NICE National Institute for Health and Care Excellence

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Adalimumab, etanercept, infliximab and abatacept for moderate rheumatoid arthritis after conventional DMARDs only have failed (partial review of TA375)

Lead team presentation

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Companies: AbbVie, Amgen, Biogen, Bristol-Myers Squibb (BMS), Celltrion Healthcare, Fresenius Kabi, Pfizer & Sandoz.

ACM1: 10 March 2021

Partial review of TA375 – process overview

- TA375 recommends biological DMARDs for severe disease but not moderate disease – not cost-effective
- Prices have reduced and there are now some biosimilars
- Pragmatic review of TA375 – just moderate population, scope unchanged
  - use of biological DMARDs as first-line therapy after 2 or more csDMARDs
  - original Assessment Group model with minor updates and price changes
  - targeted submissions invited + comments on Assessment Report
- Not all companies participating in the review
  - committee won't revisit recommendations on certolizumab pegol, golimumab or tocilizumab in moderate disease
- Confidential prices for interventions and subsequent therapies mean all results confidential and will be discussed in private part 2
  - exceptionally, indicative ICERs presented in public part 1 to aid transparency

NICE Technology Appraisal (TA) 375

- NICE TA375 includes the following recommendations:
  - Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept, all in combination with methotrexate, are recommended as options for treating rheumatoid arthritis, only if:
    - ✓ **disease is severe,** that is, a disease activity score (DAS28) >5.1 and
    - ✓ disease has not responded to intensive therapy with a combination of conventional disease-modifying antirheumatic drugs (DMARDs)
  - Adalimumab, etanercept, certolizumab pegol or tocilizumab can be used as monotherapy for people who cannot take methotrexate.
  - Continue treatment only if there is a moderate response measured using European League Against Rheumatism (EULAR) criteria at 6 months after starting therapy.

Committee concluded that biological therapies could not be considered a cost-effective use of NHS resources for patients with **moderate active disease.**

Disease background

- Rheumatoid arthritis (RA) is an inflammatory autoimmune disease that can affect any synovial joint causing swelling, stiffness, pain and progressive joint destruction.
- It is a systemic disease and can affect the whole body including the lungs, heart and eyes.
- It is usually a chronic relapsing condition which has a pattern of flare-ups followed by periods of lower disease activity; however, for some people, the disease is constantly progressive.
- Severity of disease can be classified into 4 categories, based on the disease activity score (DAS28) scoring system:
    - DAS28 >5.1: high disease activity or severe disease
    - DAS28 = 3.2 - 5.1: moderate disease activity
    - DAS28 <3.2: low disease activity
    - DAS28 <2.6: disease remission.

Source: NICE final scope for ID2710

Summary of technologies

Technology	Companies (Reference / Biosimilar)	Mechanism of action	Administration
Abatacept	• BMS (Orencia)	Inhibits activation of T lymphocytes	Subcutaneous and intravenous injection
Adalimumab	• AbbVie (Humira) • Amgen (Amgevita) • Biogen (Imraldi) • Fresenius Kabi (Idacio) • Sandoz (Hyrimoz)	Tumour necrosis factor (TNF) inhibitor	Subcutaneous injection
Etanercept	• Pfizer (Enbrel) • Biogen (Benepali) • Sandoz (Erelzi)	TNF inhibitor	Subcutaneous injection
Infliximab	• Biogen (Flixabi) • Celltrion (Remsima) • Pfizer (Inflectra) • Sandoz (Zessly)	TNF inhibitor	Intravenous injection*

*Remsima is available as a subcutaneous injection but is not considered in this review – not in TA375 scope. The manufacturer of the reference product for infliximab (Remicade) is not participating in this appraisal.

