Lead team presentation
Sarilumab for treating moderate to severe active rheumatoid arthritis after the failure of disease-modifying anti-rheumatic drugs

Clinical effectiveness

1st Appraisal Committee meeting, 15 August 2017

Committee C

Evidence Review Group: School of Health and Related Research (ScHARR), The University of Sheffield

Lead team: Andrew Renehan, David Chandler

Abbreviations (shaded rows contain comparator technologies)

ABT	Abatacept
ACR20/50/70	20%/50%/70% improvement in American College of Rheumatology Criteria
ADA	Adalimumab
BAR	Baricitinib
bDMARD	Biological DMARD
cDMARD	Conventional DMARD
CTZ	Certolizumab pegol
DAS28/44	Disease activity score in 28/44 Joints
DMARD	Disease-modifying anti-rheumatic drug
ETN	Etanercept
EULAR	European League against Rheumatism
GOL	Golimumab
HAQ-DI	Health Assessment Questionnaire–Disability Index

IFX	Infliximab
mTSS	Modified Total Sharp Score
MTX	Methotrexate
Q2W	Every 2 weeks
NRI	Non-responder imputation
QD	Once daily
QW	Weekly
RA	Rheumatoid arthritis
RTX	Rituximab
SAR	Sarilumab
SSZ	Sulfasalazine
TCZ	Tocilizumab
TNF	Tumour necrosis factor
TNFi	Tumour necrosis factor inhibitor
TOFA	Tofacitinib

Key issues: Clinical effectiveness

- Is SAR comparable to the bDMARDs in clinical effectiveness in moderate and severe RA?
- Is SAR effective as a monotherapy in TNFi-IR patients?
- Are the Committee comfortable with the conclusion that the company NMA results are unlikely to change?

Key issues: Cost effectiveness

- Do the Committee accept the ERG's changes to the company model:
  - Using a non-linear approach (Norton et al) for HAQ trajectory
  - Including the option for patients to receive treatment for severe disease when in the moderate state and their DAS28 score reaches 5.1.
- Is SAR comparable to the bDMARDs in both clinical and cost effectiveness?
- Is SAR monotherapy cost-effective?

Rheumatoid arthritis

- An inflammatory autoimmune disease that typically affects the synovial tissue of the small joints of the hands and feet but can affect any synovial joint, causing swelling, stiffness, pain and progressive joint destruction.
- Disease severity measured using the composite disease activity score (DAS28), includes assessment of 28 joints for swelling/tenderness, the patient's assessment of health and erythrocyte sedimentation rate or C-reactive protein
- Associated with increased mortality and increasing disability.
- No cure

