Foreword

This seventh report of the Dutch CF Registry has been made possible thanks to the cooperation of a great number of people with Cystic Fibrosis (CF) and the efforts of many people within the CF centres. This report includes the data relating to 1499 of the estimated 1530 people with CF and CF related illnesses in the Netherlands. So it covers 98% of the patients with CF in the Netherlands.

CF is a complex disease and there are many factors which influence the course of symptoms. The treatment given is one such factor. In order to compare and interpret the treatments given at a variety of centres a closer look at potentially related factors is needed.

Since 2014 the name of each centre has been added to its data in the annual report, in order to improve transparency. I would like to stress that the interpretation of the tables and graphs requires a great deal of care. Quality of care within a CF centre is determined by many factors and cannot be established on the basis of one statistic or graph. The Registry includes data covering a number of these factors. In addition to this, other factors also determine the quality of care. This year data has been added covering so-called indicators: statistics that tell us for example something about the number of sputum cultures and the number of lung function measurements performed per year. The guidelines state that this should occur at least every three months. The guidelines also state that from the age of 10 an annual test for CF related diabetes must be performed. An indicator covering this is also included. In addition a paragraph has been added this year containing data on the increasing number of people with CF who are likely over the age of 50.

In this report the data is presented per centre and also on a national basis. Each of the CF centres has received a summary of their data, related to the national averages. The Dutch Cystic Fibrosis Foundation organises annual gatherings of paediatric pulmonologists, chest physicians, paediatric gastroenterologists and paediatric dieticians from the centres. There the treatments, results, and differences between centres are discussed in an open and positive atmosphere. If relevant differences are observed in a number of areas, these are looked at in further depth and where possible they are developed into guidelines.

The CF centres and the NCFS continue to work towards their shared ambition: improved care, leading to a better and longer life for people with CF.

October 2015

Jacquielien Noordhoek, Chairperson of the Steering Committee of the Dutch CF Registry

Composition of the Steering Committee of the Dutch CF Registry

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Appendix 1 : Publications and requests for data from the Registry
Summary

Important findings of the Dutch CF Registry in 2014:

There are approximately **1530 people with CF** or CF related disorders in the Netherlands*. More than half of them are over the age of 17. The oldest CF patient in the Netherlands is aged 73. The number of people with CF aged 50 and older is 59.

**Diagnosis** occurred in half of the children below the age of two months. Diagnosis occurred later than at the age of 18 months in the case of 6% of patients.

There are **more men** (53.5 %) than women (46.5%) with CF in the Netherlands.

88% have at least one **F508del mutation**.

In 2014, 14 people with CF underwent **lung transplant**

At the end of 2014 there were less people with CF (22) on the waiting-list for lung transplant than in previous years.

In 2014 13 people with CF **died**. Half of them were aged under 37. Of these there were two children below the age of 18.

Nearly half of the children have a **lung function (FEV1)** higher than 90% of the predicted value.

Half of the adults have a **lung function (FEV1)** higher than 66% of the predicted value. In recent years above all the lung function in the age group between 18 and 30 has improved.

The **nutritional status** (height for weight ratio) of children with CF remains average in comparison with that of healthy children of the same age. The **growth in height** of children with CF is lower on average than that of healthy children of the same age. The average nutritional status of adults with CF has remained the same in recent years. The differences between centres have decreased.

60% of children and 40% of adults with CF use **food supplements**.

A third of all patients has a chronic **Pseudomonas aeruginosa** infection. Among adults this is 51% and among children 15%.

Almost 20% have **CF related liver disease**.

**CF related diabetes** occurs among 10% of children and 34% of adults.

One in four patients (both children and adults) has received a **course of antibiotics intravenously** in hospital. 14% of children have received intravenous treatment as part of their home treatment. Among adults this is 24%.

62% of adults are in **employment** or in education. One and a half percent are retired.

*For the purposes of the Registry the diagnosis of CF is confirmed if two mutations are identified which are known to cause CF (according to the CFTR mutation database CFTR2); and/or if the chloride content in the sweat test is 60 mmol or higher. CF has been confirmed in 1378 (92%) of the 1499 registered patients.
Introduction

The Dutch Cystic Fibrosis Foundation (NCFS) has been coordinating, managing and financing the Dutch CF Registry since 2007. The Steering committee for the Registry comprises representatives from all the CF centres and the NCFS. The Steering committee determines policy concerning the Registry.

All the information that is obtained from the National Registry is anonymised. Only the person providing treatment at the CF centre of a patient is capable of relating data to an individual patient. Each CF centre enters data relating to its patients and keeps this updated in order to follow progress over a period of time. The quality of the data is checked systematically by the research coordinator of the NCFS, by automated checks in the software, and by the statisticians of the European Registry. Strenuous checks are performed in order to be sure that patient data is not capable of being traced by other people. The Dutch and European legislation and regulations apply to this. The Dutch CF Registry is Registered with the College Bescherming Persoonsgegevens (Dutch Data Protection Agency), which supervises compliance with the legislation governing privacy. People with CF have been informed about the Registry and have given their written consent for the inclusion of the (anonymous) data in the Registry. A small number of patients (25) have declined to take part in the Registry.

Data files (registers) containing medical information about people with Cystic Fibrosis (CF) are maintained in more than 30 countries. The aim of these is to support scientific research and to improve care and treatment of patients with CF. The Dutch CF Registry also supplies data to the European CF Registry. (http://www.eCFs.eu/projects/eCFs-patient-Registry/intro)

De Dutch CF Registry has adopted the definitions used within the European CF Registry (http://www.eCFs.eu/projects/eCFs-patient-Registry/Variables-Definitions). The use of data from the Dutch or European Registry requires the approval of the Dutch Steering Committee or the European Review Committee. These comprise national and European CF specialists and experts in the area of the judicial and ethical aspects of personal data. Requests for data from the Dutch or European registries can be submitted using application forms which are available on the websites http://www.CFonderzoek.nl/CF-registratie and http://www.eCFs.eu/. Appendix 1 lists the requests for data from the registry that were made during 2014.

Each year a report is drawn up. These are available on the website of the NCFS http://www.CFonderzoek.nl/CF-registratie.

For questions or comments it is possible to contact the research coordinator of the NCFS via info@nCFs.nl
1 Methods

In the Dutch CF Registry the medical and social variables of people with CF are registered. The Steering Committee of the Dutch Registry has defined the parameters and the definitions which should be applied and in doing so it has based its decisions primarily on the variables which are measured in the European Registry. In this way a database has been created containing the data of approximately 36,000 European people with CF. The definitions which are applied for each parameter are virtually the same as those used in the American CF Registry; that contains the data of another 28,000 people with CF.

