

NUMBER 62 / DECEMBER 2013

# EUROPEAN RESPIRATORY *monograph*

CLINICAL HANDBOOKS FOR THE RESPIRATORY PROFESSIONAL

## Outcomes in Clinical Trials

Edited by Martin Kolb  
and Claus F. Vogelmeier



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Published by European Respiratory Society ©2013  
December 2013  
Print ISBN: 978-1-84984-044-6  
Online ISBN: 978-1-84984-045-3  
Print ISSN: 1025-448x  
Online ISSN: 2075-6674  
Printed by Page Bros Ltd, Norwich, UK

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# Outcomes in Clinical Trials

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Edited by  
Martin Kolb and Claus F. Vogelmeier

Editor in Chief  
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This book is one in a series of *European Respiratory Monographs*. Each individual issue provides a comprehensive overview of one specific clinical area of respiratory health, communicating information about the most advanced techniques and systems required for its investigation. It provides factual and useful scientific detail, drawing on specific case studies and looking into the diagnosis and management of individual patients. Previously published titles in this series are listed at the back of this *Monograph*.



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# Preface

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The Guest Editors describe, in their introduction to this *European Respiratory Monograph (ERM)*, a number of reasons why fewer and fewer new drugs receive regulatory approval, although the funds invested by the pharmaceutical industry for drug development are higher than ever before. Two main reasons are mentioned.

First, the phase II and III studies, which are essential for final approval by the regulatory authorities, are extremely expensive and there is no guarantee that the development costs can be recouped after marketing authorisation. Outcome parameters of early clinical trials that demonstrate a high reliability for predicting results in phase III studies are important. However, the classical outcome parameters, such as lung function measurement and symptom scores, have failed in this regard.

Secondly, drug development has stalled because targets for development are lacking. New trial outcome parameters can contribute to new target identification for therapy: targets that had not been thought of when using the classic method of drug development.

I want to congratulate the Guest Editors, Martin Kolb and Claus F. Vogelmeier, for setting up this extraordinary issue of the *ERM*. For a topic like this, most of the authors did not have a template, and the collation of the data involved substantial work and was sophisticated. Due to time constraints, it was not possible to cover the entire field of pulmonary medicine, and there are additional areas of clinical trial outcomes that might have been included in this issue if preparation time had been available.

Nevertheless, this issue of the *ERM* should be of interest for a wide readership, including basic researchers and clinicians in the field of pneumology and also people working in the pharmaceutical industry or in regulatory authorities dealing with drug approval. I am convinced that they will find this Monograph useful for further consideration of clinical trials.





# Guest Editors

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*Martin Kolb*

Martin Kolb is a German–Canadian physician who obtained his MD at the Julius-Maximilian University Medical School in Würzburg, Germany. He received extensive training in clinical and anatomical pathology in Nürnberg, Germany, before he enrolled in general internal medicine and intensive care. He specialised in respiratory medicine and was board-certified for this discipline and for internal medicine in 2002, then received his PhD equivalent the following year. Currently, Martin Kolb is Associate Professor of Medicine at McMaster University, Hamilton, ON, Canada, as well as Director of the Division of Respiriology and Research Director of the Firestone Institute for Respiratory Health, also in Hamilton. He looks after several hundred patients with interstitial lung disease in his specialty clinic and also practises in general respirology. He is on the medical staff at St Joseph’s Healthcare Hamilton, for respirology and general internal medicine.

In addition, Martin Kolb is Deputy Editor for *Respirology*, the official journal of the Asian Pacific Society of Respirology and Academic Editor for *PLoS One*. He is on the Editorial Boards of the *American Journal of Respiratory and Critical Care Medicine*, the *European Respiratory Journal (ERJ)* and the *European Respiratory Review*. Martin Kolb is on the Executive Committee for the Respiratory Cell and Molecular Biology Assembly of the American Thoracic Society (ATS) and Chair of the Lung Injury and Repair Group of the European Respiratory Society (ERS).

