National Institute for Health and Care Excellence

Health Technology Evaluation

Teprotumumab for treating thyroid eye disease [ID6432]

Response to stakeholder organisation comments on the draft remit and draft scope

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Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Thyroid Eye Disease Charitable Trust	TEDct considers evaluation of this topic to be highly appropriate.	Thank you, no action needed.
	British Thyroid Foundation	No comment.	Thank you, no action needed.
	The Royal College of Ophthalmologists	We agree with the proposed evaluation route.	Thank you, no action needed.
	British Thyroid Association, Royal College of Physicians	STA feels appropriate.	Thank you, no action needed.

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	Society for Endocrinology, Welsh Endocrine and Diabetes Society	Appropriate.	Thank you, no action needed.
	Amgen	We appreciate the opportunity to comment on the draft scope. We agree, a single technology appraisal is appropriate for this topic.	Thank you, no action needed.
	The Thyroid Trust	We support the route that is being taken to evaluate Teprotumumab for treating Thyroid Eye Disease.	Thank you, no action needed.
Wording	Thyroid Eye Disease Charitable Trust	Regarding the list of stakeholders: TED is not a macular disease, so it does not seem relevant to include the Macular Society It is also not an immunodeficiency so does not seem relevant to include Immunodeficiency UK. SeeAbility is a charity for people with learning difficulties and visual loss; since TED rarely causes visual loss this charity also does not seem very relevant as a stakeholder; this might also apply to Sense and the other charities more focused on supporting visually impaired people. In the list of professional groups, TED is not a common condition in older people, and it is unlikely that gerontologists have much knowledge of TED, so British Geriatrics Society are not really relevant stakeholders. British ophthalmic anaesthesia society are also unlikely to be relevant to this consultation. Pathological specimens are rarely taken in TED so RCPath also not particularly relevant.	The following stakeholders have been added to the stakeholders list: • SeeAbility • British Oculoplastic Surgical Society • Society for Endocrinology We aim to include all the potentially relevant stakeholders. Participation is entirely voluntary, so stakeholders are welcome to engage if

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		BOPSS (British Oculoplastic Surgical Society) should definitely be in the stakeholder list, as these are the main professionals treating and operating on people with TED; I believe they have been invited but are just missing from the document. Similarly, the **Society for Endocrinology** should be included, though there may be personnel overlap with BTA.	they feel they have a relevant contribution.
	British Thyroid Foundation	Yes	Thank you, no action needed.
	The Royal College of Ophthalmologists	Yes	Thank you, no action needed.
	British Thyroid Association, Royal College of Physicians	We note that the evaluation is for use of teprotumumab within its market authorisation (MA). As it does not yet have an MA, the premise seems odd. Do NICE have a proposed MA that will allow one to make the evaluation according to the scope of the MA?	Thank you for your comment. The proposed MA wording is available to NICE, however it is currently confidential so cannot be shared publicly. No action needed.
	Society for Endocrinology, Welsh Endocrine and Diabetes Society	More could be made of the negative impact on employment prospects of TED in long term cost implications.	Thank you. The appraisal will consider the impact of TED from the perspective of the NHS and personal social services. We have updated the background section to

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			highlight that TED can impact people's quality of life. Also, health related quality of life is one of the outcomes which will be considered in the appraisal.
	Amgen	We would suggest updating the remit to: 'To appraise the clinical and cost effectiveness of teprotumumab within its marketing authorisation for treating moderate to severe thyroid eye disease.'	Thank you, remit updated to moderate to severe TED following the scoping workshop.
	The Thyroid Trust	No comment.	Thank you, no action needed.
Timing issues	Thyroid Eye Disease Charitable Trust	This is an important consultation. However, it should also be noted that there are several other drugs for thyroid eye disease in phase 3 trials in the UK so whilst there is currently no direct comparator drug specifically for TED it is likely that several more will emerge in the near future. Hence any NICE approval of teprotumumab may need to be reviewed in the context of other drugs that become available.	Thank you for your comment. It is noted in the NICE process and methods manual that technologies will be compared against established practice within the NHS. No action needed.
	British Thyroid Foundation	No comment	Thank you, no action needed.

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	The Royal College of Ophthalmologists	Current treatment protocols cause significant delay in rehabilitation of TED patients. However, they are generally effective in preventing visual loss, so the urgency is moderate.	Thank you, no action needed.
	British Thyroid Association, Royal College of Physicians	As the product does not yet have an MA, then NICE may be ahead of the curve. However, patients with TED clearly have unmet need and it is desirable that an evaluation is made as close to approval for MA as feasible, as some UK patients are aware this drug has been available in the USA for 3 years or more.	Thank you, no action needed. Please note that, NICE aims to publish final guidance for new technologies within 90 days of receiving UK marketing authorisation.
	Society for Endocrinology, Welsh Endocrine and Diabetes Society	Urgent, this is a disease which is historically been poorly managed and predominantly affects females.	Thank you, no action needed.
	Amgen	There is an urgent need for licensed, effective therapies for TED. Current management includes off label therapies with a limited evidence base that are not suitable for all patients. Teprotumumab has demonstrated statistically significant reductions in proptosis, diplopia, and the inflammatory symptoms of TED (as measured by the clinical activity score [CAS]) in randomised controlled trials, with associated significant improvements in patient-reported quality of life scores. The evaluation timelines as currently proposed are appropriate.	Thank you, no action needed.
	The Thyroid Trust	Given that there is no alternative pharmaceutical treatment licensed for TED in the UK the Thyroid Trust believes an evaluation of a possible treatment is necessary at the earliest opportunity.	Thank you, no action needed.

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Additional comments on the draft remit	Thyroid Eye Disease Charitable Trust	No comment	Thank you, no action needed.
	British Thyroid Foundation	No comment	Thank you, no action needed.
	The Royal College of Ophthalmologists	No comment	Thank you, no action needed.
	British Thyroid Association, Royal College of Physicians	No comment	Thank you, no action needed.
	Society for Endocrinology, Welsh Endocrine and Diabetes Society	No comment	Thank you, no action needed.
	Amgen	No comment	Thank you, no action needed.
	The Thyroid Trust	No comment	Thank you, no action needed.

