ERG's critique of the Company's additional evidence submitted at the Appraisal Consultation stage

Addendum to ERG Report

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At the second Appraisal Committee meeting on 24 March 2015, the ERG agreed that in this report it had misinterpreted the company's new approach to modelling transition probabilities for patient who had discontinued treatment or who had been censored (see section 3.100 of the final appraisal determination [FAD] for details).

Consequently, the Committee did not take into account the criticisms in the ERG's written report when considering the company's new approach to modelling what happened to patients who discontinued or were censored (see section 4.22 of the FAD for details).

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BMJ Technology Assessment Group

1 SUMMARY

In response to the Appraisal Consultation Document (ACD) the company supplied a revised health economic model based on the MEAD studies comparing dexamethasone (DEX700) with watch and wait for patients with a natural lens who either do not respond to, or are not suitable for, non-corticosteroid therapies. The new analysis incorporated the corrections the ERG had made in their review of the original submission. These corrections were listed as B1, B2, B4 and B5, and C6 to C12 in the ERG report.

In addition the company made the following changes in an attempt to alleviate concerns raised by the Appraisal Committee:

- **Residential care:** in the new analysis the company uses a weighted cost that is 95% of the cost of private sector residential care and 5% of the cost of local authority residential care;
- **Patient discontinuations:** in the new analysis patients who discontinue from treatment remain in their health state prior to discontinuing for the remainder of the 3-years of treatment;
- **Alternative utility values:** in the new analysis the company uses the utility values from Czoski-Murray *et al.*[1] which have a wider range than those derived from the MEAD studies (as well as providing alternative analyses using the Brown[2] and Brown *et al.*[3] utilities);
- **Clinical continuation rule:** in the new analysis, the company applies a continuation rule for DEX700, whereby patients have to have gained at least 5 letters by Month 6 to continue treatment.

The ERG has reviewed the new health economic model and considers the following:

- **Residential care:** the ERG considers the company's revised assumption regarding provision of residential care to be reasonable;
- **Patient discontinuations:** the ERG considers it to be clinically implausible that patients discontinuing will have stable disease (i.e. will remain in their health state at discontinuation), as diabetic macular oedema (DMO) is a progressive disease where a patient's vision deteriorates over time if not treated. The new assumption creates a perverse incentive in the model whereby patients receiving DEX700, who discontinue, continue to receive the benefit of treatment but without incurring the cost of treatment. The ERG considers that the earlier assumption where patients who discontinue will revert to their natural history of vision decline is the least biased of the two assumptions;

Superseded - see section 3.100 of the FAD

- **Alternative utility values:** due to time constraints the ERG has only evaluated the implementation of the utility values from Czoski-Murray *et al.*[1] in the new analysis. The ERG considers the company's implementation of the utility for the worst-seeing eye (WSE) is flawed in the new model, e.g. it can result in the WSE contributing a higher utility value than the best-seeing eye (BSE) to a patient. The ERG considers the approach it took in the original ERG Report (scenario analysis C13) to be a more valid approach;

- **Clinical continuation rule:** as far as the ERG can ascertain, the company has implemented the clinical continuation rule as described. However, it is beyond the scope of this review for the ERG to evaluate the feasibility of its implementation.

The company presents a revised base case ICER of £14,978. Using the company's revised model and implementing the ERG's preferred approach to patient discontinuations and implementation of the utility values from Czoski-Murray *et al.*[1] increases the ICER to £127,645.

2 BACKGROUND

The Appraisal Committee noted that it preferred the revised base case analysis by the ERG (for patients with DMO who are considered to be unsuitable for or insufficiently responsive to non-corticosteroids), when the efficacy of watch and wait was based on patient-level data from the pooled MEAD sham arms. This resulted in an ICER of £1,166,271 per QALY, but the Committee deemed that this was likely to be overestimated. The revised ERG base case ICER was estimated after combining all model corrections undertaken by the ERG (analyses B1, B2, B4 and B5) and additional scenarios considered in the analyses (C6 to C12) performed by the ERG. For completeness these amendments are described below:

