National Institute for Health and Care Excellence

Multiple Technology Appraisal

Ivacaftor–tezacaftor–elexacaftor, tezacaftor–ivacaftor and lumacaftor–ivacaftor for treating cystic fibrosis [ID3834]

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

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	CF Voices	CFTR modulators have transformed the lives and futures of the majority in the CF community – patients and their families. All three medicines are essential in CF care and it is appropriate to evaluate them together.	Thank you for your comment. No action needed.
	Cystic Fibrosis Trust	An evaluation is essential to ensure people with cystic fibrosis continue to access these transformative treatments and maintain the health improvements seen. We believe the evaluation of lumacaftor/ivacaftor (Orkambi), ivacaftor/tezacaftor (Symkevi), and elexacaftor/tezacaftor/ivacaftor (Kaftrio) as a Multiple Technology Appraisal is appropriate given that the data collection reports submitted during the interim access period have considered the treatments together.	Thank you for your comment. No action needed.
	Genetic Alliance UK	Following advice from the Cystic Fibrosis Trust, we understand that a multiple technology assessment would be the most appropriate pathway for assessing these treatments. It is important to emphasise that many individuals are already receiving these treatments through an interim access agreement and	Thank you for your comment. No action needed.

Section	Stakeholder	Comments [sic]	Action
		to ensure continuity and equity of access it is important to progress with the appraisal without delay.	
	Vertex Pharmaceuticals	It is appropriate to appraise ivacaftor/tezacaftor/elexacaftor [IVA/TEZ/ELX], however, we do not believe it is proportionate to carry out a full appraisal of lumacaftor/ivacaftor [LUM/IVA] or tezacaftor/ivacaftor [TEZ/IVA]. The European Cystic Fibrosis Society (ECFS) consensus statement on standards of care for CFTR variant-specific therapy (Southern et al., 2022) stipulates that people with cystic fibrosis (PwCF) "aged six years and older, with one or two F508del variants, should have daily treatment with triple modulator therapy" (IVA/TEZ/ELX). This statement suggests that IVA/TEZ/ELX is standard of care for the vast majority of eligible PwCF in the UK and alternatives only are suitable if IVA/TEZ/ELX is not indicated or tolerated. [redacted] Equally, it is inappropriate to compare the interventions to one another given that the NICE methods clearly state technologies recommended in managed access agreements are not considered suitable comparators, and LUM/IVA and TEZ/IVA fall into this category (NICE, 2022). For this reason, we believe a single technology appraisal (STA) of IVA/TEZ/ELX to be more efficient and proportionate and suggest it would be more appropriate to ensure continued access to LUM/IVA and TEZ/IVA via a separate proportionate process, as NICE has outlined is its aim in recent announcements (NICE, 2022). Equally, we call on NICE to ensure that the appraisal of IVA/TEZ/ELX is carried out in a timely manner. In order to support a rapid and efficient	The multiple technology appraisal (MTA) process is designed to appraise single or multiple products, devices or other technologies, with 1 or more related indications. At present there is no positive NICE guidance for any of these combinations, so the MTA process is considered to be the most appropriate to ensure timely and continued access for patients. The data collection agreement also outlines that the NICE health technology appraisal(s) will include lumacaftor–ivacaftor, tezacaftor–ivacaftor and ivacaftor–tezacaftor–elexacaftor.

Section	Stakeholder	Comments [sic]	Action
		process, we strongly recommend that the committee uses the company model as the basis for decision-making rather than employing an External Assessment Group (EAG) to conduct separate modelling. This is appropriate owing to the unique nature of the appraisal in that Vertex would be submitting for three of its technologies with a model that has been validated (McGarry et al., 2020) and published in peer reviewed journals (Rubin et al., 2019). This is different from a usual MTA where using a company model is not possible as the various treatments are commercialised by different companies. References: Cystic Fibrosis Trust. UK Cystic Fibrosis Registry 2021 Annual Data Report. September 2022. Available at: https://www.cysticfibrosis.org.uk/sites/default/files/2022-10/CFT_2021-Annual-Data-Report-WEB.pdf McGarry L, Lopez A, Chandler C, Pelligra C, Alkhateeb Z, Rubin J, et al., editors. Validation of modelled 5-year survival outcomes among patients with cystic fibrosis treated with the CF transmembrane conductance regulator modulator ivacaftor using US CF Foundation Patient Registry data. International Society of Pharmacoeconomic and Outcomes Research (ISPOR); 2020 May 16-20; Orlando, Florida NICE (2022), https://www.nice.org.uk/news/blog/increasing-the-capacity-of-our-technology-appraisals-the-proportionate-way Rubin JL, O'Callaghan L, Pelligra C, Konstan MW, Ward A, Ishak JK, et al. Modeling long-term health outcomes of patients with cystic fibrosis homozygous for F508del-CFTR treated with lumacaftor/ivacaftor. Ther Adv Respir Dis. 2019;13:1753466618820186. Southern KW, Castellani C, Lammertyn E, Smyth A, et. al. Standards of care for CFTR variant-specific therapy (including modulators) for people with cystic fibrosis, Journal of Cystic Fibrosis, 2022, https://doi.org/10.1016/j.jcf.2022.10.002.	Sections 8.6.5 and 8.6.5 of NICE health technology evaluations: the manual state a guidance update after a period of managed access will be done through NICE's processes for developing guidance (of which a multiple technology appraisal is an option), and that the guidance update will include the scoping step. Thank you for your comment. The External Assessment Group will independently synthesise the evidence from the manufacturers submission about the clinical and cost effectiveness of the technologies. This may

