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AbbVie Ltd	Guideline	012	012	**Recommendation 1.5.5** Evidence Review H accurately captures that anti-VEGF and corticosteroid therapies were deemed to be cost effective only for people with CRT >400 micrometres in their technology appraisals. However, AbbVie agrees that it is vitally important to ensure subgroups (e.g., women and people of South Asian or Afro-Caribbean descent) that tend to have thinner retinas do not miss out on timely treatment. The Committee stated that "With more limited evidence for people with thinner retinas, and an awareness that macular laser can have benefits, they did not think they could make as strong a recommendation in favour of anti-VEGFs as for those in the subgroup with greater central retinal thickness" (P103, Evidence Review G). Based on this conclusion, AbbVie believes that dexamethasone intravitreal implant also should be included in the list of therapies available for patients with CRT <400 micrometres. • The flexibility outside of the NICE Technology Appraisal process being proposed by the	Thank you for your response. The committee decided that the recommendations for people with thinner retinas should be similar to those with thicker retinas. This decision was based on the results of the whole population NMA which showed most anti-VEGFs to be more effective than macular laser, and on the importance of addressing equality issues in subgroups with thinner retinas. Although the committee thought there was sufficient evidence to recommend that anti-VEGFs be considered for people with thinner retinas, they did not think there was enough evidence to make recommendations beyond what is recommended by the NICE technology appraisals for the use of intravitreal steroids. They were also concerned about the additional adverse events associated with intravitreal steroids, and therefore thought that it was important that, where possible, anti-VEGF treatment is considered before the use of steroids. As such they recommended that intravitreal steroids should be considered if someone has not responded well enough to non-corticosteroid therapy. There is also a recommendation that intravitreal steroid implants are considered for people who cannot have, or do not want, anti-VEGF treatment. This means that

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				Committee should be applied consistently across all therapies. • The whole population NMAs suggest that dexamethasone intravitreal implant is more effective than standard threshold laser therapy in terms of visual acuity at 12 months (Table 8, pp.47, Evidence Review G) and central retinal thickness at 12 & 24 months (Tables 12 & 13, pp.51-52, Evidence Review G). If the rationale to recommend anti-VEGF therapies for these patients is based on favourable whole population NMA results compared to laser therapy, dexamethasone intravitreal implant should be recommended based on the same rationale. • The Committee states that laser therapy is current standard of care for many people in the <400 micrometre CRT subgroup. This also is the case for dexamethasone intravitreal implant. Importantly, many local DMO pathways currently do not restrict the use of dexamethasone by CRT threshold – e.g., Norfolk and Waveney ICS, but this is one of many instances where this is the case. • Importantly, not all patients with CRT <400 micrometres will be able to receive / want anti-	dexamethasone can still be considered for people with thinner retinas, but that its use should be in line with the recommendations in the technology appraisal. This matches the recommendations for the group with central retinal thickness >400 micrometres.

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				VEGF therapy. At the very least, the guideline must make clear that dexamethasone intravitreal implant is available for these patients. • The use of dexamethasone intravitreal implant in this patient subgroup would be in line with the current license, which has not restriction based on central retinal thickness.	
AbbVie Ltd	Guideline	013	004	**Recommendation 1.5.9** The draft guideline as it stands currently could prevent patients that are sub-optimally responding to anti-VEGF therapies from switching to dexamethasone intravitreal implant after the anti-VEGF loading dose, ultimately having to wait an additional 6-9 months before that is possible. This could lead to worse visual outcomes for patients. Understandably, the Committee expressed concerns that a 3-month loading phase may not be sufficient to accurately assess response to treatment, as it might not account for delayed responders. However, published literature indicates that approximately 40% of eyes show only a minimal response (<5 letter gain) in best corrected	Thank you for your response. The committee discussed the timing of when to consider a switch to steroids in detail and were confident that the 12 month period is appropriate for most people. The evidence for the technology appraisal submission for ranibizumab showed improvements in visual acuity in the first 12 months after the start of anti-VEGF treatment, and few people had a reduction in 10 letters over that time period. The committee therefore thought it was important that people are given this amount of time to respond to anti-VEGF treatment. Although many people in the Gonzalez study didn't show a clinically meaningful improvement, there were still many people who did respond further by 12 months. The study also highlights how there were marked differences in BCVA response, with some

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				visual acuity after 3 months and only a minority of these eyes (~20%–30%) are expected to develop a clinically significant visual response with continued intensive anti-VEGF treatment over the following 1–3 years. (Gonzalez VH, Campbell J, Holekamp NM, et al. Early and long term responses to anti–vascular endothelial growth factor therapy on September 27, 2023 in diabetic macular edema: analysis of Protocol I data. Am J Ophthalmol 2016;172:72–9). These data would suggest that there is a significant proportion of patients that do not demonstrate an optimal response at 3 months and will continue to respond sub-optimally. Currently, clinicians have the option to switch to dexamethasone intravitreal implant following assessment at 3 months. This approach is in line with NICE TA824 which recommends dexamethasone intravitreal implant as an option for treating visual impairment caused by diabetic macular oedema in adults only if their condition has not responded well enough to, or if they cannot have non-corticosteroid therapy. "Given the limited data available, the committee could not determine which clinical features best indicates the need to switch or stop treatments" (Evidence Review H). If this is the Committee's conclusion, it would be inappropriate to	people showing considerable improvement in vision beyond the 12 week period. The committee were therefore concerned that an earlier switch to steroids if there is a limited response to anti-VEGFs to begin with could result in people experiencing the additional adverse events associated with steroids, when they would have responded to anti-VEGFs if given more time. More information about this has been added to the rationale of the guideline and the committee discussion section of the evidence review.

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				prevent clinicians using their individual judgement at the earliest possible timepoint.	
AbbVie Ltd	Guideline	013	004	**Definition of Suboptimal response for DMO** The characterisation of suboptimal response in the draft guideline is highly positive, however it could be improved further by including more quantifiable criteria. The consensus document published in the BMJ, which underpins the NHS England operational note on commissioning recommendation for medical retinal vascular medicines, suggests suboptimal response to be if the eye shows <20% reduction in CRT and <5 letters gained (where baseline VA is <85 letters) (Downey L, Acharya N, Devonport H, et al. Treatment choices for diabetic macular oedema: a guideline for when to consider an intravitreal corticosteroid, including adaptations for the COVID-19 era. BMJ Open Ophthalmology 2021). Also, it is unclear why the suboptimal treatment response criteria are not applied when assessing effectiveness of anti-VEGF therapies after the loading dose (Draft Guideline recommendation 1.5.8), especially as the Committee themselves have defined suboptimal response as being applicable after the loading dose and not at a later point. Whilst vision stabilisation (as defined in the draft guideline) following anti-VEGF loading dose might be an appropriate short-term outcome for patients with high	Thank you for your response. The committee discussed the definition of suboptimal response and noted that the definition reported in the Downey paper was based on consensus. The committee wanted to avoid too restrictive of a definition as they did not review the evidence for this. They also thought this should be partly based on clinical judgment. As suggested, we have updated the recommendations so that the definition of suboptimal response is the same for the loading phase and at later points of follow-up.

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				visual acuity at baseline, this might not be the same for patients with lower visual acuity at baseline. In these patients, staying within 5 letters (potentially 5 fewer) of what it was before treatment may not be a satisfactory short-term outcome. AbbVie's suggestion would be to apply the definition of suboptimal response consistently after loading dose and at later points of clinical follow-up. This would help to better identify those patients who are refractory to anti-VEGF therapy as early as possible and that should be switched to dexamethasone intravitreal implant, compared to those patients who might need additional time to demonstrate an optimal response and should be reassessed at 6-12 months.	
AbbVie Ltd	Guideline	013	004	**Recommendation 1.5.9** It is not clear why the Committee has recommended switching to an alternative anti-VEGF therapy based on a lack of vision stabilisation after loading dose of first anti-VEGF therapy. The conclusion in Evidence Review H from the assessment of the clinical data was that "*the evidence for switching from bevacizumab to aflibercept at 12 weeks*	Thank you for your response. The committee agree that there is limited evidence to suggest switching between different anti-VEGF therapies and this has been removed from the recommendations. The committee think a change in class is important if someone shows a limited response and have therefore retained the recommendation about considering a switch to steroids if a person shows a suboptimal response.

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				based on a lack of improvement in vision, suboptimal vision, or recent treatment of the eye did not demonstrate any evidence of benefit compared to aflibercept monotherapy. Given the limited evidence and the limitations of the study mentioned in the quality of the evidence section, the committee did not think they could recommend this specific switching criteria." As such, it is unclear why the Committee has recommended this approach of switching between anti-VEGF therapies. AbbVie's concern is that many local commissioning pathways for the treatment of DMO do not allow for the switching between anti-VEGF therapies and this recommendation has the potential to cause significant upheaval to local pathways without a strong clinical or cost effectiveness rationale to do so. Alternatively, the option of switching to dexamethasone intravitreal implant at this stage would be in line with NICE TA824, its UK marketing authorisation and current local commissioning pathways. There may also be NHS capacity benefits as the dosing of dexamethasone intravitreal implant is less frequent than the main anti VEGF therapies.	
AbbVie Ltd	Guideline	013	004	**Recommendation 1.5.10**	Thank you for your response. The committee discussed the timing of when to consider a switch to

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				Any recommendation to consider switching from anti-VEGF therapies to dexamethasone intravitreal implant based on suboptimal response at 12 months is too long – early switching can have a positive impact on visual outcomes. Data (Busch 2019) shows that in a real-world setting, eyes with DMO considered refractory to anti-VEGF therapy after 3 monthly injections which were switched to dexamethasone intravitreal implant had better visual anatomical outcomes at 12 months than those that continued treatment with anti-VEGF therapy. Noting the limitations of this study already identified in Evidence Review H, there is a strong rationale to ensure patients refractory to, or gaining suboptimal response from, anti-VEGF therapy can switch to dexamethasone intravitreal implant at the earliest opportunity. AbbVie's suggestion would be to recommend as assessment at 6 rather than 12 months. This aligns with the Operational Note: Commissioning recommendations following the national procurement for medical retinal vascular medicines published by NHS England in August 2022, which already has been implemented within the NHS in England.	steroids in detail and were confident that the 12 month period is appropriate for most people. The evidence for the technology appraisal submission for ranibizumab showed improvements in visual acuity in the first 12 months after the start of anti-VEGF treatment, and few people had a reduction in 10 letters over that time period. The committee therefore thought it was important that people are given this amount of time to respond to anti-VEGF treatment. Although the Busch study showed some improvements at 12 months for those who switched early to dexamethasone, they reported similar outcomes for BCVA at 24 months between that group and those who showed a suboptimal response at 12 months and were then switched to dexamethasone. The committee were therefore concerned that an earlier switch to steroids if there is a limited response to anti-VEGFs to begin with could result in people experiencing the additional adverse events associated with steroids when they may have responded to anti-VEGFs if given more time. If they do not respond by 12 months, then the switch to steroids is expected to provide similar longer-term benefits for visual acuity as an earlier switch,

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AbbVie Ltd	Guideline	015	001	**Recommendation 1.5.17** The Committee noted that monitoring during treatment with intravitreal therapies would be determined by the treatment protocol and so did not make recommendations for this area. Whilst protocols may vary based on treatment choice and geography, some guidance on best practice and aspirational standards would be a positive step to address known variation across Trusts and ICS footprints. Ongoing capacity challenges reduce the opportunity for consultants to conduct patient reviews, ultimately keeping patients on anti-VEGF therapy inappropriately. Switching to dexamethasone intravitreal implant at the most appropriate timepoint can be positive in the long term for both clinical outcomes and healthcare expenditure.	Thank you for your response. The committee also thought reducing variation was important but there was limited evidence to make specific recommendations. The recommendations do include guidance on when to switch to intravitreal implants in the section on treatment strategies for people with diabetic macular oedema. The committee thought that it was important to highlight the need to consider switching to intravitreal steroids if someone is showing a suboptimal response to anti-VEGFs.
Alimera Sciences Limited	Equality and Impact Assessment	002	General	Sex and Socio-Economic Factors - We would like to draw your attention to the following statement and ask for the FAc implant to be included: *'In the section on treatments for people with diabetic macular oedema, the committee recommended that*	Thank you for your response. We have updated the recommendation about people who no longer wish to continue with anti-VEGF treatment so that it now says "intravitreal steroid implant" rather than stating dexamethasone. This means that both dexamethasone and fluocinolone can be considered when deciding which intravitreal steroid implant is most appropriate, taking into account people's individual circumstances.

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				people can be offered an intravitreal dexamethasone implant (which requires fewer appointments) if they do not wish to continue with regular anti-VEGF injections. This will help patients with DMO from lower socio-economic backgrounds and may have factors, such as jobs with zero hours contracts, that mean they cannot easily attend additional appointments.' The FAc implant is a longer acting intravitreal corticosteroid treatment – lasting up to 3 years with a single injection and requiring fewer appointments. This will benefit this group of patients for the same reasons stipulated above for the dexamethasone implant, which is administered at least every 6 months as per SPC. The company request that the FAc is added to this section as an option for these patients. This will also apply to the point beneath regarding the costs associated with regular visits to the clinic.	

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Alimera Sciences Limited	Evidence Review K	General	General	This evidence review in this appendix includes: 1) Recent evidence of UWF 2) OCT evidence comes from a Cochrane Review of studies between 1998 -2012. This evidence is dated and discounts consensus and evidence from the DRCR network which discuss OCT structural parameters as well as functional outcomes described in Protocol I. [29](Dugel et al/). This has been adopted by the Northeast & Yorkshire group[9] (Reference) NHSE Retina Treatment guidelines.[6] Again, we draw your attention to the OCT imaging biomarker There are predictive morphological biomarkers to guide treatment choice in DMO. These help to identify DMO patients who may benefit from IV corticosteroid treatment or an early switch[30]. Quantifying foveal thickening" and "presence of cystoid spaces" do not thoroughly describe the disease. In the presence of DMO there is also progressive retinal damage that is functional at first stages but eventually anatomical and irreversible. The European School for Advanced Studies in Ophthalmology (ESASO) have described and validated a comprehensive description of all optical coherence	Thank you for your response. The committee used the Cochrane review which determined that OCT is the gold standard for monitoring diabetic macular oedema, and there is no need to consider updates to this. The committee agreed with this conclusion and so no further evidence was considered for the use of OCT. This review searched for evidence on the accuracy of OCT for monitoring progression, but did not aim to determine which structural parameters should be used to determine this.

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				tomography images and biomarkers numerical score for scientific use in clinical trials.[31,32]	
Alimera Sciences Limited	Guideline	012	012 - 016	Alimera strongly supports the new guidance to allow treatment of DMO in patients with CRT<400 µm as this will allow for earlier treatment. This will improve the likelihood of better visual outcomes in patients with DMO (i.e. fewer letters are gained overall, but there is the ability to maintain better visual acuity).	Thank you for your response and support for this recommendation.
Alimera Sciences Limited	Guideline	012	022	Reference should be paid to the NHS Framework Agreement for the supply of Medical Retinal Vascular Treatments for the NHS in England.[6] The commissioning recommendations from NHS England for DMO are notably different to those in this draft NICE DR guideline. It would make sense for NICE and the NHS-E team to align. Based on tender submissions from the manufacturers of anti-VEGF and steroid implants for DMO, evidence and cost based decision making factors were taken into account. The commissioning recommendations[6] state: *"When to consider intra-vitreal steroids (dexamethasone and fluocinolone acetonide) - If anti-VEGF treatment is*	Thank you for your response. We believe that the guideline is mostly aligned with the current NHS England recommendations. The committee also thought that steroids should be considered if people have a suboptimal response to anti-VEGFs, or if there are reasons that someone may not want to continue with anti-VEGF injections. This information is included within the recommendations. Although NHS England suggests that response is assessed after 6 months, the committee thought that assessment of response to anti-VEGFs should happen after the loading dose and at 12 months. This timing was discussed in detail by the committee, and they were confident that the 12 month period is appropriate for most people. The evidence for the technology appraisal submission for ranibizumab showed improvements in visual acuity in the first 12 months after the start of anti-VEGF treatment, and few people

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				contra-indicated or does not achieve a sufficient response (despite an appropriate injection frequency and regular monitoring), then intravitreal corticosteroid implants (dexamethasone intravitreal implant or fluocinolone acetonide intravitreal implant) should be considered (assuming the patient meets NICE guidance criteria TA301 and TA824, and there are no contra-indications to steroid usage). Equally, patients may achieve good efficacy with anti-VEGF, but the frequency of repeated injections may not be tolerable for the patient due to individualised patient factors. In this last scenario, intravitreal steroids, with their potentially longer duration of action, may be useful. The two main reasons for considering intravitreal steroid therapy for a patient previously treated with anti-VEGF are: inadequate efficacy with anti-VEGF intolerable anti-VEGF treatment burden. One approach is to consider a change to intravitreal steroid after six months of anti-VEGF therapy based on	had a reduction in 10 letters over that time period. The committee therefore thought it was important that people are given this amount of time to respond to anti-VEGF treatment. The NHS framework presents switching to steroids at 3-6 months as one approach to assessing response to treatment. While this decision considered the effectiveness of steroids, there was less consideration given to other factors such as adverse events. Given the additional risks associated with steroids, and that some people can show a response to anti-VEGFs beyond 6 months, the committee thought the 12 months recommendation was appropriate. They were concerned that an earlier switch to steroids if there is a limited response to anti-VEGFs to begin with could result in people experiencing the additional adverse events associated with steroids for limited benefits for visual acuity. More information about this has been added to the rationale in the guideline and to the committee discussion section of evidence review G.

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				the efficacy of therapy at this time-point and then to consider again a change to intravitreal steroid after two years of anti-VEGF therapy based on treatment burden at this stage. A consensus document is published with more detail of this approach, together with supporting data [Downey et al 2021 is cited]. Intra-vitreal steroid therapy may also be the first-line option for some patients where anti-VEGF agents are contraindicated or not available." This above guidance can only improve the burden on NHS resources in ophthalmology services but moving away from anti-VEGFs where the first treatment from this class (if given in line with guidelines) has not been effective. As this NHS-E guideline was based on a strict and confidential tender process, it should not be overlooked by the NICE DR guideline team.	
Alimera Sciences Limited	Guideline	013	007	Alimera believe that in DMO treatment the recommendation in point 1.5.9 is unsafe and concerned that the evidence review H only assessed 2 RCTs that addressed switching treatments. There was also no evidence in the anti-VEGF RCT that switching treatment	Thank you for your response. The committee agree that there is limited evidence to suggest switching between different anti-VEGF therapies and this has been removed from the recommendations. The criteria used to determine the response has also been updated to match the suboptimal response definition in the recommendation for assessing response after 12 months. The committee thought that a change in class

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				had any effect of visual outcomes. The Evidence reviews fail to account for the large body of real-world DMO evidence and NHS England national commissioning recommendations[6] that already exist around this area. The recommendation in point 1.5.9 risks patient's vision and are misleading as it is well-known that real-world outcomes with anti-VEGF are simply not replicated or reflective of outcomes in RCTs. It is important that the guidelines recommend a switch away from this class of drugs after 1 product (the cheapest) has been seen to not improve DMO outcomes Alimera believes this is necessary to avoid wasting NHS and patients time (high frequency of injections) and NHS drug budget (switching from a biosimilar anti-VEGF to another branded anti-VEGF only appears to forecast an increase in costs). Evidence review H also does not consider the large body of real-world data that does look at the switching between treatments. Whilst not RCTs, some of these RWE studies	is important and have therefore retained the recommendation about considering a switch to steroids if a person shows a suboptimal response. NICE bases its recommendations on the clinical and cost-effectiveness evidence, resource impact and committee experience. The committee are aware of recommendations in other guidance and bear that in mind when making recommendations. However, the committee did not think that the recommendations differ greatly from those produced by NHS England or the Downey paper. The committee discussed the timing of when to consider a switch to steroids in detail and were confident that the 12 month period is appropriate for most people. The evidence for the technology appraisal submission for ranibizumab showed improvements in visual acuity in the first 12 months after the start of anti-VEGF treatment, and few people had a reduction in 10 letters over that time period. The committee therefore thought it was important that people are given this amount of time to respond to anti-VEGF treatment. Although the Rennie study showed limited improvements beyond 6 months, the lack of a comparator group means that it is not clear whether people would have responded better had they

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				record what is being practiced in UK clinics (i.e., ICE-UK,[3] Medisoft,[4] and IRISS[5]). It also overlooks very recent 2023 data by Rennie et al (2023) concludes that *"Continuing [anti-VEGF] treatment beyond 6 months in suboptimal responders imposes unnecessary treatment burden without significant change in VA. In suboptimal responders, consideration of early switch to longer acting steroid treatments may help to reduce treatment burden, whilst maintaining or improving vision."*[41] Alimera believes p13 line 7 should be changed to reflect the following 2 recommendations: 1. The Downey et al (2021)[9] recommendation, which states: *"[change to corticosteroid] needs to occur while the macula is still capable of functional response, so anti-VEGF treatment should not continue so long that the window of opportunity for benefiting from a corticosteroid has passed."*	switched to steroids at 6 months. The NHS framework presents switching to steroids at 3-6 months as one approach to assessing response to treatment. While this decision considered the effectiveness of steroids, there was less consideration given to other factors such as adverse events. Given the additional risks associated with steroids, and that some people can show a response to anti-VEGFs beyond 6 months, the committee thought the 12 months recommendation was appropriate. They were concerned that an earlier switch to steroids if there is a limited response to anti-VEGFs to begin with could result in people experiencing the additional adverse events associated with steroids for limited benefits for visual acuity. If people do not respond by 12 months, then the switch to steroids is expected to provide similar longer-term benefits for visual acuity as an earlier switch. More information about this has been added to the rationale in the guideline and to the committee discussion section of evidence review G.

