

## Measuring Quality of Life in Clinical Trials in CF: Another Piece in the Jigsaw



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This article is based on a published paper that examined how researchers investigated quality of life in clinical trials of people with CF. First, this article describes the research process, the role of clinical trials and why it is important to gain the views of people with CF as to how a therapy has made them feel. Second, the article summarises the ways in which researchers have measured and reported on patient-reported quality of life in clinical trials

### **What is a randomised controlled trial (RCT)?**

Research is like doing a jigsaw puzzle. Each study corresponds to a small piece in the picture, and the full picture emerges after many studies have been completed. There are several designs for research studies and different designs can answer different questions. When asking about the *effectiveness* of a treatment, the randomised controlled trial (RCT) is the best design. The two aspects that make this a good design are, as the name implies, *control* and *randomisation*.

A controlled trial is one in which there is a treatment group and a control group. If we gave a group of people with CF a new antibiotic, and after two weeks their Forced Expiratory Volume (FEV<sub>1</sub>) had improved and they reported a decrease in coughing and the amount of sputum produced, we may think that the antibiotic was effective. However, we could not be certain that the antibiotic was responsible for the improvement. There



could be other reasons why chest symptoms improved. So if we want to be sure that the improvement was an *effect* of the treatment, it is important to have a control group. This is a group that is treated just the same as the treatment group but they take a pill that doesn't contain the antibiotic, known as a placebo (this would be called a placebo controlled trial). Alternatively, the control group may be given an existing antibiotic if the aim of the research was to compare the new antibiotic with an existing one. The control group should be made up of people with CF as similar to those in the treatment group so that any differences in FEV<sub>1</sub> or chest symptoms can be attributed to the antibiotic – as this would be the only difference between the groups.

This is where randomisation comes in. The only way to be sure that there are no differences between the groups is to allocate people to the treatment and control groups randomly (like tossing a coin, but more scientific). We then use statistics to analyse the RCT – to see if the differences in FEV<sub>1</sub> and chest symptoms between the antibiotic group and the placebo group are large enough for the antibiotic to be clinically beneficial. Or, if we are comparing an existing and a new antibiotic we can evaluate whether they produce similar improvements or whether one is more effective than the other.

### **Quality of RCTs**

Unfortunately, in the research literature there are good RCTs and not so good RCTs; and there are RCTs that are reported very well and others that are reported badly. This makes it very difficult to interpret the research information. Years ago you were much more likely to get an RCT published if the results were positive (e.g. if there was an improvement in lung function). However, some of these RCTs were not well-designed and the apparent positive results were spurious. RCTs which showed that a drug was not effective were less likely to be published. This resulted in publication bias – the evidence in the medical journals may have suggested that a treatment was effective, but this was not the whole picture - some pieces of the jigsaw were missing.

In order to remedy this situation, a group of researchers drew up a set of guidelines for reporting RCTs. This is called the CONSORT statement. It lists all aspects of a trial that should be reported (<http://www.consort-statement.org/revisedstatement.htm>). Many medical journals now use CONSORT to assess papers when deciding whether or not to publish them. A paper that meets the CONSORT criteria should be published whether the

results are positive or negative. In this way all valid pieces of the jigsaw are available, and people reviewing the evidence should be able to see as much of the picture as is available.

### **Outcome Measures**

One of the areas that CONSORT covers is the choice of outcome measures for a RCT. Before running a RCT researchers must decide how they will assess whether or not a treatment is effective. What things will they measure - FEV<sub>1</sub>? Bacterial infection? number of respiratory exacerbations? Or nutritional status? How much would they expect FEV<sub>1</sub> to improve? Which are the most important outcomes (these are called primary outcomes) and which are less important (these are secondary outcomes)? These decisions affect the number of people needed for the trial. Furthermore, we need to be sure that the chosen outcomes measure what they are supposed to measure. Also, if the treatment does have an effect (improvement or deterioration) the outcomes should be able to detect this. Several outcome measures could be chosen. Those most often used in CF RCTs are lung function (FEV<sub>1</sub>, FVC), number of chest exacerbations, weight or body mass index (BMI), side effects and, more recently, quality of life (QL).

### **Why should we measure quality of life in clinical trials?**

A person's account of how effective they believe a treatment to be is also important. We know that clinical tests (e.g. lung function and type of infection) do not always correspond very well with what patients report they can do or how they feel. Therefore, people with CF can provide additional valuable information to the clinical information that is typically collected. Some effects of treatments (including side effects) can only be known by the patient because there is no objective way to see them or measure them - for example aches and pains, tiredness or anxiety.

Asking people with CF about their symptoms and how these affect their lives, before, during or after a course of treatment is nothing new. In clinical practice a doctor will informally ask questions such as 'How is your cough?' 'Does it keep you awake at night?' 'Are you able to go to work?' What patients report is typically used to help clinicians make a decision as to the most appropriate treatment, and to assess how effective the treatment is. Quality of life measurement (measured by questionnaire or interview) is a more formal way of assessing how a treatment has impacted on several

important aspects of a person's life (e.g. chest symptoms, school / work, social life, self-esteem, body image, how energetic and happy they feel). Additionally, any adverse effects of a treatment may result in a detrimental impact on QoL.

There are three types of QoL questionnaires that tend to be used in CF research. These are (1) generic questionnaires which can be used to measure quality of life in any disease, (2) respiratory questionnaires that can be used with any chest condition and (3) there are now questionnaires that have been developed specifically to measure QoL in CF. The CF-specific questionnaires are the best to use in a RCT because they are likely to provide more meaningful information.

