

Functional imaging using computer methods to improve respiratory drug development

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1 The need for new outcome parameters

On a global scale, the prevalence of respiratory diseases is increasing of which the two most common respiratory conditions are asthma and chronic obstructive pulmonary disease (COPD). This global rise can be attributed to an enlarged exposure to certain risk factors such as air pollution, cigarette smoke and passive lifestyle. In addition, the aging population in combination with improved health care has resulted in an increase in chronic respiratory diseases. These chronic diseases severely affect the quality of life of the patient and consume a great deal of the healthcare budget. In the European Union, COPD has become the third leading cause of death. Although in general the respiratory diseases can be kept under control there is still a large need for better phenotyping and management of lung diseases such as COPD and asthma in order to further improve the patient's quality of life and reduce the overall cost. An important aspect in this regard is the pulmonary delivery of inhaled aerosols. The large majority of the treatments for respiratory diseases consist of aerosol therapy delivered via the inhalation route. Within the pharmaceutical industry it has become more and more apparent that the cost for the development of new products increases while the number of products that reaches the market declines. One of the causes for this phenomenon is the limited sensitivity of existing lung function tests to detect changes in pulmonary function in an early stage. Therefore within the field of respiratory medicine a consensus is starting to form around the need for new outcome parameters.

The need for new outcome parameters in respiratory drug development

In the past, various large-scale studies^{1,2} have been performed with a number of inhalation compounds or a combination with as primary endpoints the spirometric values, mainly forced expiratory volume in 1 second (FEV1), and the Saint George Respiratory Questionnaire (SGRQ). The FEV1 is today still considered the gold standard for airway diseases. The value represents the volume that a patient can exhale in one second using a forced manoeuvre. According to the authors of the questionnaire, the St George's Respiratory Questionnaire is 'a standardized self-completed questionnaire for measuring impaired health and perceived well-being ('quality of life') in airways disease. It has been designed to allow comparative measurements of health between patient populations and quantify changes in health following therapy.'³

The majority of these studies indicate changes after the administration of the product with marginal clinical significance. While an overall maximum change in FEV1 of 150ml is observed, the clinical implication of this value remains uncertain. Also regarding the outcome of the SGRQ, the studies demonstrate a maximum change of approximately 4, which is recognised as the lower limit for clinical significance.

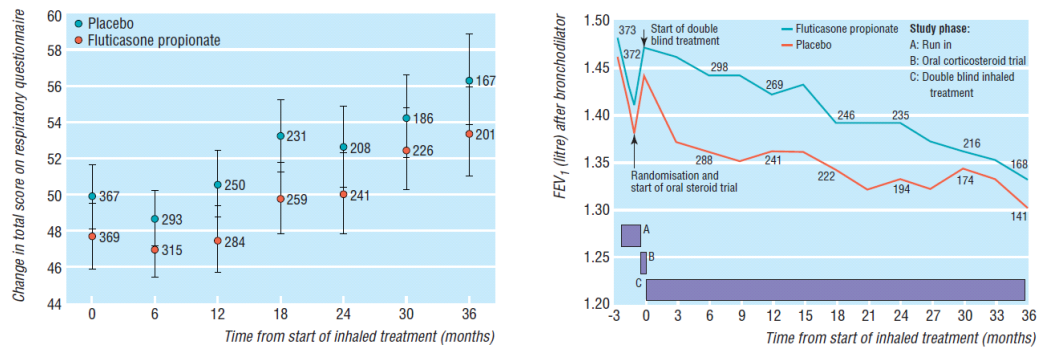


Figure 1 Changes in SGRQ score and FEV₁ for placebo and fluticasone (ISOLDE study¹)

Despite the limited effect of the studied compounds on these functional and clinical outcome parameters, a survival benefit of the fixed combination under investigation compared to the single therapies was demonstrated in the TORCH study⁴ (>6100 patients included) indicating a clear discrepancy between these two parameters.

These studies in general have broad inclusion criteria and mostly assess values averaged over the entire group or large subgroups. Most likely within each of these study populations a considerable group exists in which the products have a significant effect. However, overall these effects are probably 'washed out' by a group of non-responders. It would therefore be beneficial to develop a method that could select the appropriate candidate for a specific treatment. At present, different fields such as genetics and physiology are searching for such novel biomarkers. Imaging is also certainly one of the candidates to become a valuable endpoint in clinical trials and in clinical practice.

