Innovations in Outcomes and Designs of Clinical Trials for Respiratory Drug Development

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Abstract

Clinical trials for the development of respiratory drugs have for years been reliant upon measurements of physiologic tests, combined with the use of questionnaires. New drugs were mostly administered by inhalation and increasingly in fixed combinations. However, these lung function tests have a lack of sensitivity for patient-relevant clinical outcomes. Moreover, new insights in phenotypes and endotypes of these diseases in the basic mechanisms and the discovery of new targets for therapy, have led to the need for a more personalized patient-centered approach and precision medicine.

In recent years, a great number of techniques have been proposed but some need further validation. These include fractional exhaled nitric oxide, health-related quality of life and the use of biomarkers like blood and sputum eosinophils and neutrophils, IgE, sIgE, periostin, copeptin and specific cytokines. Additionally, exhaled breath condensate and lung deposition studies by functional residual imaging and by local bronchial pharmacokinetics can be used. In rare diseases like cystic fibrosis, Lung Clearance Index and CT and PET scan fusion images seem to be valuable outcome measurements. Lastly leverage of lung function tests can be done by using body plethysmography, measuring respiratory impedance, variability and the use of modeling and simulation.

The need for a patient-centric approach through all stages of clinical development is becoming mandatory. So, an evolution from classical randomized clinical trials (RCTs) to more efficient and patient-relevant designs will be seen more in the future. RCTs will remain necessary for regulatory submission but more efficient and adaptive designs with lower heterogeneity and the use of pragmatic trials are needed. This evolution from undefined targets to a more targeted approach will lead us closer to precision medicine.

In this overview, the unmet medical need for better outcomes and study designs in the development of treatments for respiratory diseases, are discussed.

Keywords: Respiratory drug; Respiratory diseases; Lung function tests; Respiratory trials

Introduction

Clinical trials for the development of drugs for respiratory diseases, mainly asthma and chronic obstructive pulmonary disease (COPD), have for years been relying on measurements of physiologic tests combined with the use of questionnaires. The new drug was mostly administered by inhalation and increasingly in fixed combinations.

The assessment of adequate control of disease status and progression are still mostly achieved by lung function tests, with a particular focus on forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC). Clinical and patient-reported outcomes such as dyspnea, exercise capacity, exacerbations, use of rescue medication, physical activity, health-related quality of life and mortality, have been applied more frequently as an essential part of the clinical assessment.

These lung function tests have a lack of sensitivity for patient-relevant clinical outcomes. Moreover, new insights into the phenotype (defined by clinical features that distinguish between individuals) and endotype (subtypes defined by distinct physiological mechanisms) of these diseases and into the basic mechanisms combined with the discovery of new targets for therapy have led to the need for a more personalized patient-centered approach and precision medicine.

Although progress has been made there remains an important gap in our knowledge regarding more sensitive patient-relevant outcomes that have been validated and accepted as primary outcomes by the authorities. Also, the application of more efficient designs for randomized controlled trials and the introduction of more patient-centered approaches making use of pragmatic trials and real-world evidence lag behind other therapeutic areas. In this overview, the current efforts to fulfill this unmet medical need for better outcomes and study designs in the development of treatments for respiratory diseases will be discussed.

Outcomes in Respiratory Trials

Outcomes in asthma trials

Minimal recommended outcomes for asthma trials, apart from spirometry pre and post-bronchodilator therapy are symptom scores such as the Asthma Control Questionnaire (ACQ) and Asthma...
Control Test (ACT). Exacerbations are measured by number of hospitalizations, emergency department visits, steroid and rescue medication use. Biomarkers are measured as total and allergen specific IgE (sIgE).

Alternative outcomes previously used for diagnostic reasons and for phenotyping have now increasingly been used as outcome parameters in clinical trials. Fractional exhaled nitric oxide (FENO) is an easy to measure, reproducible, non-invasive biomarker of inflammation. The measurement of NO in exhaled breath has been standardized and is measured with an easy to use, point of care device and expressed as parts per billion (ppb). Values above 50 ppb indicate that eosinophilic airway inflammation is likely.

