GIG CYMRU NHS WALES

Pwyllgor Gwasanaethau Iechyd Arbenigol Cymru (PGIAC)

Welsh Health Specialised Services Committee (WHSSC)

Specialised Services Policy Position PP198

Cystic Fibrosis Modulator Therapies

January 2021

Version 2.0

Document information	
Document purpose	Policy Position
Document name	Cystic Fibrosis Modulator Therapies
Author	Welsh Health Specialised Services Committee
Publication date	January 2021
Commissioning Team	Cardiac
Target audience	Chief Executives, Medical Directors, Directors of Finance, Directors of Planning, Medicine Management, Cystic Fibrosis Centre Manager, CF consultants.
Description	NHS Wales routinely commission this specialised service in accordance with the criteria described in this policy
Document No	PP198

Contents

Policy Statement

Welsh Health Specialised Services Committee (WHSSC) commission Cystic Fibrosis Modulator Therapies for people with Cystic Fibrosis in accordance with the criteria outlined in this document.

In creating this document WHSSC has reviewed the relevant guidance issued by NHS England and National Institute of Health and Care Excellence (NICE) and has concluded that Modulator Therapies should be made available.

Disclaimer

WHSSC assumes that healthcare professionals will use their clinical judgment, knowledge and expertise when deciding whether it is appropriate to apply this policy position statement.

This policy may not be clinically appropriate for use in all situations and does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

WHSSC disclaims any responsibility for damages arising out of the use or non-use of this policy position statement.

1. Introduction

This Policy Position Statement has been developed for the planning and delivery of Cystic Fibrosis Modulator Therapies for people resident in Wales. These therapies will only be commissioned by the Welsh Health Specialised Services Committee (WHSSC) and apply to residents of all seven Health Boards in Wales.

1.1 Plain language summary

Cystic fibrosis (CF) is an inherited, multi-system, genetic condition that causes a build-up of sticky mucus in the lungs, digestive system and other organs. People with CF can experience a range of symptoms throughout the body. In the lungs, the build-up of mucus can cause chronic infections, and in the digestive system excess mucus can cause a difficulty in digesting food. Cystic Fibrosis can have a significant impact on life expectancy and quality of life[1].

Cystic fibrosis is caused by variants in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that result in the absence or dysfunction of the CFTR protein, a cell-surface localised chloride channel that regulates salt and water absorption and secretion across epithelia in multiple organs. This dysregulation of salt and water transport across the cells leads to the accumulation of thick, sticky mucus in the airways of the lungs, loss of pancreatic function, impaired intestinal absorption, reproductive dysfunction and elevated sweat chloride concentration (Van Goor et al. 2014)[2]. The leading cause of mortality in people with cystic fibrosis is respiratory failure.

Many different gene variants are responsible for cystic fibrosis. The commonest variant is F508del, and approximately 50% of people with CF have two F508del genes (homozygous) and 40% have one F508del gene and another CF gene (heterozygous). Disease severity generally correlates with the severity of the loss of chloride transport. Complete, or near complete loss of CFTR-mediated chloride transport is referred to as 'minimal function' of CFTR protein and results in severe cystic fibrosis.

1.2 Aims and Objectives

This Policy Position Statement aims to define the commissioning position of WHSSC on the use of Modulator Therapies for people with Cystic Fibrosis.

The objectives of this policy are to:

- ensure commissioning for the use of Cystic Fibrosis Modulator Therapies is evidence based

[1] Overview | Cystic fibrosis: diagnosis and management | Guidance | NICE
[2] https://www.sciencedirect.com/science/article/pii/S1569199313001136

- ensure equitable access to Cystic Fibrosis Modulator Therapies
- define criteria for people with Cystic Fibrosis to access treatment
- improve outcomes for people with Cystic Fibrosis

1.3 The Treatments

Cystic fibrosis transmembrane conductance regulator (CFTR) modulator therapies are designed to correct the malfunctioning protein by the CFTR gene. Because different variants cause different defects in the protein, the medications that have been developed so far are effective only in people with specific gene variants.

The CFTR protein regulates the proper flow of water and salt in and out of cells lining the lungs and other organs. In people with CF, variants in the CFTR gene result in either a defective protein being produced or no protein at all. This leads to the buildup of thick, sticky mucus, which can lead to infections in the lungs and damage to the pancreas. It can also lead to problems in other parts of the body.