For the 2014 annual report the seven Dutch CF centres have entered data relating to approximately 150 variables into an Excel spreadsheet. The data has been collected during the year. In the case of lung function, the highest value during the year is recorded, in line with European definitions. Some CF centres were not able to supply all the variables, because they were not recorded at those centres.

The same reference values are maintained in relation to lung function for all centres, namely the international reference values in accordance with the Global Lung Initiative (GLI 2012; http://erj.ersjournals.com/content/early/2012/06/27/09031936.00080312.abstract?papetoc)

In calculating Z scores for growth among children (weight for height ratio and BMI) use was made of the Growth Analyser application of the Stichting Kind en Groei (Children and Growth Foundation) in Rotterdam. The reference values for the Dutch population in 2010 (Talma) were applied.

Percentages and averages or medians per centre were set for a variety of items. Important parameters for results, such as the lung function value FEV1 and the Body Mass Index for the nutritional status are presented as uncorrected values and they are only for patients with a confirmed diagnosis of CF who have not undergone a lung transplant. FEV1 and Body Mass Index are also presented per age group.

Outcome parameters and Confounder analysis

Outcome parameters such as FEV1, BMI weight for height tell us something about the quality of patient care. However there are many factors which determine FEV1, BMI and weight for height. Some of these are capable of being influenced by the centre (for example treatment), but others are a given and cannot be influenced. Those are known as confounders. The Steering committee has defined the following as possible confounders: gender, age, age of diagnosis, ethnicity, severity of the mutation class, meconium ileus, pancreatic insufficiency and previous lung transplant. Socio-economic status may be a confounder, but no data on this is included in the Registry.

In consultation with a clinical epidemiologist from the Julius Centre in Utrecht, differences between centres in FEV1, BMI, BMI Standard Deviation Score (SDS) and weight for height are corrected for most confounders (gender, age, pancreatic sufficiency, meconium ileus, severity of the mutation class (1,2,3 versus 4 and 5) and ethnicity). Separate analyses are performed for children and adults. Patients who have had a lung transplant previously are not included in the analyses.

The variable “age of diagnosis” is not included in the analysis, because insufficient data was available for a number of centres. In any case the median age upon which diagnosis occurs hardly varies between the centres whose data was available.

We looked at the differences between the centres with a multi-variable linear regression model, for both children and adults. The possible influence of confounders was tested by adding them to the model.

The differences between centres were not significant, following correction (adjustment) for possible confounders. This matches the conclusions from the analysis of the American and English CF Registry. This offers scope for a further analysis of possible predictors of differences between centres.
The results are presented in graphs accompanying the various sections dealing with lung function and nutritional status among children and adults.

The uncorrected differences between centres are shown in the figures 7, 12 and 15 for the averages for FEV1 % of predicted, BMI Z score and Weight-Height Ratio Z score of children, in relation to the largest centre as a reference point, and the differences have then been corrected (adjusted) for gender, age, meconium ileus, pancreatic sufficiency, ethnicity and severity of the mutation class (1, 2 and 3 versus 4 and 5).

In the figures 19 and 25, the differences are shown for the averages of FEV1 % from predicted and absolute BMI of adults in relation to the largest centre as reference point. The differences are presented uncorrected and adjusted for gender, age, pancreatic sufficiency and severity of the mutation class (1, 2, 3 versus 4 and 5).

All the possible confounders mentioned above do not cause significant changes in the differences between centres after multivariate correction.
2 Demographics

The ‘Guidelines for the Diagnosis and Treatment of CF’ [Richtlijn Diagnostiek and Behandeling van CF] (2007) and the report ‘Centre Care’ [Centrezorg] (NCFS 2003) recommend that people with CF should visit a CF centre once a year. The seven Dutch CF centres were treating approximately 1525 people with CF (92%) and CF related disorders in 2014. More than half (56%) of these people are aged 18 or older. The number of adults is slowly increasing, whilst the number of children has remained fairly constant over the last five years. The data from 1499 (98.4%) patients with CF and CF related disorders was included in the registry for 2014. Twentyfive people (1.6 %) did not give consent for the inclusion of their data. The data for a small number of people following lung transplant is not yet available. In all cases when the term adults is used, this refers to people aged 18 or older.

The data of all registered patients is used in presenting the following summaries.

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<tr>
<th>Year</th>
<th>2008</th>
<th>2009</th>
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<th>2011</th>
<th>2012</th>
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Number of deceased patients

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Median age of death

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Average age in years

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### Number of registered patients per centre

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<td>Adults</td>
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<td>Adults</td>
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<td>36</td>
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<tr>
<td><strong>Total</strong></td>
<td>1205</td>
<td>1299</td>
<td>1346</td>
<td>1374</td>
<td>1452</td>
<td>1476</td>
<td>1499</td>
</tr>
</tbody>
</table>

### Number of children and adults per centre

![Bar chart showing the number of children and adults per centre](chart.png)
4. Diagnosis

CF is often diagnosed at a young age but an increasing number of patients is also being diagnosed in adulthood. 50% of the current group of children were diagnosed before the age of 3 months but 6% of current patients were diagnosed at 18 years or older.

Screening

22% of children were diagnosed with CF following newborn screening for CF. Since 2008 new-born babies have been screened for CF by means of a heel prick following birth in a number of provinces. This screening is now performed with all new-born babies in the Netherlands since 1 May 2011. In 2011 the data of 43 children was added to the CF registry after the heel prick. In 2012 that number was 38, in 2013 it was 33, and in 2014 it was 18. It is very likely that a number of children who were born at the end of 2014 will have been diagnosed as having CF a few weeks later, and were not yet included in the registry for 2014. Their details will be included in the 2015 registry.

Diagnosed symptoms

The symptoms which lead to the diagnosis of CF can vary. Among children who are born with an obstruction of the intestine (meconeum ileus, MI; 19.5% of the children), CF can be diagnosed quickly. Poor growth or nutritional status have led to a diagnosis of CF in 58% of cases. 41% of the children were diagnosed because of respiratory problems and 14% because CF occurs in the family. Other symptoms and combinations were also recorded. The percentage of children being diagnosed on the basis of symptoms of CF has fallen by 20% since the introduction of heel prick screening.

MI: Meconeum Ileus

**Figure 1. Diagnosis symptoms of children with CF**
Mutations

For 97% of patients there is a result of genetic testing available. Among children this is as high as 99.5%. The percentage of patients included with an F508del mutation on both chromosomes (homozygous) is 53.6%. Among children this is 58.6 %, whilst among adults it is 49.6 %.

