, female 78-82%, age 52-53 yrs, disease duration 6 yrs, BMI 26-28, DAS28(crp) 5.6-6.1	24 wks	CZP concentration, DAS28crp	CZP concentration thresholds of at least 28.0 µg/ml (sensitivity: 86.0%; specificity: 20.2%) at week 12 and 23.2 µg/ml (sensitivity: 89.6%; specificity: 19.7%) at week 24 were associated with achievement of DAS28(CRP) remission (<2.3) at these time points. CZP thresholds of 30.4 µg/ml (sensitivity: 80.0%; specificity: 24.2%) at week 12 and 17.6 µg/ml (sensitivity: 93.3%; specificity: 17.0%) at week 24 were associated with achievement of DAS28(CRP) LDA (≤ 2.7).	Quality in Prognosis Studies Tool	1.Study participation: moderate 2.Attrition: high 3.Prognostic factor: high 4.Outcome: high 5.Confounding: high 6.Statistics: low
COMBINATION OF TNF INHIBITORS (adalimumab, etanercept)									
Chen 2015	Longitudinal observational cohort, Taiwan	RA ADA and ETN	Association between drug levels and therapeutic response	ADA 36 pts, 53 years, 89% female, disease duration 5.4 years, DAS28 6.1, MTX 89% ETN 34 pts, 58 years, 88% female, disease duration 5.4 years, DAS28 5.95 MTX 88%	12 months	EULAR response and drug level	Depending on the assay used, optimal adalimumab and etanercept cut-offs for achieving EULAR good response at 6 and 12 months was: ELISA (Progenika) 6 months ADA: 1.27 ug/ml (sens 90%, spec 100%) ETN: 1.24 ug/ml (sens80%, spec 100% ELISA (Progenika) 12 months ADA 1.05 ug/ml (sens 100%, spec 100%) ETN 0.8 ug/ml (sens 85%, spec 85%) ELISA (Sanquin) 12 months ADA 0.801 ug/ml (sens 95%, spec 100%) ETN 0.7 ug/ml (sens 84%, spec 100%)	Quality in Prognosis Studies Tool	1.Study participation: high 2.Attrition: ? 3.Prognostic factor: moderate 4.Outcome: low 5.Confounding: high 6.Statistics: moderate
Jani 2015	Prospective observational cohort (BRAGGSS), multicenter, UK	RA ADA, ETN	Random drug levels, clinical response and adherence to therapy	ADA 160 pts, age 56.2 years, 70% female, disease duration 8.6 years, DAS28 5.7, MTX 55%. ETN 171 pts, 57 years, 80% female, disease duration 7,8	12 months	Random drug levels, EULAR response, change in DAS28crp, adherence to treatment	Concentration effect curve adalimumab: drug concentration < 5ug/ml was associated with lower change in DAS28 The predictive value of drug levels at 3 months for EULAR response at 12 months was (AUC) 0.66 (95% CI 0.55-0.77) for adalimumab Drug levels < 1.0 ug/ml was associated with no response (rc 2.29 95% CI 1.13-3.44 p<0.0001) for adalimumab Concentration effect curve for etanercept did not reveal a clear therapeutic window	Quality in Prognosis Studies Tool	1.Study participation: moderate 2.Attrition: moderate 3.Prognostic factor: moderate 4.Outcome: moderate 5.Confounding: moderate 6.Statistics: low

				years, DAS28 5.9, MTX 46%					
Van Herwaarden 2015	Post hoc analysis RCT	RA, adalimumab, etanercept	To investigate whether random timed drug levels are predictive of successful dose reduction or discontinuation	118 pts,	18 months	Random timed drug level before treatment adaptation (down-titration)	Random timed adalimumab levels for patients who successfully stopped (n=11), successfully dose reduced (n=15) or were not able to reduce the dose (n=16) were 8.5 (2.8), 8.1 (5.2) and 6.8 (4.1) mg/l, respectively. there was no statistically significant difference between these levels. Random timed etanercept levels for patients who successfully stopped (n=11), successfully dose reduced (n=37) or were not able to reduce the dose (n=28) were 2.7 (1.3), 2.0 (0.9) and 2.4 (1.0) mg/l, respectively. there was no statistically significant difference between these levels. ROC analyses showed no significant predictive value of TNFi serum levels for successful dose reduction or discontinuation. In a sensitivity analysis, for adalimumab, high trough levels were associated with successful dose reduction (AUC 0.86, 95% CI 0.58 to 1.00, optimal cut-off 7.8 mg/L).	Newcastle-Ottawa for cohort studies	Sum score: ***, -, ** Selection: *** Comparability: - Outcome: **
Sanmarti 2015	Cross-sectional study	RA etanercept, adalimumab	Confirmation of the study results by Chen et al 2015, optimal cut-offs for adalimumab and etanercept	127 patients in total, 54 adalimumab, 73 etanercept. 82% female, age 61 years, disease duration 13 years, treatment duration 60 months	N/A	DAS28≤2.6, etanercept and adalimumab trough level cut-offs	Trough levels with the greatest discriminative capacity for remission (DAS28≤2.6) were 1.336 µg/mL for adalimumab (sensitivity 81.9%, specificity 81%) and 1.56 µg/mL for etanercept (sensitivity 71.1%, specificity 71.4%). For adalimumab AUC was 0.81 (95% CI 0.68 to 0.94) and for etanercept 0.747 (95% CI 0.68 to 0.85)	Newcastle-Ottawa for cohort studies	Sum score: ***, -, ** Selection: *** Comparability: - Outcome: **

Rheumatoid arthritis + other biologics

Study	Study design	Population	Scope/Intervention	Study population	Follow-up	Outcome measures	Results	Tool used for RoB assessment	Risk of Bias
				TOCILIZUMAB					
Abdallah 2017	Pooled data RCTs (SUMMACTA and	RA, tocilizumab after inadequate	PK/PD sc tocilizumab	N/A (supp tab S1)	24 weeks	PK/PD	Mean steady state toc iv 8 mg/kg every 4 weeks at 24 weeks was 18 ug/ml. For sc dosing 162 mg weekly: 40 ug/ml.	Cochrane RoB2 for RCT	Overall: low Randomisation: Low Intervention: low Missing outcome data: low

	BREVACTA), population pharmacokinetic model	DMARD response					No concentration response relation was shown for ACR response and trough concentrations for tocilizumab iv. For the weekly SC dose there was a concentration effect observed, patients in the lowest trough level quartile (mean TCZ concentration 14.6 ug/ml) had poorer ACR responses (ACR20 63%; ACR50 39%; ACR70 20%), the concentration effect relation plateaued in the second quartile (mean TCZ concentration 32.7 ug/ml, ACR20 76%, ACR50 52%, ACR70 28%)		Outcome measurement: low Selective reporting: Low
Kneepkens 2017	Prospective observational cohort, the Netherlands	RA TCZ 8mg/kg/4 weeks iv	Investigating the variation in serum TCZ concentrations and the relationschip with clinical measurements	66 pts, age 56 years, female 82%, disease duration 11 years, DAS28 5.4, MTX 64%, prednisolone 70%	24 weeks	CRP, TCZ levels, DAS28 improvement ≥1.2	At baseline, 26 patients had a CRP level above 10mg/l with a median of 37.7mg/l (21.9-49.7). TCZ concentrations above 1 mg/l were sufficient to normalize CRP levels. The cut off of 1 mg/l was also associated with a clinical relevant improvement in DAS28 (≥1.2) rc 0.080, 95%CI 0.039-0.113. 12 patients did not achieve this improvement, eight of them had a TCZ concentration below 1 mg/l	Newcastle-Ottawa for cohort studies	Sum score: ***, -, *** Selection: *** Comparability: - Outcome: ***

Axial spondyloarthritis + TNF inhibitors

Study	Study design	Population	Scope/Intervention	Study population	Follow-up	Outcome measures	Results	Tool used for RoB assessment	Risk of Bias
ADALIMUMAB									
Marsman 2016	Observational cohort, multicenter, the Netherlands ,Taiwan	AS ADA	To determine the concentration-effect relationship of ADA in AS	102 pts, 42 years, 67% male, disease duration 7 years, HLAB27 83%, ASDAScrp 3.4, BASDAI 6.2	6 months	ΔBASDAI 0-6 months and ΔASDAS 0-6 months, CRP, drug level	No significant correlation between adalimumab level at 24 weeks and ΔASDAS or ΔBASDAI was found. No therapeutic window could be identified. The median (interquartile) drug level in patients with low CRP was significantly higher than in patients with high CRP at baseline [respectively 10.6 (3.9 – 16.2) vs. 6.9 (1.0 – 12.6); p = 0.019].	Quality in Prognosis Studies Tool	1.Study participation: moderate 2.Attrition: high 3.Prognostic factor: moderate 4.Outcome: moderate 5.Confounding: high 6.Statistics: low
Senabre 2019	Cross-sectional, Spain	AS adalimumab	To assess the prevalence of anti-drug antibodies in patients with axSpa, to investigate their relationship with serum levels of	51 pts, age 47 years, disease duration 71 months, HLAB27 82%, BASDAI 4.2, ASDAScrp 2.0, ASDAsesr 2.3, adalimumab	N/A	BASDAI, ASDAS (CRP/ESR), trough levels	The adalimumab level cut-offs and area under the curve (AUC) obtained in the ROC curves were 4.6 mg/l (AUC 81.2%; 95% CI 67.5–94.9), 7.7 mg/l (AUC 82.4%; 95% CI 69.3–95.5) and 6.4 mg/l (AUC 73.5%; 95% CI 58.6–88.3) for ASDAS-CRP<2.1, ASDAS-ESR<2.1 and BASDAI<4, respectively	Newcastle-Ottawa for cohort studies	Sum score: **, **, * Selection: ** Comparability: ** Outcome: *

			adalimumab and disease activity	treatment 9.8 months					
Ding 2020	Observational cohort study, monocentric, China	AS adalimumab	To determine a concentration-effect curve for adalimumab in patients with AS	31 pts, age 31 yrs, male 94%, disease duration 7 yrs, CRP 16 mg/l, ASDAScrp 4.06, BASDAI 6.1, NSAIDs 15%	12 weeks	ADA concentrations, ASDAS	To reach clinically important improvement (ΔASDAS ≥ 1.1), concentrations of ~ 2.5 µg/mL seem to be already sufficient. Levels of ~ 8 µg/mL show major improvement (ΔASDAS ≥ 2.0). Serum levels up to 12 µg/mL show a positive association with ΔASDAS. In general, adalimumab trough concentrations between 8 and 12 µg/mL seem optimal. No significant correlation between adalimumab levels at week 12 and ΔBASDAI was found.	Quality in Prognosis Studies Tool	1.Study participation: moderate 2.Attrition: high 3.Prognostic factor: ? 4.Outcome: low 5.Confounding: high 6.Statistics: low
Senabre-Gallego FRI0295 (2020)	EULAR abstract 2020, cross-sectional	Axial SpA, adalimumab	Association between drug retention rates and adalimumab levels	51 pts, age 46,9 (18–68), 47.1% female, HLAB27+ 82,4%, disease duration 122,9 months (2-408), duration of treatment 17,8 months (1-69). Concomitant DMARD 21.6% (MTX 15.7%) BASDAI 4.0 ± 2.3; ASDAS-crp 2.1 ± 1.1 and ASDAS-esr 2.1 ± 1.0.	N/A	Adalumumab drug level, treatment retention	Multivariate analyses showed an ADA level > 3 mg/L was a protective factor for ADA discontinuation (HR 0.01 (0.00-0.59, p=0.026),	Newcastle-Ottawa for cohort studies	Sum score: **, **, ** Selection: ** Comparability: ** Outcome: **
ETANERCEPT									
Kneepkens 2015	Prospective observational cohort, monocenter, the Netherlands	AS ETN	association between drug levels and clinical response	162 pts, age 43 years, men 71%, disease duration 8 years, HLAB27 73%, ASDAScrp 3.6, NSAID 70%	24 weeks	ASDASCRP, BASDAI, drug levels	A clear therapeutic window, based on a concentration effect curve could not be identified	Quality in Prognosis Studies Tool	1.Study participation: moderate 2.Attrition: moderate 3.Prognostic factor: low 4.Outcome: low 5.Confounding: low 6.Statistics: low