Section	Stakeholder	Comments [sic]	Action
			also include an economic model submitted by the manufacturer.
	British Thoracic Society	Yes agree MTA	Thank you for your comment. No action needed.
	UK CF Medical Association	The emergence of variant specific therapy is a major milestone for people with CF and a detailed appraisal is appropriate for this new intervention. The appraisal should be inclusive (not completely variant focused) and patient facing.	Thank you for your comment. No action needed.
Wording	CF Voices	Yes. Although even with the extended data collection period, CFTR modulators will only really demonstrate their full cost effectiveness over a long period, possibly decades - when children who start treatment at age 2 or younger have grown to be adults without the significant illness and care requirements that the current population has had to endure and will continue to feel the effects of throughout their lives, despite treatment, because the damage is irreversible.	Thank you for your comment. The assessment group will take a pragmatic approach to solve data limitations. Potential methods to overcome data limitations, include implementing sensitivity analysis and scenario analysis.
	Cystic Fibrosis Trust	The wording of the appraisal is ambiguous and suggests that only the triple combination will be appraised. The remit should be clarified to read: 'to appraise the clinical and cost effectiveness of lumacaftor/ivacaftor (Orkambi),	Thank you for your comment. The scope

Section	Stakeholder	Comments [sic]	Action
		ivacaftor/tezacaftor (Symkevi), and elexacaftor/tezacaftor/ivacaftor (Kaftrio) within their marketing authorisations for treating cystic fibrosis'.	has been updated to reflect this.
	Genetic Alliance UK	The wording of the appraisal would benefit from further clarity as to what exactly is being appraised as part of the MTA. The remit should be rephrased as 'to appraise the clinical and cost effectiveness of lumacaftor/ivacaftor (Orkambi), ivacaftor/tezacaftor (Symkevi), and elexacaftor/tezacaftor/ivacaftor (Kaftrio) within their marketing authorisations for treating cystic fibrosis'.	Thank you for your comment. The scope has been updated to reflect this.
	NHS England	The agreement at the end of 2019 did indeed include all the combination CFTR modulators but E/T/I was at that time unlicensed so was not available to prescribe, people with CF (not part of a clinical trial) were not able to access the drug on the NHS until September 2020. The paragraph could be reworded for clarity.	Thank you for your comment. The scope has been updated to reflect this.
	Vertex Pharmaceuticals	NICE should refer to the technologies as follows: • Lumacaftor/ivacaftor • Tezacaftor/ivacaftor • Ivacaftor/tezacaftor/elexacaftor	Thank you for your comment. The scope has been updated to reflect this.
	UK CF Medical Association	The circumstance and timing of this review is unusual in that a detailed contract has been agreed between NHSE and the pharmaceutical company for the currently available therapies. It is important that the review does not undermine this agreement, but it is also important that these relatively new agents are thoroughly appraised. Whilst the review should be inclusive, it is important that conclusions do not conflate data across different interventions, as has occurred in the past. The results should be applicable across all the UK nations.	Thank you for your comment. No update to the scope required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	CF Voices	This is incorrect: 'In October 2019, NHS England & Improvement announced they and Vertex have concluded an access agreement to enable eligible patients in England interim access to treatment with ivacaftor/tezacaftor/elexacaftor, tezacaftor/ivacaftor, lumacaftor/ivacaftor and ivacaftor via the NHS while further data are collected.' And should read along the lines of: 'In October 2019, NHS England & Improvement announced they and Vertex have concluded an access agreement to enable eligible patients in England interim access to treatment with tezacaftor/ivacaftor, lumacaftor/ivacaftor and ivacaftor via the NHS while further data are collected. In August 2020, ivacaftor/tezacaftor/elexacaftor was added to the access agreement: https://www.england.nhs.uk/2020/08/landmark-nhs-deal-to-open-up-access-to-life-changing-cystic-fibrosis-drug/.'	Thank you for your comment. The scope has been updated to reflect this.
	Cystic Fibrosis Trust	The background information is broadly accurate, but we would like to clarify a few points. The UK Cystic Fibrosis Registry is a secure centralised database, sponsored and managed by the Cystic Fibrosis Trust. It records health data on consenting people with cystic fibrosis in England, Wales, Scotland, and Northern Ireland. Registry reports are published each year in the annual report. The 2021 Registry annual data report finds there are 10,908 people registered with cystic fibrosis[1]. The background information should be updated as there are over 2,000 known mutations that can cause cystic fibrosis[2]. Additionally, the numbers with at least one F508del mutation are higher than quoted – the 2021	Thank you for your comment. No action needed. Thank you for your comment. The scope

