

## Measuring health-related quality of life in clinical trials in cystic fibrosis

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### Abstract

The inclusion of health-related quality of life (HRQoL) as an outcome measure in cystic fibrosis (CF) clinical trials can supply important patient-reported information not captured by other endpoints. Both an appropriate HRQoL measure and sound methodology are required in order to draw valid inferences about treatments and HRQoL. This paper provides the current consensus of the HRQoL Outcomes Group. Particular consideration has been given to the appropriateness of measurement scales, the rationale for including specific domains as endpoints, the importance of considering baseline ceiling effects and the difficulties of data interpretation. Guidance is provided on HRQoL measurement in National and European CF clinical trials.

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### 1. Introduction

Health-related quality of life (HRQoL) was established as a paradigm to include the patients' perspective in clinical practice and research. Typically, HRQoL is defined as a multidimensional construct comprising (at least) physical, psychological and social well-being and functioning as perceived by the individual. The inclusion of HRQoL as an outcome measure in cystic fibrosis (CF) clinical trials is becoming more common. Both an appropriate HRQoL measure and sound methodology are required in order to draw valid inferences about treatments and HRQoL [1,2].

#### 1.1. Why is HRQoL important in clinical trials?

Asking the patient "how they are" or about the effectiveness of treatments is nothing new. HRQoL instruments, however, can provide a formal, standardised, valid and reliable way of gaining the patients' perspective as to the benefits and limitations of a specific intervention. Regulatory authorities and Good Clinical Practice (GCP) guidelines require the inclusion of HRQoL in clinical trials as an additional outcome parameter [3]. HRQoL can provide "added value" as it can supply information not captured by other endpoints. The correlations between clinical variables and HRQoL are often poor. Furthermore, there are some things that only the patient can know (for example, fatigue, nausea). HRQoL may be informative as an efficacy measure, but it is potentially also a safety measure and for these reasons HRQoL is becoming important in labelling claims.

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## 2. Considerations for measuring HRQoL in clinical trials

In the past HRQoL has been indiscriminately applied and abused. There has been a general lack of expertise and knowledge among trial investigators. HRQoL has been considered easy to measure and/or not too important. This approach has resulted in poor data quality (and potentially unreliable claims being made about treatments). This report is not intended to deter researchers from measuring HRQoL in clinical trials. The aim is to outline important issues in order to improve practice, so that those who do measure HRQoL in trials can produce scientifically and clinically valid results.

### 2.1. Measurement scales

There has been little consensus on how to measure HRQoL in CF at a conceptual or operational level. HRQoL instruments provide different information, even for similarly named domains (for example, social functioning can refer to a variety of concepts), and there is no “gold standard”. The diversity of instruments and definitions of HRQoL (defined by the items that make up the scale) have produced inconsistent findings in CF [4]. Different types of scales have previously been employed and include: global rating of change, ad hoc, generic (SIP, NHP, SF36; CHQ, PedsQL), utility (QWB, EuroQoL), non standardised profiles (SEIQoL), respiratory (CRDQ, SGRQ) and CF specific scales (CFQ [5–9], CFQoL [10], FLZ-CF [11], DISABKIDS [12])<sup>1</sup>. Only the CFQ has scales for both children and adults. Apart from CF specific scales, the only scales that have CF psychometric evaluation data for investigators to consult are the SF36 and CRQ [13,14]. When trying to evaluate *change* in a trial, stringent reliability and validity criteria are paramount. Thus far, only the respiratory scale of the CFQ has been approved by the US Food and Drug Administration (FDA) for use as an endpoint in trials. It is noteworthy that it is the CFQ domain (adolescent and adult) with the most acceptable intraclass correlation coefficient for test-retest reliability. The scale captures perceived respiratory function/symptoms which is only one aspect of the much broader construct of HRQoL.

The International Society for Quality of Life (ISOQoL) Efficacy Working Party and the FDA have provided several recommendations concerning HRQoL instruments [3]. First, investigators should examine the psychometric data for an instrument to ensure that it meets their requirements. It is essential that an instrument’s psychometric data are robust before the instrument is used in a trial. Construct validity, internal reliability, known groups validity and especially test-retest reliability must be strong. Second, a full psychometric

evaluation should be undertaken with cultural translation (especially construct validity and test-retest reliability). Third, scales should be revised for developments in the disease to ensure that they remain valid. CF disease has “evolved” and since the CF HRQoL scales were developed several years ago there has been a significant increase in survival, with greater opportunities for employment, relationships and parenting, together with an increase in CF related conditions (e.g. diabetes, osteoporosis), new medicines and treatment burden.

### 2.2. HRQoL measurement should be theoretically driven.

Investigators should have a rationale for including all outcomes in a trial and patient reported outcomes are no exception. All HRQoL domains that make up an instrument should be carefully considered to identify the additional information that each domain brings to the trial. Investigators should check that the items in specific domains are valid for the purposes of the trial. They should be able to provide a rationale for the inclusion/exclusion of specific domains as endpoints. Pilot studies can be used to inform the trial as to which domains are important in addition to the size and variation of change(s) anticipated. Ideally, *a priori* hypothesis testing should be undertaken.