Comment 2: the draft scope

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Background information	Thyroid Eye Disease Charitable Trust	In the discussion of the impact of TED, there should probably be some reference to the fact that visual loss is possible, and also to the fact that changes in appearance lead to great psychosocial distress for affected people. The statement that women are more affected due to effect of oestrogen is actually unproven- the most common age to develop Graves / TED is around perimenopause when oestrogen levels may be dropping so the link with oestrogen levels is poorly understood but likely not a direct link. It might be better simply to state that women are more commonly affected that to speculate as to why.	Thank you for your comment. The potential risks of vision loss and psychosocial distress have been added to the scope. The role of oestrogen has been removed.
	British Thyroid Foundation	No comment	Thank you, no action needed.
	The Royal College of Ophthalmologists	The reference New Guidelines for Thyroid Eye Disease (TED)| The Royal College of Ophthalmologists is very outdated.https://www.rcophth.ac.uk/news-views/guidelines-for-thyroid-eye-disease-2015/ A more up to date reference is The 2021 European Group on Graves' orbitopathy (EUGOGO) clinical practice guidelines for the medical management of Graves' orbitopathy L Bartalena, G J Kahaly, L Baldeschi, C M Dayan, A Eckstein, C Marcocci, M Marinò, B Vaidya, W M Wiersinga, EUGOGO *European Journal of Endocrinology*, Volume 185, Issue 4, Oct 2021, Pages G43–G67, https://doi.org/10.1530/EJE-21-0479 Lee, V., Avari, P., Williams, B. *et al.* A survey of current practices by the British Oculoplastic Surgery Society (BOPSS) and recommendations for delivering a sustainable multidisciplinary approach to thyroid eye disease in the United Kingdom. *Eye* **34**, 1662–1671 (2020).	Thank you for your comment. The treatment section of the scope has been updated to align with the current EUGOGO 2021 guidelines. The scope consultation confirmed that UK clinicians largely follow these guidelines. This update replaces the previous treatment section which was based on the 2015 TED guidelines developed by

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		https://doi.org/10.1038/s41433-019-0664-zapproach to thyroid eye disease in the United Kingdom The recommendations from this paper have been endorsed by TEAMeD, BOPSS, Royal College of Ophthalmologists, The Royal College of Physicians, Society for Endocrinology, British Thyroid Foundation and the British and Irish Orthoptic Society. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7608203/pdf/41433_2019_Article_664.pdf	the Royal College of Ophthalmologists.
	British Thyroid Association, Royal College of Physicians	The terms severity and activity have specific implications when used with reference to TED (e.g. patients may have mild but active disease or severe but inactive disease). 'Activity' references the features of inflammation which are likely to respond to immunomodulatory or anti-inflammatory treatments. So, this sentence "More severe cases often necessitate systemic corticosteroids and immunosuppressive therapies" Should read "More active cases or those with prominent inflammation often necessitate systemic corticosteroids and immunosuppressive therapies." After this, I would also suggest adding that "Urgent orbital decompression surgery is sometimes needed for dysthyroid optic neuropathy (DON), as well as routinely for rehabilitation in patients with significant residual proptosis or abnormal eyelid positions. Importantly, this specialist surgery is only available in about 15 regional UK centres." Although radiotherapy is approved and was NICE evaluated in 2005, use has been declining in recent years as alternative (second line) anti-inflammatory treatments to corticosteroids have become available. In addition, the UK RCT "CIRTED" study showed that radiotherapy was not superior to placebo (PMID: 29396245), meaning NICE guidance on this subject may need updating. "However, no pharmacological treatments are specifically approved for TED in the UK." Although this is technically true, NHS standard of care for patients with moderate to severe and active TED is pulsed	Thank you. The background information section has been updated to make a clearer distinction between activity and severity. It has also been updated to align with the treatment approaches outlined in the EUGOGO guidelines. Surgery requirements This sentence has been removed to avoid suggesting that there is

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		methylprednisolone in every centre that has a large-volume TED practice. The idea that there is no current treatment for TED and that the disease is an orphan indication is false and was already rejected by EMA in 2019 or 2020.	no current treatment for TED.
	Society for Endocrinology, Welsh Endocrine and Diabetes Society	Yes	Thank you, no action needed.
	Amgen	Comments on the draft background section: • In the first paragraph, we would suggest adding '(diplopia)' after 'double vision' so that the term has been explained before being mentioned later in the document. • The statement that radiotherapy contributes to the development of TED may be more specifically described by the following: "Genetic predisposition, combined with environmental factors like smoking and previous radioactive iodine therapy, contribute to the development and/or severity of TED (Bartalena et al. 1998; Bartalena et al. 2023; Khalilzadeh et al. 2011). Concurrent endocrine disorders, such as type 1 diabetes, may also play a role in its development (Gupta et al. 2023)." • In the absence of established patient registries or robust centralised datasets, the exact number of patients affected by TED within the UK remains uncertain. The British Thyroid Foundation and Royal college of Ophthalmologists estimate that there are approximately 50,000 TED patient in the UK with approximately 2,500 new cases annually. However, the data upon which these numbers are based is not readily apparent. The 50,000-estimate stated by the British Thyroid foundation is unsubstantiated on their	Thank you for your comments. The term 'diplopia' has been added. The sentence has been updated to include the term 'previous radioactive iodine therapy'. The prevalence figures have been updated to reflect that the exact number of patients affected by TED within the UK remains uncertain. A range of

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		website. Similarly, we cannot identify a source for the 2,500 new patients a year as stated by the RCOPH reference. A recent European epidemiological study estimated the prevalence of TED (using published incidence data for TED and Grave's hyperthyroidism), as approximately 10/10,000 population (range 8.97 to 15.48; Abraham-Nordling et al. 2011; Laurberg et al. 2012; Perros et al. 2017; Zaletel 2011). This would equate to 68,000 (range 60,996 to 105,264) TED patients in the UK (based on a UK population of 68 million). Previous epidemiological studies have also estimated a prevalence of 0.1% to 0.3% (equating to 68,000 to 204,000 UK patients; Lazarus 2012). The incidence (rate at which new cases occur) for TED has been estimated as 5/100,000/year, equating to 3,400 new cases of TED in the UK annually (Boulakh et al. 2022; Perros et al. 2017). • Given clinical management differs according to disease activity and severity, it may be helpful to provide an overview of how disease activity and severity are categorised (we have provided details below). • We would also suggest highlighting that TED is associated with a reduction in patient reported quality of life, psychological morbidity and impairment of daily activities including reading, driving, and socialising (Smith et al. 2023a; Smith et al. 2023b). Patients report appearance impairment and psychological impact long after the active inflammatory phase of TED has subsided (Cockerham et al. 2023). • The description of teprotumumab is appropriate.	plausible estimates has been included. The background information section has been updated to make a clearer distinction between activity and severity. It also now specifies how they are measured/categorised. The background information section now states that TED can impact quality of life and cause psychosocial distress. Thank you for providing this supplementary information to help