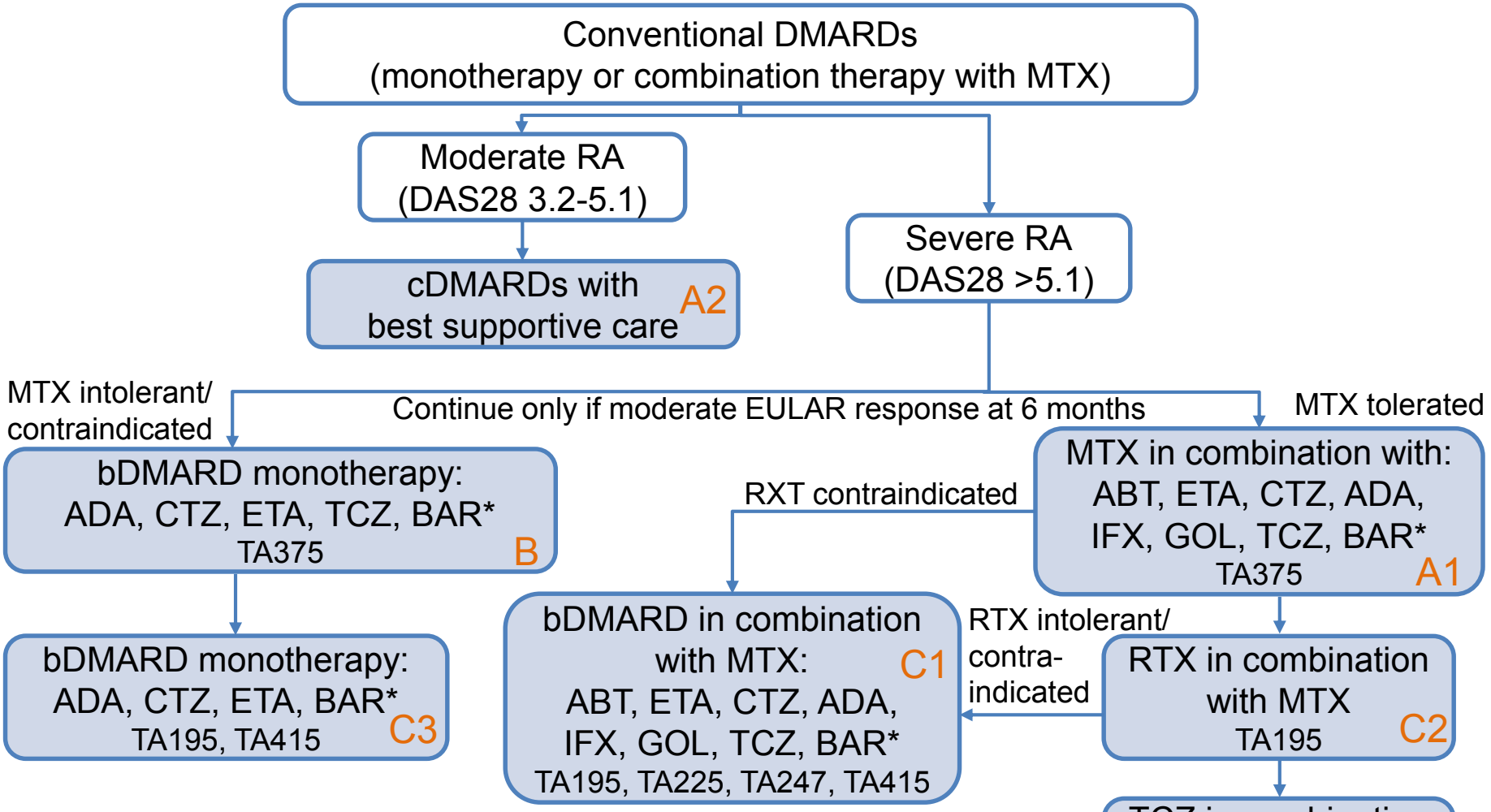
Relevant NICE technology appraisals		
TA	**Treatment**	**Population**
415 2016	CTZ + MTX	Adults whose disease has responded inadequately to, or who cannot tolerate, other DMARDs including at least 1 TNF inhibitor, only if: • disease activity is severe and RTX is contraindicated or not tolerated
	CTZ monotherapy	As above but only if: • RTX therapy cannot be given because MTX is contraindicated or not tolerated
375 2016	ADA, ETN, IFX, CTZ, GOL, TCZ, ABA (all + MTX)	Disease is severe (disease activity score [DAS28] >5.1) and has not responded to intensive therapy with a combination of cDMARDs
	ADA, ETN, CTZ, TCZ monotherapy	As above but for people who cannot have MTX because of contraindications or intolerance
247 2012	TCZ + MTX	Disease has responded inadequately to DMARDs and a TNF inhibitor and the person cannot have RTX because it is contraindicated or not tolerated, and TCZ is used as described for TNF inhibitor treatments in TA195, specifically the recommendations on disease activity or the disease has responded inadequately to 1 or more TNF inhibitor treatments and to RTX
225 2011	GOL + MTX	Adults whose RA has responded inadequately to other DMARDs, including a TNF inhibitor, if it is used as described for other TNF inhibitor treatments in TA195
195 2010	RTX + MTX	Adults with severe active RA with an inadequate response to, or are intolerant of, other DMARDs, including at least 1 TNF inhibitor.
	ADA, ETN, IFX, ABT (all + MTX)	As for RTX + MTX but for people who cannot have RTX because of contraindications or intolerance
	ADA, ETN monotherapy	As for RTX + MTX but for people who cannot have RTX because they have a contraindication to, or intolerance of MTX

Details of the technology	
Technology	Sarilumab (Kevzara; Sanofi)
Marketing authorisation	Treatment of moderate to severe active RA in adult patients • who have responded inadequately to, or • who are intolerant to one or more DMARDs − used as monotherapy or in combination with MTX
Mechanism of action	interleukin-6 inhibitor
Administration	Subcutaneous injection: once every 2 weeks. 2 doses available (as a single use pre-filled pen [PFP] or pre-filled syringe [PFS]):150 mg and 200 mg
Acquisition cost	List price per PFS/PFP: 150 mg or 200 mg: £457.69 Annual cost per patient: £11,900 Company have agreed a confidential PAS with a simple discount on the list price

Innovation

- Only IL-6 receptor inhibitor available as an auto-injectable pre-filled pen, administered subcutaneously every other week by the patient at home
- 2 doses available (200 mg and 150 mg) enabling dose reduction as needed. It is also stable out of the fridge for up to 14 days
  - TCZ is currently the only other IL-6 receptor inhibitor available. It is administered by IV infusion every 4 weeks or by SC injection once a week.
  - Once removed from the refrigerator, TCZ must be administered within 8 hours

Treatment pathway



- Shaded boxes=Potential positions of SAR in the pathway
- A1-C4 =Patient populations referred to in the company submission
- * Tofacitinib is currently being appraised by NICE at the same positions as BAR in the treatment pathway

Decision problem: Population & intervention

	Final scope issued by NICE	ERG comments
Population	Adults with moderate-to-severe, active RA, whose disease has not responded adequately to, or who are intolerant of cDMARDs or bDMARDs	None.
Intervention	Sarilumab monotherapy or in combination with cDMARDs	None.

