NICE National Institute for Health and Care Excellence

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Upadacitinib for treating moderate to severe rheumatoid arthritis [ID1400]

ACM 2 presentation

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Company: Abbvie

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Abbreviations

Abbreviation	
ABT	abatacept
ADA	adalimumab
bDMARD	biologic disease-modifying antirheumatic drug
BRC	baricitinib
BSC	best supportive care
csDMARD	conventional synthetic disease-modifying antirheumatic drug
CTZ	certolizumab pegol
DAS-28	disease activity score 28-joint count
ETN	etanercept
GOL	golimumab
HAQ-DI	health assessment questionnaire disability index
IFX	infliximab
IR	Inadequate response
IV	Intravenous
JAK	Janus kinase
MTX	methotrexate
RA	Rheumatoid arthritis
PBO	placebo
RTX	rituximab
SC	subcutaneous
SRL	sarilumab
TCZ	tocilizumab
TFC	tofacitinib
TNF-alpha	tumour necrosis factor alpha
UPA	upadacitinib

Key Issues – Moderate RA

1. What clinical effectiveness data should be used to compare UPA with BSC – company's NMA or SELECT head-head to trials?
2. Does the company's proposed positioning post ACM 1 reflect committee's preferred position for moderate RA (pos 2a + 2b: after 2 or more csDMARDs)?
3. What is committee's preferred method to account for the placebo effect in the SELECT trials?
    a) apply placebo response to BSC when it's compared with UPA or any active treatment
    b) net out placebo effect from active comparator (cttee previously agreed this company scenario may be appropriate but would underestimate costs)
4. Is the company's scenario with more people progressing from moderate to severe RA acceptable?
5. Should the company's approach to mapping HAQ-to-pain scores be considered plausible?

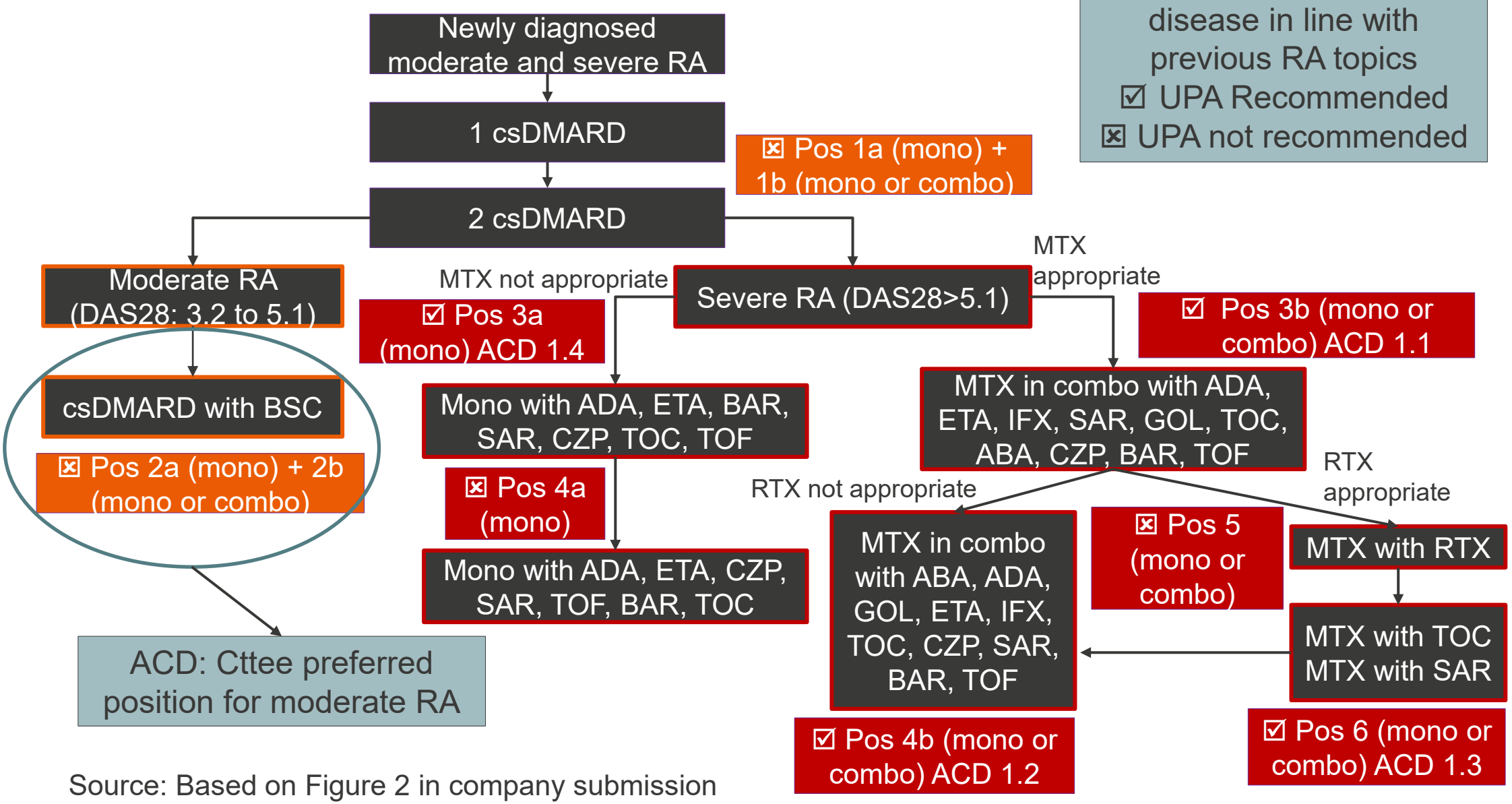
Upadacitinib (Rinvoq, Abbvie)

Description of technology	A Janus-kinase (JAK) 1 inhibitor that blocks the JAK-signal transducer and activator of transcription (STAT) pathway and inflammatory responses.
Marketing authorisation	Upadacitinib is indicated for the treatment of moderate to severe active RA in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs). It can be used as a monotherapy or in combination with methotrexate.
Dosage and administration	15 mg orally administered once daily.
Proposed place in treatment pathway for moderate RA	Upadacitinib can be used in the moderate RA population after: • 1 csDMARD • 2 or more csDMARDs Treatment options for RA also differ by methotrexate and rituximab tolerance

Treatment pathway with mapped ACD recs

Company focus on moderate population in ACD response for patients "who have run out of treatment options"

ACD: UPA is recommended for severe disease in line with previous RA topics
☑ UPA Recommended
☒ UPA not recommended



Source: Based on Figure 2 in company submission

ACD recommendations by treatment position

Cttee preferred position for moderate disease

Pos #	Disease severity	Failed treatments	Methotrexate tolerant?	Rituximab tolerant?	ACD rec
1a	Moderate	1 csDMARD	X	✓	ICERs not robust & upadacitinib unlikely to be cost-effective
1b	Moderate	1 csDMARD	✓	✓	
2a	Moderate	≥2 csDMARDs	X	✓	
2b	Moderate	≥2 csDMARDs	✓	✓	
3a	Severe	≥2 csDMARDs	X	✓	Recommended
3b	Severe	≥2 csDMARDs	✓	✓	Recommended
4a	Severe	1 bDMARD	X	✓	Not recommended
4b	Severe	1 bDMARD	✓	X	Recommended
5	Severe	1 bDMARD	✓	✓	Not recommended
6	Severe	Rituximab	✓	✓	Recommended

ACD 3.8 summary (position 1 vs. position 2 for moderate disease):

- *Clinical expert statement explained UPA more likely to be used after 2 csDMARDs*
- *EULAR guidelines: 2 csDMARD treatments should be given before considering a bDMARD but clinical expert explained guideline recommends bDMARD after 1 csDMARD if poor prognosis. Company's NMA didn't include separate analyses for this subgroup*
- *ICER for position 1 likely to be >£30,000 compared with position 2*
- *Committee concluded it was more appropriate to consider UPA at position 2 (after 2 or more csDMARDs)*

Committee preferred assumptions for moderate disease (1)