Dong 2019	Prospective observational cohort. China	AS etanercept	To investigate the effective serum level of etanercept in patients with AS	60 pts, 54/60 male, age 29 years, disease duration 4 years	24 weeks	BASDAI, ASDAS CRP/ESR, drug levels	cut-off values of effective etanercept levels when patients achieved ASDAS-CRP < 2.1 at each interval by ROC curve: values at weeks 4, 12, and 24 were 2.32, 2.12, and 2.36 μg/mL, respectively, while the sensitivity and specificity values were 53.7% and 94.4%, 60.8% and 86.7%, and 59.2% and 85.7%, respectively In addition, the area under the curve (AUC) values were 0.758 (p = 0.002, 95% confidence interval (CI), 0.635–0.881), 0.709 (p = 0.005, 95% CI, 0.571–0.846), and 0.723 (p = 0.008, 95% CI, 0.503–0.916) at weeks 4, 12, and 24, respectively	Quality in Prognosis Studies Tool	1.Study participation: moderate 2.Attrition: high 3.Prognostic factor: moderate 4.Outcome: low 5.Confounding: high 6.Statistics: moderate
GOLIMUMAB									
Martinez-Feito 2018	Prospective observational cohort, multicenter, Spain, the Netherlands	axSpA, golimumab	Association between GLM levels and clinical response, determining the optimal concentration range	49 pts, 48 years, 73% men, disease duration 10.5 years, HLAB27 69%, ASDAS 3.5, monotherapy 37%	52 weeks	Clinical response: ASDAS, ΔASDAS, GLM levels	A concentration effect curve plotting the ΔASDAS at week 52 and golimumab level showed that concentrations between 0.7 and 1.4 mg/l appeared sufficient to reach the therapeutic aim (ΔASDAS ≥1.1) among patients with levels <0.7 mg/l only one achieved major clinical improvement (ΔASDAS ≥1.1). and 59% and 62.5% of patients in the 0.7-1.5-4 and >1.4 mg/l group, respectively, achieved this treatment goal (p>0.01) Of patients with levels <0.7mg/l, 37% had ASDAS<2.1 and 63% had ASDAS≥2.1 Of patients with levels 0.7 – 1.4 mg/l, 88% had ASDAS<2.1 and 12% had ASDAS≥2.1 Of patients with levels >1.4mg/l, 75% had ASDAS<2.1 and 25% had ASDAS≥2.1	Newcastle-Ottawa for cohort studies	Sum score: ***, **, ** Selection: *** Comparability: ** Outcome: **

Peripheral spondyloarthritis including psoriatic arthritis + TNF inhibitors

Study	Study design	Population	Scope/Intervention	Study population	Follow-up	Outcome measures	Results	Tool used for RoB assessment	Risk of Bias
ADALIMUMAB									
Vogelzang 2014	Prospective observational cohort, monocenter, the Netherlands	PsA, adalimumab	Association between adalimumab drug levels and disease activity	103 pts, male 53%, age 50 years, MTX 78%, disease duration 6 years, DAS28 4.0, PASI 0.6	52 weeks	Drug level, DAS28	Concentrations of approximately 1.0 mg/L already show reasonable efficacy. Adalimumab concentrations between 5–8 mg/L appear optimal. In 48 (47%) patients, adalimumab concentrations exceeded 8 mg/L. Furthermore, 36 (35%) patients had adalimumab concentrations below 5 mg/L. (no statistics)	Quality in Prognosis Studies Tool	1.Study participation: high 2.Attrition: high 3.Prognostic factor: low 4.Outcome: low 5.Confounding: moderate 6.Statistics: low

Jani 2020	Prospective observational cohort study, multicenter (UK), OUTPASS	PsA, ETN, ADA	1- whether the presence of ADAb/drug levels predicts treatment response 2- identify a drug level threshold for optimal therapeuticresponse 3- factors associated with drug levels	ADA 97 pts, ETN 56 pts, age 51 yrs, BMI 28.9, female gender 46%, disease duration 5 yrs, DAS28: 4.9, CRP 7.5, MTX use 25%	12 months	Adalimumab and etanercept concentrations, disease activity (DAS28 (crp))	There was no significant association between ETN drug levels and ΔDAS28 over 12 months (β –0.039, 95% CI –0.31 to 0.23; p = 0.77). ADA concentrations between 4–8 µg/ml were associated with an optimal treatment response at 6 months using concentration-effect curves. Of samples with ADA levels measured in the study, distribution of levels was as follows: 19.6% (n = 19) < 4 µg/ml; 35.1% (n = 34) 4–8 µg/ml; 16.5% (n = 16) > 8 to < 11 µg/ml; and 28.9% (n = 28) ≥ 11 µg/ml.	Quality in Prognosis Studies Tool	1.Study participation: moderate 2.Attrition: high 3.Prognostic factor: high 4.Outcome: low 5.Confounding: high 6.Statistics: low

Combination of diseases and TNF inhibitors

Study	Study design	Population	Scope/Intervention	Study population	Follow-up	Outcome measures	Results	Tool used for RoB assessment	Risk of Bias
Gehin 2019	Longitudinal observational cohort (NOR-DMARD), multicenter, Norway	RA, SpA, PsA, certolizumab	Association between serum levels, antibodies and treatment response	116 SpA, 91 RA and 61 PsA. SpA: age 42 years, female 47%, disease duration 2,6 years, ASDAS crp 2.6, DMARDs 19%. RA age 54 years, female 79%, disease duration 10 years, DAS28 4.0, DMARDs 74%. PsA age 50 years, female 66%, disease duration 6.6 years, DAS28 3.9 DMARDs 67%	6 months	Clinical response (ASDAS-CRP, improvement ≥1.1, DAS28, EULAR good/moderate, improvement ≥ 0.6	Patients with certolizumab levels of 20-39.9 mg/l had the largest mean improvement in disease activity from baseline to 3 months for all diseases. - for axSpA 53% clinically important improvement of ASDAS vs. 18% and 37% for <20 mg/L and ≥ 40 mg/L, resp. - for PsA 77% ≥0.6 improvement of DAS28 vs. 47% and 77% for <20 mg/L and ≥ 40 mg/L, resp. for RA 74% ≥0.6 improvement of DAS28 vs. 44% and 55% for <20 mg/L and ≥ 40 mg/L, resp. Having a serum CZP level ≥ 20 mg/L was associated with response at 3 and 6 months for all three diagnoses combined (OR 2.3 (95% CI 1.2–4.5, p= 0.01), OR 1.9 (95% CI 1.0–3.5, p= 0.05), respectively). However, CZP levels ≥ 40 mg/L were not associated with any additional benefit, and response rates were, on the contrary, lower across all diagnoses.	Quality in Prognosis Studies Tool	1.Study participation: low 2.Attrition: high 3.Prognostic factor: low 4.Outcome: low 5.Confounding: high 6.Statistics: low

Gehin FRI0536 (2020)	EULAR abstract 2020 Observational study as part of NOR-DMARD study	RA, axial SpA, PsA, GLM	To identify the therapeutic target concentration of GLM	91 pts (RA:20, PsA:30, AxSpA:41)	3 months	Random GLM levels, treatment response (EULAR response, ASDAS, DAPSA)	The proportions of responders after 3 months among patients with golimumab concentration <1.0, 1.0-3.9 and ≥4.0 mg/L, were 19%, 49% and 74%, respectively. The likelihood of response after 3 months of treatment was significantly higher among patients with serum golimumab concentration ≥1.0 mg/L compared to those with golimumab <1.0 mg/L (OR 5.8 (95% CI 1.7-19.7), p=0.005). A higher rate of treatment discontinuation in patients with serum golimumab concentration <1.0 mg/L compared to ≥1.0 mg/L was shown (HR 3.6 (95% CI 1.9-6.9), P <0.001).	Newcastle-Ottawa for cohort studies	Sum score: **, **, ** Selection: ** Comparability: ** Outcome: **

PTC-5: Routine use of proactive TDM is not recommended in the management of inflammatory arthritis.

Study	Study design	Population	Scope/Intervention	Study population	Follow-up	Outcome measures	Results	Tool used for RoB assessment	Risk of Bias
Syversen S. et al, 2020 EULAR abstract	Randomised controlled trial	Pts starting IFX with RA, PsA, SpA, UC, CD, Psoriasis	Pts starting IFX therapy were randomly assigned to administration of IFX according to a treatment strategy based on TDM (TDM arm) or to standard administration of INX without TDM (control arm). In the TDM arm, the dose and interval were adjusted according to IFX trough levels to reach the therapeutic range	398 patients (RA 80, PsA 42, SpA 117, UC 80, CD 57, Psoriasis 22)	30 weeks	Primary endpoint: Remission at week 30.	For all diagnoses, remission at week 30 was reached in 100 (53%) and 106 (54%) of the patients in the TDM and control arm, respectively (adjusted difference, 1.5%; 95% CI, -8.2 to 11.1, p=0.78) Remission rates TDM group vs. Control group, by disease: RA: 58% vs. 50%, difference -8.3% (95% CI -30.4-13.8) PsA: 28% vs. 57%, difference 29.4% (95% CI -0.2-59.0) SpA: 40% vs. 37%, difference -3.5% (95% CI -21.4-14.4) -Reviewer conclusion: The study did not demonstrate utility of TDM as a general strategy when starting IFX, (but less infusion reactions in the TDM arm).	Cochrane RoB2 for RCT	Overall: Some concerns Randomisation: Low Intervention: High Missing outcome data: Unclear Outcome measurement: Some concerns Selective reporting: Low
Méric J-C. et al, 2011	Prospective observational study	SpA pts, routinely treated with IFX	The preliminary therapeutic decision (based on disease activity) was re-evaluated, based on an algorithm including both disease activity and IFX DL and applied at the next infusion.	32 pts % male: 50 Median age: 48 years	3 visits (V2-V4) (16 weeks?)	BASDAI improvement	-The preliminary therapeutic decision (based on disease activity alone) was modified (based on IFX DL) in 10 pts (31%). - In the 4 patients whose measurement of IFX DL modified the therapeutic decision to an increase in IFX dosage, adaptation of the IFX dose based on DL led to improvement in BASDAI in only 2 out of 4 patients, despite increased DL in all 4. -Reviewer conclusion: The study did not demonstrate utility of TDM. Small study without control group.	Newcastle-Ottawa for cohort studies	Sum score: **, , ** Selection: ** Comparability: Outcome: **

PTC-6: Reactive TDM could be considered in the management of inflammatory arthritis.

Please see evidence tables for PTC 7, 8, 9, 10 and 11, in which evidence for utility of TDM in particular clinical situations are provided.

PTC-7: Measurement of biopharmaceutical blood concentrations up to 3 months after commencement of treatment could be considered to predict future efficacy.

Study	Study design	Population	Scope/Intervention	Study population	Follow-up	Outcome measures	Results	Tool used for RoB assessment	Risk of Bias
Infliximab									
Martinez-Feito A. et al, EULAR 2019	Prospective observational	axSpA pts treated with IFX	Association between W14 IFX DL and W24 response evaluated. High or low IFX DL defined as above or below median measured IFX DL.	81 pts	24 weeks	-ASDAS clinical improvement -ΔASDAS	Predictive value (OR) for W24 response: -High W14 IFX DL: OR: 3.6; CI 95%: 1.3-10.4 (multivariable model). -W14 s-IFX ≥ 6.7 µg/mL and baseline disease activity score ≥ 3.5, combined, predicted higher ΔASDAS at W24: OR 16, 95%CI: 3.6-71.7 (adjustments NR). – W14 s-IFX ≥ 6.7 µg/mL and ADAb positivity combined, predicted W24 response (by ROC-curve analyses) with a sens. 87.5%, spec. 69.6%, PPV of 75% and NPV of 84.2% (AUC NR). Reviewer conclusion: W14 s-IFX predicted W24 response	Quality in Prognosis Studies Tool (QUIPS)	1.Study participation: High 2.Attrition: High 3.Prognostic factor: Moderate 4.Outcome: Low 5.Confounding: Moderate 6.Statistics: Low
Siljehult F. et al, 2018	Retrospective observational	RA pts treated with IFX	Evaluated s-IFX and ADAb at 14 weeks, in relation to response after 52 weeks	94 pts (72 completed 52 weeks follow-up)	52 weeks	-EULAR good/moderate	-Predictive value of W14 IFX DL ≥ 4.66 µg/mL for W52 response: AUC 0.69, spec. 91.3% sens. 39.3%. -16/18 (88.9%) of W14 good responders with IFX DL > 0.5 µg/mL were still good to moderate responders at W52. Reviewer conclusion: W14 s-IFX predicts response after 52 weeks (AUC 0.69 (not reported 95%CI or p))	Quality in Prognosis Studies Tool (QUIPS)	1.Study participation: Moderate 2.Attrition: Moderate 3.Prognostic factor: Moderate 4.Outcome: Low 5.Confounding: Moderate 6.Statistics: Low
Jurado T. et al, 2017	Restrospective observational	RA pts treated with IFX	Assess whether IFX trough levels in the induction phase are associated with clinical outcomes at week 54	66 pts Mean age: 56 y % male: 14	54 weeks	-DAS28 score, LDA, remission -EULAR response -Drug survival	W54 DAS28 score in pts stratified by W6 IFX DL: -Pts with W6 IFX DL > 4.4 µg/ml: 3.68±1.26 -Pts with W6 IFX DL < 4.4 µg/ml: 4.75±1.27 -Difference in W54 DAS28 was statistically significant, p=0.01. Proportion of pts with W54 DAS28 LDA or remission stratified by W6 IFX DL: -Pts with W6 IFX DL > 4.4 µg/ml: 20/45 (44%) -Pts with W6 IFX DL < 4.4 µg/ml: 3/19 (16%); -Difference in proportion with W54 DAS28 LDA or remission was statistically significant, p=0.02 Proportion of W54 EULAR responders stratified by W6 IFX DL: Pts with W6 IFX DL > 4.4 µg/ml: 33/45 (73%) Pts with W6 IFX DL < 4.4 µg/ml: 10/19 (53%); - Difference in proportion with W54 EULAR response was not statistically significant,p=0.08	Quality in Prognosis Studies Tool (QUIPS)	1.Study participation: Moderate 2.Attrition: Moderate 3.Prognostic factor: Moderate 4.Outcome: Low 5.Confounding: Low 6.Statistics: Low

