NICE National Institute for Health and Care Excellence

DIAGNOSTICS ASSESSMENT PROGRAMME

Therapeutic monitoring of TNF-alpha inhibitors in rheumatoid arthritis

Diagnostics Consultation Document – Comments

Diagnostics Advisory Committee date: 16 April 2019

THEME: GENERAL COMMENTS

Comment number	Name and organisation	Section number	Comment	NICE/EAG considerations
1	Grifols UK Ltd	1.2	Grifols UK Ltd will continue to support therapeutic drug monitoring (TDM) data collection through various centres currently using Promonitor within the NHS and wider geographies.	Thank you for your comment.
2	R-Biopharm AG		We took note of the DCD and have no further comments on the DCD. I would like to express my appreciation for the detailed answers to our raised comments on the DAP and have no further concerns on the DCD.	Thank you for your comment.
3	DHSC		No comments	Thank you for confirming.
4	Sanquin		No comments; attached full-text publication, Pascual-Salcedo et al. 2015 (http://dx.doi.org/10.4172/2329-6887.1000172)	Thank you for confirming and sending the full-text published study (Pascual-Salcedo et al. 2015). The evidence section of the guidance document has been updated to reflect the new evidence (sections 4.12-2.16).

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THEME: CURRENT STANDARD CARE IN THE UK AND THE GENERALIZABILITY OF INGEBIO

Comment number	Name and organisation	Section number	Comment	NICE/EAG considerations
5	Grifols UK Ltd	1.3	We feel that the INGEBIO is generalisable to the NHS practice as many centres across the UK do dose- de-escalate albeit mainly through increasing dosing interval but with a similar objective of finding the minimal effective dose for a specific patient.	Thank you for your comment which the committee considered. The committee heard from experts that although there is a considerable interest in developing local algorithms for dose reductions based on clinical judgement, it is not a standard practice in the NHS at the moment. This is captured in sections 2.13 and 5.4 of the diagnostics guidance document. A sentence has been added to section 2.13 to capture expert opinion on the high interest in developing local algorithms for dose reductions of TNF-alpha inhibitors based on clinical judgement only.
6	Grifols UK Ltd	2.13 & 2.14	From our experience and feedback from physicians across the UK dose reduction is widely adopted albeit by clinical judgement alone. The addition of TDM will help better inform the patient and clinician utilising a more quantifiable approach.	Thank you for your comment which the committee considered. The committee heard from experts that although there is a considerable interest in developing local algorithms for dose reductions based on clinical judgement, it is not a standard practice in the NHS at the moment. This is captured in sections 2.13 and 5.4 of the diagnostics guidance document. A sentence has been added to section 2.13 to capture expert opinion on the high interest in developing local algorithms for

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				dose reductions of TNF-alpha inhibitors based on clinical judgement only. The committee considered potential benefits of therapeutic monitoring of TNF-alpha inhibitors in scenarios with and without dose reductions based on clinical judgement only. This is reflected in Section 5.5 of the diagnostics guidance document.
7	Grifols UK Ltd	13 [2.13]	Agreed that no standard algorithms exist for dose reduction of TNF-alpha inhibitors but many centres across the UK extended the dose intervals in some cases up to 4 weeks with certain biologics.	Thank you for your comment which the committee considered. The committee heard from experts that although there is a considerable interest in developing local algorithms for dose reductions based on clinical judgement, it is not a standard practice in the NHS at the moment. This is captured in sections 2.13 and 5.4 of the diagnostics guidance document. A sentence has been added to section 2.13 to capture expert opinion on the high interest in developing local algorithms for dose reductions of TNF-alpha inhibitors based on clinical judgement only.
8	Grifols UK Ltd	4.8	As discussed in comment 2 [here, comment #5], it could be considered that the 'standard care' in Spain is similar to that received by patients in the NHS since treatment decisions are routinely made by clinical	Thank you for your comment which the committee considered.