	Cttee ACM 1	Company	ERG
Treatment position	after ≥2 csDMARDs is most appropriate	Move away from position 1 & 2 and refer to moderate RA only for "people who have run out of treatment options"	Company don't account for patients intensifying csDMARDs before UPA - not in line with cttee preference
Comparator	BSC (previous csDMARD including MTX ± corticosteroid).	ACM2: Mainly consider MTX (labelled as csDMARD), some analyses with placebo/BSC ACM1: pos 2a BSC, pos 2b MTX	
Clinical data	NMA	NMA	Should use SELECT head-to-head trials for moderate RA
Progression from moderate to severe	Model underestimates how many patients' disease progresses from moderate to severe, making its results less robust	Scenarios: 11% and 19% progress from moderate to severe RA at 2 years (71% & 87% at 12 years)	ERG also report these scenario analyses

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Committee preferred assumptions for moderate disease (2)

	Cttee ACM 1	Company	ERG
Placebo effect	• Not appropriate to model 0% for BSC and full response from clinical evidence for UPA • Company's scenario using 'net treatment effect' is appropriate for clinical effectiveness but not costs	Not methodologically appropriate to separate treatment effect & costs - 'net treatment effect' not applied apart from table 8	Not in line with cttee preference. ERG provide ICERs using 'net treatment effect' & treatment effects with placebo effects
Treatment sequence	Unequal treatment lengths may bias ICERs: 1) at some point active treatment in longer sequence is compared to BSC. If there is no placebo effect associated with BSC the relative effect is likely to be overestimated 2) ↓ DMARD response if used later in pathway - not captured in NMA	• No change (UPA still has longest treatment sequence) • 5% treatment waning scenario for use later in pathway	Not in line with cttee preference (treatment waning scenario has small impact on ICER)

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ACD consultation comments

Note: Slide amended after ACM 2

- Received comments from company, British Society for Rheumatology (BSR), UCB Pharma Ltd. No web comments received

Issue	Comment	ERG
Errors from company	**Issue 6**: The ACD misrepresents the intention of the company's 'net treatment effect' approach because the placebo effect is not seen in clinical practice so drug costs would likely be lower (discontinuation likely to be higher). Not methodologically appropriate to separate treatment effect from costs **Issue 8**: ACD incorrectly states the comparator and efficacy input in the company's moderate RA base case. For patients eligible for MTX the comparator was MTX then BSC (see issue 1)	**Issue 6** – The net treatment effect is correctly described **Issue 8** – ACD should specify 3.11 refers to MTX intolerant pop (position 2a) and add for MTX tolerant pop
Placebo effect	**BSR**: Disappointed with negative recommendation for moderate disease as there is high unmet need. The ERG assumption around placebo effect differs compared with previous RA appraisals - not based on published evidence. Patients having BSC and no new treatment would not have placebo response. For moderate RA, DMARDS are usually continued not stopped and re-started.	

ACD consultation comments

Issue	Comment
Agree with ACD conclusions	**UCB**: agree BSC is most appropriate comparator and is unlikely to give EULAR response, comparing sequences of different length may be misleading, transition from moderate to severe RA is underestimated, HAQ to pain mapping based on National Databank for Rheumatic Diseases is more robust, agree that using the "net treatment effect" would underestimate costs, HAQ trajectories should be considered as these have been incorporated for both UPA and BSC responders
Disagree with ACD	**UCB**: tofacitinib and baricitinib should not be classed as biologic DMARDS in the ACD as this is not in line with NICE treatment pathway, there is no consistent outcome in terms of treatment effect as the number of treatment failures increases. This contradicts the company's common effects NMA assumption.
Additional information	**UCB**: there is no consistency with TA375 in how the moderate sub-group has been modelled and it would be useful to include this context in the ACD

Model robustness for moderate RA

ACD currently states model is not robust because:

1. The validation analysis from the company show that the company's model overestimated QALY gains for biological DMARDs compared with conventional DMARDs → this primarily impacts the cost-effectiveness analysis for moderate disease, when upadacitinib is compared with conventional DMARDs (see section 3.16)
2. The company's model appeared to underestimate the number of patients with moderate disease whose disease would progress to be treated as severe disease (see section 3.14)
3. the company's 'net treatment effect' scenario likely underestimated treatment costs (see section 3.12)

ERG	1. Company managed to get outputs reasonably aligned to TA375 (included correction of 4 ERG errors in implementation of TA375 model) 2. Company provide relevant scenarios in ACD response 3. Company's 'net treatment effect' likely to underestimate net treatment costs and overestimate proportion of UPA good responders as a proportion of UPA responders. ERG provide scenarios with placebo effect.

Clinical data from trials vs. NMA

Background

Clinical effectiveness data at ACM1 was taken from company's NMA for severe RA and this was accepted by committee

NICE methods guide (section 5.2.12)

- Data from head-to-head RCTs should be presented in the reference-case analysis.
- When technologies are being compared that have not been evaluated within a single RCT, data from a series of pairwise head-to-head RCTs should be presented together with a network meta-analysis if appropriate.
- The network meta-analysis must be fully described and presented as additional to the reference-case analysis.

ERG

- For moderate RA where UPA is compared with BSC/PBO it may be more appropriate to use direct head-to-head trial evidence rather than NMA because:
  - this would be in line with NICE methods guide
  - Company NMA method for estimating placebo is uncertain & ERG cannot assess reliability
  - NMA relies on ACR mapped data but trials use EULAR response rate
- But using MONOTHERAPY trial to model position 2a (MTX intolerant population) is problematic because it compares UPA vs. MTX
- ICERs ↑ when using head-to-head trial data compared with NMA, the **net effect of the NMA is higher than the trial**.

Summary of clinical evidence

4 upadacitinib RCTs, moderate to severe RA

ERG considers Pos 2b. SELECT-NEXT may be most appropriate trial

SELECT-COMPARE
Inadequate response to MTX

Week 12	UPA+MTX (651)	ADA+MTX (327)	PBO (651)
ACR20	71%	63% *	36% **
ACR50	45%	29% **	15% **
ACR70	26%	13% **	5% **
Low DAS	49%	29% **	14% **
Remission	29%	18% **	6% **

SELECT-MONOTHERAPY
Inadequate response to MTX

Week 14	UPA (217)	MTX (216)
ACR20	68%	41% **
ACR50	42%	15% **
ACR70	23%	3% **
Low DAS	45%	19% **
Remission	28%	8% **

SELECT-NEXT
Inadequate response to csDMARDs

Week 12	UPA (221)	PBO (221)
ACR20	64%	36% **
ACR50	38%	15% **
ACR70	21%	6% **
Low DAS	48%	17% **
Remission	31%	10% **

SELECT-BEYOND
Inadequate resp or intolerance to ≥1 bDMARD

Week 12	UPA+csDM'D (164)	PBO+csDM'D (169)
ACR20	65%	28% **
ACR50	34%	12% **
ACR70	12%	7% **
Low DAS	43%	14% **
Remission	29%	10% **

NICE (number of patients in each trial arm)

* $p \leq 0.050$
** $p \leq 0.001$

Note: Slide amended after ACM 2

Summary of NMA results – csDMARD IR

- Company submitted results from 2 NMAs:
  - Disease responding inadequately to csDMARD (csDMARD-IR)
  - Disease responding inadequately to biological DMARDs (bDMARD-IR)
- Both NMAs used treatment estimates that mapped ACR responses to EULAR
- Both NMAs assume that same treatment estimates apply regardless of positioning (e.g. 1st line MTX and 3rd line MTX applied as 46% response rate)

Treatment	NMA absolute effect			Net effect						NMA absolute effect		
	csDMARD-IR									bDMARD-IR		
				vs. int csDMARD		vs. MTX		vs. BSC				
	Mod	Good	Total	Mod	Good	Mod	Good	Mod	Good	Mod	Good	Total
BSC	0%	0%	0%							0%	0%	0%
Placebo												
MTX												
Int.csDMARDs												
UPA												
UPA+MTX												

In ACD response, company base case uses 46% from csDMARD-IR NMA and 38% after UPA from bDMARD-IR NMA

1. What clinical effectiveness data should be used to compare UPA with BSC – company's NMA or SELECT head-head to trials?

