Critical Appraisal: Chronic Respiratory Diseases

London School of Economics and Political Science

The MAPPING_NCDs Consortium*

**which includes Erica Visintin, Francisca Costa, Astrid Grant, Hala Hourani, John Wright, Panos Kanavos (LSE); Mursheda Begum, Elena Pallari, Grant Lewison (KINGS); Ludovica Borsoi, Silvia Sommariva, Oriana Ciani, Rosanna Tarricone (UB).*

Disclaimer:
This research is funded under the European 7th Framework Programme with Mapping_NCD.
The results presented reflect the author's views and not those of the European Commission.

Mapping Chronic Non-Communicable Disease Research Activities and their Impact
This research has received funding from the European Community's Seventh Framework Programme under grant agreement EC/FP7/602536

CONTENTS

List of Figures

List of Tables

Abbreviations

CARDI	Cardiovascular
COPD	Chronic Obstructive Pulmonary Disease
CRDs	Chronic Respiratory Disease
CVD	Cardiovascular Disease
EC	European Commission
EU	European Union
GBD	Global Burden of Disease
ICD	International Disease Classification
IHME	Institute for Health Metrics and Evaluation
MS	Member State
RESPI	Respiratory Diseases
RFO	Research Funding Organization
UK	United Kingdom
US	United States
WHO	Word Health Organization

Executive Summary

According to the Global Burden of Disease study, CRDs are the fifth leading cause of lost DALYs across Europe in terms of NCDs (5%). Breaking down the category into its major diseases, COPD is the largest cause of lost DALYs (30.2%) by comparison with asthma (1.21%).

In the past few years, research investment in CRDs has grown. In terms of project aims, most CRD research has focused on the development of new drugs and therapies. . In respiratory medicine, drugs are becoming increasingly important. The use of antibodies and antagonists to block and change disease mechanisms, oncogenes and metabolic pathways is relevant to key disease types like Asthma, COPD, pulmonary fibrosis, and pulmonary hypertension.

The European pharmaceutical sector has five companies in among the world's top ten pharmaceutical firms. The research pipeline for the top 10 European pharmaceutical companies suggests that firms seem to specialize in certain NCD categories. For example, pipeline data shows that SANOFI-AVENTIS, preferring to focus on other areas, does not have any CRD relevant molecules under development; other firms like GSK, however, are developing several.

Overall, the European pharmaceutical sector has increased its commitment to R&D over the past four years. GSK is the only top 10 company to record a shrinking commitment to research investment. Some companies, like AstraZeneca, have recorded a massive increase in R&D spending. But most companies have recorded progressive of steady increases. By contrast, US levels of investment in R&D have been more mixed.

Interviews with stakeholders revealed several major themes with regard to the future of research in the area of CRDs. There was a recognition of the growing importance of stratified medicine, which several informants considered to be the future of research across the wider spectrum of NCDs. There was a need to find new ways of working with private sector. And there was a need to accommodate new research requirements within a wider strategic approach to the funding of NCD research which considered the needs of researchers for autonomy and the requirements of funders to demonstrate the effectiveness of their investments.

In terms of the effectiveness of research investment, CRD funding demonstrates a significant European presence. And average 56% of paper published for CRDs are of European origin, which is much higher than the percentages for the other four (38% for ONCOL, 42% for CARDI, 40% for DIABE and 35% for MENTH). The internationalism was initially lower than in the other NCDs, but has caught up and even surpassed some of them.

The UK has the highest output in terms of CRD papers, more than twice as high as the second country, France. The UK is publishing almost twice as much as expected, as are Sweden and the Netherlands. On the other hand, Austria is publishing very little, and Germany, Norway and Switzerland are doing barely half of what might be expected considering their levels of GDP.

Papers from Finland and Sweden attracted most funders, and fewer than one in five papers for CRD had no acknowledgements. These papers also had the most support from private-non-profit sources: 48% for Finland and 39% for Sweden. In 10 of the 15 countries, private-non-profit (PNP) sources out-numbered those using public moneys. Industry provided about 13% of funders on average, and international sources, 3.5% – notably the European Commission.

Levels of funding also varied with the subject matter and type of the research, with asthma and COPD receiving the most funding attention and bronchiectasis the least. Clinical papers were less

likely to be funded than basic ones. Papers with more authors tended to have more funding bodies, and that (for the 2009 papers for which five-year citation counts were available) the number of citations was positively correlated with the number of funders.

1 European Research Programs

In this section, we present a "Purposive Sample" of funded research programs and projects for CRDs. It is neither feasible nor desirable to provide a comprehensive sample of funded CRD research projects across EU31. Alternatively, a "Purposive Sample" provides a general description of the types of projects in the relevant disease area for which a selection of RFOs across the EU provide funding. A Purposive Sample is comprised of three parameters:

- a time limitation of 2006-13 in order to include projects under FP-6
- a selection of range of RFOs in the disease area across the different European Countries and the most relevant projects funded by EU or at EU Level;
- and a selection of projects in the disease area relevant to the individual conditions based on IDCs (ie. CRDs: COPD, Asthma, Cystic Fibrosis).

The point of the Purposive Sample is to provide a general description, or appreciation, of the kinds of projects that are being funded in each ICD-10 condition.

1.1 Methods For Establishing the Purposive Sample for CRDs

In establishing the purposive sample of projects for CRDs, we queried the websites of the most relevant European RFOs. These RFOs were selected for their relevance in shaping the National and European Health Policies, rather than their actual levels of funding for CRDs. We adopted this approach for the purpose of capturing grants at a variety of levels, considering that smaller CRD grants play a significant role in smaller MSs. For example, in western European MSs, there are a wide range of grants with smaller levels of annual funding that provide an opportunity to extend or disseminate the results of research already underway. In this way, the role smaller disease specific RFOs, like the British Lung Foundation, in providing these grants is important to the provision of research impact. In addition, larger research projects may also receive multiple inputs from a number of smaller funders.

By contrast, in Eastern European MSs, research funding is principally an activity of Government bodies, which award larger grants with a shorter time horizon. Where these larger block grants were awarded to fund research institutions rather than specific projects, we attempted to individuate larger projects via a multilevel query. This query consisted of the following actions:

- A search for keywords (see Appendix 2) in English and in the relevant national language(s).
- A search by subjects (allowed under the databases) in order to find any possible gaps in the website query.
- In the absence of an available database, a website search or search of annual reports for recent awards.

Given the large number of projects funded for the period 2006-2013, we considered only the projects that commenced and concluded within the time period, limiting the sample to 100 (N) projects for the European area in total. Allocating the N to MSs across the EU, we ranked MS by GDP per capita assigning certain numbers of projects for each country based on comparative levels of GDP. The number of projects assigned for each MS is outlined in the table ??. We allocated 15% of the N to the EC given the higher funding levels and large numbers of projects it awards to CRD projects. Within MSs, we allocated N projects into individual disease types by calculating the percentage of projects for CRD types in MSs . Finally, the largest sample was divided by amount of funding, and 3 categories were created in order to include at least one project for each disease type where possible. After the retrieving of all the projects, we performed a more in depth online research to individuate the maximum level of detail possible. At this stage a mixed quantitative and qualitative analysis was performed.

Results are outlined in the tables below.

The creation of a Purposive Sample involves several limitations. In the first place, the purposive sample does not retrieves and analyzes all the projects funded across EU on CRDs. Indeed, the construction of a comprehensive sample would be unfeasible. . Alternatively, we selected the main projects for relevance and proportionally including also projects with a small level of funding to individuate the main trends across all the type of funding.

Secondly, it was not possible to individuate basic from applied research projects via the database queries. Often the basic research such as microbiology and fundamental chemistry is not specifically directed to a group of diseases but may be directed towards a wide range of applications. Alternatively, we analyzed the specific purpose of the most relevant basic research looking for specific research directed towards CRDs.

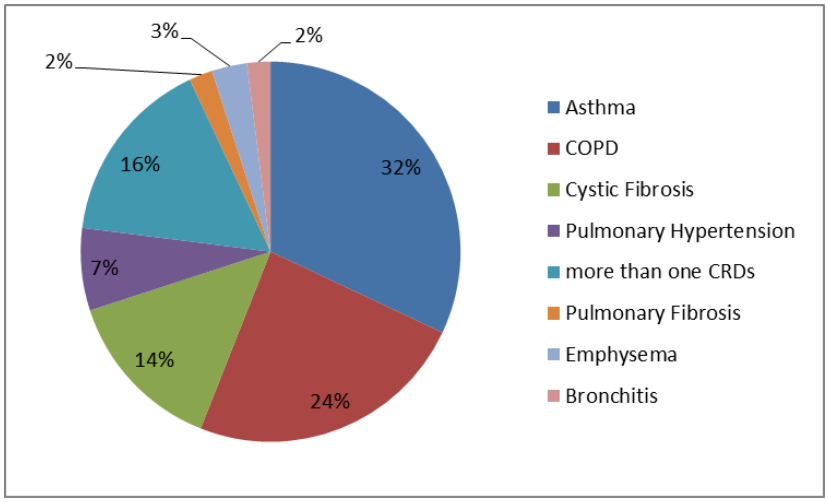
Thirdly, the website query has intrinsic limitations linked to the public availability of information. Often, RFOs do not clearly state the levels of funding for individual projects or even list the projects they are currently funded. Moreover, in some MSs, it was also not possible to individuate projects due to the lack of transparent information.

1.2 Results: CRD Research Programs

Initially, we found around 3500 individuated CRD research projects. Applying the search criteria, we identified 1924 projects across 20 European countries, from which we selected the purposive sample according to the methods outlined above. Broadly, the selection confirmed the trends highlighted in previous reports.

As shown in Figure i, the research investment favors asthma, with the 32% of projects. The second most important area is COPD to which (24%) of the project are devoted, followed by 14% for cystic fibrosis. The remaining 30% is almost equally split between other CRDs, with no smaller CRD received more than 10% of projects.

Figure i: Percentage of Projects by Disease Area



Looking at the average time Horizon of the projects, the average life of grant is of 28 months with a minimum time of 12 months and a maximum of 60 months per project. However, in the larger database the 45% of the research projects funded were extensions of previous exploratory research or were further implemented by other grants in order to reach the output expected.

The most important area in which the RFOs were interested was in relation to the therapeutic and drug developments, whereas the health care research and economic health research are almost not existent, with only 2 projects addressing these subjects. Indeed, a high number of projects (n=64)

addresses genetic or cellular biology, with the aim of finding the causes of chemical and biological mechanisms in order to develop new strategies in therapeutic and pharmaceutical care. Interestingly, in only 2 cases the primary output the projects was the approval of a patent, and in only 1 case was the translation of the theory into practice the primary outcome.

In addition, only two projects addressed the quality of life for CRDs patients, and only a small percentage (between 3% and 4%) of studies addressed the economic consequences of these diseases (n=1)

Typically, the many recipients of funding were universities or research centers (around 90%) whereas Private companies and charities conducted about 8% and 2% of projects respectively. In only one case, the lead recipient of funding was from the private sector (BioChancePLUS-4: "IgE-AAV), which addressed the issue of particles as vaccines for the treatment of asthma and other allergic diseases" funded By BMBF). In all other case, private companies and charities were members of a larger consortium led by universities.

In terms of number of institutions funded, most of the RFOs (n=89) tend to fund only 1 organization whereas larger consortiums were mainly supported by the European Commission. Indeed, 7 out of 8 EC funded projects involved a consortium or multiple partners across Europe. The only exception was BMBF in Germany, which, in the period between 2009 and 2012, funded two large joint projects in the program of "Disease oriented Competence Network Asthma and COPD". These projects had particular relevance to the shaping of national and European policy on CRDs given the larger level of funding investment involved, and the inclusion of research groups from several universities, research institutions and private companies and Charities.

In terms of the level of collaborations among RFOs, results highlighted the absence of trans-border collaboration. Indeed, the 88% of the projects were funded within the MS of RFOs, and only 7% were developed at international level, and 5% at the European level. These results may indicate a need for larger collaborations within the European Union in order to enhance the quality of research.

1.3.1 COPD

The sample includes 24 projects research on COPD (24%). Across Europe, the primary focus of COPD research is the development of new therapies and drugs (n=9), and the management of the patients during the course of the illness (n=10). This could be linked to the slow progression of COPD and the presence of acute exacerbations characterized by a worsening of the quality of life, leading to a large need of new therapies. Furthermore, 15 out of 17 projects are focused on the management of patients or new drugs and therapies. In the main, these projects build on basic research. The direct causes of COPD exacerbations are still obscure and the involvement of pathogens remains uncertain. 3 projects considered aietology. And only 2 projects are focused on social determinants and outcomes of COPD. The average length of the projects is 36 months.

1.3.2 Asthma

The sample includes 32 projects directed to study of Asthma. The primary focus of these projects is directed toward development of new drugs and therapies (n=18), followed by the study of aietology (n=9) and development of diagnostisc (n=6). Patient management (n= 1) and prevention (n=3) received less attention. Generally, 24 of 32 projects were the product of basic biological research. The average length of the projects is 24 months.

1.3.3 Cystic fibrosis

The sample includes fourteen projects for cystic fibrosis. These were funded across 9 MSs and 2 non-European Countries. The majority of the projects i (8 out of 14) were investigating new drugs and therapies. Other areas investigated included disease management (n=2), Aietology (n=3) and Diagnosis and prognosis. Two projects out of 14 involved international collaboration whereas the

others were country focused, perhaps highlighting the lack of a European network for research on cystic fibrosis. The average length of a project was 24 months.

1.3.4 Non Specific and Mixed Projects

Website queries identified that 16% of projects were directed towards more than one CRDs. The most common association was made between Asthma and COPD (n=13). Other non-specific CRDs , such as Bronchitis, emphysema and Pulmonary Hypertension, were a less common subject of mixed research, which numbered 2, 3 and 7 projects respectively. The majority of mixed projects were concerned with biological discovery in the interested of developing new drugs and treatments (n=14). The most second relevant area of mixed study was in regard of the aietology of the diseases (n=7) and diagnostics (n=5). Interestingly, 4 out of 5 diagnostic study focused on the development and improvement of imaging tools. The average length of the projects where 24 months.