Decision problem: Comparators

	Final scope issued by NICE	ERG comments

Comparators	People with moderate active RA that has not responded adequately to, or who are intolerant of therapy with cDMARDs
	• Best supportive care
	People with severely active RA that has not responded adequately to therapy with cDMARDs only
	• Biologic DMARDs in combination with MTX (ADA, ETN, IFX, CTZ, GOL, TCZ, ABT)
	• ADA, ETN, CTZ, or TCZ (each as monotherapy)
	People with severely active RA that has not responded adequately to therapy with DMARDs including at least 1 TNF inhibitor
	• RTX in combination with MTX
	• When RTX is contraindicated or withdrawn due to adverse events:
	  ○ ABT, ADA, CTZ, ETN, IFX, TCZ, or GOL, each in combination with MTX
	  ○ ADA, ETN or CTZ (each as monotherapy)
	People with severe, active disease despite treatment with bDMARDs:
	  ○ TCZ in combination with MTX, best supportive care
		Company did not consider biosimilars for ADA and RTX.

Decision problem: Outcomes and economic analyses

	Final scope issued by NICE		ERG comment
Outcomes	The outcome measures to be considered include:		No data identified on extra-articular manifestations related to sarilumab
	• disease activity • physical function • joint damage • pain • mortality	• fatigue • radiological progression • extra-articular manifestations • adverse effects of treatment • health-related quality of life	
Economic analysis	• Cost-effectiveness should be expressed in terms of incremental cost per QALY • Time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared • Costs will be considered from an NHS and Personal Social Services perspective • Patient access schemes for the intervention or comparator technologies will be taken into account • Availability and cost of biosimilar products should be taken into account		None.

Decision problem: Subgroups

	Final scope issued by NICE	ERG comment
Subgroups to be considered	If evidence allows, the appraisal will consider subgroups of people identified as: • Having had primary or secondary failure of response to the first TNFi; or • Having seronegative or seropositive antibody status • People with moderate disease activity (DAS28 between 3.2 and 5.1) and severe active disease (DAS28 greater than 5.1)	No data were identified to enable a comparison on previous TNF inhibitor failure or seropositive/seronegative antibody status

Patient perspective-1
Living with rheumatoid arthritis (National Rheumatoid Arthritis Society submission)

- A chronic disease with no cure
- A diagnosis of RA can be extremely distressing
- Impact can be life-changing
- Major affect on all aspects of life
  - *Personal confidence and future relationships in younger people*
  - *Working life and job security*
  - *Caring for young children*
  - *Retirement plans*
- Not only physical but emotional wellbeing too
- Impacts the whole family

Patient perspective – 2
What patients want from treatments

- Reduction in the physical symptoms of pain and inflammation
- Reduction in fatigue – major issue to patients
- Get the disease under control
- Aim to avoid permanent disability
- Maintain independence
  - *"get on with work and life"*
- Treatments need to have low adverse events
- Further options needed for people with moderate or severe disease, which has not responded to cDMARDs or a TNFi
- No disadvantages were identified by the patient group for sarilumab

Submissions from clinical experts

- Current evidence suggests that IL-6 inhibitors (SAR, TCZ) appear to have similar clinical effectiveness and adverse effect profiles
- Compared with some other bDMARDs, SAR is licensed as a monotherapy in people where co-administration of methotrexate is contraindicated or not tolerated
- Differences in injection device and dosing means people may find it easier to administer the drug.

Clinical effectiveness – included studies overview

Trial name	Population and number enrolled	Intervention	Comparators	Primary outcome
MOBILITY A	MTX-IR, N=306	• SAR + MTX • SAR doses: 100mg QW, 150mg QW, 100mg Q2W, 150mg Q2W, 200mg Q2W	• PBO + MTX	• ACR20 response at week 12
MOBILITY B	MTX-IR, N=1197	• SAR + MTX • SAR doses: 150mg Q2W, 200mg Q2W	•PBO + MTX	• ACR20 response at Week 24 • Change in HAQ-DI from baseline to Week 16 • Change in mTSS from baseline to Week 52
MONARCH	MTX-IR, N=369	• SAR monotherapy • dose 200mg Q2W	• ADA monotherapy • ADA dose 40mg Q2W	• DAS28-ESR at week 24
TARGET	TNFi-IR, N=546	• SAR + cDMARD • SAR doses: 150mg Q2W, 200mg Q2W	• PBO + cDMARD	• ACR20 response at Week 24 • Change in HAQ-DI from baseline to Week 12
ASCERTAIN	TNFi-IR, N=202	• SAR + cDMARD • SAR doses: 150mg Q2W, 200mg Q2W	• TCZ + cDMARD • TCZ dose 4-8mg/kg	• Safety
EXTEND	cDMARD/TNFi-IR, N=2023	• SAR + cDMARD, • SAR monotherapy	• NA, Extension study	• Safety

Clinical effectiveness Results: ACR 20

- SAR+MTX (both licenced doses) showed a statistically significant improvement in ACR20 compared with PBO+MTX in MOBILITY-A (at week 12) and MOBILITY-B (at week 24)

- SAR 200mg Q2W showed a statistically significant improvement in ACR20 compared with ADA 40mg Q2W in MONARCH (at week 24)

- SAR+MTX (both licenced doses) showed a statistically significant improvement in ACR20 compared with PBO+ cDMARD in TARGET (at week 24)

- The company did not report comparative statistics for ASCERTAIN as the study was powered for safety not effectiveness. However it noted that [redacted]

Clinical effectiveness Results: adverse events

cDMARD-IR trials

- Adverse event rates reported in MOBILITY-A and B were higher in SAR groups (53%-78%) compared with PBO (47%-61%).
- In the MONARCH trial, ADA and SAR had similar AE rates (63.6% and 64.1% respectively).