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			judgement alone and on a patient by patient basis. We note however no specific algorithm for guidance was given.	The committee noted that standard care in Spain for people with rheumatoid arthritis who have reached their treatment target involves reducing the doses of TNF-alpha inhibitors. The committee heard from experts that in the UK, although there is a considerable interest in developing local algorithms for dose reductions based on clinical judgement, it is not a standard practice in the NHS at the moment. This is captured in sections 2.13 and 5.4 of the diagnostics guidance document. A sentence has been added to section 2.13 to capture expert opinion on the high interest in developing local algorithms for dose reductions of TNF-alpha inhibitors based on clinical judgement only.

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THEME: ADDITIONAL BENEFITS OF THERAPEUTIC MONITORING

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9	Grifols UK Ltd	2.2	TDM will certainly demonstrate non-compliance which cannot be addressed by clinical judgement alone. A patient expressing no serum drug levels and no ADA would unequivocally prove non-adherence to biological therapy. Adherence rates for hospital infused biologics are typically around 91% whilst sub-cutaneous homecare therapies, adherence is around 69%.	Thank you for your comment which the committee considered. The EAG did not conduct economic analysis for people with rheumatoid arthritis for whom adherence with TNF-alpha inhibitor treatment could be an issue. This was due to the lack of clinical evidence on the effect of therapeutic monitoring of TNF-alpha inhibitors in such patients. The committee agreed that the therapeutic monitoring of TNF-alpha inhibitors could help improve adherence to TNF-alpha inhibitors by helping to identify people for whom this could be a problem, and facilitating discussion on the importance of adherence. However, clinical experts commented that concerns about adherence would not be the main reason for using therapeutic monitoring of TNF-alpha inhibitors. Paragraph 5.7 has been added to the diagnostics guidance document to reflect the committee discussion of the impact of therapeutic monitoring of TNF-alpha inhibitors on adherence.

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10	Grifols UK Ltd	5.6	We agree that TDM will certainly provide reassurance of dose reduction but also in those patients where compliance may be an issue and ultimately will assist the physician in identifying those in drug free remission, i.e No drug level.	Thank you for your comment which the committee considered. The committee agreed that the therapeutic monitoring of TNF-alpha inhibitors could help improve adherence by helping to identify people for whom adherence could be a problem. However, clinical experts commented that concerns about adherence would not be the main reason for using therapeutic monitoring of TNF-alpha inhibitors. Paragraph 5.7 has been added to the diagnostics guidance document to reflect the committee discussion of the impact of therapeutic monitoring of TNF-alpha inhibitors on adherence.

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THEME: ECONOMIC MODEL: CLINICAL DATA INPUTS

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11	Grifols UK Ltd	4.50, 4.52	Please see attached the INGEBIO full study report [commercial-in-confidence] which hopefully should answer some questions outlined by the committee. In both analysis the data seen from the TDM service for NHS Scotland would demonstrate that the overall cost of testing per patient annually would be lower than both the ICER thresholds of £20k & £30K for both UCAR and Arango analyses. With the additional analysis and data supplied, please also see attached the INGEBIO full study report, the Arango analysis dominated standard care, similar to UCAR as noted in 4.51.	Thank you for your comment and for providing the full study report from the INGEBIO study. The committee considered the comment and the additional analyses prepared by the EAG using the data from the full study report (data on clinical outcomes, and the type and frequency of testing). The committee discussed the substantial imbalances between study groups in the INGEBIO study, and lack of certainty in the clinical estimates taken from this study. The committee concluded that the degree of uncertainty in the current clinical evidence was too high for it to be able to use the model for decision-making. The guidance document has been revised throughout to reflect the evidence from the full-text study report, and additional analyses prepared by the EAG.
12	Grifols UK Ltd	4.57	Discounts applied to ADL of up to 80% should be the same in both analyses, testing dominates standard care.	Thank you for your comment which the committee considered. The EAG conducted sensitivity analyses on adalimumab discounts of up to 80%, which can be