Section	Consultee/ Commentator	Comments [sic]	Action
		Registry report finds there are 9714 (89.1%) of people with cystic fibrosis who have at least one copy of the F508del mutation[3].	has been updated to reflect this.
		People living with cystic fibrosis have an extreme treatment burden and the scope should recognise this. As cystic fibrosis can affect many different parts of the body in different ways, most people with cystic fibrosis require a significant number of medications each day. This is alongside vital physiotherapy and managing complex nutrition needs.	Thank you for your comment. No action needed.
		Some people with cystic fibrosis may need a transplant if standard treatments are no longer working as well as they should. The main transplants that people with cystic fibrosis may need are lungs or liver. For some people with cystic fibrosis, other organs may need to be transplanted (including the liver or the pancreas) because of the damage the condition can inflict on the whole of the body, and the scope should be updated to reflect this. As cystic fibrosis is a genetic condition, people who receive a transplanted organ will still have cystic fibrosis in the rest of their body and may still require cystic fibrosis treatment, even after a successful transplant. After transplant, specific care is required and the Trust is aware many people who've had lung transplants say that it feels like swapping one chronic condition for another, although with fewer symptoms and an improved quality of life.	Thank you for your comment. The scope has been updated to reflect this.
		In October 2019, NHS England concluded a deal for access to these treatments. This was originally for full access to lumacaftor/ivacaftor (Orkambi), ivacaftor/tezacaftor (Symkevi) and extended access to ivacaftor (Kalydeco). In June 2020, the deal was expanded to include elexacaftor/ ivacaftor/tezacaftor (Kaftrio) when a marketing authorisation was granted. As	Thank you for your comment. The scope

Section	Consultee/ Commentator	Comments [sic]	Action
		access was agreed for current and future possible licence extensions, in January 2022, children with cystic fibrosis aged six to 11 were able to access Kaftrio when the MHRA confirmed a licence extension. This paragraph should be reworded for clarity. The terms of the interim access agreement enable people with cystic fibrosis with rare named mutations are eligible modulator therapies under licensing decisions by the U.S Food and Drug Administration (FDA), for which use of the treatments is off label in England. An updated commissioning statement, originally published in 2021, details the named CFTR mutations that will not be considered by the Medicines and Healthcare products Regulatory Agency (MHRA), and therefore reimbursement is covered by NHS England[4]. The scope should acknowledge the comprehensive nature of the access arrangement. We are concerned about people with cystic fibrosis accessing treatments via this eligibility when the appraisal concludes, and the commissioning statement is superseded by NICE technology appraisal guidance. Continuity of access, and certainty is vital for people living with cystic fibrosis. There may be significant implications for the health of people with cystic fibrosis if treatment is stopped and patient choice is important if other treatments cannot be tolerated. [1] UK Cystic Fibrosis Registry Annual Data Report 2021, https://www.cysticfibrosis.org.uk/the-work-we-do/uk-cf-registry/reporting-and-resources [2] Cystic Fibrosis Trust, What are the causes of cystic fibrosis? https://www.cysticfibrosis.org.uk/what-is-cystic-fibrosis/what-causes-cystic-fibrosis [3] UK Cystic Fibrosis Registry Annual Data Report 2021, https://www.cysticfibrosis.org.uk/the-work-we-do/uk-cf-registry/reporting-and-resources	has been updated to reflect this. Thank you for your comment. Unless the Department of Health and Social Care indicates otherwise, NICE will not develop guidance on a technology for indications that have not been given regulatory approval in the UK (that is, for unlicensed or 'off-label' use).

Section	Consultee/ Commentator	Comments [sic]	Action
		[4] NHS England, Commissioning statement: Ivacaftor, tezacaftor/ivacaftor, lumacaftor/ivacaftor and elexacaftor/tezacaftor/ivacaftor for cystic fibrosis, https://www.england.nhs.uk/publication/commissioning-statement-ivacaftor-tezacaftor-ivacaftor-lumacaftor-ivacaftor-and-elexacaftor-tezacaftor-ivacaftor-for-cystic-fibrosis/	
	Genetic Alliance UK	The impact of current treatment options is not fully reflected in the scope. The scope states that some people with cystic fibrosis may require a lung transplant however the lungs are not the only organ affected by cystic fibrosis; other organs are sometimes required to be transplanted such as the liver or pancreas. An organ transplant does not equate to a cure, special care and treatment must be adhered to following a transplant on top of existing management options.	Thank you for your comment. The scope has been updated to reflect this.
	NHS England	There are nearer 2000 mutations in the CF gene rather than 1400 but not all are known to be disease causing	Thank you for your comment. The scope has been updated to reflect this.
	Vertex Pharmaceuticals	The background section states that “current treatments for cystic fibrosis manage the symptoms and complications rather than the cause of the disease”. This statement disregards the availability of CFTR modulators, and therefore should be amended to clarify that existing treatments can be broadly classified into two groups based on their expected clinical benefit: 1) symptom-based therapies, which comprise the existing standard of care (a term frequently used interchangeably with best supportive care), and 2) CFTR modulators, currently the only disease-modifying treatment options which target the underlying cause of disease. The final paragraph of the background section includes ivacaftor in the list of CFTR modulators granted interim access. The NHSE commissioning policy	Thank you for your comment. No action needed. Thank you for your comment. The scope

Section	Consultee/ Commentator	Comments [sic]	Action
		for ivacaftor is permanent (in contrast to the other CFTR modulators), therefore the paragraph should be amended to clarify this fact. We would also like to bring the fact to NICE's attention that LUM/IVA is currently licensed for patients aged 2 years and older, rather than the 6 years and older mentioned in the draft scope.	has been updated to reflect this. Thank you for your comment. The scope has been updated to reflect this.
	British Thoracic Society	Yes appears accurate	Thank you for your comment. No action needed.
	UK CF Medical Association	There are some minor corrections - Please use the term variant instead of mutation (or CFTR gene variant). Not all variants are CF causing and it is important to reflect this. - The correctors were available in a stepwise manner; LUM-IVA, then TEZ-IVA, then ELX-TEZ-IVA. - LUM-IVA is licenced for 2-5 year olds	Thank you for your comment. No action needed. Thank you for your comment. The scope has been updated to reflect this.