Placebo effect & treatment sequence

ACD 3.11: It is not appropriate to model both a 0% response rate for best supportive care and the full response rate from the clinical evidence for upadacitinib

Background

- Control arms (including placebo) of the UPA trials showed notable response rates
- A proportion of the UPA response from the trials would be caused by the same placebo effect
- UPA treatment sequence is longer than comparator arm (UPA has 1 additional treatment) and final treatment in UPA arm is compared with BSC
- Need to account for placebo effect in both treatment arms

Method to account for placebo effect

1. ERG preferred: assume placebo effect	Apply placebo response from the NMA to BSC when comparing with UPA & active comparator - otherwise overestimates relative effect
2. Company scenario: Net out placebo effect from active comparator	Company scenario at ACM 1 included 'net treatment effect' – lower UPA response to account for placebo effect. This was compared to 0% response in BSC. But this leads to underestimated treatment costs as fewer people responding to UPA and incur costs

Cttee concluded company's scenario may be appropriate to model clinical effectiveness of UPA but not relative costs

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Company response: Placebo effect

Company

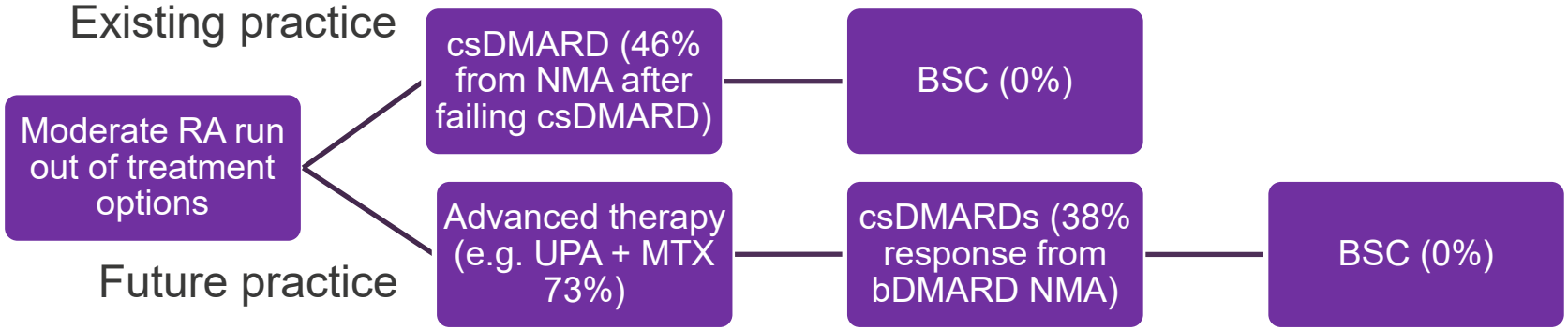
Raise 3 issues related to placebo effect:

1. Consistency with TA375 (If assume placebo response when comparing to UPA should assume placebo response for csDMARD)
2. Constraining treatment sequence to be equal does not model clinical practice (no evidence to support this)
3. No clear rationale why using longer sequences would result in overestimation – provide 5% treatment waning scenario

ERG

1. Company positioning post ACM1 & rationale for including 46% response after failing csDMARD is unclear - could be because UPA + MTX positioned before csDMARD
2. longer sequence will apply placebo effect more times than the shorter sequence so sensible to equalise to allow a like for like comparison
3. Waning scenario – small impact on ICERs

Figure 1. Company preferred sequence from TA375 (response rate %)



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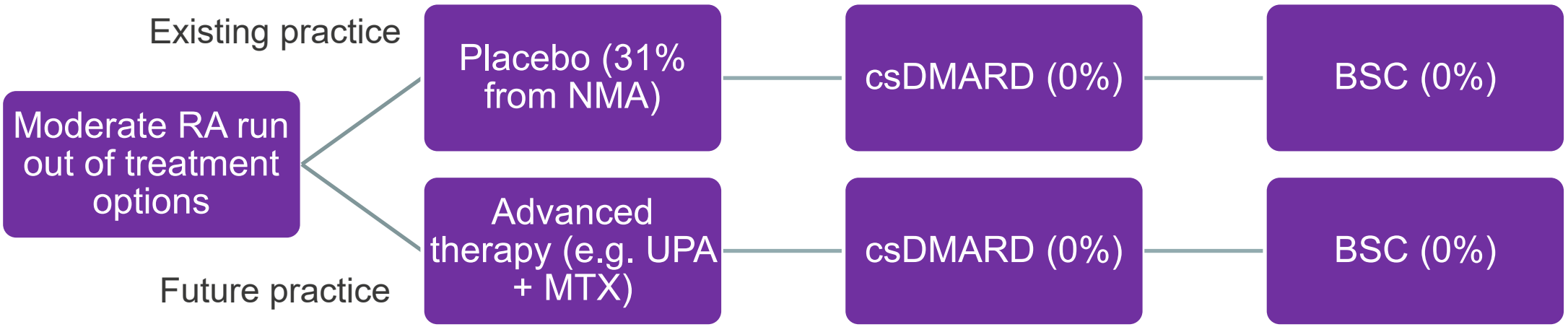
Approach advocated by committee



Note: Slide amended after ACM 2

Company's response: positioning of UPA

Company response	Treatment seq (response rate from NMA)		Comparison
	Intervention	Comparator	
Table 4	UPA + MTX ([redacted]) > MTX ([redacted], from bDMARD-IR NMA)	MTX ([redacted])	UPA + MTX vs. MTX
Table 5	UPA + MTX ([redacted])	PBO ([redacted])	UPA + MTX vs. PBO
Table 6	UPA + MTX ([redacted]) > PBO ([redacted])	PBO ([redacted])	
Table 7	UPA + MTX - PBO ([redacted]) > MTX – PBO ([redacted])	MTX – PBO ([redacted]) > PBO – PBO (0%)	UPA + MTX vs. MTX (net out PBO)
Table 8	UPA + MTX - PBO ([redacted])	PBO – PBO (0%)	UPA + MTX vs PBO (net out PBO)
Table 11	UPA ([redacted])	BSC (0%)	UPA vs. BSC
Table 12	UPA ([redacted])	PBO ([redacted])	UPA s. PBO

ERG

Company generally use MTX as comparator rather than BSC (previous csDMARD ± corticosteroid) or intensified csDMARDs. This may be consistent with company's prior positioning at ACM1 for pos 2b

2. Does the company's proposed positioning post ACM 1 reflect committee's preferred position for moderate RA?
3. What is committee's preferred method to account for the placebo effect in the SELECT trials?

Company response: Rate of transition from moderate to severe disease

ACD 3.14: The model underestimates how many patients' disease progresses from moderate to severe, making its results less robust

Background

- Company model included possibility of treatment for moderate disease progressing to treatment for severe disease
- Not in previous NICE RA models but reflects clinical practice and was modelled in TA485 for sarilumab
- Transition modelled by estimating the relationship between DAS28, which defines disease severity, and HAQ from the SELECT trials
- At ACM 1 company estimated 7% with moderate disease progress to severe after 2 years but this was much lower than 19% predicted by the UK Early Rheumatoid Arthritis Network database

Company

- New scenario analyses doubling and tripling HAQ to DAS28 coefficient from trials to reflect ↑ progression from mod to severe:
  - Double: 11% at 2 yr, max 71% by 12 yrs
  - Triple: 19% at 2 yr, max 87% by 12 yrs

ERG

- Company reports the proportion in the comparator arm progressing to severe, but not the proportion in the UPA arm
- Company's analyses are reasonable but full assessment would require arm specific data on non-responders & progression to severe disease from SELECT trials

4. Is the company's scenario with more people progressing from moderate to severe RA acceptable?

Company response: Mapping algorithm for HAQ to pain

ACD 3.15: the company's approach may be valid, but it preferred to use utilities calculated using the HAQ-to-pain mapping function used in the previous NICE technology appraisal, which was based on a much larger dataset.

