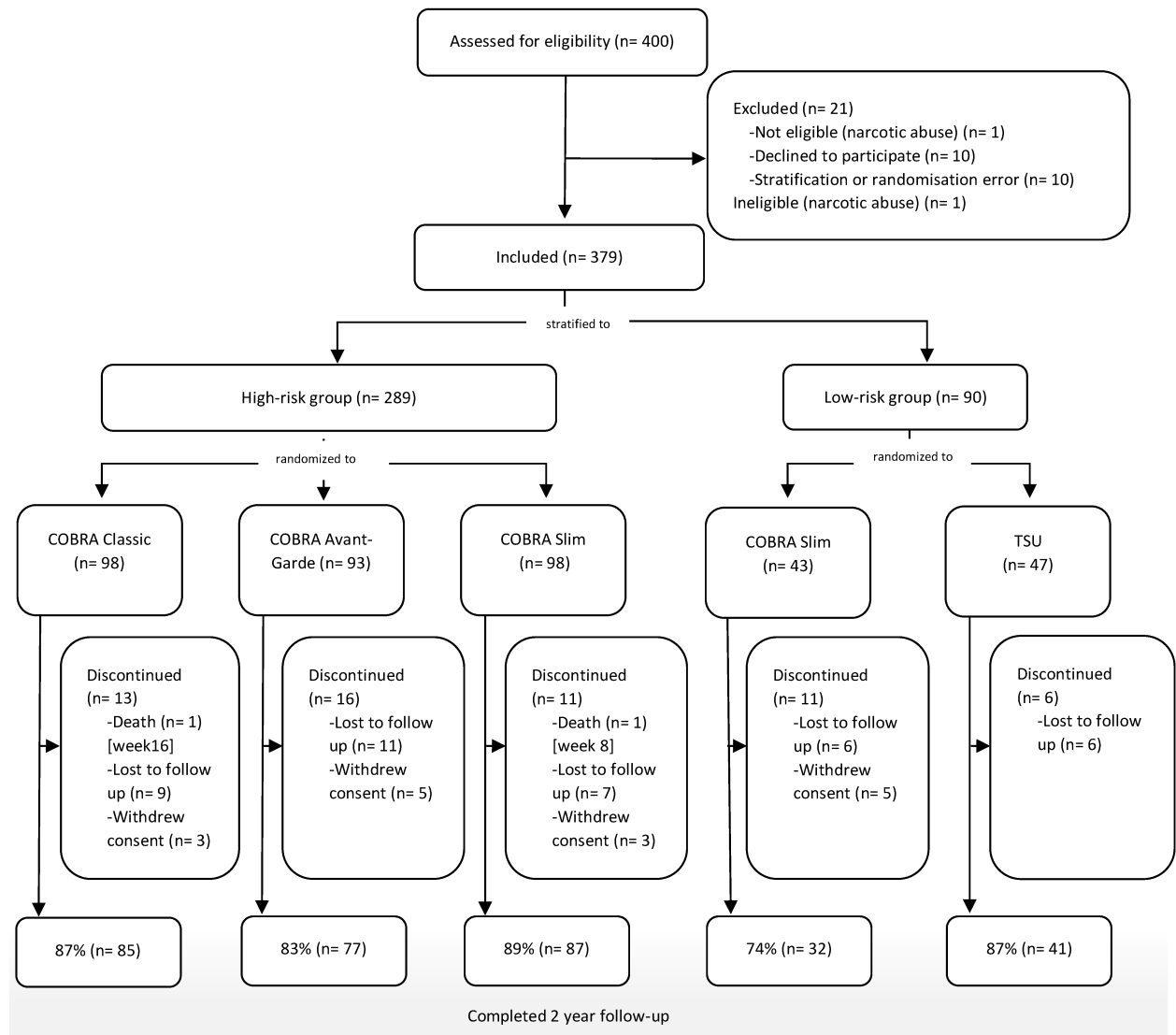


SUPPLEMENTAL MATERIAL

Supplemental Figure 1: Flow chart of participants during the 2-year trial. All randomized patients.

Supplemental Table 1: Average costs per patient (incurring in the resource) for the different categories of health care utilisation over the 2 years follow-up of complete cost cases (n=328) per treatment scheme.