Section	Consultee/ Commentator	Comments [sic]	Action
		With respect to the intervention, although it is appreciated that the HTA can only consider licenced drugs or agents coming to market, it is important to note that there are phase 3 trial data on an alternative to ELX, which is given the trial name VX-659. Also the company are investigating a once daily IVA preparation.	Thank you for your comment. No action needed.
Population	CF Voices	Lumacaftor and ivacaftor combination therapy is licensed for age 2 years +.	Thank you for your comment. The scope has been updated to reflect this.
	Genetic Alliance UK	We understand from the Cystic Fibrosis Trust that the interim access agreement allows a population of people with rarer mutations to access these treatments under the FDA license via off label usage in England. The scope should acknowledge these other mutations as we share the CF Trust's concern that this population will struggle to continue to access treatment when the commissioning statement is superseded by the NICE technology appraisal guidance. It is imperative that people living with cystic fibrosis have assurance that they will be able to continue their current treatment otherwise they are likely to face significant health implications.	Thank you for your comment. Unless the Department of Health and Social Care indicates otherwise, NICE will not develop guidance on a technology for indications that have not been given regulatory approval in the UK (that is, for unlicensed or 'off-label' use).
	Vertex Pharmaceuticals	The population is correct and defined appropriately.	Thank you for your comment. No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
	British Thoracic Society	Yes- but to ensure that the population on ETI are examined i.e 'in a combination regimen with ivacaftor for the treatment of cystic fibrosis (CF) in patients aged 6 years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene'.	Thank you for your comment. No action needed.
	UK CF Medical Association	It is important to clarify that the patients should have a clear diagnosis of CF (not just two CFTR gene variants). Some variants that have been classed as responsive to ELX-TEZ-IVA, are in fact characterised as "non-CF causing". The population should include all pwCF with a potentially eligible CFTR gene variant, not just F508del.	Thank you for your comment. NICE develops guidance on a technology for indications that have been given regulatory approval in the UK. The UK Marketing Authorisations for ivacaftor–tezacaftor–elexacaftor, tezacaftor–ivacaftor and lumacaftor–ivacafor specify the *F508del* mutation.
Subgroups	Cystic Fibrosis Trust	As access to Kaftrio came approximately one year after access to Orkambi and Symkevi and extended access to Kalydeco, it is essential the additional clinical outcomes evidence for Kaftrio, which is due to be completed by mid-2023, is included in this appraisal. The data collection period for Kaftrio was set for two years, and there is concern that this is not long enough to assess the full health economic benefit of Kaftrio when long-term clinical trials are ongoing. We encourage this appraisal to utilise all flexibilities for the evaluation of health technologies, as introduced in the new methods and processes manual published earlier this year.	Thank you for your comment. The assessment group will explore the uncertainty associated with data limitations. Potential methods include implementing sensitivity analysis and scenario

Section	Consultee/ Commentator	Comments [sic]	Action
			analysis. NICE health technology evaluations: the manual permits additional evidence to be submitted during the process where required, including if it is requested by the committee.
	Genetic Alliance UK	Kaftrio is a newer treatment compared to the other ones being assessed as part of this MTA therefore is likely to have a less mature evidence base to analyse. It is therefore important to utilise the flexibility of the new methods and processes that were introduced earlier this year.	Thank you for your comment. The assessment group will explore the uncertainty associated with data limitations. Potential methods include implementing sensitivity analysis and scenario analysis. NICE health technology evaluations: the manual permits additional evidence to be submitted during the process where required, including if it is requested by the committee.

Section	Consultee/ Commentator	Comments [sic]	Action
	NHS England	The population and subgroups should be expanded. The licensed indications are correct as listed. [redacted].	Thank you for your comment. The population has been kept broad and the treatments will be evaluated within their marketing authorisations.
	Vertex Pharmaceuticals	It is not relevant or appropriate to consider subgroups within cystic fibrosis and all patients within the licensed indications will benefit clinically from treatment (as demonstrated, for example, in Middleton et al., 2019). References: Middleton PG, Mall MA, Dřevínek P, Lands LC, McKone EF, Polineni D, et al. Elexacaftor–Tezacaftor–Ivacaftor for Cystic Fibrosis with a Single Phe508del Allele. New England Journal of Medicine. 2019;381(19):1809-19.	Thank you for your comment. The treatments will be evaluated within their marketing authorisations.
	British Thoracic Society	Important to remember some people with CF are not on full dose and also some have been tried on ETI therapy as part of IPFR –especially for rare mutations which are often from people with CF from ethnic minorities	Thank you for your comment. No action needed.
	UK CF Medical Association	A subgroup of interest is those pwCF who have a gating variant, which is responsive to IVA monotherapy. Is there benefit of switching to ELX-TEZ-IVA if they have F508del on their other chromosome?	Thank you for your comment. The scope has been updated to reflect this.
Comparators	Cystic Fibrosis Trust	The wording of this section is unclear. Clinical data from those on modulator therapies is being compared to a historic matched cohort i.e., standard treatments prior to starting modulator therapy. People with cystic fibrosis who	Thank you for your comment. Established clinical management will be defined as a

