NICE National Institute for Health and Care Excellence

Therapeutic monitoring of TNF-alpha inhibitors in rheumatoid arthritis

Diagnostics Assessment Report (DAR) - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG Response
DHSC	1			Thank you for the opportunity to comment on the above surveillance review proposal. I wish to confirm that the Department of Health and Social Care has no substantive comments to make, regarding this consultation.	Thank you for your comment
Greater Manchester Health and Care Commissioning	2			Due to both work and personal commitments, and timing of the registration as a stakeholder, I will not be able to provide constructive feedback in a required format on this occasion. On a brief reading through the papers I had the following thoughts: • If the percentage of RA patients that are classed as non-responders (both primary and secondary) is known? • Whether costing for biosimilars (note recent significantly lower cost of adalimumab) would be applied in the calculations.	The approach used in the model differs as no relevant clinical effectiveness evidence was identified which would allow such analyses was identified in the review The AG conducted a sensitivity analyses for a range of annual acquisition costs of ADL, £1000 to £9127 (the latter represents the acquisition cost of Humira®). Costing for biosimilars a sensitivity analysis was conducted assuming 20%, 40%, 60%, and 80% discount
R-Biopharm AG	3	20 of 420	Model assumptions	"Some people may flare after reducing the dose of their TNF inhibitors (Bykerk and colleagues, 2016)." This assumption does not reflect the value of TDM in dose tapering, as only patients with overexposure (e.g. drug concentrations >8 µg/mL) are to be considered eligible for dose tapering, as indicated by l'Ami MJ, Krieckaert CLM, Nurmohamed MT, et al. Ann Rheum Dis 2018;77:484–487. (In addition, the study by Bykerk includes also patients that stopped treatment, not only dose tapered patients)	None of the evidence reporting data from the INGEBIO study, reported flare rates in the intervention and control arms were not stratified according to dose (full or tapered), so the AG applied the same rate of flares to all patients (tapered and non-tapered) within each arm.

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R-Biopharm AG	4	11 of 420	Comparative study	Why was the following study excluded per population? l'Ami MJ, Krieckaert CLM, Nurmohamed MT, et al. Ann Rheum Dis 2018;77:484–487. This study adequately reflects a TDM-guided dose reduction that contributes to significant cost saving (33% of cost savings vs standard care), without significant reductions in Disease Activity Score. The population is >20 in each group and the study is a randomized controlled trial.	Thank you for your comment. The study was excluded because it did not meet one or more inclusion criteria for the systematic review. This study was excluded based on population as it did not consider it appropriate to use the mean DAS28 score at baseline to assume that all patients had achieved remission/ low disease activity at baseline and it is highly likely that a certain proportion of patients who had higher DAS28 score than the mean DAS28 score were not in remission/ low disease activity at baseline. In this trial, all patients were screened based on drug trough level of 8ưg/mL at baseline. This would imply that some eligible patients (e.g. those who were in remission) with drug level lower than 8ưg/mL would have been excluded and some ineligible patients (e.g. those who with moderate or high disease activity) with drug level meeting the cut-off would have been included. The study was also considered excludable on comparator because all the physicians in the control arm had the knowledge of drug and antidrug antibody levels to make their judgements. The AG also considered that the study was excludable on comparator

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					because all the physicians in the control arm had the knowledge of drug and antidrug antibody levels to make their judgements. The AG considered conducting a sensitivity analysis using data from the l'Ami study; however, considered it (refer to Addendum #1). Although demonstrating the potential benefit of TDM, the study assessed the concentration-response relationship. The intervention described in the study was ADL dose-interval prolongation and not TDM. The AG considered there to be limited value in conducting a sensitivity analysis using the data from l'Ami et al. (2018) due to uncertainty. This was due to the following factors: median ADL dose at Week 28 was comparable to baseline in both groups, and the small sample size (approximately 50 participants).
R-Biopharm AG	5	177	4.1.9.1.15 Training	This statement also applies for R-Biopharm and should not be presented as a 'Promonitor only' statement.	Thank you for your comment. Text has been amended to: "Based on the information provided by the companies and clinical opinion it was anticipated that minimal additional training would be required by healthcare staff to use any of the testing kits. Therefore training costs were not considered in the model."