There are four modulator therapies with market authorisation that act on the CFTR pathways and ameliorate the impact of specific defective genes that result in the absence or dysfunction of the CFTR protein, a cell-surface localised chloride channel that regulates salt and water absorption and secretion across epithelia in multiple organs.

- **Ivacaftor (Kalydeco®)**
  Ivacaftor is a CFTR potentiator, meaning it increases the activity of the defective CFTR protein. This means that ivacaftor increases the chances that the defective channel will open on the cell surface and let chloride and sodium ions pass through.

- **Lumacaftor/Ivacaftor (Orkambi®)**
  Lumacaftor/Ivacaftor is a systemic protein modulator. Lumacaftor is a corrector of the CFTR working in combination with ivacaftor as a potentiator of the CFTR.

- **Ivacaftor/Tezacaftor (Symkevi®)**
  Ivacaftor/Tezacaftor (used in combination with Ivacaftor). Tezacaftor is a corrector designed to move the defective CFTR protein to the correct position in the cell.

- **Elexacaftor/tezacaftor/ivacaftor (Kaftrio®)**
  Elexacaftor/tezacaftor/ivacaftor (used in combination with ivacaftor) is designed to act as a potentiator and a corrector.

This Policy Position Statement also includes:

- the off label use of ivacaftor in patients without a class III gating variant
- an expanded range of variants for which treatment with tezacaftor/ivacaftor for CF patients is available off label
- access to the triple therapy elexacaftor/tezacaftor/ivacaftor according to the European Marketing Authorisation (and other revisions to the market authorisations for these products) and,
- off label use of elexacaftor/tezacaftor/ivacaftor in those heterozygous for F508del and a non-minimal function variant.

1.4 What NHS Wales has decided

We have concluded that there is enough evidence to recommend the use of Modulator Therapies for people with Cystic Fibrosis, within the criteria set out in section 2.

2. Criteria for Commissioning

The Welsh Health Specialised Services Committee approve funding of Cystic Fibrosis Modulator Therapies with Cystic Fibrosis, in-line with the criteria identified in the policy.

2.1 Inclusion Criteria

The CF variants which are eligible for treatment are listed in tables 1 -4.

Patients may receive ivacaftor if they are heterozygous for a class III gating variant.

<table>
<tr><th colspan="4">Table 1: Ivacaftor as a monotherapy for patients aged 6 months and over</th></tr>
<tr><td colspan="4">In adults, adolescents, and children aged 6 years and older and weighing 25 kg or more. The recommended dose is one 150 mg tablet taken orally every 12 hours (300 mg total daily dose) with fat-containing food.</td></tr>
<tr><td colspan="4">Infants aged at least 6 months, toddlers, children, adolescents and adults should be dosed according to the patients weight but weighing 5 kg to less than 25 kg ≥5 kg to < 7 kg: 25 mg granules taken orally every 12 hours with fat-containing food ≥ 7 kg to < 14 kg: 50 mg granules taken orally every 12 hours with fat-containing food ≥ 14 kg to < 25 kg: 75 mg granules taken orally every 12 hours with fat-containing food ≥ 25 kg: See ivacaftor tablets SmPC for further details.</td></tr>
<tr><td rowspan="3">Heterozygous for the class III “gating” variants or R117H</td><td>G551D
S549R
S1251N</td><td>G178R
G551S
S1255P</td><td>S549N
G1244E
G1349D</td></tr>
<tr><td rowspan="2">Off label if heterozygous for one of the variants</td><td>E56K
P67L
D110H
R117C
E193K
R347H</td><td>L206W
R352Q
A455E
711+3A->G
E831X
S945L</td><td>K1060T
A1067T
2789+5G>A
3272-26A>G
3849+10kbC>T</td></tr>
<tr><td rowspan="2">Off label for variants of variable clinical consequence</td><td>R74W
D110E
D579G
S977F</td><td>F1052V
G1069R
R1070Q
R1070W</td><td>F1074L
D1152H
D1270N</td></tr>
<tr><td colspan="3">R117H but excluding CFSPID</td></tr>
<tr><td colspan="4">Off Label Use
Patients with a sweat chloride concentration >60mmol/L <u>without a class III variant but with a variant listed in table 1 (including variants of variable clinical consequence)</u> may receive ivacaftor off label with the same conditions and cautions as when used in those with a class III variant.</td></tr>
</table>