The percentage of patients with an F508del mutation on one chromosome and a different mutation on the other chromosome (heterozygous) is 34.9%. Among children this is 34%, whilst among adults it is 35.6%.

The percentage of patients with a non-F508del mutation on both chromosomes is 8.6%. Among children this is 7.1%, whilst among adults it is 9.8%.

The F508del mutation is present on at least one chromosome in the case of 88.5% of patients. The other mutations are much more rare. Table 1. shows an overview of the most prevalent mutations (more often than 0.5%) amongst patients whose DNA has been examined. Both ‘arms’ (alleles) of the chromosome pair have been taken into account in the calculations.

Figure 2. Proportion of combined mutations among children and adults

The break down of the percentage of patients with a homozygous F508del mutation varies between the CF centres for children (53 to 76 %) and for adults (41 to 57%).
### Table 1. Summary of the most common mutations.

The total percentage (100) comprises 1459 patients whose mutations have been analysed. No mutation investigation was performed in respect of 40 patients and their results are not known.

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Frequency (%)</th>
<th>Mutation class</th>
</tr>
</thead>
<tbody>
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<td>deltaF508</td>
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<tr>
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<tr>
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<td>R553X</td>
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</tr>
<tr>
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<tr>
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<td>0.5</td>
<td>5</td>
</tr>
<tr>
<td>W1282X</td>
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</tr>
<tr>
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<td>1</td>
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<td>Other known mutations</td>
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<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>100</strong></td>
<td></td>
</tr>
</tbody>
</table>

Almost 2000 mutations which lead to CF or what we call CF-related disorders are known worldwide. These mutations can be further divided into 'classes'. The nature of the abnormality which the mutation in the cells causes, is different for every class.

With class 1 mutations, CFTR protein is not formed so chloride channels in the cell wall are not made. The most prevalent F508del mutation is a class 2 mutation. This leads to the disrupted transport of the CFTR protein to the surface of the cells, preventing the chloride channels from developing.

With the class 3 mutations, chloride channels are formed but they are not activated, so they don't work.

With class 4 and 5 mutations, chloride channels are present but they are limited in number or they are functioning less well. These mutations are grouped together as ‘milder mutations’. However, it should be noted that it is not possible to make any predictions about the prognosis for the individual patient with CF based on the mutation class.

There are also a large number of rare mutations where it is not clear to which class they belong. A number of people also have mutations where it is uncertain if they will lead to ‘true CF symptoms’. These are talked of in terms of “CF-related disorder”*. This also applies to people with an R117H mutation, which occurs relatively frequently (2.4%, see table 1) and which is also observed a number of times per year amongst children after newborn screening. However some people with this mutation clearly have symptoms of CF.

* The diagnosis of CF applied for the registry is when two mutations are seen which are known to cause CF (according to the CFTR mutation database CFTR2), and/or the chloride level of the sweat test is 60 mmol or higher. The diagnosis of CF has been confirmed amongst 1378 (92%) of the 1499 registered patients.
Figure 3. Subdivision into class of mutation (percentage) of all patients
In allocating to classes the “mildest” class is used, where applicable.
Among 3.2% of patients no mutation investigation has been performed or the results are unknown (“missing”).
Among 9.7% of patients a mutation was found, but the exact class was not established (“unknown”).
3 Summary of children (below the age of 18)

The data of 625 children with a confirmed CF diagnosis has been used in the overviews in this section. The diagnosis was confirmed based on CF mutations and/or a positive sweat test. The diagnosis had not (yet) been confirmed for 28 children.

In the following graphs, the centres are given in a fixed order. The total for all centres is given in red on the right.

The alphabetical order of the abbreviations of the centres in all the graphs is as follows:

Amst : CF centre Amsterdam (AMC and VUMC)
Gron : CF centre UMC Groningen
Haga : CF centre HagaZiekenhuis Den Haag
Maas : CF centre Maastricht UMC
Nijm : CF centre East Netherlands (Nijmegen)
Rott : CF centre Erasmus MC Rotterdam
Utre : CF centre UMC Utrecht

5.1 Lung function

The FEV1 value is the maximum amount of air that can be exhaled in 1 second after a deep breath and is an important indicator for the functioning of the lungs. The FEV1 value is given as percentage of the predicted value (the reference value of healthy people of the same age). The median value for children between the ages of 6 and 18 is 88%. This means that 50% of the children have a value that is lower than 88% of the predicted value and 50% has a higher value. The median FEV1 value of children aged between six and 18 varies between 81% and 101% per centre and for all the children's centres together it amounts to 88.0% (in 2013 this was 88.6%).

In figure 4 the FEV1 values per centre are shown for 2013 and 2014.

The interquartile range for all centres together is 21.4% and varies from 18 to 26% per centre. Four quartiles can be distinguished per distribution. The first quartile is the value which 25% of the FEV1 values are below if all measured values are arranged in order of size, the second quartile is the value which 50% of the FEV1 values are below, and so on. The interquartile range is a measure of dispersion and indicates the difference between the third quartile (75% of all values) and the first quartile (25% of all values).
Figure 4. Median FEV1 percentage compared to reference values among healthy children per centre in total

Figure 5 shows the Median FEV1 values per age group (6 to 12 years, 12 to 18 years and 6 to 18 years).

Figure 5. Median FEV1 percentage compared to reference values among healthy children per age category and per centre

In figure 6, the percentage of children per category of lung function is shown (with an FEV1 less than 40%, between 40% and 70%, between 70% and 90%, and greater than 90%). This division has been
chosen because it is applied by other countries and it makes international comparison possible. From the figure it can be seen that nearly half of the children below 18 years has a lung function higher than 90%.

Figure 6. Percentage children per lung function category

In figure 7, the uncorrected differences between centres are given with regards to the average FEV1 % of the predicted values for children, with the largest centre as a reference point, and the differences corrected (adjusted) for gender, age, meconium ileus, pancreatic insufficiency, ethnicity and severity of the mutation class (1, 2 and 3 versus 4 and 5). All the possible confounders referred to do not cause any significant changes to the centre differences after multivariate correction.

Figure 7. Differences in average FEV1 values among children in relation to be largest centre (Utrecht) as reference point.
5.2 Micro-organisms

In the respiratory tract of people suffering from CF, micro-organisms (bacteria and fungi) are found which lead to varying degrees of infection. The occurrence of a number of important micro-organisms in children is displayed in figure 8 below. The definitions of the European CF Registry have been used since 2010. This means that a chronic infection with *Pseudomonas aeruginosa* (PA) is considered present if more than 50% of at least four sputum cultures in the last year were positive and/or there has been a significant increase in anti-pseudomonas antibodies (‘modified Leeds criteria’). The child’s physician may also decide that there is no reason to review the previously determined chronic infection with PA if there has been an insufficient number of cultures.