Table i: Research Programs for COPD (J44) 2006-2013

Funder	Recipient Type	Level of Collaboration (National – European - Global)	Partner Countries	Project Title	Research Area (focus)	Project Timeline (years)	Summary Description (Project aim)	Achieved/ Anticipated Outcomes	Amount of Funding
1. European Commission- FP7 projects	University, NGO, Private (n= 13)	European	FR, GER, HU, IT, NE, POL, SWE, SW, UK	Markers for emphysema versus airway disease in COPD	Aietology and Basic medical research	2007-2013	To identify novel markers for COPD and its main phenotypes.	Markers will be used for diagnostic approaches and as therapeutic targets for COPD.	€2,984,025.00
2. European Union- FP6 projects	University (n=1)	National	SW	Lipid- and protein-mediators critical in the pathological mechanisms underlying chronic obstructive pulmonary disease(COPD PROTEOMICS)	Aietology-Detection, screening and diagnosis – Development of new therapies/drug	2006-2008	To identify lipid- and protein-mediators critical in the pathological mechanisms underlying COPD	Developments of novel methods for clinical settings-identification of novel pharmaceutical targets for COPD.	169,324 €
3. European Commission- FP7 projects	Universiry, Private (n=6)	European	NH-DK-SW-GR-PL	COPD Pathology: Addressing Critical gaps, Early Treatment and Innovative Concepts	Development and evaluation of treatments and therapeutic interventions	2008-2010	Unravel the genetic determinants of the susceptibility to develop COPD in (ex-)smokers at high risk.	Baseline studies showed that COPD resulted from airflow obstruction or tissue damage, but not both.	2,981,143€
4. European Respiratory society, SEPAR, NYCOMED.	University (n=13)	European	SP	Chronic Obstructive Pulmonary Disease Audit	Disease/ patient management	2010–2011.	to develop a core data set that can be used to audit COPD in acute hospital admissions across Europe with a	View to raising the standards of care to a level consistent with the European management guidelines.	N/A
5. The French National Research Agency	University, Public institution (n=3)	National	FR	Inhibition of Mucus Hypersecretion In COPD Exacerbation	Disease/ Patient management	2012-2013	to study the effects of ATK on mucus hyper-secretion, inflammation and respiratory failure in our animal model.	Improve the quality of life of patients with COPD in the exacerbation phase of infectious origin.	353,005 €

6. The French National Research Agency	University, Public institution (n=2)	National	FR	HVP-PAH in COPD	Basic research-Development of new therapies/drug	2006-2009	To characterize the cellular mechanism behind the pulmonary arterial wall.	To improve the knowledge in the field and to develop original therapeutic strategies targeting TRP	240, 000 €
7. BMBF	University, private, public institution (n=5)	National	GR	PneumoGRID: GRID-based analysis of medical signal and image data for dynamic imaging of ventilation in healthy subjects and patients with chronic obstructive pulmonary disease	Development of new diagnostics	2009-2012	To categorize CBNP characteristics and their corresponding toxicology potential.	Development of new diagnostics	N/A
8. BMBF	University, private, public institution (n=6)	National	GR	COSYCONET for German COPD and Systemic Consequences - Comorbidities Network	Diseases and patient management	2009-2012	Projects concerning etiology, pathogenesis, diagnosis and therapy, imaging for lung diagnostics in clinical practice, and basic research were performed.	Development new medical technology and rise awareness for the self-management of comorbidities in COPD patients	8,500,000 €
Marató TV3	University (n=1)	National	SP	Study of bronchial bacterial colonization in COPD. Effect of antibiotic treatment on eradication and prevention of exacerbations.	Development and evaluation of treatments and therapeutic interventions	2006-2008	To study the prevalence and characteristics of colonization Bronchial in patients with those of patients without COPD	Treatment with moxifloxacin is effective in eradicating bacterial colonization, but this effect disappears at 8 weeks.	137,640.00 €
ISCIII	Public Institution (n=1)	National	SP	Cardiovascular, pulmonary and systemic alterations related to COPD: Phenotype characteristic and prognostic implications.	Disease/Patient management	2007-2010	To improve the diagnostic developing a model based on phenotype characteristics	To improve the diagnostic approach	90.000 €

ISCIII	University (n=1)	National	SP	Study of exacerbations of COPD in Spain (NACECOS) 2	Disease/Patient management	2009-2012	To improve the management of exacerbations in COPD patients	Development of new diagnostics	111,000.00 €
British Lung Foundation/ Medical Research Council	University (n=1)	National	UK	A study to explore the value of metformin as a potential new treatment for COPD exacerbations	Disease/Patient management	2010-2011	To determine whether a rapid dose escalation regimen of metformin can lower blood glucose reliably and safely in individuals during acute exacerbations of COPD.	To lead to a better resource use	€ 44,287.38/N/A
Scientific Office Scotland	University (n=1)	National	UK	Exploring the feasibility of using remote respiratory monitoring to detect and manage exacerbations of chronic obstructive pulmonary disease.	Disease/Patient management	2013	to find out if monitoring respiratory rate is potentially useful in detecting early deterioration that could lead to a hospital admission	This study shows that currently available respiratory rate monitors should not be added to tele-monitoring systems in COPD.	Scientific Office Scotland
FWO	University (n=1)	National	BE	Skeletal Muscle dysfunction in COPD due to inactivity.	Diseases/patient management	2009-2012	To discover the relation between inactivity and skeletal muscle dysfunctions and other exacerbation in patients with COPD	Skeletal Exacerbations are associated to significant mortality and acceleration of decline of lung function and HRQoL.	FWO
Swedish research Council	University (n=1)	National	SE	Molecular Mechanism in Inflammatory lung Diseases: C/EBP transcription factors in the pathogenesis of COPD	aetiology	2007-2009	to increase knowledge of the national disease chronic obstructive pulmonary disease (COPD)	to increase knowledge of the national disease chronic obstructive pulmonary disease (COPD)	Swedish research Council
Fundacao para ciencia e a tecnologia	University (n=1)	National	SP	Purinergic and cholinergic control of lung resident	Basic research-patient disease	2007	to combine functional and immuno-	Improve the management of the COPD	Fundacao para ciencia e a tecnologia

				inflammatory cells in chronic obstructive pulmonary diseases	management		cytochemical approaches I order to characterise and study the role of acetylcholine and purine receptors, and their interaction, in the control of the major lung-resident inflammatory cell types, macrophages and neutrophils, collected from COPD patients	exacerbations	
Health Research Board	University (n=1)	National	IE	Genetic Determinants of COPD	aetiology	2006-2012	To discover the genetic epidemiology of COPD	To permit earlier diagnosis and to lead to the development of treatments to modify progression	Health Research Board
National bank of Austria	University (n=1)	National	AU	Pulmonary vasculopathy in COPD patients - role of endothelin-1 and TASK	Patients and disease management	2007-2011	To clarify the mechanisms underlying the effects of ET-1 is based,	N/A	Nationl bank of Austria
Netherlands Lung foundation	University (n=1)	National	NT	The novel cyclic AMP effector Epac: new avenues in the treatment of inflammation, tissue remodelling and airway narrowing in COPD	Diagnostic, prevention and development of new drugs.	2008-2012	to increase the role of Epac1 and Epac2 (exchange protein directly activated by cAMP) in inflammation and structural changes in the airways	To lead to better availability of drugs which focus on the intracellular cyclic AMP signal substance	N/A
Swiss National Science Foundation	University (n=1)	National	SW	Risk assessment for chronic obstructive pulmonary disease in primary care: research should solve the	Diagnostic, management of patient and diseases.	2007- 2010	to develop and validate a practical disease severity index for patients with COPD in	Improvement of the severity index	591,755.00 €

				dilemma			primary care settings that predicts the future course of the illness and serves as a basis for treatment selection		
DFG	University (n=1)	National	GE	Diagnostics and therapy control in COPD by quantification of structural changes in the lungs	Diagnostic, prevention and development of new drugs.	2007-2011	To develop of methods for localized diagnostic detection and quantitative evaluation of COPD	N/A	N/A
Fondazione cassa di risparmio di Lucca	University (n=1)	National	IT	Development and promotion of new techniques for managing ultrasound examination pathology Thoracic	Development of new diagnostic	2006	To develop new and analyse the efficacy of the current method of methods for diagnosticof COPD.	Development of new diagnostic tools.	90,000€

Table ii: Research Programs for Asthma (J45) 2006-2013

Funder	Recipient Type	Level of Collaboration (National – European - Global)	Partner Countries	Project Title	Research Area (focus)	Project Timeline (years)	Summary Description (Project aim)	Achieved/ Anticipated Outcomes	Amount of Funding
Medical Research Council	University, n=1	National	UK	Exploring, Understanding and Intervening in IgE-dependent Mechanisms in Allergic Disease and Asthma	Aetiology and Basic medical research	2006-2011	To prevent cells in the body that make antibodies producing IgE instead of beneficial, protective antibodies	To develop compounds that are cheaper, more applicable to different allergic conditions, and easier to administer.	2,294,565€
European Union-FP6 projects	University, Private, public institution (n=35)	International	UK-NH-FR-GR-BG-SW-SW-IE-AU-HK-RU-PO-FL-IT-ECU	A multidisciplinary study to identify the genetic and environmental causes of asthma in the European Community	Aietology	2006-210	To identify all important gene environment interactions underlying asthma in the EU.	Cellular and genomic models to identify the molecular mechanisms of protective environments were developed as screens for novel therapeutics and commercialization.	11,327,585€
European Union-FP6 projects	University, private(n=2)	European	UK-IE	Micro-fluidic Biochips for trans-endothelial migration of eosinophils for the study of asthma	Development of new diagnostic	2006-2009	to identify therapeutic targets for asthma	Development of a biochip that facilitated the study of how eosinophils move from the blood vessels into the tissues of the lungs.	270,898€
European Commission- FP7 projects	University (n=1)	National	BE	TSLP IN ASTHMA (Human TSLP and OX40L as targets of therapeutic intervention for allergic asthma)	Development of new drugs and therapies	2010-2012	To study the potential of targeting human TSLP and human OX40L for intervening with the initiation and/or	To lead to important go-no go decisions to further advance this therapeutic strategy to the clinic.	139 000€

							progression of allergic asthma in vivo, using mouse.		
Fonds de Dotation "Recherche en Santé Respiratoire"	University (n=1)	National	FR	Allergy prevention through breastfeeding: mechanisms, epidemiology, and implications for primary prevention in the general population	Aietology and development of new diagnostic	2010	To study the opportunity to prevent the insurgence of Asthma or other allergies in children	Lead to new therapies for breastfeeding women.	100,000€
Fonds de Dotation "Recherche en Santé Respiratoire"	Public Institution (n=1)	National	FR	Impact of exposure to air pollution during fetal life on respiratory health in children: study of the role of changes in gene expression within the prospective cohort EDEN	Prevention	2010	To clarify if exposing the pregnant women to air pollutants could disrupt pregnancy and create the insorgens of Asthma and other allergies	An insight of mechanisms that could explain the effects of pollution on pregnancy.	100,000€
The French National Research Agency	Public Institution, University (n=3)	National	FR	Immunoregulatory functions of IL-17 cells and iNKT (invariant natural killer T): new therapeutic approaches for allergic asthma.	Development of new drugs and therapies	2007-2009	To identify the of generation of the L-17 and evaluate the respective capacity of influence asthma and its mechanisms	Identification for new cellular and molecular elements of disease control to develop of new therapeutic strategies.	300,000€
BMBF	Private (n=1)	National	GR	BioChancePLUS-4: "IgE-AAV" particles as vaccines for the treatment of asthma and other allergic diseases	Development of new drugs and therapies	2007-2009	To discover the role of recombinant cells to treat asthma	To develop a new drug for the treatment of Asthma	587,772€
BMBF	University (n=1)	National	GR	Development of a photo acoustic NO sensor on QCL	Development of diagnostics	2006-2010	To design and realize an optoacoustic	To Improve the current diagnostic tools	259,192€

				basis for asthma diagnosis			sensor for trace gas detection		
BMBF	University (n=1)	National	GR	Collaborative project: Genome Network environment related diseases: Genetic aetiology of bronchial asthma	Prevention	2008-2013	To understand and map human lung epithelial cells will be analysed under experimental conditions	To lead to the identification of strategically promising biomarkers and drug targets in lung inflammation	800,533€
ISCIII/FIS	University (n=1)	National	SP	Asthma and Protein suppressors of suppressors of cytokine signalling (SOCS): Evaluation of the role of SOCS in the regulation of Asthma and in the application of new therapeutic strategy for Asthma control.	Development to new drugs and therapies\basic research	2009 - 2011	To describe the expression of SOCS3 protein for develop new treatment	Interventions that regulate Th2 cytokine effector pathways are attractive as potential therapeutic targets. The implication of SOCS proteins in the regulation of the Th1/Th2 balance suggests a range of new therapeutic strategies that might reduce Th2-induced inflammation and its consequences in eosinophilia.	245,025€
ISCII	University (n=1)	National	SP	Study the epigenetic regulation of gene COX-2 in asthma	aetiology	2009 - 2012	To describe the expression of gene COX2	N/A	139.500,00€
Medical Research Council	University (n=1)	National	UK	Exploring, Understanding and Intervening in IgE-dependent Mechanisms in Allergic Disease and Asthma	Development to new drugs and therapies\basic research	2006-2011	to understand and prevent the switch of The cells in the body that make antibodies, B-cells, switch in response to certain signals	Test compounds that prevent this change in shape, collaborating with the pharmaceutical industry to develop small-molecule	2,294,565€

							from producing beneficial, protective antibodies to producing IgE	inhibitors that overcome the limitations of anti-IgE.	
Medical Research Council	University (n=1)	National	UK	Mechanisms of Deficient Innate Immune Responses in Asthma	development of new therapies for asthma exacerbations	2008-2011	to understand the mechanisms of deficient IFN production in asthma to identify specific targets for development of new therapies	To identify novel targets for development of new therapies for asthma exacerbations and determine which populations with asthma would be most likely to benefit from new therapies.	1,153,543€
Scientific Office Sotland	University (n=1)	National	UK	Measuring the risk of Beta-blocker and non-steroidal anti-inflammatory drug prescribing in Asthma	Disease and patients management	2013	To measure the risk from beta-blocker and nonsteroidal anti-inflammatory drugs (NSAIDs) in asthma	To help prescribers better judge their risks versus benefits among individual patients.	N/A
King Baudouin Foundation	University (n=1)	National	BE	Targeting the modified innate functionality of the post-asthma alveolar macrophage for relieving Respiratory Syncytial Virus-induced asthma exacerbation.	development of new therapies for asthma exacerbations	2013	To validate the theory that uncoupling of inflammatory and antiviral responsiveness may well be at the origin of RSV-induced asthma exacerbation	Validation of the theory and basis for a new therapeutic opportunity to be validated through this research project	50,000 €
Swedish research Council	University (n=1)	National		Soluble epoxide hydrolase as a novel therapeutic target for asthma	development of new therapies for asthma exacerbations	2008-2009	To investigate for a medication that prevents SEH from acting to stop the inflammation in asthmatics	N/A	663,000/111,000

Fundacao para ciencia e a tecnologia	University (n=1)	National	PT	ASTHMA - Future asthma management helped by non-invasive sampling: contributes for the definition of a rapid and non-invasive diagnostic tool.	Patient and disease management, diagnostic	2010	To use of high sensitivity and high throughput equipment and efficient sample preparation to improve diagnostic	To improve diagnostic and management of Asthma Patients	€ 90,488.00
Fundacao para ciencia e a tecnologia	University (n=1)	National	PT	Invariant natural Killer cells in allergic asthma and tolerogenic therapy	Development of new drug and therapies	2007	to study the role of NK T lymphocytes	To understand how t lymphocity can lead to a new therapy	€ 155,000.00
Estonian research Council/ Ministry of research and education	University (n=1)	National	ES	The role of microRNAs in regulation of immune responses in allergic asthma and atopic dermatitis	Development of diagnostic, basic research	2009-2013	to explore the molecular functions of miRNAs in allergic asthma and atopic dermatitis	to develop novel diagnostic and therapeutic approaches for better treat asth,s	€ 52,600.00/ 29,100.00€
Academy of Finland	University (n=1)	National	FL	NK cell in the pathogenesis of asthma	aetiology	2009	to study the role of NK T lymphocytes	To find a better clinical approach.	136,926€
Hugarian Science Fund	University (n=1)	International	HU, USA, GR	Natural killer (NK) T lymphocytes in airway inflammation	aetiology	2007-2011	to study the role of NK T lymphocytes in the pregnancy-induced exacerbation of bronchial asthma (A) and the pathogenesis of bronchiolitis obliterans	Understanding the mechanisms by which NK cells regulate allergic disease is therefore an important component of treatment approaches.	12,148€
Academy of Finland	University (n=1)	National	FI	The Functional Role of GPR154 in Asthma	Basic research, development of new therapeutics and drug	2007-2009	To explore the expression of the GPR154 in the activation of Asthma	To develop new therapeutics approach	120,000€