Summary of technologies

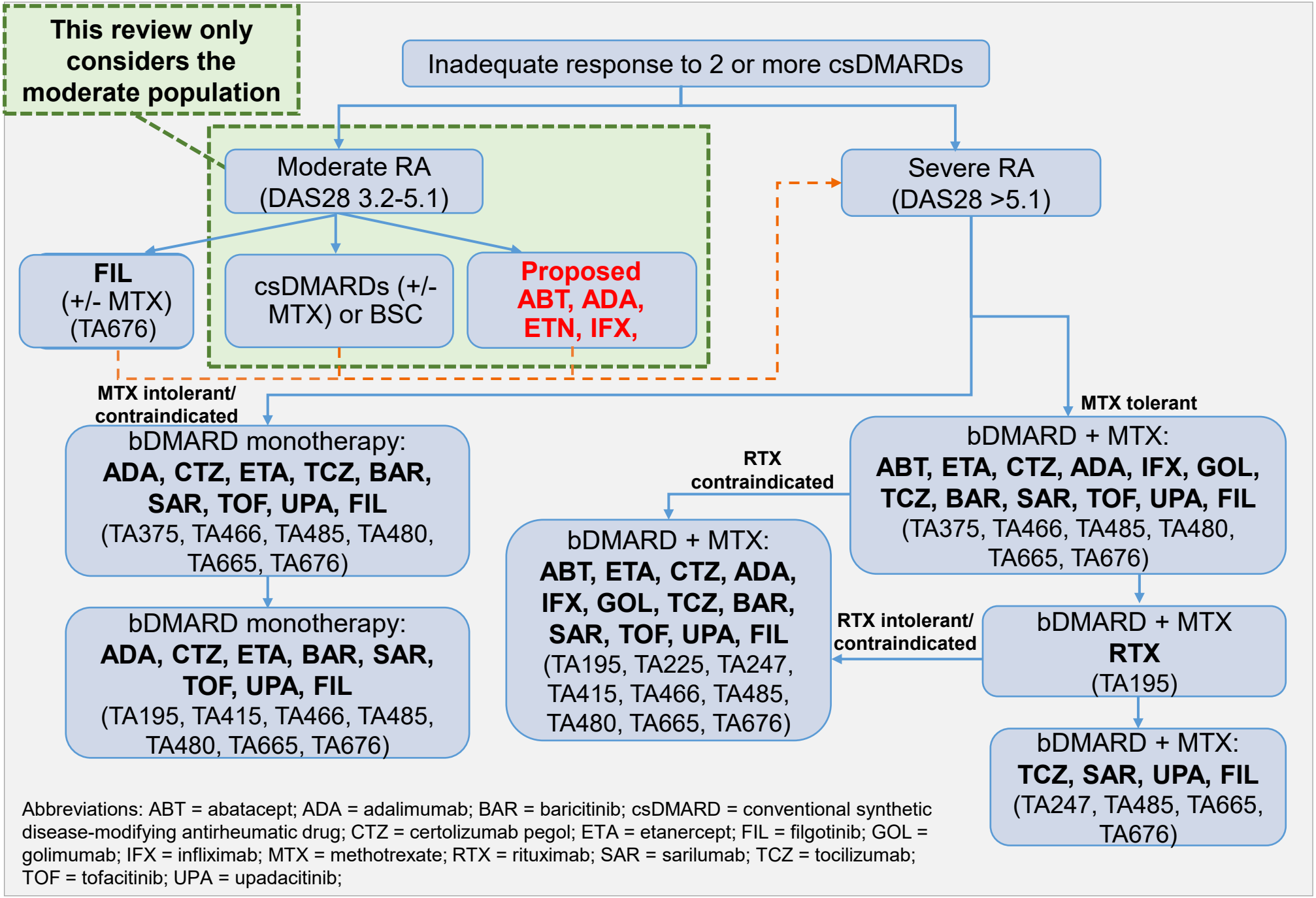
- All technologies have marketing authorisations for the treatment of moderate to severe active rheumatoid arthritis in combination with methotrexate.
- Adalimumab and etanercept can be used as monotherapy when treatment with methotrexate is not suitable.
- Technologies have confidential price discounts so prices cannot be reported here.
- Where available, prices used in model are inclusive of homecare support.

Decision problem of relevance to this MTA

Population	Interventions (includes biosimilars)	Comparators
Adults with moderate, active rheumatoid arthritis, whose disease has responded inadequately to, or who are intolerant of conventional synthetic DMARDs	• Adalimumab • Etanercept • Infliximab • Abatacept (iv and sc formulations)	• The interventions are compared with each other • Conventional synthetic DMARDs (csDMARDs), non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids.