![Figure 8. Percentage micro-organisms among children](image)

**PA**: Pseudomonas aeruginosa  
**BC**: Burkholderia cepacia  
**SM**: Stenotrophomonas maltophilia  
**SA**: Staphylococcus aureus  
**MRSA**: Methicillin resistant Staphylococcus aureus  
**HI**: Haemophilus influenzae  
**AF**: Aspergillus fumigatus  
**NTM**: Non-tuberculous Mycobacteria  
**AX**: Achromobacter xylosoxidans
*Pseudomonas aeruginosa* (PA) is particularly important for the treatment and prognosis of many children with CF. The figure below shows the percentage of children suffering from chronic PA-infection per centre. This can vary greatly per centre. The definition of chronic PA infection has proven difficult in practice, which can affect its registration. The percentage of patients with a chronic PA infection for the total group of children is 15.5%. In 2013 this was still 21.4%. The percentage of children aged six years and older with a chronic *Pseudomonas* infection which is being treated with inhaled antibiotics is 90%. In 2013 this was still 73%.

![Percentage children with pseudomonas](image)

**Figure 9. Percentage of Chronic *Pseudomonas aeruginosa* infection in children per centre**
5.3 Nutritional status

The optimisation of growth and weight is important for children suffering from CF. The body weight in relation to height is one measure for the nutritional status. The Body Mass Index (BMI) is another measure for the nutritional status. The index is calculated by dividing the weight (in kg) by the square of the height (in m).

The height and weight for the age are also given. All these measurements can be expressed as a standard score, known as the Z-score. A Z-score with a value of 0 is the average. The scores of 97% of healthy Dutch children are between the values -2 to +2.

In the registry, the measures for height and weight are included as measured at the time of the lung function examination with the highest FEV1 value. For children who have not undergone a lung function examination, the measures of the annual major examination have been used.

**Weight for height**

The median Z-scores for weight for height (figure 10) vary per centre from -0.03 to +0.53 (in 2013 these were -0.05 to +0.47). The median value for all centres combined is +0.14 (in 2013 this was +0.10). This means that 50% of children have a value that is lower than +0.14 and 50% have a higher value.

![Weight for height (Z-score) children](chart)

**Figure 10. Median Z-scores for weight for height per centre from 2012 to 2014**

In figure 11 it is possible to see the improvement in median Z score for weight for height in all children over the period from 2008 to 2014.

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Report of the Dutch CF Registry 2014
Broken down by age cohort (0 to 6 years, 6 to 12 years and 12 to 18 years) the respective median Z score for weight for height is +0.20, +0.19 and +0.09 (in 2013 these were +0.11, +0.29 and +0.02).

Correction for possible confounders, such as gender, age, severity of the mutation class, meconium ileus, pancreatic insufficiency and ethnicity, hardly shows any changes in the differences between the centres (figure 12, see section 2 for a description of the methodology).
BMI
The median Z-scores for the BMI (figure 13) vary per centre from -0.05 to +0.37 (in 2013 these were -0.15 to +0.15). The median value for all centres together is +0.10 (in 2013 this was +0.03).

Broken down by age cohort (0 to 6 years, 6 to 12 years and 12 to 18 years) the respective median Z score for BMI is 0.17, 0.13 and 0.06 (in 2013 these were 0.13, 0.16 and -0.07)

This means that the average nutritional status of children with CF was almost the same as that of healthy children of the same age and that the nutritional status of children with CF has improved considerably since 2008 (see figure 14). The nutritional status in 2014 has improved in comparison with 2013.

Figure 13. Median Z-scores for children’s BMI per centre from 2012 to 2014

Figure 14. Median Z-scores for children’s BMI from 2008 to 2014
Correction for possible confounders such as gender, age, severity of the mutation class, meconium ileus, pancreatic insufficiency and ethnicity do not have any effect on the differences between the centres (figure 15, see section 2 for a description of the methodology).

**Figure 15.** Differences between centres in average Z-scores for children’s BMI in comparison with the largest centre (Utrecht) as reference point.

**Weight and height by age**
In figures 16 and 17 the Z-scores for weight and height by age are stated per centre and in total. From this it can be seen that the average height of children with CF is lower than that of healthy children of their age.

**Figure 16.** Median Z-scores for weight by age per centre in 2013 and 2014.
Figure 17. Median Z-scores for height by age per centre in 2014.
5.4 Comorbidity

A number of children suffering from CF also suffer from what is called ‘comorbidity’. Examples of this include:

ABPA: Allergic Broncho Pulmonary Aspergillosis, an allergic reaction to the Aspergillus fungus.
CFRD: CF related diabetes. A number of patients develop a special CF related form of diabetes. In order to discover CFRD quickly, the ‘Guidelines for the Diagnosis and Treatment of Cystic Fibrosis’ [Richtlijn diagnostiek and behandeling van Cystic Fibrosis] (2007) recommend conducting an annual Oral Glucose Tolerance Test (OGTT) in children without diabetes from the age of 10. An OGTT was performed on 80% of the children who fell within this category (in 2013 this was still 60%).
DIOS: Distal Intestinal Obstruction Syndrome, a severe blockage at the end of the small intestine which is common in people suffering from CF.
Liver disease: Hepatic impairment/ transaminase disorders gradually develop in some people with CF and can lead to a severely disrupted liver function.
The definition of liver disease applied by the CF Registry is: the presence of steatosis (fattening) and/or cirrhosis (shrinking).

The percentage children with ABPA varies per centre from 3 to 22%.
The percentage children with CFRD varies per centre from 3 to 24%.
The percentage children with DIOS varies per centre from 0 to 8%.
The percentage children with Liver disease varies per centre from 6 to 36%.
5.5 Treatment

The percentages are shown below of diverse aspects of the treatment of children with a confirmed diagnosis of CF (n=625).

<table>
<thead>
<tr>
<th></th>
<th>2008</th>
<th>2009</th>
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<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
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<tr>
<td></td>
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<td>89.3</td>
<td>89.5</td>
<td>85.8</td>
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<td><strong>Use of food supplements</strong></td>
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</tr>
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<td>Energy enriched liquid food</td>
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<td>59.9</td>
<td>50.6</td>
<td>48.2</td>
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<td>13.0</td>
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<td>7.1</td>
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<td>19.7</td>
<td>19.4</td>
<td>14.4</td>
<td>20.4</td>
<td>25.2</td>
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<tr>
<td>Inhaled medication</td>
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<td>27.0</td>
<td>29.0</td>
<td>34.0</td>
<td>29.6</td>
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<tr>
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</table>
5.6 Transplants in children

The number of children that have undergone a transplant is stated below.