							Reviewer conclusion: W6 IFX DL was associated with response at W54		
Van den Bemt B. et al, 2013	Prospective observational	RA pts starting IFX	Assessed the added predictive value of combining IFX DL with disease activity and at 6 weeks for achieving EULAR good response after 6 months. IFX trough conc. measured at 2, 6 and 26 weeks	57 pts, Mean age; 57y % male: 37	6 months	-EULAR good response	The value of adding IFX DL >2.5 mg/L, to disease activity (DAS28 <4.2) at 6 weeks as predictor for response after 6 months, increased the spec. from 49% to 54% without changing the sensitivity (100%),(PPV: 45%, NPV:100%, Youden index 0.54)(compared to disease activity alone) Proportion of responders after 6 months stratified by presence of ADAb (no statistics): 0/3 of those who were ADAb pos at 6 weeks 1/9 of those who were ADAb pos at 14 weeks Reviewer conclusion: W6 IFX DL, combined with disease activity, slightly increased the predictive value for response after 6 months, compared to disease activity alone.	Quality in Prognosis Studies Tool (QUIPS)	1.Study participation: Moderate 2.Attrition: Moderate 3.Prognostic factor: Low 4.Outcome: Low 5.Confounding: High 6.Statistics: Low
Adalimumab									
Ding et al. 2020	Prospective observational	AS pts with active disease starting ADA	ADA trough was measured week 2,4 8, 12	31 pts	12 weeks	Response by week 12, def: ΔASDAS ≥ 2.0 or ASDAS < 2.1 with ΔASDAS ≥ 1.1	W12 nonresponders had significantly lower W4 and W2 ADA DL than W12 responders; W4: median 2.60 µg/mL IQR 0.30−3.55 vs. 7.07 µg/mL IQR 5.42−7.71, respectively, P < 0.0001; W2: 2.73 µg/mL IQR 0.66−3.22 vs. 4.71 µg/mL IQR 3.14−4.95, respectively, P = 0.036. W4 or W2 ADA DL below 4.28 µg/mL or 3.37 µg/mL were significantly associated with W12 non-response, W4: AUC = 0.89, P = 0.0003, sens. 83.3%, spec. 94.7%; W2: AUC = 0.88, P = 0.034, sens. 100%, spec. 70.0%; W4 ADA ADAb levels above 5.31 had a 66.7% sens. and 94.7% spec. for W12 nonresponse (AUC = 0.81, P = 0.004)	Quality in Prognosis Studies Tool (QUIPS)	1.Study participation: Moderate 2.Attrition: Low 3.Prognostic factor: Moderate 4.Outcome: Low 5.Confounding: Moderate 6.Statistics: Low

							Reviewer conclusion: The study showed predictive value of W2 and W4 ADA DL and presence of ADAb for W12 responses. Small study.		
Jani M. et al, 2015	Prospective observational	RA pts treated with ADA	The association between ADAb and TNFi non-trough levels at 3 months and the treatment response after 12 months was evaluated	ADA : 160 pts Mean age: 57 y % male: 24,5	12 months	-EULAR non-response	Predictive value for EULAR non-response at 12 months: -ADA DL <5 µg/ml at 3 months: AUC 0.66 (95% CI 0.55- 0.77) -ADA ADAb at 3 months: AUC 0.68 (95% CI 0.54-0.81) -Predictive value of both ADA DL <5 µg/ml and anti-ADA-Ab at 3 months, combined,: AUC of 0.71 (95% CI 0.57-0.85) Reviewer conclusion: Low ADA DL and ADAb at 3 months predicted 12 month non-response.	Quality in Prognosis Studies Tool (QUIPS)	1.Study participation: Low 2.Attrition: Moderate 3.Prognostic factor: Moderate 4.Outcome: Low 5.Confounding: Low 6.Statistics: Low
Etanercept									
Jani M. et al, 2015	Prospective observational	RA pts treated with ETN	The association between ADAb and TNFi non-trough levels at 3 months and the treatment response after 12 months was evaluated	ETN: 171 pts Mean age: 57 y % male: 24,5	12 months	-EULAR non-response	Predictive value for EULAR non-response at 12 months: -ETN DL <5 µg/ml at 3 months: AUC of 0.51 (95% CI 0.41, 0.61) -ETN DL <3.23 µg/ml at 3 months: AUC of 0.58 (95% CI 0.46, 0.70). Reviewer conclusion: Low serum ETN was not predictive for 12 month response	Quality in Prognosis Studies Tool (QUIPS)	1.Study participation: Low 2.Attrition: Moderate 3.Prognostic factor: Moderate 4.Outcome: Low 5.Confounding: Low 6.Statistics: Low

Daien CI. et al, 2012	Prospective observational	RA pts starting ETN	ETN DL and anti-ETN ADAb were measured at baseline and after 3 and 6 months of treatment.	19 women	6 months	-EULAR good/moderate response -ΔDAS28	Median ETN DL at 3 months in pts stratified by response after 6 months -Non-responders: 1.75 µg/ml, IQR 0–3.6, -Responders: 3.70 µg/ml, IQR 1.0–6.7, -The difference in median ETN DL was statistically significant, p = 0.03 3-month ETN DL correlated significantly with ΔDAS28 at 6 months (r = −0.62, p = 0.006). ETN DL ≥ 3.1 µg/ml at 3 months predicted 6-month response with sens. 87% and spec. of 67% (AUC NR). Reviewer conclusion: 3 months ETN DL was associated with 6 month response	Quality in Prognosis Studies Tool (QUIPS)	1.Study participation: High 2.Attrition: Low 3.Prognostic factor: Moderate 4.Outcome: Low 5.Confounding: High 6.Statistics: Low
Certolizumab									
Gehin J. et al, 2019	Prospective observational	axSpA, RA and PsA pts treated with CZP	Associations between 3 months non-trough CZP DL and response after 6 months	268 pts, axSpA: 116 RA: 91 PsA: 61 Mean age: axSpA 42 y, RA 54 y, PsA 50 y %male: axSpA 53, RA 22, PsA 34	6 months	-ASDAS clinical improvement (axSpA) -EULAR good/moderate (RA) -DAS28 0.6 (PsA)	-3-month CZP DL ≥20 mg/L associated with response after 6 months: OR 1.9 (95% CI 1.0-3.5, P = 0.05)(multivariable logistic regression) Reviewer conclusion: 3 month CZP DL associated with response after 6 months	Quality in Prognosis Studies Tool	1.Study participation: low 2.Attrition: high 3.Prognostic factor: low 4.Outcome: low 5.Confounding: high 6.Statistics: low

PTC-8: Measurement of biopharmaceutical blood concentrations could be considered to identify those with high biopharmaceutical blood concentrations in whom tapering may be indicated.

Study	Study design	Population	Scope/Intervention	Study population	Follow-up	Outcome measures	Results	Tool used for RoB assessment	Risk of Bias
Rheumatoid arthritis									
Bastida et al. 2020	PK/PD simulation study	RA virtual population treated with TCZ	Four tapering strategies were simulated on a virtual population; 1.label-dosing 2.mild empirical dose-tapering 3.intense empirical dose-tapering 4.TDM-guided dose tapering PK model used to predict individual TCZ DL. The predicted TCZ DLs were related to response by a population PKPD model.	Virtual population of 5000 individuals	12 months	Sustained remission/LDA	-Proportion of simulated pts in remission/LDA after 1 year: Mild empirical group: 80.3% TDM-guided: 78.2% Intense empirical: 69.0% -1-year flare rates: Mild empirical group: 6.5% TDM-guided: 10.6% Intense empirical: 24.8% Reviewer conclusion: The study did not demonstrate additional value of the TDM-guided vs. the mild empirical tapering strategy with regard to outcome.	Quality in Prognosis Studies Tool (QUIPS)	1.Study participation: High 2.Attrition: Unclear 3.Prognostic factor: Moderate 4.Outcome: High 5.Confounding: Moderate 6.Statistics: Low
Lamers-Karnebeek FBG. et al, 2019	Post hoc/ substudy of RCT	RA pts with LDA who discontinued ADA	Pts in LDA on stable treatment, who were randomised to discontinue ADA were included in post hoc study. Retrospective assessment of trough ADA DL and ADAb as predictors of flare.	210 pts % male: 31 Mean age: 59 y	52 weeks	-Flare (increase of >0.6 in DAS28-ESR from baseline, with current DAS28-ESR > 3.2)	-Predictive value of flare for ADA DL: AUC 0.50, 95% CI 0.42-0.58, P = 0.92. -HR for flare in pts with ADA DL ⩾ 5 vs <5 µg/ml: 0.93, 95% CI: 0.63-1.36 (adjustments not specified in manuscript). -2 out of 4 pts with high ADAb experienced a flare. -10 out of 21 pts with ADA DL <0.1ug/mL experienced a flare after a median of 24 weeks. Reviewer conclusion: The study did not demonstrate predictive value of TDM	Quality in Prognosis Studies Tool (QUIPS)	1.Study participation: Low 2.Attrition: Low 3.Prognostic factor: High 4.Outcome: Moderate 5.Confounding: High 6.Statistics: Low

L'Ami M. et al, 2018	Randomised, open-label, non-inferiority trial	RA pts treated with ADA	Pts with ADL >8 µg/mL randomised (1:1) to prolongation group (40 mg once every 3 weeks) or continuation group (standard interval)	55 pts % male: 6 Mean age: 60 y	28 weeks	- ΔDAS28-ESR	Mean ΔDAS28 after 28 weeks: -Prolongation group: –0.14±0.61. -Continuation group: 0.30±0.52 -Mean difference: 0.44 (95% CI 0.12 to 0.76, p=0.01) (in favour of prolongation group). Reviewer conclusion: The study demonstrated that tapering was safe among RA pts with ADA DL >8 µg/mL. (The study did not include ctrl. Group with lower DLs)	Cochrane RoB2 for RCT	Overall: Some concerns Randomisation: Low Intervention: High Missing outcome data: Low Outcome measurement: Some concerns Selective reporting: Low
Bouman C. et al, 2017	Post hoc analyses of data for RA pts in two different studies included; 1. An open-label RCT and 2. A prospective observational study	RA pts with LDA treated with ADA, ETN, IFX	Pts in LDA, were tapered until discontinuation or flare. Non-trough DL for ADA and ETN and trough for IFX, were measured before dose reduction. Tapering was performed independently of DL.	169 pts ADA: 42 ETN: 76 IFX: 51 % male: ADA: 36 ETN: 39 IFX: 63 Mean age: ADA: 61 y ETN: 58 y IFX: 59 y	ADA, ETN: 78 weeks. IFX: 52 weeks.	-Successful dose reduction or discontinuation without flare, (def: DAS28 incr. >1.2 or DAS28 incr. >0.6, with current DAS28 ≥ 3)	Predictive value of ADA DL for successful (without flare): -Discontinuation: AUC 0.66, 95% CI 0.50-0.83. -Dose reduction: AUC 0.51, 95% CI 0.32-0.71. Predictive value of ETN DL for successful (without flare): -Discontinuation: AUC 0.63, 95% CI 0.43-0.82. -Dose reduction: AUC 0.36, 95% CI 0.23-0.49; cut-off <2.6 mg/l sens 81%, spec 44%. Predictive value IFX DL for successful (without flare): -Discontinuation: AUC 0.44, 95% CI 0.30-0.59. -Dose reduction: AUC 0.65, 95% CI 0.50-0.81. -Sensitivity analyses: High ADA DL: AUC 0.86, 0.58–1.00; cut-off >7.8 sens 100% and spec. 86%. -ADAb were infrequent and not predictive of successful discontinuation. -Statistics: ROC-analyses. (No correction for multiple testing) Reviewer conclusion: The study did not demonstrate predictive value for successful discontinuation or dose reduction of DL or ADAb, except for sensitivity analyses for subset of pts with high ADA DL.	Quality in Prognosis Studies Tool (QUIPS)	1.Study participation: Moderate 2.Attrition: Low 3.Prognostic factor: Moderate 4.Outcome: Low 5.Confounding: High 6.Statistics: Low
Chen DY. et al, 2016[5]	Prospective observational	RA pts in LDA or remission, treated with ADA	All pts underwent ADA dose-halving. Drug levels were measured before dose reduction.	64 pts % male: 10 Mean age: 55	24 weeks	Remission LDA Persistent remission and LDA (w24) Flare (def: DAS28 ≥3.2)	Baseline median (IQR) ADA DL in pts with W24: -Persistent remission: 10.5 (8.1-11.8) µg/ml -LDA: 4.5 (2.9-5.9) µg/ml -Disease flare: 0.9 µg/ml (0.7-1.0) -Significant difference in ADA DL between pts with both remission and LDA vs. flare, P<0.001. Predictive value of ADA DL for persistent remission: AUC 0.998, 95% CI 0.94-1.00, P < 0.001; cut-off 6.4 µg/ml sens. 100%, spec. 93%. Predictive value of ADA DL for persistent LDA; AUC 0.995, CI 0.93-1.00, P < 0.001; cut-off 1.9 µg/ml sens. 94%, spec. 100%.	Quality in Prognosis Studies Tool (QUIPS)	1.Study participation: High 2.Attrition: High 3.Prognostic factor: Low 4.Outcome: Low 5.Confounding: Moderate 6.Statistics: High

							Reviewer conclusion: The study showed predictive value of low ADA DL for flare		
Axial spondyloarthritis									
Redondo C. et al, 2018	Prospective observational	AxSpA pts with LDA treated with GLM	Pts with LDA at least 6 months before tapering were included. All underwent tapering. Drug levels were measured before dose reduction.	21 pts, Mean age and % Male N/A	24 months	-Flare, (def: increase in ASDAS (from the pre-tapering visit) of ≥0.9)	-4 of 5 pts with suboptimal (<0.7µg/ml) GLM DL at the pre-tapering visit had flares during follow-up. -1 of 11 patients with GLM DL >0.7 µg/ml at pre-tapering visit had flares (P = 0.003) during follow-up. Reviewer conclusion: Numerically more pts with suboptimal GLM DL had flares, compared to pts with GLM DL <0.7µg/ml, but small sample size and no effect measures were described	Quality in Prognosis Studies Tool (QUIPS)	1.Study participation: High 2.Attrition: High 3.Prognostic factor: Low 4.Outcome: Low 5.Confounding: Moderate 6.Statistics: Moderate

PTC-9: Measurement of biopharmaceutical blood concentrations should be considered to understand clinical non-response.

