Variables, Inclusion Criteria and References used by the ECFSPR (from follow-up year 2022)

Changes valid from 2022 are in pale blue

Demographics

CF centre code;
Centre Patient code (optional);
Year of follow-up;
Year and month of birth;
Sex (Previously "Gender") - Male, Female, Other/Prefer not to say;
Ethnicity;
Vital Status of patient;
Cause of death;
Date of death.

Diagnosis

Age at diagnosis;
Sweat test type and values (x2);
First & second mutations (possible to record complex variants in cis);
Meconium Ileus;
Neonatal screening;
Nasal Potential Difference Measured? (NPD);
CF-typical NPD measurement Yes/No;
Date of NPD measurement;
Intestinal current value measured? (ICM);
CF-typical IC measurement Yes/No;
Date of IC measurement.

Complications

Distal intestinal obstruction syndrome (DIOS) this year;
Salt loss syndrome this year;
Diabetes this year;
Pneumothorax this year;
Liver disease this year;
Haemoptysis major volume of expectorate > 250ml in a day;
Occurrence of malignancy - diagnosed this year;
Pancreatic status: faecal elastase;
Pancreatic status: faecal fat;
Pregnancy this year;
Pregnancy stopped this year - reason for stop;
Pregnancy ongoing at 31/12.

n.b.From 2022 we will no longer collect "Allergic broncho-pulmonary aspergillosis this year" but we will start to collect information about whether or not centres investigate for Fungi - see "Microbiology".

Maintenance Therapy

Inhaled continuous (≥ 3 months) hypertonic saline ≥3% ;
Inhaled continuous (≥ 3 months) Mannitol;
Inhaled antibiotic this year - continuous (≥ 3 months) or on/off for a total of (≥ 6months) ;
Inhaled continuous (≥ 3 months) bronchodilators, long-acting or short-acting or both;
Oxygen therapy ≥ 3 months during the year of follow-up (inc. 24h/day, night time, exercise). Does not need to be continuously but should be from a single prescription);
Use of continuous (≥ 3 months) non-invasive positive pressure ventilation (NIPPV);
Use of continuous (≥ 3 months) rhDNase this year;
Use of continuous (≥ 3 months) Inhaled steroids;
Use of continuous (≥ 3 months) Oral steroids;
Use of continuous (≥ 3 months) azithromycin (or other macrolide) this year;
Use of continuous (≥ 3 months) ursodeoxycholic acid this year;
Use of continuous (≥ 3 months) pancreatic enzymes this year;
Use of continuous (≥ 3 months) proton pump inhibitors (PPI);
Use of CFTR Modulator Therapy (data for each of the following are collected: Ivacaftor, Lumacaftor /Ivacaftor, Tezacaftor/Ivacaftor, Elexacaftor/Tezacaftor/Ivacaftor, Other CFTR modulator;
Start and stop dates x 2 for each CFTR modulator;
Sweat chloride values - before start and during (lowest of the year) for each CFTR modulator.

Lung function and nutrition follow-up

Value of FEV1 in litres of highest FEV1% predicted of the year;
Value of FVC in litres (from same spirometry as recorded FEV1);
Height measured at date of best FEV1 (or if no available FEV1, last height of the year);
Weight measured at date of best FEV1 (or if no available FEV1, last weight of the year);
Date of recorded FEV1 or if no FEV1 recorded, date of recorded height and weight);
Lowest LCI 2.5% of the year;
Type of device used for LCI measurement;
Date of lowest LCI 2.5% this year;
Value of lowest LCI 2.5% this year.

Microbiology (*positive-chronic* or *positive-at least once/not chronic* for all pathogens)

Pseudomonas aeruginosa;
MSSA (previously Staphlycoccus aureus, no specification);
MRSA;
Chronic Burkholderia cepacia complex;
Stenotrophomonas maltophilia;
Achromobacter spp;
Haemophilus influenza;
Nontuberculous mycobacteria cultured;
Mycobacterium abscessus complex;
Mycobacterium avium complex;
Other mycobacteria;
NTMB treated this year;
Fungi investigated;
Aspergillus fumigatus;
Scedosporium spp.