Section	Consultee/ Commentator	Comments [sic]	Action
		access modulator therapies are still on standard treatment, and where appropriate, modulators will also be compared. This is a unique appraisal and there are large numbers of people with cystic fibrosis taking the modulator therapies. The 2021 UK Cystic Fibrosis Registry's annual report found that 5,321 people were taking Kaftrio, 515 on Symkevi, 942 on Orkambi and 606 on Kalydeco[5]. [5] UK Cystic Fibrosis Registry Annual Data Report 2021, https://www.cysticfibrosis.org.uk/the-work-we-do/uk-cf-registry/reporting-and-resources	treatment widely accepted by the NHS as standard of care, which is routinely funded by the NHS, including CFTR modulators.
	NHS England	Ivacaftor should be listed as a comparator. The comparators list is standard care but modulators are in addition to standard therapy and address underlying problem with the dysfunctional CFTR protein nota downstream effect	Thank you for your comment. Ivacaftor monotherapy is licensed for use in people "who have an R117H CFTR mutation or one of the following gating (class III) mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R". Ivacaftor is not considered a relevant comparator in people

Section	Consultee/ Commentator	Comments [sic]	Action
			with at least one F508del mutation.[a]
	Vertex Pharmaceuticals	The relevant comparators for IVA/TEZ/ELX are BSC and ivacaftor, in the relevant populations. The ECFS consensus statement on standards of care in CF (Southern et al., 2022) recommends that: • Children with CF with eligible CFTR gene variants should be offered treatment with ivacaftor from 4 months of age • Children with CF who are homozygous for the F508del variant, aged 2-5 years, should be offered treatment with LUM/IVA • Patients with CF aged six years and older, with one or two F508del variants, should have daily treatment with IVA/TEZ/ELX However, such modulators are not included in the NICE guideline. NICE recommends the following symptom-based therapies as BSC for the treatment of CF: • Airway clearance techniques (breathing techniques, autogenic drainage and airway clearance devices) • Mucoactive agents (dornase alpha, hypertonic sodium chloride, or mannitol dry powder) to reduce the viscosity and/or adherence of the mucus within the airway, thereby promoting better mucus clearance • Antibiotics for treating acute and chronic bacterial infections • Immunomodulatory agents (e.g. azithromycin, corticosteroids) • Nutritional support to achieve normal growth and development	Thank you for your comment. Ivacaftor monotherapy is licensed for use in people “who have an R117H CFTR mutation or one of the following gating (class III) mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R”. Ivacaftor is not considered a relevant comparator in people with at least one F508del mutation.[a]

Section	Consultee/ Commentator	Comments [sic]	Action
		• Exercise to help clear mucus from the lungs and improve overall lung function • The NHS guidance on CF treatments also indicates that bronchodilators may be used to widen the airways. Further treatments are also recommended depending on any complications which may arise such as distal intestinal obstruction syndrome, malabsorption, liver disease, low bone mineral density, CFRD and psychological illness. While not included in the list of comparators, ivacaftor is a relevant comparator for some CF populations and therefore should be added. Importantly, it is inappropriate to compare the interventions to one another given that the NICE methods clearly state technologies recommended in managed access agreements are not considered suitable comparators, and LUM/IVA and TEZ/IVA fall into this category (NICE, 2022). References: National institute for Health and Care Excellence (NICE). Cystic fibrosis: diagnosis and management NICE guideline [NG78] 2017 National institute for Health and Care Excellence (NICE). Programme Manual. 2022 Southern KW, Castellani C, Lammertyn E, Smyth A, et. Al. Standards of care for CFTR variant-specific therapy (including modulators) for people with cystic fibrosis, Journal of Cystic Fibrosis, 2022, https://doi.org/10.1016/j.jcf.2022.10.002.	Thank you for your comment. The treatments will be evaluated within their marketing

Section	Consultee/ Commentator	Comments [sic]	Action
			authorisations and compared with each other where appropriate.
	British Thoracic Society	yes	Thank you for your comment. No action needed.
	UK CF Medical Association	The comparator should be placebo, or another variant specific therapy. Both groups should receive standard care, as defined by the NICE guidelines.	Thank for your comment. Established clinical management will be defined as a treatment widely accepted by the NHS as standard of care.
Outcomes	CF Voices	Lung transplant and transplant list referrals should also be considered. While data collected by NHS and reported through the CF Registry as part of the Data Collection Agreement will form the main source for appraisal, if there is robust data from other sources about additional outcomes, these could include CFRD, Liver Disease, Renal Disease, GI complications, Pancreatitis, ENT, Fertility.	Thank you for your comment. The scope has been updated to reflect this. The assessment group will choose the outcomes to be included, based on composite endpoints

Section	Consultee/ Commentator	Comments [sic]	Action
		Disease progression and increase in complications/treatment burden/hospitalisation over time relative to a treatment naive comparator group would be useful. Health-related quality of life impacts are difficult to quantify in children and will also be challenging in those who are fortunate enough to gain access before cystic fibrosis illness substantially impacts them – where the main benefits are of prevention of future damage to health and health-related quality of life. Conversely, for the significant proportion of the population who received these drugs too late in their life to avoid ongoing ill-health, particularly as this came after years of high-profile struggle for access, understandable ambivalence will need to be taken into account. Carers are significantly impacted by a loved-one having CF and the impact on them of a patient's treatment with CFTR modulators, must be considered (see comment below).	and the available data. The list of outcomes is not exhaustive. The company can include additional outcomes at the submission stage. Thank you for your comment. Difficulty quantifying health-related quality of life for some people has been noted. This will be considered in the appraisal. Carer disutilities will be considered as per the 2022 NICE health technology evaluations: the manual if there is evidence to support this.