Study	Study design	Population	Scope/Intervention	Study population	Follow-up	Outcome measures	Results	Tool used for RoB assessment	Risk of Bias
Rheumatoid arthritis									
Mulleman D. et al, 2009	Prospective observational	RA pts routinely treated with IFX	The preliminary therapeutic decision (based on disease activity) was re-evaluated, based on an algorithm including both disease activity and IFX DL, and applied at the next infusion.	24 pts % male: N/A Mean age: 61 y	3 visits (V2-V4) (16 weeks?)	ΔDAS28	-For 7 patients, the IFX dosage was increased for the final therapeutic decision (based on TDM and disease activity), as compared with 3 patients for whom the dosage was increased at the preliminary therapeutic decision (disease activity alone). -Of the 7 patients, 6 were considered to have an inadequate control of disease activity (2 with medium and 4 with low IFX DL) and 1 was considered to have acceptable control (with medium IFX DL). -For pts with increased IFX dose (n=7), mean DAS28 decreased by about 20% ($P < 0.05$) -Reviewer conclusion: Study showed DAS28 improvement for 7 pts with increased IFX dose, but only 4 of these had the dose modified as a result of TDM. No separate analyses for those who had a dose modification as a result of TDM.	Newcastle-Ottawa for cohort studies	Sum score: **, ,* Selection: ** Comparability: - Outcome: *
Zänker M. et al, 2018	Prospective observational	RA pts with active disease treated with ADA	Pts with active RA (CDAI>19) were given additional 40 mg ADA one week after standard injection ADA DL 5.0–10.0 µg/mL was defined as the target concentration	8 pts were boosted Mean age and % male: NR	14 days	-EULAR response (moderate) (Change in CDAI and DAS28)	-Pts therapeutic ADA DL: 3/3 boosted pts achieved moderate EULAR response. -Pts sub-therapeutic ADA DL: 1/2 boosted pts achieved moderate EULAR response. -Pts supra-therapeutic ADA DL: 2/2 boosted pts achieved moderate EULAR response. -ADAb pos pts: 1 pts boosted (out of 4 ADAb pos), responded partially to boost injection -Reviewer conclusion: Study did not demonstrate utility of TDM. Very small study	Newcastle-Ottawa for cohort studies	Sum score: *, ,* Selection: * Comparability: - Outcome: *
Plasencia C. et al, 2015	Retrospective observational	RA pts treated with IFX	-IFX dose increased in pts with insufficient response (DAS28 >3.2). -Assessed retrospectively if response was related to IFX DL prior to dose	42 pts Mean age: 57y % men: 12	12 months	-EULAR response, -DAS28 score,	-Proportion of pts who achieved good response after 1st dose increase, stratified by IFX DL prior to dose increase (no, low, high): No detectable IFX DL group: 11.1% Low: 16.7% High: 12.5%	Quality in Prognosis Studies Tool (QUIPS)	1.Study participation: High 2.Attrition: Moderate 3.Prognostic factor: Moderate 4.Outcome: Low 5.Confounding: Moderate 6.Statistics: Moderate

			increase, no detectable, low (<1.1 µg/mL) or high (≥1.1 µg/mL).				-Proportion of pts who remained non-responders after 1st dose increase, stratified by IFX DL prior to dose increase (no, low, high): No detectable IFX DL group: 44.4% Low: 58.3% High: 37.5% -Proportion of pts who achieved good response after 12 months after the dose increase, stratified by IFX DL prior to dose increase (no, low, high): No: 25% Low: 0% High: 0% -Proportion of pts who remained non-responders after 12 months, stratified by IFX DL prior to dose increase (no, low, high): No: 50% Low: 77.8% High: 71.4% -Reviewers conclusion: The study did not show a clear utility of TDM for prediction of response after dose increase.		
Spondyloarthritis / Ankylosing spondylitis									
Méric J-C. et al, 2011	Prospective observational study	SpA pts, routinely treated with IFX	The preliminary therapeutic decision (based on disease activity) was re-evaluated, based on an algorithm including both disease activity and IFX DL and applied at the next infusion.	32 pts % male: 50 Median age: 48 years	3 visits (V2-V4) (16 weeks?)	BASDAI improvement	-The preliminary therapeutic decision (based on disease activity alone) was modified (based on IFX DL) in 10 pts (31%). - In the 4 patients whose measurement of IFX DL modified the therapeutic decision to an increase in IFX dosage, adaptation of the IFX dose based on DL led to improvement in BASDAI in only 2 out of 4 patients, despite increased DL in all 4. -Reviewer conclusion: The study did not demonstrate utility of TDM. Small study.	Newcastle-Ottawa for cohort studies	Sum score: **, ,** Selection: ** Comparability: - Outcome: **

Inman RD. et al, 2008	Substudy of RCT (phase III-study)	AS pts with insufficient response to treatment with GLM	Pts randomly assigned in a 1:1.8:1.8 ratio to receive placebo or GLM 50 mg or 100 mg. At week 16, pts who achieved <20% improvement from baseline entered early escape. Pts in the placebo, 50-mg and 100-mg group received GLM 50 mg, 100 mg, and continued 100 mg, respectively. The decision of dose escalation was not based on DL.	356 pts in main study, % male: 72 Mean age: 39.5 y	24 weeks	ASAS20 response	-Median serum GLM (assessed retrospectively) among the -21 pts without ASAS20 response after early escape: 1.04 µg/ml -4 pts with ASAS20 response: 0.90 µg/ml. -Reviewers conclusion: No clear difference in GLM DL between those who achieved response after dose escalation , vs. those who did not	Cochrane RoB2 for RCT	Overall: Low Randomisation: Low Intervention: Low Missing outcome data: Low Outcome measurement: Low Selective reporting: Low
Drug levels									
Ulijn E. et al, 2020[12]	Retrospective observational	RA pts who discontinued ADA after >3 months due to inefficacy and started another bDMARD	ADA and ADAb measured retrospectively in non-trough samples collected ≥8 weeks after start ADA and within 2 weeks of discontinuation.	137 pts (47 switched to second TNFi and 90 to non TNFi bDMARD) Mean age: 64,4y %male: 31%	3-6 months after switch	EULAR good response	ADA levels were not predictive for response in patients that switched to a TNFi (sensitivity/specificity 50%/52%, AUC 0.50 (95% CI 0.29-0.71)) and patients that switched to a non-TNFi (sensitivity/specificity 32%/69%, AUC 0.50 (95% CI 0.34-0.65)). Reviewer conclusion: Study did not demonstrate predictive value of DLs for response to next bDMARD	Quality in Prognosis Studies Tool (QUIPS)	1.Study participation: Moderate 2.Attrition: High 3.Prognostic factor: Moderate 4.Outcome: High 5.Confounding: High 6.Statistics: Low
L'Ami M. et al, 2019	Prospective observational	RA pts who started ETN; after switch from ADA (71% discontinued ADA due to failure)	Pts switching from ADA divided into subgroups based on ADA DL before switch: < 0.5 µg/mL, 0.5–5.0 µg/mL, and ≥ 5.0 µg/mL	Switchers: 69 pts	52 weeks	EULAR good/moderate response	Proportion of pts with EULAR good or moderate response, stratified by ADA DL prior to switch: ADA DL < 0.5 µg/mL: 72% ADA DL 0.5–5.0 µg/mL: 50% ADA DL ≥ 5.0 µg/mL: 52% Reviewer conclusion: Numerically more pts had response to ETN among pts with ADA DL < 0.5 µg/mL before switch, compared to higher DL	Quality in Prognosis Studies Tool (QUIPS)	1.Study participation: Low 2.Attrition: Moderate 3.Prognostic factor: Moderate 4.Outcome: Low 5.Confounding: High 6.Statistics: Low

Vincent FB. et al, 2016	Prospective observational multicenter study (retrospective assessments from one center)	RA and AS pts, switching to second TNFi due to failure to first TNFi	DL measured when decision of failure was made and before the switch. No modifications in dose was made (physicians' awareness of DL not specified) Response to subsequent TNFi assessed	75 pts, RA: 44 and AS: 31 First TNFi: IFX 30, ADA 15, ETN 30 Second TNFi: IFX 10, ADA 38, ETN 28 Mean age 49,7y % male: 29	3 months	-EULAR response for RA -BASDAI 20 points (0-100) improvement for AS	Mean [SD] DL of first TNFi in: Responders to 2nd (all TNFi) (n = 36): 4.4 ±7.1 Non-responders to 2nd (n = 23): 8.7 ±24.3, p=0.37 IFX DL (as 1st TNFi) in responders to 2nd TNFi: 2.9 ±6.5 IFX DL (as 1st TNFi) in non-responders to 2nd TNFi: 3.2 ±6.5, p=0.91 ADA DL (as 1st TNFi) in responders to 2nd TNFi: 10.0 ±10.5 ADA DL (as 1st TNFi) in non-responders to 2nd TNFi: 29.9 ±53.3, p=0.45 ETN DL (as 1st TNFi) in responders to 2nd TNFi: 2.8 ±3.0 ETN DL (as 1st TNFi) in non-responders to 2nd TNFi: 4.0 ±4.3, p=0.66 Reviewer conclusion: Mean [SD] DLs of the 1st TNFi were numerically lower, but not significantly different, among responders vs. non-responders to 2nd TNFi.	Quality in Prognosis Studies Tool (QUIPS)	1.Study participation: Moderate 2.Attrition: Moderate 3.Prognostic factor: High 4.Outcome: Moderate 5.Confounding: High 6.Statistics: Moderate
Anti-drug antibodies (ADAb)									
Ulijn E. et al, 2020	Retrospective observational	RA pts who discontinued ADA after >3 months due to inefficacy and started another bDMARD	ADA and ADAb measured retrospectively in non-trough samples collected ≥8 weeks after start ADA and within 2 weeks of discontinuation. ADAb within 12 weeks after discontinuation.	137 pts (47 switched to second TNFi and 90 to non TNFi bDMARD) Mean age: 64,4y %male: 31%	3-6 months after switch	EULAR good response	ADAb presence was not predictive for response in switchers to a TNFi (sensitivity/specificity 18%/75%, AUC 0.46 (95%CI 0.32-0.59)) or a non-TNFi (sensitivity/specificity 33%/70%, AUC 0.52 (95%CI 0.42-0.63)). Reviewer conclusion: Study did not demonstrate predictive value of ADAb for response to next bDMARD	Quality in Prognosis Studies Tool (QUIPS)	1.Study participation: Moderate 2.Attrition: High 3.Prognostic factor: Moderate 4.Outcome: High 5.Confounding: High 6.Statistics: Low
Vincent FB. et al, 2016	Prospective observational	RA and AS pts, switching to second TNFi due to failure to first TNFi (primary or	ADAb measured when decision of failure was made and before the switch. No modifications in dose was made (physicians'	75 pts, RA: 44 and AS: 31 First TNFi: IFX 30, ADA 15, ETN 30 Second TNFi: IFX 10, ADA 38, ETN 28 Mean age 49,7y	3 months	-EULAR response for RA -BASDAI 20 points (0-100) improvement for AS	ADAb to the 1st (failed) TNFi was present in 18 (72%) of responders and 7 (28%) of non-responders to 2nd TNFi, respectively, p 0.31. Reviewer conclusion: Presence of ADAb was numerically more frequent, but not significantly different, among responders vs. non-responders to 2nd TNFi.	Quality in Prognosis Studies Tool (QUIPS)	1.Study participation: Moderate 2.Attrition: Moderate 3.Prognostic factor: High 4.Outcome: Moderate 5.Confounding: High 6.Statistics: Moderate