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		Here we have also outlined supplementary information on disease pathophysiology and clinical management, as this may be useful for the scoping workshop: • Thyroid-stimulating immunoglobulins (TSIs) bind to and stimulate thyrotropin receptors (TSHR) expressed on the thyroid gland, leading to the excessive production of thyroid hormones. These TSHR receptors are also expressed by fat, muscle, and connective tissues around the eye (orbital fibroblasts, orbital fat cells and extra-ocular muscles; Bahn 2002; Feliciello et al. 1993). There is evidence that TSI acting through locally expressed TSHR receptors within the orbit, contributes to the inflammation and orbital tissue expansion seen in TED. However, TSHR stimulation does not appear to be the sole agent responsible for TED (Bahn 2002; Feliciello et al. 1993; Wang and Smith 2014; Winn and Kersten 2021). Insulin like growth factor 1 (IGF-1) is a growth factor that mediates growth, cellular differentiation, and proliferation throughout the body, through stimulation of IGF-1 receptors (IGF-1R). IGF-1R are expressed on cells within the orbit (orbital fibroblasts) as well as at increased levels in immune cells (T and B lymphocytes) from TED patients (Douglas et al. 2007; Douglas et al. 2008; Winn and Kersten 2021). Stimulation of IGF-1R increases the release of signalling molecules (chemoattractant) by orbital fibroblasts from patients with Grave's disease that attract immune cells (T lymphocytes), initiating an inflammatory immune reaction, and stimulate the synthesis of connective (hyaluronan) and fat tissue (adipogenesis). These events can be blocked by inhibiting the stimulation of the IGF-1R receptor using a monoclonal antibody specific for IGF-1R (Pritchard et al. 2003; Smith and Hoa 2004). There is now a substantial body of evidence within the literature to suggest that TSHR and IGF-1R are physically and functionally coupled (Krieger et al. 2015). It is hypothesised that autoantibodies directed against this receptor complex may be responsible for stimulating the downstream cellular signalling pathways that underpin the pathogenesis of TED (Krieger et al. 2015; Rees Smith et al. 2009; Tsui et al. 2008).	inform the scoping workshop.

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		• The natural history of TED remains under study however it is associated with three broad disease phases: the initial active inflammatory disease phase, the plateau/static phase, and the inactive, chronic disease phase. In the active disease phase, there is active inflammation of the tissues within the orbit. This is driven by autoantibody stimulation of the TSHR and IGF-1R complex resulting in activation of downstream cellular signalling pathways that attract and stimulate immune cells whilst simultaneously stimulating the generation and proliferation of fat and connective tissues within the orbit. These processes result in both acute inflammatory symptoms (redness, pain, and swelling) as well as causing proptosis (due to increased tissue volume and pressure within the orbit exerting outward pressure on the eye(s)) and diplopia (due to impingement of muscle that control eye movement by swollen, higher volume orbital tissues). The plateau phase is associated with diseases stabilisation and the beginning of cessation of the active inflammatory processes. The inactive phase denotes a lack of active inflammatory processes however residual symptoms such a proptosis and diplopia may persist resulting in long term disfigurement and visual and functional impairment (Bartalena et al. 2020). • Management of TED patients depend on the phase of disease as well as its severity. Within the UK the activity of TED is generally assessed using the clinical activity score (CAS) which is a composite score assessing characteristic features of orbital inflammation. Disease severity classification typically follows recommendations by EUGOGO (2021) and is subcategorised into mild, moderate to severe and sight threatening categories based on clinical features, impact on daily life, risk benefit of immunosuppression or surgical interventions (Bartalena et al. 2021). • Risk factors for progression of disease such as abnormal thyroid function, smoking and radioactive iodine treatment should be addressed in all cases. Mild active cases require supportive measures such as lubricating eye drops, selenium supplementation and sunglasses. Moderate to severe	

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		active cases are treated with intravenous corticosteroids, immunosuppressive therapies (mycophenolate, cyclosporin, azathioprine) and in some cases orbital radiotherapy. Sight threatening active cases may require a combination of corticosteroids/ immunosuppressive therapies and acute surgical intervention (orbital decompression) to relieve optic nerve pressure (Bartalena et al. 2021). • Reconstructive (non-emergency) surgery to address residual proptosis, disfigurement and visual impairment is generally reserved for the inactive phase of the disease. It is estimated that up to 20% of patients will require surgery within the first decade after diagnosis (Baeg et al. 2023; Bartalena et al. 2021; Cheng et al. 2020). • There are currently no pharmacological treatments specifically approved for TED in the UK. Clinical management currently consists of off label treatments which do not target the underlying cause of the disease, providing only transient symptom relief, with non-meaningful changes in proptosis and diplopia. Steroids are only appropriate for short-term use with extended treatment associated with high rates of adverse reactions and symptoms (Bartalena et al. 2021; Sánchez-Ortiga et al. 2009). References Abraham-Nordling M et al. Eur J Endocrinol. 2011;165:899–905. doi: 10.1530/EJE-11-0548. Baeg J et al. Front Endocrinol (Lausanne). 2023 Feb 6;13:1080204. doi: 10.3389/fendo.2022.1080204. Bahn RS. Thyroid. 2002 Mar;12(3):193-5. doi: 10.1089/105072502753600124. Bartalena L et al. Ophthalmic Plast Reconstr Surg. 2023 Dec 1;39(6S):S2-S8. doi: 10.1097/IOP.0000000000002467.	

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		Bartalena L et al. Eur J Endocrinol. 2021;185(4):G43-G67. Published 2021 Aug 27. doi:10.1530/EJE-21-0479. Bartalena L et al. Front Endocrinol (Lausanne). 2020 Nov 30;11:615993. doi: 10.3389/fendo.2020.615993. Bartalena L et al. N Engl J Med. 1998 Jan 8;338(2):73-8. doi: 10.1056/NEJM199801083380201. Boulakh L et al. Arch Ophthalmol. 2022;140:667–73. Cheng AMS, Wei Y-H, Liao S-L. Oxid Med Cell Longev. 2020:3537675. doi: 10.1155/2020/3537675. Cockerham KP et al. Ophthalmol Ther. 2021 Dec;10(4):975-987. doi: 10.1007/s40123-021-00385-8. Epub 2021 Sep 3. Erratum in: Ophthalmol Ther. 2022 Apr;11(2):923. doi: 10.1007/s40123-022-00467-1. Douglas RS et al. J Immunol. 2008 Oct 15;181(8):5768-74. doi: 10.4049/jimmunol.181.8.5768. Douglas RS et al. J Immunol. 2007 Mar 1;178(5):3281-7. doi: 10.4049/jimmunol.178.5.3281. Feliciello A et al. Lancet. 1993 Aug 7;342(8867):337-8. doi: 10.1016/0140-6736(93)91475-2. Gupta R et al. Ophthalmic Plast Reconstr Surg. 2023 Dec 1;39(6S):S51-S64. doi: 10.1097/IOP.0000000000002449. Khalilzadeh O et al. Curr Genomics. 2011 Dec;12(8):564-75. doi: 10.2174/138920211798120844. Krieger CC et al. J Clin Endocrinol Metab. 2015 Mar;100(3):1071-7. doi: 10.1210/jc.2014-3566. Laurberg P et al. J Clin Endocrinol Metab. 2012;97:2325–32. doi: 10.1210/jc.2012-1275. Lazarus JH. Best Pract Res Clin Endocrinol Metab. 2012;26:273–9. doi: 10.1016/j.beem.2011.10.05	