Section	Consultee/ Commentator	Comments [sic]	Action
	Cystic Fibrosis Trust	The description of the outcomes should be clarified as the primary objective is change in the percentage of predicted FEV_1. Cystic Fibrosis Trust urges the appraisal to consider a wide range of outcomes related to these transformative treatments, particularly those outcomes that are most significant for people with cystic fibrosis. There are numerous examples of how these treatments have made a difference to people living with cystic fibrosis, and at present, the outcomes listed, and QALY calculations may not capture them all. The 2021 UK Cystic Fibrosis Registry's annual report found that overall health and outcomes are improving, including a rise in the median FEV_1, improved nutritional status, a reduction in the proportion of adults requiring oxygen and a reduction in those receiving at least one course of IV antibiotics, as well as the number of women with cystic fibrosis who had a baby almost doubling, from 56 in 2020 to 106 in 2021[6]. The potential reduction in the treatment burden for people with cystic fibrosis who are taking modulator therapies is an important outcome of these treatments. A six-week study by the Cystic Fibrosis Foundation found that individuals on Kaftrio aged 12 and older who stopped taking mucoactive nebulisers (either hypertonic saline or dornase alfa) did not experience a decline in their lung function[7]. Cystic Fibrosis Trust is funding a longer-term trial to understand if people receiving Kaftrio can safely start to reduce the number of treatments they have to manage as part of their daily healthcare routine[8]. Simplifying the treatment burden for people with cystic fibrosis has been identified as a top priority through a collaboration between the Trust, our community, and the James Lind Alliance.	Thank you for your comment. The scope has been updated to reflect this. The assessment group will choose the outcomes to be included, based on composite endpoints and the available data. The list of outcomes is not exhaustive. Additional outcomes can be included in the clinical and cost effectiveness evidence put forward during the appraisal.

Section	Consultee/ Commentator	Comments [sic]	Action
		The Trust is aware of the significant impact living with cystic fibrosis has, and it has been recognised that parents sometimes give up work in order to care for family members to manage the significant treatment burden. The condition also has a major impact on siblings due to the all-encompassing nature of cystic fibrosis. The Trust is aware that access to these treatments, or awareness of future access to these treatments, has a significant psychological impact on growing up with cystic fibrosis. As exacerbations reduce and the disease progression slows, there are new opportunities related to education, careers, and employment as a result of increased physical health and wellbeing. The transformative nature of these treatments has been acknowledged at the highest level of NHS England at their board meeting on 1st December 2022[9] and we encourage this appraisal to recognise the significance of the improved outcomes for people with cystic fibrosis. [6] UK Cystic Fibrosis Registry Annual Data Report 2021, https://www.cysticfibrosis.org.uk/the-work-we-do/uk-cf-registry/reporting-and-resources [7] Cystic Fibrosis Foundation, Simplify Study Indicates Potential to Reduce Medication Burden for People With CF Taking Trikafta, https://www.cff.org/news/2022-11/simplify-study-indicates-potential-reduce-medication-burden-people-cf-taking-trikafta [8]Cystic Fibrosis Trust, A storm is coming!, https://www.cysticfibrosis.org.uk/news/a-storm-is-coming [9] NHS England, Public board meeting – agenda and papers – 1 December 2022, Item 8 – Medicines Access and uptake – transforming patient outcomes, https://www.england.nhs.uk/publication/nhs-england-public-board-meeting-agenda-and-papers-1-december-2022/	

Section	Consultee/ Commentator	Comments [sic]	Action
	Genetic Alliance UK	It is important to consider the impact the condition has on the wider family, not just affected individuals. Parents of affected children may have to give up work to be able to care for their child and take them to various appointments. It is also important to consider outcomes that people living with cystic fibrosis would prioritise as being more impactful to their quality of life. For example: the frequency of receiving IV antibiotics that may require a hospital visit and therefore time away from work or education; assessing whether individuals are able to reduce the number of medicines they take as part of their daily routine; the number of affected women who are able to have a baby as a result of receiving treatment. It is important to note that having multiple treatment options available allows patients to choose the best treatment option for them and therefore improves patient outcomes.	Thank you for your comment. Carer disutilities will be considered as per the 2022 NICE health technology evaluations: the manual, if there is evidence to support this. The assessment group will choose the outcomes to be included, based on composite endpoints and the available data. The list of outcomes is not exhaustive. Additional outcomes can be included in the clinical and cost effectiveness evidence put forward during the appraisal.
	NHS England	Body mass index is not appropriate for younger children – weight percentiles Lung function – should be specific – FEV1 is listed separately, suggest stick to this and add FVC as both are collected routinely If mortality is collected as an outcome then lung transplantation should be too	Thank you for your comment. The scope has been updated to reflect this. The list of

