APPENDIX 2 Adverse events; Protocol violations, and protocolized treatment deviations

Adverse events

	COBRA (n=81)	**COBRA-light (n=81)**
Skin problems, (e.g. injection site reaction, dry skin), n (%)	61 (75)	64 (79)
Mild gastro-intestinal problems (e.g. nausea, diarrhea), n (%)	50 (62)	50 (62)
Liver enzyme increases, n (%)	3 (4)	9 (11)
Leucopenia, n (%)	1 (1)	3 (4)
Fractures, n (%)	1 (1)	1 (1)
Infections, n (%)	61 (75)	61 (75)
Problems related to the eye, n (%)	9 (11)	4 (5)
Other, n (%)*	11 (14)	5 (6)

* Other adverse events not mentioned on CRF

Protocol violations and protocolized treatment deviations

	COBRA (n=81)	**COBRA-light (n=81)**
Total number of patients with at least one violation/deviation	**49**	**47**
• Patients with at least one major violation	47	33
○ First occurrence at or after week 26	5	3
• Patients with only minor violations, at or after week 26	0	2
• Patients with only protocolized deviations, at or after week 26	5	14
Total number of violations/deviations	**91**	**70**
• Major violations	71	49
○ First occurrence at or after week 26	66	46
• Minor violations	1	9
• Protocolized treatment deviations	21	12
Major violations (week 26 – 52)*		
Due to compliance physician	37	34
– decreased intensity of therapy	23	22
– increased intensity of therapy	14	12
Due to compliance patient	19	11

– decreased intensity of therapy	14	11
– increased intensity of therapy	5	0
Due to administrative mistakes	9	1
– decreased intensity of therapy	6	1
– increased intensity of therapy	3	0
Due to physician mistakes		
– increased intensity of therapy	1	0
Minor violations (week 26 – 52)*		
Delayed etanercept start	1	1
Etanercept start preceding study visit	0	1
No etanercept start due to other diseases and anxiety for exacerbation of disease activity	0	1
No etanercept start, in expectation of MTX effect	0	3
Temporary increase prednisolone due to active RA	0	3
Protocolized treatment deviations (week 26 – 52)*		
No full dose MTX due to AE's	7	1
Decreased prednisolone dose due to AE's	0	1†
Increased prednisolone dose due to active RA	3‡	1
No etanercept start due to infections or AE's	2	2
Delayed etanercept start due to infections or AE's	0	2
Stop MTX due to AE's	2	0
Stop SSZ due to AE's	4	0
Stop etanercept due to AE's	1	3
Secondary ineligibility of patient e.g. positive tuberculin test and wish to become pregnant		
- decreased intensity of therapy	2	2

*Frequently more than one violation/deviation per patient. †Prednisolone dose 5 mg/day.

‡Prednisolone dose 15 mg/day.

AE: adverse event. MTX: methotrexate; RA: Rheumatoid Arthritis. SSZ: sulfasalazine.