Functional imaging as a biomarker

In recent years imaging of the thorax has evolved substantially from an experimental tool that was only used in a limited number of centres towards a routine test for clinical assessment of the respiratory system. Especially the development of high resolution computed tomography or HRCT has greatly increased the understanding of the pathophysiology of respiratory diseases such as asthma, COPD, cystic fibrosis etc. The imaging method in itself has been increasingly used in clinical trials, though the absolute number of studies still remains limited.

Without additional post processing the HRCT scan is limited to static information of the respiratory system. This in itself is already very valuable since, due to the high resolution, certain pathologies (fibrosis, bronchiectasies,...) could be distinguished very well. Today HRCT is the method of choice to determine the extent of emphysema in COPD patients.

Recent developments in the field of flow and structural simulations have made it possible to simulate the behaviour of the flow in the airways on one hand and the tissue on the other hand in a patient specific fashion based on the HRCT images. It could therefore be hypothesised that functional parameters derived from patient specific simulations, such as the modelled airway resistance, can function as a biomarker. Changes in this biomarker could therefore be a reflection of changes that are clinically relevant.

Current use of airway models

In the literature, a number of trials, including FluidDA's studies, have been published that make use of patient specific models based on the segmentation of CT scans. These models

were able to describe the distinct flow patterns in the respiratory system. Certain studies focussed on the effect of inhalation medication and described the subsequent changes in airway calibre and function using the functional imaging approach.

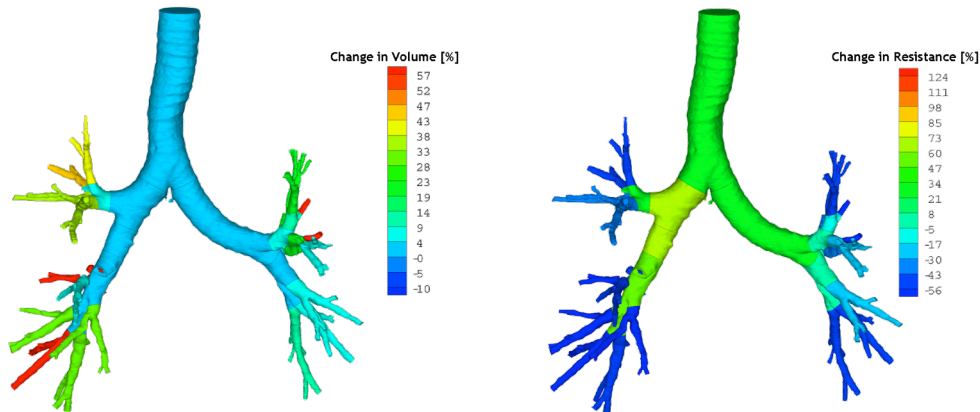


Figure 2 Assessment of changes in airway volume and resistance through functional imaging using CFD⁵

Correlations with clinical outcome parameters have been performed. The results indicated that whenever the simulations are performed accurately, a good agreement is found between the functional imaging results and the clinical parameters. Similar methods can be used to assess the respiratory structure of animals⁶ in pre-clinical research and inhalation devices⁷. Figure 3 illustrates the segmented airway structures and the corresponding lobar volumes derived from static and dynamics micro CT scans. From these examples it becomes apparent that a similar functional imaging method can be used in a pre-clinical as well as in a clinical development stage. The method could therefore potentially facilitate an improvement in translational activities. The next section will illustrate how a common technology could optimize the development cycle of new inhalation compounds.