Health-related quality of life (HRQOL) is a patient-related outcome used to assess the perceived burden of asthma [1]. Quality of life questionnaires have been validated and compared. HRQOL considers not only the impact of asthma control and severity but also the impact of comorbid conditions and the potential additional burden of treatment side effects.

Blood and sputum eosinophil and neutrophil, IgE, sIgE, peroxidin another biomarker of inflammation have been used to define inflammatory asthma phenotypes as predictors of airway asthma exacerbations and as a potential target for anti-inflammatory biotherapies [2]. Induced sputum cells and supernatant analysis is a noninvasive way to investigate airway inflammation that has been extensively used in cross-sectional and longitudinal studies. Apart from the inflammatory mediators already mentioned, it allows the measurement of more specific cytokines like II-4, II-5, II-6, and II-13 targeted by new therapies. Although there is still a lack of a golden standard for sputum induction and a quite elaborate and time-consuming sample handling process following a strict protocol and increasing experience has shown highly valid and reproducible data [3,4].

Furthermore, analysis of the components of exhaled breath condensate (EBC) such as airway pH or oxidative-related mediators may assess airway inflammation although there are still problems of dilution repeatability and reproducibility that preclude their use in clinical trials [5]. EBC is easy to collect noninvasively during normal tidal breathing for 10 minutes.

There is also a trend for the increased use of challenge agents such as histamine, methacholine and endotoxin (LPS) to study the effect of drugs in asthma. Adequate use of allergen bronchoprovocation and more recently, the use of the human viral challenge model based on the developing insights in the viral triggers for asthma exacerbations can help a more performant drug development.

Outcomes in COPD trials

According to the draft guidance of the FDA, the primary efficacy endpoints for a COPD should be improving airflow obstruction by demonstrating a change in post-dose FEV1 for a bronchodilator and change in pre-dose FEV1 for nonbronchodilator [6]. Other primary endpoints could be providing symptom relief reflecting the claimed clinical benefit (example reduce), modifying or preventing clinically meaningful measures of exacerbations, altering disease progression by the serial measurement of FEV1 over time and modifying lung structure by a sensitive radiological assessment of lung structure.

Commonly used secondary efficacy endpoints include clinically meaningful improvements in various measures of lung function, exercise capacity, symptom scores, activity scales, and health related quality of life instruments. Biomarkers can in some cases also provide support of efficacy.

Although other outcomes like exhaled nitric oxide fraction (FeNO), Exhaled Breath Condensate (EBC), eosinophils in blood and (induced) sputum and other biomarkers have been more extensively studied in asthma there is increasing interest in studies in COPD. The problem with these biomarkers and also with some scales and (electronic) Patient-Reported Outcomes (ePRO) is proper validation before they can be generally accepted as outcomes in clinical trials by the authorities especially when they are used as primary outcomes [7].

Because of a decline in approval rates for new drugs, high attrition rates and increasing costs the pharmaceutical industry has a rising interest in quick wins fast fails. One method of attempting to improve this is to focus on proof-of-concept studies [8]. For inhalation drugs the most frequently used method of drug administration in respiratory diseases not only COPD this could be done by studying lung deposition in humans and the use of modeling and simulation techniques. Lung deposition can be studied by functional residual imaging and by local bronchial pharmacokinetics through collection of bronchoalveolar lavage fluid (BALF) [9,10]. BALF is collected after advancing a bronchoscope into a wedged position in the medial segment of left or right lung and instillation of an aliquot of sterile saline. This technique can be used to test for example, a chemical or biologic drug administered by oral inhalation in order to compare local and systemic pharmacokinetics. Combining the results of the local PK data in bronchial alveolar lavage fluid (BALF) with the systemic PK and pharmacodynamics data the results can be used in a modeling and simulation exercise to develop an adequate model for further study of the drug effects in a different population.