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		Perros P et al. Orphanet J Rare Dis. 2017 Apr 20;12(1):72. doi: 10.1186/s13023-017-0625-1. Pritchard J et al. J Immunol. 2003 Jun 15;170(12):6348-54. doi: 10.4049/jimmunol.170.12.6348. Rees Smith B et al. Horm Metab Res. 2009 Jun;41(6):448-55. doi: 10.1055/s-0029-1220913. Sánchez-Ortiga R et al. Endocrinol Nutr. 2009;56(3):118-122. doi:10.1016/S1575-0922(09)70841-1. Smith TJ et al. Front Endocrinol (Lausanne). 2023a Nov 9;14:1283374. doi: 10.3389/fendo.2023.1283374. Smith TJ et al. JAMA Ophthalmol. 2023b Feb 1;141(2):159-166. doi: 10.1001/jamaophthalmol.2022.3225. Erratum in: JAMA Ophthalmol. 2023 Feb 1;141(2):213. doi: 10.1001/jamaophthalmol.2023.0109. Smith TJ, Hoa N. J Clin Endocrinol Metab. 2004 Oct;89(10):5076-80. doi: 10.1210/jc.2004-0716. Tsui S et al. J Immunol. 2008 Sep 15;181(6):4397-405. doi: 10.4049/jimmunol.181.6.4397. Wang Y, Smith TJ. Invest Ophthalmol Vis Sci. 2014 Mar 20;55(3):1735-48. doi: 10.1167/iovs.14-14002. Winn BJ, Kersten RC. Ophthalmology. 2021 Nov;128(11):1627-1651. doi: 10.1016/j.ophtha.2021.04.024. Zaletel K et al. Croat Med J. 2011;52:615–21. doi: 10.3325/cmj.2011.52.615.	
	The Thyroid Trust	As a patient group, we feel it should be emphasised that TED can have a severe impact on quality of life for patients due to the impact on their physical appearance. This in turn can have a detrimental effect on an individual's mental health, their ability to work and to socialise.	Thank you, the long-term impacts of TED (e.g., loss of vision, physical appearance and psychosocial

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			impacts) have been added to the background section.
Population	Thyroid Eye Disease Charitable Trust	No comment	Thank you, no action needed.
	British Thyroid Foundation	No comment	Thank you, no action needed.
	The Royal College of Ophthalmologists	Also, previously NICE in a consultation document for orbital radiotherapy gave the UK prevalence of TED to be 400,000.	Thank you. The previous consultation was conducted in 2005, and the current draft scope incorporates data from the most recent available sources. The updated scope also acknowledges the uncertainty surrounding the estimate of TED prevalence in the UK. No action needed.
	British Thyroid Association, Royal College of Physicians	Yes	Thank you, no action needed.

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	Society for Endocrinology, Welsh Endocrine and Diabetes Society	Yes	Thank you, no action needed.
	Amgen	We would suggest updating the population to 'People living with moderate to severe thyroid eye disease.'	Thank you, population has been updated to 'moderate to severe'.
	The Thyroid Trust	Yes	Thank you, no action needed.
Subgroups	Thyroid Eye Disease Charitable Trust	No comment	Thank you, no action needed.
	British Thyroid Foundation	No comment	Thank you, no action needed.
	The Royal College of Ophthalmologists	Patients with severe proptosis that will otherwise need orbital decompression surgery as there is no current effective medical treatment Patients with predominantly muscle involvement on orbital imaging Patients with severe diplopia as there is current effective medical treatment Patients with severe inflammation where conventional immunosuppression is contra indicated. Subgroups suggested in the scope are very generic.	Thank you, subgroups have been updated considering the comment. "Predominantly muscle involvement on orbital imaging" not included as this is related to differential diagnosis of TED or other underlying

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			conditions which has been covered.
	British Thyroid Association, Royal College of Physicians	We suggest including specifically these additional subgroups: Patients who are not treatment naïve such as those who remain active following pulsed methylprednisolone Cigarette users. (There is already evidence that they respond less well to existing therapies).	Thank you, subgroups have been updated considering the comment on patients who are not treatment naïve. “Cigarette users” not included to keep subgroups inclusive at this stage.
	Society for Endocrinology, Welsh Endocrine and Diabetes Society	How is initial severity coded into groups is this based on CAS -which reflects inflammation, or are we using proptosis, or quality of life.	Thank you, no action needed. The scope now states that severity is typically categorised using the European Group on Graves Orbitopathy (EUGOGO, 2021) guidelines.
	Amgen	The marketing authorisation excludes mild disease, so it will not be possible to evaluate this as a subgroup. An inclusion criterion of the OPTIC trial was a diagnosis of Graves’ disease; therefore, we will be unable to present analyses for people without Graves’ disease. Due to data limitations, we are unlikely to be able to provide a subgroup analysis according to the duration of active symptoms.	Thank you. Severity has been removed from the subgroups to align with the updated population. Graves disease subgroups have been removed to align with trial population. Otherwise, the subgroups are kept

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			inclusive at this stage. The company is invited to justify if/why any subgroups are not relevant or feasible in its submission.
	The Thyroid Trust	Maybe include subgroups for patients with Treated and Untreated TED.	Thank you, treated /untreated TED has been added as a subgroup.
Comparators	Thyroid Eye Disease Charitable Trust	Dexamethasone is listed as a possible systemic treatment. We do not believe that this happens in the UK, and it is not part of widely used guidelines such as EUGOGO. Also, triamcinolone should not be listed as a systemic medication; it is only used as an intraorbital or eyelid injection in TED. In the same section, rituximab and mycophenolate are not the only immunosuppressants in use. Some NHS departments may still be using azathioprine, mycophenolate or ciclosporin, though this is less common since the EUGOGO consensus recommended use of mycophenolate, so you may wish to add these to the list.	Thank you, comparators have been updated to align with current UK practice and EUGOGO guidelines. Dexamethasone has been removed as a comparator. Triamcinolone is listed as a corticosteroid (rather than a 'systemic corticosteroid'). Tocilizumab and ciclosporin have been added to the list. Azathioprine has been removed as consultees indicated during the scoping workshop

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			discussion that it is not widely used in the UK practice.
	British Thyroid Foundation	No comment	Thank you, no action needed.
	The Royal College of Ophthalmologists	Should include Orbital Radiotherapy in addition to comparators already listed?	Thank you, comparators have been updated to reflect current UK practice and EUGOGO guidelines. Previously listed as 'radiotherapy', this has been revised to 'orbital radiotherapy' to avoid any confusion.
	British Thyroid Association, Royal College of Physicians	Yes	Thank you, no action needed.
	Society for Endocrinology, Welsh Endocrine and Diabetes Society	We do not think many places use dexamethasone, tocilizumab and ciclosporin may be used and are not included	Thank you. Dexamethasone has been removed, while tocilizumab and ciclosporin have been added to the updated list of comparators.