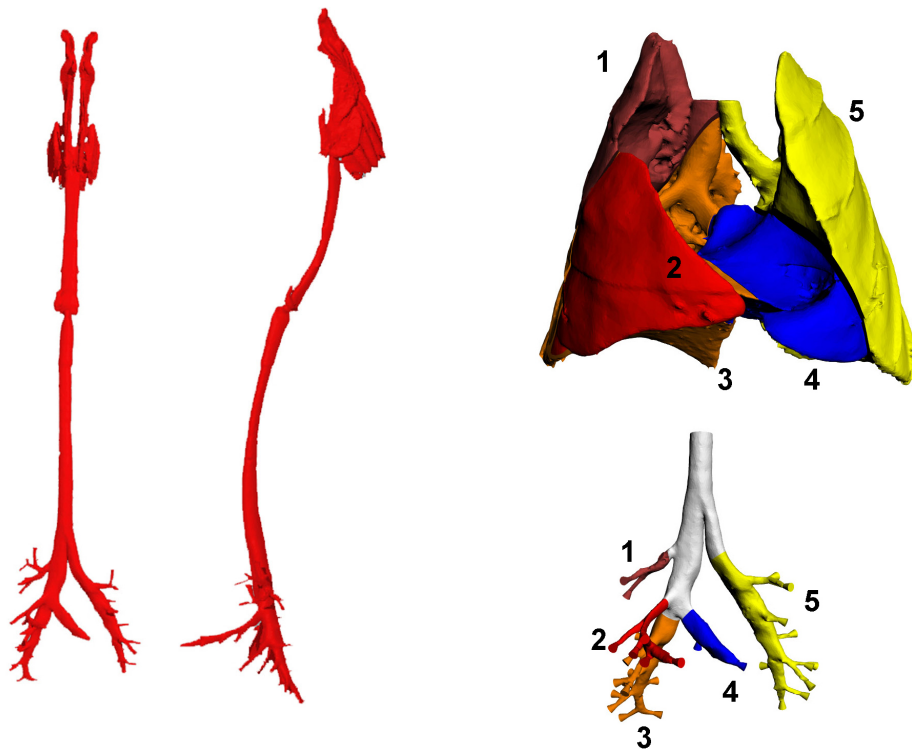
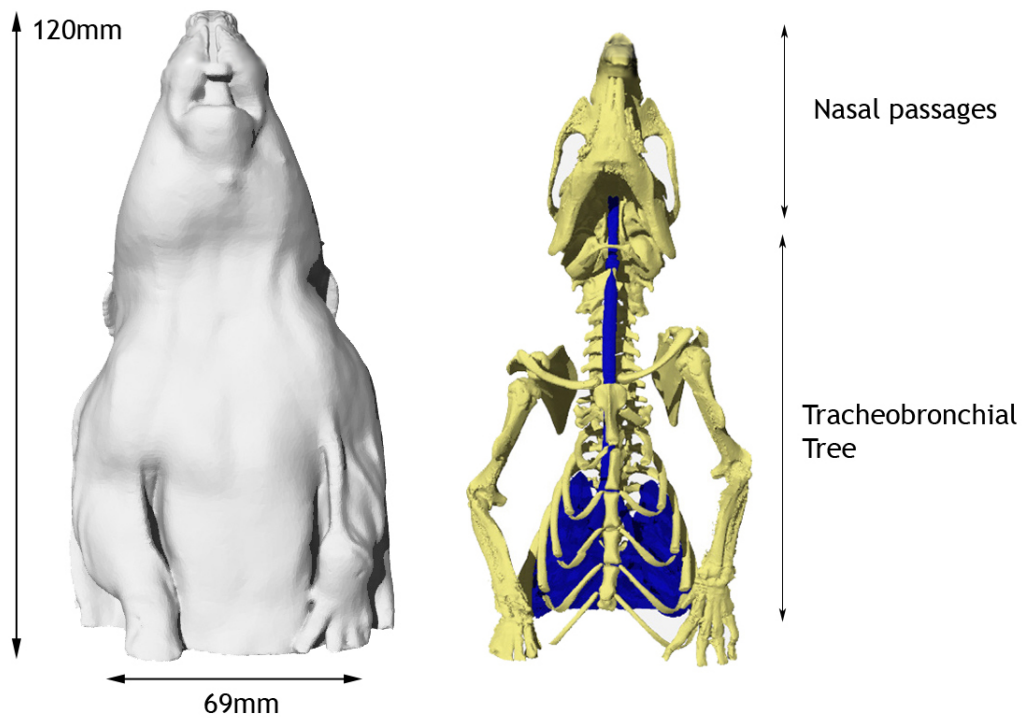


Figure 3 Segmentation of Sprague Dawley rat respiratory system ⁶

2 Optimizing drug development

Respiratory diseases, especially the severe and chronic, have a significant impact on the patients' quality of life. These people often have to reduce their social activities and their working hours. This implies that, due to the increasing numbers of patients, on one hand the healthcare costs are high and even increasing while on the other hand the active, working population reduces. This leads to an unsustainable situation over time, as the economic growth would have to be unrealistically large to cover the rise in cost. Moreover the pharmaceutical companies and regulatory bodies are faced with insensitive outcome parameters that correlate weakly with the clinical outcome so that it becomes increasingly difficult to develop and register novel respiratory products that have a proven clinical effect.