TNFI-IR trials

- [redacted]

Company NMA overview

- No direct evidence for all comparators.
- Company performed NMA separately for:
  - cDMARD-IR (further separated into combination therapy and monotherapy)
  - bDMARDs-IR
- Efficacy outcome measures included:
  - ACR response
  - HAQ-DI
  - EULAR
  - DAS28
  - mTSS

Company NMA results for the cDMARD-IR population (combination)

	ACR at week 24	EULAR good response at Week 24	EULAR moderate-to-good response at Week 24
SAR 200 mg combination vs cDMARDs combination	statistically superior	statistically superior	statistically superior
SAR 200 mg combination vs bDMARDs combination	Comparable efficacy	statistically superior to ABT, IFX, TCZ 4mg IV, RTX, SAR 150mg combinations Comparable efficacy to GOL, TCZ 8mg IV combinations	statistically inferior to CTZ Comparable efficacy to GOL, IFX, TCZ 4mg IV and 8mg IV, RTX and SAR 150mg combinations

**ACR20/50 only

Company NMA results for the cDMARD-IR population (monotherapy)

	ACR at week 24	EULAR good response at week 24	EULAR moderate-to-good response at week 24
SAR 200 mg monotherapy vs cDMARDs monotherapy	statistically superior	statistically superior	statistically superior
SAR 200 mg monotherapy vs bDMARDs monotherapy	statistically superior to ADA, sirukumab 50 mg** Comparable efficacy to CTZ, ETN, sirukumab 100mg, TCZ 8mg and tofacitinib	statistically superior to ADA Comparable efficacy to TCZ 8mg	statistically superior to ADA Comparable efficacy to TCZ 8mg

Company NMA results for the TNFi-IR population

	ACR at week 24	EULAR good response at week 24	EULAR moderate-to-good response at week 24
SAR 200mg combination vs cDMARDs *combination*	statistically superior	statistically superior	statistically superior
SAR 200mg combination vs bDMARDs *combination*	statistically superior to baricitinib 2mg combination, sirukumab 50mg combination on ACR50 only. Comparable efficacy to other bDMARD combinations on all ACR outcomes	statistically superior to RTX combination Comparable efficacy to ABT, SAR 150mg combinations	statistically inferior to TCZ 8mg, RTX combinations Comparable efficacy to ABT, GOL, SAR 150mg combinations

- The company did not identify any evidence for SAR monotherapy in the TNFi-IR population.

Company NMA – ERG comments (I)

The ERG considers that some uncertainty remains with the company's base case NMA results because:

- Using a fixed effect model underestimates uncertainty in the treatment effects.
- MOBILITY B and TARGET trial designs may overestimate the relative treatment effect of SAR combination therapy compared with cDMARDs.

Company NMA – ERG comments (II)

- The ERG requested a number of changes to the company NMA :
  - See page 72-73 of ERG report.
- The company provided the results for the cDMARD-IR population on ACR responses only.
- Company concluded that the updated results were in line with the original analysis and the conclusion that SAR 200mg in combination with cDMARD showed comparable efficacy to other bDMARDs was unchanged.
- ERG agreed but noted that the results from the requested NMA may be numerically different from the original NMA in the CS

Key issues: Clinical effectiveness

- Is SAR comparable to the bDMARDs in clinical effectiveness in moderate and severe RA?
- Is SAR effective as a monotherapy in TNFi-IR patients?
- Are the Committee comfortable with the conclusion that the company NMA results are unlikely to change?

Lead team presentation
Sarilumab for treating moderate to severe active rheumatoid arthritis after the failure of disease-modifying anti-rheumatic drugs