- csDMARDs include methotrexate, leflunomide, sulfasalazine and hydroxychloroquine.
- Filgotinib (NICE TA676) has recently been recommended in moderate disease. Final guidance was published in Feb 2021, so it is not in the scope for this review.

Treatment pathway (based on current NICE guidance for RA)



Abbreviations: ABT = abatacept; ADA = adalimumab; BAR = baricitinib; csDMARD = conventional synthetic disease-modifying antirheumatic drug; CTZ = certolizumab pegol; ETA = etanercept; FIL = filgotinib; GOL = golimumab; IFX = infliximab; MTX = methotrexate; RTX = rituximab; SAR = sarilumab; TCZ = tocilizumab; TOF = tofacitinib; UPA = upadacitinib;

Patient expert perspectives

- Rheumatoid arthritis (RA) can be extremely painful and affect many parts of the body in addition to the joints.
- RA can cause significant disability and mobility issues which can result in high care needs for daily activities.
- RA affects the ability to work, everyday activities and relationships
    - young adults often feel less desirable, less confident and fear reduced fertility.
- Three out of four people diagnosed with RA are of working age.
- Patients need access to effective treatments at an earlier stage.
- Patients with refractory disease for whom the treatment benefit with many drugs is lost over time want a suite of biologics to treat or maintain the condition.
- Effective treatments can reduce depression and anxiety and enable people to remain in work.

"Even so called moderate disease has a massive, negative impact on quality of life."

"you…find yourself hoping that your condition becomes much worse and joint destruction visible in order to be considered for advanced therapies."

"These technologies have literally given people their lives back when csDMARDs are not fully effective at controlling disease activity."

Clinical expert perspectives

- "One size fits all" approach is not appropriate for patients with moderate RA and results in suboptimal care and unmet need: vital to respond to heterogeneous disease and population (age, multiple morbidities etc), drug safety and practical considerations
    - Better treatment of RA is generally associated with improved quality of life and outcomes including multimorbidity and cardiovascular events.
- "EULAR recommendations are exemplary" and evidence-based: they stress that a patient with a DAS28 >3.2 should have access to an advanced therapy.
- Biologic DMARDs are safe and improve the quality of life of people with RA when they can be "used optimally over a lifetime of the evolution of the disease".
- Data from UK patients with moderate disease activity (DAS28 range of 3.2-5.1) indicates that after 1 year of treatment, the likelihood of achieving a target low DAS28 <3.2, or a low HAQ by switching between or combining csDMARDs is poor.

"The current NICE guidance which the present MTA seeks to update has undoubtedly had an adverse impact on people with disabilities related to moderate rheumatoid arthritis over the last two decades."

NRAS survey: impact of living with RA in people not currently treated with advanced therapies

- Target population: people with RA, over the age of 16, with a disease duration of 2 years or more and living in the UK
- 612 respondents: mean age 59 years, 88% female:
  - Disease duration: 37.7% 2 to 5 years; 27.9% 5 to 10 years; 34.2% 10+ years
  - 86.4% were taking at least one csDMARDs[a] and 15.4% were on corticosteroids
  - 90% had at least one RA flare and 23% had six or more flares in the past year
  - Average (range) disease activity score (e.g. DAS28) was not reported
- Key author's messages:
  - In established RA patients not on advanced therapies, patient-reported outcome measures indicate high levels of suffering
  - A patient acceptable state on the Rheumatoid Arthritis Impact of Disease (RAID)[b] tool is very uncommon (12.4% patients)
  - High levels of pain, physical disability, sleep difficulties and fatigue are prominent symptoms

Source: Nikiphorou et al. (in publication).
[a] as a monotherapy in 262 patients (42.8%) and as a combination therapy in 267 patients (43.6%);
[b] 7 domains: pain, functional disability, fatigue, sleep, physical well-being, emotional well-being, and coping; each domain is scored on a 10-item numerical rating scale, with zero being a good or low activity score and 10 a high or severe activity score. Patient acceptable state is defined as a RAID total score below 2.