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R-Biopharm AG	6	171	4.1.9.1.9 Assay costs provided by the manufacturers	We confirm the personal communication of Clinical expert Timothy McDonald that the R-Biopharm tests can be run in singlicate as well, a confirmation that is provided to customers only upon request. The cost of reflex testing is the cost of the drug level test + the cost of the anti-drug antibody level test for the R-Biopharm test kits. It can be easily calculated from the price statements of the individual kits. In addition, we did not specifically receive a question from NICE to provide the cost of reflex and concurrent testing. In addition, the Grifols pricing discounts should not be included. It does not contribute to the DAP and is clearly a marketing statement and thus a conflict of interest. This document is not supposed to contain hidden offers.	The tables (Table 54 and Table 55) and related text has been corrected to show the range of costs per the instructions for use documents and other information provided by the manufacturers.
R-Biopharm AG	7	173	Table 54	The information regarding the RIDASCREEN is incorrect. A Standard curve and 2 controls needs to be included, and as such the number of samples analysed per assay can be maximally 88 in singlicate testing and 40 in duplicate testing. This is also true for other tests listed. We did not specifically receive a question from NICE to provide the cost of singlicate and duplicate testing, respectively. Instead, we provided information on the total cost of one ELISA plate that consists of 96 wells.	The tables (Table 54 and Table 55) and related text has been corrected to show the range of costs per the instructions for use documents and other information provided by the manufacturers.
R-Biopharm AG	8	173	Table 55	I like to argue the Promonitor concurrent testing procedure. Up to my knowledge, they do not offer a test that measures 80 samples for IFX and ATI using one ELISA assay consisting of a 96 wells. I also doubt that Theradiag is offering an ELISA assay that is testing 96 samples concurrently as they need to run controls and standard(s) as well.	Table 55 has been removed and one table has been provided to show the range of costs per the instructions for use documents and other information provided by the manufacturers.

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R-Biopharm AG	9	General comment	Economic Analysis	The use of UCAR and ARANGO (or INGEBIO) as the primordial source of evidence consists of serious limitations, as the authors adequately addressed in their manuscript. The study was not a pure TDM vs standard care trial and was non-randomized. In the control group, an almost equal amount of patients is dose tapered compared to the interventional group and it is not clear how many times dose tapering in the interventional group could be assigned to the use of TDM. Likewise, it is unclear how many times dose tapering is not performed because of TDM (e.g. in case a patient has low drug concentrations). The lack of availability of these data hampers the analysis. Can't these data be obtained from the authors? The use of a well-designed study in which only patients with high drug concentration are tapered, offers the advantage to focus purely on the utility of TDM. This has been done by l'Ami MJ, Krieckaert CLM, Nurmohamed MT, et al. Ann Rheum Dis 2018;77:484–487. It is thus surprising to see that this study has not been discussed in depth in the DAP.	Thank you for your comment. The limitations related to the INGEBIO study are discussed in the report. Data were not available in the publications identified i.e. abstracts or the posters provided by the authors. Reference response to Comment #4 regarding the reasons that the l'Ami study was excluded from the review. In addition, the l'Ami study was considered for use in a sensitivity analysis (refer to Addendum #1). Although demonstrating the potential benefit of TDM, the study assessed the concentration-response relationship. The intervention described in the study was ADL dose-interval prolongation and not TDM. The AG considered there to be limited value in conducting a sensitivity analysis using the data from l'Ami et al. (2018) due to uncertainty. This was due to the following factors: median ADL dose at Week 28 was comparable to baseline in both groups, and the small sample size (approximately 50 participants). In addition the proportion of participants with high drug level was not reported.
R-Biopharm AG	10	68		No product numbers listed for the RIDASCREEN ELISAs (G09041 – G09044)	Thank you. We have added to the erratum.

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Amgen	11	60	Table 10	Solymbic can be removed from the documentation- this is not available in the EU. Amgevita is the licenced product in the UK and European market	Thank you. Footnote added to the table
Amgen	12	164	Table 50	Solymbic can be removed from the documentation- this is not available in the EU. Amgevita is the licenced product in the UK and European market	Thank you. Footnote added to the table – reference the addendum including revisions for clarification
Amgen	13	233	Appendix 1	Solymbic can be removed from the documentation- this is not available in the EU. Amgevita is the licenced product in the UK and European market	The searches were as broad as possible due to the paucity of evidence, in an attempt to capture any possibly relevant literature from any country. It is not possible to remove this term from the searches as the searches were carried out in July 2018. Any irrelevant abstracts were discarded at the screening stage.
Amgen	14	237	Appendix 1	Solymbic can be removed from the documentation- this is not available in the EU. Amgevita is the licenced product in the UK and European market	Thank you. See response to Comment 13
Amgen	15	239	Appendix 1	Solymbic can be removed from the documentation- this is not available in the EU. Amgevita is the licenced product in the UK and European market	Thank you. See response to Comment 13
Amgen	16	241	Appendix 1	Solymbic can be removed from the documentation- this is not available in the EU. Amgevita is the licenced product in the UK and European market	Thank you. See response to Comment 13
Amgen	17	244	Appendix 1	Solymbic can be removed from the documentation- this is not available in the EU. Amgevita is the licenced product in the UK and European market	Thank you. See response to Comment 13
Amgen	18	248	Appendix 1	Solymbic can be removed from the documentation- this is not available in the EU. Amgevita is the licenced product in the UK and European market	Thank you. See response to Comment 13