Cost effectiveness

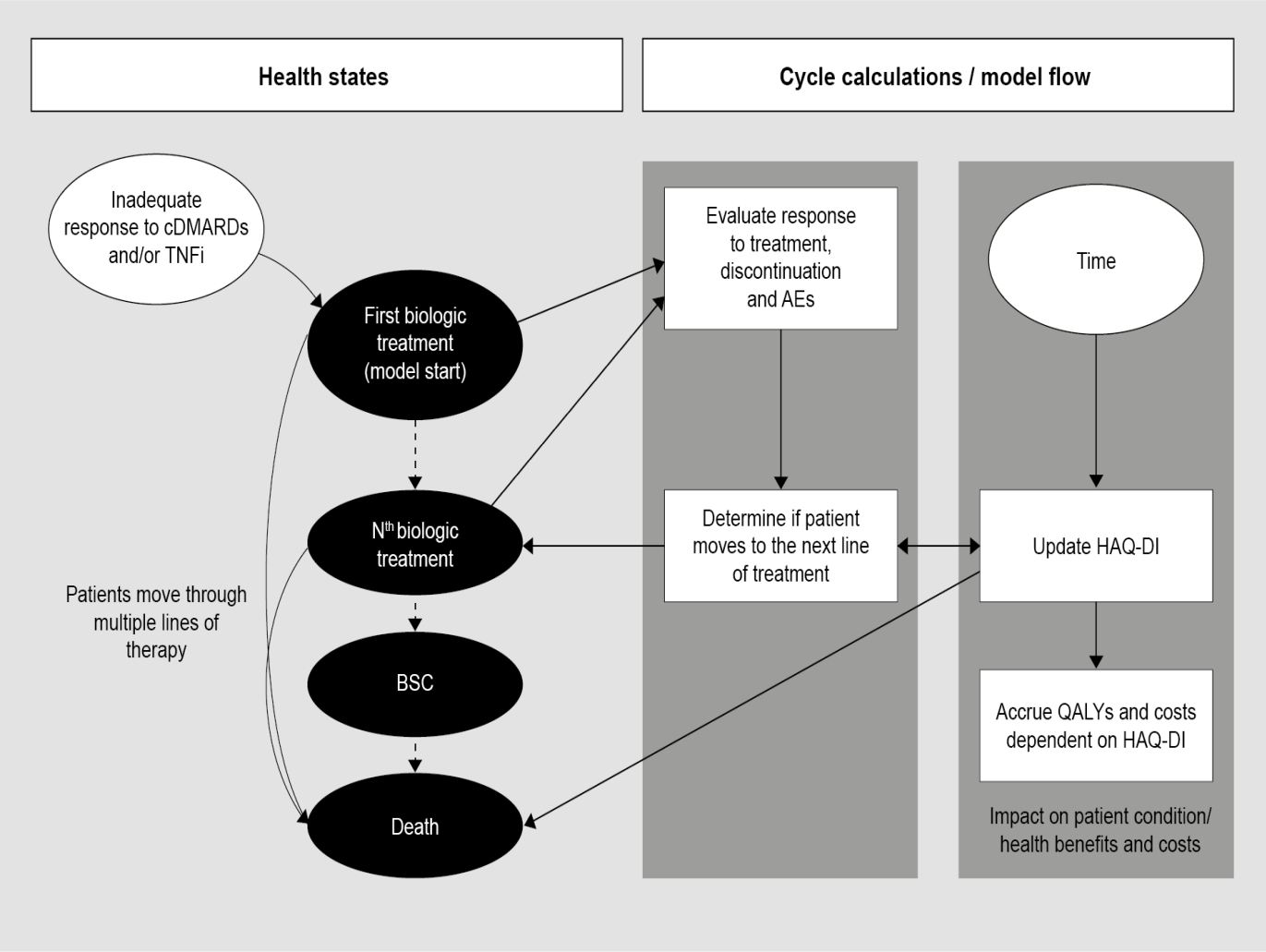
1st Appraisal Committee meeting, 15 August 2017

Committee C

Evidence Review Group: School of Health and Related Research (ScHARR), The University of Sheffield

Lead team: Nigel Langford

Company cost effectiveness model structure



- Patient-level Markov model
- 6 month cycle length and 100 year time horizon
- Utilities estimated from HAQ-DI using TA375 algorithm
- Estimated treatment effect (EULAR response) from company NMA

Key: BSC=best supportive care; HAQ-DI=Health Assessment Questionnaire Disability Index; TNFi=tumour necrosis factor inhibitor

Treatment sequences

- Different treatment sequences were evaluated for each of the populations.
- The model treatment sequences included a ‘TNFi bundle’ in the base case. The ‘TNFi bundle’ used the pooled efficacy of TNFis with the price weighted according to the estimated market share of each TNFi.
- The ERG noted that sequences were not consistent with those accepted in TA375 and at clarification the company updated these sequences as requested by the ERG
  - The ERG noted that for the TNFi-IR RTX-ineligible population the company had mistakenly added a second line of biologics.
  - In the ERG exploratory analyses these have been corrected
  - Full treatment sequences on page 87-89, tables 42-48 of ERG report

Company cost effectiveness model: Resources and costs

- Company model included costs associated with drug acquisition, administration and monitoring, and hospitalisation and serious infection
- SAR has a confidential PAS
- PASs for CTZ and GOL were incorporated (not confidential)
- Biosimilars for RTX and ADA were not included in the company's analyses
- Administration costs based on TA375 and inflated to 2015/16 prices

Treatment effectiveness

- The company used absolute EULAR responses to inform treatment effectiveness (mapped from ACR responses in the trials identified in the NMA)
- The company assumed, due to lack of evidence, that the effectiveness of treatments in TNFi-IR patients who are MTX-ineligible would be the same as those treatments for TNFi-IR MTX-eligible.
- [redacted]

Absolute EULAR responses estimated by the company : cDMARD-IR

- [redacted]

Absolute EULAR responses estimated by the company: cDMARD-IR – MTX ineligible

- [redacted]

Absolute EULAR responses estimated by the company: TNFi-IR

- [redacted]