Academy of Finland	University (n=1)	National	FI	TYKS Viral Inception of Asthma: Prospective study infancy to school-age.	Aetiology, development of new therapeutics and drugs	2010-2013	To investigate the immunological events in young first-time wheezing children affected by rhinovirus	Results gave basis for the prevention of asthma and for the development of new treatment strategies a	113,740€
Lung Foundation Netherlands	University (n=1)	National	NT	The effect of Activated Protein C in asthma	Basic research, development of new therapeutics and drug	2009-2012	To clarify the role of the protein C system during asthma, as well as to the possible application of recombinant	Variants of APC or APC may be used to work the treatment of asthma.	N/A
Lung Foundation Netherlands	University (n=1)	National	NT	Validation of the risk score PIAMA and implementation of a risk assessment tool to predict asthma in the primary school age in 0-4 year old children with asthma symptoms within the Youth Health Care.	Diagnostics	2009-2013	external validation and update PIAMA Risk Score performed	The PIAMA Risk Score showed a good external validity in the multi-ethnic Generation R study.	N/A
LungFoundation Netherlands	University (n=1)	Lung foundation	University (n=1)	The Th17 response in asthma: Protection against atopy but development of non-allergic (intrinsic) asthma	Aetiology, basic research	2012-2013	To investigate the role of dust-induced IL17 for treating Asthma and other airways inflammation	dust-induced IL-17 Contributes to the development of non-allergic airway inflammation.	N/A
Swiss National Science Foundation	University (n=1)	National	SW	Protective Factors in Asthma and Allergy: the role of farm milk - a potential tool for prevention	Prevention	2009-2012	To determine what underlies the epidemiologically observed protective effect of farm milk	Consumption of raw milk during the first year of life had the strongest impact on up-regulation a series of receptors	162,415.00

							consumption on the development of asthma and allergy and to prospectively assess the association between milk and asthma.	of innate immunity at age one year of the child	
Swiss Narional Science Foundation	University (n=1)	National	SW	T cell interaction with tissue cells in allergic inflammation	Prevention	2010-2013	To analyse T cell in vivo.	to develop new pathophysiological insights into interaction of the immune system cells, particularly recently identified effector	537'000.00
Christian Doppler Research Association	University (n=1)	National	AU	CD-Laboratory for Allergy	Prevention		To find a vaccines for the treatment of allergic asthma	To find a vaccines for the treatment of allergic asthma	N/A
Swedish research Council	University (n=1)	National	SW	Studies of the effect of allergens on epithelial cells and dendritic cells - basis for an in vitro test for respiratory sensitization	Development diagnostics	2010-2012	To identify biomarkers involved in respiratory allergy and to develop a test for sensitization to replace animal experiments.	To develop a new test enhancing the current diagnostic tools for asthma	210,000
Research Council of Lithuania	Public Institution (n=1)	National	LT	Autoimmune diseases in patients with T-cell populations significance of the disease	Aetiology, basic research development of new therapeutics and drug	2010 -2011	Understand the mechanism of T-cell in allergic patients	To improve the therapeutic approach	N/A

Table iii: Research Programs for Cystic Fibrosis (E84) 2006-2013

Funder	Recipient Type	Level of Collaboration (National – European - Global)	Partner Countries	Project Title	Research Area (focus)	Project Timeline (years)	Summary Description (Project aim)	Achieved/ Anticipated Outcomes	Amount of Funding
European Union- FP6 projects	University, private public institution (n=21)	International	UK, IE, IT, CZ, GR, FR, IS,PL, BE,SW,NT	European Coordination Action for Research in Cystic Fibrosis	Patient management-development of therapy	2006-2009	To translate research results into optimise d clinical management and therapy development to promote good standards of care	To translate research results into optimise d clinical management and therapy development to promote good standards of care	€1,757,500
Health Research Board	Public Institution (n=1)	National	IE	The role of Stenotrophomonas maltophilia in cystic fibrosis lung disease	Development of new therapies and drug	2012	To Investigate the role of a specific S. maltophilia derived proteases in inducing inflammation in the CF lung as well as its ability to inactivate important protective proteins in the lung	To find the way for new antimicrobials to treat an otherwise multi-resistant organism.	N/A
Fundacao para ciencia e a tecnologia	University (n=1)	National	PT	Diagnosis, Prognosis and Treatment of Cystic Fibrosis.	Diagnosis, Prognosis and Treatment	2007	To identify the mutation specific in each patient and target the basic defect underlying CF.	To find patient-tailored therpies based on taiolored-diagnostic tools	€170,000
Swiss Narional Science Foundation	University (n=1)	National	SW	Clinical impact and pathophysiological mechanisms of rhinovirus infections in cystic fibrosis lung disease	Development of new therapies and drug	2009-2012	To understand of defective or harmful inflammatory pathways induced by viral infection in CF	identification of new therapeutic targets for CF	€301693

The research Council of Norway	Private (n=1)	National	NW	Designed alginate products providing symptom relief for patients suffering from Cystic Fibrosis (CF)	Disease and patient management	2006 - 2008	To design functionality alginates formulated into products/medical devices providing symptom relief	To enhance the management of the disease	€300,000
Swedish research Council	University (n=1)	National	SW	Methods for treatment of cystic fibrosis	Development of new therapies and drug	2007-2009	to test a number of drugs that can prevent the mutated protein is destroyed or compensate for the error by using an alternative mechanism to transport chloride ions.	Improve the current methods for the treatment of CF.	€996,000
King Baudouin Foundation	University (n=1)	National	BE	Development of an animal model for fetal gene therapy of cystic fibrosis	Development of new therapies and drug	2011	To develop a mouse model for prenatal gene delivery in the fetal lung and nose as a treatment option for cystic fibrosis using both lentivirus and adeno-associated viral vectors.	To individuate a new drugs for the treatment of CF	€120,000
British Lung Foundation	University (n=1)	National	UK	Do physiotherapy joint and muscle movement techniques improve posture, pain, secretion clearance, lung measurements or quality of life during an inpatient stay for a chest infection in adults with cystic fibrosis?	Patient management	2008-2009	To assess the best way to deal with the adult cystic fibrosis	Physiotherapy should be offered to patients with a variety of medical respiratory conditions, with the aim of breathlessness management and symptom control, mobility and function improvement or	€16,948

								maintenance, and airway clearance and cough enhancement or support.	
Wellcome trust	University (n=1)	National	UK	Combination therapy of quorum sensing inhibitors and biofilm blockers for the treatment of Pseudomonas aeruginosa infection in those with cystic fibrosis.	Development of new drug and therapies	2009-2010	To investigate the efficacy of combination therapy in infections in Cystic fibrosis Patients	Clinical application of these therapies may be slow and progress limited by a lack of experience of similar approaches with which to satisfy regulatory bodies.	€139,298
Fondazione Cassa di Risparmio di Puglia, Ministry of health and Telethon .	University (n=1)	National	IT	Cistic Fibrosis Transmembrane conductance Regulator	Aetiology-basic research	2008	To determine the influence of CFTR and P2Y1 activation on apical membrane NHE3 by protein-protein interactions via NHERF using an experimental cell model in which we can control the expression of both NHE3 and CFTR.	To better understand the relationship between extracellular nucleotides and CFTR, the role of extracellular nucleotides in epithelial pathophysiology and their putative role as therapeutic agents	85,750€/58,360€/30,000€
The French National Research Agency	University, Public Institution, private (n=5)	International	FR, TW	Control of cell nonoperation In-vivo Cavitation Regulated: from fundamental to in vivo applications.	Development of new therapies and drug	2009-2012	to promote innovative technological developments in treatment of Hereditary pathologies	To give a new perspective in the development of drugs	€943,872
The French National Research	Public Institution (n=1)	National	FR	New synthetic strategies aimed at diversity to	Development of new therapies and	2011-2013	to develop a new link building strategy based on	Discovery of new drugs to orally treat the cystic	**€943,872**

Agency				accelerate the discovery of therapeutic agents against cystic fibrosis	drug		an iterative functionalization of inactivated CH bonds in heterocycles.	fibrosis	
Italian Ministry of health	Public Institution (n=1)	National	IT	Study of microRNAs in EBC and in epithelial cells obtained by means brushing nasal come Expression modulators of CFTR in patients with cystic fibrosis	Aetiology, basic research	2007	to search for mutations, both in CF patients and controls, within the 3'UTR region of CFTR gene that could affect the interaction and therefore the regulatory activity of miRNAs, by acting as disease-causative mutations or as modifier factors of CF phenotype	This may be due not only to the action of miRNAs, but also to an effect on the accessibility to various factors involved in the conformation, translation and stability of CFTR mRNA.	€102,000
DFG	University (n=1)	National	GR	Senescence of Staphylococci: The roles of Clp ATPases in bacterial metabolism, survival and persistence during late stationary phase	Aetiology, basic research	2006-2010	To characterize S. aureus ClpC through an analyses of regulatory modifications with a metabolomics approach	To unravel the putative role of Clp ATPases in chronic persistent course of disease.	N/A

Table iv: Research Programs for Non-Specific CRDs (2006-2013)

Funder	Recipient Type	Level of Collaboration (National – European - Global)	Partner Countries	IDC-10 Disease Area(s)	Project Title	Research Area (focus)	Project Timeline (years)	Summary Description (Project aim)	Achieved/ Anticipated Outcomes	Amount of Funding
Wellcome Trust	University (n=2)	National	UK	Pulmonary Hypertension	Totally automated blood pressure monitoring at home to improve care of patients with heart failure or pulmonary hypertension.	Patient Management	2010-2011	To study the use real-time monitoring of patients in hospital and the use the use of mobile-phone based telehealth to improve the management of chronic disease.	To lead to improved patient condition, slower progression of the disease and reduced re-hospitalisation	1,018,810
FWO	University (n=1)	National	BE	Pulmonary Hypertension	Role of endothelial progenitor cells and multipotent adult progenitor cells in experimental pulmonary hypertension and peripheral arterial insufficiency.	Aietology, Development of new therapies and drug	2006-2009	To investigate the he role of the circulating progenitor cells in PH.	these experiments may yield opportunities for critical new treatment strategies.	N/A
Fundacao para ciencia e a tecnologia	University (n=1)	National	PT	Pulmonary Hypertension	Pathophysiological role and therapeutic potential of urocortin 2 in pulmonary hypertension	Development of new therapies and drug	2012	To analyze the effects of UCN-2 treatment in an animal model of RV.	UCN-2 pathway has a relevant role on the pathophysiology of PAH and RV failure, representing a potential therapeutic target.	83,098
ISCII	University-public Institution – Charity (=3)	National	SP	Pulmonary Hypertension	Study of new therapeutic targets in the treatment of pulmonary hypertension associated with chronic obstructive pulmonary disease	Development of new therapies and drug/patient management	2010-2012	To investigate the relations between HP and COPD to develop a new targeted therapy	to develop a new targeted therapy	328,515 €.

DFG	University, public institution (n=2)	National	GR	Pulmonary Hypertension	Influence of BMP receptor type 2 signalling on hemodynamics and structure of pulmonary vessels in primary pulmonary hypertension	Aetiology	2008-2010	to facilitate a better understanding of the complex signal transduction system and BMP to put this in the proper context of vascular development and -autoregulation the lungs.	to better understand the mechanism may lead to new targeted therapies	N/A
The French National Research Agency	Public Institution (n=1)	National	FR	Pulmonary Hypertension	Pan-genomic research of susceptibility alleles of pulmonary arterial hypertension	Development of new therapies and drug		to identify new genetic susceptibility factors, different from those already known.	New therapeutic Drug for PH	400,000
European Union- FP6 projects	University, Public Institution, Private (n=30)	European	UK, GR, BE, GE, SP, SW, AU, DK, FL, IE, IT	Pulmonary Hypertension	Pulmonary Hypertension: Functional Genomics and Therapy of Lung Vascular Remodelling	Development of new therapies and drug	2006-2009	To investigate the underlying mechanisms in PH	promotion of innovative therapies, and benefit the European infrastructure for scientific and technical competence in the field of PH.	11,399,999
Swiss Narional Science Foundation	University (n=1)	National	SW	Non-specific/ mixed CRDs	Interactions between the pulmonary vascular and broncho-alveolar networks: mechanisms and therapeutic implications	Development of new drugs and therapies	2007-2011	To investigate both experimentally and clinically the effect of commonly used anesthetic drugs and other therapies	Progress in identifying the close interaction between the pulmonary hemodynamic and the lung function	254'637.00
European Commission- FP7 projects	University, public Institution (n=10)	International	UK, IT, GR, SP, GE,SR, BE.	Across different CRDs disease	Health Risk from Environmental Pollution Levels in Urban Systems	Aetiology	2009-2011	To investigate the correlation between pollution and development of illness in the	Risk maps starting from pre-existent environmental and health data, by development of new epidemiological and	1,399,836.55

								urban population	statistical approach	
The French National Research Agency	Public Institution (n=1)	National	FR	Across different CRDs	Simulation, Analysis and Measurement of Airway Obstruction in Lung	Development of medical technology	2007-2009	to understand the impact of changes in the structure and geometry of the bronchi on the overall properties of the respiratory system and their impact in terms of spontaneous or artificial ventilation optimization of mechanical ventilation.	better control of the pressures put in play throughout the air shaft, especially in pathophysiological conditions in which fluid-structure interaction phenomena could compromise the effectiveness of spontaneous ventilation, assisted or controlled.	612,538
ISC III	University (n=4)	European	FR, UK<, AU	Emphysema	Study erythropoietin receptor (EpoR) in lung tissue and progenitor cells from the bone marrow of patients with emphysema	Development of new therapies and drug	2009 - 2011			74,052
SEPAR	University (n=1)	National	SP	Bronchitis	Defects MBL (mannose-binding lectin) in the etiology and course of bronchiectasis.	Aietology	2007-2009	to assess the effect of MBL deficiency on disease severity in bronchiectasis	To understand the undelie mechanism of brinchiectasis	12,000.00 €
FWD	University (n=1)	National	AU	Pulmonary Hypertension	L-arginine and tetrahydrobiopterin as a therapy for pulmonary arterial hypertension	Development of new therapies and drugs	2008-2011	to investigate the effects of combination therapy with L-arginine and BH4 in a rat model of PAH	Combination therapy of L-arginine and BH4 in a rat model of severe PAH improves hemodynamic parameters.	N/A
FWD	University (n=1)	National	AU	Across different CRDs	Effect of beta-carotene on primary lung cells	Aietology, and Development of new therapies and drugs	2007-2011	To investigate the effects of beta-caratone on the development of lung tissues	The development of new drugs preventing the insurgence of Airways infllamation	N/A