### 2.3. Ceiling effects should be considered

Many people with CF report a good HRQoL even when they have severe disease. It is not uncommon to have relatively large numbers of patients scoring very highly on some HRQoL domains at baseline. These ceiling effects are important because investigators are presumably looking for a change, usually an improvement in HRQoL. Therefore, there must be the potential to demonstrate improvement if an improvement occurs. Using baseline HRQoL scores as inclusion/exclusion criteria should be considered especially if HRQoL is the primary outcome. If HRQoL is a secondary outcome, a sample size calculation or the analysis and interpretation of results needs to take into account the subgroup of patients who would not be expected to respond.

### 2.4. Data analyses and interpretation

It is a high hurdle to expect a drug or non-pharmacological intervention to improve all HRQoL domains in a scale with wide ranging concepts. If 10 domains in a scale are measured and only 1 or 3 or 6 change – how should these data be interpreted? Can it be claimed that HRQoL has improved? In the CF literature there are claims made that a treatment improves HRQoL when only 1 of many domains that were measured actually improved. Theoretically driven data can remove this interpretation difficulty, as investigators will already have an *a priori* hypothesis for the domains to be measured in the trial.

The interpretation of the results should not be based solely on *p* values, especially if HRQoL is a secondary outcome, when the trial tends not to be powered for HRQoL.

<sup>1</sup> SIP = Sickness Impact Profile, NHP = Nottingham Health Profile, SF-36 = Short-Form 36, CHQ = Child Health Questionnaire, PedsQL = Pediatric Quality of Life Inventory, QWB = Quality of Wellbeing Scale, SEIQoL = Schedule for the Evaluation of Individual Quality of Life, CRDQ = Chronic Respiratory Disease Questionnaire, SGRQ = St George’s Respiratory Questionnaire, CFQ = Cystic Fibrosis Questionnaire, CFQoL = Cystic Fibrosis Quality of Life Questionnaire, FLZ-CF = Questions on Life Satisfaction–CF specific.

This presents difficulties for HRQoL interpretation. The data should be described and the clinical importance of the findings should be discussed. Knowledge of what constitutes a clinically important difference is helpful, although the minimal clinically important difference (MCID) is not without problems. For example, there can be confusion over the interpretation of individual or population MCIDs.

A potential way forward is to measure outcomes in terms of “responders”. A responder is a person for whom the treatment is deemed to have been successful. Responder criteria are the rules which determine whether a person is a responder. The criteria may vary from one patient subgroup to another, for example, dependent on the severity of the disease and/or the patient’s symptoms. When designing such a trial, investigators need to define: (a) what they expect the treatment to do, (b) the population expected to respond to treatment, and (c) the criteria defining a responder. The report should compare the proportions of responders in each treatment arm.

### 2.5. Combining data (children and adults)

There is a relatively small population of CF patients. As a result, data from children and adult patients have been combined in analyses, often when it was inappropriate to do so. Investigators need to ensure that child and adult domains with the same name (e.g. physical function) are measuring the same concept and that the number and content of the items are comparable. This is especially important in long term trials; investigators need to be sure that if an adolescent enters a trial and is reassessed as an adult – that the adolescent and adult scales are equivalent. Currently, there are no comparable CF-specific scales for children and adults. Therefore, data for children and adults should not be combined in a single analysis.

### 3. Current consensus of the HRQoL Outcomes Group

Agreement was reached on a number of issues reflecting the use of HRQoL in CF trials currently and in the future.

- The use of HRQoL should be theoretically driven.
- A CF specific scale should be used where possible.
- Existing CF scales are good at describing HRQoL and for use in clinical practice. Further consideration of their suitability and value in clinical trials is warranted.
- Research may continue with available measures that best meet the criteria set out below. At the same time, for European trials, we should ensure instrument development that will meet optimal clinical trial criteria.
- At present it is feasible to measure HRQoL in:
  - (a) A national trial with adults *or* children, where scales exist that have robust psychometric properties (including construct validity and test-retest reliability).
  - (b) In international trials different translations of a measure could be used, but stratification by country would be required where translations were not direct copies of the original or agreement between the measures not demonstrated.
  - (c) At present, HRQoL should not be measured in Eu-

ropean trials where both child and adult scores are combined for the purposes of data analysis.

- If possible, the primary source of information should be the patient. Who reports (patient or proxy), when and how often, will depend on the nature of the trial, but careful consideration should be given to these issues.
- Using current developmentally appropriate scales, children may report HRQoL reliably and consistently from the age of 8 years. Further study should look at possible ways of assessing HRQoL in children younger than 8 years. In children, the collection of self-reports and parent/caregiver reports may provide additional information, especially regarding the observable aspects of HRQoL such as physical function. These responses should not be regarded as interchangeable and/or combined in data analysis.
- Scales should be short. (It is unethical to overburden the patient; it may cause them to drop out of a trial or compromise data quality).
- Ceiling effects should be considered and inclusion/exclusion criteria defined.
- Patient responses tend to be more reliable if focusing on their present state rather than on longer recall periods. However, the time-frame should be compatible with the anticipated effect of the intervention to allow potential changes in HRQoL to be determined.
- Trial investigators should seek advice on HRQoL measurement, analysis, interpretation and data reporting.

### 4. Conclusion

HRQoL measurement, if undertaken appropriately, can provide a standardised, valid and reliable way of gaining the patients’ perspective as to the benefits and limitations of a specific intervention. It can supply important information not captured by other endpoints. The current consensus of the HRQoL Outcomes Group should provide guidance, and help researchers avoid the many pitfalls, regarding HRQoL measurement in National and European CF clinical trials.

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### Conflict of interest

No author has a conflict of interest.

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