Hospitalisation, Pulmonary Exacerbations, IV Antibiotics

Total days on iv antibiotics at home and in hospital this year (CF-related reasons);

Total days on iv antibiotics in hospital this year (CF-related reasons);
Total days in hospital this year (any reason);

Number of PExs treated with intravenous antibiotics during the year.

Transplant

Liver transplant at any time;
Year of latest liver transplant (before or during this year);
Lung transplant at any time;
Year of latest lung transplant (before or during this year);
Kidney transplant at any time;
Year of latest lung transplant (before or during this year);
Other transplant at any time;
Year of latest other transplant (before or during this year).

End

Criteria and References used by the ECFS Patient Registry

1 Diagnosis / Reversal of Diagnosis: Criteria, References

i. Two sweat tests value > 59 mmol/L chloride: CF diagnosis accepted.

ii. One sweat test value > 59 mmol/L chloride + DNA Analysis/Genotyping – two identified disease-causing CF mutations in trans: CF diagnosis accepted.

iii. If the sweat value is less than or equal to 60 mmol/L chloride, or not reported, then at least 2 of the following must be fulfilled:

a. DNA Analysis/Genotyping: two identified disease-causing CF mutations in trans;
b. NPD (Transepithelial (Nasal) Potential Difference) or ICM (Intestinal current measurement): result consistent with a diagnosis of CF;
c. Clinical presentation: typical features of CF.

iv. **Diagnosis reversal***
CF diagnosis should be reversed if any of the following cases are true:

a. DNA Analysis: unable to identify any disease causing CF mutations;
b. NPD (nasal potential difference) &/or ICM (intestinal current measurement): result not consistent with diagnosis of CF;
c. Normal values from repeated sweat testing (confirm with the clinical team).

** See also ECFSPR SOP - Standard Operating Procedure - regarding reversal of diagnosis and previously submitted data (find it on the homepage of the data collection software ECFSTracker, together with other useful information).*

References (links)

1) ECFS best practice guidelines: the 2018 revision
2) European Cystic Fibrosis Society Standards of Care: Best Practice guidelines (2013)

2 Sweat Test: Parameters, Values to be reported, References

i. Diagnostic standards: the quantity of sweat should indicate an adequate rate of sweat production;

ii. a. The sweat sample should be processed immediately after sweat collection;
b. Chloride concentration measurement is the preferred analysis for Diagnostic sweat tests. For sweat tests in relation to CFTR modulator therapy, Chloride is the only accepted value;
c. Chloride value: report the Chloride value in millimols per litre (mmol/L). If duplicate tests were completed on the same day, for Diagnostic sweat tests, **report the highest positive value;**
d. A sweat chloride value >59 mmol/L is consistent with a diagnosis of CF;
e. A sweat chloride value <30 mmol/L makes the diagnosis of CF unlikely (However, specific CF causing mutations can be associated with a sweat test below 30 mmol/L).
n.b. *The acceptable range for Chloride values is 1-160 mmol/L.* ***Anyone who has a Chloride value above 160 mmol/L should be re-tested;***

iii. As already mentioned above, the ECFSPR will consider only Titration/Chloride values in analyses.

References (links)

1) ECFS best practice guidelines: the 2018 revision
1) European Cystic Fibrosis Society Standards of Care: Best Practice guidelines (2013)

3 Nutrition: Method, Values and Dates to be reported, References.

i. The height and weight reported to the ECFSPR should be from the same day as the reported FEV1 (of hightest FEV1% predicted of the year);

ii. If spirometry was not done, the last weight and height measurements of the year, and the date they were measured, should be recorded;

iii. Height and weight should be measured in accordance with EuroCareCF guidelines:
Weight: removal of outer clothing, shoes and socks;
Height: removal of shoes and socks, stadiometer - top of head in contact with head board, slight pressure.

iv. Z-scores for height, weight & BMI are calculated with the CDC reference values [Kuczmarski et al (2002)].