Academy of Finland	University	National	FL	Across different CRDs	HY Lung structure and function studied by x-ray imaging	Development of new Diagnostic	2008-2009	To develop a novel method was developed for functional lung imaging	The results are combined with detailed information of the structural and mechanical properties of the lung tissue obtained with x-ray scattering imaging techniques and microtomography imaging	195,450 €
European Commission – FP5 program	University, private, Public Institution(n=17)	European	SP, FR, GR, IT, NT, UK, SK, PL	Across different CRDs	Polarized helium lung imaging network (PHELINET).	Development of new Diagnostic	2007-2011	To develop and apply "innovative and non-invasive lung magnetic resonance imaging (MRI) techniques for clinical diagnosis and validation of lung therapy".	To develop and apply "innovative and non-invasive lung magnetic resonance imaging	3,702,750 €
DFG	University (n=1)	National	GR	Across different CRDs	Controlled release of active ingredients from nanostructured carrier systems in the lungs	Development of new therapies and drugs		to develop controlled release formulations for administration by inhalation of vasoactive drugs		
Medical research council	University (n=1)	National	UK	Bronchitis	An investigation of L-ficolin in adult bronchiectasis:- a potential innovative new therapy	Development of new therapies and drugs	2006-2011	To provide first class training in organizing and running a clinical study, processing sputum and sera, ELISA, cell and bacterial culture, purification of leukocytes from peripheral blood, analysis of apoptosis and phagocytosis,	To offer a fresh new therapy for this disabling disease, one that is natural and not an antibiotic	186,570

								Western blotting, DNA extraction and PCR, and data analysis and presentation.		
Italian Ministry of Health	University (n=1)	National	IT	Pulmonary fibrosis	Pulmonary fibrosis and cutaneous scleroderma : pathogenetic mechanisms , early diagnosis and medication effects antifibrogenetic	Diagnosis and treatment	2006-2010	N/A	N/A	145,000
Italian Ministry of Health	University (n=1)	National	IT	Pulmonary fibrosis	Lymphatic and vascular remodeling in pulmonary fibrosis	Development of new therapies and drugs	2010	N/A	N/A	80,000
Italian Ministry of Health	University (n=1)	National	IT	Across different CRDs	Role of the NK-1 receptor and receptors activated by proteases in the development of bronchial lesions mediated by cigarette smoke	Aietology , Development of new therapies and drugs	2012	N/A	N/A	€ 40,000
Italian Ministry of Health	University (n=1)	National	IT	Across different CRDs	Role of protease receptors (PAR - 1,2,3,4) in inflammation of the respiratory system .	Development of new therapies and drugs		N/A	N/A	€ 36.200,00
Medical research council	University (n=1)	National	UK	Across different CRDs	Histone acetyl transferase (HAT) inhibitors in COPD/asthma	Aietology	2007-2011	To analyse the mechanism behind the transferase inibitors	to discover new drug leads for chronic inflammatory lung diseases	€ 570058
Italian Ministry of Health	University (n=1)	National	IT	Across different CRDs	Interventions to ensure equity of access to diagnostic prodecure in solitary pulmonary nodule	Diagnostic-economic impact		To understand the different approach to the clinical problem in various regions of the Country	To reduce in the overall number of diagnostic procedures that a patient will have to undergo by eliminating those that do not add significant new	€ 30.000,00

									information.	
Fonds de Dotation "Recherche en Santé Respiratoire"	University (n=1)	National	FR	Across different CRDs	Mechanisms of pulmonary inflammation to metal nanoparticles : role of the inflammasome and purinergic signaling	Aietology, prevention	2010	To understand the relation between nanopaticoles and the insurgence of CRDs	To understand the health problems created by pollution and enhance the prevention of these.	€ 100000
Hugarian Science Fund	University (n=1)	National	HU	Emphysema	Structural and functional correlates of experimental emphysema	aietology	2007-2012	the development and progression of emphysema in animal models, by using sensitive lung function techniques	To understand the mechanism of Emphysema	19.117 million (HUF)
DFG	University (n=1)	National	GR	Emphysema	Regeneration destructed alveoli by administration of recombinant growth factors as a new approach to therapy for Emphysema- Molecular Mechanisms	Development of new drugs and therapies	2006-2009	To understand in the laser-capture micro dissection, the gene expression versus non-regenerating alveolar septa.	to identify potentially therapeutically useful Bowl events of the regeneration process	N/A
Fondazione del Monte di Bologna e Ravenna	University (n=1)	National	IT	Across different CRDs	Research on the interaction between pollution and CRDs	Aietology	2011	The correlation between CRDs and the quality of life in Italian city	To improve the knowledge of the bad effects of pollution and suggest policy changes.	185000
British Lung Foundation	University (n=1)	National	UK	Pulmonary fibrosis	An external pilot trial of Omeprazole in Idiopathic Pulmonary Fibrosis	Efficacy of drugs	2012-2013	To objectively measured cough frequency	Assess the efficacy of Omeprazole	139,567
ISCIII	University (n=1)	National	SP	Across different CRDs	Effect of treatment with continuous positive airway pressure (CPAP) on the blood pressure in patients with resistant hypertension . Multicenter randomized study.	Development of new therapies and drug	2010-2012.	To assess the effect of CPAP treatment on blood pressure values and nocturnal blood pressure patterns in patients with	PAP treatment for 12 weeks compared with control resulted in a decrease in 24-hour mean and diastolic blood pressure and an improvement in the	591.909 €

								resistant hypertension and OSA.	nocturnal blood pressure pattern. There is a need of improvements in these tools.	

1.3 Discussion and Conclusion

In the past few years, research investment in CRDs has grown. In terms of project aims, most have focused on the research and development of new drugs and therapies. For example, the European Commission's 6th and 7th Framework Programmes have sponsored a large array of new projects for the purpose of advancing CRD therapy and treatments such as GA2LEN (Global Allergy and Asthma European Network). In respiratory medicine, drugs are becoming increasingly important. The use of antibodies and antagonists to block and change disease mechanisms, oncogenes and metabolic pathways is relevant to key disease types like Asthma, COPD, pulmonary fibrosis, and pulmonary hypertension (Canonica, 2007). Projects like GA2LEN aim to improve knowledge regarding Allergies and Asthma together with the factors correlated to the prevalence of these diseases. However, these larger EC projects also involve an emphasis on collaboration than smaller projects lack. As part of the GA2LEN project, researchers are also building a more sophisticated network of researchers, experts and patients associations. In this way the ECs sponsorship FP6 and FP7, the EC had purposefully developed collaborations that extend beyond individual MSs and gain from a pan European exchange of information and expertise.

For COPD, projects clearly focus on new therapies and drugs. Such a focus may be associated with the slow progression of COPD and the presence of acute exacerbations characterized by a worsening of the quality of life which produce a need for new therapies. However, they may also be room for research on the association between the pathogenic roles of key risk factors like cigarette smoke, inflammation, and protease/antiprotease balance. Although the cigarette-inflammation-protease approach neatly captures key features of COPD epidemiology and pathology, this approach has not yet led to a reduction in COPD prevalence or morbidity, to the development of any therapy proven to modify the disease process itself, or to an adequate understanding of how risk factors other than cigarette smoking may contribute to COPD pathogenesis. Others suggest more focus on the socials and economic consequences of COPD are necessary. Equally, others argue that there may also be room for socio-economic research on reducing the availability of tobacco via legislative means.

For asthma, the focus of projects is mainly on understanding the aietology of the disease, and developing new drugs in response. In particular, a large amount of research has been directed towards tailored treatments for patients with severe asthma. Here, the emphasis is on personalized medicine, or the use of more rational and precise treatments that are targeted to individual patients. For some, the notion of "treatment for everyone" with asthma is applicable only to first-episode patients, but not to those with severe asthma. (Weiss, 2012) Indeed, the effectiveness of new treatments also partially depends on the accuracy of the methods for tailoring patients. (Drazen, 2011; Weiss 2012)

For cystic fibrosis, the majority of the projects are attempting to develop new drugs and therapies using a "bottom-up" approach based on knowledge of the mechanisms of disease. This approach involves identifying pathogenic markers of early response to treatment and implementing tests that can predictive their efficacy on the individual patient. Again, the emphasis is on personalized medicine. However, for the majority of the projects on personalized drug development for cystic fibrosis, the results are still uncertain. It is not clear when treatments will become available in clinical practice

For projects that focus on more than one CRD, the most common association is Asthma and COPD. Although these disease types are treated and managed in related ways, prevention programs are very different. For COPD, the priority is to intervene for the reduction of smoking, which remains the key risk factor for the disease. Asthma, however, is not yet completely understood. Neither the causes of its induction, nor the exact influence of genetic and / or environmental development of the disease are accurately know, Consequently, experts are not yet able to recommend a program of specific measures for primary prevention. (Croxton et al, 2002)

For non-specific CRDs, there seems to be an absence of focus on pulmonary hypertension, for which there is currently no cure. Novel therapies, prevention measures and early interventions for in patients at risk are needed. (ERS,2011)

Chronic illnesses, like CRDs, detract from the ability of suffers to maintain a normal life. For this reason perhaps, our results highlight that the research seems to be oriented toward developing drugs and treatments. There has been less focus on imaging and diagnosis.

2 Private Sector Investment in CRDs

Investments in NCD research funding originate from a variety of sources: national governments, regional organizations, charities, non-governmental organizations and supranational organizations. While policy-makers regard the management of NCDs as an increasingly important issue and are engaged in sponsoring research and facilitating cooperation between these organizations for the purpose of developing useful collaborations; less is known about the industry response to NCDs in terms of research and development. In this section of the CA, we consider the background and specifics of private sector investment in NCD research, and in particular, CRDs.

2.0.1. Background: Private Sector Investment in Research and Development

Across the various sectors of industry, the world's top companies are increasing their commitment to research and development (R&D). After the 2009 financial crisis, the world's top 2500 companies, which account for 90% of the world's industrial investment in research and development, enjoyed a brief rebound in sales for the years 2010-11. Although growth stalled in 2012-13, companies continued to invest in R&D, which, overall, increased 4.9% in 2013 (Hernandez et al 2014, 6). Currently, the top 100 world companies are responsible for 53.1% of the total investment in R&D, which includes 31 companies based in the EU, 39 in the US and 17 in Japan. These companies are also responsible for about one third of all patents filed for approval in the US and EU, with the Electronic and Electrical Equipment sector (Samsung and IBM) being the most active (Hernandez et al 2014, 12)

The Pharmaceuticals & Biotechnology sector is one of the largest investors in R&D, claiming about a 18.0% share of total R&D investment for 2014 (Hernandez et al 2014, 47). However, the sector has a much less significant share of patents to R&D investment ratios. For example, the Electronic and Electrical Equipment sector, which enjoys the highest ratio, is about ten times larger than the ratio for Pharma & Biotech. Today, the production of safe and effective compounds requires substantial investment and cooperation between diverse companies across the sector, particularly bio-tech companies (Hernandez et al 2014, 39-40). Indeed, biotech companies are outstripping traditional pharmaceutical companies in terms of investment in R&D, which has increased 20.4%, against pharmaceutical, which has itself decreased investment by 0.2% (Hernandez et al 2014, 47).

Although the Pharmaceutical and Biotechnology sector is among the largest in terms of global R&D investment; analysts have become concerned about the nature and quality of those investments. Decreased patent ratios, stalling investment in general R&D and the increasing role of biotech companies in discovering new molecules and bringing them to market are symptomatic of wider systemic shifts across the industry. The sector, they argue, is in the grip of major changes, which are weighing heavily on the capacity of industry to undertake investment in R&D and respond to the growing challenge of NCDs. These shifts are tectonic and include: changed paradigms for scientific research, new measures of productivity and a declining tolerance for risk (Cockburn, 2006; Pammolli et al., 2011).

Today, new drug discovery is a high-risk and time-consuming process. Only 1 out of every 5000-10,000 compounds screened becomes an approved drug. And it takes an average of 10 to 15 years at an average cost of more than US$1 billion to develop a successful medicine (Merck 2015). Significant can losses occur where outputs are dependent on research interaction at the interface of various disciplines, and where there is no guarantee that new compounds will advance to clinical trials. Increased possibility of R&D failure is one of the main factors in the raised estimates of the costs per new molecular entity (NME), on the basis which analysts now question whether industry is in the grip of an R&D productivity crisis (Cockburn, 2006; Pammolli et al., 2011).

In past, analysts lauded the contribution of industry to the advancement of science and medical technologies. Today, however, where they measure productivity in terms of the ratio of the

"output" of a process to some measure of "inputs", like rising R&D expenditures and falling or static counts of new drug approvals; they have identified a sharp decline in research productivity over the past decade (Cockburn 2007, 1). As such, old confidences in the industry and its product development pathway are fading. In 2004, the FDA expressed "growing concern that many of the new basic science discoveries made in recent years may not quickly yield more effective, more affordable, and safe medical products for patients," citing falling numbers of applications for approval of new drugs, and placing the blame squarely on an "increasingly challenging, inefficient, and costly" product development path (cited in Cockburn 2007, 3). In the 21st century, industry analysts are concerned that the decreasing levels of productivity confronts policy makers with tough questions. Where tax-payers continue to provide significant amounts financial support to industry led R&D, analysts are now asking whether these "poor outcomes justify continued public investment at its current scale?" (Cockburn 2007, 2-3)

2.0.2. Mapping the Private Sector Research Pipeline

In this context, mapping private sector investment in NCD research funding becomes quite important. However, such a mapping exercise also involves unique challenges. For example, the details and strategic focus of public and third sector NCD research funding programmes are readily accessible and, in many cases, a matter of public record. By contrast, the activities of the private sector are not. Governed by the profit motive, the specifics of private sector investment in NCD research are more usually confidential. So, what is the commitment of European pharmaceutical companies to R&D investment in CRDs. How can we map the ways (types of technologies) in which industry has responded to the challenge of CRDs? And how can we assess, or make sense, of this response.

In order to map the industry response (activity, investment and initiatives) to CRDs in terms of research investment, we describe the research pipeline for major European pharmaceutical companies in terms of Molecules in Phase I, Phase II, Phase III, Submission and Approval. Data was collected from the four most recent annual reports available at the companies' global websites (2014-2011). Where data was not available for 2014, the range 2013-2010 was applied. Information was readily available on the web. Results are expressed in terms of phases of development for individual molecules, which are set out in the tables below. The tables also include the total amount of R&D expenses for the available period and the percentage of sales or revenues allocated to R&D.

In order to assess the industry response, we compare the top 20 US and European headquartered companies in terms of annual R&D investment against unmet US and European need for CRDs. Table v details the top 20 pharmaceutical companies based in the US and Europe by investment in R&D. In the sections that follow, we discuss unmet need for NCDs in both Europe and the US, mapping and analyzing the commitment of each company to CRDs in terms of their individual research pipelines.