Background

- Company mapped HAQ to pain scores using a mapping algorithm and SELECT trial data
- The committee preferred to use mapping based on the National Databank for Rheumatic Diseases dataset because it was based on a much larger dataset (over 100,000 observations) and had been used in previous TAs

ERG

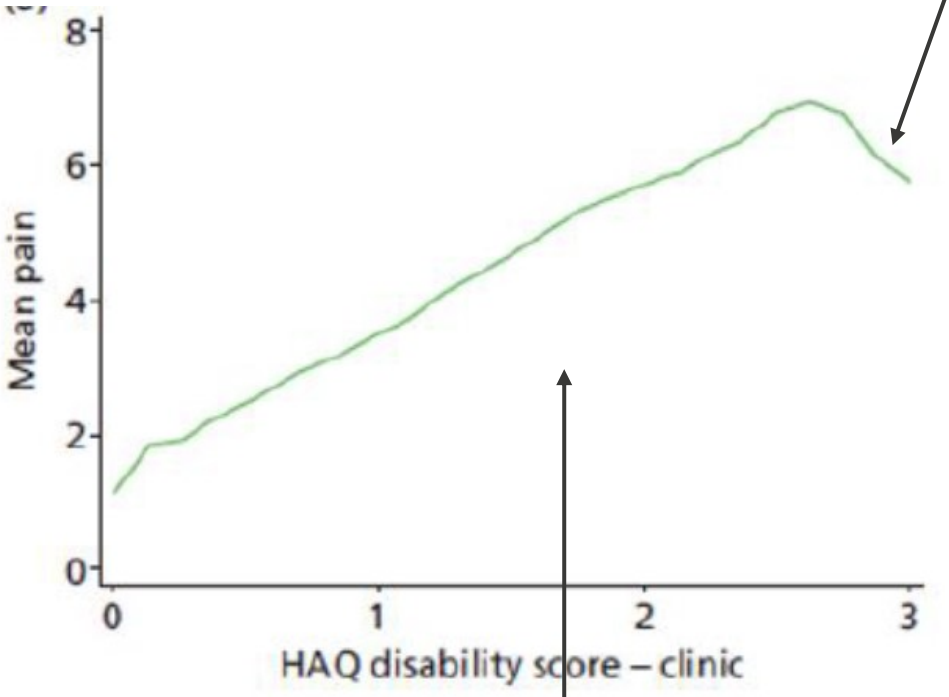
No change but include scenarios using company approach

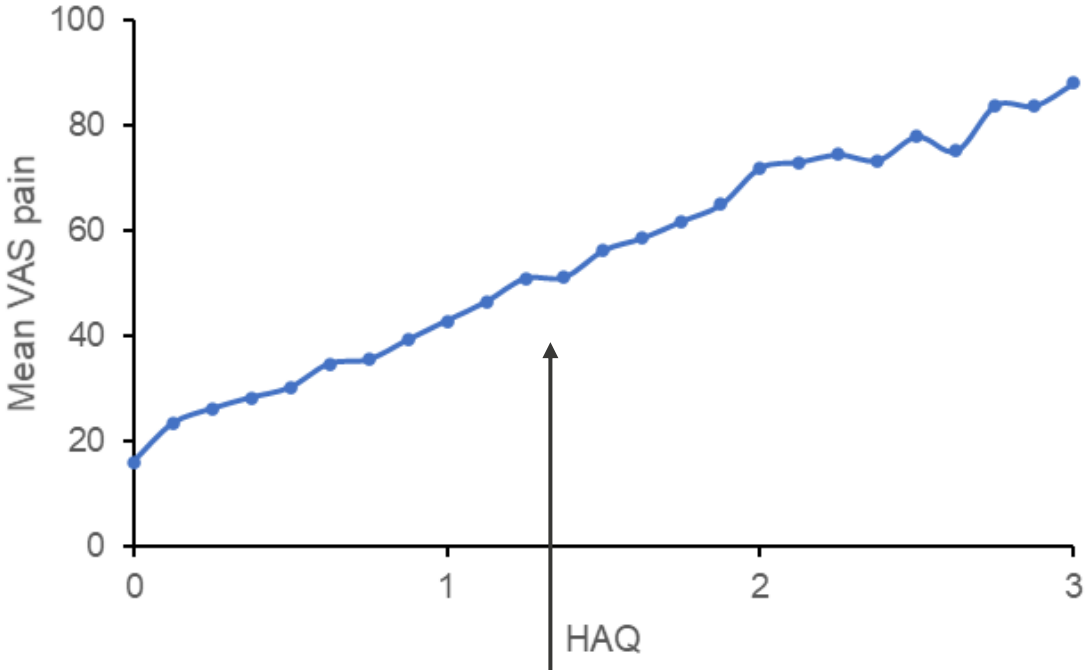
Company

- Algorithm based on data from the National Databank for Rheumatic Diseases provides counterintuitive results that HAQ scores at the highest end of the spectrum (indicating lowest functionality) are associated with a reduction in pain – this is not addressed in ACD
- SELECT trial-based algorithm based on 3,599 patients and 7,963 observations and should also be considered plausible

7. Mapping algorithm from HAQ to pain

Company: Counterintuitive results of reduction in pain associated with lowest functionality





HAQ-to-pain mapped based on committee preferred National Databank for Rheumatic Diseases

Company preferred HAQ-to-pain mapped based on SELECT trials

5. Should the company's approach to mapping HAQ-to-pain scores be considered plausible?

Company's cost-effectiveness results

Original PAS for UPA and list price for all other treatments

Company prefer not to 'net out' placebo effect in base case submitted with ACD response

	ICER (UPA + MTX vs. MTX)
Company Base Case	£25,110
Company scenarios	
1. Assume no transition to severe RA	£29,557
2. Assume 5% waning	£25,462
3. Assume 5% waning and double HAQ to DAS28	£18,428
4. Assume 5% waning and triple HAQ to DAS28	£13,492

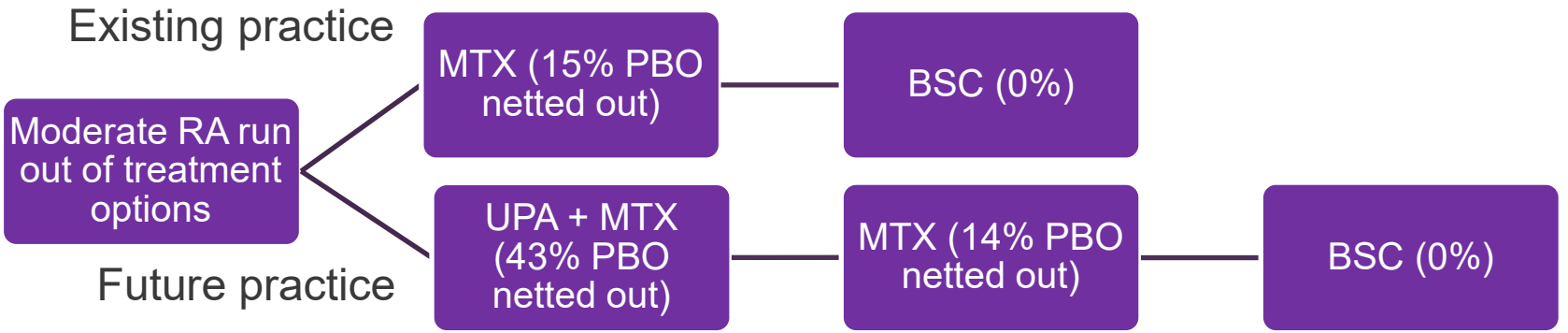
Proposed change to PAS received late last week. All ICERs in this presentation were calculated using the **original** PAS.

Due to time constraints, only the ICERs presented in part 2 include the updated (proposed) PAS discount.

Company's scenario

Original PAS for UPA and list price for all other treatments

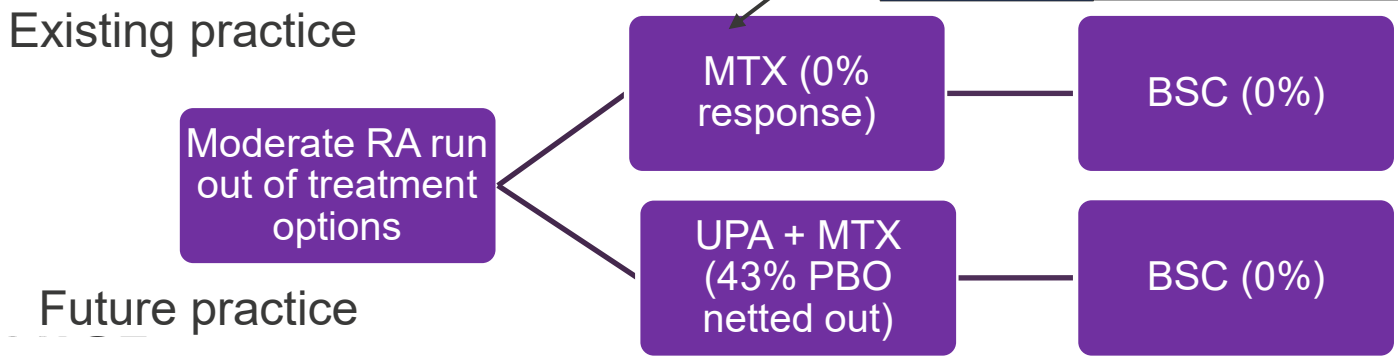
Table 7 (company ACD response). Scenario assuming placebo effect in trials not seen in clinical practice (company preferred)