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				Specifically, they concluded anti-VEGF therapy should be assessed after the initial three to six monthly injections and a change in therapy considered if the eye shows <20% reduction in CRT and <5 letters gained from baseline. If anti-VEGF therapy is continued, it should be assessed again at 24 months (or earlier if services have been interrupted) and, if injections in the preceding 12 months have been more frequent than every 8 weeks, a change in therapy should be considered. Response to corticosteroid therapy was recommended to be assessed at 8-week intervals and clinicians should consider the benefits of a longer acting versus shorter acting corticosteroid implant (including minimising the treatment burden for patients and clinics and ensuring continuity of	

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				treatment during exceptional circumstances such as pandemics where timely retreatment may not be possible) against the possible disadvantages including potential adverse events. 2. NHS Framework Agreement for the supply of Medical Retinal Vascular Treatments for the NHS in England[6] which states: *"When to consider intra-vitreal steroids (dexamethasone and fluocinolone acetonide) - If anti-VEGF treatment is contra-indicated or does not achieve a sufficient response (despite an appropriate injection frequency and regular monitoring), then intravitreal corticosteroid implants (dexamethasone intravitreal implant or fluocinolone acetonide intravitreal implant) should be considered (assuming the patient meets NICE guidance*	

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				criteria TA301 and TA824, and there are no contra-indications to steroid usage). Equally, patients may achieve good efficacy with anti-VEGF, but the frequency of repeated injections may not be tolerable for the patient due to individualised patient factors. In this last scenario, intravitreal steroids, with their potentially longer duration of action, may be useful. The two main reasons for considering intravitreal steroid therapy for a patient previously treated with anti-VEGF are: inadequate efficacy with anti-VEGF intolerable anti-VEGF treatment burden. One approach is to consider a change to intravitreal steroid after six months of anti-VEGF therapy based on the efficacy of therapy at this time-point and then to consider again a change to intravitreal steroid after two	

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				years of anti-VEGF therapy based on treatment burden at this stage. A consensus document is published with more detail of this approach, together with supporting data [Downey et al 2021 is cited]. Intra-vitreal steroid therapy may also be the first-line option for some patients where anti-VEGF agents are contraindicated or not available." The guideline development team should note the real-world pragmatism of the above guidelines but also their strong evidence-based recommendations. Alimera believes these will afford patients a much better chance to retain their vision (efficacy) and also reduce unnecessary consumption of NHS resources and patient's time (burden).	
Alimera Sciences Limited	Guideline	013	008	Alimera believe, similarly to the comments made on pojnt 1.5.9 p13 line 7, that assessing response to treatment after 12 months is not supported by the current evidence base. In the recent publication by Rennie et al (2023) concludes that "*Continuing [anti-VEGF] treatment beyond*	Thank you for your response. The committee discussed the timing of when to consider a switch to steroids in detail and were confident that the 12 month period is appropriate for most people. The evidence for the technology appraisal submission for ranibizumab showed improvements in visual acuity in the first 12 months after the start of anti-VEGF treatment, and few people

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				6 months in suboptimal responders imposes unnecessary treatment burden without significant change in VA. In suboptimal responders, consideration of early switch to longer acting steroid treatments may help to reduce treatment burden, whilst maintaining or improving vision."[41] As mentioned before, evidence based real-world recommendations from Downey et al (2021) and also the NHS Framework Agreement for the supply of Medical Retinal Vascular Treatments for the NHS in England[6] should be considered instead. The switch to an alternative therapeutic treatment (i.e., intravitreal corticosteroid) must be considered after the loading phase and insufficient response to anti-VEGF treatment. Switching to another treatment which has the same mode of action and expecting improvements in outcomes is simply not backed by robust clinical data to	had a reduction in 10 letters over that time period. The committee therefore thought it was important that people are given this amount of time to respond to anti-VEGF treatment. Although the Rennie study showed limited improvements beyond 6 months, the lack of a comparator group means that it is not clear whether people would have responded better had they switched to steroids at 6 months. The NHS framework presents switching to steroids at 3-6 months as one approach to assessing response to treatment. While this decision considered the effectiveness of steroids, there was less consideration given to other factors such as adverse events. Given the additional risks associated with steroids, and that some people can show a response to anti-VEGFs beyond 6 months, the committee thought the 12 months recommendation was appropriate. They were concerned that an earlier switch to steroids if there is a limited response to anti-VEGFs to begin with could result in people experiencing the additional adverse events associated with steroids for limited benefits for visual acuity. If people do not respond by 12 months, then the switch to steroids is expected to provide similar longer-term benefits for visual acuity as an earlier switch. More information about this has been added to the rationale

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				support switching after 12 months. Further, there are no analyses by NICE to show patients will have a delayed response to anti-VEGF, so keeping them on therapy past this point will put the patient at risk of not maintaining or gaining vision as a direct consequence of delaying a switch to an alternative therapy. A huge body of literature on DMO pathogenesis explains that in many patients with DMO the disease is *not solely mediated by VEGF* levels. The literature discusses how acute inflammation and vascular dysfunction may characterise early DMO, and more chronic inflammatory mechanism may predominate in later disease DMO is *therefore not solely because of increased VEGF level*.[18] Clinically it is not possible to determine which pathway is predominating i.e.., pro-angiogenic or pro-inflammatory mechanisms.[10,18,19] With the above in mind, using a second anti-VEGF in these patients is very illogical as a sign of no response to the first anti-VEGF would clearly	in the guideline and to the committee discussion section of evidence review G. The committee agree that there is limited evidence to suggest switching between different anti-VEGF therapies and this has been removed from the recommendations. The recommendation about switching to steroid treatment has been updated so that it now says "intravitreal steroid implant" rather than stating dexamethasone.

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				highlight that VEGF alone may not be the mediator for DMO in this patient. As such, Alimera strongly recommends the guideline development team consider and note Downey et al (2021) guidance developed by retinal specialists from 8 NHS trusts:[10] • a significant proportion of eyes with DMO are insufficiently responsive to anti-VEGF therapies, whereby up to 40% show a minimal response i.e., <5 BCVA letter gain after three months. From this cohort, only a minority of these eyes (20-30%) go on to develop a clinically significant response in terms of visual outcomes over the following 1-3 years.[10,20] It is therefore considered that an early response to anti-VEGF therapy is predictive of long-term response to anti-VEGF agents in the majority of patients.	

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				• The outlined criteria in this guidance could give rise to using the wrong medicine in a significant number of patients, predisposing patients to a high risk of irreversible vison loss. Alimera therefore *strongly* recommends *both* Dex and FAc steroid implants should be offered at this point to reflect the *ineffective prior anti-VEGF treatment*. This is especially important bearing in mind the CEA developed by the guideline team is seriously flawed for the following reasons, which has resulted in inaccurate and misleading determinations and recommendations in the draft guidance around the use of the FAc implant in clinical practice. • The decision problem (DP) and the NMA used to answer the DP in the economic model do not discriminate regarding prior treatments	

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				i.e., anti-VEGF agents are used as first line therapy in DMO and corticosteroid therapies (the FAc and Dex implant) are used as second line therapy for those with insufficient response to non-corticosteroid therapy. • The reported mean differences reported in BCVA in the pairwise comparison of the presented economic model support the argument of clinical equivalence between the FAc implant and the Dex implant. This is not reflected in the guidelines. • The CEA model assumes 1 injection *per year* for FAc, where in pharmacokinetics (PK) studies, RCTs and RWE (specifically UK) the reality is typically 1 injection in a 36 month or *3-year period*.[1] This represents a gross *overestimate* of injection frequency for FAc.	

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				These inaccuracies undermine the accuracy of the reported estimates significantly. • Alimera have submitted a revised CEA model to the DR guidelines development team including an evidence-based assumption of 1 injection over 3 years. The value "0.33" is proposed for sheet "DataStore" in specific cells F172, F198, F224, F250, and F276 respectively. • Using the correct FAc injection frequency as above showed the FAc implant to be more cost effective and cheaper than the Dex implant. Adding the confidential PAS led to further dominance for FAc over Dex implant. The guidance should therefore reflect this by giving the FAc implant *at least* a similar position to that of the Dex implant throughout.	

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				• The CEA model also grossly *underestimates* the injection frequency of Dex implant, assuming from 1.78 (year 1) down to 1 injection per year across 5 years of treatment. This does not reflect RCT or RWE evidence. To treat DMO in line with RCT evidence and SPC, a *minimum* of 2 Dex implants are required per year to deliver the patient outcomes achieved in RCT studies for BCVA and CRT. • It is unintuitive and incorrect for the CEA to use the RCT outcome values for BCVA and CRT outcomes and not use the frequency of injections in these studies that achieved those outcomes. • In Dex implant real-world data sources, the injection frequency for Dex implant ranges between 2.2 per year[33] and 2.3 per year.[34] As	

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				such, in the revised model Alimera have submitted to the DR guidelines team, a value "2.0" proposed for sheet "DataStore" in specific cells F173, F200, F226 respectively. NB: this is still a *conservative* injection frequency of 2 Dex implants per year when compared to RWE.[33,34] • With the above CEA input values added to the CEA, which Alimera believe reflect clinical practice and the evidence base for RCT and RWE, the FAc implant *appears to dominate Dex implant*. This throws into question any decision making that has influenced the position of both Dex and FAc implants in the guideline development and stepwise prescribing recommendations of this draft. • Alimera calls NICE and the DR guidelines team to look seriously at these incorrect	

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				assumptions and look closer at already published NHS and consensus guideline publications[6,10,19] that appear to offer a better researched and evidenced stepwise recommendation for both Dex and FAc implants after anti-VEGF have failed. • TA613[2] is currently being reappraised by NICE (FAc implant in eyes with a phakic lens) with recommendations from the technical assessment expected early 2024. To ensure robustness of the NICE DR guideline, and that it is current and aligned with *all* NICE TAs for DMO treatments, it is proposed that current draft guidance timelines should be paused until such a time that recommendations from the NICE TA613 reappraisal have been made, which is Alimera believe has been set as precedent for	

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				other disease area guidelines by NICE in the past. In conclusion, and based on the above information, Alimera believes that the current statement: • *"1.5.10 Assess response to treatments after 12 months. Consider switching to a dexamethasone intravitreal implant if the response is suboptimal. [2023]"* • *Must* be changed to reflect the above evidence base and corrected cost effectiveness analysis (submitted to NICE DR guidelines team in Sept 2023) to read as follows: ***"1.5.10 Assess response to treatments after 6 months. Consider switching to either dexamethasone or fluocinolone acetonide intravitreal implant if the response is suboptimal. [2023]"***	
Alimera Sciences Limited	Guideline	013	010 - 012	Whilst this point is accurate with regards to TA824, Alimera believe as a very minimum a point should be	Thank you for your response. Following the update of the technology appraisal for fluocinolone (TA953), we have updated the recommendation about switching to steroid treatment so that it now says "intravitreal

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				added perhaps like the following **"*TA613 recommendations for FAc implant are currently being reappraised by NICE following the conclusions on Dex implant in TA824. See https://www.nice.org.uk/guidance/indevelopment/gid-ta11387/documents*"** The current and ongoing STA (Fluocinolone acetonide intravitreal implant for treating chronic diabetic macular oedema in phakic eyes after an inadequate response to previous treatment (Review of TA613) [ID6307]) will likely publish recommendations from the technical assessment expected early 2024. To ensure robustness of the guideline, and that it is current and aligned with *all* NICE TAs for DMO treatments, it is proposed that current draft guidance timelines should be paused until such a time that recommendations from the NICE TA613 reappraisal have been made.	steroid implant" rather than stating dexamethasone. This means that fluocinolone can also be considered when anti-VEGF treatment is not effective.

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				As this TA613[2] review is a cost comparison appraisal versus Dex implant as the main comparator, and also in light of this guideline development team's own CEA analysis (once corrected), it may be concluded that *both* Dex and FAc implants are useful after anti-VEGF treatment *irrespective* of the patient's lens status. Alimera suggest if the guideline timelines cannot be paused for the publication of ID6307, *at the very least* a holding statement like the one above should be added with an explanation that the recommendation for the FAc implant is under review for the addition of the *phakic* population after an inadequate response to previous treatment to the NICE recommendation already reference for the *pseudophakic* population.	
Alimera Sciences Limited	Guideline	013	013 - 017	The recommendation to refer to the technology appraisal guidance TA301[14] for the FAc implant is accurate at present but Alimera believe as a very minimum a point should be added perhaps like the following ***"TA613 recommendations for FAc implant are currently being reappraised by NICE following the conclusions on Dex implant in TA824. See https://www.nice.org.uk/guidance/indevelopment/gid-ta11387/documents"***	Thank you for your response. Following the update of the technology appraisal for fluocinolone (TA953), we have updated the recommendation about switching to steroid treatment so that it now says "intravitreal steroid implant" rather than stating dexamethasone. This means that fluocinolone can also be considered when anti-VEGF treatment is not effective.

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				The current and ongoing STA (Fluocinolone acetonide intravitreal implant for treating chronic diabetic macular oedema in phakic eyes after an inadequate response to previous treatment (Review of TA613) [ID6307]) will likely publish recommendations from the technical assessment expected early 2024. To ensure robustness of the guideline, and that it is current and aligned with *all* NICE TAs for DMO treatments, it is proposed that current draft guidance timelines should be paused until such a time that recommendations from the NICE TA613 reappraisal have been made. As this TA613[2] review is a cost comparison appraisal versus Dex implant as the main comparator, and also in light of this guideline development team's own CEA analysis (once corrected), it may be concluded that both Dex and FAc implants are useful after anti-VEGF treatment irrespective of the patient's lens status. Alimera suggest if the guideline timelines cannot be paused for the publication of ID6307, *at the very least a holding statement should be added* with an explanation that the	

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				recommendation for the FAc implant is under review for the addition of the *phakic* population after an inadequate response to previous treatment to the NICE recommendation already reference for the *pseudophakic* population.	
Alimera Sciences Limited	Guideline	013	018 - 019	Alimera believe point 1.5.13 is incomplete and does not reflect RCT, real-world or current UK and NHS guidance for DMO treatment.[6,9,13] This statement should clearly include both FAc and Dex implants and reflect be a broader statement around the challenges currently effecting stained ophthalmology services, which is documented in the public domain by NHS England, Public Health England and the lay press.[37,38,39,40] The burden of treatment with intravitreal injections (IVIs) is huge on NHS trusts, clinicians and patients. This is documented in numerous sources and has only been made worse by the COVID-19 pandemic.[9,36] The frequency of IVIs was a huge factor in the recommendations from TA824, which stated:	Thank you for your response. Following the update of the technology appraisal for fluocinolone (TA953), we have updated the recommendation about switching to steroid treatment so that it now says "intravitreal steroid implant" rather than stating dexamethasone. This means that fluocinolone can also be considered when anti-VEGF treatment is not effective.

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				• *"There is an unmet need for an effective treatment given less frequently: 3.1 The patient expert explained the nature of their experience with current treatment…The patient expert highlighted that having frequent eye injections causes fear, but there is no alternative* [to anti-VEGF treatment] *because laser therapy has not been very effective for them. They emphasised that reducing the number of times they need treatment, especially for an eye injection, would be of huge benefit for their quality of life. They also explained that for this population, there are no other effective treatment options if anti-vascular endothelial growth factor (anti-VEGF) treatments do not work. The patient expert highlighted that although treatments might not improve their diabetic macular oedema, they can stop it from getting worse, which is still very*	

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				important to people with the condition. The company… emphasised that the impact of dexamethasone intravitreal implant would mean less frequent hospital visits and injections compared with anti-VEGF treatments. The committee was aware that some people with diabetic macular oedema may require help from a carer to travel to appointments. The patient expert emphasised that people with diabetic macular oedema may be unsure about using steroids because it could affect their diabetes management…The committee concluded that there is an unmet need for another treatment option for diabetic macular oedema in people who have a phakic lens. It added that people with diabetic macular oedema and clinicians would welcome an effective new treatment option that is used less frequently.	

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				• In light of the above, and the fact that RCT and RWE the FAc implant is injected fewer times than the Dex implant across a similar treatment period (approximately 1 injection every 36 months versus at least 6 Dex injections over 36 months) suggests that FAc treatment may have more profound impact on the issue of highly frequent IVIs with anti-VEGFs. • This is also supported by NICE's own reviews of 2 new anti-VEGF treatments in TA799 and TA820. These confirmed that all licenced anti-VEGFs for the treatment of DMO are expected to have similar injection frequency to each other over a 3 year period. This is confirmed by the NICE resource impact template for TA820 which outlines between *16-18 injections may be required across a 3-year period for all available*	

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				anti-VEGFs included in the costing analysis template. Patients should be allowed access to alternative treatments. If patients are considering for a switch to Dex intravitreal implant they should also be given the option to be treated with a FAc implant. One FAc implant can be injected and last for up to 3 years further minimising the injection burden for the patient and reducing resource use burden in the NHS ophthalmic clinics. • The UK literature speaks to the need for more efficacious intravitreal therapies with an extended duration of effect so the NHS can adapt to high ocular service demand in the face of scarce resources[10,21.] • In terms of patient treatment burden ocular injections can be a source of fear, stress, and anxiety in patients with retinal disease. *"Keeping*	

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				the same level of vision with fewer injections" (TA824[16]) is an understood patient preference. The FAc implant which has up to 36-month duration of effect aligns with patient preferences and improves adherence. The frequency of treatment injections in DMO is correlated to visual outcomes[22]. Nonadherence to onerous intravitreal treatment regimens was found to correlate with a loss of up to 15 BCVA letters. Failing vision influences the patient's ability to effectively manage diabetic disease comorbidities as it makes the tasks difficult. It impacts on health-related quality of life, where it was reported in the literature that a 1-line average improvement in vision was associated with "clinically meaningful changes in Health-Related Quality of Life[23]. The ability to drive is impacted directly by underlying	

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				DR,[24,25] causing further reduction in independence and HRQoL. The complexity of DMO clinical management demands a multiplicity of partial solutions to address the needs of the broader DMO patient population. Therapeutic access thus needs to be flexible enough to change as patient circumstances and clinical presentations alter. It has been demonstrated that the FAc implant can significantly reduce treatment burden in the overall patient DMO patient population as demonstrated by the UK RWE for the FAc implant. (i.e., ICE-UK[3], Medisoft[4], and IRISS[5], Dobbler[26]). TA613[2] recommendations for FAc implant are currently being reappraised by NICE following the conclusions on Dex implant in TA824. The current and ongoing STA (Fluocinolone acetonide intravitreal implant for treating	

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				chronic diabetic macular oedema in phakic eyes after an inadequate response to previous treatment (Review of TA613) [ID6307]) will likely publish recommendations from the technical assessment expected early 2024. To ensure robustness of the guideline, and that it is current and aligned with *all* NICE TAs for DMO treatments, it is proposed that current draft guidance timelines should be paused until such a time that recommendations from the NICE TA613 reappraisal have been made. In conclusion, and based on the above information, Alimera believes that the current statement. *"1.5.13 If a person does not want to continue with regular anti-VEGF injections, consider switching treatment to a dexamethasone intravitreal implant [2023]"* should be changed to reflect the evidence base and corrected cost effectiveness analysis (submitted to NICE on Sept 2023) to read as follows:	

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				"1.5.13 If a person does not want to continue with regular anti-VEGF injections, consider switching treatment to either dexamethasone or fluocinolone acetonide intravitreal implant [2023]."	
Alimera Sciences Limited	Guideline	013	021 - 023	Alimera wish to see parity between FAc and Dex implants in this guideline. Patients should be taken through the options when not suitable for 'non-corticosteroid therapy' and this should include FAc implant with the other alternatives being considered. One FAc implant can be injected and lasts for up to 3 years thereby minimising the injection burden for the patient and reducing resource use burden in the NHS ophthalmic clinics. • The UK literature speaks to the need for more efficacious intravitreal therapies with an extended duration of effect so the NHS can adapt to high	Thank you for your response. Following the update of the technology appraisal for fluocinolone (TA953), we have updated the recommendation about switching to steroid treatment so that it now says "intravitreal steroid implant" rather than stating dexamethasone. This means that fluocinolone can also be considered when anti-VEGF treatment is not effective.

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				ocular service demand in the face of scarce resources[10,21.] • In terms of patient treatment burden Ocular injections can be a source of fear, stress, and anxiety inn patients with retinal disease. "Keeping the same level of vision with fewer injections" [16]. is an understood patient preference[29].The FAc implant which has up to 36-month duration of effect aligns with patient preferences and improves adherence. The frequency of treatment injections in DMO is correlated to visual outcomes[22]. Nonadherence to onerous intravitreal treatment regimens was found to correlate with a loss of up to 15 BCVA letters[23]. Failing vision influences the patient's ability to effectively manage diabetic disease comorbidities as it makes the tasks difficult. It impacts on health-related quality of life, where it was r3eported in	

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				the literature that a 1-line average improvement in vision was associated with "clinically meaningful changes in Health-Related Quality of Life[23]. The ability to drive is impacted directly by underlying DR[24,25], causing further reduction in independence and HRQoL. The complexity of DMO clinical management demands a multiplicity of partial solutions to address the needs of the broader DMO patient population. Therapeutic access thus needs to be flexible enough to change as patient circumstances and clinical presentations alter. It has been demonstrated that the FAc implant can significantly reduce treatment burden in the overall patient DMO patient population as demonstrated by the UK RWE for the FAc implant. (i.e., ICE-UK[3], Medisoft[4], and IRISS[5], Dobbler[26.]).	