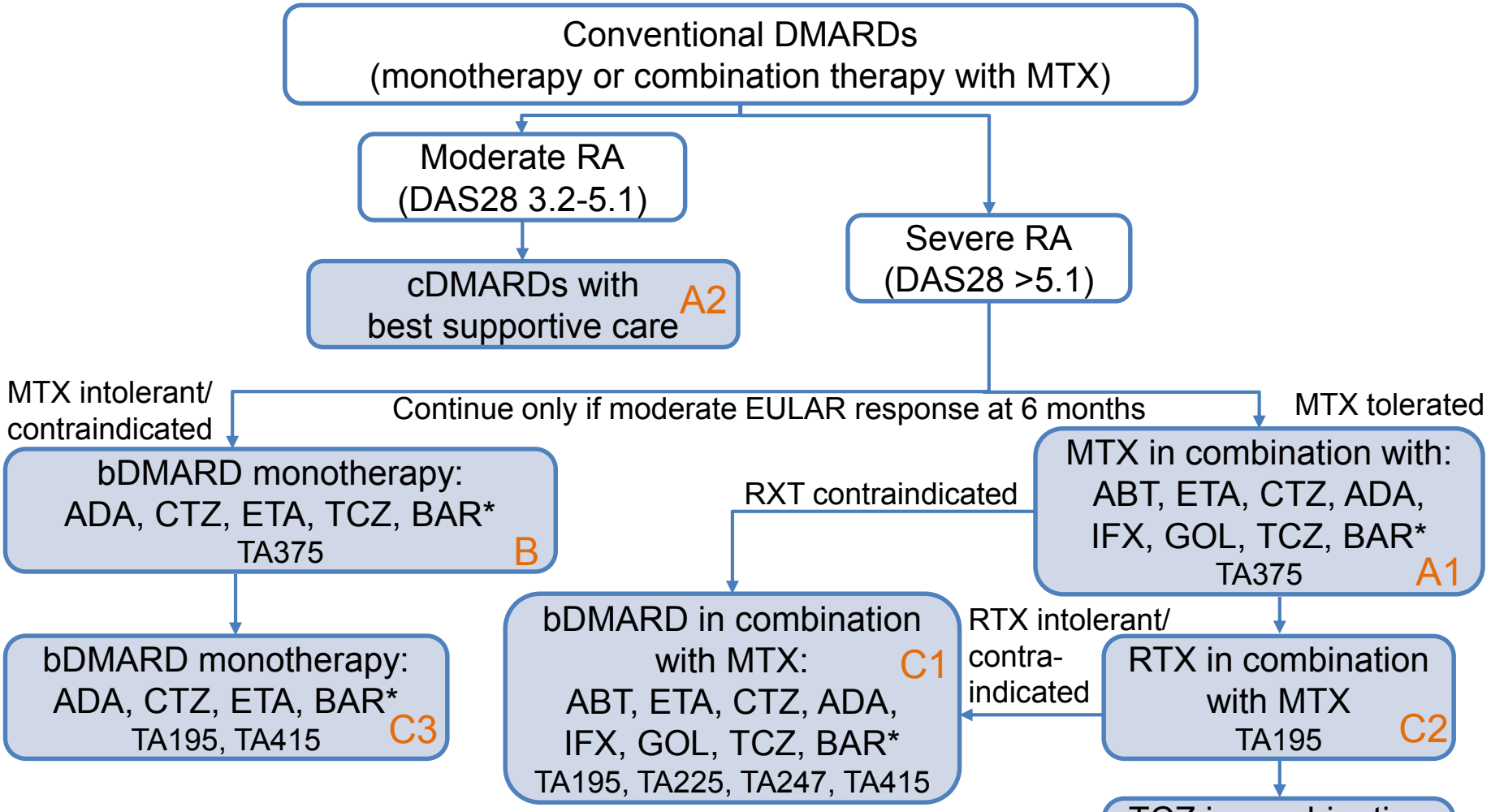
Treatment effectiveness: HAQ score

- In the company model, after 6 months, patients are assumed to be assessed for response to treatment.
- Patients who achieved a moderate or good EULAR response were assumed to have an associated reduction in HAQ score which is assumed independent of treatment.
- The ERG noted that the company have used a linear approach to HAQ score progression
- The Appraisal Committee in TA375 favoured a non-linear approach advocated by the AG
- ERG concluded that a linear approach would have a significant favourable effect for SAR when compared with cDMARDs.
- The ERG further noted that the linear method is not likely to significantly affect the conclusions in the comparison of SAR with bDMARDs, due to similar efficacy levels

Company cost effectiveness model: Utilities

- EQ-5D utility data was not available for all comparators across all patient populations. Company used literature review to inform health-related quality of life (HRQoL).
- The ERG noted that Hernandez *et al.*, which estimated EQ-5D based on patient characteristics used in TA375 was not included in the company's analysis.
- The company used Malottki et al because they were concerned that the method used in TA375 may double count the effects of pain since the HAQ-DI assessment already includes pain.
- Following a request at clarification by the ERG the company implemented the mapping of Hernandez *et al*
- The rates of serious infections for SAR and BSC were taken from the pivotal studies MOBILITY-B for cDMARD-IR + MTX, MONARCH for cDMARD-IR MTX-IR and TARGET for the remaining populations.