Table 2 Lumacaftor/ivacaftor as a combination therapy: for patients aged 2 years and over	
12 years and older Two lumacaftor 200 mg/ivacaftor 125 mg tablets every 12 hours	
6 to 11 years Two lumacaftor 100 mg/ivacaftor 125 mg tablets every 12 hours	
2 to 5 years and weighing less than 14 kg One lumacaftor 100 mg/ivacaftor 125 mg sachet every 12 hours 2 to 5 years and weighing 14 kg or greater One lumacaftor 150 mg/ivacaftor 188 mg sachet every 12 hours	
Named Variants	Homozygous for the F508del variant

Table 3 Tezacaftor/ivacaftor as a combination therapy

In adults, adolescents and children aged 6 years and older

The recommended dose is:

Age	**Morning (1 tablet)**	**Evening (1 tablet)**
6 to < 12 years weighing < 30 kg	tezacaftor 50 mg/ivacaftor 75 mg	ivacaftor 75 mg
6 to < 12 years weighing ≥ 30 kg	tezacaftor 100 mg/ivacaftor 150 mg	ivacaftor 150 mg
≥ 12 years	tezacaftor 100 mg/ivacaftor 150 mg	ivacaftor 150 mg

The morning and evening dose should be taken approximately 12 hours apart with fat-containing food (see Method of administration).

Named Variants	Homozygous for the F508del variant		
	Heterozygous for the F508del variant combined with one of the following variants:		
License includes anyone with one of these variants with F508del, but can be used off license if heterozygous without F508del	P67L	R117C	L206W
	R352Q S945L D1152H 3849+10kbC→T	A455E S977F 2789+5G→A	D579G R1070W 3272-26A→G
Off label heterozygous for one of these variants	E56K P67L D110H R117C E193K R347H	L206W R352Q A455E 711+3A->G E831X S945L	K1060T A1067T 2789+5G>A 3272-26A>G 3849+10kbC>T
Off label use for variants of variable clinical consequence	R74W D110E D579G	S977F F1052V R1070W	F1074L D1152H D1270N

Off label use
Patients with a sweat chloride concentration >60mmol/L without F508del but with a variant listed in table 3 (including variants of variable clinical consequence) may receive ivacaftor/tezacaftor off label with the same conditions and cautions as when used in those with an F508del gene.

Table 4 Elexacaftor/tezacaftor/ivacaftor as a combination therapy	
Adults and adolescents aged 12 years and older The recommended dose is two tablets (each containing elexacaftor 100 mg, tezacaftor 50 mg and ivacaftor 75 mg) taken in the morning and one ivacaftor tablet (containing ivacaftor 150 mg) taken in the evening, approximately 12 hours apart. It is for oral use and the tablet should be swallowed whole. It should be taken with fat-containing food.	
Named Variants	Homozygous for the F508del variant
	Heterozygous for the F508del variant combined with a minimal function variant (as defined in Annex ii)

Marketing Authorisations/Summary of Product Characteristics

The marketing authorisations for each product cover side effects, contra-indications, drug interactions, and the need to consider variation in dosing when Ivacaftor is given in combination with other products as well as age (and weight) specific dosing.

Summaries of Product Characteristics (SmPCS) are available from The Electronic Medicines Compendium (emc) for the following:

- Ivacaftor (Kalydeco®)
- Ivacaftor/lumacaftor (Orkambi®)
- Ivacaftor/tezacaftor (Symkevi®): Used in combination with ivacaftor
- Elexacaftor/tezacaftor/ivacaftor (Kaftrio®): tablets used in combination with ivacaftor.

Off label use

For those heterozygous for F508del with a sweat chloride concentration >60mmol/L but without a minimal function variant (as defined in Annex ii), elexacaftor/tezacaftor/ivacaftor can be used off label with the same conditions and cautions as when used in those heterozygous for F508del and a minimal function variant.

Governance arrangements

For the off label use of elexacaftor/tezacaftor/ivacaftor any provider organisation treating patients with this intervention will be required to assure itself that the internal governance arrangements have been completed before the medicine is prescribed. These arrangements may be through the Hospitals Drugs and Therapeutics Committee (or similar) and NHS Wales may ask for assurance of this process.

The risks and benefits of the off-label use of elexacaftor/tezacaftor/ivacaftor should be clearly stated and discussed with the patient to allow informed consent. Providers should consult the General Medical Council Guidelines on prescribing unlicensed medicines before any off-label medicines are prescribed.