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				In conclusion, and based on the above information, Alimera believes that the current statement. *"1.5.14 When people with centre-involving diabetic macular oedema have visual impairment and cannot have non-corticosteroid therapy, consider a dexamethasone intravitreal implant. [2023]"* should be changed to reflect the evidence base and corrected cost effectiveness analysis (submitted to NICE on Sept 2023) to read as follows: ***"1.5.14 When people with centre-involving diabetic macular oedema have visual impairment and cannot have non-corticosteroid therapy, consider switching treatment to either dexamethasone or fluocinolone acetonide intravitreal implant [2023]."*** It is considered that the draft guidance cannot be finalised until final recommendation from the NICE TA613[2] reappraisal (FAc implant in patients with a phakic lens) is	

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				formally published. TA613 reappraisal recommendations are expected early 2024.	
Alimera Sciences Limited	Guideline	014	002 - 004	The use of OCT to assess response to therapy is increasingly standard practice in the UK but does not just look at CRT (central retinal thickness) and often treat/no treat or switch therapies are taken on the presence or absence of intra-retinal/sub-retinal fluid. This area has not been adequately addressed in these guidelines.	Thank you for your response. Although we looked for evidence on the most effective diagnostic tool, we did not look at whether the presence of intraretinal or sub-retinal fluid should indicate a change or stop in treatment. Therefore, the committee were unable to make recommendations on this.
Alimera Sciences Limited	Guideline	017	011 – 016	This is not the standard definition of sub-optimal or insufficient response. This normally includes <5 letter VA gain and <20 % decrease in retinal thickness.[10.]	Thank you for your response. The committee discussed the definition of suboptimal response and noted that there are a number of ways it can be defined. They decided to focus on the main characteristics they thought were important to indicate the need for additional treatment.
Alimera Sciences Limited	Guideline	039	013 - 014	It is accepted that OCT is the primary diagnostic recommended, but there is a need to quantify what insufficient response looks like with regards to macular oedema /intraretinal fluid risk.	Thank you for your response. Although we looked for evidence on the most effective diagnostic tool, we did not look at what best indicates an insufficient response to treatment. Therefore, the committee were unable to make recommendations on this.
Alimera Sciences Limited	Guideline	039	020 - 021	The company support the statement that OCT is already standard practice for diagnosing macular oedema.	Thank you for your response and support for this recommendation.
Alimera Sciences Limited	Guideline	039	027 - 028	The company agree with this statement and would go further by saying that all treatments available should be discussed.	Thank you for your response and support for this recommendation.

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Alimera Sciences Limited	Guideline	040	003 - 012	The company agree with this paragraph and the importance of making patients aware of all treatment options. It is a stressful time for patients with DMO. They are not only dealing with their diabetes and underlying disease, but also the potential loss of sight. Addressing their personal needs and circumstances is important from a treatment perspective and with longer acting treatments like FAc the reduction in injections and hospital visits may be a better option for both patient and carers. Sivaprasad and Oyetunde 2016[27] reported that patients' most desired improvement to their treatment regimen was to have fewer injections and to require fewer appointments, to achieve the same visual results. Effects that reduce stress and that may also be of benefit.	Thank you for your response and support for this guideline.
Alimera Sciences Limited	Guideline	040	031	The company would ask that this should be expanded to include both Dex and FAc implants.	Thank you for your response. Following the update of the technology appraisal for fluocinolone (TA953), we have updated the recommendation about switching to steroid treatment so that it now says "intravitreal steroid implant" rather than stating dexamethasone. This means that fluocinolone can also be considered when anti-VEGF treatment is not effective.
Alimera Sciences Limited	Guideline	041	010 - 011	There is extensive real-world evidence and trials available through DRCR.net that counter the statement around limited data on the effectiveness of visual acuity at 24 months. The FAME phase 3 trials[28] (assessing the efficacy and safety of the FAc implant) reported outcomes to month 36 and there is significant UK real-world	Thank you for your response. Although there was evidence for visual acuity at 24 months, this was more limited than the data that was available at 12 months. More information about this is included in section 1.1.12.3 of the evidence review (Imprecision and clinical importance of effects). Data from both the

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				experience reporting outcomes after 3 years of follow-up in UK NHS practices[4,5.]	DRCR and FAME trials were included within this analysis and therefore formed part of the committee's decision making. Real world evidence is used in some circumstance, but this review focused on RCTs, and the committee felt that the available RCT data from DRCR and FAME alongside their clinical opinion trials provided sufficient basis for decision-making in this instance The committee did not believe that the inclusion of observational real-world evidence would have affected the recommendations made by the committee as the included RCTs highlight the associated risk of adverse events (development of cataract, increased intraocular pressure and vitreous haemorrhage) with steroid treatment for DMO Although this means that the Bailey 2022 and Khoramnia 2022 studies were not included in this review, the included RCT evidence showed that steroids can have benefits with regards to visual acuity for people with centre-involving diabetic macular oedema. however, the benefits of greater improvements in vision observed in Anti-VEGF treatment compared to steroids as well as the reduced risk of adverse events was considered important by the committee This is why the guideline recommends that they be considered for people who have a suboptimal

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					response to anti-VEGF treatment, or for people who do not want, or cannot have anti-VEGF treatment.
Alimera Sciences Limited	Guideline	041	020 - 022	This recommendation for anti-VEGF treatments should be expanded to say 'as a 1st line treatment' as this is just the start of the treatment pathway for patients with diabetic macular oedema. It should be made clearer that after one treatment from the anti-VEGF class has failed, evidence does not support switching to another anti-VEGF with the same mode of action.	Thank you for your response. The committee agree that there is limited evidence to suggest switching between different anti-VEGF therapies and this has been removed from the recommendations.
Alimera Sciences Limited	Guideline	042	007 - 009	The company strongly supports the new guidance to allow treatment of DMO in patients with CRT<400 µm as this will allow for earlier treatment which is highly likely to maintain better visual outcomes for patients (less vision gain but maintain what they have if vision is good) which is a favourable outcome for patients with DMO.	Thank you for your response and support for this recommendation.
Alimera Sciences Limited	Guideline	042	014 - 024	Assessing response to treatment The company consider that this is not a wide consensus and would suggest referring to other groups like the NHS England guideline[6] or Downey et al (2021)[9], which allows the assessment to switch to intravitreal corticosteroid if an insufficient response after the loading phase of anti-VEGF is observed at 6 months. Also, for a patient with no VA/OCT improvement after 6 months of injections,	Thank you for your response. NICE bases its recommendations on the clinical and cost-effectiveness evidence, resource impact and committee experience. The committee are aware of recommendations in other guidance and bear that in mind when making recommendations. However, the committee did not think that the recommendations differ greatly from those produced by NHS England or the Downey paper. The evidence for the technology appraisal submission for ranibizumab showed improvements in visual acuity in the first 12 months after the start of anti-VEGF treatment, and few people

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				subjecting them to a further 6 months of injections (perhaps with additional laser) may be futile and misses the opportunity for the clinician to switch to alternative therapy (i.e., intravitreal corticosteroid). With regards to the above comments, the 2 following guidelines should be taken into account: 1. The Downey et al (2021)[9] recommendation, which states: "[change to corticosteroid] needs to occur while the macula is still capable of functional response, so anti-VEGF treatment should not continue so long that the window of opportunity for benefiting from a corticosteroid has passed." Specifically, this group of retina experts from 8 NHS trusts concluded anti-VEGF therapy should be assessed after the initial three to six monthly injections and a change in therapy considered if the eye shows <20%	had a reduction in 10 letters over that time period. The committee therefore thought it was important that people are given this amount of time to respond to anti-VEGF treatment. The NHS framework presents switching to steroids at 3-6 months as one approach to assessing response to treatment. While this decision considered the effectiveness of steroids, there was less consideration given to other factors such as adverse events. Given the additional risks associated with steroids, and that some people can show a response to anti-VEGFs beyond 6 months, the committee thought the 12 months recommendation was appropriate. They were concerned that an earlier switch to steroids if there is a limited response to anti-VEGFs to begin with could result in people experiencing the additional adverse events associated with steroids for limited benefits for visual acuity. More information about this has been added to the rationale in the guideline and to the committee discussion section of evidence review G.

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				reduction in CRT and <5 letters gained from baseline. If anti-VEGF therapy is continued, it should be assessed again at 24 months (or earlier if services have been interrupted) and, if injections in the preceding 12 months have been more frequent than every 8 weeks, a change in therapy should be considered. Response to corticosteroid therapy was recommended to be assessed at 8-week intervals and clinicians should consider the benefits of a longer acting versus shorter acting corticosteroid implant (including minimising the treatment burden for patients and clinics and ensuring continuity of treatment during exceptional circumstances such as pandemics where timely retreatment may not be possible) against the possible	

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				disadvantages including potential adverse events. 2. NHS Framework Agreement for the supply of Medical Retinal Vascular Treatments for the NHS in England[6] looks at DMO and when to consider intravitreal corticosteroids with the treatment pathway. The company requests that the DR guidelines reflect the recommendations made with regards to consideration of intravitreal corticosteroid treatment and draw your attention to the wording as follows: *"When to consider intra-vitreal steroids (dexamethasone and fluocinolone acetonide) - If anti-VEGF treatment is contra-indicated or does not achieve a sufficient response (despite an appropriate injection frequency and regular monitoring), then intravitreal corticosteroid*	

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				implants (dexamethasone intravitreal implant or fluocinolone acetonide intravitreal implant) should be considered (assuming the patient meets NICE guidance criteria TA301 and TA824, and there are no contra-indications to steroid usage). Equally, patients may achieve good efficacy with anti-VEGF, but the frequency of repeated injections may not be tolerable for the patient due to individualised patient factors. In this last scenario, intravitreal steroids, with their potentially longer duration of action, may be useful. The two main reasons for considering intravitreal steroid therapy for a patient previously treated with anti-VEGF are: inadequate efficacy with anti-VEGF intolerable anti-VEGF treatment burden. One approach is to consider a change to intravitreal steroid after six months	

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				of anti-VEGF therapy based on the efficacy of therapy at this time-point and then to consider again a change to intravitreal steroid after two years of anti-VEGF therapy based on treatment burden at this stage. A consensus document is published with more detail of this approach, together with supporting data [Downey et al 2021 is cited]. Intra-vitreal steroid therapy may also be the first-line option for some patients where anti-VEGF agents are contraindicated or not available."	
Alimera Sciences Limited	Guideline	042 – 043	025 – 032	and 1-5 respectively 1. The economic modelling underpinning the recommendations of this guidance document is flawed on several points. This has resulted in inaccurate and misleading determinations and	Thank you for your comment. Regarding the economic modelling, we have discussed with the committee and agree that both corticosteroid therapies should not be included in the comparison in the economic analysis, given the model is built to compare first line therapies only. We take on board your other comments about the model but have decided with committee input to remove the corticosteroids from the economic analysis since it is imperative to justify the choice of alternative

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				recommendations in the draft guidance around the use of the FAc implant in clinical practice. • The decision problem (DP) and the NMA used to answer the DP in the economic model do not discriminate regarding prior treatments i.e., anti-VEGF agents are used as first line therapy in DMO and corticosteroid therapies (the FAc and Dex implant) are used as second line therapy for those with insufficient response to non-corticosteroid therapy. • The reported mean differences reported in BCVA in the pairwise comparison of the presented economic model support the argument of clinical equivalence between the FAc implant and the Dex implant. This is not reflected in the guidelines. • The CEA model assumes 1 injection *per year* for FAc, where in pharmacokinetics (PK)	interventions to make appropriate comparisons in any economic analysis. Fluocinolone and dexamethasone are used as second line therapies and are only considered as first line treatments for patients in whom other first line treatments are not suitable or who had not responded to previous treatments (mainly laser), which would be a different population to that considered in this economic analysis. We have updated the health economic report. Corticosteroids were included in the NMA as the committee were interested in seeing the comparative effects of different treatments. However, they were aware of limitations regarding the evidence base and that steroids wouldn't be used as first-line treatment. The studies that included steroids used them as first-line treatment, and removing the steroids from the network would remove some of the comparisons from the NMA. The committee were also concerned about the additional adverse events associated with steroids compared to anti-VEGFs. This is why steroids were not considered as first-line treatment and have only been recommended in line with the TA guidance.

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				studies, RCTs and RWE (specifically UK) the reality is typically 1 injection in a 36 month or *3-year period*.[1] This represents a gross *overestimate* of injection frequency for FAc. These inaccuracies undermine the accuracy of the reported estimates significantly. • Alimera have submitted a revised CEA model to the DR guidelines development team including an evidence-based assumption of 1 injection over 3 years. The value "0.33" is proposed for sheet "DataStore" in specific cells F172, F198, F224, F250, and F276 respectively. • Using the correct FAc injection frequency as above showed the FAc implant to be more cost effective and cheaper than the Dex implant. Adding the confidential PAS led to further dominance for FAc over Dex implant.	

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				The guidance should therefore reflect this by giving the FAc implant *at least* a similar position to that of the Dex implant throughout. • The CEA model also grossly *underestimates* the injection frequency of Dex implant, assuming from 1.78 (year 1) down to 1 injection per year across 5 years of treatment. This does not reflect RCT or RWE evidence. To treat DMO in line with RCT evidence and SPC, a *minimum* of 2 Dex implants are required per year to deliver the patient outcomes achieved in RCT studies for BCVA and CRT. • It is unintuitive and incorrect for the CEA to use the RCT outcome values for BCVA and CRT outcomes and not use the frequency of injections in these studies that achieved those outcomes.	

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				• In Dex implant real-world data sources, the injection frequency for Dex implant ranges between 2.2 per year[33] and 2.3 per year.[34] As such, in the revised model Alimera have submitted to the DR guidelines team, a value "2.0" proposed for sheet "DataStore" in specific cells F173, F200, F226 respectively. NB: this is still a *conservative* injection frequency of 2 Dex implants per year when compared to RWE.[33,34] • With the above CEA input values added to the CEA, which Alimera believe reflect clinical practice and the evidence base for RCT and RWE, the FAc implant *appears to dominate Dex implant*. This throws into question any decision making that has influenced the position of both Dex and FAc implants in the	

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				guideline development and stepwise prescribing recommendations of this draft. • Alimera calls NICE and the DR guidelines team to look seriously at these incorrect assumptions and look closer at already published NHS and consensus guideline publications[6,10,19] that appear to offer a better researched and evidenced stepwise recommendation for both Dex and FAc implants after anti-VEGF have failed. TA613[2] is currently being reappraised by NICE (FAc implant in eyes with a phakic lens) with recommendations from the technical assessment expected early 2024. To ensure robustness of the NICE DR guideline, and that it is current and aligned with *all* NICE TAs for DMO treatments, it is proposed that current draft guidance timelines should be paused until such a time that recommendations from the NICE TA613 reappraisal have been made, which is Alimera believe has been set as precedent for other disease area guidelines by NICE in the past.	

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Alimera Sciences Limited	Guideline	043	008	Alimera request this sentence is reviewed to include fluocinolone acetonide implant and to ensure parity to access to these two corticosteroid implants as the benefits equally apply to *both* Dex implant and FAc Implant DMO therapies.	Thank you for your response. The recommendation and rationale have been updated and now say "intravitreal steroid implant". This means both dexamethasone and fluocinolone can be considered.
Alimera Sciences Limited	Guideline	044	023 – 027	Alimera believe this statement is very unlikely to occur with regards to macular laser and that the evidence available supports this recommendation and assessment. It would be extremely challenging for a clinician to consent a patient to laser therapy (which damages the retina) if they have good vision. This may happen with PDR, but it is more likely that clinicians will watch and wait unless the oedema is focal and away from fovea	Thank you for your response. The committee were aware that this does not always happen in current practice. However, they noted that when macular laser is given to people with good vision it can reduce the number of people who progress to having visual impairment, ultimately benefiting the patient. The committee were also aware of emerging evidence on subthreshold laser which can have less of an impact on the retina than standard threshold laser. In the committee's experience, if macular laser is delivered correctly it can have long-term benefits when given early. Therefore, they thought it was important to highlight this in the recommendations.
Alimera Sciences Limited	Guideline	044	029 - 030	Alimera believe that NHS clinics are already at full capacity, and this will have an impact. Over the next few years, it is likely UK eye centres will have to manage the treatment of patients with dry AMD/GA with monthly intravitreal injections of complement inhibitors. This will include a significant proportion of elderly patients and is expected to further overwhelm current NHS clinic capacity.	Thank you for your comment. We have noted that although there may be an increase in numbers of people who are initially offered anti-VEGFs, this impact might be mitigated with the additional option of macular laser for people who have thinner retinas and the recommendations around switching treatment if there is a suboptimal response after 12 months.

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Alimera Sciences Limited	Guideline	045	003	Alimera believe that NHS clinics are already at full capacity, and this will have an impact. Over the next few years, it is likely UK eye centres will have to manage the treatment of patients with dry AMD/GA with monthly intravitreal injections of complement inhibitors. This will include a significant proportion of elderly patients and is expected to further overwhelm current NHS clinic capacity.	Thank you for your comment. We have noted that although there may be an increase in numbers of people who are initially offered anti-VEGFs, this impact might be mitigated with the additional option of macular laser for people who have thinner retinas and the recommendations around switching treatment if there is a suboptimal response after 12 months.
Alimera Sciences Limited	Guideline	047	021 - 022	We draw your attention again to the following information: Assessing response to treatment The company consider that this is not a wide consensus and would suggest referring to other groups like the NHS England guideline[6] and the Downey et al (2021) guideline[9], which allows the assessment to switch to intravitreal corticosteroid if an insufficient response after the loading phase of anti-VEGF is observed at 6 months. Also, for a patient with no VA/OCT improvement after 6 months of injections, subjecting them to a further 6 months of injections (perhaps with additional laser) may be futile and misses the opportunity for the clinician to	Thank you for your response. NICE bases its recommendations on the clinical and cost-effectiveness evidence, resource impact and committee experience. The committee are aware of recommendations in other guidance and bear that in mind when making recommendations. However, the committee did not think that the recommendations differ greatly from those produced by NHS England or the Downey paper. The evidence for the technology appraisal submission for ranibizumab showed improvements in visual acuity in the first 12 months after the start of anti-VEGF treatment, and few people had a reduction in 10 letters over that time period. The committee therefore thought it was important that people are given this amount of time to respond to anti-VEGF treatment. The NHS framework presents switching to steroids at 3-6 months as one approach to assessing response to treatment. While this decision considered the effectiveness of steroids, there was

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				switch to alternative therapy (i.e., intravitreal corticosteroid). With regards to the above comments, the 2 following guidelines should be taken into account: 1. The Downey et al (2021)[9] recommendation, which states: "[change to corticosteroid] needs to occur while the macula is still capable of functional response, so anti-VEGF treatment should not continue so long that the window of opportunity for benefiting from a corticosteroid has passed." Specifically, this group of retina experts from 8 NHS trusts concluded anti-VEGF therapy should be assessed after the initial three to six monthly injections and a change in therapy considered if the eye shows <20% reduction in CRT and <5 letters gained from baseline. If anti-VEGF therapy is continued, it	less consideration given to other factors such as adverse events. Given the additional risks associated with steroids, and that some people can show a response to anti-VEGFs beyond 6 months, the committee thought the 12 months recommendation was appropriate. They were concerned that an earlier switch to steroids if there is a limited response to anti-VEGFs to begin with could result in people experiencing the additional adverse events associated with steroids for limited benefits for visual acuity. More information about this has been added to the rationale in the guideline and to the committee discussion section of evidence review G.

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				should be assessed again at 24 months (or earlier if services have been interrupted) and, if injections in the preceding 12 months have been more frequent than every 8 weeks, a change in therapy should be considered. Response to corticosteroid therapy was recommended to be assessed at 8-week intervals and clinicians should consider the benefits of a longer acting versus shorter acting corticosteroid implant (including minimising the treatment burden for patients and clinics and ensuring continuity of treatment during exceptional circumstances such as pandemics where timely retreatment may not be possible) against the possible disadvantages including potential adverse events. NHS Framework Agreement for the supply of Medical Retinal Vascular Treatments for the NHS in England[6]	

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				looks at DMO and when to consider intravitreal corticosteroids with the treatment pathway. The company requests that the DR guidelines reflect the recommendations made with regards to consideration of intravitreal corticosteroid treatment and draw your attention to the wording as follows: *"When to consider intra-vitreal steroids (dexamethasone and fluocinolone acetonide) - If anti-VEGF treatment is contra-indicated or does not achieve a sufficient response (despite an appropriate injection frequency and regular monitoring), then intravitreal corticosteroid implants (dexamethasone intravitreal implant or fluocinolone acetonide intravitreal implant) should be considered (assuming the patient meets NICE guidance criteria TA301 and TA824, and there are no contra-indications to steroid usage). Equally, patients may achieve good efficacy with anti-VEGF, but the frequency of repeated injections may not be tolerable for the patient due to individualised patient factors. In this last scenario, intravitreal steroids, with their potentially longer duration of action, may be useful. The two main reasons for considering intravitreal steroid therapy for a patient previously treated with anti-VEGF are: inadequate efficacy with anti-VEGF intolerable anti-VEGF treatment burden. One approach is to consider a change to intravitreal steroid after six months of anti-VEGF therapy based on the efficacy of therapy at this time-point and then to consider again a change to intravitreal steroid after*	

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				two years of anti-VEGF therapy based on treatment burden at this stage. A consensus document is published with more detail of this approach, together with supporting data [Downey et al 2021 is cited]. Intra-vitreal steroid therapy may also be the first-line option for some patients where anti-VEGF agents are contraindicated or not available."	
Alimera Sciences Limited	Guideline	047	021 - 026	The company believes there are anatomical and functional biomarker recommendations from various working groups i.e., DRCR.net.[29] These guidelines have been adopted into Downey et al[10] as well as NHSE Operational note: updated commissioning recommendations for medical retinal vascular medicines following the national procurement for ranibizumab biosimilars.[6] We also draw attention to current OCT imaging biomarkers. There are predictive morphological biomarkers to guide treatment choice in DMO. These help to identify DMO patients who may benefit from IV	Thank you for your response. While there was evidence for various markers, there was very limited consistent high-quality evidence for specific biomarkers. Therefore, based on the evidence in our review, the committee didn't think there was enough evidence to recommend specific biomarkers. However, they did agree that this is a very important gap in the evidence, and so they made recommendations for research.