- **Analysis B1:** the annual probability of fellow-eye involvement (FEI) corrected to [redacted];
- **Analysis B3**: the probability of cataract for DEX700 in Years 1, 2 and 3 was amended to [redacted], [redacted], and [redacted], respectively; the annual probability of cataract for patients with DMO receiving no treatment or watch and wait was amended to 2.32%;
- **Analysis B4**: the cost of a fluorescein angiography was amended to £144;
- **Analysis B5**: the unit cost of intermediate vitreous procedures applied to the management of vitreous haemorrhage and retinal detachment was amended to £989; the management of retinal detachment was estimated to be an intermediate / major vitreous day case procedure in 80% and 20% of cases, respectively, with a mean cost of £1,080;
- **Analysis C6**: the numbers of total visits associated with treatment and monitoring each year were amended to take into account that some re-treatment visits included monitoring visits;
- **Analysis C7**: costs associated with IOP checks were removed from the analysis;
- **Analysis C8**: the unit cost of private residential care (£532 weekly) was used;
- **Analysis C9**: a cost of depression of £2,252 was utilised;
- **Analysis C10**: a mean cost of medication for raised IOP of £88.77 was used, using the cost of generic prostaglandins and assuming that, medication for raised IOP comprises 70% generic prostaglandins; 10% generic beta-blockers; and 20% equal use of remaining treatments listed by the company;
- **Analysis C11**: trabeculectomy was the only surgical procedure considered for the management of raised IOP; 50% of procedures were assumed to be intermediate and 50% major glaucoma day case procedures; cost was £1273;
- **Analysis C12**: 6 extra IOP visits were added to patients with DMO who were treated for raised IOP.

The analysis submitted by the company has been conducted using the head-to-head MEAD trial data, which was noted as being preferred by the Committee, and incorporated the model corrections (B1, B2, B4 and B5) made by the ERG in their review of the company's original submitted model. When the ERG verified these changes it was evident that the revised model also included additional

scenarios (C6 to C12) that were considered by the ERG when estimating the most plausible base case ICER of £1,166,271.

Another correction proposed by the ERG related to the type of residential care received by patients with severe vision loss. The ERG's view was that the unit cost of private residential care should replace the unit cost of local authority residential care in the company's economic analysis (Analysis C8, ERG Report, page 268). This revised cost was £532 per week in 2013 prices, giving an annual cost of residential care of £27,664; the company's original estimate was £52,283 per annum based on local authority residential care.

The new analysis presented by the company has used a weighted cost comprised of 95% of the cost of private sector residential care and 5% of the cost of local authority residential care, giving an annual cost of residential care of £28,985. The ERG considers this new assumption to be reasonable.

In addition to the revision of residential care, the new analysis submitted by the company in response to the ACD includes three updated modelling assumptions. These are discussed in detail below.

Alternative transition matrices for patients who discontinue from treatment

For reasons described in the ACD appendices, the company believed that the natural history transition matrix from Mitchell *et al*.[4] is likely to overestimate the BCVA of patients who discontinued due to a lack or loss of efficacy or who were censored from the study, due to requiring off-protocol treatment. The company's solution to this issue was to present an analysis that used a "last transition carried forward" (LTCF) approach. For all patients who discontinued from the study or were censored, the last observed transition (i.e. the change in BCVA between the last two visits before discontinuation or censoring) was applied in every subsequent cycle from the point of discontinuation to the end of the initial 3-year treatment period. Patients would then return to the natural history transition matrix for the remaining time horizon (15 years).

The ERG does not consider this assumption to be plausible because DMO is a degenerative condition. This assumption would imply that treating DMO is unnecessary because a patient's vision would remain stable. Moreover, the ERG is unclear how the total costs presented in Scenario 2 (presented in Table 5 of the ACD response) for both DEX700 and watch and wait can increase from Scenario 1 (natural history transition matrices maintained). Firstly, the only costs incurred in the model post-discontinuation are the costs associated with severe vision loss. If a patient remains in the same health state throughout the treatment period once they discontinue, they will not incur these costs because they cannot transition to the severe vision loss health state. Secondly, the ERG is unclear as to why the QALYs for both DEX700 and watch and wait have reduced under the updated scenario, in which patients cannot transition to a worse BCVA health state during the initial 3-year treatment period.

Superseded – see section 3.100 of the FAD

An exploratory analysis previously undertaken by the ERG (Analysis C3, ERG Report, pages 182 and 315) in patients with DMO who are considered unsuitable for, or insufficiently responsive to non-corticosteroids, which set discontinuation rates of both DEX700 and watch and wait at zero, showed that the number of QALYs for both interventions was reduced, while the total costs for both interventions increased compared with the base case analysis. The impact was more significant for watch and wait than for DEX700, as incremental costs of watch and wait versus DEX700 increased and incremental QALYs decreased. This suggested that the patient group in the MEAD trials receiving sham did not have better natural history than expected; therefore, the effect of sham (and, consequently, watch and wait) may not have been overestimated in the economic analysis as the company has described. If not, the ERG considers there may be a potential error in the model programming.

Overall, the ERG does not consider the assumption of alternative transition matrices for patients who discontinue from treatment to be plausible, despite patients returning to the natural history after the initial 3-year treatment period. Even though the natural history data taken from Mitchel *et al*.[4] may not be entirely representative of the DMO population for this STA, the ERG regards these data to be more appropriate than the LTCF approach.