To illustrate this we consider the different phases in the drug development cycle and their respective cost. A previous study by Adams and Brantner⁸ has indicated that the cost for developing a new compound in the respiratory field amounts to a staggering 1134 million dollars (with the dollar value of the year 2000!). This makes respiratory drug development the most expensive one, followed by medication for cancer (1042 million \$) and neurological diseases (1016 million \$). Figure 4 shows a graphical representation of the drug development cycle and the cost involved, including the pre-clinical as well as the clinical phases. From this image it could be observed that the majority of the cost could be attributed to the clinical phases. It is well known that large clinical trials, that are often performed globally, are very expensive. In the respiratory field the need for very large clinical studies is closely related to the lack of sensitive outcome parameters as discussed above. Furthermore the transition from pre-clinical to clinical is often problematic due to the change in species (animal to human) and the lack of a common denominator.

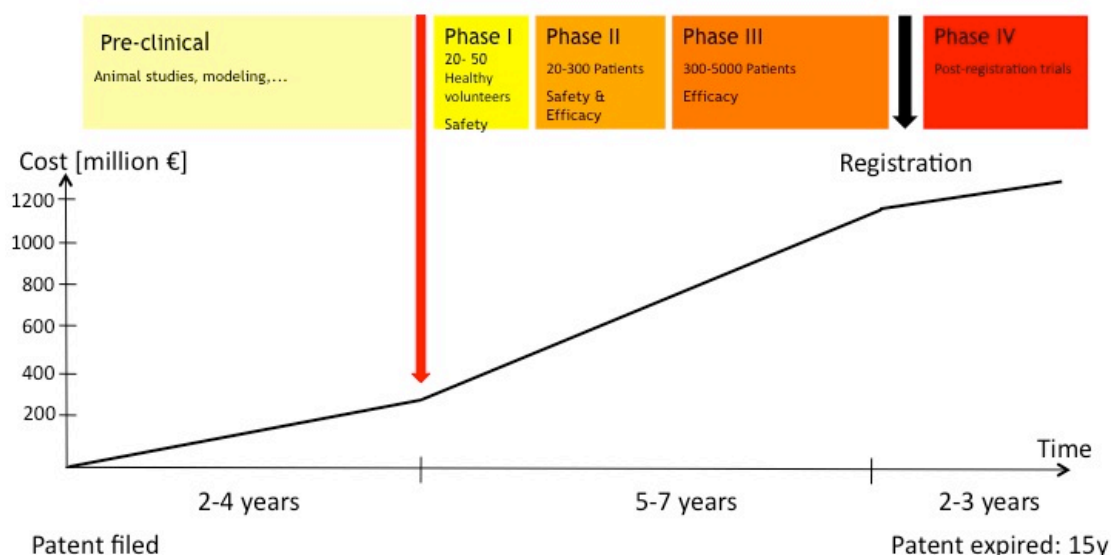


Figure 4 Drug development cycle and indication of cost expenditure based on 8

The field of translational medicine is constantly searching for parameters that could facilitate the transition of a novel compound from the pre-clinical to the clinical stage. Imaging and in particular functional imaging using computer methods is one of the components that could contribute to this goal. As described above previous studies have used this technique to describe animal respiratory structures, optimize device design and implement in clinical trials. Figure 5 illustrates the translational approach for the

implementation of functional imaging and computer methods in the drug development cycle. The common parameters allow for an optimization approach between the pre-clinical and the clinical stages. The patient or animal specific virtual models could be used in a pre-clinical setting to test different inhalation profiles, different devices and their respective deposition patterns. Considering the great deal of information contained in these models, the patient him or herself should not be involved or to a very small extent. This, in combination with the more sensitive outcome parameters in the clinical studies has the large potential of reducing the cost of drug development to a certain extent.