Liver transplant before 2014 0
Liver transplant on the waiting-list at 31/12/2014 1
Liver transplant in 2014 0

Lung transplant before 2014 5
Lung transplant on the waiting-list at 31/12/2014 0
Lung transplant in 2014 0

5.7 Deceased patients

Two children with CF died during 2014.
5. Adults (18 years and older)

In the overviews in this section, the details of 666 adults without lung transplant and with a confirmed diagnosis of CF have been used. The diagnosis was confirmed based on CF mutations and/or a positive sweat test. The diagnosis had not yet been confirmed for 85 adults. 11.5% of the adults with CF were diagnosed above the age of 18.

In the following graphs, the centres are displayed in a fixed order. The total for all centres is listed in red on the right. The alphabetical order of the abbreviations of all the centres in the graphs is as follows:

Amst : CF centre Amsterdam (AMC)
Gron : CF centre UMC Groningen
Haga : CF centre HagaZiekenhuis Den Haag
Maas : CF centre Maastricht UMC
Nijm : CF centre East Netherlands (Nijmegen)
Rott : CF centre Erasmus MC Rotterdam
Utre : CF centre UMC Utrecht

6.1 Lung function

The FEV1 value is the maximum amount of air that can be exhaled after a deep breath in 1 second and is an important indicator for the functioning of the lungs. The FEV1 value is shown as a percentage of the predicted value (the reference value of healthy people of the same age). The median value is 65.9%. This means that 50% of the adults had a value which was lower than 65.9% of the predicted value. In 2013 this median value was 64.1%.

The median FEV1 value for adults varies between 61 and 75 % per centre (in 2013 this was between 60 and 74 % per centre).

In figure 19 the FEV1 values per centre are stated for 2013 and 2014.

The interquartile range for all centres combined is 32 % and varies from 26 to 42 % per centre. *Four quartiles* can be distinguished per distribution. The first quartile is the value below which 25% of the FEV1-values lie if all measured values are arranged by size, the second quartile is the value which 50% of the FEV1 values lie below, etc. The interquartile range is a measure of dispersion and indicates the difference between the third quartile (75% of all values) and the first quartile (25% of all values).
Correction for possible factors which could have an influence on FEV1 outcome (confounders such as gender, age, pancreatic insufficiency and severity of the mutation), hardly shows any changes in the differences between the centres (Figure 20, see section 2 for a description of the methodology).

Figure 19. Median FEV1 percentage in comparison with reference values of healthy adults per centre.

Figure 20. Differences in average FEV1 values in adults between the centres in comparison with the largest centre (Haga) as reference point.
The percentage of adults per category of lung function (with an FEV1 lower than 40 %, between 40 and 70 %, between 70 and 90 % and greater than 90 %) is presented in figure 21. This division has been chosen because it is applied by other countries and it makes international comparison possible. It is encouraging to see that the groups with an FEV1 < 70% are gradually decreasing and that the groups with a higher FEV1 are gradually increasing. The percentage of patients with an FEV1 < 40 % varies from 11 to 23% per centre.

Figure 21. Percentage adults per lung function category.
6.2 Micro-organisms

In the respiratory tract of people suffering from CF, micro-organisms (bacteria and fungi) are found which lead to varying degrees of infection.

The occurrence of a number of important micro-organisms in adults is shown in the figure below. The definitions of the European CF Registry have been used since 2010. This means that a chronic infection with *Pseudomonas aeruginosa* (PA) is considered present if more than 50% of the sputum cultures in the last year were positive and/or there has been a significant increase in anti-pseudomonas antibodies (‘modified Leeds criteria’). The patient’s physician may also decide that there is no reason to review the previously determined chronic infection with PA if there has been insufficient number of cultures.

![Percentage micro-organisms adults](chart)

**Figure 22. Percentage micro-organisms in adults**

- **PA**: *Pseudomonas aeruginosa*
- **BC**: *Burkholderia cepacia*
- **SM**: *Stenotrophomonas maltophilia*
- **SA**: *Staphylococcus aureus*
- **MRSA**: Meticilline resistant *Staphylococcus aureus*
- **HI**: *Haemophilus influenzae*
- **AF**: *Aspergillus fumigatus*
- **NTM**: Non-tuberculous *Mycobacteria*
- **AX**: *Achromobacter xylosoxidans*

The percentage of adults with a chronic *Pseudomonas* infection remains around 50%.
The percentage of adults where *Burkholderia*, MRSA or Mycobacteria appear in cultures, remains low.
Pseudomonas aeruginosa (PA) in particular has a lot of impact on the treatment and prognosis for many adults suffering from CF. The percentage of adults suffering from chronic PA infection per centre is given in figure 23. This is 51% for the total group of adults, but it can vary greatly per centre. The percentage of adults treated with inhaled antibiotics, which are generally used to combat PA, is 59.7% (page 31).

The percentage of adults with a chronic Pseudomonas infection who are being treated with inhaled antibiotics, is 83%.

Figure 23. Percentage Chronic *Pseudomonas aeruginosa* infection in adults per centre
6.3 Nutritional status

The preservation and improvement of a good nutritional status is important in adults suffering from CF. The nutritional status in adults is indicated by the Body Mass Index (BMI). The BMI is calculated by dividing the body weight (in kilograms) by the square of the height (in metres). The median BMI values for adults vary per centre (figure 24) from 20.8 to 22.1 (in 2013 this varied from 21.2 to 22.0). The total of all the centres combined is 21.6 (in previous years this was also 21.6; figure 24). This means that 50% of adults have a value lower than 21.6. BMI values between 18.5 and 25 are regarded as normal.

![Figure 24. Median BMI values for adults per centre from 2012 to 2014.](image)

Correction for possible confounders, such as gender, age, pancreatic insufficiency and severity of the mutation class, hardly shows any changes in the differences between the centres (figure 26, see section 2 for a description of the methodology).
Figure 26. Differences in average BMI values for adults compared to the largest centre (Haga) as a reference point.
6.4 Comorbidity

A number of adults with CF suffer from what we call comorbidity. Examples of this are:

ABPA: Allergic Broncho Pulmonary Aspergillosis, an allergic reaction to the Aspergillus fungus. CFRD: CF-related diabetes. Mainly in adults, a special form of CF-related diabetes can develop. In order to discover CFRD quickly, the ‘Guidelines for the Diagnosis and Treatment of Cystic Fibrosis’ [Richtlijn diagnostiek en behandeling van Cystic Fibrosis] (2007) recommend conducting an annual Oral Glucose Tolerance Test (OGTT) in adults who do not suffer from diabetes. An OGTT was carried out amongst 60 percent of the adults who fell under that category. This was 50% in 2013 and 37% in 2012.