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	Amgen	The comparators listed are generally aligned with our understanding of treatments used in the NHS, with some exceptions: • Clinical expert advice is that rituximab is not widely used in NHS practice. • Triamcinolone and dexamethasone are local injections and are only used when systemic corticosteroids are contraindicated due to the significant risk of adverse events. As such, our understanding is that they are not routinely used and are not appropriate comparators (Bartalena et al. 2021). • It is unclear how 'best supportive care' would be defined, and as such we suggest removing it as a comparator. People who choose to have no treatment would not have teprotumumab, so would not be included in the population. All other available treatments have already been listed separately as comparators, so it is unclear what would fall under 'best supportive care.' We would suggest sub-dividing the comparators according to the point in the pathway at which they are used, as different therapies are used according to level of disease activity and severity, and number of previous therapies. For example, surgery is only used for very severe, sight-threatening TED ([redacted]) or inactive TED [redacted] Advice from expert clinicians practising in England suggests that the 2021 European Group on Graves' orbitopathy (EUGOGO) clinical practice guidelines for the medical management of Graves' orbitopathy (Bartalena et al. 2021) are generally followed in the UK. However, experts advised that neither rituximab nor tocilizumab are used for active moderate to severe	Thank you. Using input from the consultation and scoping workshop, the comparators have been updated. They are now aligned with current UK practice, which largely follows EUGOGO guidelines. Best supportive care and dexamethasone have been removed as comparators. Rituximab and tocilizumab have been included as stakeholders suggest they may be used in some regions for specific patient populations.

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		TED in the UK, despite being listed in the EUGOGO guidelines. This is due to a combination of lack of data, availability, and lack of familiarity.
		
		Taking this into account, our understanding of the treatment pathway for **active** moderate to severe TED, split by line of therapy, is as follows:
		• No prior treatment:
		  ○ Systemic methylprednisolone with or without mycophenolate
		• Inadequate response / deterioration on 1st treatment:
		  ○ Repeat dose of methylprednisolone (with addition of mycophenolate if not already received)
		  ○ Radiotherapy
		  ○ Oral prednisone/ prednisolone with cyclosporine or azathioprine
		
		Our understanding of the comparators for **inactive** moderate to severe TED is aligned with the rehabilitative surgical interventions listed in the draft scope and the EUGOGO guidelines:
		• Eyelid surgery
		• Orbital decompression surgery
		• Strabismus surgery
		
		References:
		
		Bartalena L et al. Eur J Endocrinol. 2021;185(4):G43-G67. Published 2021 Aug 27. doi:10.1530/EJE-21-0479	

	The Thyroid Trust	We have nothing to add here.	Thank you, no action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
Outcomes	Thyroid Eye Disease Charitable Trust	In the economic analysis section: TEDct would recommend that emphasis is placed on psychosocial impact of this disease as well as visual function, because can be the most debilitating aspect of the condition. Patients with TED may stop working, lose social confidence and develop depression due to the impact of the condition even if measurable visual function is good.	Thank you. The outcome section has been updated considering the comment.
	British Thyroid Foundation	We would like to add 'psychosocial impact of the disease' to the list of outcomes to be considered unless this is properly covered by 'health related QoL'? 'Diplopia response' – ensure it is clear how this will be measured and by whom	Thank you. The outcome section has been updated considering the comment.
	The Royal College of Ophthalmologists	Use of healthcare resources in management of adverse events Frequency of non-responders or flare post treatment requiring re-treatment Patients still requiring rehabilitation surgery post treatment The use of a composite score widely used in many prospective TED studies associated with EUGOGO should be used to reflect the healthcare benefits. Improving radiological proptosis and decreased inflammation on MRI scans are a more reliable measurement than clinical measurements of proptosis on exopthalmometry and is now incorporated as an end point measurement in many current TED CTIMP trials.	Thank you. Impact on healthcare resource use is routinely considered in technology appraisals. "Frequency of non-responders or flare post treatment requiring re-treatment" could be captured by the outcome of retreatment

Section	Consultee/ Commentator	Comments [sic]	Action
		A clear strategy to prevent permanent adverse events e.g. Sensorineural hearing loss is needed with monitoring of audiology before during and after treatment. The long-term adverse event profile is not known so a robust surveillance strategy needed	which is already included in the scope. “need for rehabilitation” has been added. NICE does not specify any particular measurement scales that should be used to assess outcomes.
	British Thyroid Association, Royal College of Physicians	We feel duration of response is a critical factor here as there is already some evidence that there is disease recrudescence in some patients once teprotumumab is discontinued. •Reduction in subsequent use of surgical interventions is a hard outcome that has high value to patients, and we suggest including it.	Thank you for your comment. ‘Duration of response’ and ‘reduction in the need for subsequent surgical intervention’ have been added to the outcomes list.
	Society for Endocrinology, Welsh Endocrine and Diabetes Society	Health related quality of life – assume GOQOL is being used.	Thank you. NICE does not specify any particular measurement scales that should be used to assess outcomes.
	Amgen	The following outcomes listed in the scope are appropriate, and were collected as part of the teprotumumab clinical trial programme (Douglas et al. 2020): • change in disease activity (measured by CAS) • proptosis response • change in proptosis	Thank you. The outcomes are kept inclusive at this stage. Following the consultation and scoping workshop:

Section	Consultee/ Commentator	Comments [sic]	Action
		• diplopia response • adverse effects of treatment • health-related quality of life (in the OPTIC trial this was measured by the GO-QOL questionnaire). Orbital pain, eyelid swelling, and functional vision were not collected as separate outcomes but are components of the CAS. Furthermore, change in disease severity (as per the EUGOGO definition) was not collected as an outcome, however individual components that indicate the level of severity were collected (e.g. proptosis and diplopia). Overall response was measured, which is defined as a reduction in 2 or more CAS points (measure of activity) and a reduction in proptosis of 2 mm or more. Retreatment time was not collected as an outcome as part of the teprotumumab clinical trial programme. There are no additional outcomes that we would suggest including. References Douglas et al. N Engl J Med. 2020;382(4):341-352. doi:10.1056/NEJMoa1910434	Orbital pain, eyelid swelling, and functional vision have been removed as outcomes. Retreatment time is included as 'retreatment'. The company is invited to justify if/why any outcomes are not relevant or feasible in its submission.
	The Thyroid Trust	Add: Improvement in mental health	Thank you for your comment. The outcomes in the draft scope have been updated considering the comment. Mental health impacts may also be captured in the 'health

Section	Consultee/ Commentator	Comments [sic]	Action
			related quality of life' outcome.
Equality	Thyroid Eye Disease Charitable Trust	No comment	Thank you, no action needed.
	British Thyroid Foundation	No comment	Thank you, no action needed.
	The Royal College of Ophthalmologists	Many of the outcome measures used in clinical TED trials e.g. Clinical Activity Score are less reliable in non-white patients so can bias towards a lower score and cause these groups not to qualify for treatment if there is an absolute cut off. Clinician discretion must be allowed. Teprotumumab can be difficult to administer in diabetic patients due to hyperglycaemia side effect so a multidisciplinary approach with endocrinology involvement is needed to facilitate safe administration in this subgroup.	Thank you. The limitations of CAS and the risks of using it to assess eligibility for treatment were explored during the scoping workshop. A sentence has been added to the scope to highlight these limitations. This is an implementation issue and is not an equality issue that can be addressed by the NICE technology appraisal process.