		secondary failure or intolerance)	awareness of ADAb status not specified) Response to subsequent TNFi assessed	% male: 29					
Plasencia C. et al, 2013	Ambispective observational study	SpA starting second TNFi due to failure (93%) and/or AE (19%) to first TNFi		42 pts Mean age: 50 % male: 55 -1st TNFi: 20 IFX, 5 ADA, 17 ETN -2nd TNFi: 9 IFX, 19 ADA, 8 ETN, 6 GLM	6 months	-ASDAS -ASDAS high disease activity	ASDAS (mean ± SD) 6 months after switch to second TNFi, stratified by presence of ADAb to first TNFi: -Pts with previous ADAb: 1.62 ± 0.93 -Pts without previous ADAb: 2.79 ± 1.01 -Significant difference in mean ASDAS, p = 0.002 Proportion of pts with ASDAS high disease activity 6 months after switch to second TNFi, stratified by presence of ADAb to first TNFi: -Pts with previous ADAb: 3 out of 11 (27.3%) -Pts without previous ADAb: 25 out of 31 (80.6%) -Proportion of pts with ASDAS high disease activity significantly different, p = 0.002 Reviewer conclusion: Presence of ADAb to previous TNFi was significantly associated with response to subsequent TNFi	Quality in Prognosis Studies Tool (QUIPS)	1.Study participation: Moderate 2.Attrition: Moderate 3.Prognostic factor: Moderate 4.Outcome: Low 5.Confounding: Moderate 6.Statistics: Moderate
Jamnitski A. et al, 2011	Prospective observational	RA pts with active disease starting ETN after switch from IFX or ADA due to failure (n=76) or AE (n=12).	Switchers divided into groups with/without ADAb to previous IFX or ADA. ADAb measured prior to start ETN.	-89 pts (in switcher group) Mean age: 53 y % male: 12	28 weeks	-ΔDAS28 -EULAR response	Response to ETN, stratified by presence of ADAb to 1st TNFi: -Switchers with ADAb to 1st TNFi: ΔDAS28=2.0±1.3; -Switchers without ADAb to 1st TNFi: ΔDAS28=1.2±1.3; -Difference in ΔDAS28 was statistically significant, p=0.017 (after adjustment for baseline DAS28). - EULAR response among switchers with ADAb to first TNFi: 29% good, 62% moderate and 9% were non-responders, compared to 24% good, 43% moderate and 33% non-responders in the switchers without ADAb. In the post hoc analysis only the percentage of EULAR non-responders was different between two groups (p=0.014). -Statistics: Mann-Whitney test and multiple regression models adjusted for baseline DAS28. Reviewer conclusion: Switchers with ADAb to first TNFi had better responses when switching to ETN.	Quality in Prognosis Studies Tool (QUIPS)	1.Study participation: Low 2.Attrition: Low 3.Prognostic factor: Moderate 4.Outcome: Low 5.Confounding: Low 6.Statistics: Moderate

Bartelds GM. et al, 2010	Prospective observational	RA pts with active disease starting ADA, after switch from IFX	IFX ADAb was determined before the start of ADA. ADA ADAb was determined at time points between baseline and 28 weeks.	-52 pts switched from IFX Mean age: 52 y % male: 17	28 weeks	-ΔDAS28	Response ΔDAS28 (mean ± SD) to ADA in pts stratified by previous IFX ADAb: -Switchers without previous IFX ADAb: 0.9±1.4 -Switchers with previous IFX ADAb: 1.2±1.3 -Mean ΔDAS28 did not differ significantly between switchers with and without IFX ADAb; p=0.969 (adjusted, "multiple regression analyses") Reviewer conclusion: No difference response (ΔDAS28) to ADA (second TNFi), between switchers with vs. without ADAb to IFX (first TNFi)	Quality in Prognosis Studies Tool (QUIPS)	1.Study participation: Low 2.Attrition: Low 3.Prognostic factor: Moderate 4.Outcome: Low 5.Confounding: Low 6.Statistics: Low
Bingham C. et al, 2009	Prospective observational	RA pts who have failed IFX, starting ETN	IFX ADAb measured at baseline and after 16 weeks of ETN-treatment	201 pts -Primary IFX-failure: 29 -Secondary failure: 172 Mean age: 57y % male: 20	16 weeks	-EULAR good/moderate response	Proportion of pts (n,%) with baseline IFX ADAb, stratified by response to ETN: -ETN responders: 42 (36%) -ETN non-responders: 24 (29%) -Subanalyses of pts with high levels (≥ 1600 ng/mL; above the quantifiable limit) of IFX ADAb at baseline: included 18 (15%) ETN-responders and 7 (8%) non-responders Reviewer conclusion: No clear difference in proportion of IFX ADAb at baseline among ETN-responders, vs. non-responders.	Quality in Prognosis Studies Tool (QUIPS)	1.Study participation: Low 2.Attrition: Low 3.Prognostic factor: Low 4.Outcome: Low 5.Confounding: Moderate 6.Statistics: Moderate
Van Der Bijl A. et al, 2008	Prospective observational	RA pts who have failed previous IFX-treatment, starting ADA	Pts with previous treatment failure to IFX due to lack or loss of response or intolerance. Response to ADA evaluated after 16 weeks.	41 pts, 37 completed 16 weeks Mean age: 55y % male: 12	16 weeks	EULAR and ACR20/50 response	Proportion of pts with W16 ACR20 response to ADA, stratified by presence of IFX ADAb: -Switchers with previous IFX ADAb: 47% -Switchers with previous IFX ADAb: 43% Proportion of pts with W16 ACR50 response to ADA, stratified by presence of IFX ADAb: -Switchers with previous IFX ADAb: 47% -Switchers with previous IFX ADAb: 7% Proportion of pts with W16 EULAR good/moderate response to ADA, stratified by presence of IFX ADAb: -Switchers with previous IFX ADAb: 53% -Switchers with previous IFX ADAb: 53% Reviewer conclusion: No clear difference in response to ADA, in previous IFX ADAb pos vs. neg, (except for ACR50 response)	Quality in Prognosis Studies Tool (QUIPS)	1.Study participation: Moderate 2.Attrition: Low 3.Prognostic factor: High 4.Outcome: Low 5.Confounding: High 6.Statistics: Moderate

Mazilu D. et al, 2014	Prospective observational	RA pts treated with RTX, IFX, ADA or ETN, included at time of inadequate response	Pts tested for both serum drug level and ADAb at the time of their first sign of inadequate response (baseline) Def. Flare: one of the following: an increase in SDAI, an increase in ESR and/or CRP, increase in DAS score to moderate or high disease activity, and a lower class in EULAR response.	154 pts incl. Final cohort: 72 pts. RTX: 25 IFX: 20 ETN: 18 ADA: 9 Mean age and % male: NR	2 years. Disease activity/persistence of flare was evaluated after 6 months for RTX, 2 months for IFX, 3 months for ETN.	-DAS28 -SDAI -EULAR good/moderate response.	RTX: Disease activity 6 months after first sign of inadequate response, stratified by RTX DL at baseline (time of first sign of inadequate response); -Mean (SD) DAS28 2.93 ± 1.20 in pts with detectable RTX at baseline, vs. 3.27 ± 1.47 in pts with undetectable RTX at baseline (P = 0.01). -Mean (SD) SDAI 12.23 ± 14.1320 in pts with detectable RTX at baseline, vs. 14.83 ± 20.51 in pts with undetectable RTX at baseline (P = 0.033). -EULAR response achieved in 12/16 pts with detectable RTX at baseline, vs. 3/9 pts with undetectable RTX at baseline (P=0.038). IFX: Disease activity 2 months after first sign of inadequate response, stratified by IFX DL at baseline (time of first sign of inadequate response); -Mean (SD) DAS28 3.67 ± 1.24 in pts with detectable IFX at baseline, vs. 5.59 ± 1.07 in pts with undetectable IFX at baseline (P = 0.002). -Mean (SD) SDAI 17.26 ± 12.29 in pts with detectable IFX at baseline, vs. 44.33 ± 18.22 in pts with undetectable IFX at baseline (P = 0.001). -EULAR response achieved in 7/7 pts with detectable IFX at baseline, vs. 1/11 pts with undetectable RTX at baseline (P=0.002). IFX ADAb detected in 9/20 IFX-pts; All 9 had no EULAR response after 2 months. ETN: Disease activity 3 months after first sign of inadequate response stratified by ETN DL at baseline (time of first sign of inadequate response); -Mean (SD) DAS28 7.17 ± 1.21 in pts with detectable ETN at baseline, vs. 3.57 ± 1.65 in pts with undetectable ETN at baseline (P =0.003). -Mean (SD) SDAI 19.06 in pts with detectable ETN at baseline, vs. 58.73 in pts with undetectable ETN at baseline (P =0.026). -EULAR response achieved in 12/15 pts with detectable ETN at baseline, vs. 0/3 pts with undetectable ETN at baseline (P=0.023). ADA: sample size too small Reviewer conclusion: Statistically significant differences in disease activity and/or response at time of evaluation, in pts stratified by DL at baseline. Pts with detectable DLs at baseline had lower disease activity at evaluation.	Quality in Prognosis Studies Tool (QUIPS)	1.Study participation: High 2.Attrition: Moderate 3.Prognostic factor: Moderate 4.Outcome: Moderate 5.Confounding: High 6.Statistics: Low

PTC-10: Measurement of ADAb should be considered in the case of immunogenic biopharmaceuticals, alongside biopharmaceutical blood concentrations, at the time of clinical non-response.

Study	Study design	Population	Scope/Intervention	Study population	Follow-up	Outcome measures	Results	Tool used for RoB assessment	Risk of Bias
Senabre Gallego JM. et al, 2019	Cross-sectional observational study	Pts with axial SpA	Measurement of ADAb (bELISA: specific detection)	51 pts	>3 months	Clinical response	ASDAS-CRP<2.1: ADAb+(4%); ASDAS-CRP≥2.1: ADAb+(52%); p<0.001 ASDAS-ESR<2.1: ADAb+(0%); ASDAS-CRP≥2.1: ADAb+(46%); p<0.01 BASDAI<4: ADAb+(0%); BASDAI≥4: ADAb+(47%); p<0.001 Results were not adjusted for confounders	Newcastle-Ottawa for cohort studies	Sum score: **, **,* Selection: ** Comparability: ** Outcome: *
Burmester GR. et al, 2017	Post-hoc analysis of several RCT	RA pts treated with TCZ	Measurement of ADAb (by bELISA, specific detection)	8974 pts from the different RCT	TCZ-SC (up to 3.5yr) Tcz-IV (up to 5yr)	Clinical response	Incidence of ADAb: - 1.5% (n=47) pts who received TCZ-SC developed ADAb - 1.2% (n=69) pts who received TCZ-IV developed ADAb Among all patients who developed ADAb with neutralising potential following TCZ treatment, none experienced loss of efficacy, regardless of administration route. Results were not adjusted for confounders	AMSTAR-2	HIGH *3x YES* *3x partial-YES* *9x NO* *1x N/A*
Hoxha A. et al, 2016	Open-label multicenter prospective study	Pts with RA, AS or PsA treated with ADA	Measurement of ADAb (sandwich ELISA: specific detection) at 4, 12 and 24 weeks	58 pts	24 weeks	Treatment failure within 24 weeks	ADAb at week 4 were significantly associated with lack of response and/or loss of efficacy (treatment failure) within 24 weeks: OR 4.5, 95% CI 1.1-18.2; p=0.035 Results were not adjusted for confounders	Newcastle-Ottawa for cohort studies	Sum score: **, -,* Selection: ** Comparability: - Outcome: *

Arstikyte I. et al, 2015	Retrospective observational study	Pts with RA or SpA treated with ADA, IfFX or ETN	Measurement of ADAb (sandwich ELISA: specific detection) Blood samples collected at: IFX: at 42 (12-66) months after treatment initiation AdDA: at 6 (3-18) months after treatment initiation ETN: at 30 (12-54) months after treatment initiation	143 pts (62 with RA and 81 with SpA). ADA: 25 pts (17.4%) ETN: 61 pts (42.7%) IFX: 57 pts (39.9%)	2 years	- Dose increasing - Stop treatment	15 (10%) pts developed ADAb: IFX: 14 (25%) pts developed ADAb Patients with ADAb have lower odds to continue with the same dose of IFX: OR 0.2 (95% CI 0.05-0.69); p<0.05 Association between ADAb and the stop of the treatment: OR 9.28 (95% CI 1.64-52.52); p<0.05 ADA: 1 (4%) pts developed ADAb ETN: 0 (0%) pts developed ADAb Results were not adjusted for confounders	Quality in Prognosis Studies Tool (QUIPS)	1.Study participation: high 2.Attrition: high 3.Prognostic factor: High 4.Outcome: Low 5.Confounding: High 6.Statistics: Moderate
Krintel SB. et al, 2013	Prospective observational study	TNFi naïve pts with RA treated with IFX	Measurement of ADAb after 6, 14 and 52 weeks (biochip platform: specific capture but non-specific detection)	218 pts	52 weeks	Treatment response	- There was no significant association between ADAb status after 6 (p=0.1) and 14 (p=0.6) weeks of treatment and withdrawal due to treatment failure during the 52-week follow-up. - ADAb+ pts were less likely to achieve sustained minimal disease activity (DAS28<3.2) compared with ADAb- pts (HR=0.49, 95% CI 0.27-0.92, p=0.023). - ADAb+ pts were less likely to achieve sustained remission (DAS28<2.6) compared with patients without ADAb (HR=0.53, 95% CI 0.28-0.98; p=0.04). Results were not adjusted for confounders	Newcastle-Ottawa for cohort studies	Sum score: **, -,* Selection: ** Comparability: - Outcome: *
Plasencia C. et al, 2012	Ambispective observational study	Pts with SpA treated with IFX	Measurement of ADAb (by bELISA, specific detection)	94 pts	A mean of 7 years	- Clinical response - TNFi survival	- ΔASDAS was lower in ADAb+ pts at any time: At 6 months: 0.48±0.73 vs 1.47±1.66; p=0.029 At 1 year: 0.81±1.20 vs 1.56±1.67; p=0.098 At >4 years: 0.45±0.82 vs 1.43±1.25; p=0.022 - The median IFX survival time was 4.25 years (95% CI: 3.06 to 5.43) in ADAb+ pts vs. 8.19 years (95% CI: 7.54 to 8.85) in ADAb- pts (p<0.001) Results were not adjusted for confounders	Newcastle-Ottawa for cohort studies	Sum score: ***, -,** Selection: *** Comparability: - Outcome: **