Table v: Top 20 European and US Pharmaceutical Companies by R&D investment (2013)*

Pharma Co. Rank	World Co. Rank	Company	Country	Total R&D Investment (Mil EURO)	Pipeline Data Available
1	5	NOVARTIS	Switzerland	7173.5	Yes
2	6	ROCHE	Switzerland	7076.2	Yes
3	8	JOHNSON & JOHNSON	US	5933.6	Yes
4	12	MERCK US	US	5165.0	Yes

5	14	SANOFI-AVENTIS	France	4757.0	Yes
6	15	PFIZER	US	4750.2	Yes
7	21	GLAXOSMITHKLINE	UK	4154.3	Yes
8	23	ELI LILLY	US	4010.8	Yes
9	34	BAYER	Germany	3259.0	Yes
10	37	ASTRAZENECA	UK	3202.8	Yes
11	38	AMGEN	US	2960.6	Yes
12	39	BOEHRINGER INGELHEIM	Germany	2743.0	Yes
13	40	BRISTOL-MYERS SQUIBB	US	2705.4	Yes
14	52	ABBVIE	US	2059.3	Yes
15	65	CELGENE	US	1603.4	Yes
16	66	NOVO NORDISK	Denmark	1567.4	Yes
17	68	GILEAD SCIENCES	US	1537.1	Yes
18	70	MERCK DE	Germany	1504.3	**No**
19	95	ABBOTT LABORATORIES	US	1052.9	Yes
20	96	BIOGEN IDEC	US	1047.1	Yes

**'The 2014 EU Industrial R&D Investment Scoreboard' available at: http://iri.jrc.ec.europa.eu/scoreboard.html*

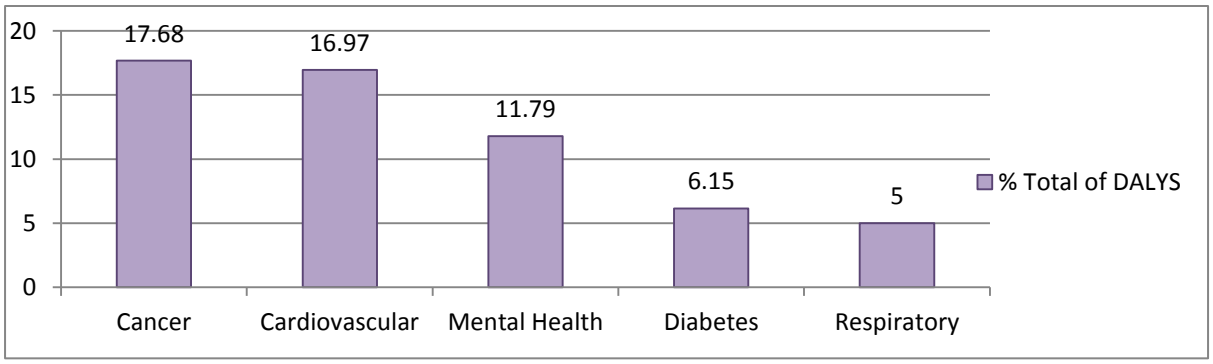
2.1 Unmet Need for CRDs and the Pharmaceutical Sector (EUR)

For governments around the world, the prevention and management of CRDs is an important public health issue for the future. Indeed, by 2020, the World Bank/World Health Organization projects that COPD will be the fifth highest disease in terms of the worldwide burden of disease (Rabe et al 2007, 532). Still, for some time now, COPD, and CRDs in general, have remained relatively unknown to both governments and the public. Even today, there are very few European based RFOs concerned exclusively with CRD research. And in United States, concerns about the visibility of CRDs have even prompted the U.S. National Heart, Lung, and Blood Institute and the World Health Organization to form the Global Initiative for Chronic Obstructive Lung Disease (GOLD) (Pauwels et al 2001, 1256). At the global level, the 53rd World Health Assembly (WHA) has attempted to redress the lack of attention to CRDs by requesting that the WHO Director General to give immediate priority to the prevention and control of CRDs. And in addition, the WHO has attempted to establish a comprehensive worldwide approach to the surveillance, diagnosis, prevention and control of CRDs with the formation of the Global Alliance against Chronic Respiratory Diseases (GARD), a voluntary alliance of organizations, institutions and agencies, including GOLD, for the purpose of delivering on the common aims of improving global lung health and increasing wider public awareness about the threat and debilitating effects of CRDs (Bousquet et al 2007, 217-218)

In terms of specifics, the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) is the world leading data base for recoding epidemiological levels and disease trends worldwide. Maintained by the Institute for Health Metrics and Evaluation (IHME) at the University of

Washington, the database provides rigorous and comparable freely available measurement of the world's major health problems, of which CRDs is one. The purpose of the GBD data base is to provide policymakers with sufficient the evidence to make informed decisions on the allocation of resources for the improvement of population health. For our purpose, the GBD offers an accurate comparative picture of the levels of unmet need that the major NCD categories represent. According to the GBD, CRDs are a serious public health problem in Europe. They are the fifth leading cause of lost DALYs across Europe in terms of NCDs.

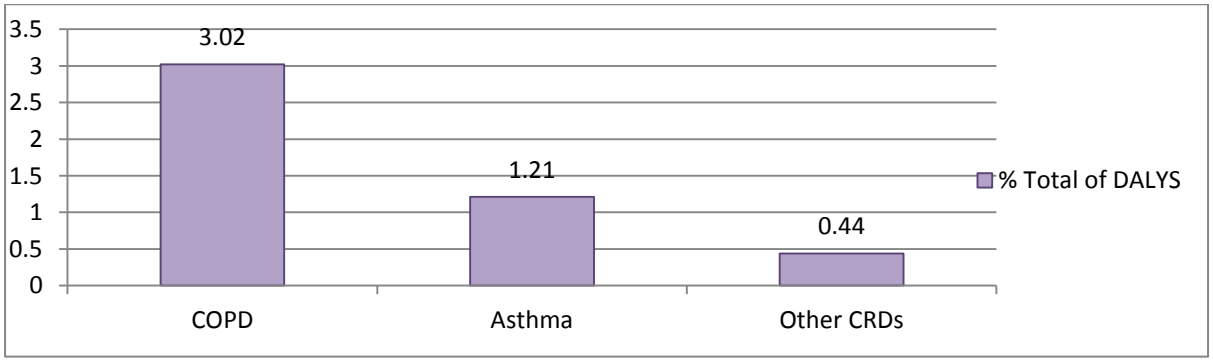
Figure ii: NCDs in Europe (2010) Percentage of Lost DALYs by Disease Category*



*Sourced at: http://vizhub.healthdata.org/gbd-compare/

Breaking down the CRD category into its major diseases, the database reveals that COPD is the largest cause of lost DALYs

Figure iii: CRDs in Europe (2010) Percentage of Lost DALYs by Disease*



*Sourced at: http://vizhub.healthdata.org/gbd-compare/

Using the European burden of disease as a basis, we analyzed the commitment of the European pharmaceutical sector to CRDs and its major disease categories. With the analysts suggesting that CRDs typically receive less attention than other NCD categories from national governments and the general public, it is reasonable to assume that they might also receive less attention in the private sector. But, as we found, this was not always the case. The research pipeline for the top 10 European pharmaceutical companies suggests that firms seem to specialize in certain NCD categories. For example, pipeline data shows that SANOFI-AVENTIS, preferring to focus on other areas, does not have any CRD relevant molecules under development; other firms like GSK, however, are developing several. In the second place, we though it reasonable to assume that we should expect to see a relatively similar commitment from major companies to the disease categories of COPD and asthma. Although COPD is by far the biggest source of lost DALYs within the CRD category, analysts have suggested that there is a greater potential for developing pharmaceutical products for the treatment asthma than for the treatment of COPD. And indeed, where companies chose to focus their attention on CRDs, they did seem to have similar numbers of products available in each disease category.

2.2 European Pharmaceutical Sector: Research Pipeline for CRDs

The European pharmaceutical sector has five companies among the world's top ten pharmaceutical firms. And indeed, across Europe, the sector is major investor in R&D. According to the European Federation of Pharmaceutical Industries, the European pharmaceutical sector invested an estimated €30,630 million in R&D across Europe for the year 2013 (EFPI 2014). The industry also employs about 690,000 people and supports between three and four times than number of jobs across the EU area. The EFPI also asserts that the sector has suffered from the impact of European austerity measures introduced in response to the financial and debt crisis of 2008-9 (EFPI 2014).

2.2.1. NOVARTIS (EUR)

Novartis is a Swiss based company headquartered in Basel. It was formed in 1996 through the merger of Sandoz and Ciba-Geigy. In 2003, Novartis reintroduced the Sandoz brand as a single subsidiary in which it consolidated its generic drugs businesses. Novartis divested its agrochemical and genetically modified crops business in 2000 with the spinout of Syngenta in partnership with AstraZeneca, which also divested its agrochemical business. Today, Novartis focuses its business on three leading divisions: pharmaceuticals (Novartis), eye care (Alcon) and generics (Sandoz). Novartis is currently expanding its presence in the emerging markets of Asia, Africa and Latin America, where there is fast-growing demand for access to high-quality medicines and healthcare. The company has more than 119.000 employees in over 150 countries.

Table vi: NOVARTIS (EUR) Total Research and Development Investment

Mil USD	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	9900	17.1	9640	16.6	9120	16.1	9240	15.8
% Change	+2.6		+5.5		-1.3		+	

Since 2012, Novartis has marginally increased its commitment to R&D activities, and has several CRD relevant molecules in advanced stages of development, which pertain equally to major disease categories of COPD and asthma. Novartis also lists CRDs as an area of therapeutic interest.

Table vii: NOVARTIS (EUR) Research Pipeline CRDs

Year	Product Name	Indication	Phase
2012	Seebri (glycopyrronium bromide)	COPD	Approved
2014	Fevipiprant	Asthma	II
2011	Indacaterol, mometasone fuorate	Asthma and COPD	II
2013	BCT197	COPD	II
2014	QGE031	Asthma	II

2.2.2. ROCHE (EUR)

ROCHE is Swiss pharmaceutical company headquartered in Basel, Switzerland. Founded in 1896 by Fritz Hoffmann-La Roche, it is the largest European pharmaceutical company in terms of investment in R&D. Today, Hoffman's descendants own close to half the company's bearer shares with voting rights (45%). ROCHE owns several important biotechnology companies, like Genentech and Ventana in the US, and Chugai Pharmaceuticals in Japan. In its early years, ROCHE gained a reputation for being the first company to mass-produce synthetic vitamin C in 1934. Today, it is a market leader in cancer research. Since 2012, ROCHE's total investment in R&D had been increasing at an average of 3.19%

Table viii: ROCHE (EUR) Total Research and Development Investment

Mil USD	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	8900	18.6	8700	18.6	8500	18.6	8100	19.0
% Change	+2.29		+2.35		+4.93			

Despite being the largest pharmaceutical company in Europe, ROCHE has only one CRD relevant molecule in its research pipeline, which pertains to asthma. However, ROCHE does not list CRDs as research area in which its scientists are currently active. Instead, ROCHE is focused on other disease areas such as oncology, neuroscience and infectious diseases, immunology and cardiovascular diseases.

Table ix: ROCHE (EUR) Research Pipeline CRDs

Year	Product Name	Indication	Phase
2014	Lebrikizumab	Asthma	III

2.2.3. SANOFI-AVENTIS (EUR)

Sanofi-Aventis is a French pharmaceutical company currently headquartered in Paris. It was formed in 2004 when Sanofi-Synthélabo acquired Aventis via a hostile takeover bid in which the French government played a major role in resolving. Today, the company is focused on the seven strategic growth platforms: diabetes, vaccines, consumer healthcare, rare diseases & multiple sclerosis. They have 45000 employees across 40 countries.

Table x: SANOFI-AVENTIS (EUR) Total Research and Development Investment

Mil Euro	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	4824	14.3	4770	14.5	4922	14.1	4811	14.4
% Change	+1.1		-3.2		+2.3			

Historically, Sanofi-Aventis claims to have concentrated its efforts on alleviating and curing common chronic and acute diseases. However, it does not list CRDs as an area of interest. Instead, its focus is on cardiovascular medicine, thrombosis, oncology, internal medicine, metabolic disorders, diseases of the central nervous system and vaccines. Its commitment to R&D investment has remained relatively steady over the period.

2.2.4 GLAXO SMITH KLINE (EUR)

GSK is a British multinational pharmaceutical company currently headquartered in Brentford. It was established in 2000 by a merger of Glaxo Wellcome and SmithKline Beecham. GSK has a portfolio of products for major disease areas such as asthma, cancer, infections, mental health, diabetes and digestive conditions. In March 2015, they acquired Novartis's vaccines business (excluding influenza vaccines). Today. GSK has more than 100000 employees across 110 countries.

Table xi: GLAXO SMITH KLINE (EUR) Total Research and Development Investment

Mil GBP	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	3100	13.5	3400	12.8	3500	13.2	4000	14.6
% Change	-8.82		-2.86		-12.5			

As its statement of focus suggests, GSK has a number of molecules in development that are relevant to CRDs. According to its annual reports, GSK has a larger commitment to COPD than to Asthma, but it does have one molecule in development that is focusses on severe Asthma. With multiple products in development, GSK has the second largest commitment to CRDs of the top 10 European pharmaceutical companies. Curiously, however, GSK seems to have progressively decreased its commitment to R&D activities over the period (2011-4)

Table xii: GLAXO SMITH KLINE (EUR) Research Pipeline CRDs

Year	Product Name	Indication	Phase
2014	Losmapimod	COPD	II
2014	Danirixin	COPD	II
2014	2269557	Asthma and COPD	II
2014	2245035	Asthma	II
2014	961081	COPD	II
2014	Vilanterol	COPD	III
2013	Relvar/Breo Ellipta (Fluticasone fuorate/vintaerol)	COPD and Asthma	Approved in US
2013	Anoro Ellipta (umeclidinium + vinaterol)	COPD	Approved in US
2014	Mepolizumab	Severe asthma	Field
2013	Incruse Ellipta (Umeclidinium)	COPD and hyperhydrosis	Field

2.2.5 BAYER (EUR)

Founded in 1863, Bayer is a German chemical and pharmaceutical company headquarter in Leverkusen, Germany. In the Aftermath of World War One, Bayer became part of IG Farben, which in the aftermath of World War Two, was broken up following its participation in Nazi war crimes. In 1978, the company retook the name 'Bayer'. Today, Bayer is active in healthcare, but also has major divisions in material and crop science. The company is mainly focused on familiar over-the-counter consumer health care products and prescription medicines. The company has about 118900 employees across 75 countries.

Table xiii: BAYER (EUR) Total Research and Development Investment

Mil EURO	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	3574	8.5	3190*	7.9	3013	7.6	2932	8.0
% Change	+12.0		+5.9		+2.8			

**For 2013 R&D Expenditure, there was a discrepancy between the 2014 and 2013 annual report. The table records the figure reported in 2014*

Consistent with its focus on consumer healthcare products, Bayer does not have any CRD relevant molecules in development. The company is, however, progressively increasing its commitment to R&D investment.

2.2.6 ASTRAZENECA (EUR)

AstraZeneca is a British-Swedish company with its headquarters in London. Founded in 1999 by the merger of Astra AB (Swedish) and the Zeneca Group (British), AstraZeneca focusses on three areas of healthcare: CVDs, Oncology, CRDs, Inflammation and Autoimmunity. The company is also active in the Infection, Neuroscience and Gastrointestinal disease areas. AstraZeneca also collaborates and cooperates with other leading companies in the sector. In 2012, it announced a collaboration with the American company Amgen on inflammatory disease treatments. The same year, it announced a joint acquisition of the biotechnology company Amylin Pharmaceuticals with American company Bristol Myers Squibb. Today, the company has about 57500 employees across 100 countries.