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Amgen	19	252	Appendix 1	Solymbic can be removed from the documentation- this is not available in the EU. Amgevita is the licenced product in the UK and European market	Thank you. See response to Comment 13
Amgen	20	255	Appendix 1	Solymbic can be removed from the documentation- this is not available in the EU. Amgevita is the licenced product in the UK and European market	Thank you. See response to Comment 13
Amgen	21	261	Appendix 1	Solymbic can be removed from the documentation- this is not available in the EU. Amgevita is the licenced product in the UK and European market	Thank you. See response to Comment 13
Amgen	22	264	Appendix 1	Solymbic can be removed from the documentation- this is not available in the EU. Amgevita is the licenced product in the UK and European market	Thank you. See response to Comment 13
Amgen	23	267	Appendix 1	Solymbic can be removed from the documentation- this is not available in the EU. Amgevita is the licenced product in the UK and European market	Thank you. See response to Comment 13
Amgen	24	272	Appendix 1	Solymbic can be removed from the documentation- this is not available in the EU. Amgevita is the licenced product in the UK and European market	Thank you. See response to Comment 13
Amgen	25	274	Appendix 1	Solymbic can be removed from the documentation- this is not available in the EU. Amgevita is the licenced product in the UK and European market	Thank you. See response to Comment 13
Amgen	26	410	Appendix 4	Solymbic can be removed from the documentation- this is not available in the EU. Amgevita is the licenced product in the UK and European market	Thank you. See response to Comment 13
Amgen	27	20		Up to date discount levels for Amgevita can be provided upon request in order to update cost model	Thank you. A sensitivity analysis has been conducted in which the ADL price has been discounted by 20%, 40%, 60%, 80% (refer to Addendum #2)

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Amgen	28	18		Update to reflect launched status of biosimilars	Thank you. It was stated in the report that the information provided was correct in November 2018.
Cambridge Life Sciences Ltd	29	173	Table 54/55	LisaTracker price provided is list price however we rarely sell at list price as discounts are offered on volume and purchasing of associated independent quality control sera for drug and anti-drug assays.	Thank you. The text and this table has been updated considering also the comments above
Pfizer	30			Thank you for the email and the opportunity to review these resources. Pfizer have reviewed the documents and have no comments at this time.	Thank you.
Grifols UK Ltd	31	17	Cost of Testing	The costs of the TDM service based at Glasgow for the nationally commissioned service potentially should have been considered for expert advice.	Thank you for raising this. We considered a range of costs for inclusion in the analysis and the Team considered that the most applicable estimates were used (considering the possibility that an initial phlebotomy appointment may vary between centres in scenario analysis).
Grifols UK Ltd	32	17	Concurrent vs Reflex testing	The TDM service based at Glasgow has some preliminary analysis which demonstrates that a reflex strategy should be adopted. Since a large proportion of patients, circa 40%, had high drug levels for both IFX and ADL and reported high total antibodies for both aIFX and aADL. These were deemed to be false positive results and negated the need for a total aADL or aIFX test in patients with high drug levels. The approach was to then reflex only if serum drug levels (DL's) were low. It is understood that the same blood sample would be used to test for antidrug antibodies (ADA's) and wouldn't require a further blood sample. Please note the majority of testing performed	Thank you for your comment. The summary has been corrected to reflect the relevant section of the main report; i.e. in a scenario in which reflex testing is performed, an additional phlebotomy appointment (which is the key driver of the testing cost) would not be required (assuming that storage of blood samples is common practice at test laboratories). When modelling reflex testing the AG considered 4.6% and 35.8% as the lower