Bartelds GM. et al, 2011	Prospective observational cohort study	Pts with RA treated with ADA	Measurement of ADAb (by RIA, specific detection) at 4, 16, 28, 40, 52, 78, 104, 130, and 156 weeks	272 pts	3 years	- Treatment failure - Treatment discontinuation	- Minimal disease activity (DAS28<3.2): ADAb+ pts less often achieved sustained minimal disease activity compared with ADAb- pts: Unadjusted model: p<0.001 Adjusted model: Correction for confounding variables (methotrexate dosage, ESR, and C-reactive protein): HR=3.6; 95% CI, 1.8-7.2; p<0.001 - Clinical remission: ADAb+ pts less often achieved clinical remission compared with ADAb- pts: Unadjusted model: p<0.001 Adjusted model: Correction for confounding variables (methotrexate dosage, ESR, and C-reactive protein): HR=7.1; 95% CI, 2.1-23.4; p<0.001 - Discontinuation due to treatment failure: ADAb+ pts more often discontinued the treatment than ADAb- pts [29 (38%) vs. 28 (14%), respectively]: Unadjusted model: p<0.001 Adjusted model: Correction for confounding variables (methotrexate use, number of previous DMARDs, and C-reactive protein): HR=3.0; 95% CI, 1.6-5.5; p<0.001	Quality in Prognosis Studies Tool (QUIPS)	1.Study participation: low 2.Attrition: moderate 3.Prognostic factor: low 4.Outcome: Low 5.Confounding: moderate 6.Statistics: low
Pascual-Salcedo D. et al, 2011	Retrospective observational study	Pts with RA	Measurement of ADAb (by bELISA, specific detection)	85 pts	>4years	- Treatment discontinuation - Clinical response	- IFX discontinuation was higher in pts who developed ADAb [23 (82.1%) out of 28 vs 22 (39.3%) out of 57; p<0.001]. - ADAb+ pts had higher DAS28 values at 6-month follow-up [4.85 (1.24) vs 3.67 (1.12); p=0.004], 1 year [4.95 (1.24) vs 3.13 (1.17); p=0.002] and >4 years [4.00 (1.35) vs 3.46 (1.22), p=0.004] Results were not adjusted for confounders	Newcastle-Ottawa for cohort studies	Sum score: ***, -,** Selection: *** Comparability: - Outcome: **
Bendtzen K. et al, 2006	Retrospective observational study	Pts with RA treated with IFX	Measurement of ADAb (by RIA, specific detection) at 1.5, 3 and 6 months	106 pts	>6 months	- Treatment discontinuation - Dose increasing due to inadequate response	- Early formation of ADAb was also associated with subsequent discontinuation of therapy (within 18 months); (any discontinuation: p=0.0001): Therapy failure: p=0.009 Infusion reaction: p=0.001 - Detection of ADAb at an early time point (3 months) was associated with later dose increases (within 18 months) necessitated by inadequate clinical response (p=0.0005) Results were not adjusted for confounders	Newcastle-Ottawa for cohort studies	Sum score: **, -,* Selection: ** Comparability: - Outcome: *

Wolbink GJ. et al, 2006	prospective observational study	Pts with RA treated with IFX	Measurement of ADAb (by RIA, specific detection)	51 pts	1 year	Clinical response	ADAb- pts were significantly more often classified as responders when compared with ADAb+ pts (20 of 29 without antibodies [69%] versus 8 of 22 with antibodies [36%] considered responders); p=0.04 Results were not adjusted for confounders	Quality in Prognosis Studies Tool (QUIPS)	1.Study participation: moderate 2.Attrition: high 3.Prognostic factor: low 4.Outcome: Low 5.Confounding: high 6.Statistics: low

Study	**Study design**	**Population**	**Scope/Intervention**	**Study population**	**Follow-up**	**Outcome measures**	**Results**	**Tool used for RoB assessment**	**Risk of Bias**
ADALIMUMAB									
Bartelds 2007	Prospective observational cohort, monocentric, the Netherlands	RA ADA	Association antibodies with drug level and clinical response	121 pts, 79% female, age 53, baseline DAS28 5.3, diseases duration 12 years, MTX use 79%	28 weeks	Drug levels and antibodies	Adalimumab concentrations were significantly lower in patients with detectable anti-adalimumab antibodies than in patients without antibodies. Median 1.2, range 0.0 – 5.6 mg/l vs. median 11.0, range 2.0 – 33 mg/l (p<0.001)	Quality in Prognosis Studies Tool (QUIPS)	1.Study participation: moderate 2.Attrition: moderate 3.Prognostic factor: high 4.Outcome: Low 5.Confounding: high 6.Statistics: low
Ding 2020	Observational cohort study, monocentric, China	AS adalimumab	To determine a concentration-effect curve for adalimumab in patients with AS	31 pts, age 31 yrs, male 94%, disease duration 7 yrs, CRP 16 mg/l, ASDAScrp 4.06, BASDAI 6.1, NSAIDs 15%	12 weeks	ADA concentrations, anti-drug antibodies	Patients who were antibody negative had significantly higher adalimumab levels than patients who were antibody positive (week 4: median 7.53 µg/mL IQR 5.94−8.30 vs. 3.57 µg/mL IQR 2.33−6.42, respectively, p=0.001; week 8: 11.35 µg/mL IQR 9.76−16.03 vs. 5.85 µg/mL IQR 2.69−10.07, p=0.001; week 12: 16.57 µg/mL IQR 11.97−19.37 vs. 7.41 µg/mL IQR 3.07−12.22, p=0.0005)	Quality in Prognosis Studies Tool (QUIPS)	1.Study participation: moderate 2.Attrition: high 3.Prognostic factor: ? 4.Outcome: Low 5.Confounding: high 6.Statistics: low
Rosas 2017	Cross-sectional study, monocentric, Spain	AS adalimumab	To determine whether obesity affects serum levels of adalimumab	57 pts, male 65%, age 47 years, BMI 27.6, disease duration 9.8 years, HLAB27 77%, treatment duration 1.44 years,	N/A	adalimumab level, antibodies	When the groups of patients with and without positive anti-ADA antibodies (n=4, 7%) were compared, patients with positive antibodies showed a significantly lower mean ADA concentration (<0.024 vs. 8.0 [4.3] mg/L, p<0.001)	Quality in Prognosis Studies Tool (QUIPS)	1.Study participation: low 2.Attrition: high 3.Prognostic factor: moderate 4.Outcome: Low 5.Confounding: high 6.Statistics: moderate

				BASDAI4.05, ASDAS(esr) 2.36					
Kneepkens 2015 (2)	Prospective observational cohort, multicentric, the Netherlands, Taiwan	AS ADA	Association between drug level and clinical response	151 pts, 42 years, 68% male, disease duration 8 years, HLAB27 83%, ASDAS 3.5, BASDAI 6.4, NSAIDs 65%	24 weeks	drug levels, antibodies	Adalimumab levels were significantly different for patients without and with antibodies: 12.7 (8.2-18) and 1.2 (0-2.0), respectively (p<0.001).	Quality in Prognosis Studies Tool (QUIPS)	1.Study participation: moderate 2.Attrition: moderate 3.Prognostic factor: moderate 4.Outcome: moderate 5.Confounding: moderate 6.Statistics: low
Van Kuijk 2010	Prospective observational cohort, monocentric, the Netherlands	PsA, adalimumab	Relationship between clinical response and serum levels	22 pts, male 14/8, age 43 years, disease duration6.3 years, MTX 55%, DAS28 4.9, PASI 5.7	12 months	Drug level, anti-drug antibodies	Patients with anti-adalimumab antibodies had lower median adalimumab concentrations than those without: 1.7 vs 8.1 mg/l (p=0.007) at 3 months, and 1.7 vs 9.8 mg/l (p=0.031) at 12 months.	Quality in Prognosis Studies Tool (QUIPS)	1.Study participation: high 2.Attrition: high 3.Prognostic factor: moderate 4.Outcome: Low 5.Confounding: high 6.Statistics: low
Vogelzang 2014	Prospective observational cohort, monocentric, the Netherlands	PsA, adalimumab	Association between adalimumab drug levels and disease activity	103 pts, male 53%, age 50 years, MTX 78%, disease duration 6 years, DAS28 4.0, PASI 0.6	52 weeks	Drug level, anti-drug antibodies	At week 28, patients who had detectable ADA had significant lower median adalimumab concentrations: 1.3 mg/L (0.0–3.2 IQR) compared with 8.7 mg/L (5.7–11.5 IQR) in patients without ADA, p<0.001. At 52 weeks median adalimumab concentration in patients with detectable ADA, was significantly lower (p=0.0001) than in patients without detectable ADA (respectively, median 0.9 mg/L, IQR 0.0–2.9 vs median 9.4 mg/L, IQR 5.7–12.1).	Quality in Prognosis Studies Tool (QUIPS)	1.Study participation: high 2.Attrition: high 3.Prognostic factor: low 4.Outcome: Low 5.Confounding: high 6.Statistics: low
INFLIXIMAB									
Dervieux 2012	Cross-sectional study	RA IFX (median 6 mg/kg/8 wks	Correlation between drug level, MTX polyglutamates and disease activity	61 pts, 64 years, 77% female, disease duration 11 years, MTX dose 15 (10-20) mg, treatment duration 70 months, CDAI 8	N/A	Drug level, anti-drug antibodies	Patients with anti-drug antibodies (n=11, 18%) had lower IFX levels than patients without antibodies (median 5.0 vs. <0.5 ug/ml, p<0.001).	Quality in Prognosis Studies Tool (QUIPS)	1.Study participation: moderate 2.Attrition: ? 3.Prognostic factor: ? 4.Outcome: Low 5.Confounding: high 6.Statistics: low
ETANERCEPT									

Dong 2019	Prospective observational cohort, monocentric, China	AS etanercept	To investigate the effective serum level of etanercept in patients with AS	60 pts, 54/60 male, age 29 years, disease duration 4 years	24 weeks	drug levels, anti-drug antibodies	Cut-off drug level values of effective (ASDAS-CRP < 2.1) etanercept treatment based on results of ROC curves at weeks 4, 12, and 24 were 2.32, 2.12, and 2.36 µg/mL, respectively. Etanercept levels were significantly higher in patients who were antibody-negative than those who were antibody-positive at weeks 4, 12, and 24, respectively (2.46 ± 0.63 vs 1.97 ± 0.98 µg/mL, p = 0.044; 2.55 ± 0.94 vs 2.10 ± 0.58 µg/ mL, p=0.023 and 2.85±1.09 vs 2.22±0.74 µg/mL, p= 0.042)	Quality in Prognosis Studies Tool (QUIPS)	1.Study participation: moderate 2.Attrition: high 3.Prognostic factor: moderate 4.Outcome: Low 5.Confounding: high 6.Statistics: moderate
CERTOLIZUMAB									
Jani 2017	Prospective observational cohort (BRAGGSS) multicentric, UK	RA CZP	Association between random certolizumab levels, antidrug antibodies and treatment response	115 pts, age 58 years, female 70%, disease duration 7 years, DAS28 5.9 MTX use 53%	12 months	Random drug levels, anti-drug antibodies	Antidrug antibodies levels were strongly correlated (in multivariate analysis) with drug levels. -0.044 (-0.059 – -0.028), p<0.0001. The presence of antibodies was significantly associated with lower drug levels over 12 months using GEE (β=−0.037, 95% CI −0.055 to −0.018, p<0.0001.	Quality in Prognosis Studies Tool (QUIPS)	1.Study participation: low 2.Attrition: moderate 3.Prognostic factor: low 4.Outcome: Low 5.Confounding: low 6.Statistics: low
RHEUMATOID ARTHRITIS AND TNF-INHIBITORS (ADA, IFX, ETN)									
Chen 2015 (2)	Observational cohort, Taiwan	RA ADA and ETN	Association between drug levels and therapeutic response	ADA 36 pts, 53 years, 89% female, disease duration 5.4 years, DAS28 6.1, MTX 89% ETN 34 pts, 58 years, 88% female, disease duration 5.4 years, DAS28 5.95 MTX 88%	12 months	Anti-drug antibodies and drug level	Adalimumab: patients with negative antibodies had significantly higher drug levels at 6 and 12 months, median 4.25 and 4.19 ug/ml, respectively vs. 0.51 and 0.35 ug/ml, respectively, for those with positive antibodies (measured with ELISA) (p<0.001 for both). There was an inverse correlation between antibody levels (bridging ELISA) and drug trough levels (Progenika) (r=−0.667, p<0.001; r= −0.575, p<0.001, at the 6th and 12th month, respectively. Similarly, there was an inverse correlation between antibody levels (RIA) and drug trough levels (Sanquin) at the 12 months of anti-TNF therapy (r=−0.612, p<0.001).	Quality in Prognosis Studies Tool (QUIPS)	1.Study participation: high 2.Attrition: high 3.Prognostic factor: ? 4.Outcome: Low 5.Confounding: high 6.Statistics: low