ICER £23,465 (includes 5% waning)

Table 8 (company ACD response). Scenario assuming placebo effect in trials not seen in clinical practice (committee preferred)

ERG: Company assume 0% for MTX but only net out PBO from UPA + MTX. NICE request scenarios netting out MTX from UPA + MTX



ICER £19,086 (includes 5% waning)

ERG comments – netting out MTX

- When netting out the MTX effects the balance between moderate and good response for UPA+MTX shifts markedly towards good responses (there is only 1 moderate responder for every 3 good responders)
- Simple netting out of EULAR response rates both reduces the proportion of patients who incur upadacitinib costs and among those who do incur these costs, many more are modelled as having a good response (may not be reasonable)
- Simple netting out may not be appropriate because:
  - Net costs possibly being underestimated (ACD section 3.12)
  - It biasing the analysis due to it increasing the proportion of UPA EULAR responses that are good responses, when correctly netting out the control arm effect would be expected to do the opposite.
  - The SELECT trial head-to-head results not being amenable to a simple netting out, meaning that the NICE reference case cannot be presented
- A more correct approach may be to use the SELECT trials' patient distributions of EULAR scores and to attempt to shift these leftward such that few patients in the control arm achieve a moderate EULAR response

Treatment sequence: progression mod to severe RA

ERG expert opinion: for those progressing to severe RA most will be treated with cheapest advanced DMARD [ADA]. Those tolerant of RTX will tend to have it next (even if MTX intolerant). Interleukin may be used 3rd line but since JAKs and interleukins act through similar pathways, those who had previous UPA may get treatment with a different method of action such as ABT.

Clinical expert: both scenarios plausible. For sequence 5 SRL and ABTsc could be interchangeable. UPA and SRL do not have same mode of action but both target IL-6. Decision would depend on other factors such as infectious risk, cost, liver abnormalities. For sequence 6 UPA probably more likely than SRL.

	1st line	2nd line	3rd line	4th line	
ERG	***Scenario 5**. Patients with severe RA previously treated with upadacitinib when in moderate RA will be treated with subcutaneous abatacept rather than sarilumab*				
Comparator	ADA + MTX	RTX + MTX	SRL + MTX	BSC	2b
UPA arm	ADA + MTX	RTX + MTX	ABTsc + MTX	BSC	
ERG	***Scenario 6**. Patients with severe RA not previously treated with upadacitinib when in moderate RA will be treated with upadacitinib rather than sarilumab*				
Comparator	ADA + MTX	RTX + MTX	UPA + MTX	BSC	2b
UPA arm	ADA + MTX	RTX + MTX	SRL + MTX	BSC	

Note: for position 2a (MTX intolerant) the treatment sequence is the same but without MTX

ERG cost-effectiveness results – moderate RA

Position 2b: UPA + MTX vs. PBO/BSC after ≥ 2 csDMARDs

Notes: Position 2b (both MTX and RTX tolerant) presented first as larger population. ERG's method to implement 'net effect' simpler than company's approach but results similar. Original PAS.

	ERG placebo effect			Company 'net effect'		
	ΔCost	ΔQALY	ICER	ΔCost	ΔQALY	ICER
ERG base case from ACM 1	[redacted]	[redacted]	£28,356	[redacted]	[redacted]	£15,881
Clinical effectiveness data (head-to-head trial not NMA)						
1.SELECT-COMPARE NRI	[redacted]	[redacted]	£31,484	[redacted]	[redacted]	*
2.SELECT-NEXT NRI	[redacted]	[redacted]	£36,952	[redacted]	[redacted]	*
3.SELECT-COMPARE NRI (mod RA)	[redacted]	[redacted]	£34,134	[redacted]	[redacted]	*
4.SELECT-NEXT NRI (mod RA)	[redacted]	[redacted]	£43,157	[redacted]	[redacted]	*
UPA for moderate RA impacts treatment sequence for severe RA						
5.ABT_{SC} after UPA for mod RA	[redacted]	[redacted]	£31,247	[redacted]	[redacted]	£21,229
6.UPA if no UPA for mod. RA	[redacted]	[redacted]	£35,385	[redacted]	[redacted]	£25,946
7.Apply 5 and 6	[redacted]	[redacted]	£38,166	[redacted]	[redacted]	£31,341
Other scenarios						
8.Company HAQ to pain mapping	[redacted]	[redacted]	£24,420	[redacted]	[redacted]	£13,518
9.Treatment waning 5%	[redacted]	[redacted]	£29,596	[redacted]	[redacted]	£17,554
10.Double HAQ to DAS28 coefficient	[redacted]	[redacted]	£22,734	[redacted]	[redacted]	£5,874
11.Triple HAQ to DAS28 coefficient	[redacted]	[redacted]	£17,893	[redacted]	[redacted]	Dominant

* Not amenable to simple netting out due to higher moderate response for PBO / BSC than for UPA + MTX;
Abbreviations: ABT, abatacept; NRI, non-responder imputation

ERG cost-effectiveness results – moderate RA

Position 2a: UPA mono vs. PBO/BSC after ≥ 2 csDMARDs

Note: Position 2a (MTX intolerant & RTX tolerant) is smaller population. Only the SELECT-MONOTHERAPY trial is available but this compared UPA vs. MTX. This is an issue because modelling in position 2a should reflect MTX intolerant population