Treatment pathway



- Shaded boxes=Potential positions of SAR in the pathway
- A1-C4 =Patient populations referred to in the company submission
- *Tofacitinib is currently being appraised by NICE at the same positions as BAR in the treatment pathway

Base-case results

- The company undertook analyses on the following groups:
  - cDMARD-IR patients with severe RA who can tolerate MTX (A1)
  - cDMARD-IR patients with severe RA who cannot tolerate MTX (B)
  - TNFi-IR patients with severe RA who can tolerate RTX and MTX (C2)
  - TNFi-IR patients with severe RA who cannot tolerate RTX (C1)
  - TNFi-IR patients with severe RA who cannot tolerate MTX (C3)
  - TNFi-IR patients who have received RTX and MTX (C4)
  - cDMARD-IR patients with moderate RA and DAS28 between 4.0 and 5.1 who can tolerate MTX (A2).
- In the company's original base case SAR+MTX was estimated to either dominate all its comparators or result in ICERs lower than £20,000 per QALY in all populations except in:
  - cDMARD-IR patients with moderate RA and a DAS28 score higher than 4.0 **(£22,275 per QALY gained)**
  - TNFi-IR patients for whom RTX was an option **(£104,012 per QALY gained)**
- The ERG identified a number of issues which the company resolved at clarification (see section 5.3 pages 104-105 of ERG report).

ERG exploratory analyses

1) ***Progression of HAQ score for patients on cDMARDs and BSC****:*

- The ERG implemented a non-linear HAQ progression based on the latent classes' approach (Norton et al.) which was also implemented in the model developed by the AG in TA375

2) ***Transition from moderate to severe RA***

- At clarification the company updated its model to assume that those with moderate disease would progress to severe disease. The ERG noted that this progression would provide a more accurate representation of clinical practice although it acknowledged this assumption was not included by the AG in TA375
- The ERG identified 2 issues with the company's methods which it corrected in the exploratory analyses:
  - Calculating the DAS28 score of the patient at each cycle based on their DAS28 score at baseline, the change in HAQ score from baseline and the coefficient for HAQ score calculated by the company in their regression and used in their amended model
  - Assuming patients would transition to the severe state at the point when their DAS28 score increases above 5.1 without waiting until they have reached the end of the moderate sequence

Impact of the confidential PASs

- CTZ and GOL have non-confidential PASs
  - Incorporated into the previous analyses
- ABA and TCZ have confidential simple discount PASs
- ERG updated the company and ERG exploratory analyses to incorporate these discounts
  - Population C3 not included in confidential appendix as results do not change (TCZ and ABA not relevant comparators for this population)
- All results are deterministic, ERG noted that probabilistic unlikely to change conclusion.

cDMARD-IR patients with severe RA who can tolerate MTX (A1)

Sequences*	Total QALYs	Total costs	Incr. QALYs	Incr. costs	ICER (per QALY)	Pairwise vs SAR (per QALY)
Company results following clarification						
TCZ (SC) + MTX#	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	**Dominated**
TCZ (IV) + MTX#	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	**Dominated**
SAR + MTX	[redacted]	[redacted]	[redacted]	[redacted]	-	**-**
TNFi bundle + MTX	[redacted]	[redacted]	[redacted]	[redacted]	£79,199	**£79,199**
ABT (SC) + MTX#	[redacted]	[redacted]	[redacted]	[redacted]	£206,188	**£126,110†**
ERG exploratory analyses						
TCZ (SC) + MTX#	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	**Dominated**
TCZ (IV) + MTX#	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	**Dominated**
SAR + MTX	[redacted]	[redacted]	[redacted]	[redacted]	-	
TNFi bundle + MTX	[redacted]	[redacted]	[redacted]	[redacted]	£151,563	**£151,563**
ABT (SC) + MTX#	[redacted]	[redacted]	[redacted]	[redacted]	£311,453	**£214,071**

*Sequences as defined in Table 42 of ERG report
#Does not include confidential PAS
†Approximate ICER calculated by the ERG based on incrementals

cDMARD-IR patients with severe RA who cannot tolerate MTX (B)

Sequences*	Total QALYs	Total costs	Incr. QALYs	Incr. costs	ICER (per QALY)	Pairwise vs SAR (per QALY)
Company results following clarification						
TNFi bundle	[redacted]	[redacted]	[redacted]	[redacted]	-	**£17,123‡**
SAR	[redacted]	[redacted]	[redacted]	[redacted]	£17,123	**-**
TCZ (SC) #	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	**£2,596,000†**
TCZ (IV) #	[redacted]	[redacted]	[redacted]	[redacted]	£1,578,976	**£1,578,976**
ERG exploratory analyses						
TNFi bundle	[redacted]	[redacted]	[redacted]	[redacted]	-	**£34,422‡**
SAR	[redacted]	[redacted]	[redacted]	[redacted]	£34,422	**-**
TCZ (SC) #	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dom.	**£2,541,618**
TCZ (IV) #	[redacted]	[redacted]	[redacted]	[redacted]	£1,676,280	**£1,676,280**

*Sequences as defined in Table 43 of ERG report
#Does not include confidential PAS
†Approximate ICER calculated by the ERG based on incrementals
‡ICER in the south western quadrant representing cost savings per QALY lost

TNFi-IR patients with severe RA who can tolerate RTX & MTX (C2)