Table xiv: ASTRAZENECA (EUR) Total Research and Development Investment

Mil USD	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	5579	21.3	1429	20.9	1320	18.1	1867	21.6
% Change	+290.4		+8.3		-29.2			

Of the top 10 European pharmaceutical companies, AstraZeneca has the largest commitment to CRDs by products in development. It demonstrates a greater commitment to COPD, but has some products in development that are exclusive to asthma and is also focused on products for severe asthma. In 2014, the company massively increased its commitment to R&D, almost quadrupling its aggregate investment of 2012, making it the third-largest European investor in R&D for 2014. The increase may be related to its joint acquisition of Amylin Pharmaceuticals.

Table xv: ASTRAZENECA (EUR) Research Pipeline CRDs

Year	Product Name	Indication	Phase
2011	Oxis (formoterol)	COPD	III
2011	Symbicort (budesonide+formoterol)	COPD and Asthma	III
2011	AZD1981	COPD and Asthma	II
2011	AZD2423, 5423, 8683	COPD	II
2011/12	AZD5069, MEDI-8968	Asthma	II
2014	PT003, 001	COPD	III
2013	Benralizumab	Severe asthma	III
2014	Tralokinumab	Asthma	III
2012	AZD2115, 7594, MEDI8968	COPD	II
2012	AZD8848, MEDI4212, 9929, 1419	Asthma	I
2014	Brodalumab	Asthma	III
2013/14	MEDI7814, AZD4721, 7624, PT010, 8999	COPD	I
2014	AZD0548, 9412	Asthma and COPD	II

2.2.7 BOEHRINGER-INGELHEIM (EUR)

Originally founded in 1885 by Albert Boehringer, Boehringer Ingelheim is a German pharmaceutical company headquartered in Ingelheim, Germany. Today, Boehringer Ingelheim remains a family owned company. Its focus is on CRDs, metabolism, immunology, oncology and central nervous system diseases. The company claims a reputation for providing effective products for the treatment of COPD. It has about 47700 employees across 146 affiliates.

Table xvi: BOEHRINGER-INGELHEIM (EUR) Total Research and Development Investment

Mil EURO	**2013**		**2012**		**2011**		**2010**	
Total R & D Expense	**Amount**	**% of Sales**	**Amount**	**% of Sales**	**Amount**	**% of Sales**	**Amount**	**% of Sales**
	2743	19.5	2795	19.0	2516	19.1	2453	19.5
% Change	-1.9		+11.0		+2.5			

Despite its claims in relation to CRDs and COPD, the company has significantly less CRD relevant products in development than larger competitors such as GSK and AstraZeneca. Nevertheless, its commitment to R&D investment has increased steadily since 2010.

Table xvii: BOEHRINGER-INGELHEIM (EUR) Research Pipeline CRDs

Year	Product Name	Indication	Phase
2014	Striverdi (olodaterol)	COPD	Approved
	Tiotropium	Asthma	Submitted

2.2.8 NOVO-NORDISK (EUR)

Founded in 1989 through the merger of the smaller Danish companies Nordisk Insulinlaboratorium and Novo Terapeutisk Laboratorium, Novo Nordisk is a Danish pharmaceutical company currently headquartered in Bagsvaerd, Denmark. The company's major product lines address the disease areas of diabetes, hemostasis and also growth hormone therapy and hormone replacement therapy. The company manufactures pharmaceutical under various brand names, which include Levemir, NovoLog, Novolin R, NovoSeven, NovoEight and Victoza. Today, the company has about 39000 employees across 75 countries. Importantly, the company records its results in Danish currency.

Table xviii: NOVO-NORDISK (EUR) Total Research and Development Investment

Mil DKK	2014		2013		2012		2011	
Total R & D Expense	**Amount**	**% of Sales**	**Amount**	**% of Sales**	**Amount**	**% of Sales**	**Amount**	**% of Sales**
	13800	15.5	11700	14.0	10900	14.0	9300	14.5
% Change	+17.94		+7.33		+17.2			

With its focus on other disease areas, Novo Nordisk does not have any CRD relevant molecules in development. But, since 2011, the company has progressive increased its commitment to R&D.

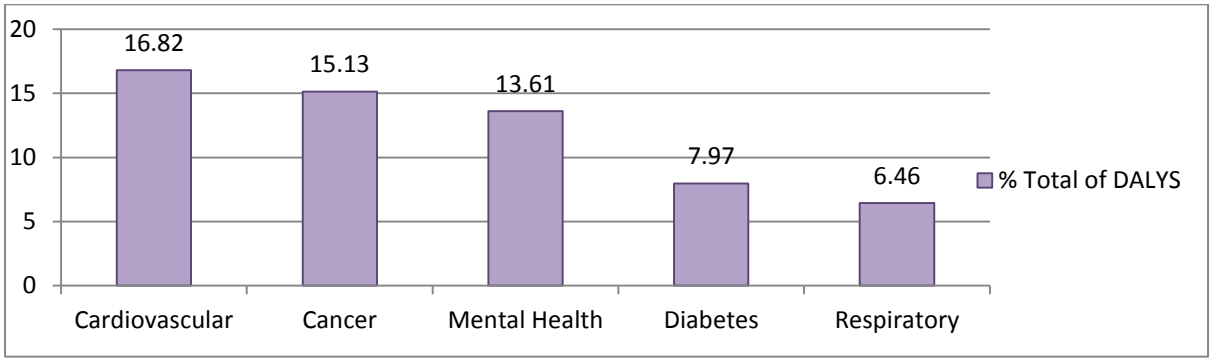
Table xix: NOVO-NORDISK (EUR) Research Pipeline CRDs

Year	Product Name	Indication	Phase
	Nil		

2.3 Unmet Need for CRDs and the Pharmaceutical Sector (US)

In the United States, the burden of disease associated with CRDs is higher than that of Europe. But, considered in relation to other NCD categories, it yet remains the fifth largest cause of lost DALYs across the continent. According to the GBD, the US seems to have larger problems with categories like diabetes and mental health than Europe; and the situation for CVDs and Cancer is somewhat reversed. In the US, CVDs are the largest disease category in terms of lost DALYs, but the levels of lost DALYs in Europe and the US are about the same. In the US, however, there is less burden of disease associated with cancer.

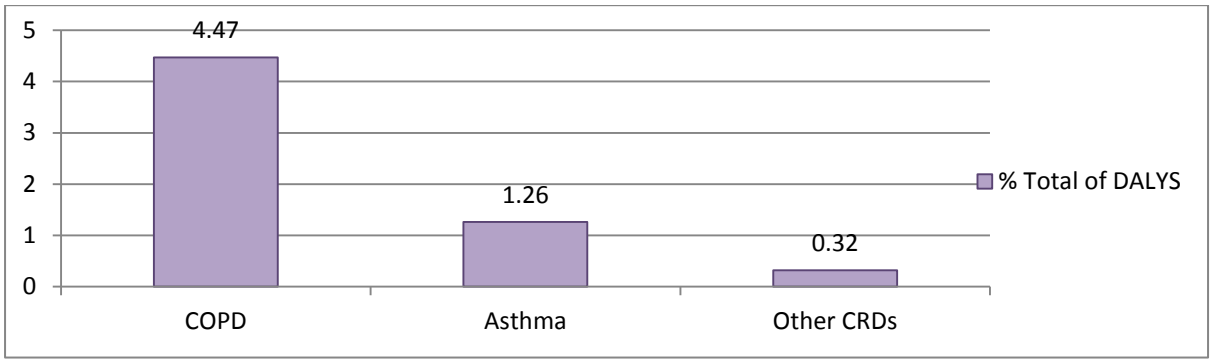
Figure iv: NCDs in United States (2010) Percentage of Lost DALYs by Disease Category*



*Sourced at: http://vizhub.healthdata.org/gbd-compare/

Breaking the CRD category into disease areas, COPD remains the largest contributor to lost DALYs in the US. Interestingly, the US and Europe have broadly similar levels of disease burden associated with asthma. Still, the US has a significantly higher level of disease burden associated with COPD.

Figure v: CRDs in United States (2010) Percentage of Lost DALYs by Disease*



*Sourced at: http://vizhub.healthdata.org/gbd-compare/

2.4 US Pharmaceutical Sector: Research Pipeline for CRDs

Five of the world's top ten pharmaceutical companies have their headquarters in the US, which is also the world's largest market for pharmaceuticals, and a world leader for investment in R&D. U.S. firms carryout the majority of global R&D and hold the intellectual property rights on most new medicines. Considered as an aggregate, the US research pipeline has approximately 3,400 compounds currently under development in the United States, which is significantly more than any other region (PHRMA 2015). According to Pharmaceutical Research and Manufacturers of America, the US biopharmaceutical industry employs more than 810,000 people, supporting another approximately 3.4 million jobs nationally. In addition, the US biopharmaceutical sector is one of the most R&D-intensive sectors in the United States and around the world. In the US, the industry invests more than 10 times the amount of R&D per employee than all manufacturing industries overall (PHRMA 2015).

Based on the GBD data, the US pharmaceutical sector should demonstrate relatively similar levels of product commitment to CRDs, and perhaps also a similar levels of commitment to COPD and asthma. Research Pipeline Data was available for the top ten US Pharmaceutical companies. But, broadly, we found that US companies had significantly less CRD-relevant molecules in their research pipeline than European based companies. While commitment to CRDs, where it was found, was

evenly distributed between asthma and COPD; in many cases, US firms were not at all active in developing new molecules for CRDs.

2.4.1. JOHNSON AND JOHNSON

Founded in 1886, Johnson & Johnson is a U.S. medical devices, pharmaceutical and consumer healthcare products company currently headquartered in New Brunswick, New Jersey. Its consumer division provides well known over the counter medicines and a range of baby care and skin care products. Its medical devices division, which we consider in the next section, specialises in orthopedics, neurological disease, diabetes care, infection prevention, and cardiovascular disease. And its pharmaceutical division focusses on oncology, immunology, neuroscience, diabetes and cardiovascular diseases.

Table xx: Johnson & Johnson (US) Total Research and Development Investment

Mil USD	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	8494		8183	11.5	7665	11.4	7548	11.6
% Change	+3.8		+6.8		+1.6		+10.2	

With its focus in other areas, Johnson & Johnson does not have any CRD relevant molecules in development. As a side note, however, in December 2012, the company received approval for tuberculosis drug, Sirturo (bedaquiline), which is the first new medicine to combat the infection in over forty years. The company has been progressively increasing its commitment to R&D investment since 2010.

Table xxi: Johnson & Johnson (US) Research Pipeline CRDs

Year	Product Name	Indication	Phase
	Nil		

2.4.2. MERCK (US)

Merck US is headquartered in Kenilworth, New Jersey. The company was established in 1891 as a US subsidiary of the German company Merck, which was originally founded in 1668. During the First World War, the US government confiscated Merck and reestablished it as an independent American company. In 2013, Merck invested $7,500 million in R&D, which represents the largest amount in the sector both globally and the US. However, Merck's overall investment level in R&D has been progressively falling over the period (2010-2014), with a major fall of 22.7% in 2011.

Table xxii: MERCK (US) Total Research and Development Investment

(Mil USD)	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	7180		7503	17.0	8200	17.35	8500	17.69
% Change	-4.3		-8.54		-3.53		-22.73	

Consistent with its position as the largest US pharmaceutical company by R&D investment, Merck has the largest number of pharmaceutical technologies for CRD in its research pipeline of any other US company. Merck's outputs for CRDs are also evenly distributed between the major disease types, namely Asthma and COPD; and they are also in advanced stages of development. However, the company's output for CRDs is still much less than that of comparatively smaller European companies like AstraZeneca and Glaxo.

Table xxiii: MERCK (US) Research Pipeline CRDs

Year	Product Name	Indication	Phase
2014	MK-1029	Asthma	Phase II
	SCH 527123 (Selective CX CR2 Chemokine Receptor 2 antagonist)	COPD	Phase II
	Dulera (Mometasone Furoate, Formoterol Fumarate Dihydrate)	COPD and Asthma (inhaled medicine used to control and prevent asthma)	Phase III
2014	Grastek (Timothy Grass Pollen Allergen Extract)	Grass pollen allergy	Approved
2014	Ragwitek (Short Ragweed Pollen Allergen Extract)	Grass pollen allergy	Approved

2.4.3. PFIZER

Founded in New York in 1849 by Charles Pfizer and Charles F. Erhart, Pfizer is American pharmaceuticals company currently headquartered in New York. Since 2004, the company's shares have been listed a component of the Dow Jones Industrial Average. Recently, Pfizer has also been the subject prosecutions for illegal and off-label marketing in relation to the arthritis drug Bextra, paying the US government multi-billion dollar settlements. Pfizer produces medicines for a wide range of disease areas, including: oncology, diabetes, cardiovascular disease and neurology

Table xxiv: PFIZER (US) Total Research and Development Investment

Mil USD	2014		2013		2012		2011	
Total R & D Expense	**Amount**	**% of Sales**	**Amount**	**% of Sales**	**Amount**	**% of Sales**	**Amount**	**% of Sales**
	8393		6678	12.9	7870	13.7	8681	14.2
% Change	+25.6		-15.1		-9.34		-8.45	

Although the company does not claim CRDs as an area of research interest, Pfizer has several CRD relevant molecules in development, which are aimed at major disease areas of COPD and asthma. Interestingly, the company's commitment to R&D had been progressively decreasing since 2010 to the point that its levels of investment have been diminished by about a third over the relevant time period. In 2014, however, investment in R&D jumped by over 25%.

Table xxv: PFIZER (US)Research Pipeline CRDs

Year	Product Name	Indication	Phase
	PF-03715455	COPD	Phase I
	PH-797804	COPD	Phase II
2011	PF-03526299/ PF-03893787	Asthma	Phase I

2.4.4. ELI LILLY

Eli Lilly was founded in 1877 by Eli Lilly, a pharmaceutical chemist and veteran of the American Civil War, who was company president until his death in 1898. Eli Lilly was the first pharmaceutical company to mass produce break-through drugs like insulin, polio vaccine and penicillin. Today, the company remains the largest manufacturer and distributor in the world of psychiatric medications. In 2009, Eli Lilly paid a $515 million fine in relation to the off-label marketing of the dementia drug, Zyprexa. Today, the company's focus is on the disease areas of autoimmunity, cardiovascular disease, musculoskeletal disorders, neuroscience, oncology and diabetes.

Table xxvi: ELI LILLY (US) Total Research and Development Investment

Mil USD	2014		2013		2012		2011	
Total R & D Expense	**Amount**	**% of Sales**	**Amount**	**% of Sales**	**Amount**	**% of Sales**	**Amount**	**% of Sales**
	4773		5531.3	23.9	5278.1	23.4	5020.8	20.7
% Change	-13.7		+4.79		+5.12		+2.7	

Focused on other disease areas, Eli Lilly does not have any CRD relevant molecules in development. The company's levels on investment in R&D have steadily increased since 2010, but dropped substantially (14%) in 2014.