Patient and professional org. comments

- NICE guideline on management of RA in adults recommends to treat active RA with the aim of achieving a target of remission or low disease activity.
- Studies indicate that patients with moderate disease have a similar response to treatment with TNF inhibitors compared with patients with severe disease. Without access to advanced treatments many 'moderate' patients will have progressive disease with increasing morbidity.

"All those with 'moderate' RA who would benefit from biologic therapies would fulfil the criteria for disability as defined in the Equality Act 2010. Most of these individuals are unable to work but with treatment the majority would be able to return to work. It could be argued that denying treatment…that would enable them to work is discriminatory."

- National Rheumatoid Arthritis Society (NRAS) 2019 survey*:

"These findings question the use of DAS28…as the only [measure] to direct treatment escalation decisions…The patient global component does not reveal the breadth and severity of impact on RA on patients' everyday lives that measures such as RAID and composite PROM tools assess."

"Patients not currently treated with advanced therapies experience profound difficulties in everyday living with RA, across a broad range of measures."

*Source: Nikiphorou et al. (in publication)

Impact on carers

- It can be very hard for carers and children to cope with seeing a family member in pain or seeing the rapid deterioration of the health of a partner or parent with early RA
- Children may often become carers for parents living with RA or younger siblings. The parents worry about being a burden to their children or family

"This disease does very much impact…the whole family."

"Imagine not being able to pick up your baby and change its nappy."

"…dreams of being able to travel and look after grandchildren can suddenly seem unachievable."

We would like to thank the National Rheumatoid Arthritis Society (NRAS), British Society for Rheumatology, patient and clinical experts for their submissions.

Treatment efficacy of interventions used in model

Clinical evidence is not revisited for this review

EULAR response	ABA iv + MTX	ADA + MTX	MTX†	ETA + MTX	IFX + MTX	TCZ + MTX
Good	26.3%	28.1%	9.7%	53.0%	25.6%	57.2%
Moderate	41.4%	40.5%	35.5%	32.4%	42.8%	33.0%
No response	32.3%	31.4%	54.8%	14.6%	31.6%	9.8%

- Good response > moderate > no response
- Subcutaneous abatacept and rituximab are assumed to have the same efficacy of intravenous abatacept.
- If there is no EULAR response to a bDMARD after 6 months the next treatment in the strategy is used.
- Note that efficacy values are midpoint estimates. Uncertainty around these estimates was considered by the committee when recommending treatments for severe disease in TA375.

†Slide has been updated after the committee meeting to replace 'csDMARDs' with 'MTX' in the table. csDMARDs have zero efficacy.

TA375 Assessment Group original model

- Individual patient-based discrete event simulation model, lifetime time horizon
- The model assumed that after first biological DMARD treatment had failed, NICE guidance was followed (in line with the final scope).

General approach to modelling treatment effect in RA

- Based on change in Health Assessment Questionnaire (HAQ) score over time.
- HAQ scores range from 0 to 3 (scale with step values of 0.125):
    - An improvement in function is related to a decrease in HAQ
    - A better response to treatment is related to larger change in HAQ or HRQoL.

AG's approach to modelling treatment effect

- Initial response to treatment was modelled using the EULAR response data from the AG's network meta-analysis of clinical trials. Initial change in HAQ after a good and moderate EULAR response were estimated.
- HAQ progression after initial response estimated for csDMARDs and bDMARDs.
- Model assumed that after stopping treatment, initial improvement in HAQ lost.

Committee's preferred assumptions in TA375

Abbreviated protocol specified that these should be used in this review

Assumption	Committee's preference
Response measure	EULAR
Trials in NMA	Main analysis from the AG
HAQ progression **a) csDMARDs** **b) bDMARDs**	a) Disease progression whilst on treatment with csDMARDs modelled using the AG's adjusted ERAS dataset b) No change in HAQ whilst on bDMARDs (no progression of disease when on treatment)
Utility values	AG method of obtaining EQ-5D using a function from a mixture model developed using the NDB and ERAS datasets
Discount rate	3.5% for costs and benefits
HAQ/mortality	Only baseline HAQ associated with mortality, not HAQ increase
Adverse events	As per AG base case
Monotherapy without methotrexate	Results for bDMARDs with methotrexate to be generalised to bDMARD monotherapy in those who cannot tolerate it (if monotherapy included in the marketing authorisation)

ERAS = Early Rheumatoid Arthritis Study, NDB = US National Data Bank for Rheumatic Diseases

Updates to model as part of review

1. The model has been amended so that patients with moderate disease (who do not have biological DMARDs) can have biological DMARDs when their disease becomes severe, reflecting current clinical practice (not possible in the original model).
2. Amending treatment sequences to follow current NICE guidance (following comments on assessment report).