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				corticosteroid treatment or an early switch[30]. Quantifying foveal thickening" and "presence of cystoid spaces" do not thoroughly describe the disease. In the presence of DMO there is also progressive retinal damage that is functional at first stages but eventually anatomical and irreversible. The morphological biomarkers visible in OCT may predict treatment response and guide treatment decisions The European School for Advanced Studies in Ophthalmology (ESASO) have described and validated a comprehensive description of all optical coherence tomography images and biomarkers numerical score for scientific use in clinical trials[31,32.]	
Alimera Sciences Limited	Guideline	047 - 048	027 – 028	1.4 - Clinical evidence does not support this claim. In primary or first line therapy, insufficient response can be detected after 3 loading injections (please see 'DRCR.net Protocol I EARLY post hoc analysis')[20]. There is a likelihood, that the success or failure of switching anti-VEGF can even be assessed after 3 months but certainly 6 months (with or without switching if there has been an	Thank you for your response. The committee discussed the timing of when to consider a switch to steroids in detail and were confident that the 12 month period is appropriate for most people. The evidence for the technology appraisal submission for ranibizumab showed improvements in visual acuity in the first 12 months after the start of anti-VEGF treatment, and few people

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				insufficient response) after initial anti-VEGF therapy started.	had a reduction in 10 letters over that time period. The committee therefore thought it was important that people are given this amount of time to respond to anti-VEGF treatment. The committee were concerned that an earlier switch to steroids if there is a limited response to anti-VEGFs to begin with could result in people experiencing the additional adverse events associated with steroids when they may have responded to anti-VEGFs if given more time. If they do not respond by 12 months, then the switch to steroids is expected to provide similar longer-term benefits for visual acuity as an earlier switch,
Alimera Sciences Limited	Guideline	050	008 - 010	The company believe there is RWE evidence which suggest that IVI corticosteroids can be used in vitrectomised eyes;	Thank you for your response. The committee considered whether to recommend intravitreal steroids with vitrectomy but did not think that the evidence supported this. NICE does consider real world evidence in certain circumstances, such as if there is insufficient evidence for decision making. However, a number of RCTs were identified that compared vitrectomy with intravitreal steroids against vitrectomy alone, and they did not show clear benefits of the addition of steroids. While observational evidence was considered for some of the reviews in this guideline, it was not thought that there would be sufficient evidence

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					to affect the committee's decisions on recommendations for this review.
Alimera Sciences Limited	Guideline	General	General	Alimera's strongest concerns on this draft guideline are around the following areas. 2. The economic modelling underpinning the recommendations of this guidance document is flawed on several points. This has resulted in inaccurate and misleading determinations and recommendations in the draft guidance around the use of the FAc implant in clinical practice. • The decision problem (DP) and the NMA used to answer the DP in the economic model do not discriminate regarding prior treatments i.e., anti-VEGF agents are used as first line therapy in DMO and corticosteroid therapies (the FAc and Dex implant) are used as second line therapy for those with insufficient response to non-corticosteroid therapy.	Thank you for your comment. 1. Regarding the economic modelling, we have discussed with the committee and agree that both corticosteroid therapies should not be included in the comparison in the economic analysis, given the model is built to compare first line therapies only. We take on board your other comments about the model but have decided with committee input to remove the corticosteroids from the economic analysis since it is imperative to justify the choice of alternative interventions to make appropriate comparisons in any economic analysis. Fluocinolone and dexamethasone are used as second line therapies and are only considered as first line treatments for patients in whom other first line treatments are not suitable or who had not responded to previous treatments (mainly laser), which would be a different population to that considered in this economic analysis. We have updated the health economic report. Corticosteroids were included in the NMA as the committee were interested in seeing the comparative effects of different treatments. However, they were aware of limitations regarding the evidence base and that steroids wouldn't be used as first-line treatment.

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				• The reported mean differences reported in BCVA in the pairwise comparison of the presented economic model support the argument of clinical equivalence between the FAc implant and the Dex implant. This is not reflected in the guidelines. • The CEA model assumes 1 injection *per year* for FAc, where in pharmacokinetics (PK) studies, RCTs and RWE (specifically UK) the reality is typically 1 injection in a 36 month or *3-year period*.[1] This represents a gross *overestimate* of injection frequency for FAc. These inaccuracies undermine the accuracy of the reported estimates significantly. • Alimera have submitted a revised CEA model to the DR guidelines development team including an evidence-based assumption of 1 injection over 3 years. The value "0.33" is	The studies that included steroids used them as first-line treatment, and removing the steroids from the network would remove some of the comparisons from the NMA. The committee were also concerned about the additional adverse events associated with steroids compared to anti-VEGFs. This is why steroids were not considered as first-line treatment and have only been recommended in line with the TA guidance. 2 and 3. The committee agree that there is very limited evidence to suggest switching between different anti-VEGF therapies and this has been removed from the recommendations. They think a change in class is important and have therefore retained the recommendation about considering a switch to steroids if a person shows a suboptimal response. After edits following consultation, the recommendations now state that anti-VEGFs should be offered initially, followed by adjuvant laser if there is a suboptimal response. Intravitreal steroids should then be considered if the response remains suboptimal. This reflects the guidance in the TAs for the anti-VEGFs and for dexamethasone and fluocinolone.

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				proposed for sheet "DataStore" in specific cells F172, F198, F224, F250, and F276 respectively. • Using the correct FAc injection frequency as above showed the FAc implant to be more cost effective and cheaper than the Dex implant. Adding the confidential PAS led to further dominance for FAc over Dex implant. The guidance should therefore reflect this by giving the FAc implant *at least* a similar position to that of the Dex implant throughout. • The CEA model also grossly *underestimates* the injection frequency of Dex implant, assuming from 1.78 (year 1) down to 1 injection per year across 5 years of treatment. This does not reflect RCT or RWE evidence. To treat DMO in line with RCT evidence and SPC, a *minimum* of 2 Dex implants are	NICE bases its recommendations on the clinical and cost-effectiveness evidence, resource impact and committee experience. The committee are aware of recommendations in other guidance and bear that in mind when making recommendations. However, the committee did not think that the recommendations differ greatly from those produced by NHS England or the Downey paper. The evidence for the technology appraisal submission for ranibizumab showed improvements in visual acuity in the first 12 months after the start of anti-VEGF treatment, and few people had a reduction in 10 letters over that time period. The committee therefore thought it was important that people are given this amount of time to respond to anti-VEGF treatment. The NHS framework presents switching to steroids at 3-6 months as one approach to assessing response to treatment. While this decision considered the effectiveness of steroids, there was less consideration given to other factors such as adverse events. Given the additional risks associated with steroids, and that some people can show a response to anti-VEGFs beyond 6 months, the committee thought the 12 months recommendation was appropriate. They were concerned that an earlier switch to steroids if there is a limited response to anti-VEGFs to begin with could result in people experiencing the additional adverse events associated

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				required per year to deliver the patient outcomes achieved in RCT studies for BCVA and CRT. • It is unintuitive and incorrect for the CEA to use the RCT outcome values for BCVA and CRT outcomes and not use the frequency of injections in these studies that achieved those outcomes. • In Dex implant real-world data sources, the injection frequency for Dex implant ranges between 2.2 per year[33] and 2.3 per year.[34] As such, in the revised model Alimera have submitted to the DR guidelines team, a value "2.0" proposed for sheet "DataStore" in specific cells F173, F200, F226 respectively. NB: this is still a *conservative* injection frequency of 2 Dex implants per year when compared to RWE.[33,34]	with steroids for limited benefits for visual acuity. More information about this has been added to the rationale in the guideline and to the committee discussion section of evidence review G. Although the Kodijikian study showed initial improvements in visual acuity in comparison to anti-VEGFs, the final visual acuity following each treatment was similar. This means that an early switch to steroids if there is a limited response to anti-VEGFs to begin with could result in people experiencing the additional adverse events associated with steroids for limited benefits for visual acuity. This supports the committee's view that 12 months are important to ensure that people have the time to respond to anti-VEGF treatment. The committee also thought that the frequency of injections is important, as stated in the Rennie study. Information is included in the rationale of the guideline about the importance of following guidance in the SPC to reflect this. Some questions within this guideline were answered with the use of observational evidence, but those that compared interventions were answered using RCT evidence. The recommendations were based on a combination of this evidence and the committee's clinical knowledge and experience, and so included

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				• With the above CEA input values added to the CEA, which Alimera believe reflect clinical practice and the evidence base for RCT and RWE, the FAc implant *appears to dominate Dex implant*. This throws into question any decision making that has influenced the position of both Dex and FAc implants in the guideline development and stepwise prescribing recommendations of this draft. • Alimera calls NICE and the DR guidelines team to look seriously at these incorrect assumptions and look closer at already published NHS and consensus guideline publications[6,10,19] that appear to offer a better researched and evidenced stepwise recommendation for both Dex and FAc implants after anti-VEGF have failed.	their awareness of how people are treated, and the impact on their eye disease, in practice.

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				• TA613[2] is currently being reappraised by NICE (FAc implant in eyes with a phakic lens) with recommendations from the technical assessment expected early 2024. To ensure robustness of the NICE DR guideline, and that it is current and aligned with *all* NICE TAs for DMO treatments, it is proposed that current draft guidance timelines should be paused until such a time that recommendations from the NICE TA613 reappraisal have been made, which is Alimera believe has been set as precedent for other disease area guidelines by NICE in the past. 3. Alimera does not consider the guideline on switching therapies as safe or supported by RCT data (i.e. it is based on 2 relatively inconclusive RCTs). The following points support this concern:	

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				• There is a lack of any robust clinical data that switching from one anti-VEGF therapy to another anti-VEGF offers any additional clinical benefit. • A change in class may prove a better option. Moving away from anti-VEGF treatments to intravitreal steroids may also significantly decrease the injection frequency required for the patient, NHS and clinician, potentially reducing cost and burden of treatment. The company feels that this area has not been adequately addressed in Evidence Review H due to: i) Only RCT evidence being evaluate with no UK RWE to reinforce or refute its findings ii) Only 2 RCTs being assessed with one reporting no change in VA outcomes in	

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				switching from one anti-VEGF (bevacizumab) to another (Aflibercept). Based on this evidence, there is not enough data to make these recommendations. iii) No assessment has been conducted of the large volume of real-world data from clinical audits and clinical guidance. These are important as they clearly show: A. Real-world VA outcomes with anti-VEGF are *inferior* to those achieved in RCTs. B. Real-world studies in UK NHS clinical practice (i.e., ICE-UK[3], Medisoft[4], and IRISS[5]) show switching from initial anti-VEGF	

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Stakeholder	Document	Page No	Line No	Comments	Developer's response
				treatment/laser to intravitreal corticosteroid leads to *improved* VA and CRT outcomes. C. There is clinical guidance (i.e., NHS England guidance[6], Royal College of Ophthalmology Guidelines[7], European Guidelines[8], Northeast and Yorkshire Retina Guidelines[9]) on switching between anti-VEGF therapy and when to consider a switch to intravitreal corticosteroid. D. In around 50% of cases, an insufficient response	

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				to anti-VEGF therapy, i.e., defined as <5 letter gain or <20% reduction in CRT, occurs after the initial loading phase.[10] iv) Delaying a switch from anti-VEGF to intravitreal corticosteroids until 12 months is not supported by any clinical data that we are aware of. Indeed, real-world data suggests that mean gains in VA over 12 months are suboptimal (<5 letters) and that mean injections are also suboptimal. For instance, in a UK audit of anti-VEGF use, Zou et al. 2021[11] showed a mean letter gain of 1.6 letters after 6 anti-VEGF injections achieved over a 9–12-month period. This was consistent with larger audits over a 12-month period (see	

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				Kodjikian et al. 2018[12] and Ciulla et al. 2020[13]) and also a new paper focussing on phakic patients specificaly.[41] In the latter publication by Rennie et al (2023) concludes that their "*Data confirms previous real-world evidence around response to anti-VEGF treatment, importance of baseline VA and frequency of injections in predicting outcomes in a UK setting. Continuing treatment beyond 6 months in suboptimal responders imposes unnecessary treatment burden without significant change in VA. In suboptimal responders, consideration of early switch to longer acting steroid treatments may help to reduce treatment burden, whilst maintaining or improving vision*."[41]	

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				v) Stopping anti-VEGF and switching to intravitreal corticosteroids is not currently practiced in-line with the supporting evidence base or following guidance from in NICE TA 301[14],TA349[15] and TA824[16.] Note: If there had been improved implementation of NICE TA301 and TA349 prior to the COVID-19 pandemic, more patients may have benefitted from long-acting intravitreal corticosteroid treatments that do not require frequent injections and therefore are less onerous on the clinic and the patient. This new guideline should ensure clearer stopping and switching rules for anti-VEGF treatment and when it is appropriate to switch to pharmacological treatments with a different mode of action, such as	

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				fluocinolone acetonide (ILUVIEN)[1] and dexamethasone intravitreal implant (OZURDEX).[17] Thus, basing the guidance solely on RCT data is flawed and not in-line with clinical guidance and practice/real-world evidence in the UK and around the World. 3. The Evidence reviews fail to account for the large body of real-world DMO evidence and NHS England clinical guidelines that already exist around this area and maybe misleading as it is well-known that real-world outcomes with anti-VEGF are not replicated or reflective of outcomes in RCTs. It is important that the guidelines recommend a switch away from anti-VEGFs as a class after 1 product (the cheapest) has been observed not to improve DMO outcomes. Alimera believes this is necessary to avoid wasting NHS and patients time due to the high frequency of injections required, and also NHS drug budget - switching from a biosimilar anti-VEGF to	

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				another branded anti-VEGF only appears to forecast an *increase in cost*. • Recommendations from evidence-based consensus publications involving expert clinicians from many NHS trusts need to be reviewed by the clinical guidelines team and recommendations noted from these clinical experts.[9,19] • Downey et al (2021) offers excellent guidance on the above focussing on how the NHS can manage treatment options by focussing 2 deciding factors BURDEN of treatment and EFFICACY of treatment. The recommendations from this consensus work across 8 NHS trusts in the north of England outlined that ophthalmology clinics may be able to improve clinical outcomes in DMO by promptly identifying eyes not responding	

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				sufficiently to intravitreal anti-VEGF treatment and considering a possible change to intravitreal corticosteroid treatment where a risk-to- benefit assessment supports this. The authors reviewed real world data and concluded it showed that a corticosteroid implant may offer greater clinical efficacy than continued anti-VEGF therapy in a non-response scenario but the timeliness of such a change is important to avoid compromising long-term visual outcomes— specifically they stated *"[change to corticosteroid] needs to occur while the macula is still capable of functional response, so anti-VEGF treatment should not continue so long that the window of opportunity for benefiting from a corticosteroid has passed."* The authors reflected upon lens status in this guideline,	

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				concluding that whilst development of cataract development in phakic eyes was a risk factor with both FAc and DEX treatments, they state, *"cataracts—which are typically already present or developing in a significant proportion of patients with DMO—can be resolved with routine surgery".* This reinforces the argument that lens status is not the main focus of treatment for DMO and preserving retina function is key. • Specifically, they concluded anti-VEGF therapy should be assessed after the initial three to six monthly injections and a change in therapy considered if the eye shows <20% reduction in CRT and <5 letters gained from baseline. If anti-VEGF therapy is continued, it should be assessed again at 24 months (or earlier if services have been interrupted) and,	

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				if injections in the preceding 12 months have been more frequent than every 8 weeks, a change in therapy should be considered. Response to corticosteroid therapy was recommended to be assessed at 8-week intervals and clinicians should consider the benefits of a longer acting versus shorter acting corticosteroid implant (including minimising the treatment burden for patients and clinics and ensuring continuity of treatment during exceptional circumstances such as pandemics where timely retreatment may not be possible) against the possible disadvantages including potential adverse events. The guideline development team should note the real-world pragmatism of the above guidelines but also their strong evidence-based recommendations. Alimera believes these will afford patients a much better chance to retain their vision (efficacy) and also reduce unnecessary	

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				consumption of NHS resources and patient's time (burden).	
Alimera Sciences Limited	Guideline	General	General	Alimera's strongest concerns on this draft guideline are around the following areas. 4. The economic modelling underpinning the recommendations of this guidance document is flawed on several points. This has resulted in inaccurate and misleading determinations and recommendations in the draft guidance around the use of the FAc implant in clinical practice. • The decision problem (DP) and the NMA used to answer the DP in the economic model do not discriminate regarding prior treatments i.e., anti-VEGF agents are used as first line therapy in DMO and corticosteroid therapies (the FAc and Dex implant) are used as second line therapy for those with insufficient response to non-corticosteroid therapy.	Thank you for your comment. Regarding the economic modelling, we have discussed with the committee and agree that both corticosteroid therapies should not be included in the comparison in the economic analysis, given the model is built to compare first line therapies only. We take on board your other comments about the model but have decided with committee input to remove the corticosteroids from the economic analysis since it is imperative to justify the choice of alternative interventions to make appropriate comparisons in any economic analysis. Fluocinolone and dexamethasone are used as second line therapies and are only considered as first line treatments for patients in whom other first line treatments are not suitable or who had not responded to previous treatments (mainly laser), which would be a different population to that considered in this economic analysis. We have updated the health economic report. Corticosteroids were included in the NMA as the committee were interested in seeing the comparative effects of different treatments. However, they were aware of limitations regarding the evidence base and that steroids wouldn't be used as first-line treatment.

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				• The reported mean differences reported in BCVA in the pairwise comparison of the presented economic model support the argument of clinical equivalence between the FAc implant and the Dex implant. This is not reflected in the guidelines. • The CEA model assumes 1 injection *per year* for FAc, where in pharmacokinetics (PK) studies, RCTs and RWE (specifically UK) the reality is typically 1 injection in a 36 month or *3-year period*.[1] This represents a gross *overestimate* of injection frequency for FAc. These inaccuracies undermine the accuracy of the reported estimates significantly. • Alimera have submitted a revised CEA model to the DR guidelines development team including an evidence-based assumption of 1 injection over 3 years. The value "0.33" is	The studies that included steroids used them as first-line treatment, and removing the steroids from the network would remove some of the comparisons from the NMA. The committee were also concerned about the additional adverse events associated with steroids compared to anti-VEGFs. This is why steroids were not considered as first-line treatment and have only been recommended in line with the TA guidance. The committee agree that there is very limited evidence to suggest switching between different anti-VEGF therapies and this has been removed from the recommendations. They think a change in class is important and have therefore retained the recommendation about considering a switch to steroids if a person shows a suboptimal response. After edits following consultation, the recommendations now state that anti-VEGFs should be offered initially, followed by adjuvant laser if there is a suboptimal response. Intravitreal steroids should then be considered if the response remains suboptimal. This reflects the guidance in the TAs for the ant-VEGFs and for dexamethasone and fluocinolone.

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				proposed for sheet "DataStore" in specific cells F172, F198, F224, F250, and F276 respectively. • Using the correct FAc injection frequency as above showed the FAc implant to be more cost effective and cheaper than the Dex implant. Adding the confidential PAS led to further dominance for FAc over Dex implant. The guidance should therefore reflect this by giving the FAc implant *at least* a similar position to that of the Dex implant throughout. • The CEA model also grossly *underestimates* the injection frequency of Dex implant, assuming from 1.78 (year 1) down to 1 injection per year across 5 years of treatment. This does not reflect RCT or RWE evidence. To treat DMO in line with RCT evidence and SPC, a *minimum* of 2 Dex implants are	NICE bases its recommendations on the clinical and cost-effectiveness evidence, resource impact and committee experience. The committee are aware of recommendations in other guidance and bear that in mind when making recommendations. However, the committee did not think that the recommendations differ greatly from those produced by NHS England or the Downey paper. The evidence for the technology appraisal submission for ranibizumab showed improvements in visual acuity in the first 12 months after the start of anti-VEGF treatment, and few people had a reduction in 10 letters over that time period. The committee therefore thought it was important that people are given this amount of time to respond to anti-VEGF treatment. The NHS framework presents switching to steroids at 3-6 months as one approach to assessing response to treatment. While this decision considered the effectiveness of steroids, there was less consideration given to other factors such as adverse events. Given the additional risks associated with steroids, and that some people can show a response to anti-VEGFs beyond 6 months, the committee thought the 12 months recommendation was appropriate. They were concerned that an earlier switch to steroids if there is a limited response to anti-VEGFs to begin with could result in people experiencing the additional adverse events associated

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				required per year to deliver the patient outcomes achieved in RCT studies for BCVA and CRT. • It is unintuitive and incorrect for the CEA to use the RCT outcome values for BCVA and CRT outcomes and not use the frequency of injections in these studies that achieved those outcomes. • In Dex implant real-world data sources, the injection frequency for Dex implant ranges between 2.2 per year[33] and 2.3 per year.[34] As such, in the revised model Alimera have submitted to the DR guidelines team, a value "2.0" proposed for sheet "DataStore" in specific cells F173, F200, F226 respectively. NB: this is still a *conservative* injection frequency of 2 Dex implants per year when compared to RWE.[33,34]	with steroids for limited benefits for visual acuity. More information about this has been added to the rationale in the guideline and to the committee discussion section of evidence review G. Although the Kodijikian study showed initial improvements in visual acuity in comparison to anti-VEGFs, the final visual acuity following each treatment was similar. This means that an early switch to steroids if there is a limited response to anti-VEGFs to begin with could result in people experiencing the additional adverse events associated with steroids for limited benefits for visual acuity. This supports the committee's view that 12 months are important to ensure that people have the time to respond to anti-VEGF treatment. The committee also thought that the frequency of injections is important, as stated in the Rennie study. Information is included in the rationale of the guideline about the importance of following guidance in the SPC to reflect this. Some questions within this guideline were answered with the use of observational evidence, but those that compared interventions were answered using RCT evidence. The recommendations were based on a combination of this evidence and the committee's clinical knowledge and experience, and so included

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				• With the above CEA input values added to the CEA, which Alimera believe reflect clinical practice and the evidence base for RCT and RWE, the FAc implant *appears to dominate Dex implant*. This throws into question any decision making that has influenced the position of both Dex and FAc implants in the guideline development and stepwise prescribing recommendations of this draft. • Alimera calls NICE and the DR guidelines team to look seriously at these incorrect assumptions and look closer at already published NHS and consensus guideline publications[6,10,19] that appear to offer a better researched and evidenced stepwise recommendation for both Dex and FAc implants after anti-VEGF have failed.	their awareness of how people are treated, and the impact on their eye disease, in practice.