Incorporation of alternative utility values

To reduce the uncertainty around the ICER resulting from the narrow range of utility values derived from the MEAD data, the company performed an analysis using utility values from Czoski-Murray *et al*.[1] which have a wider range than those derived from the MEAD studies. These have been preferred by the Committee in previous technology appraisals in DMO[5-7], before the utility dataset used in this company's submission, which were based on a new preference-based measure derived from the NEI-FQ-25. The company also presented additional analyses using utility data from Brown[2] and Brown *et al*.[3]; however, due to time constraints the ERG will only consider the values from Czoski-Murray *et al*.[1] in this response.

Czoski-Murray *et al*.[1] report BSE utilities only; therefore the range of utility values in the WSE has been estimated assuming that the change in the WSE is 30% of the change in the BSE, as per the assumptions made in previous technology appraisals.[5-7]

The ERG notes that the utility values in the WSE are estimated assuming that the change comprises a 30% reduction from near perfect vision (ETDRS letters 86-100) for each of the BCVA health states in the model. The ERG does not consider this to be reasonable, especially as the transitions for each eye have been modelled independently; assuming a 30% reduction from near perfect vision when

Superseded – see section 2.100 of the EAD

modelling utility of WSE is in essence modelling of the vision in only one eye because the true BSE health state has been replaced with near perfect vision for every patient.

The ERG also notes that in the company's model the BSE and WSE are randomly allocated across health states at baseline, plus that their states may swap due to treatment, so that the WSE can have better vision than the BSE from the start to the end of the model.

The ERG considers the WSE utility values calculated by the company to be implausible, for example if a patient had their BSE in health state 4 (0.6110) and their WSE in health state 3 (0.7561) the WSE is not contributing less to the overall patient utility (Company ACD response, Table 1, page 6). The ERG's preferred approach would be to assume that the contribution of WSE and BSE to the overall utility was 3/13 and 10/13, respectively, based on the assumption that the impact of WSE on overall utility equalled 30% of the impact of the BSE.

Furthermore the ERG believes that the company's updated model has the same limitation seen in the revised model with utility updates provided by the company at clarification. As discussed previously in the ERG Report (page 308), the WSE effectively contributed more than the BSE to the overall patient's utility, because both eyes were considered to be equally contributing (by 50%) to the patient's utility.

These limitations have been amended in the exploratory analysis undertaken previously by the ERG **(**Analysis C13, ERG Report, page 251**)**; therefore the ERG is unclear as to why the company did not follow this approach. Consequently the ERG has corrected the BSE and WSE utility values applied in the model so the overall utility "consists" of 10/13 BSE utility and 3/13 of WSE utility based on the BSE values reported in Czoski-Murray *et al*.[1]

Incorporation of a clinical continuation rule for DEX700

The company has applied a clinical continuation rule for DEX700, whereby patients are assumed not to receive further treatment with DEX700 if they do not achieve a gain of at least 5 letters (i.e. do not respond to treatment) by Month 6 following their first injection of DEX700.

In the MEAD studies, of the 347 patients who were randomised to DEX700, nine had discontinued or were censored prior to the Month 6 visit, leaving 338 patients remaining in the DEX700 treatment arm at Month 6. Of these 338 patients, 105 (31.1%) did not achieve a gain of at least five letters by Month 6 and have therefore been discontinued from treatment with DEX700 within the revised analysis. These patients have been assigned the transition probabilities associated with the natural history of vision, in line with Mitchell *et al*.[4]

For completeness the ERG notes the DEX700 re-treatment criterion used to assess patient eligibility in MEAD was the following (ERG Report, page 79):

- retinal thickness in the 1mm central macular subfield by OCT was >175µm (this retinal thickness threshold was reduced from >225 µm as of May 2010 in a protocol amendment based on investigator feedback that a more aggressive DMO treatment approach is adopted in current practice); or
- investigator interpretation of the OCT suggesting evidence of residual retinal oedema consisting of intraretinal cysts or any regions of increased retinal thickening (within or outside of the centre subfield).

As expected, the same numbers of patients were discontinued due to adverse events and other reasons in the revised and original model when the continuation rule was applied (5 out of 347 [1.44%] patients at Month 6). The ERG also notes that the same transition matrices are used in the revised and original model.

However, patients who discontinue DEX700 due to a lack or loss of efficacy at Month 6, increased from 4 out of 347 (1.15%) patients in the original model, to 109 out of 347 (31.41%) patients in the revised analysis when the clinical continuation rule was applied. In other words, the proportion of patients remaining on treatment (excluding those who have discontinued due to adverse events or a lack or loss of efficacy) has been reduced from 97.41% to 68.59%. The ERG notes that these proportions in the revised model are consistent with those reported in the company's ACD response.

Results of the company's revised analysis

The company considered 15 scenarios that contributed to the revised base case; these are presented within the company's ACD response (Table 5). For completeness, the ERG has presented the scenarios in Table 1 that lead to the revised base case ICER of £14,978.