Outcomes in trials for rare pulmonary diseases

These diseases include mainly Idiopathic Pulmonary Fibrosis (IPF), Cystic fibrosis (CF) and Pulmonary Arterial Hypertension (PAH). They represent a major health care burden in the developed world. Recently improved insight into the mechanisms and genetics of disease is leading to the development of new targeted therapies. In clinical studies, the most commonly used outcomes are still lung function (FEV1, FVC), pulmonary exacerbations and health related quality of life. There are also an increasing number of validated biomarkers, patient reported outcomes, and imaging techniques. In many cases however, we are still struggling with evaluation of early stage and proof-of-concept studies.

For the study of treatments for IPF, there is still an ongoing debate about selection of the optimal primary endpoint, whether it is all cause mortality, progression free survival (PFS) or Forced V ital Capacity (FVC) [8]. In general, no single endpoint is suitable to all types of therapies and composite endpoints are used in many studies. In early phase studies, there is no clarity about outcomes able to detect meaningful disease change. Exploratory omics based research in populations of carefully phenotyped patients with IPF will hopefully lead to the identification of candidate outcome measures. Without such measures the drug development pipeline in IPF remains incomplete.

As secondary outcome parameters used are:

- Six Minute Walk Test (6MWT) and other physiologic outcomes
- Biomarkers
• As PRO, the St. George's Respiratory Questionnaire validated for IPF (SGRQ)
• Quantified high-resolution computed tomography (HRCT) scores
• Positron emission tomography (PET) scans

Additionally, in CF for example, the Lung Clearance Index (LCI) based on multiple-breath inert gas washout (MBW) testing seems to be a valuable tool that also can be used easily in infants [11]. Also, the combination of CT and PET scan in fusion images using fluorodeoxyglucose (FD) PET/CT is a useful tool for detecting inflammatory changes resulting from treatment for pulmonary exacerbations in pediatric patients with CF. These changes correlated with lung function, sputum neutrophil counts, and CF-CT scores, quantified by using standardized uptake values (SUVs) [12].

**Leverage of lung function tests as outcomes**

One technique for improving the value of measuring respiratory function is body plethysmography. This allows assessment of lung volumes such as functional residual capacity (FRC), total lung capacity (TLC) and residual volume (RV). Also, diffusion capacity can be measured with this technique by using dilutional gas methods [13].

Body plethysmography is safe and noninvasive but requires certain equipment and skilled personnel. In body plethysmography, the patient sits inside an airtight box inhales or exhales to a particular volume and then a shutter drops across their breathing tube so that the subject makes respiratory efforts against the closed shutter causing their chest volume to expand. Therefore, body plethysmography is not usually performed in larger clinical trials. This is unfortunate because body plethysmography also allows assessment of airway resistance (Raw) by the direct measurement. Raw is less dependent on patient effort compared with forced volumes and provides an assessment of airway caliber [8].

Another technique to assess pulmonary mechanics and Raw is the forced oscillation technique (FOT). FOT is a noninvasive test which provides unique information about lung mechanics that is not available from spirometry or body plethysmography example, the mechanical impedance of the respiratory system and lung inhomogeneity. FOT employs small amplitude pressure oscillations superimposed onto normal breathing and therefore, it is noninvasive and independent from performance of different respiratory maneuvers. Also, these measurements have been standardized [8].

A different approach is the calculation of the variability in time series of lung function measurements. Temporal fluctuation patterns assessed throughout a specified follow-up period can reflect patient-relevant outcomes and serve as intermediate or surrogate markers. This implies that variability over short periods is related to variability over longer time periods called self-similarity. Kaminisky and colleagues found recently that variability in twice daily peak expiratory flow (PEF) time series and long range autocorrelation were associated with the primary outcome of treatment failure in randomized controlled trials [14]. This methodology has the potential to improve trial efficiency.

A last technique for leverage of lung function parameters is modeling and simulation [15]. In a Phase I, single ascending dose randomized crossover trial in 34 patients classical FEV1 was used as the outcome parameter. Due to the large ‘within-subject’ variability, the analysis failed to detect a clear dose-response relationship. Development of a kinetic-pharmacodynamic (K-PD) model appropriately predicted the data and made extraction of dose-response information possible. The model improved signal-to-noise ratio of the efficacy signal, allowing the selection of doses for a subsequent dose-finding study.