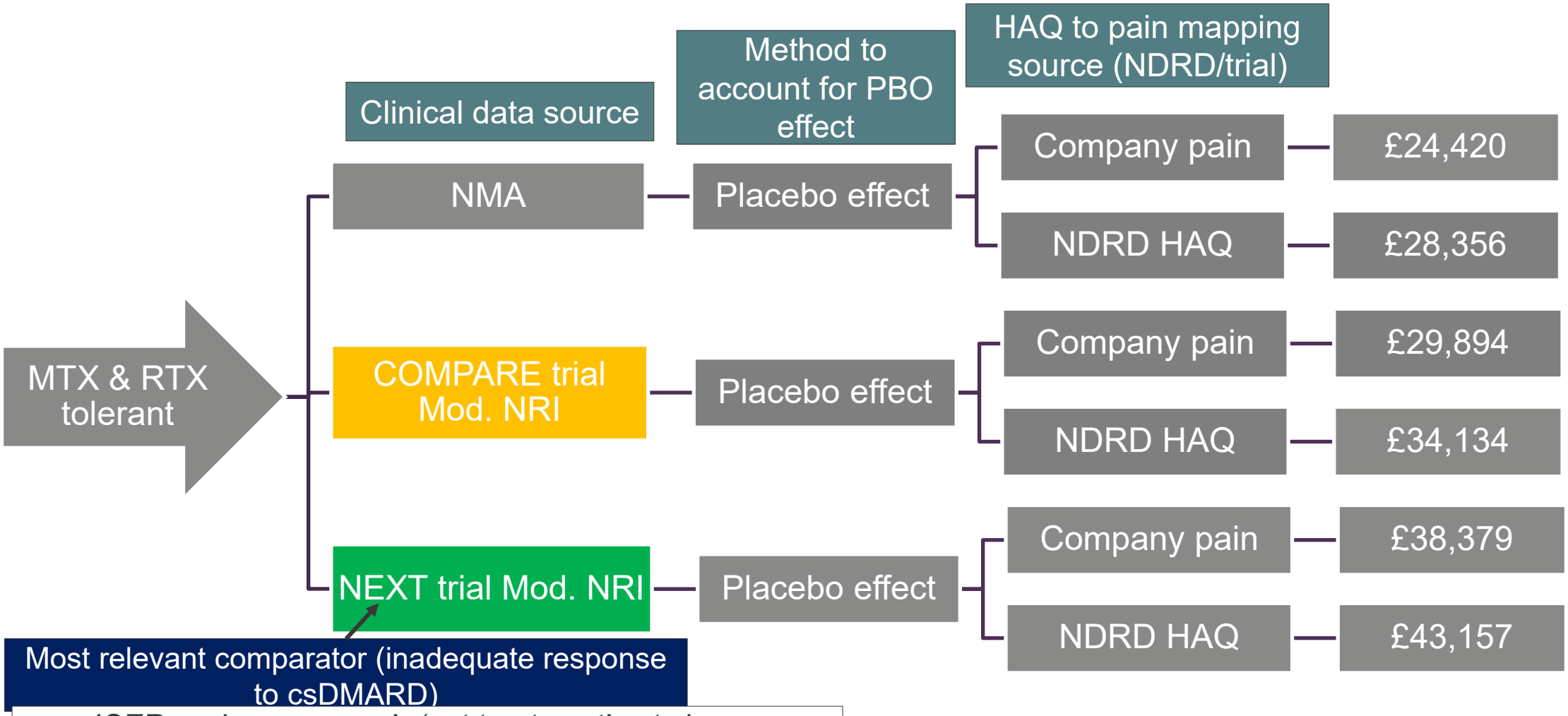
Original PAS

	ERG placebo effect			Company 'net effect'		
	ΔCost	ΔQALY	ICER	ΔCost	ΔQALY	ICER
ERG base case from ACM 1	[redacted]	[redacted]	£32,092	[redacted]	[redacted]	£18,194
Clinical effectiveness data (head-to-head trial not NMA)						
1.SELECT-MONOTHERAPY NRI	[redacted]	[redacted]	£40,566	[redacted]	[redacted]	£18,199
2.SELECT-MONOTHERAPY NRI (mod RA)	[redacted]	[redacted]	£38,425	[redacted]	[redacted]	*
UPA for moderate RA impacts treatment sequence for severe RA						
3.ABT_{SC} after UPA for mod RA	[redacted]	[redacted]	£34,732	[redacted]	[redacted]	£22,080
4.UPA if no mod. RA UPA	[redacted]	[redacted]	£40,693	[redacted]	[redacted]	£29,791
5. Apply 6 and 7	[redacted]	[redacted]	£43,311	[redacted]	[redacted]	£34,009
Other scenarios						
6.Company HAQ to pain mapping	[redacted]	[redacted]	£27,567	[redacted]	[redacted]	£15,308
7.Treatment waning 5%	[redacted]	[redacted]	£32,369	[redacted]	[redacted]	£18,541
8.Double HAQ to DAS28 coefficient	[redacted]	[redacted]	£25,109	[redacted]	[redacted]	£11,480
9.Triple HAQ to DAS28 coefficient	[redacted]	[redacted]	£23,155	[redacted]	[redacted]	£5,514

* Not amenable to simple netting out due to ↑ moderate response for PBO/BSC vs UPA

ERG scenarios UPA + MTX vs. BSC (Pos 2b)

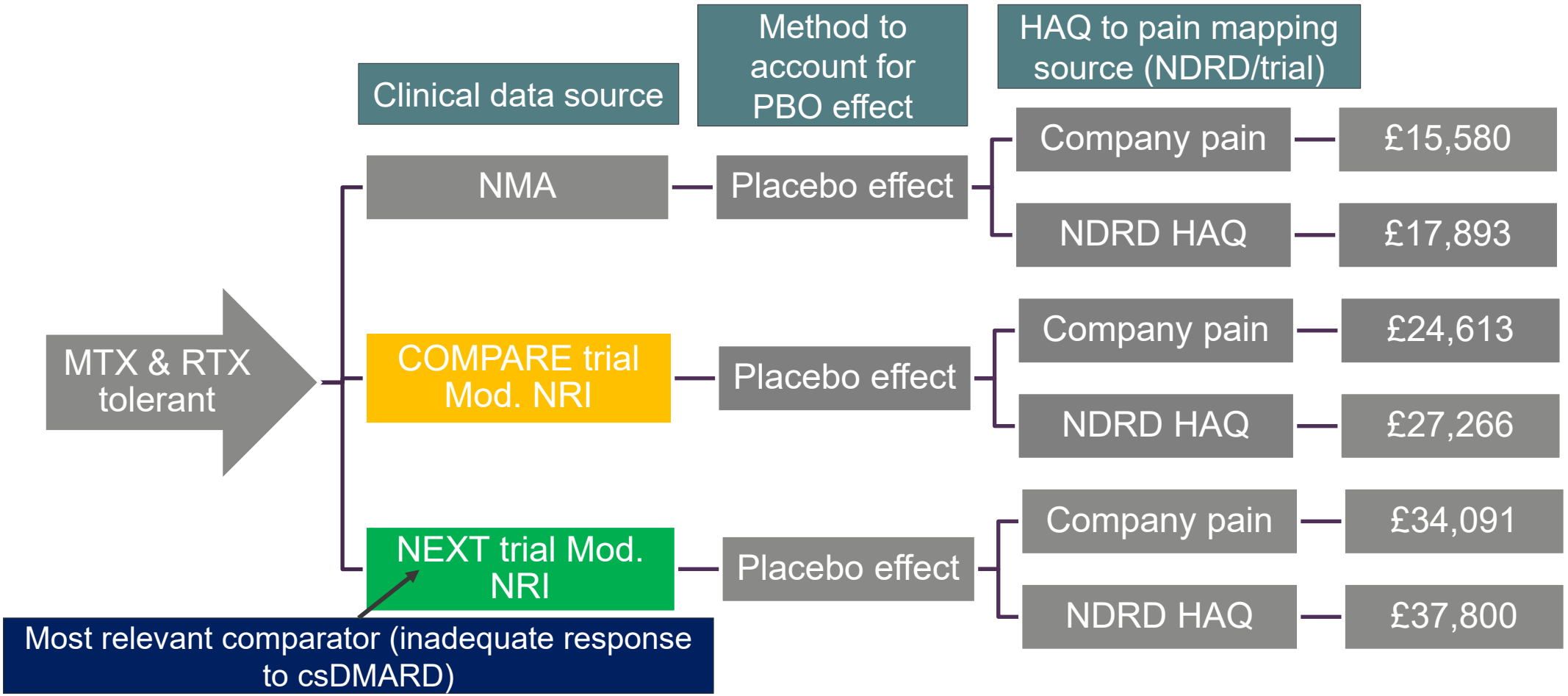
Note: all ICERs **based on ERG base case** (no changes to alternative treatment seq for severe RA based on UPA for mod RA or transition from mod to severe)



ICERs using company's 'net treatment' not shown.
Original PAS for UPA and list price for all other treatments

ERG scenarios UPA + MTX vs. BSC (Pos 2b)