Section	Consultee/ Commentator	Comments [sic]	Action
		It is also very important to remember that TED is a disfiguring disease so that there is often a significant perception gap between the clinician (with a visual function focus) and patient perspective of their own disease severity so the routine use of a validated QOL instrument e.g. GOQOL is essential to justify the use of interventional treatment in clinically 'mild' TED. This was also recommended in the European consensus.	The outcomes have been updated considering the comment. NICE does not specify any particular measurement tool, but the value of GOQOL was discussed at the scoping workshop.
	British Thyroid Association, Royal College of Physicians	No comment	Thank you, no action needed.
	Society for Endocrinology, Welsh Endocrine and Diabetes Society	No comment	Thank you, no action needed.
	Amgen	The level of disease activity in TED is measured by the CAS (Bartalena et al. 2021). One of the key limitations with the CAS is that any signs of inflammation, such as redness, are more difficult to detect in people who have black skin. Wang et al. (2024) discuss that "the clinical activity score (CAS) system was developed in 1999 in Amsterdam and was amended by the European Group on Graves' Orbitopathy (EUGOGO). Though the original studies did not specify the racial demographics of the included patients, a later analysis showed that over 95% of the TED patients referred in the EUGOGO centres were Caucasian". They conclude that the data suggests that black patients present with fewer external exam findings	Thank you for your comment. The limitations of CAS in *non-white* populations and the risks of using it to assess eligibility for treatment were explored during the scoping workshop. A sentence has been

Section	Consultee/ Commentator	Comments [sic]	Action
		suggestive of active TED compared to white patients, but the rate of compressive optic neuropathy and decompression surgery are similar. Therefore, CAS scoring may underappreciate disease activity in black patients (Wang et al. 2024). [redacted] which is often defined clinically according to the CAS, it is important to ensure that any recommendations do not make it more difficult for people with black or brown skin to access teprotumumab. There is a risk that their CAS assessment does not reflect their clinical disease activity level (i.e. they may be assessed as having inactive disease when they have clinically active disease), and as such a risk of them being excluded from accessing teprotumumab due to their race. References: Bartalena L et al. Eur J Endocrinol. 2021;185(4):G43-G67. Published 2021 Aug 27. doi:10.1530/EJE-21-0479 Wang et al. Front Ophthalmol (Lausanne). 2024 Jan 23;3:1309850. doi: 10.3389/fopht.2023.1309850.	added to the scope to highlight these limitations. This issue has been noted and the appraisal committee will consider whether its recommendations could have a different impact on people protected by the equality legislation than on the wider population.
	The Thyroid Trust	We would hope that any research studies and testing will include a higher number of women given that they are disproportionately affected by TED.	Thank you for your comment. Issues related to differences in prevalence or incidence of a disease cannot typically be addressed in a technology appraisal.

Section	Consultee/ Commentator	Comments [sic]	Action
Other considerations	Thyroid Eye Disease Charitable Trust	No comment	Thank you, no action needed.
	British Thyroid Foundation	No comment	Thank you, no action needed.
	The Royal College of Ophthalmologists	Access to safety monitoring (audiology) within the NHS setting Long term safety profile Duration of therapeutic effect Likelihood rehabilitation surgery will be needed – or re-treatment.	Thank you. Need for rehabilitation surgery has been added to the outcomes list.
	British Thyroid Association, Royal College of Physicians	Lost employment should be considered in the economic model. TED often prevents people from driving owing to double vision leading to loss of employment. Furthermore, disfigurement around the eyes leading to lack of confidence for people in public-facing roles, whether as a receptionist or a teacher, also leads to early loss of employment for many patients with TED. This is a life-changing condition for many people with moderate to severe disease.	Thank you. The impact of the condition on health related quality of life will be included in the cost effectiveness analyses for the appraisal. The outcomes in the draft scope have been updated considering the comment.
	Society for Endocrinology, Welsh Endocrine and Diabetes Society	No comment	Thank you, no action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
	Amgen	No comment	Thank you, no action needed.
	The Thyroid Trust	Impact of TED on patients' mental health.	Thank you. the outcomes in the draft scope have been updated considering the comment.
Questions for consultation	Thyroid Eye Disease Charitable Trust	These seem appropriate	Thank you, no action needed.
	British Thyroid Foundation	The severity of TED should be assessed and determined following all assessments, ophthalmic and orthoptic. We believe that some of the most significant unmet needs are those caused by the psychosocial impact of the disease. More data in needed in this area to improve understanding about patients' needs and how to address them.	Thank you. Outcomes in the draft scope have been updated in draft scope considering the comment.
	The Royal College of Ophthalmologists	1 Is the population defined appropriately? A previous NICE consultation document on orbital radiotherapy stated the prevalence of TED in the UK to be 400,000. OBJ	Thank you. The previous consultation was conducted in 2005, and the current draft scope incorporates data from the most recent available data sources. The updated scope also acknowledges the uncertainty surrounding

Section	Consultee/ Commentator	Comments [sic]	Action
			the estimate of TED prevalence in the UK. No further action is required.
		2 How is the activity of thyroid eye disease assessed and determined in the NHS? The Clinical Activity Score (CAS) is the most widely used activity score in the UK, but this can be subject to bias especially in non-white patients' progression of inflammation is defined as increasing proptosis on exopthalmometry, increasing ocular motility restriction and worsening visual acuity 3 How is the severity of thyroid eye disease assessed and determined in the NHS? What criteria are currently used? The EUGOGO severity criteria- mild, moderate-severe, sight threatening. [1] Gorman Diplopia score GOQOL quality of life score[2] 4 What is established clinical management for TED in the NHS?	Thank you. The limitations of CAS have been added to the scope. Thank you. The use of EUGOGO to categorise TED has been added to the scope.