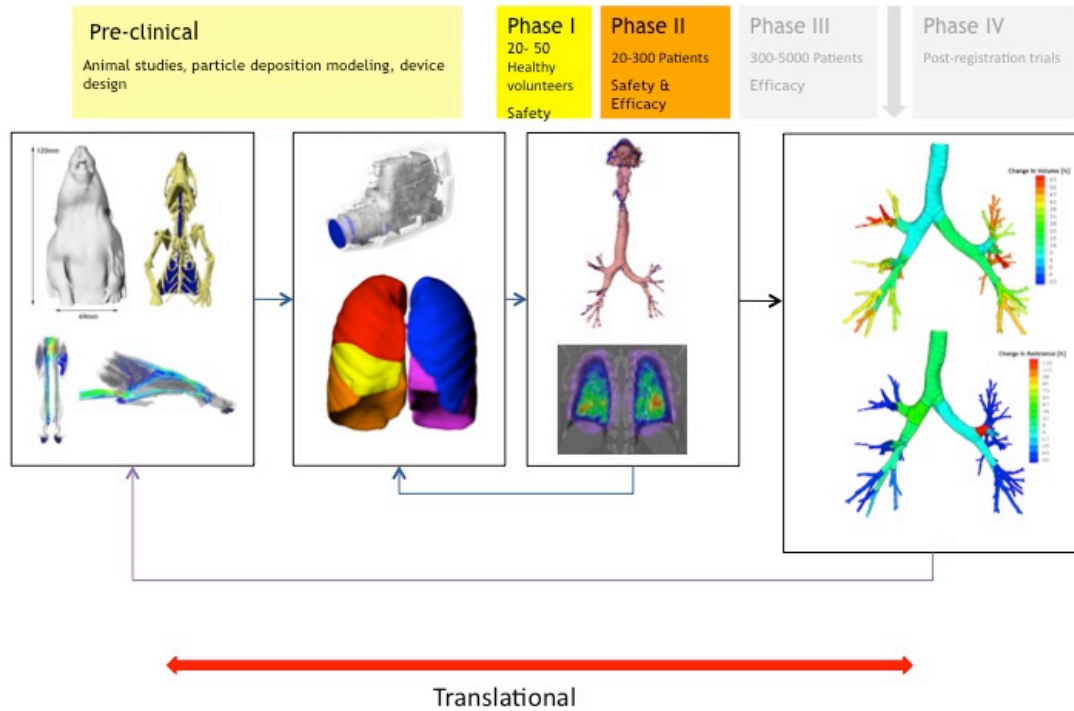


Figure 5 Functional imaging throughout drug development cycle

Figure 6 illustrates how patient specific imaging simulation could assist in decreasing the cost for drug development. It could be observed that if the change in slope of the 'cost' line could be altered by this translational approach the cost, even when they increase linearly, are reduced. Furthermore the more sensitive outcome parameters have the potential to reduce the number of patients needed to demonstrate efficacy thereby reducing the development time and moving the registration forward. This increases the time for the pharmaceutical company to sell and market their product under the protection of the patent. When costs for the development of new compounds are reduced, the price for these products could be lowered without affecting profit margins. The latter would allow for continuous research & development of new compounds in the pharmaceutical industry, while the healthcare system remains sustainable.

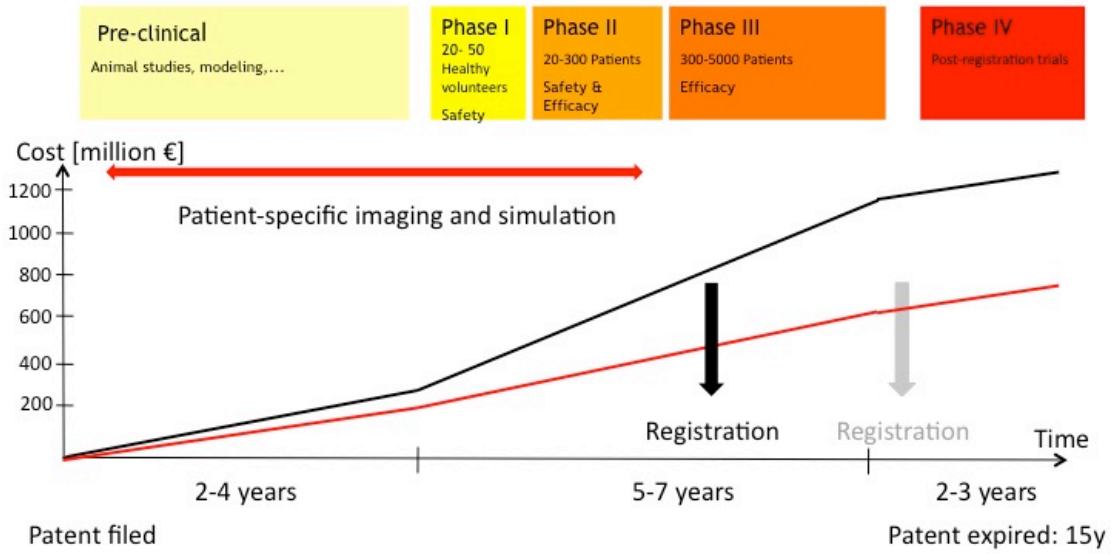


Figure 6 Possible cost reduction in drug development through patient specific imaging and simulation

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