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				found in Addendum 4 of the diagnostics assessment report. The guidance document has been revised to reflect the results of updated sensitivity analyses (section 5.53).
13	Grifols UK Ltd	4.61	As comment 11 [here: also comment #11] based on the new information for Arango supplied in the previous response.	Thank you for your comment and for providing the full study report from the INGEBIO study. The economic model has been updated with clinical data from the full study report and the updated health state costs. However, exploratory analyses for infliximab and etanercept were not repeated. The committee concluded that the degree of uncertainty in the current clinical evidence from INGEBIO was too high for it to be able to use the model for decision-making.
14	Grifols UK Ltd	5.8	A full text peer reviewed publication is in the process, please see attached the full INGEBIO study report.	Thank you for submitting the full INGEBIO study report. The EAG's analyses and the guidance document have been revised to reflect data from this report. A note was added stating that peer-review publication is in progress (section 5.10 of the diagnostics guidance document)

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THEME: ECONOMIC MODEL: COST INPUTS

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15	Grifols UK Ltd	4.41	A reflex strategy is adopted by NHS Scotland. This is where the drug levels are measured first, with retention of the serum sample in case an ADA is analysis is required, and then reflexed to a Free or Total antibody if the drug levels are below 7ug/ml for Adalimumab(ADL) or 4ug/ml for Infliximab (IFX). Analysis of nearly 2,000 samples of RWE has demonstrated that the model assumptions costs per sample were nearly 7 fold higher than sample costs for NHS Scotland [redacted] for drug level and [redacted] for ADA level. The number of tests performed is roughly 2-3 drug levels and 1 ADA level per patient annually. This reduces the cost from a concurrent strategy as most of the ADA levels were required and when utilising the Total ADA level assays, not Promonitor which measures Free Levels, around 40% were reporting high Total ADA level in the presence of High drug levels for both IFX and ADL	Thank you for your comment which the committee considered. The EAG's updated model (Addendum 4 of the diagnostics assessment report) assumed reflex testing, with the proportion of anti-drug antibodies testing based on the INGEBIO full study report (commercial-in-confidence). The costs used in the model were based on a published microcosting study by Jani et al. 2016, adjusted for single testing of the samples (Jani et al. 2016 assumed double testing of each sample). The committee heard that an additional phlebotomy appointment may be needed to measure trough drug levels. This additional appointment would not be needed if drug levels of TNF-alpha inhibitors could be measured at any time in the administration cycle. This was explored in sensitivity analyses. Sections 4.41 and sections 4.49-4.53 of the diagnostics guidance document have been revised to reflect the updated analyses, assuming reflex testing.

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THEME: ECONOMIC MODEL: COST INPUTS

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16	Grifols UK Ltd	4.45	We feel the costs associated with the low disease activity were more than likely on the elevated side at £18,889, similar to that of High disease activity. In addition, the Arango analysis costs associated with high disease activity were £3,254 higher than those patients in the UCAR analysis.	Thank you for your comment which the committee considered. The EAG found an error in their calculations of the health state costs. The updated model (Addendum 4 of the diagnostics assessment report) used corrected health state costs. The guidance document has been adjusted to report the correct health state costs (section 4.45) and updated costs-effectiveness results (sections 4.49-4.53).

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THEME: ANALYTICAL PERFORMANCE

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17	Grifols UK Ltd	5.11	The analytical performance of the ELISA's was challenged in DG22. Now with the introductions of the WHO standard, a whole plethora of validation evidence was performed at Queen Elizabeth University Hospital with Promonitor drug level assays being the assay of choice due to the low common variance in both the manual and automated use, <8%. It is our understanding other manufacturers have now changed various aspects of their assays to bring them closer in line with the WHO standard.	Thank you for your comment which the committee considered. The diagnostics guidance document notes that despite recent progress there is still variability between results generated by the different ELISA tests, and between different laboratories, especially for TNF-alpha inhibitors other than infliximab. The committee concluded that there is potential uncertainty in the analytical performance of the ELISAs (section 5.12 of the diagnostics guidance document). The committee decided that no changes to the guidance document in relation to the analytical validity of the tests were needed.