Until recently, QoL has mostly been measured as a secondary outcome in RCTs, suggesting that it is not as important as the primary outcome (which tends to be lung function). However, some studies are measuring patient-reported QoL as the primary outcome. Two treatments (or delivery systems) may similarly improve lung function but people with CF may report that one treatment makes them feel better and / or gives them a better quality of life. This is important information for the management of CF.

### **Systematic Review Methods**

A systematic review is a research study which systematically searches for all papers on a particular subject and then summarises them; this is like describing part of the jigsaw. We decided to do a systematic review of RCTs in CF where researchers had looked at quality of life as an outcome. We searched a number of computer-based databases which list published papers, and selected those written in English, reporting RCTs exclusively on people with CF where conclusions were made about the effect of treatment on quality of life or on well-being. For each RCT we assessed several factors including:

- The purpose of the trial;
- The rationale for measuring quality of life;
- The type of questionnaire used to measure quality of life;
- The participants in the trial;
- The linking of clinical and QoL outcomes;
- The validity of the conclusions.

## Results

We found 16 trials. The treatments were as follows: antibiotics (5 trials), steroids (1 trial), mucolytic therapies (6 trials), exercise (3 trials) and pancreatic enzymes (1 trial). Table 1 provides a brief description of the trial and the authors' conclusions concerning the clinical and QoL outcomes.

When running a trial it is important to know why quality of life is being measured, and to have some idea of how and why it could change following treatment. Only 4 papers provided a rationale for measuring QoL and only 4 papers justified their method of measuring it.

Six trials recruited children, 4 trials recruited adults and 6 included both children and adults. There was only one trial that had QoL as a primary outcome. This compared home and hospital administered antibiotics. In this situation, where patients may prefer to administer IVs at home, it is important to establish that the treatment effectiveness is not compromised and to investigate the effects on QoL.

Few papers gave enough information about the results to enable the readers to understand how QoL was affected or how the QoL and clinical results were related. Most authors presented definite statements about quality of life, but no RCT provided conclusive data to back up these statements.

## Conclusion

A good RCT provides important information for clinicians and contributes to what we call 'evidence-based medicine'. The quality of the evidence depends on the quality of the RCT and the quality of the published paper. Knowing that a treatment affects QoL is insufficient in itself; clinicians need to understand the *nature* of these effects. For example, papers should describe the QoL scores that people had at the start of the RCT (before any trial treatment) and at the end. There are other factors that affect the quality of the data. Some people recruited to a RCT will drop out, resulting in missing data. Obviously, the trial results are more reliable if there are only a small proportion of missing values. All papers should describe how they have dealt with problems like this.



Our review highlights many of the pitfalls in QoL measurement in CF clinical trials and provides constructive information concerning QoL in trial design and the reporting of QoL data. Hopefully it will help to shape our thinking and ensure that we consider all the pieces of the jigsaw. Indeed, as part of the EuroCareCF project (Clinical research – Work package 3), a working group has been formed to look at how best to include the reports of people with CF as an outcome measure in clinical trials. For more information, visit: <http://www.eurocarecf.eu>.

The original paper can be obtained on-line:

Abbott J, Hart A. (2005). Measuring and reporting quality of life outcomes in clinical trials in cystic fibrosis: a critical review. *Health and Quality of Life Outcomes*;3;19. <http://www.hqlo.com/contents/3/1/19>



**Table 1 Summary of authors' conclusions from RCTs measuring QoL**

<b>Brief description</b>	<b>Authors' main conclusion</b>	<b>Authors' conclusion about QoL outcome</b>
<b>ANTIBIOTICS</b>		
Tobramycin versus placebo	Tobramycin improved lung function	Tobramycin improved QoL
Azithromycin versus placebo	Azithromycin improved lung function	QoL similar for each group
Azithromycin versus placebo	Azithromycin improved lung function	Azithromycin improved all aspects of QoL
Azithromycin versus placebo	Azithromycin improved lung function and weight but had more side effects.	Azithromycin improved physical functioning only
Home versus hospital IV antibiotics	No clinical compromise associated with home therapy	Home IVs worse for fatigue and mastery, but better for personal, family, sleeping, eating
<b>STEROIDS</b>		
Corticosteroids versus placebo	No benefit	No benefit for well-being
<b>MUCOLYTIC THERAPIES</b>		
DNase versus placebo	DNase improved FEV <sub>1</sub>	DNase did not improve overall well-being but improved some symptoms
DNase versus placebo	DNase improved lung function	DNase improved breathlessness and well-being
DNase versus placebo	DNase improved lung function	DNase improved well-being
DNase versus placebo	No benefit	No benefit for well-being
Daily versus alternate day DNase versus saline	Daily treatment better than saline for lung function	No benefit
Normal or hypertonic saline	Hypertonic saline improved lung function	An improvement, but inconclusive results
<b>EXERCISE</b>		
Aerobic training or resistance training or standard care	Aerobic training improved fitness. Resistance training improved weight, lung function and leg strength	Aerobic training improved QoL
Anaerobic training versus normal activity	Training improved performance	Training improved QoL
Aerobic versus upper-body strength training	Strength and aerobic training may increase upper-body strength and physical work capacity	No benefits
<b>PANCREATIC ENZYMES</b>		
4 versus 1 capsule daily	No difference	No benefit for well-being