Prescribing

Ivacaftor, Lumacaftor/Ivacaftor and Tezacaftor/Ivacaftor and Elexacaftor/tezacaftor/ivacaftor should only be prescribed by physicians in Specialist Paediatric or Adult CF Centres, within NHS Wales and NHS England commissioned CF services and in line with the respective market authorisations above.

If the patient's genotype is unknown, an accurate and validated genotyping method should be performed before starting treatment to confirm the presence of an indicated variant in the CFTR gene. CF clinical teams will need to review existing patients prior to changing or initiating new medications.

2.2 Continuation of Treatment

Healthcare professionals are expected to review a patient's health at regular intervals to ensure they are demonstrating an improvement to their health due to the treatment being given.

If no improvement to a patient's health has been recorded, then clinical judgement on the continuation of treatment must be made by the treating healthcare professional.

2.3 Acceptance Criteria

The service outlined in this specification is for patients ordinarily resident in Wales, or otherwise the commissioning responsibility of the NHS in Wales. This excludes patients who whilst resident in Wales, are registered with a GP practice in England, but includes patients resident in England who are registered with a GP Practice in Wales.

2.4 Exceptions

If the patient does not meet the criteria for treatment as outlined in this policy, an Individual Patient Funding Request (IPFR) can be submitted for consideration in line with the All Wales Policy: Making Decisions on Individual Patient Funding Requests. The request will then be considered by the All Wales IPFR Panel.

If the patient wishes to be referred to a provider outside of the agreed pathway, and IPFR should be submitted.

Further information on making IPFR requests can be found at: Welsh Health Specialised Services Committee (WHSSC) | Individual Patient Funding Requests

2.5 Clinical Outcome and Quality Measures

The Provider must work to written quality standards and provide monitoring information to the lead commissioner and the CF Registry.

All providers must submit the minimum dataset data to the UK CF Registry within the required timescales. There is an expectation that data from all of Welsh CF patients will be entered onto the CF registry, but where it is not possible to obtain consent for registration and data entry the reasons should be documented for future audit.

Data collection as part of the access agreement (see Annex iii) will be used by NICE to inform further evaluation of Lumacaftor/Ivacaftor and to support a clinical and cost effectiveness evaluation of Tezacaftor/Ivacaftor.

NICE will extend data collection to support a clinical and cost effectiveness evaluation of elexacaftor/tezacaftor/ivacaftor.

The centre must enable the patient's, carer's and advocate's informed participation and to be able to demonstrate this. Provision should be made for patients with communication difficulties and for children, teenagers and young adults.

2.6 Responsibilities

Referrers should:

- inform the patient that this treatment is not routinely funded outside the criteria in this policy, and
- refer via the agreed pathway.

Clinician considering treatment should:

- discuss all the alternative treatment with the patient
- advise the patient of any side effects and risks of the potential treatment
- inform the patient that treatment is not routinely funded outside of the criteria in the policy, and
- confirm that there is contractual agreement with WHSSC for the treatment.

In all other circumstances an IPFR must be submitted.

3. Documents which have informed this policy

The following documents have been used to inform this policy:

- **National Institute of Health and Care Excellence (NICE) guidance**
  - Cystic fibrosis: diagnosis and management, NICE Guideline NG78, October 2017.
  - Lumacaftor–ivacaftor for treating cystic fibrosis homozygous for the F508del mutation, NICE TA398, July 2016

- **NHS England policies**
  - https://www.england.nhs.uk/wp-content/uploads/2020/08/Policy-statement-CFTR-Modulator-Therapies-Licensed-mutations-DHUP-04-09-2020.pdf, NHS England August 2020.

- **All Wales Medicines Steering Group (AWMSG)**
  - Ivacaftor (Kalydeco®)
  - Tezacaftor/ivacaftor (Symkevi®)
  - Lumacaftor/ivacaftor (Orkambi®).

This document should be read in conjunction with the following documents:

- **NHS Wales**
  - All Wales Policy: Making Decisions in Individual Patient Funding requests (IPFR).

4. Date of Review

This policy statement will be reviewed after NICE has completed the evaluation for Lumacaftor/Ivacaftor, Ivacaftor/Tezacaftor and elexacaftor/tezacaftor/ivacaftor.

5. Putting Things Right

5.1 Raising a Concern

Whilst every effort has been made to ensure that decisions made under this policy are robust and appropriate for the patient group, it is acknowledged that there may be occasions when the patient or their representative are not happy with decisions made or the treatment provided.