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				• TA613[2] is currently being reappraised by NICE (FAc implant in eyes with a phakic lens) with recommendations from the technical assessment expected early 2024. To ensure robustness of the NICE DR guideline, and that it is current and aligned with *all* NICE TAs for DMO treatments, it is proposed that current draft guidance timelines should be paused until such a time that recommendations from the NICE TA613 reappraisal have been made, which is Alimera believe has been set as precedent for other disease area guidelines by NICE in the past. 5. Alimera does not consider the guideline on switching therapies as safe or supported by RCT data (i.e. it is based on 2 relatively inconclusive RCTs). The following points support this concern:	

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				• There is a lack of any robust clinical data that switching from one anti-VEGF therapy to another anti-VEGF offers any additional clinical benefit. • A change in class may prove a better option. Moving away from anti-VEGF treatments to intravitreal steroids may also significantly decrease the injection frequency required for the patient, NHS and clinician, potentially reducing cost and burden of treatment. The company feels that this area has not been adequately addressed in Evidence Review H due to: vi) Only RCT evidence being evaluate with no UK RWE to reinforce or refute its findings vii) Only 2 RCTs being assessed with one reporting no change in VA outcomes in	

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				switching from one anti-VEGF (bevacizumab) to another (Aflibercept). Based on this evidence, there is not enough data to make these recommendations. viii) No assessment has been conducted of the large volume of real-world data from clinical audits and clinical guidance. These are important as they clearly show: E. Real-world VA outcomes with anti-VEGF are *inferior* to those achieved in RCTs. F. Real-world studies in UK NHS clinical practice (i.e., ICE-UK[3], Medisoft[4], and IRISS[5]) show switching from initial anti-VEGF	

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				Kodjikian et al. 2018[12] and Ciulla et al. 2020[13]) and also a new paper focussing on phakic patients specificaly.[41] In the latter publication by Rennie et al (2023) concludes that their "*Data confirms previous real-world evidence around response to anti-VEGF treatment, importance of baseline VA and frequency of injections in predicting outcomes in a UK setting. Continuing treatment beyond 6 months in suboptimal responders imposes unnecessary treatment burden without significant change in VA. In suboptimal responders, consideration of early switch to longer acting steroid treatments may help to reduce treatment burden, whilst maintaining or improving vision*."[41]	

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				consumption of NHS resources and patient's time (burden).	
Alimera Sciences Limited	Guideline	General	General	Diabetic Retinopathy: management and monitoring – Economic model report for evidence reviews E and G 6. The economic modelling underpinning the recommendations of this guidance document is flawed on several points. This has resulted in inaccurate and misleading determinations and recommendations in the draft guidance around the use of the FAc implant in clinical practice. • The decision problem (DP) and the NMA used to answer the DP in the economic model do not discriminate regarding prior treatments i.e., anti-VEGF agents are used as first line therapy in DMO and corticosteroid therapies (the FAc and Dex implant) are used as second line therapy for those with insufficient response to non-corticosteroid therapy.	Thank you for your comment. 1. Regarding the economic modelling, we have discussed with the committee and agree that both corticosteroid therapies should not be included in the comparison in the economic analysis, given the model is built to compare first line therapies only. We take on board your other comments about the model but have decided with committee input to completely remove the corticosteroids from the economic analysis. Corticosteroids were included in the NMA as the committee were interested in seeing the comparative effects of different treatments. However, they were aware of limitations regarding the evidence base and that steroids wouldn't be used as first-line treatment.

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Alimera Sciences Limited	Guideline	General	General	References 1. ILUVIEN 190 micrograms intravitreal implant in applicator Summary of Product Characteristics 2021. https://www.medicines.ie/medicines/iluvien-190-micrograms-intravitreal-implant-in-applicator-34861/spc#tabs 2. National Institute for Health and Care Excellence (NICE) Technology appraisal guidance [TA 613] Fluocinolone acetonide intravitreal implant for treating chronic diabetic macular oedema in phakic eyes after an inadequate response to previous therapy. Published: 20 November 2019. Available at: https://www.nice.org.uk/guidance/ta613 3. Holden SE, Kapik B, Beiderbeck AB, Currie CJ. Comparison of data characterizing the clinical effectiveness of the fluocinolone intravitreal	Thank you for your responses. We have checked these references where they are included in each of your comments and responded accordingly.

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				33. Iacono P, Parodi MB, Scaramuzzi M, et al. Morphological and functional changes in recalcitrant diabetic macular oedema after intravitreal dexamethasone implant. Br J Ophthalmol 2017;101:791–5. doi:10.1136/bjophthalmol-2016-308726 34. Mitchell P, Arnold J, Fraser-Bell S, et al Dexamethasone intravitreal implant in diabetic macular oedema refractory to anti-vascular endothelial growth factors: the AUSSIEDEX studyBMJ Open Ophthalmology 2023;8:e001224. doi: 10.1136/bmjophth-2022-001224 35. National Institute for Health and Care Excellence (NICE). TA820 Resource Impact Template available at: https://www.nice.org.uk/guidance/ta820/resources [accessed 22/9/23] 36. Wickham et al Eye 2020; 34; 1189–1192. https://www.nature.com/articles/s41433-020-0957-2, accessed 3/3/21. 37. BBC news, available at: https://www.bbc.co.uk/news/health-52968845, accessed 3/3/21 38. HSIB, available at: https://www.hsib.org.uk/news/latest-hsib-report-	

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				highlights-devastating-impact-of-delays-and-pressure-on-national-glaucoma-services/, accessed 3/3/21. 39. NHS England, Winter pressures and 2021/22 Planning letter available at: https://www.england.nhs.uk/coronavirus/wp-content/uploads/sites/52/2020/12/important-for-action-operational-priorities-winter-and-2021-22-sent-23-december-2020.pdf, accessed 3/3/21 40. Office for Health Improvement and Disparities. Atlas of variation in risk factors and healthcare for vision in England – Full document. 2021. Available at: https://fingertips.phe.org.uk/profile/atlas-of-variation [accessed 22/9/23] 41. Rennie C, Lotery A, Payne J, Singh M, Ghanchi F. Suboptimal outcomes and treatment burden of anti-vascular endothelial growth factor treatment for diabetic macular oedema in phakic patients. Eye (Lond). 2023 Aug 4. doi: 10.1038/s41433-023-02667-w. Epub ahead of print. PMID: 37542174.	
Bayer plc	Economic Report	026 075	Table 17	**Economic report – tables 17 and 57 (monitoring visits)**	Thank you for your comment. The first table includes where the data are sourced from and, in cases where an average has been used, a link to the table in the

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			Table 57	Table 17 and table 57 report monitoring frequencies for the available anti-VEGFs. In line with NICEs processes, the basis of these numbers should be supported by clinical evidence. **However, the 'evidence' in the tables appear to be largely assumptions from past appraisals, some several years old. This represents a lowering of standards for this guidelines update.** Assumptions from an appraisal for one treatment have been used as the 'evidence' source for another treatment e.g. assumptions from TA799 (faricimab) and TA820 (brolucizumab) are used as inputs for aflibercept. As experience with anti-VEGFs has increased, clinical practice has changed and with it the frequency of monitoring. As a consequence of these changes assumptions from early appraisals should not automatically be considered relevant. This guideline does not consider how treatment has changed and implicitly, without validation, gives equal weighting to assumptions from different appraisals irrespective of their timing. **Requested change** It should be made clear in the tables where evidence is not available and where assumptions have been relied upon i.e. by inclusion of an asterix in the table cells with a footnote stating that RCT evidence is not available. The	appendix where all of the individual source data is detailed. Where one of the sources for a treatment (e.g. aflibercept from TA799) is taken from the technology appraisal of another treatment (TA799), it is the inputs that were used for the correct treatment, and this has now been clarified in the tables. When more than one alternative source available, the average across sources was considered in the base-case analysis.

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				year in which the appraisal was conducted should also be added to the tables.	
Bayer plc	Economic Report	029 073	Table 22 Table 56	**Economic report – tables 22 and 56 (injection frequency)** Table 22 in the economic report includes injection numbers over years 1-5 for anti-VEGFs. In line with NICEs processes, the basis of these injection numbers should be supported by clinical evidence. **However, the 'evidence' in the tables appear to be largely assumptions from past appraisals, some several years old and therefore not reflective of current treatment practices. This represents a lowering of standards for this guidelines update.** As an example, assumptions from an appraisal for one treatment have been used as the 'evidence' source for another treatment e.g. assumptions from TA799 (faricimab) and TA820 (brolucizumab) are used as inputs for injection frequencies for aflibercept. The weakness and inaccuracy of this approach is highlighted by the injection numbers in year 5 for aflibercept which are assumed as 2.37 (TA799) and 1 (TA820). Furthermore, TA799 provides two different assumed injection frequencies in year 5 for aflibercept i.e. 2.00 and 2.37. In total, TA799 has been used 3 times as evidence for	Thank you for your comment. The first table includes where the data are sourced from and, in cases where an average has been used, a link to the table in the appendix where all of the individual source data is detailed. Where one of the sources for a treatment (e.g. aflibercept from TA799) is taken from the technology appraisal of another treatment (TA799), it is the inputs that were used for the correct treatment, and this has now been clarified in the tables. When more than one alternative source available, the average across sources was considered in the base-case analysis.

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				aflibercept. All assumptions are then averaged to form the basecase input for aflibercept. As experience with anti-VEGFs has increased, treatment practices have changed i.e. the fixed dosing and PRN (as needed) regimens used in the earlier years have largely been replaced with a Treat & Extend regimen. As a consequence of these changes assumptions from early appraisals should not automatically be considered relevant. This guideline does not consider how treatment has changed and implicitly, without validation, gives equal weighting to assumptions from different appraisals irrespective of their timing. **Requested change** It should be made clear in the tables where evidence is not available and where assumptions have been relied upon i.e. by inclusion of an asterix in the table cells with a footnote stating that RCT evidence is not available. The year in which the appraisal was conducted should also be added to the tables.	
Bayer plc	Guideline	008 – 012	011 – 015 & 022	**Throughout the document there are statements that "if more than one anti-VEGF is available, use the cheapest [2023]"**	Thank you for your comment. The committee discussed this and also thought that there are wider considerations than the unit cost of each anti-VEGF. They therefore decided to remove the information

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				These statements are entirely focused on unit price, and as there can ever be only one 'cheapest' anti-VEGF it restricts usage to a single product. The restriction: 1) ignores clinical appropriateness i.e. the ability of the physician to select the most suitable treatment for the individual 2) ignores NHS capacity - the 'cheapest' agent may require more frequent injections/monitoring versus alternative treatments 3) considers unit price only and doesn't consider total cost which is calculated by multiplying unit price by the number of injections and then adding monitoring costs. 4) deviates from wording used in STAs and NHS commissioning policy which encompass considerations other than unit cost. 5) negatively affects continuity of care as the wording could be taken to imply that the patient's treatment should be switched in response to changing anti-VEGF prices and which treatment has the cheapest unit price on any given day 6) affects the ability to maintain a market with multiple treatment options as the 'winner takes all' nature of the wording makes being the second cheapest anti-VEGF commercially unviable	about using the cheapest anti-VEGF. As you mention in your comment, additional information about what factors should be considered when choosing an anti-VEGF are already included in some of the technology appraisal recommendations.

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				7) disadvantages patients with DMO relative to wAMD i.e. wAMD NHSE commissioning guidance allows flexibility of physician/patient choice Furthermore, the wording conflicts with the NHS constitution which states that all recommended treatments should be available as options and that "if the doctor responsible thinks the technology is the right treatment, it should be available for use, in line with NICE's recommendations (clause 74). Stipulating use of one anti-VEGF (i.e. the cheapest) removes the optionality required under the constitution. It is important that clinicians continue to determine, in discussion with their individual patients, which medical retinal vascular treatments are clinically appropriate for them, and they should be able to access all available treatments (in line with national guidance and the legal requirement for all NICE recommended products to be funded). We consider that the statement is likely to have a consequence of adversely affecting patient care and could have the unintended result of increasing the burden on the NHS. We suggest the statement is amended in line with wording used previously in STAs and NHS commissioning policy. Proposed wording is in italics below.	

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				If a range of suitable treatments are available (including aflibercept, brolucizumab, faricimab, ranibizumab), chose the least expensive treatment that is clinically acceptable. Take into account administration costs, frequency of injection, NHS capacity, and commercial arrangements.	
Bayer plc	Guideline	013 - 017	008 - 009 012 - 013	**Section 1.5.10 Assess response to treatments after 12 months. Consider switching to dexamethasone intravitreal implant if the response is suboptimal** It would appear clinically appropriate to consider a different treatment after 12 months if the patient might benefit. However, the hyperlink which takes the reader to the "Terms used in this Guideline" is not aligned with the recommendation as it defines 'suboptimal response' in relation to the period after loading rather than 12 months. It is important that patients are not switched prematurely i.e. before they have been given sufficient time to respond to anti-VEGF treatment. Evidence from clinical trials shows that patients continue to improve beyond the loading phase (1-5). Anatomic response to therapy appears to develop more gradually, and the reduction in CRT may not peak until later in the course of treatment (6,7).	Thank you for your response. The committee agreed with your suggestion and the reference to the loading phase has now been removed from the definition of a suboptimal response.

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				Suggested change To align the hyperlink with the recommendation in section 1.5.10 we suggest the wording in the hyperlink target is changed from "loading dose" to "12 months". **References** 1. DRCR.net, Elman MJ, Aiello LP, Beck RW, et al. Ophthalmology 2010;117(6):1064–1077. 2. Rajendram R, Fraser-Bell S, Kaines A, et al. Arch Ophthalmol. 2012;130(8):972–979. 3. Nguyen QD, Brown DM, Marcus DM, et al. Ophthalmology 2012;119(4):789–801. 4. Pieramici D et al. Ophthalmol Retina 2018; 2 (6): 558–566. 5. Bressler NM et al. Am J Ophthalmol 2018; 195: 93–100. 6. Massin P, Bandello F, Garweg JG, et al. Diabetes Care 2010;33(11):2399–2405. 7. Kriechbaum K, Prager S, Mylonas G, et al. Eye (Lond) 2014;28(1):9–15.	
Bayer plc	Guideline	General	General	[This text was identified as confidential and has been removed].	Thank you for your response. Where the guideline refers to anti-VEGFs, it mentions the class of drug rather than specific drug names or doses. As such, based on our current wording, people will be able to

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					prescribe the 8mg dose once it receives UK marketing authorisation. We were unable to refer to the PHOTON study in the guideline as it had not been published at the time the evidence was being considered. The cost of the 8mg dose is not included in the economic analysis as it was not available at the time of the analysis.
BNF Publications	Guideline	005	014 – 018	Rec. 1.1.10 – This recommendation states 'fibrates' yet Evidence review D uses the Cochrane review by Kataoka et. Al, for these recommendations. The two studies within this Cochrane review both used fenofibrate in doses of: - fenofibrate 200mg/day (FIELD study) - fenofibrate 160mg/day plus simvastatin 20-40mg/day (ACCORD-lipid study) Evidence review D page 8 line 65 on included studies, said that 'A systematic search was conducted to identify studies that were not covered by the Do et al. 2023 and Kataoka et al 2023. Cochrane reviews. This search looked for studies evaluating the effectiveness of statins and studies evaluating fibrates other than fenofibrate.' And line 71 'for fibrates the systematic search identified 106 records. These were screened on title and abstract, with no full-text papers ordered as relevant studies.' We therefore wanted to clarify if rec. 1.1.10 refers to the consideration of fenofibrate only, or is the intention that	Thank you for your response. This has been updated throughout the guideline and evidence review to clarify that we are recommending fenofibrate as opposed to all fibrates.

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				any fibrate (i.e. fenofibrate, as well as bezafibrate, ciprofibrate, and gemfibrozil) can be considered for use for people with non-proliferative retinopathy and type 2 diabetes to reduce the progression of diabetic retinopathy? If rec. 1.1.10 does mean any fibrate can be considered for this use, we would welcome the reasoning behind this decision, given that the studies quoted in Evidence review D refer only to the use of fenofibrate.	
BNF Publications	Guideline	012	012	Rec. 1.5.5 - This recommendation for considering anti-VEGFs in patients who have centre-involving diabetic macular oedema, central retinal thickness of less than 400 micrometres and visual impairment, is broadly covered by the indication of 'Diabetic macular oedema' in current licensed product information for Aflibercept, Brolucizumab, Faricimab, and Ranibizumab. These drugs all have a technology appraisal to cover use in central retinal thickness greater than 400 micrometres (which is rec. 1.5.6) but not for central retinal thickness of less than 400 micrometres. We wanted to know if NICE plan to publish new technology appraisals (TAs) or update existing TAs to take account of rec. 1.5.5?	Thank you for your response. NICE regularly monitors its recommendations to ensure they are up to date and decide what action to take if they are no longer valid or accurate. NICE guidelines can make advisory recommendations on the use of treatments for a wider population than those covered by the TAs if there is evidence of clinical evidence, and further justification such as to reduce inequalities. We include discussion of inequalities in the equality impact assessment and in the committee discussion section of the evidence review.
British Society for Paediatric	Guideline	General	General	Many children never develop DR but some do. It would be helpful if there could be a mention of evidence relating to	Thank you for your response. Our reviews found no specific evidence for children and so it was difficult for the committee to make specific recommendations for

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Endocrinology and diabetes (BSPED)				DR in children and young people (CYP) (see cross reference to research questions).	children and adolescents. For this reason, the committee included age as a subgroup in some of the research recommendations. This should provide more detailed evidence specifically for children in the future. However, the committee were confident that the recommendations in this guideline will also apply to children if they develop diabetic retinopathy.
British Society for Paediatric Endocrinology and diabetes (BSPED)	Guideline	General	023	Please consider including a research question on frequency of monitoring of DR in CYP; whilst some CYP develop DR, many do not. In COVID, DR monitoring was reduced in frequency. Did this impact the frequency of DR? Is there a way of informing risk stratified monitoring? E.g. those at high risk (young age of diagnosis/longer diabetes duration/ high HbA1c for more frequent (annual) checks, and those at lower risk, DR monitoring less frequently?	Thank you for your response. We included age as one of the subgroups in some of our research recommendations, such as the risk factors for progression to PDR and DMO. However, as we did not directly search for monitoring frequency and DR screening in children, we are unable to make research recommendations for this as we are not aware of the current evidence base.
College of Optometrists	Guideline	003	005	Could this be made clearer to state all clinicians in primary (community) and secondary care services (Hospital eye services)	Thank you for your response. The committee discussed this but think that the title of this section of the guideline, along with the statement that the recommendation applies to all clinicians, means that all relevant clinicians are covered. They therefore decided against updating the wording of this recommendation.
College of Optometrists	Guideline	004	016	1.1.5 Please add that the patient's primary care optometrist (who would be involved in their regular eye care) should also be provided with the same information	Thank you for your response. The committee thought it was important that primary care professionals are made aware of the patient's disease severity. This means it can be taken into account when prescribing

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				about the severity of their diabetic eye disease and how it is being managed.	medicines that are associated with a rapid drop in blood glucose and can have an adverse effect on disease progression. However, they also thought it was important for a range of people to have access to this information which is why they stated that this information was for healthcare professionals involved in diabetes care, rather than stating specific roles. This definition includes primary care optometrists.
College of Optometrists	Guideline	008	011	1.4.5 We would recommend amending this to say the 'cheapest appropriate' [anti-VEGF].	Thank you for your comment. The committee discussed this and decided that there are wider considerations than the unit cost of each anti-VEGF. They therefore decided to remove the information about using the cheapest anti-VEGF. Additional information about what factors should be considered when choosing an anti-VEGF are already included in some of the technology appraisal recommendations.
College of Optometrists	Guideline	008	018	1.4.6 We would recommend amending this to say the 'cheapest appropriate' [anti-VEGF].	Thank you for your comment. The committee discussed this and decided that there are wider considerations than the unit cost of each anti-VEGF. They therefore decided to remove the information about using the cheapest anti-VEGF. Additional information about what factors should be considered when choosing an anti-VEGF are already included in some of the technology appraisal recommendations.
College of Optometrists	Guideline	012	022	1.5.6 We would recommend amending this to say the 'cheapest appropriate' [anti-VEGF].	Thank you for your comment. The committee discussed this and decided that there are wider considerations than the unit cost of each anti-VEGF.