[1] https://www.ncbi.nlm.nih.gov/books/NBK285551/table/tyd-graves-complica.degreeofoc/

[2] Terwee CB, Dekker FW, Mourits MP, Gerding MN, Baldeschi L, Kalmann R, Prummel MF, Wiersinga WM. Interpretation and validity of changes in scores on the Graves' ophthalmopathy quality of life questionnaire (GO-QOL) after different treatments. Clin Endocrinol (Oxf). 2001 Mar;54(3):391-8. doi: 10.1046/j.1365-2265.2001.01241.x. PMID: 11298093

Section	Consultee/ Commentator	Comments [sic]	Action
		This study[3] that most of the ophthalmologists surveyed were using the guidelines recommended by the European Group on Graves Orbitopathy https://academic.oup.com/ejendo/article/185/4/G43/6654384?login=false 5 Where do you consider teprotumumab will fit into the existing care pathway for TED? Patients with severe disease with intractable diplopia and Proptosis with predominantly muscle involvement Patients unsuitable for orbital decompression surgery to address disfiguring proptosis 5 What are the long-term monitoring and management practices for people with TED in the NHS? Patients either undergo rehabilitation surgery – orbital decompression for proptosis, strabismus surgery for intractable double vision, eyelid surgeries to address residual disfigurement e.g. eyelid retraction or live with their condition without intervention once it is stable. 6 Please select from the following, will teprotumumab be: D. Other (please give details):	Thank you. No action required. Thank you. No action required.

[3] Lee V, Avari P, Williams B, Perros P, Dayan C; British Oculoplastic Surgery Society (BOPSS) and TEAMeD. A survey of current practices by the British Oculoplastic Surgery Society (BOPSS) and recommendations for delivering a sustainable multidisciplinary approach to thyroid eye disease in the United Kingdom. Eye (Lond). 2020 Sep;34(9):1662-1671. doi: 10.1038/s41433-019-0664-z. Epub 2019 Dec 13. PMID: 31836832; PMCID: PMC7608203.
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Section	Consultee/ Commentator	Comments [sic]	Action
		In specialist Thyroid Eye Disease centres with multidisciplinary management including endocrinology and otology/ audiology access 7 For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention. Currently steroids are usually given by ophthalmologists and rehabilitation surgery done by ophthalmologists. Treatment with teprotumumab will likely require access to a more multidisciplinary team. 8 What are the most significant unmet needs in the treatment of TED? The long delay between onset of disease to when patients can safely undergo rehabilitation surgery to reverse the morbidity as the eye disease and thyroid disease should be quiescent. This is likely to take at least 2-3 years and longer with NHS waiting lists 9 Are their groups within the population that should be considered separately? For example, are there subgroups in which the technology is expected to be more clinically or cost effective? Are the subgroups listed appropriate? As stated above the subgroups are very generic. There needs to be clear guidance when teprotumumab can be given in mild stable disease. 10 Would teprotumumab be a candidate for managed access? Yes	Thank you. No action required. Thank you. No action required. Thank you. No action required. The subgroups have been updated. Thank you. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		11 Do you consider that the use of teprotumumab result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits. Detailed direct and indirect care costs, employment status, use of anti-depressant medications in addition to standard healthcare QOL instruments	Thank you. No action required.
	British Thyroid Association, Royal College of Physicians	Is the population defined appropriately? • Yes, with the above additions How is the activity of thyroid eye disease assessed and determined in the NHS? What criteria are currently used? • By CAS score (Mourits M et al.) How is the severity of thyroid eye disease assessed and determined in the NHS? What criteria are currently used? •By EUGOGO criteria (mild, moderate, severe, sight threatening using a combination of disease manifestations and their effect on QoL) What is established clinical management for TED in the NHS? •TED is a heterogeneous disease and there is not a short answer, but first-line for mild disease- eye drops and selenium; moderate to severe and active disease- pulsed methylprednisolone. Where do you consider teprotumumab will fit into the existing care pathway for TED? •Likely second line for patients with active disease who have failed methylprednisolone, or have contraindications to it, and have moderate to severe residual proptosis (23mm or more).	Thank you, no action needed. Thank you. This has been reflected in the scope. Thank you. This has been reflected in the scope. Thank you. This has been reflected in the scope.

Section	Consultee/ Commentator	Comments [sic]	Action
		What are the long-term monitoring and management practices for people with TED in the NHS? •Very variable. Once disease is inactive 'burned out' after 18-24 months many are left in primary care follow up. Please select from the following, will teprotumumab be: C. Prescribed in secondary care with routine follow-up in secondary care For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention. •Self-evidently, surgical interventions may have different follow up patterns to medical interventions. As most TED clinics take place in ophthalmology clinic areas, medical interventions are often remote from the clinic and the ophthalmology teams. Physician involvement is essential as immunomodulating therapies become more sophisticated. What are the most significant unmet needs in the treatment of TED? •TED has huge psychological effects (including increased suicide rate-PMID: 29084476), even in what doctors refer to as mild disease and yet no NHS service has integrated psychologist input. Are there groups within the population that should be considered separately? For example, are there subgroups in which the technology is expected to be more clinically or cost effective? •No additional comment	Thank you. No action required. Thank you. No action required Thank you. No action required Thank you. No action required Thank you. outcomes in the draft scope have been updated considering the comment.

Section	Consultee/ Commentator	Comments [sic]	Action
		Are the subgroups listed appropriate? •Additional subgroups mentioned above Would teprotumumab be a candidate for managed access? •Definitely. There is a danger teprotumumab will be used by people who are not skilled enough to perform orbital decompression surgery as a form of medical decompression. This is highly likely to be uneconomical. Do you consider that the use of teprotumumab result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? •Employment is a huge issue as discussed above	Thank you. No action required Thank you. Subgroups have been updated. Thank you. No action required Thank you. Health related quality of life will be considered in the appraisal.
	Society for Endocrinology, Welsh Endocrine and Diabetes Society	Population is defined appropriately Criteria used in NHS is variable, CAS is the commonest, but this deals with inflammation, assessment is also needed of orbital movements/proptosis and also quality of life	Thank you, no action needed. Thank you. No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
		Existing management of NHS is largely methylprednisolone (if severe enough) and surgery when less active. Teprotumumab has the potential to reduce the need for surgery and have faster improvements than standard treatment Teprotumumab has potential for preventing surgery in active disease and improving QOL. It also may have a role in reducing the need for surgery in people with inactive disease. This latter group is a large proportion of patients and should be a key consideration of this scope Monitoring should be whilst on the agent and in the year following. Hearing impact needs perhaps longer-term monitoring. Teprotumumab to my mind should be prescribed in secondary care with follow up there.	Thank you. No action needed. Thank you. Need for rehabilitation surgery has been added to the outcomes. Thank you. No action needed. Thank you. No action needed.
	Amgen	Is the population defined appropriately? • Please see comment in 'Population' section above. How is the activity of thyroid eye disease assessed and determined in the NHS? What criteria are currently used? • The clinical activity score (CAS) is a validated scoring system for measuring disease activity, and is scored according to levels of pain, redness, and swelling (Bartalena et al. 2021). However, please see our note in the equalities section regarding the limitations of the CAS system.	Thank you. No action needed. Thank you. This has been reflected in the scope.