DIOS: Distal Intestinal Obstruction Syndrome, a severe blockage at the end of the small intestine which is common in people suffering from CF.

Liver disease: Hepatic impairment/ transaminase disorders gradually develop in some people with CF and can lead to a severely disrupted liver function. The definition of liver disease applied by the CF Registry is: the presence of steatosis (fattening) and/or cirrhosis (shrinking).

Figure 27. Percentage of specific comorbidity in adults

The percentage adults with ABPA varies per centre from 0 to 17 %.
The percentage adults with CFRD varies per centre from 17 to 50 %.
The percentage adults with DIOS varies per centre from 0 to 9 %.
The percentage adults with Liver disease varies per centre from 15 to 36 %.
6.5 Treatment

The percentages below represent diverse aspects of the treatment of adults with CF.

<table>
<thead>
<tr>
<th></th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of pancreatic enzymes</td>
<td>79.8</td>
<td>82.6</td>
<td>80.5</td>
<td>76.8</td>
<td>80.3</td>
<td>76.7</td>
<td>79.0</td>
</tr>
<tr>
<td>Use of protonpump inhibitors</td>
<td>49.7</td>
<td>47.1</td>
<td>48.8</td>
<td>46.5</td>
<td>48.8</td>
<td>53.0</td>
<td>53.8</td>
</tr>
<tr>
<td>Use of food supplements</td>
<td>37.6</td>
<td>42.5</td>
<td>41.2</td>
<td>40.3</td>
<td>47.7</td>
<td>38.2</td>
<td>40.8</td>
</tr>
<tr>
<td>Energy enriched liquid food</td>
<td>32.0</td>
<td>41.5</td>
<td>39.7</td>
<td>38.4</td>
<td>45.0</td>
<td>35.4</td>
<td>39.0</td>
</tr>
<tr>
<td>Nutrition via a tube or stoma</td>
<td>6.8</td>
<td>12.3</td>
<td>9.2</td>
<td>7.5</td>
<td>7.8</td>
<td>7.3</td>
<td>5.4</td>
</tr>
<tr>
<td>Use of ursodeoxycholic acid</td>
<td>31.2</td>
<td>29.6</td>
<td>29.1</td>
<td>29.3</td>
<td>29.2</td>
<td>29.3</td>
<td>28.7</td>
</tr>
<tr>
<td>Nebulisation with mucus thinners</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RhDNase</td>
<td>50.9</td>
<td>54.6</td>
<td>60.3</td>
<td>60.7</td>
<td>63.8</td>
<td>63.0</td>
<td>64.4</td>
</tr>
<tr>
<td>Acetylcysteine</td>
<td>32.0</td>
<td>9.6</td>
<td>6.5</td>
<td>5.3</td>
<td>3.8</td>
<td>3.9</td>
<td>2.9</td>
</tr>
<tr>
<td>Hypertonic saline</td>
<td>7.2</td>
<td>17.6</td>
<td>26.5</td>
<td>27.5</td>
<td>26.7</td>
<td>28.9</td>
<td>27.5</td>
</tr>
<tr>
<td>Intravenous antibiotics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In hospital</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>24</td>
<td>22.4</td>
<td>22.5</td>
<td>23.4</td>
</tr>
<tr>
<td>at home</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>25</td>
<td>22.4</td>
<td>22.7</td>
<td>21.8</td>
</tr>
<tr>
<td>Antibiotics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tobramycin nebulisation solution</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>10.2</td>
<td>12.4</td>
<td>15.0</td>
</tr>
<tr>
<td>Colistin</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>31.3</td>
<td>29.8</td>
<td>26.4</td>
</tr>
<tr>
<td>Dry powder antibiotics</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>28.1</td>
<td>28.3</td>
<td>21.6</td>
</tr>
<tr>
<td>Aztreonamylsine inhalation</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>10.9</td>
<td>18.3</td>
<td>16.3</td>
</tr>
<tr>
<td>Inhaled antibiotics</td>
<td>- 54.4</td>
<td>52.8</td>
<td>56.1</td>
<td>58.8</td>
<td>58.7</td>
<td>59.7</td>
<td></td>
</tr>
<tr>
<td>Macrolides</td>
<td>58.6</td>
<td>63.8</td>
<td>64.4</td>
<td>63.7</td>
<td>69.3</td>
<td>64.1</td>
<td>67.9</td>
</tr>
<tr>
<td>Use of corticosteroids</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral</td>
<td>16.3</td>
<td>17.2</td>
<td>14.8</td>
<td>16.4</td>
<td>12.3</td>
<td>19.4</td>
<td>12.6</td>
</tr>
<tr>
<td>Inhalation medication</td>
<td>47.4</td>
<td>44.8</td>
<td>49.4</td>
<td>45.9</td>
<td>44.4</td>
<td>51.7</td>
<td>56.0</td>
</tr>
<tr>
<td>Use of bronchodilators</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhalation medication</td>
<td>62.8</td>
<td>59.4</td>
<td>63.6</td>
<td>65.5</td>
<td>65.4</td>
<td>56.3</td>
<td>60.2</td>
</tr>
<tr>
<td>Use of extra oxygen</td>
<td>-</td>
<td>8.2</td>
<td>8.1</td>
<td>7.2</td>
<td>5.3</td>
<td>5.1</td>
<td>5.4</td>
</tr>
<tr>
<td>Non-invasive ventilation</td>
<td>2.2</td>
<td>3.1</td>
<td>1.6</td>
<td>1.2</td>
<td>0.3</td>
<td>1.2</td>
<td>0.4</td>
</tr>
<tr>
<td>Kalydeco (number of users)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>8</td>
</tr>
</tbody>
</table>
6.6 Transplants in adults

The number of adults who have undergone transplants is presented below.

Liver transplant before 2014 5
Liver transplant on waiting-list as at 31/12/2014 1
Liver transplant in 2014 0

Lung transplant before 2014 86
Lung transplant on waiting-list at 31/12/2014 22
Lung transplant in 2014 14

N.B.: A small number of patients have previously undergone a lung transplant and they are not included in the Dutch CF Registry.

6.7 Deceased patients

In 2014 eleven adults with CF died.
### 6.8. Social-economic context

The percentages for work/study are presented for 632 adults.