Note: all ICERs **include** 19% (2 yrs) transition from mod to severe

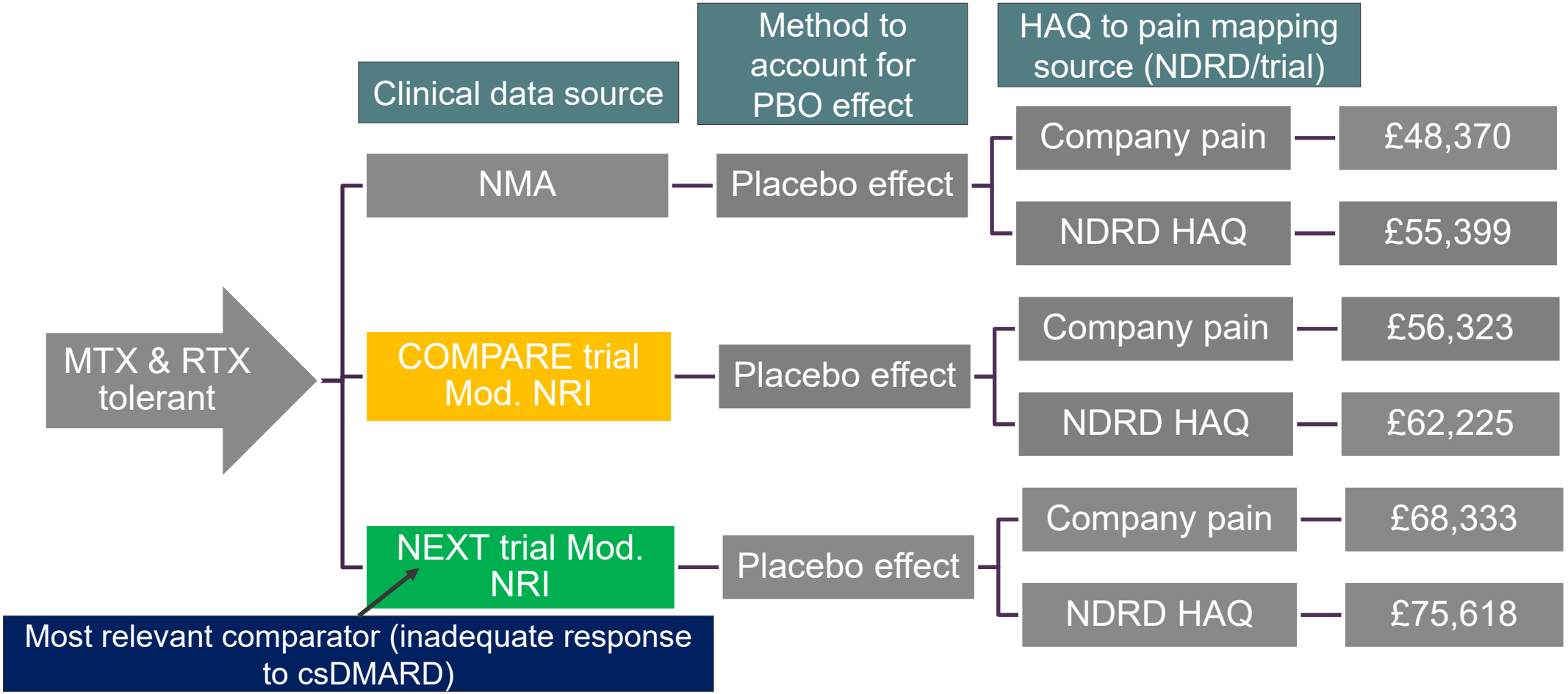


ICERs using company's 'net treatment' not shown.
Original PAS for UPA and list price for all other treatments

ERG scenarios UPA + MTX vs. BSC (Pos 2b)

Note: all ICERs **include**:

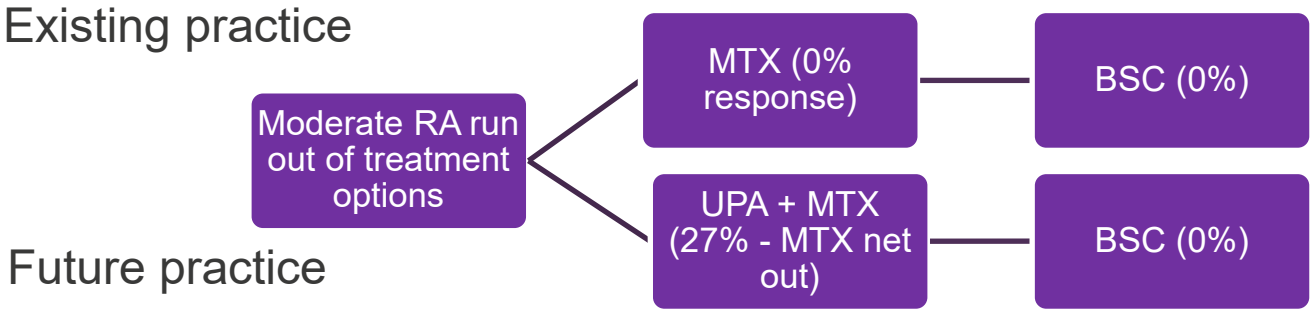
- ERG's alternative treatment seq for severe RA based on UPA for mod RA
- 19% (2 yrs) transition from mod to severe



ICERs using company's 'net treatment' not shown.
Original PAS for UPA and list price for all other treatments

Scenarios for UPA + MTX vs. MTX (Pos 2b)

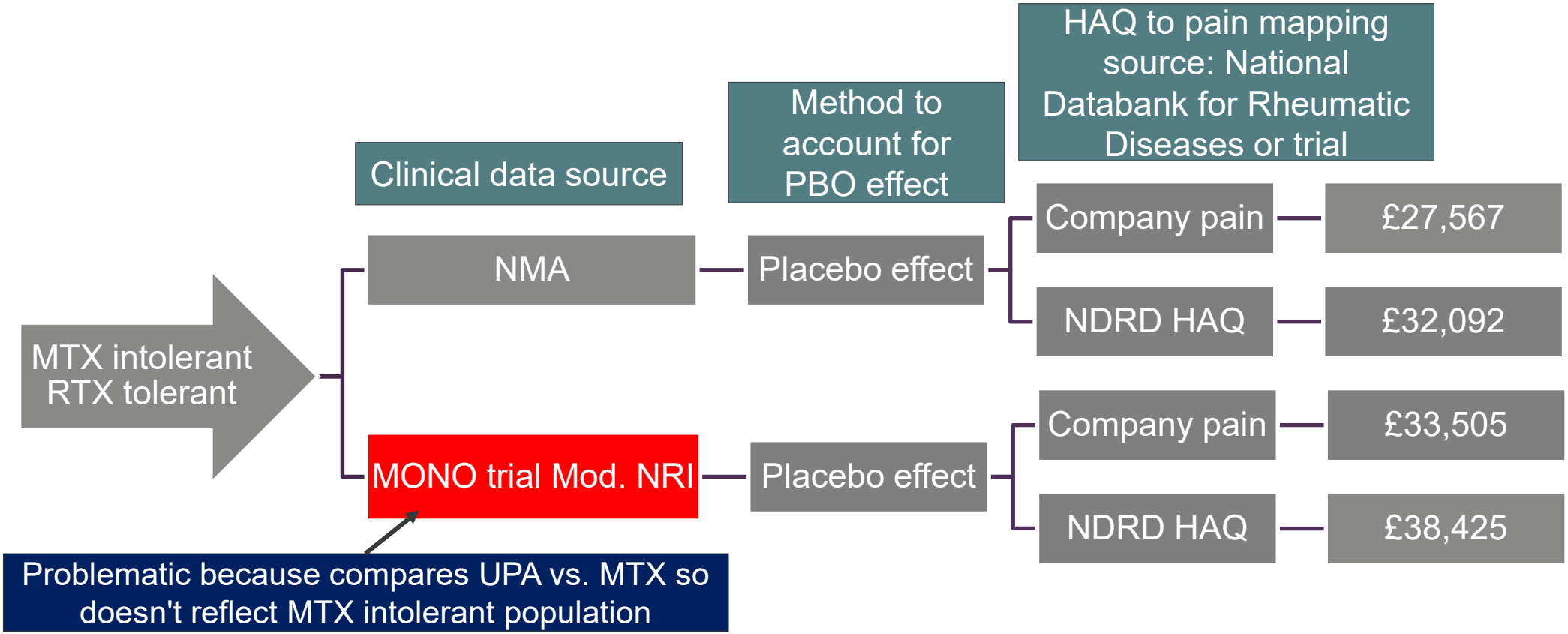
NICE requested analyses based on company's scenario assuming placebo effect in trials not seen in clinical practice but with MTX netted out of UPA + MTX. All ICERs in table based on NMA results and 'net treatment effect'



HAQ to pain mapping source	ICER (Original PAS)
Scenario 1: ERG base case	
Company	£14,551
NDRD HAQ	£16,815
Scenario 2: 19% progress from mod to severe	
Company	Dominant
NDRD HAQ	Dominant
Scenario 3: 19% progress from mod to severe & alternative treatment sequences severe RA	
Company	£82,293
NDRD HAQ	£94,509

ERG scenarios UPA vs. BSC (Pos 2a)

