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Review

Lung clearance index: Evidence for use in clinical trials in cystic fibrosis

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Abstract

The ECFS-CTN Standardisation Committee has undertaken this review of lung clearance index as part of the group's work on evaluation of clinical endpoints with regard to their use in multicentre clinical trials in CF.

The aims were 1) to review the literature on reliability, validity and responsiveness of LCI in patients with CF, 2) to gain consensus of the group on feasibility of LCI and 3) to gain consensus on answers to key questions regarding the promotion of LCI to surrogate endpoint status.

It was concluded that LCI has an attractive feasibility and clinimetric properties profile and is particularly indicated for multicentre trials in young children with CF and patients with early or mild CF lung disease. This is the first article to collate the literature in this manner and support the use of LCI in clinical trials in CF.

Keywords: Clinimetric properties; Multiple breath washout; Lung clearance index; Outcome measures; Surrogate endpoints

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1. Introduction

In the cystic fibrosis (CF) community, there is a need to focus on developing and evaluating endpoints for clinical trials in early disease. The European Cystic Fibrosis Society Clinical Trial Network (ECFS-CTN) has established a Standardisation Committee consisting of researchers with expertise in specific outcome measures. The Standardisation Committee is undertaking a rigorous evaluation of potential outcome measures for multicentre clinical trials in CF. This article summarises the group's work on lung clearance index (LCI).

A full description of the classification of outcome measures is provided in the first document in the series of articles from the ECFS-CTN Standardisation Committee (CFTR biomarkers group) [1]. Briefly, outcome measures fall into three classes: clinical endpoints, surrogate endpoints and biomarkers. Clinical endpoints reflect how a patient feels, functions or survives and detect a tangible benefit for the patient [2,3]. A surrogate endpoint is a laboratory measurement used to predict the efficacy of therapy when direct measurement of clinical effect is not feasible or practical. Ideally, surrogate endpoints should shorten the period of follow-up required. The link between the surrogate endpoint and long-term prognosis must be proven. Forced expiratory volume in one second (FEV_1) is still the only accepted surrogate outcome for the European Medicines Agency (EMA) and the North American Food and Drug Association (FDA). A biomarker is defined as "a

Table 1
Definitions and justification for clinimetric properties.

Clinimetric property	Definition	Justification of importance
Reliability	Degree to which a measurement is consistent and free from error	Important to quantify error (systematic and random) so that true changes can be discerned from changes due to normal fluctuations
Validity	Concurrent validity: Degree to which a test correlates with a "gold standard" criterion test which has been established as a valid test of the attribute of interest Convergent validity: Degree to which a test correlates with another test which measures the same attribute Discriminate validity: Degree to which a test differentiates between groups of individuals known to differ in the attribute of interest Predictive validity: Degree to which an attribute can be predicted using the result of a predictor test/or degree to which prognosis can be predicted	The gold standard outcome measures are often not feasible. Therefore it is important to know how an alternative outcome measure compares to the gold standard, and how different outcome measures compare. It is important to know the ability of outcome measures to discriminate between different groups
Responsiveness	Degree to which a test changes in response to an intervention known to alter the attribute of interest	Important attribute of tests used in clinical practice or research to assess treatment benefit (e.g. to identify improvements response to an intervention)