High-risk			
	COBRA Classic n=88	COBRA Avant-Garde n=77	COBRA Slim n=88
Health care	Mean costs € (SD)		
Rheumatologist consultations	839.63 (82.3)	853.26 (55.5) *	872.75 (90.4)
Hospitalizations†	6 386.85 (6 575.1) [n=28]	6 131.87 (5 150.7) [n=21] **	6 813.47 (6 461.5) [n=24]
Laboratory (safety blood sample)	201.05 (30.9)	208.05 (25.8) *	216.8 (22.4)
RF	8.68 (1.7)	8.70 (1.6) *	9.11 (1.0)
Anti CCP	42.63 (8.8)	43.24 (8.0) *	45.47 (5.6)
X-rays hands and feet	213.10 (35.1)	215.42 (28.7)	220.23 (26.2)
Medication			
csDMARDs	321.73 (144.4)*	559.82 (184.1) **	265.68 (163.0)
MTX	164.41 (76.9)	139.11 (59.9) **	184.81 (87.2)
SSZ†	125.44 (69.8) **	-	82.53 (25.4) [n=3]
LEF†	241.25 (174.4) [n=13]	422.93 (207.3) **	281.07 (144.3) [n=27]
HCQ†	-	-	43.03 (48.9) [n=2]
GCS	504.51 (320.8) **	293.88 (143.7)	292.78 (178.9)
bDMARDs†	10 482.98 (6 677.1) [n=17]**	9 988.42 (5691.8) [n=13]	7 623.04 (2 671.3) [n=11]
Analgesics†	89.72 (109.9) [n=73]	97.02 (140.8) [n=68]	141.69 (247.0) [n=76]
Low-risk			
	COBRA Slim n=34	Tight-Step-Up n=41	
Health care	Mean costs € (SD)		
Rheumatologist consultations	884.05 (62.7)	889.33 (84.1) *	
Hospitalizations†	3 627.28 (2 778.4) [n=10]	4 302.19 (3 210.4) [n=8] **	
Laboratory (safety blood sample)	214.17 (22.7)	217.95 (27.6) *	
RF	8.84 (1.6)	9.01 (1.0) *	
Anti CCP	44.13 (7.2)	44.98 (5.2) *	
X-rays hands and feet	214.59 (28.3)	219.66 (24.1) *	
Medication			
csDMARDs	260.67 (178.5)	285.99 (196.9)	
MTX	191.96 (97.8)	181.69 (98.2)	
SSZ†	-	24.89 (0.7) [n=2] **	
LEF†	313.22 (143.5) [n=9]	307.99 (191.5) [n=15] **	
GCS†	266.88 (107.2)	104.01 (197.8) [n=23] **	
bDMARDs†	5 162.0 (3393.1) [n=7]	13 224.45 (9 861.5) [n=5] **	
Analgesics†	104.60 (243.5) [n=28]	205.67 (243.5) [n=38] *	

Data are expressed as mean and standard deviation unless otherwise specified.

*p<0.05 **p<0.001 in mean cost difference with Kruskal Wallis or Mann-Whitney U, taking COBRA Slim as reference

RF= rheumatoid factor, anti-CCP= anti-citrullinated peptide antibody, csDMARDs= conventional synthetic disease modifying anti-rheumatic drugs, MTX= methotrexate, SSZ= sulfasalazine, LEF= leflunomide, HCQ= hydroxychloroquine, GCS=glucocorticoids, bDMARDs= biological disease modifying anti-rheumatic drugs, Analgesics= including paracetamol, non-steroidals, tramadol and opioids

†Not everyone incurred in these resources and therefore the n is different.

Supplemental Table 2: Disutilities (EQ-5D) per adverse event with their reference cohort which was used for discounting. Lowest literature available disutility was assumed.