2.4.5. AMGEN

Founded in 1980, Amgen is a US biopharmaceutical company currently headquartered in Thousand Oaks, California. Amgen is focused on kidney disease, cancer, rheumatoid arthritis, bone disease and other serious illnesses.

Table xxvii: AMGEN (US) Total Research and Development Investment

Mil USD	2014		2013		2012		2011	
Total R & D Expense	**Amount**	**% of Sales**	**Amount**	**% of Sales**	**Amount**	**% of Sales**	**Amount**	**% of Sales**
	4297		4100	22.5	3400	20.4	3200	20.9
% Change	+4.8		+20.5		+6.25		+15.39	

Amgen does not have any CRD relevant molecules in its production pipeline. However, the company has substantially increased its investment in R&D. Since 2010, the company's level of R&D investment has increased by over one third.

2.4.6 BRISTOL MYERS SQUIBB

Founded in New York in 1858 by Edward R. Squibb, Bristol-Myers Squibb is a US based pharmaceutical company currently headquartered in New York City. During the American Civil War, the company was an important source of medicines for the Union Army, manufacturing the famous Squibb pannier, a compact wooden medicine chest for use by US army surgeons on the battlefield which filled with about 50 medicines, including chloroform for use in amputations. Today, Bristol-Myers Squibb manufactures pharmaceutical products in a number of disease areas including: cancer, HIV/AIDS, cardiovascular disease, diabetes, hepatitis, rheumatoid arthritis, fibrotic diseases and psychiatric disorders.

Table xxviii: BRISTOL MYERS SQUIBB (US) Total Research and Development Investment

Mil USD	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	4534		3731	30.3	3904	28.59	3839	21.79
% Change	+21.5		-4.43		+1.69		+7.66	

The company does not have any CRD relevant molecules in development for major disease areas like COPD and asthma. However, it does have one relevant molecule for Fibrotic Lung Disease. Since 2010, the company's investment levels in R&D have been relatively steady, but jumped by over 20% in 2014.

Table xxix: BRISTOL MYERS SQUIBB (US) Research Pipeline CRDs

Year	Product Name	Indication	Phase
	LPA1 Antagonist (Lysophosphatidic acid receptor 1)	Fibrotic Lung Disease	Phase II

2.4.7 ABBVIE

Formed in 2011, Abbvie is a US biopharmaceuticals company headquartered in Chicago, Illinois. Abbvie was formed via a divestment from Abbot Laboratories. Whereas Abbott Laboratories focuses on diagnostic equipment, medical devices and consumer health care products; AbbVie operates as a research-based biopharmaceutical company. The company claims the development of two important breakthrough medications for the treatment of HIV. Today the company's research focus is on areas such as: immunology, oncology, neuroscience, kidney and disease, and women's health

Table xxx: ABBVIE (US) Total Research and Development Investment

Mil USD	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	3297		2900	15.43	2800	15.23	2600	14.90
% Change	+13.6		+3.57		+7.69		+4.0	

Focused on other areas, Abbvie does not have any CRD relevant molecules under development, but its commitment to R&D investment has been steadily increasing since 2010.

2.4.8 CELGENE

Founded in 1986, Celgene is a US based biopharmaceutical company currently headquartered in Summit, New Jersey. Celgene's research focus is on the areas of cancer, immune and inflammatory disorders. Major compounds in development concern the treatment of hematological and solid tumor cancers, together with chronic lymphocytic leukemia, non-Hodgkin's lymphoma, small cell lung cancer and prostate cancer.

Table xxxi: CELGENE (US) Total Research and Development Investment

Mil USD	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	2430		2226	34.99	1724	32.01	1600	34.04
% Change	+9.16		+29.1		+7.75		+41.8	

Although largely focused on other disease areas, Celgene's research pipeline includes one CRD relevant molecule. However, the company does not have any relevant products under development in the area of COPD and asthma. Celgene has recorded the second largest percentage increase in terms of investment in R&D of the top US pharmaceutical companies. Since 2011, its level of investment has increased by over 50%

Table xxxii: CELGENE (US) Research Pipeline CRDs

Year	Product Name	Indication	Phase
	Tanzisertib (CC-930) Kinase inhibitor. Also in Phase II for Discoid Lupus.	Idiopathic pulmonary fibrosis	Phase II

2.4.9 GILEAD

Founded in June 1987 by the then 29 year old Michael Riordan, Gilead Sciences is US based biotechnology currently headquartered in Foster City, California. Gilead's research focus in on HIV/AIDS, liver diseases, cancer, CRDs and CVDs. The company also boasts the first complete treatment regimen for HIV infection via a single pill taken once-daily, together with the first oral antiretroviral pill for reducing the risk of HIV acquisition.

Table xxxiii: GILEAD (US) Total Research and Development Investment

Mil USD	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	2854		2120	19.6	1760	18.72	1230	15.19
% Change	+34.62		+20.45		+43.1		+14.63	

Gilead lists treatments for serious respiratory conditions such as influenza, cystic fibrosis and other diseases of the lungs as a principal focus of its research and development investment. However, it only has one molecule under development. Gilead has narrowly recorded the largest percentage increase of US pharmaceutical companies in terms of investment in R&D. Since 2011, its level of investment has more than doubled, an increase of 132%

Table xxxiv: GILEAD (US) Research Pipeline: CRDs

Year	Product Name	Indication	Phase
	Simtuzumab Monoclonal antibody, it is also being studied in various Phase II studies for liver fibrosis and solid tumors	Idiopathic pulmonary fibrosis (IPF)	Phase II

2.3.10 ABBOT

Following the divestment of AbbVie in 2011, Abbott has refashioned itself as pharmaceutical company focused largely on consumer healthcare and prescription medicines. Since 2011, Abbot's investment in R&D activities has fallen substantially.

Table xxxv: ABBOT (US) Total Research and Development Investment

Mil USD	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	1345		1452	6.66	1544	7.18	1512	7.06
% Change	-7.3		-5.95		+2.11		-40.59	

Consistent with it consumer healthcare focus, Abbot does not have any CRD relevant molecules under development. Since 2010, the company's investment in R&D has substantially decreased, which is perhaps related to its divestment of AbbVie

2.3.11 BIOGEN IDEC

Biogen Idec is a global biotechnology company based in Cambridge, Massachusetts, that specializes in the development of treatments for neurodegenerative, hematologic and autoimmune diseases. Founded in Geneva in 1978, Biogen became the third largest biotechnology company in the world after merging with San Diego, California-based IDEC Pharmaceuticals in 2003.

Table xxxvi: BIOGEN IDEC (US) Total Research and Development Investment

Mil USD	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	1893	19.50	1444	20.80	1335	24.20	1220	24.2
% Change	+31.0		+8.20		+9.4			

With its focus in other areas, BIOGEN does not have any CRD relevant molecules under development. Since 2010, the company's investment in R&D has increased substantially, by almost 50%

2.5 Discussion: The Pharmaceutical Research Pipeline for CRDs

Overall, the European pharmaceutical sector has increased its commitment to R&D over the past four years. GSK is the only top 10 company to record a shrinking commitment to research investment. Some companies, like AstraZeneca, have recorded a massive increase in R&D spending. But most companies have recorded progressive of steady increases. By contrast, US levels of investment in R&D have been more mixed. Companies at the top of the scale, like Merck and Pfizer, have steady reduced their levels of investment. At the lower end of the scale, companies like Gilead and Celgene have massively increased their commitment.

Despite being the world leader for R&D investment in the pharmaceutical and biotechnology sector, major US companies have significantly less CRD-relevant molecules in their research pipelines than European based companies. In several cases, US firms were not at all active in developing new molecules for CRDs. By contrast, European based pharmaceutical companies have a much greater commitment to CRDs in terms of pipeline development. Certainly, the top 10 European companies seem to specialize in specific NCD categories, and major companies such as SANOFI-AVENTIS do not have any CRD relevant molecules under development at all. However, compared with the US, other large European firms like GSK, Novartis and AstraZeneca have quite a number of products in development. Indeed, these three firms consolidate more molecules in their research pipelines than do the top ten US firms collectively. Where the number of molecules under development in the United States is set against broadly similar levels of patent need in the US and Europe, there are grounds for concluding that US R&D commitment to CRD is lacking and perhaps even broadly insufficient to tackle to scale of the problem that these diseases represent.

In the broader context of the academic literature, the observation that US R&D investment in CRDs underestimates the scale of the problem that disease areas like COPD and asthma represent in terms of unmet need also raises an important issue. For example, in the 1980s, analysts argued that, given significant levels of industry contribution to scientific advancement, public resources may well have been better directed to facilitating research in the industry sector rather than academic institutions (Koenig 1983, 35). At the time, where conventional wisdom would have suggested that pharmaceutical companies would primarily invest in developmental and applied research in order to advance their economic interests; and similarly, where commonplace thinking of the time would have also suggested that both the industry and wider society was dependent on blue sky scientific research undertaken in a predominantly academic environment; analysts cast doubts on these ideas, finding that industry investments had contributed significantly to the vast body of scientific research in the public domain, which was guiding and influencing researchers everywhere (Koenig 1983; Nairn and Rozek 1988). Measuring the quality and quantity of industry published research in mainstream scientific journals, analysts found that industry investment in R&D has contributed significantly to advancement of broad based scientific research and the general public welfare through the 1970s and 1980s (Nairn and Rozek 1988, 139). In the 1980s, analysts argued that the high citation rates of industry published papers represented "non-trivial degree" of contribution to the basic biomedical research literature (Koenig 1983, 35). Consequently, they suggested that encouraging industry investment in R&D via special tax treatments of expenditures, might even represent a more effective contribution to the public interest than investment in the public sector universities (Koenig 1983, 35). Indeed, these earlier analysts even questioned whether academic institutions were the proper environment in which to sponsor basic scientific research given the pressing social interest in translating that research into pragmatic health technologies. Thus, given

the significant contribution of industry to scientific advancement, earlier analysts asked whether public resources were better directed to industry (Koenig 1983, 35).

Today, however, in the case of CRDs at least, where industry investment in R&D seems insufficient to the level of patient need, there seem to be grounds for questioning the conclusions of these earlier analysts, and perhaps even some additional grounds for exploring new models of working between academic and industry based researchers.

2.6 Medical Devices Industry Investment in CRDs

A Medical Device (MD) is an instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application intended by the manufacturer to be used for human beings for the purpose of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,
- investigation, replacement or modification of the anatomy or of a physiological process,
- control of conception,
- and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means (Council Directive 93/42/EEC on Medical Devices).

The objective of this section of the CA is to provide a detailed map of CRD relevant outputs of the Medical Devices Industry across the EU. In order to map MDs industry R&D investments, we identified a list of top 16 medical device manufacturers worldwide ranked by total revenue (updated to October 9, 2014). Based on website interrogations and annual reports, general information and total R&D expenses for each MD company have been collected for the period 2011 to 2014.

Table xxxvii: Top 16 Medical Devices Companies by Research and Development Investment (2014)*

MD Co. Rank	World Co. Rank	Company	Country	Total revenues (Bil USD)	Total R&D Investment (Mil USD)
1	34	Johnson & Johnson	United States	28.7	8,494
2	9	General Electric Co.	United States	18.1	4,233
3	249	Medtronic Inc	United States	17.1	1,477
4	54	Siemens AG	Germany	17.0	4,065
5	346	Baxter International Inc	United States	16.4	1,421
6	283	Fresenius Medical Care AG & Co. KGAA	Germany	15.2	369
7	472	Koninklijke Philips NV	Netherlands	11.8	1,635
8	327	Cardinal Health Inc.	United States	11.0	NA
9	52	Novartis AG (Alcon)	Switzerland	10.7	903

10	349	Covidien plc[1]	Ireland	10.4	546
11	719	Stryker Corp.	United States	9.3	614
12	610	Becton, Dickinson and Co.	United States	8.3	550
13	1047	Boston Scientific Corp.	United States	7.2	817
14	732	Essilor International SA	France	7.2	188
15	753	Allergan Inc. (Actavis)[2]	Ireland	6.7	1,085.9
16	957	St. Jude Medical Inc.	United States	5.6	692

*http://www.mddionline.com/article/top-40-medical-device-companies;

2.7 Search Methods

In order to identify new products associated with these companies, we under took three searches. In the first place, we searched a database of clinical studies (i.e. clinicaltrials.gov) for recently (≥2011) closed and ongoing clinical studies funded by each MD company identified above.

Secondly, we searched databases of new approved MDs (i.e. FDA premarket approval, de novo database, EuroScan) have been searched according to the same time frame (2011-2015).

Thirdly, at the European Level, we searched a database of CE marked products exists since 2009, called EUDAMED. This database is only accessible to government agencies in charge for the market surveillance in each country (e.g. Ministero della Salute in Italy). In the US, by contrast, the relevant authority, the Food and Drug Administration (FDA), has a whole section on the website with approval dossiers for all medical devices. Although there is not a direct link between technologies approved in the US and technologies licensed in the EU, knowledge of the most recent innovations overseas does provide some indication of the most up-to-date technologies that are available to improve clinical practice for the management for CRDs.

Therefore, the FDA premarket approval (PMA) and de novo databases have been searched for new approved products between 2011 and 2015. The 510(k) clearance has not been considered as this refers to products "substantially equivalent" to others already on the market. In this case, unlike the previous steps, the search has been performed according to indication in cancer, respiratory disease, cardiovascular disease, diabetes, mental health.

In addition to the FDA databases, we also searched the EuroScan Database. In Europe there is not an equivalent of the FDA online databases for new approved devices. We therefore relied on the EuroScan database. EuroScan is the International Information Network on New and Emerging Health Technologies, a collaborative network of member HTA agencies for the exchange of information on important emerging new drugs, devices, procedures, programmes, and settings in health care. Many European HTA agencies are members of the network (e.g. Agenas from Italy, NIHR

[1] Medtronic plc (NYSE: MDT)) has completed the acquisition of Covidien plc (NYSE: COV) in 2015
[2] Actavis plc (NYSE: ACT) has completed the acquisition of Allergan, Inc. (NYSE: AGN) in 2015

Horizon Scanning Centre from UK, Osteba from Spain, SBU from Sweden etc.). As for the FDA databases, the search has been performed according to indication in the five NCD areas.

Where results were generated, we report results in relation to the associated companies.

2.7.1. JOHNSON & JOHNSON (US)

Johnson & Johnson operates as an investment holding company with interests in health care products. It engages in research and development, manufacture and sale of personal care hygienic products, pharmaceuticals and surgical equipment. The company, through its subsidiaries operates in three business segments: Consumer, Pharmaceutical and Medical Devices and Diagnostics

Table xxxviii: JOHNSON & JOHNSON (US) Total R&D Investment

Mil USD	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	8,494	11.4%	8,183	11.5%	7,665	11.4%	7,548	11.6%
% Change	3.8%		6.8%		1.6%			

Although J&J's commitment to R&D has been steadily increasing over the relevant period, searches did not reveal any results for the company in terms of Clinical Trials, FDA premarket approval (PMA), EUDAMED or the EuroScan Database

2.7.2. GENERAL ELECTRIC CO (US)

General Electric Co. is a technology and financial services company that develops and manufactures products for the generation, transmission, distribution, control and utilization of electricity. Its products and services include aircraft engines, power generation, water processing, security technology, medical imaging, business and consumer financing, media content and industrial products. The company operates through eight segments: Power & Water, Oil & Gas, Energy Management, Aviation, Healthcare, Transportation, Home & Business Solutions and GE Capital. The Healthcare segment provides healthcare technologies such as medical imaging and information technologies, medical diagnostics, patient monitoring systems, disease research, drug discovery and biopharmaceutical manufacturing technologies. This segment predicts and detects disease earlier; monitoring its progress and informing physicians, and helping physicians tailor treatment for patients.