<table>
<thead>
<tr>
<th>Work/study</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unemployed</td>
<td>6.5</td>
<td>7.8</td>
<td>10.8</td>
<td>14.9</td>
<td>10.4</td>
</tr>
<tr>
<td>Working full-time</td>
<td>18.8</td>
<td>19.6</td>
<td>17.6</td>
<td>14.9</td>
<td>15.3</td>
</tr>
<tr>
<td>Working part-time</td>
<td>22.6</td>
<td>20.3</td>
<td>21.5</td>
<td>22.2</td>
<td>26.7</td>
</tr>
<tr>
<td>Fulltime house husband/wife</td>
<td>1.9</td>
<td>1.5</td>
<td>1.7</td>
<td>1.0</td>
<td>1.4</td>
</tr>
<tr>
<td>Student</td>
<td>20.5</td>
<td>22.7</td>
<td>27.3</td>
<td>24.5</td>
<td>20.1</td>
</tr>
<tr>
<td>Retired</td>
<td>0.9</td>
<td>0.4</td>
<td>0.5</td>
<td>1.4</td>
<td>1.4</td>
</tr>
<tr>
<td>Unable to work</td>
<td>16.4</td>
<td>13.7</td>
<td>13.2</td>
<td>10.7</td>
<td>12.8</td>
</tr>
<tr>
<td>Unknown</td>
<td>12.4</td>
<td>14.0</td>
<td>7.4</td>
<td>10.4</td>
<td>11.9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Marital status</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Living alone/never married</td>
<td>55.8</td>
<td>53.0</td>
<td>43.0</td>
</tr>
<tr>
<td>Married/cohabiting</td>
<td>36.2</td>
<td>34.0</td>
<td>41.4</td>
</tr>
<tr>
<td>Divorced</td>
<td>1.1</td>
<td>1.4</td>
<td>1.6</td>
</tr>
<tr>
<td>Widow/widower</td>
<td>0.1</td>
<td>0.3</td>
<td>0.2</td>
</tr>
<tr>
<td>Unknown</td>
<td>6.8</td>
<td>11.3</td>
<td>13.8</td>
</tr>
</tbody>
</table>
6.9 CF patients aged 50 and over

In 2014 there were 59 people aged 50 or more with a confirmed CF diagnosis. Of these, 12 people have previously had a lung transplantation. The oldest patient is aged 73.

61% are men and 39% are women.

The percentage of patients with an F508del mutation on both chromosomes (homozygous) is 27.1%. The percentage of patients with an F508del mutation on one chromosome and a different mutation on the other chromosome (heterozygous) is 50.8%. The percentage of patients with a non-F508del mutation on both chromosomes is 13.6%. The mutation is not known in respect of 8.5%.

45% of those aged 50 and older has at least one class 5 mutation.

The median Lung function is 66% (excluding patients who have had a lung transplant, 60%). The BMI is 23 (excluding patients who have had a lung transplant, 22.9).

- 23% use extra food supplements
- 36% have a Chronic Pseudomonas infection
- 40% use inhalation antibiotics
- 41% have CF related diabetes (CFRD)

- 81% are living with a partner
- 53% are working, or have worked and are retired
- 28% of the women have at least one child
7. Lung function in children and adults, men and women

In figure 28 the median FEV1 (percentage of predicted value) is stated per age category from 6 to 73 years. The decline in lung function among young adults between 18 and 30 is lower than previously. The median FEV1 for all age groups combined is 76.1%. In 2013 this was 75.9%.

![Figure 28. Lung function (median FEV1 % of predicted value) per age category](image)

**Figure 28. Lung function (median FEV1 % of predicted value) per age category**

In figure 29 the median FEV1 (percentage of predicted value) is presented per age category from 6 to 73 years for men and women. Up to the age of 15 the FEV1 is higher among girls. Between 15 and 27 this is higher among boys. After this the differences continue to alternate. In the age group 60+ the number involved is small (6 women, 5 men) which makes the median differences large.

![Figure 29. Lung function (median FEV1 % of predicted value) per age category for men and women.](image)

**Figure 29. Lung function (median FEV1 % of predicted value) per age category for men and women.**
8. Indicators

Introduction

Based on European and national guidelines a number of instruments have been developed which provide insight into the quality of care for people with CF.

Under the NCFS Quality Mark the quality of care is tested in relation to 60 criteria from the perspective of people with CF.

An important question is whether the introduction of a guideline actually achieves the intended effects in terms of quality of care. Indicators are used in order to measure this.

Indicators are measurable elements within the provision of care which provide an indication of the extent and quality of care provided. An indicator functions as a signal: it is not a direct measure of quality, but points towards a particular aspect of how things function, and it can give rise to further investigation. This goes to the heart of quality of care: actually measuring quality of care and, based on that measurement, introducing improvements where necessary, with the aim of improving quality of care in a targeted way.

Each year a number of indicators are measured with the use of the registry. Until last year hospitals were obliged to supply this information to the organisation “Zichtbare Zorg (ZiZo)” (Visible Care). However a large amount of the data was also collected for the Dutch CF Registry.

In order to prevent duplication of recording and to make information more accessible to a wide section of the public it was agreed that all information relating to the indicators concerning CF should be included in the annual report of the CF Registry of the NCFS.

Indicators can give care providers insight into the results of their own process and they assist internal direction and help improve it. Indicators established for this purpose are referred to as internal indicators. Indicators can also be used in order to compare the performance of CF centres with each other (benchmarking). The provision of structural feedback on the results of care and the introduction of benchmarking can enable continuous improvement of processes.

Indicators can also serve another purpose. The government, the Health Inspectorate (Inspectie voor de Gezondheidszorg - IGZ) and patients/consumers want to evaluate whether care providers deliver sufficient quality, so they look for suitable indicators. Indicators intended for this purpose are also known as external indicators. The external indicators can also be used in negotiations with the insurance companies. The external indicators that have been developed are already used by Dutch healthcare insurers for the procurement of care services.

The following indicators for CF care have been developed on the basis of the recommendations in the Dutch (2007) and European (2014) guidelines.

In the following graphs the centres are presented in a fixed order. The total for all centres is stated on the right, in red.

The following alphabetical order and abbreviations are used in all the graphs:

- Amst: CF centre Amsterdam (AMC and VUMC)
- Gron: CF centre UMC Groningen
- Haga: CF centre HagaZiekenhuis The Hague
- Maas: CF centre Maastricht UMC
- Nijm: CF centre East Netherlands (Nijmegen)
- Rott: CF centre Erasmus MC Rotterdam
- Utre: CF centre UMC Utrecht
Results of the indicators

1. Lung function

Lung function is an important measure of the disease severity and prognosis for people with Cystic Fibrosis. The percentage of predicted FEV1 (forced expiratory volume in 1 second) is a good, widely used measure for this.