**Use of biomarkers as outcomes**

In the last decade, major advances have been made in the field of biomarker research in various lung diseases including asthma, chronic obstructive pulmonary disease, lower respiratory tract infections, lung cancer and interstitial lung diseases. Multiple biomarkers have been implemented in the clinical practice of respiratory physicians. In parallel with the evolving field of personalized medicine the number of clinical trials that utilize biomarkers is increasing every year. The concepts of biomarker-stratified patient selection and targeted therapy have been established and their efficiency successfully proven [8].

Eosinophil granulocytes are widely used in clinical trials as a biomarker for eosinophilic asthma as indicators for the level of T-helper cell (Th) type 2 activation. Together with total and allergen specific IgE, eosinophil granulocytes, either in peripheral blood or in induced sputum are used as an inclusion criterion. Eosinophil granulocytes serve as a biomarker to allow an enrichment design study.

A further widely used biomarker in asthma is the fraction of exhaled nitric oxide (FeNO). In inflammation, nitric oxide is produced by inducible nitric oxide synthases in different inflammatory cells example, in eosinophil granulocytes. FeNO measurement is conducted in patients with suspected asthma in monitoring of disease activity and to adjust treatment with inhaled corticosteroids. Periostin was introduced as a biomarker that is induced by IL-13 and produced by the bronchial epithelium. It can be used as a surrogate marker for T-helper cell type 2 (Th2) activities. In COPD blood eosinophils are also used as predictors of exacerbations and copeptin as a marker for increased cardiovascular risk [16].

Although there is considerable interest in using biomarkers as surrogate markers for disease outcome no pulmonary clinical trial has been published so far that has tested a biomarker as a primary end point indicating disease progression. Omics technologies are expected to speed up discovery of and increase the number of biomarkers used in lung diseases and can be the key to opening the door to personalized medicine. However, advances in omics technologies have not been incorporated into current clinical trial design in pulmonary medicine. Integrating omics in our clinical trial designs will allow trialists to focus treatments on patients likely to respond and to identify clinically relevant surrogate outcome and drug effect biomarkers [8]. When used longitudinally such a biomarker may grade the patient's progress through a course of treatment. Biomarkers may also provide pharmacogenomics information, identifying which dose of a medication will be effective in a particular patient. The new paradigm suggests that current models for clinical trial design miss potentially efficacious medications since the stratification of patients does not account for sub phenotypes or endophenotypes, imaging a respiratory trial with drug and placebo showing no significant difference on the primary outcome of forced vital capacity (FVC). However peripheral blood mononuclear cells were collected from each patient at the beginning and at the end of the trial and subjected to gene expression profiling by microarray analysis of isolated RNA. If there is a group of patients with distinct patterns of biomarkers that cluster together at the far end of the distribution showing a greatly improved pulmonary function this suggests that the drug was effective in this subpopulation [8].
Another group of biomarkers are imaging biomarkers. Here too, the translation from bench to bedside lags behind. Quantitative computed tomography has been used in COPD, asthma, and Cystic Fibrosis. CT morphometry can be useful for the quantification of airway remodeling. Magnetic resonance imaging may identify abnormal heterogeneity by inhalation contrast. Molecular imaging methods (PET/CT) can demonstrate pulmonary neutrophilic activity as has been explained already.

One of the most promising techniques is certainly Functional Respiratory Imaging (FRI) [9]. FRI combines high resolution computed tomography (HRCT) imaging with advanced engineering to construct 3D biomarkers, using computational fluid dynamics. FRI has the unique capability of producing highly clinical relevant patient specific biomarkers presenting 3D visualization of the patient’s airway and lung geometry, regional airway resistance and aerosol deposition patterns.

For all types of biomarkers, validation and acceptance by regulatory authorities remains hard to achieve.