Table 1: Summary of the company's scenario analysis contributing the revised base case ICER

Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Company Scenario 1: ERG corrected base case, provision of residential care 95% private sector and 5% local authority					
Watch and wait	£10,523	5.7531	-	-	-
DEX700	£17,276	5.7589	£6,753	0.0058	£1,170,914
Company Scenario 2: Alternative transition matrices for patients who discontinue from treatment only (using VFQ-UI utilities)					
Watch and wait	£14,834	5.6999	-	-	-
DEX700	£20,388	5.7374	£5,554	0.0374	£148,403
Company Scenario 3: Alternative transition matrices for patients who discontinue from treatment using Czoski-Murray *et al*. 2009[1] utilities					

Watch and wait	£14,834	6.5400	-	-	-
DEX700	£20,388	6.6505	£5,554	0.1105	£50,280
Company Scenario 11: Alternative transition matrices for patients who discontinue from treatment and clinical continuation rule using Czoski-Murray *et al*. 2009[1] utilities (revised base case)					
Watch and wait	£14,834	6.5400	-	-	-
DEX700	£17,357	6.7085	£2,523	0.1685	£14,978
Abbreviation used in the table: DEX700, dexamethasone 700µg; ICER, incremental cost-effectiveness ratio; LTCF, last transition carried forward; QALY, quality-adjusted life year					

Under the company's revised assumptions the base case ICER is £14,978. If the Committee deemed all of the company's revised assumptions to be valid, then DEX700 could be considered a cost-effective treatment option compared with watch and wait based on a willingness to pay threshold of £20,000 per QALY.

3 ADDITIONAL WORK CARRIED OUT BY THE ERG

The ERG has reviewed the company's revised analysis and regards three of the four additional assumptions to be reasonable. For reasons described previously, the ERG does not consider the degenerative nature of DMO to be represented if patients who discontinue from treatment remain in their health state prior to discontinuing for the remainder of the 3-years of treatment. Therefore the ERG recommends that this assumption should not be included in the revised base case.

The ERG accepts that Czoski-Murray *et al.*[1] utilities may reflect the health-related quality of life of patients in the model more accurately than the utility measure derived from NEI-FQ-25. However, the ERG considers that these values were not implemented correctly by the company in the revised model. The ERG has corrected these estimates within the scenario analysis presented below. The ERG also considers the clinical continuation rule, whereby patients need to have gained at least 5 letters by Month 6 to continue DEX700 treatment to be reasonable, but is unable to comment on the practicality of its implementation. In addition, the ERG considers the company's revised cost of residential care to be reasonable.

To illustrate the impact of each component of the revised analysis in turn, Table 2 below presents the scenarios which contribute to the revised ERG base case of £127,645 per QALY.

Table 2: ERG scenario analysis in response to the revised model

Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
ERG scenario 1: 95% private residential care using VFQ-UI (note the ERG is unable to construct a scenario using correct Czoski-Murray *et al*. 2009[1] values because this model is constructed using the regression equation not the utility update)					
Watch and wait	£10,523	5.7531	-	-	-
DEX700	£17,276	5.7589	£6,753	0.0058	£1,170,914
ERG scenario 2: LTCF using VFQ-UI and 95% private residential care					
Watch and wait	£14,834	5.6999	-	-	-
DEX700	£20,388	5.7374	£5,554	0.0374	£148,403
ERG scenario 3: Clinical continuation using VFQ-UI and 95% private residential care					
Watch and wait	£10,523	5.7531	-	-	-
DEX700	£15,870	5.7610	£5,347	0.0079	£678,142
ERG scenario 4: Clinical continuation using corrected Czoski-Murray *et al*. 2009[1] and 95% private residential care (ERG revised base case)					
Watch and wait	£10,523	5.9649	-	-	-
DEX700	£15,870	6.0068	£5,347	0.0419	£127,645
Abbreviation used in the table: DEX700, dexamethasone 700µg; ERG, Evidence Review group; ICER, incremental cost-effectiveness ratio; LTCF, last transition carried forward; QALY, quality-adjusted life year					

Superseded - see section 3.100 of the FAD

4 OVERALL CONCLUSIONS

The ERG's revised base case ICER of £127,645 is substantially higher than the NICE willingness to pay threshold of £20,000 to £30,000 per QALY gained.

While the ERG did not review using the alternative utilities from Brown[2] and Brown *et al.*[3], based on the scenario analyses provided by the company (company scenarios 12 and 13, respectively), which presented higher ICERs compared with the ICERs resulting from use of utility data from Czoski-Murray *et al*.[1], it seems likely that use of these alternative utility values would similarly result in higher ICERs than the current ERG revised base case ICER.

5 REFERENCES

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