In the European Standards of Care consensus the conclusion has been reached that Lung function is an important measure in evaluating severity of illness (morbidity) and deaths (mortality) from CF. FEV1 percentage of predicted value is the clearest clinical predictor of mortality and is used as the primary outcome parameter in many clinical trials (Kerem, 1992; Ramsey, 1994; Grasemann, 1995; Flume, 2007, Smith 2014).

In figure 4 (page 14) the median highest FEV1 value is presented for children per centre, and the total for all centres. In figure 19 (page 27) these values are presented for adults.

2. Nutritional status

In approximately 80% of all patients, CF is accompanied by an exocrine pancreatic disorder. In addition patients with CF require a higher level of calories, sometimes up to 150% of normal. For this reason additional pancreatic enzymes and a well-balanced high calorie diet with vitamin supplements are important. The nutritional status of the patient is an important indicator for the prognosis, alongside lung function.

The optimisation of growth and weight is important among children with CF. The bodyweight in relation to height is one measure of the nutritional status. This index is calculated by dividing the weight (in kg) by the square of the height (in m). This measure can be expressed in a standard score, known as a Z score. A Z score with the value 0 is average. The scores of 97% of healthy Dutch children lie between the values of -2 to +2.

In the registry, the measures for height and weight are included as measured at the time of the lung function examination with the highest FEV1 value. For children who have not undergone a lung function examination, the measures of the annual major examination have been used.

The median Z-score for weight for height per centre is presented in figure 10 (page 18).

Maintaining or improving a good nutritional status is also important among adults with CF. The median BMI value for adults per centre is presented in figure 24 (page 31).

3. Indicator for infrastructure

In order to build up sufficient experience and expertise, the care and treatment of patients with CF should form part of the day-to-day activities of team members. This involves a minimum number of 50 children or adults with CF per location being treated, who are being offered continuous/chronic care. (Kerem, 2005, Conway 2014). The complexity of the illness means that specialised CF teams are necessary in the centres.

A CF centre can only add value if there are demonstrably more facilities and expertise present than outside the centre. Within the centre there should be a minimum level of specialisation present among the staff. All specialists should have sufficient patient contact and should be able to demonstrate participation each year in additional training. The centre should be sufficiently accessible to enable ease of use of the centre’s expertise by patients. In addition the care offered by the centre should be of a high level of quality which is capable of being measured. Protocols for diagnosis and treatment should be present and the provision of this care must also be measurable. The European Cystic Fibrosis Society issues guidelines that a centre must comply with (Kerem, 2005, Conway 2014). These conditions for a good infrastructure for a CF centre are looked into as part of the examination for the NCFS Quality Mark.

The number of patients per centre is registered each year. Figure 30 displays the number of children and adults per centre.
Figure 30. The number of children and adults per centre.

4. Process indicators

Routine investigation of various parameters contributes to the early detection of infections, abnormalities in nutritional status, etc. This enables the provision of more effective care, and ultimately improvement in the prognosis. According to guidelines an examination at an outpatient clinic should take place at least four times per year. As part of this, in addition to looking at patient history and a physical examination, a sputum sample/cough sample will be taken and from the age of 6 onwards a lung function examination will be carried out. Figure 31 shows the percentage of children per centre that have visited the outpatient clinic at least four times per year.

Figure 31. Percentage of children per centre that have visited the outpatient clinic at least four times per year
Figure 32 shows the percentage of adults per centre who have visited the outpatient clinic at least four times per year.

![Outpatient clinics at least 4 times per year](image)

Figure 32. Percentage of adults per centre that have visited the outpatient clinic at least four times per year.

Figure 33 shows the percentage of children per centre from whom a sputum sample/cough sample has been taken at least four times per year.

![Sputum cultures taken at least 4 times, percentage children](image)

Figure 33. Percentage of children per centre from whom a sputum sample/cough sample has been taken at least four times per year.
Figure 34 shows the percentage of adults per centre from whom a sputum sample/cough sample has been taken at least four times per year.

Figure 34. Percentage of adults per centre from whom a sputum sample/cough sample has been taken at least four times per year.

Figure 35 shows the percentage of children per centre whose lung function has been measured at least four times per year.

Figure 35. Percentage children per centre who have had a lung function test 4 times per year.
Figure 36 shows the percentage of adults per centre whose lung function has been measured at least four times per year.

Figure 36. Percentage adults per centre who have had a lung function test 4 times per year.

Children and above all adults can develop a special form of CF related diabetes (CFRD). In order to detect CFRD quickly the Guideline for diagnosis and treatment of cystic fibrosis (“Richtlijn diagnostiek and behandeling van Cystic Fibrosis”) (2007) recommends annual performance of the Glucose Tolerance Test (GTT) among children from age 10 onwards and adults without diabetes. Figure 37 shows the percentage of children per centre who had a GTT in 2014. The percentage is calculated for children above the age of 10, without CFRD, and with a pancreatic insufficiency.

Figure 37. Percentage children per centre that performed a GTT in 2014.
Figure 38 shows the percentage of adults per centre that had a GTT in 2014. The percentage is calculated among adults, without lung transplant, without CFRD and with a pancreatic insufficiency.

**Figure 38.** Percentage adults per centre that performed a GTT in 2014.
Appendix 1: Publications and requests granted in 2014 for data from the Dutch CF registry

Cost-effectiveness of newborn screening for cystic fibrosis determined with real-life data.
van der Ploeg CP, van den Akker-van Marle ME, Vernooij-van Langen AM, Elvers LH, Gille JJ, Verkerk PH, Dankert-Roelse JE; CHOPIN study group.

Factors associated with FEV1 decline in cystic fibrosis: analysis of the ECFS patient Registry.

Request: child lung diseases KU Leuven
Cystic Fibrosis among the Asian population: prevalence and clinical characteristics. Status: to be published.

Request CFTR2 mutation database
Update on mutations in Dutch patients with CF. Status: processed in database: http://www.CFtr2.org

Request ECFS DiagnosticWorking Group
Comparisons of registries with and without Newborn Screening
Status: to be published.

Request Vertex
Overview of Gating (plus 3) mutations in the Netherlands
Status: processed in the request for reimbursement from Zorginstituut Nederland.

Request H. Olesen et al.
Prevalence of CF related liver disease in Europe. Status: to be published.

For a Dutch contribution to data requests from the European CF Registry, see: https://www.eCFs.eu/projects/eCFs-patient-Registry/overview-data-applications