The patient or their representative should be guided by the clinician, or the member of NHS staff with whom the concern is raised, to the appropriate arrangements for management of their concern.

If a patient or their representative is unhappy with the care provided during the treatment or the clinical decision to withdraw treatment provided under this policy, the patient and/or their representative should be guided to the LHB for NHS Putting Things Right. For services provided outside NHS Wales the patient or their representative should be guided to the NHS Trust Concerns Procedure, with a copy of the concern being sent to WHSSC.

5.2 Individual Patient Funding Request (IPFR)

If the patient does not meet the criteria for treatment as outlined in this policy, an Individual Patient Funding Request (IPFR) can be submitted for consideration in line with the All Wales Policy: Making Decisions on Individual Patient Funding Requests. The request will then be considered by the All Wales IPFR Panel.

If an IPFR is declined by the Panel, a patient and/or their NHS clinician has the right to request information about how the decision was reached. If the patient and their NHS clinician feel the process has not been followed in accordance with this policy, arrangements can be made for an independent review of the process to be undertaken by the patient's Local Health Board. The ground for the review, which are detailed in the All Wales Policy: Making Decisions on Individual Patient Funding Requests (IPFR), must be clearly stated

If the patient wishes to be referred to a provider outside of the agreed pathway, an IPFR should be submitted.

Further information on making IPFR requests can be found at: Welsh Health Specialised Services Committee (WHSSC) | Individual Patient Funding Requests

6. Equality Impact and Assessment

The Equality Impact Assessment (EQIA) process has been developed to help promote fair and equal treatment in the delivery of health services. It aims to enable Welsh Health Specialised Services Committee to identify and eliminate detrimental treatment caused by the adverse impact of health service policies upon groups and individuals for reasons of race, gender re-assignment, disability, sex, sexual orientation, age, religion and belief, marriage and civil partnership, pregnancy and maternity and language (Welsh).

This policy has been subjected to an Equality Impact Assessment.

The Assessment demonstrates the policy is robust and there is no potential for discrimination or adverse impact. All opportunities to promote equality have been taken.

Annex i Abbreviations and Glossary

Abbreviations

IPFR Individual Patient Funding Request

WHSSC Welsh Health Specialised Services

CF Cystic Fibrosis

CFTR Cystic Fibrosis Transmembrane Conductance Regulator

Glossary

Individual Patient Funding Request (IPFR)

An IPFR is a request to Welsh Health Specialised Services Committee (WHSSC) to fund an intervention, device or treatment for patients that fall outside the range of services and treatments routinely provided across Wales.

Welsh Health Specialised Services Committee (WHSSC)

WHSSC is a joint committee of the seven local health boards in Wales. The purpose of WHSSC is to ensure that the population of Wales has fair and equitable access to the full range of Specialised Services and Tertiary Services. WHSSC ensures that specialised services are commissioned from providers that have the appropriate experience and expertise. They ensure that these providers are able to provide a robust, high quality and sustainable services, which are safe for patients and are cost effective for NHS Wales.

Annex ii CFTR Minimal Function Variants

Nonsense Variants				
Q2X	L218X	Q525X	R792X	E1104X
S4X	Q220X	G542X	W882X	W1145X
W19X	Y275X	G550X	W882X	R1158X
G27X	C276X	Q552X	W846X	R1162X
Q39X	Q290X	R553X	Y849X	S1196X
W57X	G330X	E585X	R851X	W1204X
E60X	W401X	G673X	Q890X	L1254X
R75X	Q414X	Q685X	S912X	S1255X
L88X	S434X	R709X	Y913X	W1282X
E92X	S466X	K710X	Q1042X	Q1313X
Q98X	S489X	Q715X	W1089X	Q1330X
Y122X	Q493X	L732X	Y1092X	E1371X
E193X	W496X	R764X	W1098X	Q1382X
W216X	C524X	R785X	R1102X	Q1411X
Canonical splice variants				
185+1G>T	711+5G>A	1717-8G>A	2622+1G>A	3121-1G>A
296+1G>A	712-1G>T	1717-1G>A	2790-1G>C	3500-2A>G
296+1G>T	1248+1G>T	1811+1G>C	3040G>C	3600+2insT
405+1G>A	1249-1G>A	1811+1.6kbA>G	(G970R)	3850-1G>A
405+3A>C	1341+1G>A	1811+1643G>T	3120G>A	4005+1G>A
406-1G>A	1525-2A>G	1812-1G>A	3120+1G>A	4374+1G>T
621+1G>T	1525-1G>A	1898+1G>A	3121-2A>G	
711+1G>T		1898+1G>C		
Small insertion/deletion (ins/del) frameshift variants				
182delT	1078delT	1677delTA	2711delT	3737delA
306insA	1119delA	1782delA	2732insA	3791delC
306delTAGA	1138insG	824delA	2869insG	3821delT
365-366insT	1154insTC	1833delT	2896insAG	3876delA
394delTT	1161delC	2043delG	2942insT	3878delG
442delA	1213delT	2143delT	2957delT	3905insT
444delA	1259insA	2183AA>G	3007delG	4016insT
457TAT>G	1288insTA	2184delA	028delA	4021dupT
541delC	1343delG	2184insA	3171delC	4022insT
574delA	1471delA	2307insA	3171insC	4040delA