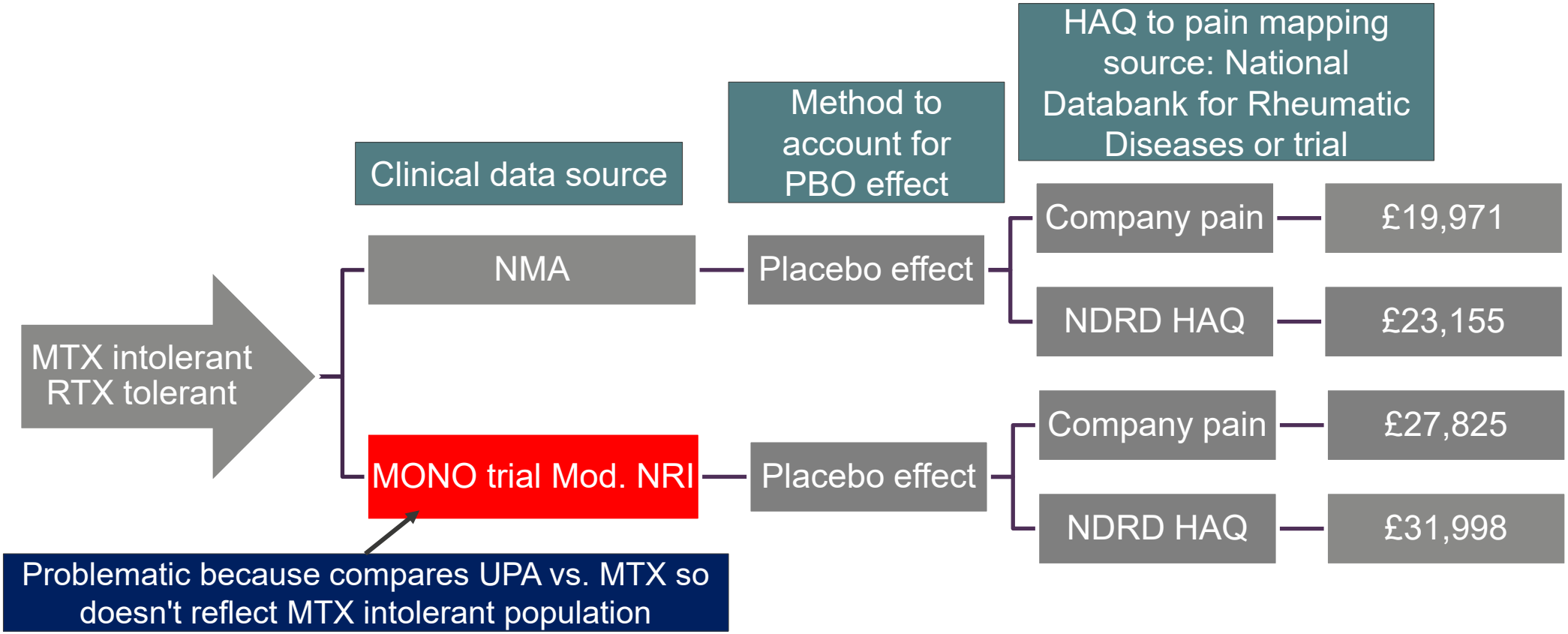
Note: all ICERs **based on ERG base case** (no changes to alternative treatment seq for severe RA based on UPA for mod RA or transition from mod to severe)



ICERs using company's 'net treatment' not shown. Original PAS for UPA and list price for all other treatments

ERG scenarios UPA vs. BSC (Pos 2a)

Note: all ICERs **include** 19% (2 yrs) transition from mod to severe

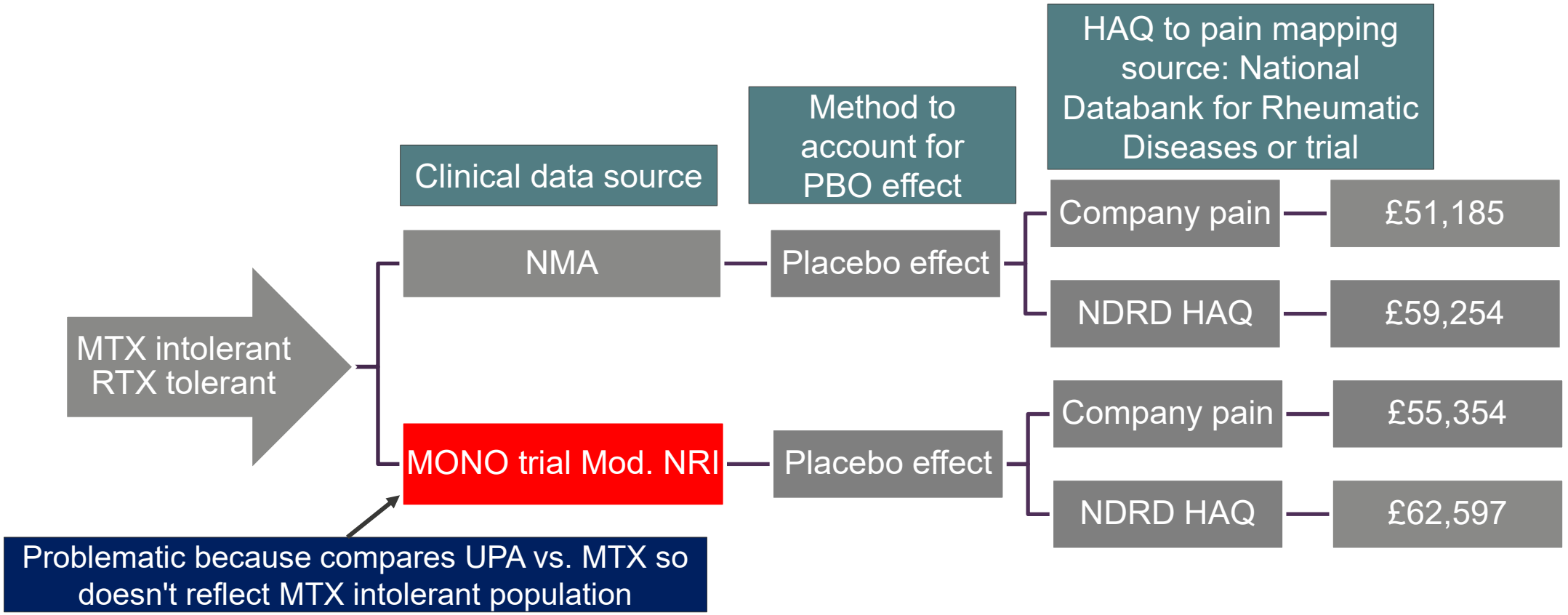


ICERs using company's 'net treatment' not shown.
Original PAS for UPA and list price for all other treatments

ERG scenarios UPA vs. BSC (Pos 2a)

Note: all ICERs **include**:

- ERG's alternative treatment sequences to treat severe RA based on UPA for mod RA
- 19% (2 yrs) transition from mod to severe



ICERs using company's 'net treatment' not shown.
Original PAS for UPA and list price for all other treatments

Other considerations – partial review of TA375

- Partial review of TA375, ID2710 - Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for moderate rheumatoid arthritis after conventional DMARDs only have failed (partial review of TA375) to start imminently
- To be considered by the NICE appraisal committee in January 2021 (subject to change)
- Company (Abbvie) ‘open to accepting a recommendation for Upadacitinib for moderate RA, subject to re-assessment if future guidance from the partial review of TA375 changes the treatment pathway for moderate disease’

Key Issues – Moderate RA

1. What clinical effectiveness data should be used to compare UPA with BSC – company's NMA or SELECT head-head to trials?
2. Does the company's proposed positioning post ACM 1 reflect committee's preferred position for moderate RA (pos 2a + 2b: after 2 or more csDMARDs)?
3. What is committee's preferred method to account for the placebo effect in the SELECT trials?
   a) apply placebo response to BSC when it's compared with UPA or any active treatment
   b) net out placebo effect from active comparator (cttee previously agreed this company scenario may be appropriate but would underestimate costs)
4. Is the company's scenario with more people progressing from moderate to severe RA acceptable?
5. Should the company's approach to mapping HAQ-to-pain scores be considered plausible?

Back up slides

Clinical data from trials vs. NMA

Net effect of UPA vs. PBO from NMA is somewhat larger than observed in trials. Some net effects results in negative numbers therefore cannot calculate some ICERs using 'net treatment effect' to account for PBO effect

	EULAR response rates									
			Control		UPA+MTX		UPA		Net	
SELECT trial	Wk	Control	Mod	Good	Mod	Good	Mod	Good	Mod	Good
csDMARD-IR NMA	-	PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
COMPARE EULAR NRI	26	PBO	24%	17%	19%	54%	-	-	-5%	37%
COMPARE EULAR NRI (mod RA only)	26	PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NEXT EULAR NRI	12	PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NEXT EULAR NRI (mod RA only)	12	PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MONO EULAR NRI	14	MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MONO EULAR NRI (mod RA only)	14	MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ACR, American College of Rheumatology; ; EULAR, European League Against Rheumatism; LOCF, last observation carried forward; NRI, non-responder imputation

Source: table 1 in ERG critique of company's ACD response (moderate RA from May version of ERG critique)