Sequences*	Total QALYs	Total costs	Incr. QALYs	Incr. costs	ICER (per QALY)
Company results following clarification					
RTX	[redacted]	[redacted]	[redacted]	[redacted]	-
SAR	[redacted]	[redacted]	[redacted]	[redacted]	**Ext. dom.**
RTX,TCZ‡#	[redacted]	[redacted]	[redacted]	[redacted]	**£39,994**
SAR,TCZ#	[redacted]	[redacted]	[redacted]	[redacted]	**£130,691**
ERG exploratory analyses					
RTX	[redacted]	[redacted]	[redacted]	[redacted]	
SAR	[redacted]	[redacted]	[redacted]	[redacted]	**Ext. dom.**
RTX,TCZ‡#	[redacted]	[redacted]	[redacted]	[redacted]	**£69,947**
SAR,TCZ#	[redacted]	[redacted]	[redacted]	[redacted]	**£171,466**

*Sequences as defined in Table 44 of ERG report
#Does not include confidential PAS for TCZ
†Approximate ICER calculated by the ERG based on incrementals
‡Currently recommended sequence

TNFi-IR patients with severe RA who cannot tolerate RTX (C1)

Sequences*	Total QALYs	Total costs	Incr. QALYs	Incr. costs	ICER (per QALY)	Pairwise vs SAR (per QALY)
Company results following clarification						
SAR + MTX	[redacted]	[redacted]	[redacted]	[redacted]	-	
TCZ (IV) + MTX#	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dom.	**£141,995†**
TNFi Bundle + MTX	[redacted]	[redacted]	[redacted]	[redacted]	£64,602	**£64,602**
ABT (SC) + MTX#	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	**£80,889†**
TCZ (SC) + MTX#	[redacted]	[redacted]	[redacted]	[redacted]	£69,306	**£69,306**
ERG exploratory analyses						
TNFi bundle+ MTX	[redacted]	[redacted]	[redacted]	[redacted]	-	**£34,979‡**
ABT (SC) + MTX#	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	**Dominated**
SAR + MTX	[redacted]	[redacted]	[redacted]	[redacted]	£34,979	**-**
TCZ (IV) + MTX#	[redacted]	[redacted]	[redacted]	[redacted]	£198,863	**£198,863**
TCZ (SC)+MTX#	[redacted]	[redacted]	[redacted]	[redacted]	£777,770	**£205,638**

*Sequences as defined in Table 45 of ERG report
#Does not include confidential PAS
†Approximate ICER calculated by the ERG based on incrementals
‡ICER in the south western quadrant representing cost savings per QALY lost

TNFi-IR patients with severe RA who cannot tolerate MTX (C3)

Sequences*	Total QALYs	Total costs	Incr. QALYs	Incr. costs	ICER (per QALY)
Company results following clarification					
TNFi Bundle	[redacted]	[redacted]	[redacted]	[redacted]	**-**
SAR	[redacted]	[redacted]	[redacted]	[redacted]	**£17,794**
ERG exploratory analyses					
TNFi Bundle	[redacted]	[redacted]	[redacted]	[redacted]	
SAR	[redacted]	[redacted]	[redacted]	[redacted]	**£31,433**

*Sequences as defined in Table 46 of ERG report

TNFi-IR patients with severe RA who have received RTX + MTX (C4)

Sequences*	Total QALYs	Total costs	Incr. QALYs	Incr. costs	ICER (per QALY)	Pairwise vs SAR (per QALY)
Company results following clarification						
SAR + MTX	[redacted]	[redacted]	[redacted]	[redacted]	-	
TCZ (IV) + MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	**£141,995†**
TCZ (SC) + MTX	[redacted]	[redacted]	[redacted]	[redacted]	£133,548	**£133,548**
ERG exploratory analyses						
SAR + MTX	[redacted]	[redacted]	[redacted]	[redacted]	-	-
TCZ (IV) + MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	**£245,465**
TCZ (SC) + MTX	[redacted]	[redacted]	[redacted]	[redacted]	£219,153	**£219,153**

*Sequences as defined in Table 47 of ERG report
#Does not include confidential PAS
†Approximate ICER calculated by the ERG based on incrementals

cDMARD-IR patients with moderate RA (DAS28 between 4.0 and 5.1) who can tolerate MTX (A2)

Sequences*	Total QALYs	Total costs	Incr. QALYs	Incr. costs	ICER (per QALY)
Company results following clarification					
MTX	[redacted]	[redacted]	[redacted]	[redacted]	-
SAR + MTX	[redacted]	[redacted]	[redacted]	[redacted]	**£38,254**
ERG exploratory analyses					
MTX	[redacted]	[redacted]	[redacted]	[redacted]	
SAR + MTX	[redacted]	[redacted]	[redacted]	[redacted]	**£63,438**

*Sequences as defined in Table 48 of ERG report

Key issues: Cost effectiveness

- Do the Committee accept the ERG's changes to the company model:
  - Using a non-linear approach (Norton et al) for HAQ trajectory
  - Including the option for patients to receive treatment for severe disease when in the moderate state and their DAS28 score reaches 5.1.
- Is SAR comparable to the bDMARDs in both clinical and cost effectiveness?
- Is SAR monotherapy cost-effective?

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