Martin Kolb’s major research area is focused on mechanisms of lung injury, repair and fibrosis, particularly in idiopathic pulmonary fibrosis. He has a strong interest in growth factor biology, extracellular matrix and mesenchymal cell progenitors. In his lab he uses a variety of animal models to study disease mechanisms and also the efficacy of novel drugs in the preclinical setting. In addition, he leads activities in biomarker development for lung fibrosis and he participates as Principal Investigator and Steering Committee member in numerous clinical trials on interstitial lung disease. Martin Kolb has over 80 peer-reviewed publications and has received funding from the Canadian Institutes of Health Research (CIHR), the National Institutes of Health, the Canadian Foundation for Innovation, the Ontario Thoracic Society and others. He has received career awards from the Parker B. Francis Families Foundation, the Dept of Medicine at McMaster University and the New Investigator Award from the CIHR.



*Claus F. Vogelmeier*

Claus F. Vogelmeier is Professor of Medicine and Head of the Dept for Pulmonary Medicine at the Philipps University of Marburg, Germany. After qualifying in medicine from the University of Munich, Claus Vogelmeier started his professional career at the hospital of the University of Munich. He is board-certified in internal medicine, pulmonary medicine, cardiology and allergology. Claus Vogelmeier spent two years as a postdoctoral fellow at the Pulmonary Branch of the National Heart, Lung and Blood Institute, Institutes of Health, in Bethesda, MD, USA. He was nominated Professor of Medicine at the Philipps University of Marburg in 2001.

Claus Vogelmeier is an active member of several respiratory societies, including the ATS and the ERS. From 2002 until 2008 he was Section Editor of the *ERJ*. From 2009 until 2011 he was President of the German Respiratory Society. In 2009 he also became Chairman of the German Asthma and Chronic Obstructive Pulmonary Disease Network. Since 2010, he has been a member of the Science and the Writing Committees of the Global Initiative for Chronic Obstructive Lung Disease (GOLD).

Claus Vogelmeier has a long-standing scientific and clinical interest in obstructive lung diseases, with topics ranging from pathogenetic aspects to novel diagnostic methods and clinical studies.

# Introduction

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The last 50 years have seen a constant decline in approval rates for new therapeutic compounds with respect to the money spent in research and development across all medicine subspecialties. Almost 50% of the costs of developing new drugs are incurred during the clinical stages of the development, particularly in phase II and III trials. Therefore, many pharmaceutical companies aim to reduce expenses for these costly steps in drug development. One method of attempting this is to focus on proof-of-concept studies, which allow them to obtain either “quick wins” or “fast fails” of new products. When “wins” are only achievable over a prolonged period of time, rapid failures are much more cost effective. For some of the chronic lung disease areas, e.g. idiopathic pulmonary fibrosis and pulmonary hypertension, the newer clinical trials involve large phase II trials that have enrolled sufficiently high numbers of patients to allow a meaningful efficacy analysis. They also use the design of two parallel arms in one phase III trial to get independent study results for faster regulatory approval. In order for these new strategies in clinical research and drug development to be successful, the outcomes used for clinical trials are increasingly critical.

While the traditional end-points for clinical studies of lung diseases have been based on functional parameters, there are concerns that this method may oversimplify the complexity of diseases, particularly in the context of chronic lung disease. The value of functional outcomes as surrogate markers for disease activity and progression has been increasingly questioned by scientists, carers, regulatory agencies and funding bodies. Novel tools and methods to measure and quantify biomarkers and patient-reported outcomes have allowed these parameters to emerge from their status as interesting secondary end-points and become potential primary outcomes for clinical trials. Wireless technology and advances in electronic devices make electronic patient-reported outcomes and e-health an option, not only for improved management of patients, but also for better clinical research. Nevertheless, the relevance and validity of these novel outcomes and tools still need to be proven.

This issue of the *European Respiratory Monograph* describes the current status of commonly used as well as investigational end-points in all relevant areas of pulmonary medicine. It includes comprehensive chapters on the most prevalent respiratory disorders, from asthma to chronic obstructive pulmonary disease, lung fibrosis, cystic fibrosis and critical care problems. In the second half of this book, we provide a detailed description of specific outcomes, their value, their limitations and the future promise they might hold. We have gathered a high-profile group of authors from the international societies who are all experts in their respective fields and provide an up-to-date presentation of outcomes in clinical trials in pulmonary medicine. As editors, we hope that this issue will provide a useful summary of the state of the art to the interested reader, and form the basis for seeking additional information from the extensive literature cited in each chapter.