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				thus far has been from gastroenterology but this approach can be extrapolated into rheumatology.	and upper bounds for the proportion of patients with low drug level when modelling reflex testing.
Grifols UK Ltd	33	17 & 18	Frequency of TNF Testing	Based on the ongoing review of the service with NHS Scotland the frequency of testing could be up to 4 tests per year as a 'worst case scenario' in the first year of treatment. The testing conducting during the induction phase would be to establish serum DL's associated to clinical response specific to each individual patient. Once established and in remission we agree that testing should be conducted once per annum or, as and when, required to taper dose based on EULAR recommendations. Currently no evidence is available for a 'treat to target' protocol which is being considered. Based on the adjusted threshold values imputed into the adapted model 'ELISA PenTAG DAR model 7 Jan 2019 (no ACIC)_UpdatedArangoIssue1' and based on the costs for DL's and ADA's from NHS Scotland and averaging out frequency of testing to 2 per patient annually, in any combination of DL or ADA, neither of the thresholds from either UCAR 2017 or Arango 2017 would potentially be met, see below table. We'd estimate the cost of testing to be between £50 -£100 per year per patient. Further clarification can be sought from NHS Greater Glasgow and Clyde regarding costs as this information is confidential. *Threshold analysis:* **Ucar** £1,000 £9,187 20K £364 £391 30K £394 £421 **Arango** £1,000 £9,187 20K £111 £155 30K £107 £151	In the threshold analysis, the total annual cost of TNF testing is estimated for the cost-effectiveness thresholds of £20,000 and £30,000 per QALY under a range of the annual acquisition costs of adalimumab (£1000 to £9187). In the cost-utility analysis, the frequency of testing can be set either to one per year or six-monthly.
Grifols UK Ltd	34	20	Major assumptions	ADL dose tapering is implemented by increasing the interval from 2 to 3 week intervals, could this be increased further to	The AG conducted a sensitivity analysis where dose tapering is implemented by increasing the interval to 4 weeks.

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				4/5 weeks as demonstrated with other biologics such as Enbrel.	
Grifols UK Ltd	35	24	Table 4	We are able to provide results from the INGEBIO trial published by Arango 2017 for duration in remission only (as opposed to duration in remission or low disease activity [LDA]).The figures are as below: Group / Mean / N / Standard deviation / Sum / Median control 360,00 52 226,181 18720 401,00 intervention 362,22 98 213,997 35498 437,50 Total 361,45 150 217,542 54218 431,00 This gave an adjusted threshold analysis as follows: *Threshold analysis:* Ucar: £1,000 £9,187; 20K £364 £391; 30K £394 £421. Arango: £1,000 £9,187; 20K £111 £155; 30K £107 £151	Thank you for providing these data, refer to Addendum #4
Grifols UK Ltd	36	26, 28, 31 &32	Table 5,6,7	Based on the adjustments for Arango 2017,outlined in comment 35, intervention would dominate standard care if the findings are accepted.	Please refer to Addendum #5
	37	36 & 37	Cost of Treatment	Grifols had taken into consideration to the introduction of biosimilars into NHS landscape, and the reduction in acquisition costs of these treatments, by adopting a singlicate strategy with a cost per diagnostic of £8.80. We anticipated that the net savings would be less given the substantial price reductions, hence the volume discounts applied to Promonitor reduce cost per diagnostic. However, utilising TDM for biologics with higher acquisitions costs would remain significantly 'cost effective'	The AG has explored the effect of singlicate testing and reduction in price of tests kits depending on uptake of testing. The model is capable of estimating ICERs under different assumptions on the uptake of testing. In addition the

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Grifols UK Ltd	38	131 & 138	Table 35 & 3.5	No strategy was considered for Drug level only testing and then reflexing to ADAb and only considered drug level testing in remission at 2 and 3 years.	The AG has considered concurrent and reflex testing scenarios in line with the NICE scope
Grifols UK Ltd	39	144	4.1.3.1	The Results section of the DAP41 claims that "*One non-randomised trial (the INGEBIO study, only reported in three abstracts) compared TDM with standard care had serious limitations in relation to the NICE scope: one-third of participants with RA, analyses were mostly not by intention-to-treat, follow-up only 18 months,…*". However, DAP41 authors should bear in mind that in the case of non-inferiority studies as the INGEBIO Study, the analysis should be done as per-protocol or complete case, instead of Intention-To-Treat (ITT) (as opposite to other type of studies), because the "per-protocol" approach is a more conservative methodology due to the design of a non-inferiority design. Actually, ITT is almost considered incorrect.	The ITT is the method of choice for superiority studies, but there is controversy for non-inferiority studies. However, only raw data from the study were used in the model the analysis reported in the paper (measure of association), was not used. Refer to: https://www.ncbi.nlm.nih.gov/pubmed/16397861