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					They therefore decided to remove the information about using the cheapest anti-VEGF. Additional information about what factors should be considered when choosing an anti-VEGF are already included in some of the technology appraisal recommendations.
College of Optometrists	Guideline	014	012	1.5.16 Please add that the patient should be advised to have regular eye examinations with a primary care optometrist. Patients may not appreciate the difference between primary eye care/regular sight tests and the diabetic screening service (DESP). It should be noted that there are other eye conditions which have a significantly higher prevalence in diabetes, such as glaucoma, and these are not detected as part of the DESP service (See Zhao D, Cho J, Kim MH, Friedman DS, Guallar E. Diabetes, fasting glucose, and the risk of glaucoma: a meta-analysis. Ophthalmology. 2015 Jan;122(1):72-8. doi: 10.1016/j.ophtha.2014.07.051). In addition people who have received treatment for proliferative eye disease or maculopathy may be more reliant on maximising their visual acuity and visual field, which can be achieved by ensuring they have a current prescription for an optical device.	Thank you for your response. The committee agreed that it is very important to consider other eye conditions that are not covered by DESP. We have added more information to the rationale about the importance of regular appointments at an optician for eye conditions not covered by screening or hospital eye services.
College of Optometrists	Guideline	035	005 - 012	– Key Recommendations for Research Suggested addition to the guidance: Panretinal photocoagulation can cause permanent visual field loss. Patients who drive should be advised of the risk to their peripheral vision before pan retinal photocoagulation	Thank you for your response. One of the outcomes in our reviews related to peripheral visual field loss, but no evidence was identified. However, the committee were aware this is a potential issue and so have included functional impact on vision and peripheral

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				treatment. People who are group two drivers (HGV, PCV) may be adversely effected by this recommendation, and may result in them being unable continue in their occupation as a driver. Anti-VEGF should be considered for people employed as drivers where panretinal photocoagulation may have an adverse effect on a their occupation and quality of life. Taxi drivers may also be effected by local licensing requirements. The cost benefit analysis is likely to be different where a person may not be able to work in their current occupation as a result of the treatment, and as such an anti-VEGF may be a more appropriate first line option.	vision and visual field changes as outcomes in the recommendations for research.
College of Optometrists	Guideline	036	018 - 020	Key Recommendations for Research - We would recommend amending this to say the 'cheapest appropriate' [anti-VEGF].	Thank you for your comment. The committee discussed this and decided that there are wider considerations than the unit cost of each anti-VEGF. They therefore decided to remove the information about using the cheapest anti-VEGF. Additional information about what factors should be considered when choosing an anti-VEGF are already included in some of the technology appraisal recommendations.
College of Optometrists	Guideline	043	022 - 026	Key Recommendations for Research - Please define what level of vision is considered 'good vision'. We recommend defining as better than 0.30 logMAR (Snellen 6/12)	Thank you for your response. This has been defined in the recommendation (79 letters or better).
Diabetes UK	Guideline	003	005	We are concerned by the use of the term good diabetes management. This suggests that if you follow instructions you can achieve perfect control, disregarding the many factors that can affect blood glucose control. We would	Thank you for your response. The committee discussed the wording for this recommendation and used the term 'good long term management' because it reflects the wider factors that can ultimately affect

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				recommend following the NHS 'Language Matters' guidance which favours the use of language which is person-centred, more inclusive and values based. This has been shown to help lower anxiety, build confidence, educate and help to improve self-care. Therefore, the wording of this section could be changed to 'should discuss with the person the benefits that keeping their HbA1c within the target range set by their healthcare team can have on long-term benefits for their vision.' Reference: https://www.england.nhs.uk/long-read/language-matters-language-and-diabetes/#principles-and-practice	HbA1c and can impact on someone's vision. They decided not to update the recommendation to the suggested wording as it focuses on HbA1c rather than the wider factors that can affect HbA1c control.
Diabetes UK	Guideline	003	012	We would suggest notifying local eye screening services alongside the person's ophthalmologist. We know there are areas in the UK where adults and children aged over 12 years are not automatically referred under an ophthalmologist and are only referred if an issue is found when attending their local eye screening programme.	Thank you for your response, The committee discussed your suggestions but think it is mostly people who are already under the care of hospital eye services who are most at risk following a rapid, substantial drop in HbA1c. As such, they did not think that local eye screening services need to be notified in the same way as an ophthalmologist.
Diabetes UK	Guideline	003	012	We are pleased to see reference to the possible adverse effects of a rapid and substantial drop in HbA1c levels, called early worsening. It is clear that this an acknowledged issue among clinicians and we appreciate that there is a lack of evidence to support more specific recommendations, other than to proceed with caution and	Thank you for your response, and support for this recommendation and research recommendation. The committee discussed your suggestions but think it is mostly people who are already under the care of hospital eye services who are most at risk following a rapid, substantial drop in HbA1c. As such, they did not

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				ensure that there is close monitoring by an ophthalmologist. We therefore are similarly pleased to see the associated research recommendation. We would suggest that local eye screening services are notified alongside the person's ophthalmologist. We know there are areas in the UK where adults and children aged over 12 years are not automatically referred under an ophthalmologist and are only referred if an issue is found when attending their local eye screening programme.	think that local eye screening services need to be notified in the same way as an ophthalmologist.
Diabetes UK	Guideline	004	001 - 019	This section of the guideline emphasises the importance of healthcare professionals in the diabetes and ophthalmology departments being fully aware of all the relevant information on the patient, in order to be able to take informed decisions on the best treatment. It is recognised that this is not always the case, so we welcome that it is highlighted. However, it's important that this is facilitated within the hospital, and we hope that this recommendation is acted on to improve communication across the specialties. A survey carried out by the Macular Society in 2021 had as one of its conclusions that better connections between diabetic clinics, eye clinics and low vision support are needed.	Thank you for your response and support for these recommendations. The committee also thought that better communication between services is important, which is why this information has been included in the guideline.

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Diabetes UK	Guideline	007	020	We welcome this recommendation as we know some ophthalmologists do not treat low risk proliferative diabetic retinopathy until it progresses into the high-risk phase. Given the low risks associated with modern laser treatment, we would agree with the decision to treat all patients diagnosed with proliferative diabetes retinopathy.	Thank you for your response and support for this recommendation.
Diabetes UK	Guideline	012	012 - 016	We welcome that the guideline recognises that some people, such as some women and those from South Asian and Afro-Caribbean descent, tend to have thinner retinas and therefore would be disadvantaged if the 400 micrometres threshold for anti-VEGF treatment was applied. This should ensure those who fall into this category do not experience worse outcomes because it takes longer for them to receive treatment.	Thank you for your response and support for this recommendation.
Diabetes UK	Guideline	013	013 - 017	To note the review of the NICE technology appraisal on fluocinolone acetonide intravitreal implant for treating diabetic macular oedema which is underway and may impact on this recommendation.	Thank you for your response. Following the update of the technology appraisal for fluocinolone (TA953), we have updated the recommendation about switching to steroid treatment so that it now says "intravitreal steroid implant" rather than stating dexamethasone. This means that fluocinolone can also be considered when anti-VEGF treatment is not effective.
Diabetes UK	Guideline	019	006 - 009	We support this research recommendation on rapid substantial reduction in HbA1c and the rsk of short-term	Thank you for your response and support for this research recommendation.

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				progression of diabetic retinopathy or diabetic macular oedema.	
Diabetes UK	Guideline	General	General	We would recommend the inclusion of guidance on reasonable adjustments to take into account any disabilities. As visual impairment can often be present with diabetic retinopathy, guidance should be included for clinicians to discuss how patients can manage their diabetes if they are experiencing vision loss.	Thank you for your response. As reasonable adjustments are a legal requirement, we expect that these are being implemented and therefore don't include specific mention of them as part of the recommendations. However, we have considered these issues in some detail during the development of this update. In developing the recommendations, the committee took into account the health inequalities issues identified as part of the equalities impact assessment that accompanies this work.
Diabetes UK	Guideline	General	General	We would suggest that clinicians refer to resources and support services provided by patient organisations such as Macular Society and Diabetes UK when discussing blood glucose management and prevention of diabetic retinopathy progression. https://www.macularsociety.org/research/features/report-finds-lack-of-support-for-sight-loss-due-to-diabetes/ https://www.diabetes.org.uk/guide-to-diabetes/complications/retinopathy	Thank you for your response. NICE does not routinely recommend specific resources within guidelines, as the most appropriate source of information may change over time. However, there are links to the homepages of the Macular Society and Diabetes UK in the information for the public that is published alongside the guideline.
JDRF - Juvenile Diabetes	Guideline	018	General	Supporters have shared with JDRF that they have concerns that medical technology companies do not always necessarily take into account individuals with	Thank you for your response. In this guideline we did not look and search for evidence on devices for managing diabetes. We are

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Research Foundation				diabetic retinopathy when producing information leaflets or packaging or with regards to the useability of devices. JDRF suggests that there should be an additional research recommendation to examine the useability of devices by those with retinopathy.	therefore unable to make research recommendations on these topics.
JDRF - Juvenile Diabetes Research Foundation	Guideline	019	006 - 009	Some supporters of JDRF have commented on experiencing sight loss following rapid HbA1c improvement. This phenomenon is not widely understood and we welcome the recommendation for research in this area.	Thank you for your response and support for this recommendation.
JDRF - Juvenile Diabetes Research Foundation	Guideline	General	General	JDRF notes that this is the first consultation on diabetic retinopathy and is supportive of the current draft guidelines.	Thank you for your response and support for this guideline.
Macular Society	Equality Impact Assessment	General	General	This assessment covers the important equality issues in diabetic retinopathy monitoring and management.	Thank you for your response and support of this assessment.
Macular Society	Guideline	003	012	We are pleased to see reference to the possible adverse effects of a rapid and substantial drop in HbA1c levels, called early worsening. It is clear that this an acknowledged issue among clinicians and we appreciate that there is a lack of evidence to support more specific recommendations, other than to proceed with caution and	Thank you for your response and support for these recommendations.

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				ensure that there is close monitoring by an ophthalmologist. We therefore are similarly pleased to see the associated research recommendation.	
Macular Society	Guideline	004	001 - 019	This section of the guideline emphasises the importance of healthcare professionals in the diabetes and ophthalmology departments being fully aware of all the relevant information on the patient, in order to be able to take informed decisions on the best treatment. It is recognised that this is not always the case so we welcome that it is highlighted. However, it's important that this is facilitated within the hospital and we hope that this recommendation is acted on to improve communication across the specialties. A survey carried out by the Macular Society in 2021 had as one of its conclusions that better connections between diabetic clinics, eye clinics and low vision support are needed.	Thank you for your response and support for these recommendations. The committee also thought that better communication between services is important, which is why this information has been included in the guideline.
Macular Society	Guideline	007	020	We welcome this recommendation as we know some ophthalmologists do not treat low risk proliferative diabetic retinopathy until it progresses into the high-risk phase. Given the low risks associated with modern laser treatment, we would agree with the decision to treat all patients diagnosed with proliferative diabetes retinopathy.	Thank you for your response and support for this recommendation.

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Macular Society	Guideline	012	012 - 016	We welcome that the guideline recognises that some people, such as some women and those from South Asian and Afro-Caribbean descent, tend to have thinner retinas and therefore would be disadvantaged if the 400 micrometres threshold for anti-VEGF treatment was applied. This should ensure those who fall into this category do not experience worse outcomes because it takes longer for them to receive treatment.	Thank you for your response and support for this recommendation.
Macular Society	Guideline	013	013 - 017	To note the review of the NICE technology appraisal on fluocinolone acetonide intravitreal implant for treating diabetic macular oedema which is underway and may impact on this recommendation.	Thank you for your response. Following the update of the technology appraisal for fluocinolone (TA953), we have updated the recommendation about switching to steroid treatment so that it now says "intravitreal steroid implant" rather than stating dexamethasone. This means that fluocinolone can also be considered when anti-VEGF treatment is not effective.
Macular Society	Guideline	019	006 - 009	We support this research recommendation on rapid substantial reduction in HbA1c and the risk of short-term progression of diabetic retinopathy or diabetic macular oedema.	Thank you for your response and support for this research recommendation.
Macular Society	Guideline	General	General	We would suggest that clinicians refer to resources and support services provided by patient organisations such as Macular Society and Diabetes UK when discussing blood glucose management and prevention of diabetic retinopathy progression.	Thank you for your response. NICE does not routinely recommend specific resources within guidelines, as the most appropriate source of information may change over time. However, there are links to the homepages of the Macular Society and Diabetes UK in

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				https://www.macularsociety.org/research/features/report-finds-lack-of-support-for-sight-loss-due-to-diabetes/ https://www.diabetes.org.uk/guide-to-diabetes/complications/retinopathy	the information for the public that is published alongside the guideline.
NHS England	Guideline	003	005	1.1.2 Agree with the recommendation however, clarity is needed. Is this for patients with Diabetic retinopathy AND diabetic macular oedema and currently under hospital eye services? If so, this is reasonable and recommended. If this is not the case, patients with mild diabetic retinopathy currently in screening and not under an ophthalmologist, does this recommend referral to hospital eye services for this cohort of patients?	Thank you for your response. The recommendations in this guideline only cover people who are already managed under hospital eye services. The description of the guideline has now been updated to clarify this. As such, the recommendations do not apply to people with mild NPDR who fall under the screening programme,
NHS England	Guideline	003	013	We are concerned that this does not specific the person should be under the care of an ophthalmologist at the time of referral and without this specification there will be many referrals made to ophthalmology that are not relevant.	Thank you for your response. The recommendations in this guideline only cover the population who are already managed under hospital eye services. People in this group should therefore already be under the care of an ophthalmologist. The description of the guideline has now been updated to clarify this.
NHS England	Guideline	004	009	1.1. 4 Agree with this recommendation but this would require access for all ophthalmologists to the GP/primary care/General hospital records of the patients HbA1c, renal function and blood pressure. Provision of this access is	Thank you for your response, We have clarified in the rationale the importance of provision of access to both primary and secondary care information. The committee discussed your comment and noted that the intention is not to have to

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				paramount for this recommendation. It is more challenging in standalone eye units. If this is not provided, it is not appropriate for patients and eye services for Hospital eye services to test for these at every visit. This should be made clear in the recommendation.	test for this information at every visit. Instead, there are a range of ways that this information can be accessed. The committee thought that it local services should decide on the best method of provision of access.
NHS England	Guideline	005	004	1.1.6 – 1.1.9 Good suggestion but clarity on the responsible clinician for the management of blood pressure/statins is needed, presumably GP?	Thank you for your response. Based on other stakeholder responses, the information about statins has been removed from the guideline. The committee noted that there are a range of clinicians responsible for a person's diabetes management, and so they decided against being more specific about who is in responsible for this.
NHS England	Guideline	005	015	1.1.10 Clarity on who should prescribe this medication is required	Thank you for your response. We have updated the recommendation to state that the person's ophthalmologist should consider prescribing fenofibrate. More information about this has also been added to the rationale.
NHS England	Guideline	006	021	1.3.2 Moderate NPDR that are R1 are still in screening, will this translate to the screening guidance? This would increase the number of referrals to HES and added resource is required to manage this.	Thank you for your response. This guideline covers diagnosis, management and monitoring of diabetic retinopathy in hospital eye services. Screening is therefore out of scope for this guideline and so these recommendations will not apply to people who are R1 and still in screening.
NHS England	Guideline	007	010	1.4.1 Anti-VEGF for PDR as first line is not NICE approved/funded and no long-term data as a primary	Thank you for your response. The committee agreed that panretinal photocoagulation is first-line treatment for people with PDR. We have added more information

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				treatment. PRP remains the first line treatment for PDR but there is a role for AntiVEGF to treat neovascularisation of iris to facilitate PRP, pre-operatively for NVG and VR surgery. It should only be used as an adjunct rather than a stand-alone treatment. Resources would be required for additional failsafe should this be a first-line option on top of the obvious drug/delivery costs. -	to the recommendation and the rationale to highlight that this is the case for most people.
NHS England	Guideline	008	008	1.4.5 Very supportive of the use of anti-VEGF as an adjunct if PDR remains active after complete PRP, however, please do add the need to rule out tractional retinal detachment before treating with anti-VEGF. The only licensed drug would be ranibizumab currently. Avastin is off-label use, other anti-VEGF not licensed for PDR. I agree that this should be the case and supportive of this – ranibizumab biosimilar/avastin. However, I suspect there may be challenges with implementation	Thank you for your response. As suggested, we have added information to the recommendation on anti-VEGFs for people with PDR to include a caution for tractional retinal detachment. The recommendation now says that people who have tractional retinal detachment should be monitored closely in collaboration with a vitreoretinal specialist.
NHS England	Guideline	008	012	1.4.6 Fully supportive of this recommendation but need to add no tractional Retinal detachment present. Again, very supportive of this, however, may have challenges with implementation.	Thank you for your response. As suggested, we have added information to the recommendation on anti-VEGFs for people with PDR to include a caution for tractional retinal detachment. The recommendation now says that people who have tractional retinal detachment should be monitored closely in collaboration with a vitreoretinal specialist.
NHS England	Guideline	009	006	1.4.8	Thank you for your response.

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				Clarity would be appreciated for the term 'in-between appointments' for a diagnostic appointment. The explanation is also unclear (Page 38) with recommendation that anyone who had treatment require a slit lamp assessment, but also recommending it as a monitoring tool in the diagnostic clinic 'in between' appointments. Is this 'in between' period between the intervals recommended. I believe a short section clarifying the use of diagnostic clinics will be helpful as well. The inability to detect rubeosis is an important limitation in diagnostic clinics but the monitoring of lower risk cases, ie. Moderate NPDR/DMO is suitable in a diagnostic clinic model as practiced in the screening programme to an extent and conversion to face to face when significant progression or change noted as mentioned in the document.	We have updated the recommendation by removing the clinical setting as the committee discussed how ultrawide-field fundus imaging can be used in both diagnostic and hospital clinics. This should remove any confusion over where monitoring can be done.
NHS England	Guideline	011	001	1.4.15 Vitrectomy should also be considered for patients with recurrent haemorrhages due to persistent vitreoretinal traction even if proliferative disease is now quiet.	Thank you for your response. The committee agreed that recurrent vitreous haemorrhages may not always be related to active proliferative diabetic retinopathy. They therefore amended the recommendation to clarify that this could also be caused by vitreomacular traction.
NHS England	Guideline	012	General	1.5.5 This goes directly against previous guidelines where Avastin was not part of the recommendation as off-license – is that the intention.	Thank you for your response.The recommendation has been edited to indicate which treatments are licensed, and notes that use of any other anti-VEGF would be off-label.

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NHS England	Guideline	012	012	There is no mention of diagnostic hubs or asynchronous monitoring of patients which is now becoming the way in which most diabetic patients are being managed when stable.	Thank you for your response. While we looked at evidence for monitoring frequencies, diagnostic hubs and asynchronous monitoring were out of scope for this update. As a result, the committee were unable to make recommendations on these.
NHS England	Guideline	014	012	Specify that the retina should have been stable for the previous 12 months before discharge.	Thank you for your response The committee discussed the recommendation on monitoring frequencies, and think that by stating that people have to be eligible for the screening programme, it covers that the retina should be stable before considering discharge.
NHS England	Guideline	General	General	We strongly suggest the document makes reference to making reasonable adjustments. This is a legal requirement as stated in the Equality Act 2010. Adjustments aim to remove barriers, do things in a different way, or to provide something additional to enable a person to receive the assessment and treatment they need. Possible examples include; allocating a clinician by gender, taking blood samples by thumb prick rather than needle, providing a quiet space to see the patient away from excess noise and activity. We recommend including reference to the Reasonable Adjustment Digital Flag (RADF) and the RADF Information Standard which mandates all providers and commissioners of health services and publicly funded	Thank you for your response. As reasonable adjustments are a legal requirement, we expect that these are being implemented and therefore don't include specific mention of them as part of the recommendation. However, we have considered these issues in some detail during the development of this guideline. In developing the recommendations, the committee took into account the health inequalities issues identified as part of the equalities impact assessment that accompanies this work.

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				social care to identify, record, flag, share, meet and review Reasonable Adjustments, including details of their underlying conditions. DAPB4019: Reasonable Adjustment Digital Flag - NHS Digital	
NHS England	Guideline	General	General	We recommend including reference to the importance of Communication: Using simple, clear language, avoiding medical terms and 'jargon' wherever possible. Some people may be non-verbal and unable to describe verbally how they feel. Pictures may be a useful way of communicating with some people, but not all.	Thank you for your response. The committee discussed the importance of shared decision making, tailoring health care to personal needs and ensuring that information is provided in a clear and suitable format. The committee therefore included recommendations linking to the sections covering communication in the NICE guideline on patient experience in adult NHS services (CG138) and the shared decision making NICE guideline (NG197).
NHS England	Guideline	General	General	We recommend including reference to the importance of Communication: Using simple, clear language, avoiding medical terms and 'jargon' wherever possible. Some people may be non-verbal and unable to describe verbally how they feel. Pictures may be a useful way of communicating with some people, but not all.	Thank you for your response. The committee discussed the importance of shared decision making, tailoring health care to personal needs and ensuring that information is provided in a clear and suitable format. The committee therefore included recommendations linking to the sections covering communication in the NICE guideline on patient experience in adult NHS services (CG138) and the shared decision making NICE guideline (NG197). The committee also discussed specific considerations for people with learning disabilities for example, making

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					adjustments to how information is provided and coaching for patients who are having radiotherapy. The committee's discussions of health inequalities are included in the committee discussion section of the evidence review and in the equalities and health inequalities assessment (EHIA) of this update
NHS England	Guideline	General	General	[This text was identified as confidential and has been removed].	Thank you for your response. This is out of scope for this guideline. However, we will pass your comments onto the surveillance team who monitor the type 2 diabetes guideline for update.
NHSE - NHS Diabetic Eye Screening Programme	Guideline	003	013	We are concerned that this do-es not specific the person should be under the care of an ophthalmologist at the time of referral and without this specification there will be many referrals made to ophthalmology that are not relevant.	Thank you for your response. This guideline covers diagnosis, management and monitoring of diabetic retinopathy in hospital eye services. As such, these people should already be under the care of an ophthalmologist. The description of the guideline has now been updated to clarify this.
NHSE - NHS Diabetic Eye Screening Programme	Guideline	014	012	Specify that the retina should have been stable for the previous 12 months before discharge.	Thank you for your response The committee have discussed the recommendation, and think that by stating people have to be eligible for the screening programme, it covers that the retina should be stable before considering discharge.
RCPCH - consultation panel for paediatrics, endocrinolog	Guideline	General	General	We have the following comments about diabetic retinopathy in children and adolescents with diabetes mellitus : #Prevalence of diabetic retinopathy in type 1 diabetes mellitus (T1DM) 10-13 years 1%, 14-15 years 5.8%, 16-18 years 17.7%	Thank you for your response. In this guideline we looked at the risk factors associated with progression of PDR and DMO, however we did not look at prevalence or the natural course of diabetic retinopathy. We were therefore unable to include this evidence in our reviews.