663delT	1497delGG	2347del	3271delGG	4279insA
849delG	1548delG	2585delT	3349insT	4326delTC
935delA	1609del C	2594delGT	3659delC	

Non-small (>3 nucleotide) insertion/deletion (ins/del) frameshift variants		
CFTRdele1	CFTRdele16-17b	1461ins4
CFTRdele2	CFTRdele17a,1	1924del7
CFTRdele2,3	CFTRdele17a-18	2055del9>A
CFTRdele2-4	CFTRdele1	2105-2117del13insAGAAA
CFTRdele3-10,14b-16	CFTRdele19-21	2372del8
CFTRdele4-7	CFTRdele21	2721del11
CFTRdele4-11	CFTRdele22-2	2991del32
CFTR50kbde	CFTRdele22,23	3121-977_3499+248del2515
CFTRdup6b-10	124del23bp	3667ins4
CFTRdele11	602del14	4010del4
CFTRdele13,14a	852del22	4209TGTT>AA
CFTRdele14b-17b	991del5	

Missense Variants			
A46D	V520F	Y569D	N1303K
G85E	A559T	L1065P	
R347P	R560T	R1066C	
L467P	R560S	L1077P	
I507del	A561E	M1101K	

Annex iii Data Collection Requirements

Assessment	Rationale	Recommended Frequency: Baseline/Pre treatment	Recommended Frequency: 3 Monthly	Recommended Frequency: 6 Monthly	Recommended Frequency: Annually	Data collection tool
Genotype (rarer mutation patients only)	**Baseline characteristics**	**Yes**	**No**	**No**	**No**	**CF Registry**
Poly-T status (R117H patients only. Patients are not required to have genetic retesting if genotyping has already been performed.)	Baseline characteristics	Yes	No	No	No	CF Registry
CFTR modulator start date	Baseline characteristics	Yes	No	No	No	CF Registry
ppFEV1 (Clinic/hospital home spirometry)	Assessment of lung function	Yes	Yes	No	No	CF Registry
BMI (for patients aged 18 years and over)	Assessment of non-respiratory symptoms	Yes	Yes	No	No	CF Registry

Height and weight (for patients aged 18 years and over)	Assessment of non-respiratory symptoms	Yes	Yes	No	No	CF Registry
Lung transplant events	Assessment of pulmonary exacerbation	No	No	Yes	No	CF Registry
Use of intravenous antibiotics - hospital and home	Proxy for assessment of pulmonary exacerbation	No	No	Yes	No	CF Registry
Microbiology	Assessment of treatment efficacy	No	No	Yes	No	CF Registry
IV and Non-IV hospital admissions	Proxy for assessment of hospital admissions	No	No	Yes	No	CF Registry
CF related diabetes status	Assessment of non-respiratory symptoms	No	No	Yes	No	CF Registry
Treatment discontinuation status and reasons for treatment discontinuation - all treatment not just CFTRm.	Assessment of treatment discontinuation rates	No	No	Yes	No	CF Registry

Mortality	Assessment of overall survival	No	No	Yes	No	CF Registry
Faecal elastase	Assessment of pancreatic insufficiency	No	No	No	Yes	CF Registry

Assessment	**Rationale**	**Recommended frequency**	**Data collection tool**
Quality of life (CFQR) (upload of domain scores/total score)	Assessment of patient quality of life	Collected prior to initiation of therapy and 6 monthly thereafter	UK CF Registry
Sweat chloride	Assessment of sweat chloride	Annually	UK CF Registry