Section	Consultee/ Commentator	Comments [sic]	Action
		How is the severity of thyroid eye disease assessed and determined in the NHS? What criteria are currently used?	
		• The severity of the disease is categorised into mild, moderate to severe, and sight threatening (i.e. very severe) as per the 2021 European Group on Graves' orbitopathy (EUGOGO) clinical practice guidelines for the medical management of Graves' orbitopathy (Bartalena et al. 2021).	Thank you. This has been reflected in the scope.
		What is established clinical management for TED in the NHS?	
		• For all patients with TED regardless of disease activity or severity, clinical management involves controlling thyroid function, and there is emerging evidence around the benefits of lowering cholesterol. Patients will also be advised on smoking cessation and will be offered eye drops or artificial tears.	Thank you. This has been reflected in the scope.
		• Our understanding of the pharmacological treatment pathway according to TED severity and activity is outlined in full in the 'Background' and 'Comparators' sections above.	Thank you. No action required.
		Where do you consider teprotumumab will fit into the existing care pathway for TED?	
		• The results of the OPTIC trial support teprotumumab as an efficacious therapy in treating patients with active moderate to severe TED, and we believe this is where it would add most value for patients and the NHS (Douglas et al. 2020).	Thank you. No action required.
		• Teprotumumab has proven efficacy for relevant outcome measures (proptosis response, CAS, diplopia, QoL; Douglas et al. 2020), whereas current treatments are suboptimal in terms of efficacy and lack a robust evidence base to support their use (Bartalena et al. 2021; Sanchez-Ortiga et a. 2009).	

Section	Consultee/ Commentator	Comments [sic]	Action
		What are the long-term monitoring and management practices for people with TED in the NHS? • Regular endocrinologist reviews in conjunction with monitoring in primary care are required to ensure thyroid function is controlled. • For patients with moderate to severe disease, ophthalmology/oculoplastic reviews are required to monitor response to initial active disease treatment. Following this, there is monitoring of residual symptoms when TED becomes inactive. This can involve, for example, review of residual proptosis and visual function, and discussion around the need for rehabilitative surgery. • Rehabilitative surgery can take 18 months to 3 years from time of initial TED diagnosis. This is due to; A) the need to bring the active disease under control to an inactive state (clinicians will not operate on active disease unless it is a sight threatening emergency); B) logistical and NHS capacity issues. • Eventually patients would be discharged from hospital care assuming a successful response to treatment or surgery if required. Please select from the following, will teprotumumab be: A. Prescribed in primary care with routine follow-up in primary care B. Prescribed in secondary care with routine follow-up in primary care C. Prescribed in secondary care with routine follow-up in secondary care D. Other (please give details): For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention. • C for teprotumumab, comparators and subsequent treatments	Thank you. No action required. Thank you. No action required. Thank you. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		What are the most significant unmet needs in the treatment of TED? • Achieving disease inactivation and addressing key symptoms (diplopia and proptosis) represent the main objectives of the most recent treatment guidelines for TED patients. • No treatments are currently approved for TED. Off label treatments, such as steroids, are typically used. These treatments do not target the underlying cause of the disease, providing only transient symptom relief, with non-meaningful changes in proptosis and diplopia. Steroids are only appropriate for short-term use with extended treatment associated with high rates of adverse reactions and symptoms (Bartalena et al. 2021; Sanchez-Ortiga et al. 2009). • The lack of evidence of efficacy for long term outcomes on proptosis and diplopia results in high proportions of patients (≥20%) requiring ≥1 surgical intervention (Wu et al. 2017). Are there groups within the population that should be considered separately? For example, are there subgroups in which the technology is expected to be more clinically or cost effective? • Please see comments in 'Subgroups' section above. Are the subgroups listed appropriate? • Please see comments in 'Subgroups' section above. Would teprotumumab be a candidate for managed access? • At this point, we consider this unlikely.	Thank you. No action required. Thank you. No action required. Thank you. No action required. Thank you. No action required. Thank you. Outcomes in the draft scope have been updated

Section	Consultee/ Commentator	Comments [sic]	Action
		Do you consider that the use of teprotumumab result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? • TED has a significant impact on appearance and self-perception, as well as vision changes. However, the sensitivity of generic measures such as the EQ-5D has been questioned in some contexts, including in some ophthalmological conditions (Dawoud et al. 2022). • Proptosis is a key factor affecting appearance in TED and there may be benefits in reducing proptosis that are not captured in the QALY. Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits. • We have conducted a systematic literature review looking at the sensitivity of generic preference-based measures in TED and analogous conditions. This will be submitted as part of our evidence package. References: Bartalena L et al. Eur J Endocrinol. 2021;185(4):G43-G67. Published 2021 Aug 27. doi:10.1530/EJE-21-0479 Dawoud D et al. Qual Life Res. 2022;31(7):2167-2173. doi:10.1007/s11136-022-03101-6 Douglas et al. N Engl J Med. 2020;382(4):341-352. doi:10.1056/NEJMoa1910434 Sanchez-Ortiga, R et al., Endocrinol Nutr, 2009. 56(3): p. 118-22. Wu CY, et al. Ophthalmic Plast Reconstr Surg. 2017;33(3):189-195. doi:10.1097/IOP.0000000000000699	considering the comment.

Section	Consultee/ Commentator	Comments [sic]	Action
	The Thyroid Trust	No comment.	Thank you, no action needed.
Additional comments on the draft scope	Thyroid Eye Disease Charitable Trust	No comment	Thank you, no action needed.
	British Thyroid Foundation	No comment	Thank you, no action needed.
	The Royal College of Ophthalmologists	There are likely many more TED patients who will benefit from Teprotumumab than those currently receiving immunosuppression (around 30%) and undergoing rehabilitation surgery. Clear guidance is needed with need for clinician discretion as to eligibility. Also, Teprotumumab has never been used in a clinical trial of for the most severe (sight threatening) category affecting between 2-8% of all TED patients. Further scientific evidence is needed.	Thank you. The remit of this scope is to treat moderate to severe TED. Input from the consultation and scoping workshop suggests that severity is typically categorised using the EUGOGO guidelines.
	British Thyroid Association, Royal College of Physicians	No comment	Thank you, no action needed.
	Society for Endocrinology, Welsh Endocrine and Diabetes Society	No comment	Thank you, no action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
	Amgen	No comment	Thank you, no action needed.
	The Thyroid Trust	We would like to see links made to the Women's Health Strategy and related policies, due to the fact that TED primarily affects women (at a female-to-male ratio of 5:1). We have been in discussions with the SPAD at the Dept of Health & Social Care regarding inclusion of thyroid conditions in the Women's Health Strategy.	Thank you. The higher prevalence among women has been noted in the background information section.

The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope

- Immunodeficiency UK
- Macular Society UK
- British Oculoplastic Surgery Society