Section	Consultee/ Commentator	Comments [sic]	Action
			outcomes is not exhaustive. Additional outcomes can be included in the clinical and cost effectiveness evidence put forward during the appraisal.
	Vertex Pharmaceuticals	We propose adding the following important outcomes in CF: • Lung transplants • Sweat chloride (SwCl) • Lung clearance index 2.5 (LCI 2.5) Given that PEx are acute infections, including acute infections as a separate outcome is duplicative; we therefore propose removing acute infections. We also request NICE removes exercise tolerance as this is not a relevant outcome for cystic fibrosis	Thank you for your comment. The scope has been updated to reflect this. The list of outcomes is not exhaustive. Additional outcomes can be included in the clinical and cost effectiveness evidence put forward during the appraisal.
	British Thoracic Society	Ideally it would be useful to look at additional measures if possible such as : Time gained back in education/ employment for people with CF and their carers Body composition Diabetic control Numbers of transplant and those being removed from transplant lists Energy/fatigue Aware that quality of life data and sweat chloride levels would be sueful Sinus and bowel symptoms	Thank you for your comment. The scope has been updated to reflect this. The list of outcomes is not exhaustive. Additional outcomes can be included in the clinical and cost effectiveness

Section	Consultee/ Commentator	Comments [sic]	Action
		Pregnancies- number and outcome	evidence put forward during the appraisal.
	UK CF Medical Association	QoL should be higher in the hierarchy of outcomes, both generic and disease specific. Another important patient facing outcome is treatment burden and the review should report changes in this outcome if available. Pulmonary exacerbations are important but challenging to measure reliably, need more detail on this outcome (PEx clearly defined). Frequency and severity of pulmonary infections is challenging to measure and a better proxy outcome is need for extra antibiotics (oral, nebulised or IV). Hospitalisation is an important outcome, but “other treatments” is unclear; is this extra antibiotics? Forced Expiratory Volume in one second (FEV1) is the best characterised surrogate outcome in the field of CF and one that is relevant to people with CF. Changes should be recorded as both absolute and relative. Other respiratory function measures are less informative although there is emerging confidence with respect to LCI measurement in younger patients. Adverse effects need to be reported openly and comprehensively.	Thank you for your comment. The list of outcomes include in the scope are in no particular order and will all be considered. Thank you for your comment. The scope has been updated to reflect this. The list of outcomes is not exhaustive. Additional outcomes can be included in the clinical and cost effectiveness evidence put forward during the appraisal.

Section	Consultee/ Commentator	Comments [sic]	Action
Equality	Cystic Fibrosis Trust	As above, at present the draft scope and remit does not acknowledge the comprehensive nature of the interim access agreement, particularly for those people accessing modulator therapies under licensing decisions by the U.S FDA. Without inclusion in this appraisal, the recommendations could lead to a different impact for this community and make it more difficult for this specific group to access the technologies in practice. Access may be dependent on via individual funding requests (IFRs) which could lead to variation across the UK and could cause adverse effects if this community of people with cystic fibrosis cannot access these transformative treatments.	Thank you for your comment. The scope has been updated to reflect this. Unless the Department of Health and Social Care indicates otherwise, NICE will not develop guidance on a technology for indications that have not been given regulatory approval in the UK (that is, for unlicensed or 'off-label' use).
	NHS England	We do not believe that the draft remit and scope need changing to meet these aims. It should be noted that people without a F508 del mutation make up a higher-proportion of the non-white population with CF.	Thank you for your comment. No action needed. Issues related to differences in prevalence or incidence of a disease cannot be addressed in a technology appraisal.
	Vertex Pharmaceuticals	Whilst we do not see any equality considerations, an appraisal approach of subgrouping the population may raise equality concerns.	Thank you for your comment. No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
	British Thoracic Society	See above on ethic minorities and also those digitally or geographically disadvantaged	Thank you for your comment. No action needed.
	UK CF Medical Association	The incidence of F508del varies between different populations, being most high in Northern European countries. By restricting this HTA to people with one or two F508del, there is a risk of discriminating against ethnic groups with lower frequency of this variant. Although CF is less common in populations from outside of Northern Europe, including all variants that are eligible for variant specific therapy may reduce discrimination.	Thank you for your comment. NICE develops guidance on a technology for indications that have been given regulatory approval in the UK. The UK Marketing Authorisation for ivacaftor–tezacaftor–elexacaftor, tezacaftor–ivacaftor and lumacaftor–ivacafor include the *F508del* mutation. Issues related to differences in prevalence or incidence of a disease cannot be addressed in a technology appraisal.