References

1) Kromeyer-Hauschild K, Wabitsch M, Kunze D, Geller F, Geiss HC, Hesse V et al. Percentiles of body mass index in children and adolescents evaluated from different regional German studies. Monatsschr Kinderheilkd 2001; 149:807-818.
2) Lai H-C, Corey M, FitzSimmons S, Kosorok MR, Farrell M. Comparision of growth status of patients with cystic fibrosis between the United States and Canada. Am J Clin Nutr 1999; 69:531-538.
3) Public Use File BGS98, German National Health Interview and Examination Survey 1998, Robert-Koch-Institut, Berlin, Germany, 2000.
4) Wiedemann B, Paul KD, Stern M, Wagner TO, Hirche TO, on behalf of the German CFQA Group. Evaluation of body mass index percentiles for assessment of malnutrition in children with cystic fibrosis. Eur J Clin Nutr 2007; 61, 759-768.
5) Kuczmarski RJ, Ogden CL, Guo SS et al. 2000 CDC Growth Charts for the United States: methods and development. Vital Health Stat 2002; 11(246): 1-190.

4 Spirometry: Criteria, Method, Values to be reported, References.

The ECFS Patient Registry collects data on spirometry values to obtain standardised data for comparison with other centres/countries and for use in specific epidemiological studies. **n.b.** Some of the conditions for this (see below) may not be met at every clinical visit for all patients. **All spirometry tests should be carried out in accordance with the ATS/ERS guidelines** (www.thoracic.org/statements/resources/pfet/PFT2.pdf), however The ECFSPR accepts that it is not always possible to carry out spirometry pre-bronchodilator and post-bronchodilator results can be recorded.

For the spirometry values reported to the ECFSPR the following criteria should be met:

i. Pre-test preparation

a. All recorded spirometry tests should be pre-bronchodilator* values (but see above):
   i. short-acting bronchodilators: at least 4 hours pre-test;
   ii. long-acting bronchodilators: at least 12 hours pre-test.

b. Date of birth, gender and height should be recorded for calculation of predicted values. In addition, the ECFS Patient Registry asks for the weight to be measured at the same time, and recorded.

** In accordance with the official criteria of PortCF.*

ii. Values to report:

a. FEV1 in litres: must be the FEV1 in litres (to 2 decimals) of the **highest FEV1% predicted of the year**, in accordance with local reference values;
b. The FEV1 and FVC measurements must be reported in litres (L), to max 2 decimal points;
c. FVC in litres: must be the FVC measured at the same time as the FEV1 of the highest FEV1% predicted of the year and it must be greater than or equal to the FEV1 measurement.
d. For the reported spirometry values, the date of the test and the patient's height and weight at that date should also be recorded in order to calculate the percent of predicted values and other values;
e. Only tests deemed valid according to ATS/ERS guidelines to be reported.

iii. Calculation of percent of predicted values:

a. A common set of reference values - the Global Lung Function Initiative equations (See (a) below) - is used for calculations;

References

1) Global Lung Function Initiative equations described by Quanjer PH et al. (Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J 2012; 40: 1324–1343).
2) Miller et al. Standardisation of spirometry. Eur Respir J 2005; 26: 319–338.
3) Miller et al. General considerations for lung function testing. Eur Respir J 2005; 26: 153–161.
4) Cystic Fibrosis Foundation Patient Registry User Guide, Version 4.0. 2006.
5) Rosenfeld et al. Task Force to Evaluate Choice of Spirometric Reference Equations for the National Patient Registry: Summary and Recommendations. Cystic Fibrosis Foundation Registry Committee; 2005.

5 Chronic infection in the lower airways: Definition, References.

i. Chronic Pseudomonas aeruginosa infection: A patient should be considered chronically infected if the modified Leeds criteria are met - (a) below - and/or anti-pseudomonas antibodies are detected - (b) below.
A patient should be defined as chronically infected if he/she fulfils the criteria now, or has done so in recent years, and the physician has no reason to think that the status has changed.

a. Modified Leeds criteria - chronic infection: >50% of the samples (sputum/other) collected during the last 12 months should be positive; at least 4 samples collected.

b. Significantly raised levels of anti-pseudomonas antibodies according to local laboratories.

ii. Chronic infection with other gram-negative or gram-positive bacteria should meet the same criteria as described above.