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y and diabetes				Reference: Massin et al undertook retinal photographic screening of 504 T1DM children at summer camp. **#** Prevalence of Diabetic Retinopathy six years after diagnosis**:** Children under age 11 (8%), pre pubertal children (12%), adolescents (25%), pubertal adolescents (19%)**.** Reference: Donaghue et al found that retinopathy was commonly found in children with T1DM six years after diagnosis.	
RCPCH - consultation panel for paediatrics, endocrinology and diabetes	Guideline	General	General	**#**Prevalence of diabetic retinopathy in type 2 diabetes (T2DM) in children: In young people, T2DM develops at around 13.5 years during the peak of physiological puberty insulin resistance. Data reported by the National Paediatric Diabetes Audit show that T2DM accounts for 1.5% of the 25,000 young (under age 25 years) diabetic persons in England and Wales.	Thank you for your response. In this guideline we looked at the risk factors associated with progression of PDR and DMO, however we did not look at prevalence or the natural course of diabetic retinopathy. We were therefore unable to include this evidence in our reviews.
RCPCH - consultation panel for paediatrics, endocrinology and diabetes	Guideline	General	General	**#**Duration of diabetes is a major risk factor in the development of diabetic retinopathy in children. those with T2DM had shorter duration, older age at diagnosis and higher rates of obesity and hypertension. **#** compared to adult patients with diabetes. The progression may be rapid especially in those with poor glycaemic control. Adolescence is a time when efforts should be	Thank you for your response. For the review on risk factors for progression of diabetic retinopathy, we used a Cochrane review. This review did not find any evidence specifically for the development of diabetic retinopathy in children, and so the committee were unable to make recommendations on this. The committee were aware of the importance of screening but were unable to make recommendations on this as the guideline is aimed at people who are in hospital

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				directed to screening for early signs of diabetic retinopathy and modifiable risk factors . **#**Those children found to have diabetic retinopathy had higher blood pressure than those without diabetic retinopathy. .reference: Gallego et al examined the relationship between blood pressure and the development of early DR in adolescents with childhood onset T1DM	eye services. Duration of diabetes was considered in the review, but there was limited evidence to support it as a major risk factor for progression.
RCPCH - consultation panel for paediatrics, endocrinology and diabetes	Guideline	General	General	**#** Patients on the "intensive" insulin regimen therapy are less likely to have retinopathy Reference: Within the DCCT was a cohort of 195 adolescents. Compared with conventional treatment, those on intensive treatment reduced the risk of and progression of background (nonproliferative) retinopathy by 53%. **#** High BMI has been shown to be a risk factor for developing retinopathy in Adolescence **#** There has been recent research interest in the role of Vitamin D in the development of Diabetic retinopathy in children. Reference: Kaur et all found 25-hydroxyvitamin D levels were more likely to be reduced in children and adolescents with diabetic retinopathy , and postulate this reduction to be due to the inflammatory and angiogenic effects of vitamin D deficiency	Thank you for your response. The committee agreed that intensive blood glucose management is effective and recommended that this is highlighted to patients. Although the DCCT study conducted a subgroup analysis based on age, the data on BMI and adolescents that could be meta-analysed was not reported and so we were unable to include this in our review. However, as the study reported that effects were similar to the full group analysis, the committee were confident that the recommendations will still apply to children and young people. The Kaur study included people who had diabetes, but not necessarily those who already have non-proliferative diabetic retinopathy and so this did not meet the inclusion for our review.

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RCPCH - consultation panel for paediatrics, endocrinology and diabetes	Guideline	General	General	**#** Screening for diabetic retinopathy in children and adolescents: There are various recommendations in the literature regarding the age at which screening for diabetic retinopathy should commence: American Diabetic Association: Screening to commence 3-5 years after diagnosis, and once the patient is 10 years old. American Academy of Paediatrics: Initial examination at 3-5 years after diagnosis, if over age 9, and annually thereafter. Adolescents with reasonable metabolic control to be screened every 2 years. Those with duration of diabetes >10 years, poor control or significant diabetic retinopathy should be screened more frequently ISPAD Clinical Practice Consensus Guideline 2009 Annual screening from age 11 after 2 years duration, and from age 9 years for those with 5 years duration. Ophthalmological monitoring is recommended before initiation of intensive treatment and at 3 month intervals for 6-12 months thereafter for patients with long-standing poor glycaemic control particularly if retinopathy severity is at or past the moderate non-proliferative stage at the time of Intensification.	Thank you for your response. This guideline covers diagnosis, management and monitoring of diabetic retinopathy in hospital eye services. Screening is therefore out of scope for this guideline and so the committee were unable to make recommendations on this.

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				American Academy of ophthalmology and Preferred Practice Pattern Type 1 diabetes mellitus 5 years after diagnosis then annually Type 2diabetes mellitus at diagnosis then annually Pregnancy (typ1or type 2) soon after conception and early in the first trimester Canadian Diabetes Association: Type 1 diabetes: 5 years after diagnosis in all individuals ≥15 years Type 2 diabetes: children, adolescents and adults at diagnosis	
RCPCH - consultation panel for paediatrics, endocrinology and diabetes	Guideline	General	General	**CARE RECOMMENDATIONS** 1) Children and adolescents with diabetes should be under the care of a multidisciplinary team with experience in managing the many aspects of this chronic condition. This care includes blood pressure monitoring, dietary advice, monitoring of BMI, advice regarding smoking and pregnancy. The importance of control in reducing the risk of onset and progression of diabetic retinopathy and preventing visual loss should be discussed. Responsibility for referral to the screening service lies with the general practitioner. 2) Children and adolescents with T1DM should undergo dilated fundus photography annually from age 12 years; emergence of cases with early onset diabetic retinopathy may help to guide initiating screening at earlier age of 10 in future.	Thank you for your response. Our reviews found no specific evidence for children and so it was difficult for the committee to make specific recommendations for children and adolescents. For this reason, the committee included age as a subgroup in some of the research recommendations. This should provide more detailed evidence specifically for children in the future. However, the committee were confident that the recommendations in this guideline will also apply to children if they develop diabetic retinopathy. The committee agree about the importance of screening, but this guideline covers diagnosis, management and monitoring of diabetic retinopathy in hospital eye services. Screening is therefore out of

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				3) Children and adolescents with T2DM should undergo dilated fundus Photography at diagnosis then annually. 4) Regular screening is important for early detection of treatable diabetic retinopathy. Screening intervals for diabetic retinopathy vary according to the individual's age and type of diabetes. 5) Optimal glycaemic control reduces the onset and progression of sight-threatening diabetic retinopathy. 6) Diabetic retinopathy often goes unnoticed until vision loss occurs; therefore, people with diabetes should get a comprehensive dilated eye exam regularly. In addition, the patients must be aware this issue. Reference; The Canadian Diabetes Association. 7) Patients with type 2 diabetes, retinopathy may be present in 21% to 39% soon after clinical diagnosis, but is sight threatening in only about 3% .Reference; The Canadian Diabetes Association. **Screening methods:** standard field, stereoscopic-colour fundus photography with interpretation by a trained reader (gold standard). Direct ophthalmoscopy or indirect slit-lamp fundoscopy through dilated pupil Digital fundus photography **If retinopathy is present** Diagnose retinopathy severity and establish appropriate monitoring intervals (1 year or less)	scope for this guideline and so the committee were unable to make recommendations on this.

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				Treat sight-threatening retinopathy with laser, pharmacological or surgical therapy Review glycaemic, blood pressure and lipid control, and adjust therapy to reach targets. **If retinopathy is not present** Type 1 diabetes: rescreen annually Type 2 diabetes: rescreen every 1 to 2 years Review glycaemic, blood pressure and lipid control, and adjust therapy to reach targets as per guidelines* Screen for other diabetes complications **Risk factors** for the development or progression of diabetic retinopathy are longer duration of diabetes, elevated A1C, increased blood pressure, dyslipidaemia, anaemia, pregnancy (with type 1 diabetes), proteinuria and severe retinopathy itself. **Treatment** Treatment modalities for diabetic retinopathy include retinal photocoagulation, intraocular injection of pharmacological agents and vitreoretinal surgery.	
Roche Products Limited	Economic model report	026	Table 17	The number of monitoring visits reported for faricimab in table 17 do not align with the committee's preferred assumptions from TA799. The committee agreed that that no additional monitoring visits will be needed in years 1 and 2, then from years 3 onward 2 separate monitoring visits will occur when injection frequency decreases.	Thank you for your comment. Table 17 reports average monitoring visits (across two sources [both from TA799] for faricimab, shown in appendix) in total, including those that occur at the same time as a treatment. As such, the model inputs differed.

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Roche Products Limited	Economic model report	052	Table 44	State whether list price or confidential prices were applied in the table title.	Thank you for your comment. This has now been clarified throughout.
Roche Products Limited	Economic model report	053	Table 45	[This text was identified as confidential and has been removed].	Thank you for your comment. We have now checked with the updated confidential discount for faricimab. The new confidential price for faricimab does not make a difference in the NMB rankings.
Roche Products Limited	Economic model report	054	Figure HE008	State whether list price or confidential prices are applied in the figure title.	Thank you for your comment. This has now been clarified throughout.
Roche Products Limited	Economic model report	056	Table 47	State whether list price or confidential prices are applied in the table title.	Thank you for your comment. This has now been clarified throughout.
Roche Products Limited	Economic model report	057	Table 48	State whether list price or confidential prices are applied in the table title.	Thank you for your comment. This has now been clarified throughout.
Roche Products Limited	Economic model report	057 - 058	Table 49	[This text was identified as confidential and has been removed].	Thank you for your comment. We have now checked with the updated confidential discount for faricimab. The new confidential price for faricimab does not make a difference in the NMB rankings.

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Roche Products Limited	Economic model report	059	Table 51	State whether list price or confidential prices are applied in the table title.	Thank you for your comment. This has now been clarified throughout.
Roche Products Limited	Economic model report	060	Table 52	[This text was identified as confidential and has been removed].	Thank you for your comment. We have now checked with the updated confidential discount for faricimab. The new confidential price for faricimab does not make a difference in the NMB rankings.
Roche Products Limited	Economic model report	062	HE3.4.1	Section HE3.4.1 states "Given the number of available treatments in DMO, it is unlikely that a treatment with an ICER nearer to £30,000 would be considered a cost-effective use of resources." Despite there being many treatment options for DMO, if there are other benefits not fully captured in the QALY calculations, ICERs nearer to £30,000/QALY may represent a cost-effective use of resource. In the case of DMO, effective and safe treatments associated with fewer injections are capacity saving, releasing pressure in stretched ophthalmology services, enabling care to be optimised, and leading to better outcomes for patients, clinicians and the health care system. This is a significant benefit, not necessarily fully accounted for in the QALY calculations, which a NICE appraisal committee would likely take into consideration when determining their acceptable cost per QALY threshold.	Thank you for your comment. Interventions with an ICER of less than £20,000 per QALY gained are generally considered to be a cost-effective use of resources, and the guideline committee use this threshold while making recommendations. It may be acceptable to the committee to recommend an intervention with an ICER above £20,000 per QALY, but in these cases there would need to be evidence of additional uncaptured benefits, or particular certainty around estimates. However, to avoid confusion, we have deleted the sentence.

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				As such, please consider amending this statement to reflect the fact that the appraisal committee may take other benefits not captured in the QALY calculations into consideration and consider removing the statement that an ICER nearer to £30,000/QALY is unlikely to be acceptable.	
Roche Products Limited	Economic model report	General	General	The confidential discount for faricimab was updated on September 1st. All analysis in which the confidential price of faricimab has been taken into account should be updated to reflect the new cost at which faricimab is available.	Thank you for your comment. We have now checked with the updated confidential discount for faricimab. The new confidential price for faricimab does not make a difference in the NMB rankings.
Roche Products Limited	Economic model report	General	General	Ensure all tables, figures and text describing analyses clearly state whether list or confidential prices are applied.	Thank you for your comment. This has now been clarified throughout.
Roche Products Limited	Evidence Review G	034	Table 4	In the RCT by Wykoff *et al*, the relevant secondary efficacy endpoint of mean change in central retinal (subfield) thickness has not been included in the "Outcomes" column, and is therefore missing from the NMA relating to "Central retinal thickness".	Thank you for your response. The data on central retinal thickness from the Wykoff study has now been included, and the analysis has been updated. The addition of this data has not affected the committee's conclusions on the evidence or changed the recommendations.
Roche Products Limited	Evidence Review G	051	Table 12	Missing analysis of central retinal thickness outcomes for faricimab	Thank you for your response. Results from the Sahni paper have now been added into the analysis. The addition of this data has not affected the committee's conclusions on the evidence or changed the recommendations

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Roche Products Limited	Evidence Review G	053	Table 14	Missing analysis of central retinal thickness outcomes for faricimab	Thank you for your response. Results from the Sahni paper have now been added into the analysis. The addition of this data has not affected the committee's conclusions on the evidence or changed the recommendations
Roche Products Limited	Evidence Review G	057	General	Missing pairwise meta-analysis of faricimab vs ranibizumab (Sahni J, *et al.* **Simultaneous Inhibition of Angiopoietin-2 and Vascular Endothelial Growth Factor-A with Faricimab in Diabetic Macular Edema: BOULEVARD Phase 2 Randomized Trial.** Ophthalmology. 2019 Aug;126(8):1155-1170. doi: 10.1016/j.ophtha.2019.03.023. Epub 2019 Mar 21. PMID: 30905643.)	Thank you for your response. Results from the Sahni paper have now been added into the analysis. The addition of this data has not affected the committee's conclusions on the evidence or changed the recommendations
Roche Products Limited	Evidence Review G	General	Section 1.1.5	A relevant clinical trial has been omitted from the effectiveness evidence; the phase II BOULEVARD study, comparing the effectiveness of faricimab with ranibizumab. (Sahni J, *et al.* **Simultaneous Inhibition of Angiopoietin-2 and Vascular Endothelial Growth Factor-A with Faricimab in Diabetic Macular Edema: BOULEVARD Phase 2 Randomized Trial.** Ophthalmology. 2019 Aug;126(8):1155-1170. doi: 10.1016/j.ophtha.2019.03.023. Epub 2019 Mar 21. PMID: 30905643.)	Thank you for your response. Results from the Sahni paper have now been added into the analysis. The addition of this data has not affected the committee's conclusions on the evidence or changed the recommendations

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Royal College of Nursing	Guideline	General	General	The Royal College of Nursing invited members who work in this area of health to review the draft guideline on our behalf. The comments below reflect the views of our members who reviewed the draft guidelines.	Thank you for your responses. We have replied to each of your comments.
Royal College of Nursing	Guideline	General	General	Should there be reference to the psychological wellbeing of patients undergoing management and monitoring of retinopathy? Maybe including these in how diagnosis /information management plans could be delivered in a sensitive way.	Thank you for your response, The committee agreed that it is important that a person's individual circumstances are taken into consideration when discussing treatment. This includes providing information in a format most appropriate for each person, and tailoring treatment choices to the individual. For this reason, the guideline refers to the sections on communication in the NICE guidelines on patient experience in adult NHS services (CG138).
Royal College of Nursing	Guideline	General	General	Would the guideline refer/ signpost /connect with visually impaired guidance so that clinicians would ensure that appropriate referrals and support is given?	Thank you for your response. NICE does not routinely recommend specific resources within guidelines, as the most appropriate source of information may change over time. However, there are links to the homepages of the Macular Society and Diabetes UK in the information for the public that is published alongside the guideline.
Royal College of Nursing	Guideline	General	General	The guidelines seem very comprehensive and there seems to be clear evidence of extensive analysis and examination of the condition.	Thank you for your response and support for this guideline.
Royal College of Ophthalmologists	Guideline	004	004	1.1.3 - Amend to **'ideally** have access to a person's HbA1c and blood pressure results'.	Thank you for your response. These recommendations are guidelines based on what the committee think every service should be aiming for. As such, all recommendations reflect what ideally should be

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					happening in practice. We therefore believe it is unnecessary to change the wording of this recommendation.
Royal College of Ophthalmologists	Guideline	004	005	1.1.3 - Amend to 'discuss the importance of good systemic control to reduce the risk of their diabetic retinopathy progressing to proliferative retinopathy or macular oedema, with the person'	Thank you for your response, The recommendations are written using NICE style which aims to be patient-centred rather than disease-focused. We have tried to avoid the use of the phrase 'good control' as this can sound as if the person is not managing their disease well, when there may be other factors that are affecting why they do not have lower HbA1c or blood pressure.
Royal College of Ophthalmologists	Guideline	006	001 - 015	1.2 It is best practice to control diabetic macular oedema before intraocular surgery like cataract surgery. If a retinal view is not possible pre op, early post op check for macular oedema and/or other sight threatening retinopathy (STR) is recommended. On findings of DMO/ STR patients should be offered individualised treatment as per the guidelines (for DMO and proliferative retinopathy) It is important to emphasise importance of communication and 'hand over' of patients after any intra-ocular surgical episodes – (cataract, glaucoma) to retina specialist for monitoring and managing retinopathy.	Thank you for your response and support for the recommendation. The committee also thought that communication between services is important. This supported their decision to include information in the recommendation about the importance of obtaining information about a person's eye disease before surgery as that would impact on postoperative medication and follow-up. More information about the importance of communication between independent cataract surgery centres and the ophthalmologist managing a person's retinopathy is also included in the rationale.
Royal College of	Guideline	007	009 - 016	1.4.1 Panretinal photocoagulation is the standard of care for PDR. Anti-VEGF may be used as supplemental therapy to PRP in certain cases such as	Thank you for your response. The committee recognised that panretinal photocoagulation is considered the standard of care for

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Ophthalmologists				neovascularisation of the iris, angle and neovascular glaucoma, preceding vitreoretinal surgery or in non-regressing retinal neovascularisation despite complete PRP.	proliferative diabetic retinopathy. In our discussions, we have emphasised the need for healthcare providers to engage in comprehensive conversations with patients at different stages of the disease. The committee believed that all treatment options should be thoroughly explored and explained to patients, ensuring they are well-informed about their choices. Furthermore, we have expanded on our recommendation to include specific guidance that clinicians should discuss with patients that panretinal photocoagulation is the first-line treatment option for most individuals. We have updated the rationale section to provide detailed information supporting the importance of discussing all available treatment options with patients, considering their individual circumstances, and conveying the specific role of panretinal photocoagulation as the primary treatment choice for most individuals.
Royal College of Ophthalmologists	Guideline	007	012	1.4 Suggest rewording of first bullet point to reflect that standard treatment is panretinal laser photocoagulation and the next two bullet points are offered under special circumstances. It may be better if 1.4.2 is put ahead of 1.4.1.to make that clear. Anti-VEGF treatment for PRP is not routinely funded or used in the NHS except as supplemental therapy to PRP (see above). The bullet	Thank you for your response. The committee recognised that panretinal photocoagulation is considered the standard of care for proliferative diabetic retinopathy. In our discussions, we have emphasised the need for healthcare providers to engage in comprehensive conversations with patients at different stages of the disease. The

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				point – no treatment (observation) for PDR, has no further elaboration (and is in contradiction to 1.4.2 where laser is to be offered to ALL patients with PDR. Most clinicians would consider 'observation' for PDR to be high risk however there are cases/ circumstances where this can be acceptable – the national guidelines need to provide signposting for such – e.g., treatments declined by patients, stable treated eyes, adverse events etc.	committee believed that all treatment options should be thoroughly explored and explained to patients, ensuring they are well-informed about their choices. Furthermore, we have expanded on our recommendation to include specific guidance that clinicians should discuss with patients that panretinal photocoagulation is the first-line treatment option for most individuals. We have updated the rationale section to provide detailed information supporting the importance of discussing all available treatment options with patients, considering their individual circumstances, and conveying the specific role of panretinal photocoagulation as the primary treatment choice for most individuals. We have also highlighted that in some circumstances panretinal photocoagulation may be inappropriate, and that in these cases, other options should be discussed.
Royal College of Ophthalmologists	Guideline	007	014	Amend to 'no treatment with close observation may sometimes be appropriate for low risk patients'	Thank you for your response. The committee also thought that observation can be appropriate for low-risk patients. However, observation or no treatment is still an important part of the discussion and shared decision making process with a patient which is why the recommendation does not state that observation should only be discussed with those who are low risk.