Adverse event	Disutility	Source of disutility/assumptions
Allergy	0.02	Olesen 2016
Allergic rhinitis	0.03	Al-Digheari 2018
Alopecia	0.031	Hagiwara 2018
Anaemia	0.01	Park 2015
Angina	0.04	Sullivan 2006
Anxiety disorders	0.04	Sullivan 2005
Aphthosis	0.14	Lloyd 2006-assumed same stomatitis
Arrhythmia	0.02	ICER 2017
Arthralgia	0.041	Hagiwara 2018
Arthritis	0.04	George 2014
Arthrosis	0.04	Arrospide 2019
Asthma	0.11	Hernandez 2018
Back pain (chronic)	0.09	Tsiplova 2016
Blindness/low vision	0.05	Sullivan 2006
Bone marrow suppression	0.218	Nafees 2008 assumed same as thrombocytopenia
Breast cancer	0.12	Wood 2017
Cataract	0.02	Sullivan 2005 and 2006
Cervicalgia	0.041	Hagiwara 2018 assumed same as arthralgia
Cholelithiasis	0.03	Sullivan 2006
COPD	0.02	Hong 2015
COPD minor exacerbation	0.108	Einarson 2015
COPD major exacerbation	0.287	Einarson 2015
Cough	0.05	Doyle 2008
Chronic bronchitis	0.04	Sullivan 2011
Cystitis	0.218	Stein 2017 assumed same as UTI
Depression	0.03	Park 2019
Diabetes	0.06	Nafees 2008 assumed as hyperglycaemia
Diarrhoea	0.176	Stein 2017
Dyspepsia	0.10	Mahadeva 2010
Dyspnoea	0.219	Lachaine 2015a
Ear infection	0.218	Stein 2017 assumed same as infection
Edema	0.085	Hagiwara 2018
Eczema	0.06	Moberg 2009
Fatigue	0.115	Lloyd 2006
Fever	0.15	Lloyd 2006
Fibromyalgia (very mild)	0.1	Luo 2011
Fractures of wrist or hip	0.04	Hagino 2009
Fractures (all others)	0.07	Matza 2014 assumed as surgery for stabilization of bone
Foot deformity (acquired)	0.02	Sullivan 2005
Gastric ulcer	0.11	Groeneveld 2001
Gastritis	0.01	Sullivan 2005
Gastroenteritis	0.04	Sullivan 2006
Hip/knee pain	0.17	Kontodimopoulos 2009
Hyperglycaemia	0.06	Nafees 2008
Hypertension	0.02	ICER 2017
Hypotension	0.02	ICER 2017

Infection	0.218	Stein 2017
Interstitial lung disease	0.218	Stein 2017 assumed same as pneumonitis or pulmonary infiltrates
Irritable bowel syndrome	0.13	Akehurst 2002
Insomnia	0.28	Wu 2014
Knee replacement surgery	0.1	Øystein 2013
Leucocytosis	0.09	Hagiwara 2018
Leukopenia	0.09	Nafees 2008
Liver disturbances	0.16	Arrospide 2019
Lower respiratory tract infection	0.218	Stein 2017 assumed same as pneumonia
Migraine	0.03	Sullivan 2005, 2006 and 2011
Myalgia	0.123	Hagiwara 2018
Mycosis	0.218	Stein 2017 same as fungal infection
Nausea	0.051	Nafees 2008
Neck/shoulder pain	0.08	Burstrom 2001
Neutropenia	0.09	Nafees 2008
Oesophagitis	0.01	Areia 20014
Oral mucositis	0.087	Hagiwara 2018
Osteoporosis	0.03	Guillemin 2013
Pain	0.29	Wu 2014
Pericarditis/pleuritis	0.218	Stein 2017 assumed same as infection
Prolonged ileus/ bowel obstruction	0.11	Worbes-Cerezo 2019
Prostatic disorder	0.02	Sullivan 2006
Pruritus	0.03	Sullivan 2011
Psoriasis	0.02	Sullivan 2011
Pulmonary embolism	0.02	Tavoly 2016
Renal cell carcinoma	0.09	de Groot 2018
Renal insufficiency	0.15	Park 2016
Renal/ureteral calculus	0.02	Sullivan 2011
Septic bursitis	0.218	Stein 2017 assumed as sepsis
Stomatitis	0.14	Tabberer 2006
Thrombocytopenia	0.09	Nafees 2008
Upper respiratory tract infection	0.218	Stein 2017 assumed same as infection
Urinary tract infection	0.218	Stein 2017
Urticaria	0.03	Sullivan 2011 assumed same as pruritus

COPD=chronic obstructive pulmonary disease

UTI=urinary tract infection

ICER=The Institute of Clinical and Economic Review