Section	Consultee/ Commentator	Comments [sic]	Action
Other considerations	CF Voices	Carers are significantly impacted by a loved-one having CF and the impact on them of a patient's treatment with CFTR both physically and mentally must be considered, if not as a measurable outcome that will be captured in the QALY – by the Committee in evidence. Emotional and financial impacts are also considerable, while admittedly less measurable, and the overall impact should be considered from studies such as the Vertex QoL study, any relevant CF Trust studies and CF Voices 'Quality of life and mental health in carers of patients with cystic fibrosis in the UK: study using validated questionnaires and interviews', which will be submitted at appraisal. EQ-5D being used to measure carer QOL impacts is disappointing, given that alternative measures specifically designed to measure carer QOL have been developed and we argue are more responsive. However, as NICE's work to improve measuring carer impact was not completed in the recent review and is ongoing, EQ-5D remains the tool recommended and as such we fear it likely that carers impacts are going to be underrepresented.	Thank you for your comment. Carer disutilities will be considered as per the 2022 NICE health technology evaluations: the manual, if there is evidence to support this.
	NHS England	In terms of the QALY calculation the increase in pregnancies and increased ability to gain/continue employment should be taken in to account in terms of quality of life improvement. A decreased risk of diabetes and for those who have diabetes improved diabetic control (HbA1C) could also be assessed. For exocrine pancreatic sufficient patients risk of acute pancreatitis may be lower with kaftrio. The need for escalation of other high cost therapies e.g. new start of nebulised antibiotics or mucolytics, could also be assessed.	Thank you for your comment. Any clinical benefit not captured in QALY calculations will be considered qualitatively by the committee.
	Vertex Pharmaceuticals	None.	Thank you for your comment. No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
	UK CF Medical Association	It is important, given the stage of this exercise, that the panel consider evidence from real world studies, especially high quality registry trials.	Thank you for your comment. No action needed.
Questions for consultation	CF Voices	Q1: These 3 CFTR modulators are the now the core, central treatment pathway for treating cystic fibrosis – the first drugs to slow the progression of the disease, rather than treat symptoms, for the vast majority of patients. Benefits are going to bef substantially greater for those starting treatment at a young age now and in the future who will not require an NHS care pathway in the same manner or timelines as their predecessors have and continue to do. CFTR modulators will continue to mould a changing care pathway both for adults now living longer with more illness associated with older age and the children of today and the future. Q3: The wider social impacts over time of the CF population being able to live longer, healthier, economically productive and independent lives may not be captured in QALY's but is the really fundamental importance of CFTR modulators. As the true extent of these benefits are wider than the NICE remit in many ways and will only be seen in future years, the access scheme data will not fully display the benefits. On the other hand, shielding due to Covid may inflate short term benefits somewhat. There is no data source that can be used to take account of these factors.	Thank you for your comment. No action needed.
	Vertex Pharmaceuticals	Where do you consider these technologies will fit into the existing care pathway for treating cystic fibrosis? • The technologies are being used as an add-on to BSC as described in the recent update to the ECFS guidelines (Southern et al., 2022), and as such as soon as patients are eligible, they are treated with	Thank you for your comment. No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
		IVA/TEZ/ELX, while LUM/IVA and TEZ/IVA are only used for a small number of patients in whom triple therapy is not indicated or tolerated. • What is established clinical management for cystic fibrosis in the NHS? • IVA/TEZ/ELX is established clinical management for all patients aged 6 years and above with an F/any genotype • LUM/IVA is established clinical management for patients with F/F genotypes aged 2-5 years • Otherwise, BSC constitutes SoC Do you consider that the use of these technologies could result in any potential substantial health- related benefits that are unlikely to be included in the QALY calculation? • Day-to-day care of people with CF imposes a considerable burden on their caregivers and families. Multiple studies have demonstrated that caregiving for people with CF has a substantial impact on caregiver QoL, particularly for caregivers of paediatric patients and during pulmonary exacerbation (PEx) episodes. CFTR modulators have been shown to provide broad societal and humanistic benefits by reducing the life-limiting impact of CF on patients, as well as improving caregiver quality of life. As a result, the QALY should also include a treatment-specific caregiver utility. References: Suthoff E, Mainz JG, Cox DW, Thorat T, Grossoehme DH, Fridman M, et al. Caregiver burden due to pulmonary exacerbations in patients with cystic fibrosis. The Journal of Pediatrics. 2019;215:164-71 Sawicki GS, Sellers DE, Robinson WM. High treatment burden in adults with cystic fibrosis: challenges to disease self-management. Journal of cystic fibrosis. 2009;8(2):91-6.	Thank you for your comment. No action needed. Thank you for your comment. Carer disutilities will be considered as per the 2022 NICE health technology evaluations: the manual, if there is evidence to support this.

Section	Consultee/ Commentator	Comments [sic]	Action
		Daly C, Ruane P, O'Reilly K, Longworth L, Vega-Hernandez G. Caregiver burden in cystic fibrosis: a systematic literature review. Therapeutic advances in respiratory disease. 2022;16:17534666221086416.	
Additional comments on the draft scope	Cystic Fibrosis Trust	Cystic Fibrosis Trust would like to emphasise the unique nature of this appraisal. Typical appraisals centre on whether a treatment should be used in the NHS. The treatments within this MTA have been available to people with cystic fibrosis via the interim access agreement since 2019, and therefore this appraisal is about continuing access. People with cystic fibrosis are experts in their condition and reiterate the importance of understanding the transformative nature these treatments have had for our community.	Thank you for your comment. No action needed.
	NHS England	NHS England notes that the proposed scope does not include the approximately 120 patients with non-licensed mutations who are currently eligible for E/T/I under the interim NHS England commissioning position. There are also a number of patients who are currently eligible for T/I (around 30 patients) who are also out of scope for this appraisal.	Thank you for your comment. The scope has been updated to reflect this. Unless the Department of Health and Social Care indicates otherwise, NICE will not develop guidance on a technology for indications that have not been given regulatory approval in the UK (that is, for unlicensed or 'off-label' use).

Section	Consultee/ Commentator	Comments [sic]	Action
[a] At the second committee meeting to discuss ivacaftor–tezacaftor–elexacaftor, tezacaftor–ivacaftor and lumacaftor–ivacaftor for treating cystic fibrosis, the committee concluded that ivacaftor should be included as a comparator in the F/Gating population because people with a gating mutation may be eligible for IVA if they also have an F508del mutation			

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

None