Improvement in Design of Respiratory Studies

Adaptive trial design

The goal of adaptive trials is to increase the efficiency of randomized clinical trials, potentially benefiting trial subjects and patients with reduced cost and enhanced likelihood of finding a true benefit of the therapy being studied [17]. These designs can be used for exploratory and confirmatory clinical trials. The emphasis in exploratory clinical trials is on finding safe and effective doses assigning a larger proportion of patients to treatments with a relevant effect reducing the number of patients in groups with a poor effect, and to select the best doses for confirmatory trials.

In confirmatory trials, prospectively planned changes to the course of an ongoing trial are made based on an interim analysis of data in a blinded or unblinded way, without undermining the statistical validity of the study.

There are four major categories of adaptations

- Seamless phase 2-3 designs
- Sample-size reestimation
- Group sequential designs
- Population-enrichment designs

An example of a seamless phase 2-3 design is the Indacaterol to Help Achieve New COPD Treatment Excellence (INHANCE) trial [18]. It was an adaptive two stage, confirmatory randomized clinical trial of several doses of inhaled indacaterol, a once daily long acting β2 agonist for the treatment of COPD, in comparison with placebo formoterol or tiotropium. Two of the four indacaterol doses were to be selected for further testing at stage 2 along with placebo and tiotropium. The final analysis would be based on the combined data from the two stages. The two most important statistical considerations for a design of this type are the dose-selection rule at the interim analysis and the statistical inference at the final analysis. The dose selection must be made by an external data and safety monitoring committee. This committee selected two doses for the second stage of the trial. The final analysis was performed when 285 additional patients had been enrolled and evaluated. The difference between each indacaterol dose and either placebo or tiotropium was significant with respect to the primary and key secondary end points. This example shows several conditions that are essential for the successful implementation of an adaptive design. First, the highly quantitative precise and easily obtained early readout of end point data made it possible to eliminate two of the trial groups quickly and enroll many more patients in study groups of primary interests. Second, the preliminary planning for this trial was meticulous with detailed dose selection criteria a communication plan for disseminating interim results a hypothesis testing strategy that controlled the type I error and detailed simulations of the operating characteristics before the initiation of the trial.

Decrease in variability between sites

Variability in data from different research sites decreases the likelihood of finding unbiased study results. Decrease in variability between sites can be obtained by several means like training of sites in study protocol and assessments, supporting local site staff with experienced trial nurses and coordinators, using one type of equipment for measuring important outcomes delivered by one vendor, electronic recording of data through one software system and using one set of standard operating procedures. This is often difficult to accomplish completely for all sites. For smaller studies, using a network of satellites can help to create a sort of virtual monocentric site applying all these methods in the most appropriate way. This can lead to a faster and a more efficient conduct of the study decreasing the sample size and the costs.

Precision medicine

Personalized medicine is an evolving field in which treatments are tailored to the individual patient. Much of the current focus of precision medicine involves developing new drugs for personalized treatment of cancer and other diseases [19].

Increased attention to precision medicine has certainly emerged in scientific literature, lay press and public health. The announcement of the precision medicine initiative has led to a variety of responses. The initiative aims to empower clinicians, patients and investigators to work together toward more personalized care and improved clinical outcomes. It includes the development of a large patient cohort from which both clinical and omics data would be collected.

Enthusiasm about the field has been heightened by a rapid reduction in the cost of high throughput genomic sequencing and a dramatic increase in the identification of potential molecular targets for therapy. Biomarker tests for molecularly targeted therapies can help physicians to select the most effective therapy for a patient’s condition and avoid treatments that could be ineffective or harmful [20].

If it is developed and maintained in a rigorous evidence based fashion with well-designed and well executed studies, precision medicine could rapidly advance the care of patients by tailoring treatment to individual patients’ conditions. This would improve clinical outcomes and quality of life while reducing costs by averting the use of ineffective or harmful therapies.