Modelling bDMARDs on progression to severe disease

- To model patients progressing to severe disease (DAS28 score >5.1) having treatment with bDMARDs, information on the relationship between the change in HAQ score and the change in DAS28 score was needed.
- A systematic review was conducted, supplemented by company submissions and papers identified by AG's clinical experts.
- From the results, the AG considers that the best estimate of change in DAS28 score associated with a 0.125 change in HAQ score was 0.48.
  - Sensitivity analyses use a lower estimate of [redacted] and upper estimate of 0.70.
- AG considers that there is uncertainty in the relationship between changes in HAQ scores and changes in DAS28 scores
  - HAQ score was increasing in only a few studies identified, so the AG assume that the relationship with decreasing HAQ scores would also apply when HAQ scores are increased.

Comments on Assessment report

General comments:

- Additional scenario analyses should be considered to quantity the uncertainty in the cost-effectiveness results including varying:
  - the rate of HAQ progression;
  - the time duration over which HAQ deteriorates;
  - the use of alternative utility mapping functions;
  - direct health effects to carers; and the societal perspective.
- The committee should consider recommending TNF inhibitors for the management of moderate RA after the failure of one csDMARD used in monotherapy to align with clinical practice and other RA guidelines.
- Despite all studies in the systematic review reporting an average DAS28 score within the moderate range of RA, patients were on average closer to the upper end of the threshold, representing the more severe RA patients.

The comments in the first 2 bullet points above are not within the scope of this pragmatic, partial review

Key comments on AG model

AG updated model before consultation

- The moderate treatment sequence (from TA375) replicates the severe sequence and is longer than that modelled in the filgotinib appraisal (NICE TA676) for patients with moderate RA.
- Rituximab is not licensed in moderate RA and tocilizumab is not participating in this appraisal

	Moderate	Progression to severe (DAS28 score >5.1)
Tx	**bDMARD1 → RTX → TCZ → csDMARDs**	**csDMARDs**
Cx	MTX† → csDMARDs	ADA → RTX → TCZ → MTX → csDMARDs

AG updated model after consultation

- The AG has amended the treatment sequence in line with all current NICE TA RA guidance.

	Moderate	Progression to severe (DAS28 score >5.1)
Tx	**bDMARD1 → csDMARDs**	**ADA* → RTX → TCZ → MTX → csDMARDs**
Cx	MTX† → csDMARDs	ADA → RTX → TCZ → MTX → csDMARDs

- The AG conducted a sensitivity analysis to remove methotrexate after tocilizumab (in line with TA676) which had little impact on the ICER.