Jani 2015	Prospective observational cohort (BRAGGSS) multicentric, UK	RA ADA, ETN	Random drug levels, clinical response and adherence to therapy	ADA 160 pts, age 56.2 years, 70% female, disease duration 8.6 years, DAS28 5.7, MTX 55%. ETN 171 pts, 57 years, 80% female, disease duration 7,8 years, DAS28 5.9, MTX 46%	12 months	Random drug levels, anti-drug antibodies	Presence of antidrug antibodies was significantly associated with lower adalimumab levels (r -0.51 p< 0.0001). Median Adalimumab levels for anti-drug antibodies positive vs. negative patients at 3, 6 and 12 months of treatment, respectively, where 4.6, 2.1 and 1.7 ug/ml vs. 12.0, 12.0 and 12.0 ug/ml (no statistics). In analysis for predictors of low drug levels, for adalimumab, anti-drug antibodies remained the strongest predictor (regression coefficient 1.27 95%CI 0.44-2.09 p=0.003).	Quality in Prognosis Studies Tool (QUIPS)	1.Study participation: moderate 2.Attrition: moderate 3.Prognostic factor: moderate 4.Outcome: moderate 5.Confounding: moderate 6.Statistics: low
Eng 2015	Cross-sectional, multicentric, DANBIO registry	RA, ADA and IFX	Evaluation of correlation between anti-drug antibodies and drug levels in patients with clinical remission (DAS28(CRP) <2.6) at time of inclusion	IFX 44 pts, age 63 years, female 61%, DAS28 1.6, MTX 89%, disease duration 11 years, treatment 55 months, remission 17 months. ADA 49 pts, age 54 years, female 57%, DAS28 1.6, MTX 82%, disease duration 16 years, treatment 68 months, remission 20 months	N/A	Serum levels in patients with and without antibodies (RIA)	Median drug levels for IFX in antibody positive (n=8, 18%) were 1.6 ug/ml, and for antibody negative patients 4.7 ug/ml (p=0.048) Median drug levels for ADA antibody positive patients (n=1, 2%) 0.7 ug/ml, and for antibody negative patients 9.7 ug/ml (no statistics)	Quality in Prognosis Studies Tool (QUIPS)	1.Study participation: low 2.Attrition: ? 3.Prognostic factor: ? 4.Outcome: Low 5.Confounding: high 6.Statistics: moderate
Moots 2017	Cross-sectional study, multinational	RA adalimumab, etanercept and infliximab	Relationship of anti-drug antibodies and efficacy and patient reported outcome with drug levels	ETN n=200, age 57 years, female 78%, treatment duration 14.6 months, MTX 61.5% ADA n=199, age 54 years, female	N/A	Drug level, anti-drug antibodies	The mean (± SD) serum trough ETN concentration was 1.8 (1.03) µg/mL; the effect of anti-drug antibodies on serum trough drug concentration could not be determined for patients treated with ETN since no patient was positive for anti-drug antibodies. For adalimumab, patients without detectable anti-drug antibodies, mean drug concentration was 7.7 mg/ml, vs. 1.5 mg/ml for patients with detectable antibodies	Quality in Prognosis Studies Tool (QUIPS)	1.Study participation: moderate 2.Attrition: high 3.Prognostic factor: ? 4.Outcome: moderate 5.Confounding: high 6.Statistics: low

				81%, treatment duration 13.5 months, MTX 70% IFX n=196, age 61 years, female 80%, treatment duration 13.1 months, MTX 64%			(p<0.0001). For infliximab, patients without detectable anti-drug antibodies, mean drug concentration was 9.8 mg/ml, vs. 0.2 mg/ml for patients with detectable antibodies (p=0.0003).		
SPONDYLARTHRITIS AND TNF-INHIBITORS (ADA, IFX, ETN)									
Arends 2010	Longitudinal observational cohort, monocentric, the Netherlands	AS, ADA, IFX ETN	Association drug level and disease activity	20 pts per drug (total 60 pts) age 42 63% male, disease duration 8 years, 84% HLA-B27+, DMARDs 23%, baseline BASDAI 5.9, CRP 17 ESR 25 ASDAS 3.8	12 months	drug level, antibodies	Serum levels at 3, 6 and 12 months were 30.6, 36.3 and 23.4 for IFX, 3.1, 2.8 and 2.9 for ETN and 5.7, 5.5 and 8.0 for ADA, respectively. Patients with antibodies had lower drug levels than patients without. For IFX: 0.1, 0.0 and 0.6 ug/ml at 3, 6 and 12 months, respectively, for patients with detectable antibodies and 20.3, 30.7 and 15.1 ug/ml for patients without antibodies. (p<0,05 at 6 & 12 months) For ADA: 1.5, 1.5 and 0.0 ug/ml for patients with and 6.4, 6.8 and 8.0 ug/ml for patients without detectable antibodies at 3, 6 and 12 months, respectively (p<0,05 at 6 & 12 months).	Quality in Prognosis Studies Tool (QUIPS)	1.Study participation: moderate 2.Attrition: high 3.Prognostic factor: high 4.Outcome: Low 5.Confounding: high 6.Statistics: moderate
Ancuta SAT0277 (2018)	Abstract EULAR 2018, cross-sectional	axSpA IFX ADA ETN	To evaluate the immunogenicity of TNF inhibitors and the potential effect on serum drug levels	ADA: 28 pts IFX: 19 pts ETA: 40 pts	N/A	Drug level, anti-drug antibodies (ELISA, Progenika)	11 patients had detectable anti-drug antibodies, 8 under ADA (28.57%) and 3 under IFX (15.78%), with significant decrease in drug levels (3.97 µg/mL vs. 0.07 µg/mL ADA, p<0.05; 1.82 µg/mL vs. 0.05 µg/mL IFX, p<0.05)	Quality in Prognosis Studies Tool (QUIPS)	1.Study participation: high 2.Attrition: high 3.Prognostic factor: high 4.Outcome: moderate 5.Confounding: high 6.Statistics: high
RA, SpA AND TNF-INHIBITORS (ADA, IFX, ETN, CPZ, GLM)									
Gehin 2019	Observational cohort (NOR-DMARD), multicentric, Norway	RA, SpA, PsA, certolizumab			6 months	Drug level, anti-drug antibodies	Stratified by diagnosis, median (IQR) CZP level was 35.0 (21.3–45.3) mg/L in axSpA patients, 34.7 (17.6–44.6) mg/L in RA and 31.0 (13.6–39.9) mg/L in PsA. Anti-drug antibody-positive patients had significantly lower CZP levels than antibody-negative patients, i.e.,	Quality in Prognosis Studies Tool	1.Study participation: low 2.Attrition: high 3.Prognostic factor: low 4.Outcome: low 5.Confounding: high 6.Statistics: low

							median (IQR) 1.0 (0.2–6.8) vs. 34.4 (21.2–44.7) mg/L (p < 0.01).		
Chen 2015 (1)	Observational cohort, Taiwan	RA AS GLM	Association between GLM levels and anti-drug antibodies	RA 33 pts, 88-100% female, disease duration 7 years, DAS28 6.27-6.51 AS 43 pts, 39 yerars, 77-91% male, BASDAI 6.3-6.5, ADASCRP 4, MTX 11-24%	24 weeks	GLM levels and anti-drug antibody status	Antibody positive RA patients (15%) had barely detectable drug levels (median 0.022 ug/ml) in contrast to antibody negative patients (median 1.05 ug/ml) (p<0.001) No numbers for AS, since only one antibody positive patient	Quality in Prognosis Studies Tool	1.Study participation: high 2.Attrition: ? 3.Prognostic factor: moderate 4.Outcome: low 5.Confounding: high 6.Statistics: moderate
OTHER BIOLOGICALS									
Wells 2019	Open label, randomised study, multicenter	RA, sarilumab 150 or 200 mg every 2 weeks	Assess immunogenicity of sarilumab in RA	132 pts (65 with 150mg, 67 with 200) ; 80% female ; Age 52,4 ; duration disease 10,5y ; DAS28 5,9	30 weeks: 24 weeks of treatment + 6 weeks of follow-up	Anti-drug antibodies, drug level	Mean (standard deviation) sarilumab concentrations at steady state (week 12) in antibody-negative and antibody-positive patients were 5.36 (SD 6.25 [n = 41]) and 2.10 (SD 2.76 [n = 13]) at 150 mg q2w and 15.62 (13.95 [n = 45]) and 9.39 (9.26 [n = 10]) at 200 mg q2w, respectively. (no statistics)	Cochrane RoB2 for RCT	Overall: some concerns Randomisation: Low Intervention: some concerns Missing outcome data: Low Outcome measurement: some concerns Selective reporting: Low
Thurlings 2010	Porspective observational cohort, bicentric, the Netherlands	RA, rituximab (2x 1000 mg)	Whether persistence of synovial B lineage cells and lack of clinical response are associated with low rituximab serum levels	58pts, female71-80%, DAS28 6.0-6.5, MTX 75-100%	24 weeks	drug levels at week 4, 12/16 and 24, anti-rituximab antibodies	Rituximab levels in anti-drug antibody-positive patients were lower than in antibody-negative patients, from 4 weeks after treatment (p=0.003, p=0.096, p=0.001 and p,0.001 after 4, 12, 16 and 24 weeks, respectively.	Quality in Prognosis Studies Tool	1.Study participation: high 2.Attrition: high 3.Prognostic factor: high 4.Outcome: high 5.Confounding: high 6.Statistics: moderate

PTC-11: Measurement of ADAb should be considered in the case of a hypersensitivity reaction, mainly related to infusions.

Study	Study design	Population	Scope/Intervention	Study population	Follow-up	Outcome measures	Results	Tool used for RoB assessment	Risk of Bias
Burmester GR. et al, 2017	Post-hoc analysis of several RCT	RA pts treated with TCZ	Measurement of ADAb (by bELISA, specific detection)	8974 pts from the different RCT	TCZ-SC (up to 3.5yr) TCZ-IV (up to 5yr)	Adverse effects	Incidence of ADAb: - 1.5% (n=47) pts who received TCZ-SC developed ADAb - 1.2% (n=69) pts who received TCZ-IV developed ADAb There was no clear impact of ADAb and safety (very low incidence of infusion reactions, hypersensitivity, injection-site reactions): - Hypersensitivity (leading to withdrawal): TCZ-SC=0.03%; TCZ-IV=0.2% - Injection-site reactions: TCZ-SC=0.1% Results were not adjusted for confounders	AMSTAR-2	HIGH *3x YES* *3x partial-YES* *9x NO* *1x N/**A***
Arstikyte I. et al, 2015	Retrospective observational study	Pts RA or SpA treated with ADA, IFX or ETN	Measurement of ADAb (Sandwich ELISA: specific detection) Blood samples collected at: IFX: at 42 (12-66) months after treatment initiation ADA: at 6 (3-18) months after treatment initiation ETN: at 30 (12-54) months after treatment initiation	143 pts (62 with RA and 81 with SpA). AdA: 25 pts (17.4%) ETN: 61 pts (42.7%) IFX: 57 pts (39.9%)	2 years	Infusion reactions	ADAb development: 14 by IFX, 1 by ADA, 0 by ETN <u>IFX</u> Association between ADAb and infusion reaction: OR 5.88 (95% CI 1.04-33.28); p<0.05 Results were not adjusted for confounders	Quality in Prognosis Studies Tool	1.Study participation: high 2.Attrition: high 3.Prognostic factor: high 4.Outcome: low 5.Confounding: high 6.Statistics: moderate