One step forwards in the direction of precision medicine in asthma was shown recently in a study with dupilumab a fully human anti-interleukin-4 receptor a monoclonal antibody that inhibits interleukin-4 and interleukin-13 signaling, key drivers of type-2-mediated inflammation [21].
Adults with uncontrolled persistent asthma, who are receiving medium to high dose inhaled corticosteroids, plus a long-acting β2 agonist, require additional treatment options as add-on therapy. In a randomized, double-blind, placebo-controlled, parallel-group, pivotal phase 2b clinical trial the efficacy and safety of dupilumab as an add-on therapy in 769 patients with uncontrolled persistent asthma was studied. Dupilumab increased lung function and reduced severe exacerbations irrespective of baseline eosinophil count and had a favorable safety profile.

Pragmatic trials

Many current trials may not adequately inform practice because they were performed with relatively small sample sizes at sites with experienced investigators and highly selected participants, overestimating benefits and underestimating harm. This leads to the belief that more pragmatic trials designed to show the real world effectiveness (RWE) of the treatment in broad patient groups are required. Pragmatic trials require that participants be like patients who would receive the intervention if it became usual care [22].

One barrier to unselected participant recruitment however, is informed consent. To guarantee that everyone who is eligible is included this requirement would need to be waived in some cases. A pragmatic approach is easier when an intervention is implemented at a group level rather than at an individual level. Cluster randomization which involves groups of patients (in the same health care facility) who are randomly assigned to the same intervention, is popular in pragmatic trials.

Good trials also include a variety of investigators with a representative mix of experience appropriate to the intervention under study. Efforts that are made to minimize biases in open trials include focusing outcomes on major events, such as death and emergency hospital admissions. Pragmatic end points should also be important to patients like symptoms, disability, and quality of life.

In a controlled effectiveness trial, the Salford Lung Study conducted in 75 general practices 2,799 patients with COPD were randomly assigned to a once-daily inhaled combination of fluticasone furoate at a dose of 100 μg and vilanterol at a dose of 25 μg (the fluticasone furoate-vilanterol group) or to usual care (the usual-care group) [23].

The primary outcome was the rate of moderate or severe exacerbations among patients who had had an exacerbation within one year before the trial. Secondary outcomes were the rates of primary care contact and secondary care contact. The rate of moderate or severe exacerbations was significantly lower by 8.4%.

There was no significant difference in the annual rate of COPD related contacts to primary or secondary care. The strength of the trial derives from its innovative design. It took place in a single urban area with primary and secondary care connected through an EHR, integrated with a new data recording system to enable the collection of a trial relevant data set. All treatment was carried out by the usual caregivers, while patients were simultaneously monitored remotely with the use of the EHR for the early detection of safety events.

Collecting real world evidence for external validation is driven by an increase of the patient centric approach. Along these lines, there is also an increasing use of outcomes relevant to patients and patient engagement. The use of Big Data derived from HER and large registries linked to integrate RWE adds to this approach. Also, the collection of outcome data through the use of patient’s own devices (Bring Your Own Device-BYOD), electronic Patient Reported Outcomes (ePRO) and electronic Clinical Outcome Assessment (eCOA) are helpful in realizing the goal of outcomes that matters to patients and patient engagement [24].

Conclusion

We can conclude that there exists a low performance of classical primary respiratory endpoints in exploratory and confirmatory studies showing a lack of sensitivity for patient relevant clinical outcomes. So, there is a high need for more sensitive outcomes in respiratory drug development. In recent years, a great number of emerging new and existing techniques have been put forward but further validation is needed before they can be accepted generally certainly as primary outcome parameters in randomized trials. Until now, they demonstrated most value in translational and exploratory development.

There is a clear need to extend these findings to confirmatory trials, and to apply them in the collection of real world evidence. The need for a patient centric approach through all stages of clinical development is becoming mandatory. So, an evolution from classical randomized clinical trials with low external validity and delays which will remain necessary for regulatory submission to more efficient and adaptive designs will be seen in the future.

The use of more patient relevant outcomes and more efficient designs must help to make the right drugs available to patients faster. Moreover, the evolution of the clinical use of respiratory drugs with undefined targets to new drugs with a more targeted approach will lead us closer to precision medicine for respiratory diseases. Finally, all these efforts will move therapeutic research and clinical care from a provider-centric approach to a patient-centric approach.

References


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