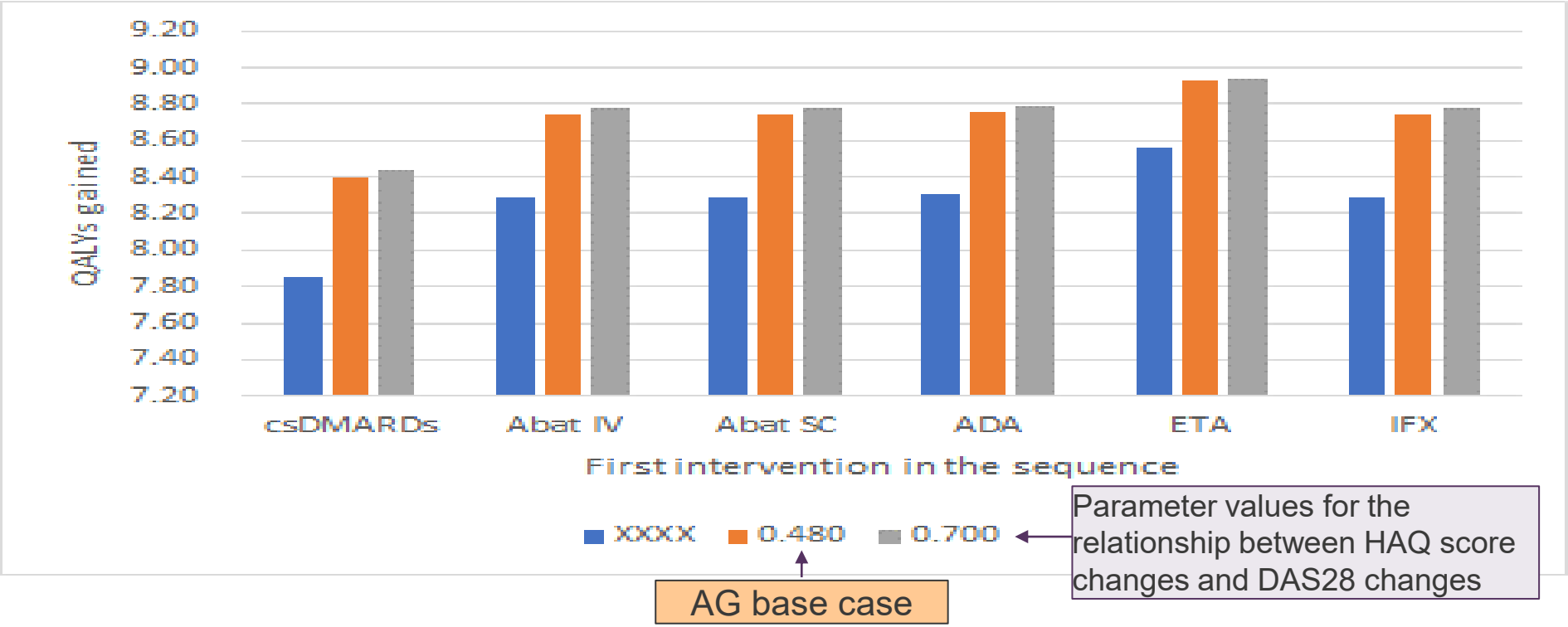
Tx = Treatment, Cx = Comparator

*Note that if first bDMARD in moderate disease was ADA, IFX would be used instead of ADA after progression to severe RA.

†**Slide has been updated after the committee meeting to add MTX to the treatment sequences**

Cost effectiveness results

- Because of the confidential discounts for the interventions and some subsequent therapies, the cost-effectiveness results are confidential and will be discussed in part 2 of meeting.
- QALYs gained by each strategy using the efficacy values (midpoint estimates) are presented:



The value used for the estimated change in DAS28 score associated with a 0.125 change in HAQ score has a minimal impact on the ICER. This is because increased QALY gains are associated with increased costs because of the earlier use of bDMARDs.

Cost effectiveness results

- Exact ICERs cannot be reported here. However, ICER ranges indicative of cost-effectiveness (AG base case) are below based on the updated treatment pathway.
- AG base case analyses use the cheapest formulation of each intervention. The availability of biosimilar adalimumab varies by region. Scenarios exploring the range of adalimumab prices are presented in part 2.

Treatment sequences used in model

	Moderate	Progression to severe (DAS28 score >5.1)
Treatment	bDMARD1 → csDMARDs	ADA → RTX → TCZ → MTX → csDMARDs
Comparator	MTX† → csDMARDs	ADA → RTX → TCZ → MTX → csDMARDs

First bDMARD in the moderate pathway (+MTX)	ICER compared with csDMARD (£/QALY gained)
Adalimumab	<£20,000
Infliximab	<£20,000
Etanercept	>£30,000
Abatacept (iv and sc)	>£30,000

†Slide has been updated after the committee meeting to add MTX to the treatment sequence

Key issues

- Is the Assessment Group's amended model appropriate for the decision problem being considered in this MTA?
- Are there any equality issues?
- Are abatacept, adalimumab, etanercept and infliximab with methotrexate cost-effective options for the treatment of moderate active RA (results discussed in part 2)?
- Are adalimumab and etanercept monotherapy cost-effective options for the treatment of moderate active RA (results discussed in part 2)?