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Royal College of Ophthalmologists	Guideline	008	001 - 002	1.4.3 - Whilst we understand the risks of undertreatment with PRP, we would suggest that you remove the requirement to have a **complete** panretinal photocoagulation within 4 weeks of offering treatment. Complete PRP as defined in this guideline is not necessarily appropriate for all patients in 4 weeks especially if the patient responds successfully to initial lase and could affect the visual field. The definition of complete PRP (as used elsewhere in the document) implies that no further PRP would be possible, and that a next step could be supplemental anti-VEGF treatment. In reality, many patients do respond to a good amount of initial laser (but not a 'complete' PRP as per your definition) and may never require any further fill-in PRP Also amend the first part of the sentence to 'Start panretinal photocoagulation within 2 weeks of offering it **for high risk patients**.' (ie we did not feel that all patients, such as those with very early NVE seen on wide field imaging would need to have their PRP within 2 weeks of diagnosis). Increasing use of ultra-wide field imaging means low risk pathology is being increasingly seen.	Thank you for your response. The committee discussed your comment but thought that the requirement for complete panretinal photocoagulation is suitable. They discussed how people who need fewer photocoagulation treatments tend to be low-risk, and not have proliferative disease. These people therefore would not be covered by the recommendations in this section of the guideline. The time to start photocoagulation has now been updated from 2 weeks to 4-6 weeks which the committee feel is appropriate and achievable for everyone.
Royal College of Ophthalmologists	Guideline	008	003 - 004	1.4.4 - Amend to 'For people with high-risk characteristics or who have difficulty attending 4 appointments, offer to start panretinal photocoagulation on the same day where possible.'	Thank you for your response. These recommendations outline what services should be aiming to achieve. However, the committee recognised that there may be exceptions where this is not possible. Therefore if the

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					recommendation to start panretinal photocoagulation on the same day is impractical due to other factors it should be completed at the earliest opportunity.
Royal College of Ophthalmologists	Guideline	008	008 - 011	1.4.5 Thank you for including this recommendation it is good to see this include. However, we are concerned about the use of the words cheapest anti VEGF thought out the document. "If more than one anti-VEGF is available, use the cheapest." It is used a few times in the guidelines. This probably refers to unit cost of anti VEGF drug. However, what is relevant is total cost of treatment package (visits/ assessments and injection package costs in addition to cost of the injections Suggest rewording to: If more than one anti-VEGF treatment package is available, use the cheapest treatment package that results in least burden to the patients and clinical services.	Thank you for your comment. The committee discussed this and also thought that there are wider considerations than the unit cost of each anti-VEGF. They therefore decided to remove the information about using the cheapest anti-VEGF. Additional information about what factors should be considered when choosing an anti-VEGF are already included in some of the technology appraisal recommendations.
Royal College of Ophthalmologists	Guideline	008	017	1.4.6 Reword for clarity to 'where severity of the cataract is preventing PRP treatment	Thank you for your response. We have updated the recommendation as suggested to clarify that anti-VEGF should be used when severity of the cataract is preventing PRP treatment
Royal College of Ophthalmologists	Guideline	008	002	1.4 Suggest merging this section with section on monitoring diabetic retinopathy and oedema for clarity and ease of reference as patients can have proliferative diabetic retinopathy in one eye and DMO in the other etc.	Thank you for your response. The committee considered the organisation of the guideline in detail, but decided that merging the two sections may be confusing. However, they agreed that it was important

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				The patient should be considered holistically. In addition, it is not always clear when a patient becomes proliferative. Perhaps rename the combined section 'Monitoring the diabetic eye'. Then the use of ultrawide field imaging plus OCT can be discussed together. A key point is that we feel that ultrawide field imaging **should be used** along with OCT in imaging clinics to monitor diabetic retinopathy. (ie stronger than 'considered')	to highlight that both eyes should be assessed and treated based on their active pathologies. An additional recommendation has been added to the guideline to explain this. Evidence for the use of OCT was reviewed in relation to diabetic macular oedema. Evidence for ultrawide field fundus imaging was only identified for people who had proliferative diabetic retinopathy, and not macular oedema. Therefore, the committee did not have enough evidence to recommend the use of both monitoring techniques in a single section on monitoring the diabetic eye.
Royal College of Ophthalmologists	Guideline	009	003 – 005	1.4.7 – Reword to in a face to face eye clinic consider using ultrawide-field fundus imaging and use OCT alongside clinical examination when assessing the eyes of **patients**	Thank you for your response. The evidence review only considered the use of ultrawide-field imaging for people who have proliferative diabetic retinopathy. The committee thought that the use of OCT was important for people who have diabetic macular oedema – there is a recommendation that reflects this in the section of the guideline on 'Monitoring diabetic macular oedema'.
Royal College of Ophthalmologists	Guideline	009	006 – 009	1.4.8 – Suggest amending to: In a diagnostic clinic ultrawide-field fundus imaging **should be used** alongside OCT when assessing the eyes of patients for the presence of proliferative diabetic retinopathy.	Thank you for your response. While the evidence we reviewed supported the use of UWF imaging for people with proliferative diabetic retinopathy, this was based on the results of a single study. As a result, the committee thought there was only enough evidence to recommend that people consider the use of this imaging modality. The committee noted that there are

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					a number of techniques to monitor proliferative diabetic retinopathy, and so decided against specifying what other tests ultrawide-field imaging should be used alongside.
Royal College of Ophthalmologists	Guideline	010	023	1.4.15 – High risk – missed word	Thank you for your response, The committee did not think it was necessary to include the term "high risk" in this recommendation because it already specifies that individuals must have had complete panretinal photocoagulation treatment. They believe that this group of recommendations include everyone who should be considered for, or offered, vitrectomy.
Royal College of Ophthalmologists	Guideline	010	001 – 014	1.4.11 and 1.4.12 – Care is driven by most active pathology. Again, we suggest the recommendations on discharge for proliferative diabetic retinopathy and maculopathy are combined.	Thank you for your response. The committee considered the organisation of the guideline in detail, but decided that merging the two sections may be confusing. However, they agreed that it was important to highlight that both eyes should be assessed and treated based on their active pathologies. An additional recommendation has been added to the guideline to explain this.
Royal College of Ophthalmologists	Guideline	010	003 – 005	1.4.11 – Reword to 'For the first 12 months of inactive pathology following the last laser treatment, monitor under the care of hospital eye services using an individualised monitoring frequency.	Thank you for your response. The committee discussed your suggestion but noted that determining inactive pathology would involve the use of an angiogram, which isn't always practical. They thought that the end of treatment was a clear way to communicate when someone should be considered for

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					discharge to the diabetic screening programme and so have decided to keep the recommendation the same.
Royal College of Ophthalmologists	Guideline	010	006	1.4.11 – Patients who have regression of proliferative retinopathy with no additional laser treatment required for at least 12 months can be considered for discharge back to the diabetic screening programme, as long as there is no other pathology requiring ongoing hospital eye service review.	Thank you for your response. We have kept the recommendation to state until end of treatment to ensure that people receive a complete course of treatment. This is to avoid variation in treatments. We have included the stipulation that a person should not be discharged back to screening if they have features that would make them ineligible. A link to the criteria for eligibility for the screening programme has also been included.
Royal College of Ophthalmologists	Guideline	010	021 – 023	1.4.14 and 1.4.15 – Change 'macular involving' to macula involving (Macula as noun)	Thank you for your response. The recommendation and other similar recommendations have been reworded,
Royal College of Ophthalmologists	Guideline	010	022 – 025	1.4.15 Consider vitrectomy for people who have active proliferative diabetic retinopathy despite complete PRP who are having recurrent vitreous haemorrhages, (ie the current wording implies that would only be the case if they also had a non foveal involving tractional detachment but recurrent vitreous haemorrhages on their own could be an indication)	Thank you for your response. The committee agreed that recurrent vitreous haemorrhages may not always be related to active proliferative diabetic retinopathy. They therefore amended the recommendation to clarify that this could also be caused by vitreomacular traction.
Royal College of	Guideline	012	005 – 006	1.5.3 We felt that may be too strong a recommendation to say 'offer' suggest rewording to 'Consider offering laser treatment to people with non-centre-involving clinically	Thank you for your response. The committee thought it was important that people are offered macular laser at this point to slow their progression to centre-involving

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Ophthalmologists				significant macular oedema if deemed clinically appropriate.'	macular oedema and complications such as vision loss. This is covered in the rationale of the guideline. We don't tend to use the term 'if clinically appropriate' in recommendations, as we would not recommend the use of any treatments that aren't considered appropriate.
Royal College of Ophthalmologists	Guideline	012	015	1.5.5 See comment above re use of word cheapest. Consider rewording to 'cheaper pathway' or remove entirely. Also, if a treatment requires more injections/visits than another treatment, there may not necessarily be the capacity available to give that option	Thank you for your comment. The committee discussed this and decided that there are wider considerations than the unit cost of each anti-VEGF. They therefore decided to remove the information about using the cheapest anti-VEGF. Additional information about what factors should be considered when choosing an anti-VEGF are already included in some of the technology appraisal recommendations.
Royal College of Ophthalmologists	Guideline	012	022	1.5.5 We are pleased to see the recommendation for considering treatment of eyes with a thickness of less than 400 micrometers who have visual impairment (as per your definition).	Thank you for your response and support for this recommendation.
Royal College of Ophthalmologists	Guideline	013	005 - 007	1.5.9 Request this section is amended. In almost all cases of DMO anti-VEGF treatment alone is used as a monotherapy so phrase 'alone' is not needed. Furthermore, the assessment for response after loading phase is not limited to vision improvement /stabilisation but also includes macular thickness. The 'suboptimal' response criteria apply. It is better to use consistent terminology – assessing treatment response after loading (to check remission is induced – refer to definition of	Thank you for your response. Following discussion with the committee, we have removed the word "alone" from the recommendation about anti-VEGF treatment. The definition of suboptimal response has also been updated to match the definition used for the loading phase. The committee discussed the timing of when to consider a switch to steroids in detail and were

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				suboptimal response). If this is not successful remission, then consider - Switch to a different AntiVEGF - switch to steroid implants -additional rescue laser treatment We felt that 12 months could be too long to wait to consider switching. For instance If there was no response to anti-VEGF treatment after 6 months it may be appropriate to consider switching to steroid treatment. We felt that the term 'intravitreal steroid treatment' rather than specifically dexamethasone would be more appropriate.	confident that the 12 month period is appropriate for most people. The evidence for the technology appraisal submission for ranibizumab showed improvements in visual acuity in the first 12 months after the start of anti-VEGF treatment, and few people had a reduction in 10 letters over that time period. The committee therefore thought it was important that people are given this amount of time to respond. As suggested, we have updated the recommendation about switching to steroid treatment so that it now says "intravitreal steroid implant" rather than stating dexamethasone.
Royal College of Ophthalmologists	Guideline	013	008 - 009	1.5.10 Do not refer to specific drug.	Thank you for your response. As suggested, we have updated the recommendation about switching to steroid treatment so that it now says "intravitreal steroid implant" rather than stating dexamethasone.
Royal College of Ophthalmologists	Guideline	013	018 - 020	1.5.13 Amend to 'If a person does not want to continue with regular anti-VEGF injections -- consider steroid implants; alternatively macular laser treatment can be considered.'	Thank you for your response. As suggested, we have updated the recommendation about switching to steroid treatment so that it now says "intravitreal steroid implant" rather than stating dexamethasone. Macular laser hasn't been added as an alternative option at this stage, as this is recommended earlier in the treatment pathway, while this recommendation is for when a person's macular oedema has progressed further and requires anti-VEGF or steroid treatment.

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Royal College of Ophthalmologists	Guideline	013	021 - 023	1.5.14 Amend to 'When people with centre-involving diabetic macular oedema have visual impairment and cannot have non-corticosteroid therapy, consider a steroid intravitreal implant.' (ie avoid the specific use on the name dexamethasone)	Thank you for your response. As suggested, we have updated the recommendation about switching to steroid treatment so that it now says "intravitreal steroid implant" rather than stating dexamethasone.
Royal College of Ophthalmologists	Guideline	014	General	1.5.15 As per earlier comments, we think a combined 'monitoring the diabetic eye; section, combining the comments about proliferative diabetic retinopathy and maculopathy may be most appropriate as an individual patient may well have both.	Thank you for your response. The committee considered the organisation of the guideline in detail, but decided that merging the two sections may be confusing. However, they agreed that it was important to highlight that both eyes should be assessed and treated based on their active pathologies. An additional recommendation has been added to the guideline to explain this.
Royal College of Ophthalmologists	Guideline	014	012 - 016	1.5.16The status of both eyes should be taken into consideration; hence we think combining the sections is appropriate. Patients who have resolved DMO for at least 12 months and no other features that would require hospital eye service review could be considered for discharge to the diabetic screening programme.	Thank you for your response. The committee considered the organisation of the guideline in detail, but decided that merging the two sections may be confusing. However, they agreed that it was important to highlight that both eyes should be assessed and treated based on their active pathologies. An additional recommendation has been added to the guideline to explain this. The committee discussed the recommendation on monitoring frequencies, and think that by stating that people have to be eligible for the screening

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					programme, it covers that the retina should be stable before considering discharge.
Royal College of Ophthalmologists	Guideline	016	023	Terms used in this guideline: the HRC definition section There is a missing word. The line should read 'any optic disc neovascularisation with a vitreous or preretinal haemorrhage.'	Thank you for your response. We have updated the definition of high-risk characteristics as suggested.
Royal College of Ophthalmologists	Guideline	017	General	Recommendations for research We are pleased to see so many suggestions for further research. However, there needs to be some prioritisation to ensure the community seeks to answer the questions with the most impact for patients. In addition, we suggest the following: 1. Preventing end organ damage: a. Does use of wearable devices for optimising control lead to prevention of Sight threatening retinopathy? 2. Reversal of end organ damage; a. Can retinal vascular bed be restored to normal? Can cell therapy restore retinal health after ischaemic macular damage?	Thank you for your response. In this guideline we did not search for evidence on preventing end organ damage or the use of wearable devices. We are therefore unable to make research recommendations on these topics.
Royal College of	Guideline	General	General	Thank you for the opportunity to provide feedback on these well-written guidelines. It is based on collection of evidence (appendices). However, the level of evidence for	Thank you for your response, NICE does not routinely refer to the level of evidence within the recommendations. However, the rationale sections

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Ophthalmologists				each recommendation is not discernible where the recommendations written in the draft guideline document. Several recommendations are based on the opinion/ consensus of the committee, and it would be useful for the readers to have this information along with the recommendations.	explain where a recommendation has been made based on the evidence or based on committee consensus. This information will be included directly under each set of recommendations when the guideline is published on the NICE website. This should make it easier to determine how the recommendations have been made.
Royal College of Ophthalmologists	Guideline	General	General	The guidelines seem to relate mostly to patients who would be under hospital eye service. However, a much larger cohort is in the screening programme- with mild retinopathy.	Thank you for your response. This guideline covers diagnosis, management and monitoring of diabetic retinopathy in hospital eye services. Screening is therefore out of scope for this guideline and so the committee were unable to make recommendations on this.
Royal College of Ophthalmologists	Guideline	General	General	The recommendations on prevention of progression of retinopathy (section 1) are most relevant and likely to have a significant impact for patients with mild retinopathy as progression to more advanced stages (i.e. end organ damage) can be reduced if not prevented. We are very pleased that reference to the use of fibrates is made in these guidelines.	Thank you for your response and support for these recommendations.
Royal College of Ophthalmologists	Guideline	General	General	"If more than one anti-VEGF is available, use the cheapest." This sentence has been used a few times in the guidelines. This probably refers to unit cost of anti VEGF drug – however what is relevant is total cost of treatment package. Treatment package costs include number of visits/ assessments and injection costs in	Thank you for your comment. The committee discussed this and also thought that there are wider considerations than the unit cost of each anti-VEGF. They therefore decided to remove the information about using the cheapest anti-VEGF. Additional information about what factors should be considered

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				addition to cost of the drug. Please make sure this is reflected in the whole document.	when choosing an anti-VEGF are already included in some of the technology appraisal recommendations.
Royal College of Ophthalmologists	Guideline	General	General	There is lack of mention on management of patients with vision impairment due to diabetic retinopathy – due to their complex spectrum of other comorbidities and need for medications, these group of patients need more tailored approach for support (e.g. patients on insulin treatment unable to read syringe markings, neuropathy patients risk of falls, renal patients etc.)	Thank you for your response, This guideline is on treatment of diabetic retinopathy rather than the wider complications of diabetes which are addressed in the diabetes guideline. The committee were aware of the importance of tailoring support to an individual person's needs and so the guideline refers to the sections on communication in the NICE guidelines on patient experience in adult NHS services (CG138) and shared decision-making (NG197). These considerations have also been highlighted in in our equality impact assessment.
University of York	Economic Report	General	General	(RQ5) - The economic model built to address guideline RQ5 uses an NMA by Simmonds et al. as the basis for BCVA outcomes and long-term transition probabilities. This NMA reports a comparison of mean difference in BCVA at one year on PRP and anti-VEGFs, and found a small decline in BCVA in patients treated with PRP at 12 months, and a small improvement in BCVA on anti-VEGFs at this time point. Our clinical advisory group noted that changes in ETDRS score of this magnitude were not clinically meaningful or consistently measurable. The Simmonds et al. study comprises part of a larger HTA (NIHR132948), which also includes a longitudinal analysis	Thank you for your comment. We have taken your feedback into account and explored a key scenario analysis, detailed in the economic report, whereby treatment effects from the NMA were applied in the first year for all interventions. For PRP, visual acuity was then assumed to stabilise beyond the first year. For anti-VEGFs, a linear decline of transition probabilities was assumed between the first and second years, with visual acuity stabilising from the second year onwards. Although the committee considered this scenario almost equally plausible to the base-case analysis, it

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				of individual participant data obtained from the Protocol S, CLARITY, and PROTEUS studies (in press). Protocol S includes 305 patients with up to five years of follow up, and as the only study which collected data for more than 12 months, was used to inform longer-term trends in BCVA on anti-VEGFs and PRP. Regression models constructed using the trial IPD showed that one-year trends were not maintained, and any differences in BCVA observed between the interventions at one year had vanished by approximately year 3 of follow-up. This is followed by stability of visual outcomes on both interventions at approximately baseline BCVA values on both treatments, with some suggestion of slow ongoing decline on anti-VEGFs. This expectation was supported by the project advisory group, which included three clinical experts. Detailed results from the IPD analyses will be available as pre-prints in November 2023. This project also includes an economic evaluation, comprising a discrete event simulation which integrates both PDR and diabetic macular oedema, and uses detailed individual participant data to inform patient outcomes on a two-eye basis. The model implements the regression analysis described above, with patients at first experiencing a small decline or improvement in BCVA for PRP and anti-VEGFs respectively, followed by a return to approximately baseline levels by five years, from which	was nevertheless kept as an important scenario in the end due to the following reasons: * Protocol S compared ranibizumab to PRP for the treatment of PDR. In both arms of Protocol S, about 40 to 45 percent of eyes had active neovascularization at two years. * We modelled PDR and DMO separately given our review question: "What is the effectiveness of anti-vascular endothelial growth factor agents and laser photocoagulation (alone or in combination) for the treatment of non-proliferative and proliferative diabetic retinopathy **without macular oedema**". * We didn't include 'the risk of developing PDR in the DMO model' and 'the risk of developing DMO in the PDR model'. This was a limitation, but the data isn't well reported to be able to include. Even when DMO was included as an adverse event within the diabetic retinopathy trials, it was very unclear if it meant they had DMO requiring treatment. We captured the impact on BCVA and not having DMO as explicit health state and it was assumed that any impact of developing this would be captured within their BCVA transition probabilities. As part of the limitations of the analysis, we wrote that: "Generally, the available data on DMO

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				point outcomes are maintained for the remainder of the time horizon. Our model generates a negligible QALY benefit in favour of PRP, but the two treatments can be considered to generate essentially equal health outcomes. As anti-VEGFs are associated with significantly higher costs than PRP, we conclude that they are unlikely to represent a cost-effective use of NHS resources for the early treatment of PDR. A manuscript detailing this analysis is to be submitted for publication imminently, and further details cannot currently be shared. Our main concern relates to the way that the treatment effect in terms of BCVA was implemented in the guideline model for PDR. The model assumes that 12-month outcomes from the Simmonds et al. NMA are indicative of a long-term treatment effect which can be repeatedly applied throughout the patient lifetime. This results in the ongoing divergence of visual outcomes between the two treatment arms, and generates significant QALY benefit in favour of anti-VEGFs. We are concerned that this represents a misinterpretation of the trial data and results in clinically implausible outcomes for patients on either treatment. In continuously applying one-year outcomes, patients on PRP invariably develop severe visual impairment, whilst those on anti-VEGFs experience very large and permanent improvements in visual acuity. No scenario analyses were presented in which the one-year	or PDR are separated by condition, and therefore it was not possible to reflect the reality that an eye can start with either DMO or PDR and later develop the other condition which would have an impact on the treatments a person may receive, and on costs and QALYs accumulated over a person's lifetime. However, any impact of developing either of these conditions was expected to be captured within the BCVA transition probabilities. Furthermore, this is consistent with the approach taken in previous models published for both populations." * Protocol S compared ranibizumab to PRP, and in the absence of other evidence, it may be flawed to assume that the other anti-VEGFs would follow exactly the same disease progression pattern as ranibizumab. * It may also be flawed that patients who switch their treatment would not receive any treatment benefit of switching, given the assumption of stability in visual acuity. Treatment effect may also sustain if patients receive treatment, so assuming visual acuity to stabilise so early in the disease pathway may not be a fully reasonable approach.

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				treatment benefits were maintained and not re-applied year on year. This means that the natural conclusion of the RQ5 guideline model is that anti-VEGFs are highly cost-effective compared to PRP. We are concerned that the guideline model will be in disagreement with the HTA model despite being based on the same trial data. It also appears to be in disagreement with the draft clinical guideline, which recommends the use of anti-VEGFs only in patients whose PDR remains active following complete PRP. We recommend the assumption of a repeated application of the one-year treatment effect is reconsidered. We also recommend exploring scenarios where the main benefit of treatment using either PRP or anti-VEGFs is ongoing stability of BCVA, and further scenarios in which patients who discontinue cease to receive this benefit and experience decline per Maturi et al (as already implemented).	* The committee agreed to keep similarity between the base-case analyses of both PDR and DMO models given our review questions.

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Document Processed	Organisation name – Stakeholder or respondent	Disclosure on tobacco funding / links	Number of comments extracted	Comments/Action
Yes	Stakeholder - Bayer plc	[**Current Situation** • Bayer does not have direct or indirect links with, or funding from, manufacturers, distributors or sellers of smoking products but Bayer provides pesticides for crops, which would therefore include tobacco crops. • Bayer is a member of the Cooperation Centre for Scientific Research Relative to Tobacco (CORESTA) (http://www.coresta.org/) within the scope of recommendations of pesticides used for protection of tobacco plants. • It is also a member of country and EU business federations such as the Confederation of British Industry (CBI) and 'Business Europe', which include tobacco companies. **Past Situation** In 2006, Bayer and its subsidiary Icon Genetics piloted a new process for producing biotech drugs in tobacco plants. Icon Genetics was acquired by Nomad Bioscience GmbH from Bayer in 2012.]	**NIL**	**No Further action required**