Krintel SB. et al, 2013	Prospective observational study	TNFi naïve pts with RA treated with IFX	Measurement of ADAb after 6, 14 and 52 weeks (biochip platform: specific capture but non-specific detection)	218 pts	52 weeks	Risk of withdrawal due to adverse drug reactions	ADAb+ : 118/218 pts - ADAb+ pts after 6 weeks of treatment had an increased risk of withdrawal due to adverse drug reactions during the 52-week follow-up compared with ADAb- pts (HR = 5.06, 95% CI 2.36-10.84; P < 0.0001). - ADAb+ pts after 14 weeks of treatment had an increased risk of withdrawal due to adverse drug reactions during the 52-week follow-up compared with ADAb- pts (HR = 3.30, 95% CI 1.56-6.99; P = 0.0009). - ADAb+ pts during the 52-week follow-up had an increased risk of adverse drug reactions compared with ADAb- pts [21 (18%) vs 7 (7%), P < 0.018]. - ADAb+ pts during the 52-week follow-up had an increased risk of infusion reactions [17 (14%) vs 0 (0%), P < 0.001]. 12/17 pts (71%) who withdrew due to infusion reactions had detectable ADAb after 6 weeks of treatment. Results were not adjusted for confounders	Newcastle-Ottawa for cohort studies	Sum score: **, -,* Selection: ** Comparability: - Outcome: *
Plasencia C. et al, 2012	Ambispective observational study	Pts with SpA treated with IFX	Measurement of ADAb (by bELISA, specific detection)	94 pts	A mean of 7 years	Association of ADAb With Safety	-ADAb associated with hypersensitivity reactions: OR(95%IC)=17(3.29-87.85) -Infusion-related reactions were seen in 11/94 pts, most of whom had detectable ADAb (8 (72.7%) vs 3 (27.3%), p=0.001). ADAb levels (median, IQR) at the times of the infusion reactions were significantly higher in the patients who developed infusion reactions (12931, 853-82437 AU/ml vs 2454, 449-7718 AU/ml; p=0.028). OR(95%IC)=11.2(3.8-40.9), p<0.001. Results were not adjusted for confounders	Newcastle-Ottawa for cohort studies	Sum score: ***, -,** Selection: *** Comparability: - Outcome: **
Pascual-Salcedo D. et al, 2011	Retrospective observational study	Pts with RA treated with IFX	Measurement of ADAb (by bELISA, specific detection)	85 pts	>4years	Relation between infusion-related reactions and ADAb	9 (10.5%) pts, all of them with high-serum ADAb levels, developed infusion-related reactions. ADAb levels at the time of infusion reaction were higher in the patients who developed reactions (20565 AU/ml) than in those patients with detectable ADA, but without infusion related reactions [10152 AU/ml]; p=0.041. Results were not adjusted for confounders	Newcastle-Ottawa for cohort studies	Sum score: ***, -,** Selection: *** Comparability: - Outcome: **

De Vries MK. et al, 2009	Prospective observational study	Pts with AS treated with ADA	Measurement of ADAb (by RIA, specific detection)	35 pts	6 months	Association of ADAb With Safety	31% (11/35) of patients developed ADAb within 6 months of treatment. 1 of them had an allergic reaction with flushing, dyspnea and undetectable serum ADA levels. OR(95%IC)=7.00(0.26-186.26); p>0.05 Results were not adjusted for confounders	Newcastle-Ottawa for cohort studies	Sum score: ***, -,*** Selection: *** Comparability: - Outcome: ***
Braun J. et al, 2008	RCT A placebo controlled, double-blind trial	Pts with AS treated with IFX	Measurement of IFX and antibodies-to-IFX at baseline and after 1.5, 3 and 6 months	277 pts	2 years	Safety of IFX	61% of ADAb+ pts developed infusion reactions. ADAb associated with hypersensitivity reactions: OR(95%IC)=9.64(3.84-24.25) Results were not adjusted for confounders	Cochrane RoB2 for RCT	Overall: some concerns Randomisation: Low Intervention: low Missing outcome data: Low Outcome measurement: some concerns Selective reporting: some concerns
Bender NK. et al. 2007	Prospective observational study	Pts with RA treated with ADA	Measurement of ADAb (by bELISA, specific detection).	15 pts	72 weeks	Correlation of ADAb and adverse events	2/15 patients (with ADAb) developed exantheme. ADAb associated with hypersensitivity reactions: OR(95%IC)=0.18(0.01-4.26), p>0.05 Results were not adjusted for confounders	Newcastle-Ottawa for cohort studies	Sum score: **, -,* Selection: ** Comparability: - Outcome: *
Abe T et al. 2006	RCT A placebo controlled, double-blind trial (the first 14 weeks) + open label trial (during 32 weeks)	Placebo and Pts with RA treated with IFX (during the double-blind trial: 3mg/kg or 10mg/kg; during the open label trial: 3mg/kg)	Measurement of ADAb (by RIA, specific detection) at baseline, at 14 weeks and at 20 weeks after the last infusion	129 pts	32 weeks	Safety of IFX	ADAb associated with hypersensitivity reactions: OR(95%IC)=1.31(0.64-2.69), p>0.05 Results were not adjusted for confounders	Cochrane RoB2 for RCT	Overall: high Randomisation: Low Intervention: high Missing outcome data: Low Outcome measurement: some concerns Selective reporting: high

Bendtzen K. et al, 2006	Retrospective observational study	Pts with RA treated with IFX (naïve to TNFi)	Measurement of ADAb (by RIA, specific detection) at baseline and after 1.5, 3 and 6 months	106 consecutive RA pts	>6 months	Discontinuation of therapy	30% of pts developed ADAb at 3 months. 22/106 (20%) pts discontinued therapy due to infusion reaction (within 18 months). Early formation of ADAb (3 months) was associated with subsequent discontinuation of therapy due to infusion reaction (within 18 months): p=0.001 OR(95%IC)=2.96(1.16-7.77); p<0.05 Results were not adjusted for confounders	Newcastle-Ottawa for cohort studies	Sum score: **, -,* Selection: ** Comparability: - Outcome: *
Wolbink GJ. et al, 2006	prospective observational study	Pts with RA treated with IFX	Measurement of ADA (by RIA, specific detection)	51 pts	1 year	Association of ADA with infusion reactions	22/51 pts developed ADA within 1 year of treatment. 3 pts developed infusion reactions (these 3 pts also developed ADA). OR(95%IC)=10.59(0.52-216.54); p>0.05 Results were not adjusted for confounders	Quality in Prognosis Studies Tool	1.Study participation: moderate 2.Attrition: high 3.Prognostic factor: low 4.Outcome: low 5.Confounding: high 6.Statistics: low

PTC-12: Measurement of ADAb is not recommended in the case of an injection-site reaction.

Study	**Study design**	**Population**	**Scope/Intervention**	**Study population**	**Follow-up**	**Outcome measures**	**Results**	**Tool used for RoB assessment**	**Risk of Bias**
Burmester GR. et al, 2017	Post-hoc analysis of several RCT	RA pts treated with TCZ	Measurement of ADAb (by bELISA, specific detection)	8974 pts from the different RCT	TCZ-SC (up to 3.5yr) TCZ-IV (up to 5yr)	Adverse effects	Incidence of ADAb: - 1.5% (n=47) pts who received TCZ-SC developed ADAb - 1.2% (n=69) pts who received TCZ-IV developed ADAb There was no clear impact of ADAb and safety (very low incidence of infusion reactions, hypersensitivity, injection-site reactions): - Hypersensitivity (leading to withdrawal): TCZ-SC=0.03%; Tcz-IV=0.2% - Injection-site reactions: TCZ-SC=0.1% Results were not adjusted for confounders	AMSTAR-2	**HIGH** ***3x YES*** ***3x partial-YES*** ***9x NO*** ***1x N/A***

PTC-13: Cost-effectiveness of TDM should be considered according to local context and standard of care.

Study	Study design	Population	Scope/Intervention	Study population	Follow-up	Outcome measures	Results	Tool used for RoB assessment	Risk of Bias
Krieckaert et al, 2015	Modeling approach (Markov Model) (The Netherlands)	RA ADA	Modelling to evaluate the cost-effectiveness of personalized treatment based on clinical response and drug level compared to usual care. Protocol, after 6 months of treatment : *A. EULAR good or moderate Response + DL <5mg/L : stop treatment* *B. EULAR good or moderate Response + DL [5-12mg/L] : continue* *C. EULAR good or moderate Response + DL >12mg/L : reduction of frequency* *D. No EULAR Response + DL>5mg/L : other bDMARD (not Anti-TNFa)* *E. No EULAR Response + DL<5mg/L : switch to another anti-TNF*	5000 simulations based on 272 patients, (81% female, mean age 54 (+/- 12); 74% MTX)	36 months	Quality Adjusted Life Years (QALYs), Costs	1.The simulations show a higher effectiveness for the cohort receiving personalized care. A personalized treatment permits a cost saving with a gain of QALYs in 72 % of simulations. The other 28% of simulations in this group were cost-savings but involve a loss of QALYs. 2. Considering a small loss of QALYs is usually acceptable, the probability of cost-effectiveness of personalized treatment was close to 100% versus usual care 3. For the whole cohort, after 3 years, the incremental cost effectiveness ratio was −666,541 euro per QALY gained using the societal perspective (- 2450.5 euro/patient, 816.8 euro/patient/year) and –646,266 euro per QALY from a healthcare perspective (- 2,376 euro/patient, -792 euro/patient/year)	Consensus on health Economic Criteria (CHEC)	Moderate 14x Yes 5x No
Jani et al, 2016	Microcosting study (England)	All rheumatic diseases Anti-TNF	To identify the direct medical costs associated with providing TNFi drug level and ADAb testing in clinical practice	Trough level analysis, in duplicate for each patient Analysis of 40 samples per batch	/	Cost of measurements /patient (both drug levels and ADAb)	Costs for monitoring one patient once by measurement of drug level and ADAb = £152.52/patient (147.68-159.24) Incremental costs due to: New appointment to acquire blood sample at trough level (67% of total cost ; £105.5/patient) Consumables *(ELISA kits, reagents, pipettes, well plates…)* (23% of total cost ; £37.47/patient)	Consensus on health Economic Criteria (CHEC)	Moderate 9x Yes 5x No 5x N/A

							Labour *(work time of clerical assistant, medical lab assistant, biomedical scientist)* (10% of total cost)		
Laine et al, 2016	Modeling approach (Markov Model) (Helsinki, Finland)	RA ADA ; IFX	Cost estimation of drugs levels and ADAb combined measurement compared to non-testing.	100 hypothetical patients per group Simulation from database (1137 samples for IFX ; 436 samples for ADA)	3 to 6 months	Cost	Cost of testing 100 patients = 20,000 Euro *(each drug test costs 200 euro)* In the non-testing cohort, ineffective treatment of 5 patients monitored every 3 months or 2,5 patients monitored every 6 months is estimated to cost 22,065 Euro Based on the fact that TDM can prevent ineffective treatment, it can be cost-saving as soon as 2,5-5 /100 patients are treated non-optimally for 3-6 months *(22,065 – 20,000 = 2,065 euro)*	Consensus on health Economic Criteria (CHEC)	High 6x Yes 13x No

abbreviations:

ABT: abatacept; ACPA: anti-citrullinated protein antibody; ACR: American college of rheumatology; ADA: adalimumab; ADAb: anti-drug antibodies; AE: adverse event; anti-ccp: anti cyclic citrullinated peptide; AS: ankylosing spondylitis; ASAS: assessment in spondyloarthritis international society; ASDAS: ankylosing spondylitis disease activity score; AU: arbitrary units; AUC: area under the curve; BASDAI: Bath ankylosing spondylitis disease activity index; bELISA: bridging enzyme-linked immunosorbent assay; BMI: body mass index; c: concentration; CD: Crohn's disease; CDAI: clinical disease activity index; cELISA: competitive enzyme-linked immunosorbent assay; ; Cmax: maximal concentration; Cmin: minimal concentration; Ctrough: trough concentration; DL: drug level; ESR: erythrocyte sedimentation rate; EULAR: European alliance of associations for rheumatology; CI: confidence interval; CPZ: certolizumab pegol; CRP: C-reactive protein; DAS28: disease activity in 28 joints; DAS44: disease activity in 44 joints; (b)DMARD: (biological) disease modifying anti-rheumatic drug; ECLIA: electrochemiluminescence assay; EIA: enzyme immunoassay; ELISA: enzyme-linked immunosorbent assay; ETN: etanercept; EQ-5D: EuroQol 5 dimensions; GEE: general equation estimation; GLM: golimumab; HAQ: health assessment questionnaire; HLA-B27: human leucocyte antigen B27; HMSA: homogeneous mobility shift assay; HR: hazard ratio; IBD: inflammatory bowel disease; ICC: intra-class correlation coefficient; IFMA: immunofluorometric assay; IFX: infliximab; IQR: interquartile range; LC-MS/MS: liquid chromatography coupled with tandem mass spectrometry; LEF: leflunomide; LFA: lateral-flow assay; LDA: low disease activity; LOCF: last observation carried forward; MTX: methotrexate; N/A: not available; NPV: negative predictive value; NSAID: non-steroidal anti-inflammatory drug; OR: odds ratio; PASI: psoriasis area severity index; PD: pharmacodynamics; PDUS: power Doppler ultrasound; PG: polyglutamates; PK: pharmacokinetics; POC: point-of-care method; PPV: positive predictive value; QALY: quality adjusted life years; QB: Quantum blue point-of-care method; PsA: psoriatic arthritis; pts: patients; RA: rheumatoid arthritis; rc: regression coefficient; RCT: randomized clinical trial; RF: rheumatoid factor; RGA: cell-based reporter gene assay; RIA radioimmunoassay; RoB: risk of bias; ROC: receiver operator curve; RTX: rituximab; SD: standard deviation; SDAI: simplified disease activity index; SF-36: short form 36; SJC: swollen joint count; (ax)SpA: (axial) spondyloarthritis; SPR: surface plasmon resonance point-of-care method; TCZ: tocilizumab; TDM: therapeutic drug monitoring; TJC: tender joint count; TSS: total Sharp score; IV: intravenous; SC: subcutaneous; TNFi: tumour necrosis factor inhibitor; UC: ulcerative colitis; W: week;