References

1) Lee TWR, Brownlee KG, Conway SP, Denton M, Littlewood JM. Evaluation of a new definition for chronic Pseudomonas aeruginosa in cystic fibrosis patients. J Cystic Fibrosis
2) Proesmans M, Balinska-Miskiewiscz, Dupont L et al. Evaluating the "Leeds criteria" for Pseudomonas aeruginosa infection in a cystic fibrosis centre. Eur Resp J 2006;27:937-943.
3) Doring G, Conway SP, Heijerman HG, et al. Antibiotic therapy against Pseudomonas aeruginosa in cystic fibrosis: a European consensus. Eur Respir J 2000;16:749-767.

6 Liver Disease: Definitions

The ECFSPR has adopted the definitions for Liver Disease used by the Cystic Fibrosis Registry in the UK. These definitions discriminate patients with severe liver disease (with portal hypertension) from milder cases (cirrhosis without portal hypertension).

- **Cirrhosis with Hypertension**: scarring of the liver related to underlying CF, typically in a biliary pattern. Severe liver disease may include portal hypertension and/or hypersplenism;
- **Cirrhosis without Hypertension**: scarring of the liver related to underlying CF;
- **Liver disease without cirrhosis**: this includes fatty liver or viral hepatitis but not biliary cirrhosis.

7 Pancreatic Status: Pancreatic Insufficiency, References

i. **Indcator of Pancreatic Insufficiency - Faecal Fat** (2 determinations are mandatory)

a. Young children: Stool fat (van de Kamer) > 4-5 g/d;

b. Children older than 10 years and adults: Stool fat (van de Kamer) >7g/d and/or faecal pancreatic elastase-1 < 200 ug/g.

Please note

- Faecal fat excretion values of infants below 3 months are contradictory.
- Other than pancreatic causes of steatorrhoea must have been excluded.

ii. **For the ECFSPR, pancreatic status will be assessed as follows:**

- Pancreatic insufficiency: Faecal elastase <200 µg/g (twice), and faecal fat high* (twice);
- Pancreatic sufficiency: Faecal elastase ≥200 µg/g (twice) and Faecal fat normal* (twice).

** Refer to 7.i.a and 7.i.b above*

References

1) Sinaasappel M, Stern M, Littlewood J, Wolfe S, Steinkamp G, Heijerman HGM, Robberecht E, Döring G. Nutrition in patients with cystic fibrosis. A European consensus. J Cystic Fibrosis 2002; 1:51-75.
2) Walkowiak J, Nousia-Arvanitakis S, Henker J, Stern M, Sinaasappel M, Dodge JA. Invited review: Indirect pancreatic function tests in children. J Pediatr Gastroenterol Nutr 2005; 40:107-114.

8 Salt Loss Syndrome: Definition and Reference

Primary metabolic alkalosis with blood pH > 7.45, serum sodium < 130 mmol/l and serum chloride < 90 mmol/l (all 3 of these to be manifest).

Reference

1) Fustik S, Pop-Jordanova N, Slaveska N, Koceva S, Efremov G. Metabolic alkalosis with hypoelectrolytemia in infants with cystic fibrosis. Pediatr int 2002; 44: 289-92.

9 Transplantation: Indications

i. For patients who had a transplant during the year of follow up*:
   a. Use the best FEV1 before transplantation;
   b. Record therapy, complications and microbiology from before transplantation.

ii. For patients who had a transplant before the current follow-up year:
   a. Record all available information.

*Direct Data Entry Hospitals (not National Registries): if a patient is transferred to a different hospital for transplant and that hospital submits data to the ECFSPR, the transplant centre must not re-register the patient. The Core Data will be transferred through the data collection software to the transplant centre.