Table xxxix: GENERAL ELECTRIC CO (US) Total R&D Investment

Mil USD	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	4,233	2.8%	4,750	3.3%	4,520	3.1%	4,601	3.1%
% Change	-10.9%		5.1%		-1.8%			

Searches did not reveal any results for the company in terms of Clinical Trials, FDA premarket approval (PMA), EUDAMED or the EuroScan Database. Since 2011, the company's commitment to R&D investments has decreased marginally.

2.7.3. MEDTRONIC INC (US)

Medtronic Plc was formerly known as Medtronic, Inc. The Group's principal activities are manufacturing, developing and marketing medical technology and providing device-based medical therapies. It operates in eight segments: Cardiac Rhythm Disease Management (CRDM), Spinal, CardioVascular, Neuromodulation, Diabetes, Surgical Technologies, Physio-Control. The company targets chronic diseases, providing therapeutic and diagnostic devices used for the treatment of diabetes, neurological, gastroenterological, urological, and movement disorders, spinal and neurosurgery, neurodegenerative disorders and ear, nose and throat (ENT) surgery. It also provides external and manual defibrillators.

Table xl: MEDTRONIC INC (US) Total R&D Investment

Mil USD	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	1,477	8.7%	1,557	9.4%	1,490	9.2%	1,508	9.5%
% Change	-5.1%		4.5%		-1.2%			

The company's commitment to R&D investment has marginally decreased over the period. But searches revealed results for the company in terms of Clinical Trials.

Table xli: MEDTRONIC INC (US) Company Clinical Trials CRDs*

Year	Device	Study Name	Application	Study Status
2013-ongoing	EP catheter connected to external pulse stimulator	Mapping for Acute Transvenous Phrenic Nerve Stimulation Study (MAPS Study)	Apnea	Ongoing

*https://clinicaltrials.gov/ . For the search strategy see Appendix 3

Results were also found for FDA premarket approvals. However, there were no results for EUDAMED or the EuroScan Database

Table xlii: MEDTRONIC INC (US) PMA Medical Devices: CRDs*

Year of Approval	Product Name	Application
2015	MELODY TRANSCATHETER PULMONARY VALVE (TPV), ENSEMBLE TRANSCATHETER VALVE DELIVERY SYSTEM (DS)	Pulmonary hypertension

*http://www.accessdata.fda.gov/scripts/cdrh/devicesatfda/. For the search strategy, see the Appendix 4

2.7.4. SIEMENS AG (EUR)

Siemens AG is engaged in the electrical, engineering and electronics business. It operates through the following segments: Energy, Healthcare, Industry, Infrastructure and Cities, Equity Investments, and Siemens Financial Services (SFS). The Healthcare segment includes medical products such as

medical imaging, in vitro diagnostics, interventional systems, and clinical information technology systems.

Table xliii: SIEMENS AG (EUR) Total R&D Investment

Mil USD	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	4,065	5.7%	4,291	5.7%	4,238	5.4%	3,925	5.3%
% Change	-5.3%		1.3%		8.0%			

Despite a 5% reduction for 2014, the company's commitment to R&D has slightly increase since 2011. Still, searches did not reveal any results for the company in terms of Clinical Trials, FDA premarket approval (PMA), EUDAMED or the EuroScan Database

2.7.5. BAXTER INTERNATIONAL INC (US)

Baxter International, Inc. develops, manufactures and markets products for disease such as hemophilia, immune disorders, infectious diseases, kidney disease, trauma, and other chronic and acute medical conditions through its subsidiaries. It produces a combination of medical devices, pharmaceuticals and biotechnology products, operating through two divisions: BioScience and Medical Products.

Table xliv: BAXTER INTERNATIONAL INC (US) Total R&D Investment

Mil USD	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	1,421	8.5%	1,246	8.2%	1,156	8.1%	946	6.8%
% Change	14.0%		7.8%		22.2%			

Baxter's commitment to R&D has increased substantially over the relevant period, a gain of about 50% percent since 2011. However, searches did not reveal any results for the company in terms of Clinical Trials, FDA premarket approval (PMA), EUDAMED or the EuroScan Database

2.7.6. FRESENIUS MEDICAL CARE AG & CO. KGAA (EUR)

Fresenius SE & Co. KGaA engages in the provision of healthcare related products and services. It operates through the following divisions: Fresenius Medical Care, Fresenius Kabi, Fresenius Helios, Fresenius Vamed, and Corporate/Other. Fresenius Medical Care provides dialysis products and services for patients with chronic kidney failure. Fresenius Kabi offers IV drugs including intravenously administered generic anesthetics, anti-infectives, analgesics, and drugs for the treatment of oncological and other critical diseases; and infusion solutions and blood volume substitutes for infusion therapy. Fresenius Helios operates hospitals. The Fresenius Vamed manages projects and provides services for hospitals and other healthcare facilities. The Corporate/Other segment comprises holding activities of the company and the activities of the information technology service provider Fresenius Netcare.

Table xlv: FRESENIUS MEDICAL CARE AG & CO. KGAA (EUR) Total R&D Investment

Mil USD	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	369	1.6%	348	1.7%	305	1.6%	267	1.6%
% Change	6.0%		14.1%		14.2%			

The company's commitment to R&D investment has increased progressively over the period. Searches revealed results for the company in terms of Clinical Trials. However, searches did not yield results for FDA premarket approval (PMA), EUDAMED or the EuroScan Database

Table xlvi: FRESENIUS MEDICAL CARE AG & CO. KGAA (EUR) Company Clinical Trials CRDs*

Year	Device	Study Name	Application	Study Status
2014-2015	IgE adsorber	Extracorporeal SPecific IgE Removal From the Plasma of Allergic Asthma Patients (ESPIRA-study)	Asthma	Completed

*https://clinicaltrials.gov/. For the search strategy see Appendix 3

2.7.7. KONINKLIJKE PHILIPS NV (EUR)

Koninklijke Philips NV is a technology company that is engaged in the healthcare, lighting and consumer well-being markets. It operates through the following divisions: Healthcare, Consumer Lifestyle, Lighting, and Innovation, Group and Services. The Healthcare division offers imaging systems, patient care and clinical informatics, home healthcare solutions, and customer services.

Table xlvii: KONINKLIJKE PHILIPS NV (EUR) Total R&D Investment

Mil USD	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	1,635	7.6%	1,733	7.4%	1,810	7.3%	1,610	7.1%
% Change	-5.7%		-4.3%		12.4%			

The company's levels of R&D investment have remained steady. Searches revealed several results for the company in terms of Clinical Trials. However, no results were found for FDA premarket approval (PMA), EUDAMED or the EuroScan Database

Table xlviii: KONINKLIJKE PHILIPS NV (EUR) Company Clinical Trials: CRDs*

Year	Device	Study Name	Application	Study Status
2011-2012	BiPAP auto Advanced	Evaluation of the Philips Respironics BiPAP autoSV Devices in Subjects With	Sleep-disordered	Completed

		Sleep Disorders	breathing	
2010-2013	BiPAP autoSV Advance	BiPAP autoSV Advanced in Central Apnea Patients	Apnea	Completed
2010-2013	REMstar Auto with A-Flex	Validation of Breathing Event Detection of the Philips Respironics Sleep Therapy System REMstar Auto A-Flex Compared to Clinical Polysomnography	Apnea	Completed
2011-2013	servo ventilation auto vs CPAP vs servo ventilation manual	BiPAP AutoSV Therapy in Patients With Chronic Pain and SDB	Sleep-disordered breathing	Completed
2015-ongoing	AVAPS-AE Non-invasive ventilation therapy	A Pilot, Multi-Center, Randomized, Open-Label, Parallel Group Study to Assess the Effects of a Novel Application of Averaged Volume Assured Pressure Support Ventilation (AVAPS-AE) Therapy on Re-hospitalization in Patients With Sleep-Disordered Breathing With Co-morbid COPD	Sleep-disordered breathing	Ongoing

*https://clinicaltrials.gov/. For the search strategy see Appendix 3

2.7.8. CARDINAL HEALTH INC (US)

Cardinal Health, Inc. is a healthcare services company providing pharmaceutical and medical products and services for pharmacies, hospitals, surgery centers, physician offices and other healthcare providers, which focus on patient care, cost reduction, enhancing efficiency and improving quality. The company operates its business through two divisions: Pharmaceutical and Medical. The Pharmaceutical division distributes branded and generic pharmaceutical, over-the-counter healthcare and consumer products through its pharmaceutical distribution business to retailers, hospitals, and other healthcare providers. The Medical division distributes a broad range of medical, surgical and laboratory products to hospitals, surgery centers, laboratories, physician offices and other healthcare providers.

Table xlix: CARDINAL HEALTH INC (US) Total R&D Investment

Mil USD	**2014**		**2013**		**2012**		**2011**	
Total R & D Expense	**Amount**	**% of Sales**	**Amount**	**% of Sales**	**Amount**	**% of Sales**	**Amount**	**% of Sales**
	NA		NA		NA		NA	
% Change								

Investment information was not available. And searches did not reveal any results for the company in terms of Clinical Trials, FDA premarket approval (PMA), EUDAMED or the EuroScan Database

2.7.9. NOVARTIS AG (ALCON) (EUR)

Novartis AG develops, manufactures, and markets healthcare products. It operates through the following divisions: Pharmaceuticals, Alcon, Sandoz, Vaccines and Diagnostics, and Consumer Health. The Alcon segment offers surgical, ophthalmic pharmaceuticals, and vision care products.

Table I: NOVARTIS AG (ALCON) (EUR) Total R&D Investment

Mil USD	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	903	8.3%	939	8.9%	950	9.3%	869	8.7%
% Change	-3.8%		-1.2%		9.3%			

Investment in R&D has remained steady over the period. Searches did not reveal any results for the company in terms of Clinical Trials, FDA premarket approval (PMA), EUDAMED or the EuroScan Database

2.7.10. COVIDIEN PLC (EUR)

Covidien Plc engages in the development, manufacture and sale of healthcare products for use in clinical and home settings. It operates through three divisions: Medical Devices, Pharmaceuticals and Medical Supplies. The Medical Devices division includes the development, manufacture and sale of endomechanical instruments, energy devices, soft tissue repair products, vascular products, oximetry and monitoring products, airway and ventilation products, and other medical products. The company was founded in 2007 and was acquired by Medtronic in 2015.

Table Ii: COVIDIEN PLC (EUR) Total R&D Investment

Mil USD	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	546	5.1%	508	5.0%	623	5.3%	554	4.8%
% Change	7.5%		-18.5%		12.5%			

Investment in R&D remains steady. Searches did not reveal any results for the company in terms of Clinical Trials, FDA premarket approval (PMA), EUDAMED or the EuroScan Database

2.7.11. STRYKER CORP (US)

Stryker Corp. engages in the provision of medical technology products and services. It operates through the following divisions: Orthopaedics, MedSurg, and Neurotechnology and Spine. The Orthopaedics division provides reconstructive and trauma implant systems. The Medsurg division deals with surgical instruments and equipment, endoscopy, patient handling, and reprocessed medical devices. The Neurotechnology and Spine division pertains to spinal implants and neurovascular products.

Table Iii: STRYKER CORP (US) Total R&D Investment

Mil USD	2014	2013	2012	2011

Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	614	6.3%	536	5.9%	471	5.4%	462	5.6%
% Change	14.6%		13.8%		1.9%			

Investment in R&D has progressively increased since 2011. But searches did not reveal any results for the company in terms of Clinical Trials, FDA premarket approval (PMA), EUDAMED or the EuroScan Database

2.7.12. BECTON DICKINSON AND CO. (US)

Becton, Dickinson & Co. is a global medical technology company. The company is engaged in the development, manufacture and sale of medical devices, instrument systems and reagents used by healthcare institutions, life science researchers, clinical laboratories, the pharmaceutical industry and the general public. The company operates through three worldwide business divisions: BD Medical, BD Diagnostics and BD Biosciences. The BD Medical division produces medical devices that are used in a wide range of healthcare settings.

Table liii: BECTON DICKINSON AND CO. (US) Total R&D Investment

Mil USD	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	550	6.5%	494	6.1%	471.8	6.1%	476.5	6.1%
% Change	11.3%		4.7%		-1%			

Investment in R&D has increased. Searches did not reveal any results for the company in terms of Clinical Trials, FDA premarket approval (PMA), EUDAMED or the EuroScan Database

2.7.13. BOSTON SCIENTIFIC CORP. (US)

Boston Scientific Corp. engages in the development, manufacture and marketing of medical devices that are used in a broad range of interventional medical specialties. The company's products and technologies are used to diagnose or treat a wide range of medical conditions, including heart, digestive, pulmonary, vascular, urological, women's health, and chronic pain conditions.

Table liv: BOSTON SCIENTIFIC CORP. (US) Total R&D Investment

Mil USD	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	817	11.1%	861	12.1%	886	12.2%	895	11.7%
% Change	-5.1%		-2.8%		-1%			

Investment in R&D has decreased marginally since 2011. But searches revealed results for the company in terms of Clinical Trials

Table lv: BOSTON SCIENTIFIC CORP. (US) Company Clinical Trials CRDs*

Year	Device	Study Name	Application	Study Status
2014-ongoing	Alair System (Bronchial Thermoplasty)	Bronchial Thermoplasty (BT) Global Registry	Asthma	Ongoing
2011-ongoing	Alair System	Post-FDA Approval Clinical Trial Evaluating Bronchial Thermoplasty in Severe Persistent Asthma	Asthma	Ongoing

*https://clinicaltrials.gov/. For the search strategy see Appendix 3

Results were also found for the EuroScan Database. However, searches did not reveal results for FDA premarket approval (PMA) or EUDAMED

Table lvi: BOSTON SCIENTIFIC CORP. (US) EuroScan International Network CRDs*

Year of Approval	Agency	Product Name	Application
2014	NECA H-SIGHT	Alair® Bronchial Thermoplasty System (Bronchial Thermoplasty)	Asthma

*http://euroscan.org.uk/technologies/public/search?advance-search=on For the search strategy, see the Appendix 6

2.7.14. ESSILOR INTERNATIONAL SA (EUR)

Essilor International SA designs, manufactures and sale of ophthalmic lenses and ophthalmic optical instruments. The company operates through three business divisions: Lenses & Optical Instruments, Equipment, and Sunglasses & Readers.

Table lvii: ESSILOR INTERNATIONAL SA (EUR) Total R&D Investment

Mil USD	2014		2013		2012		2011	
Total R & D Expense	**Amount**	**% of Sales**	**Amount**	**% of Sales**	**Amount**	**% of Sales**	**Amount**	**% of Sales**
	188	3.3%	164	3.2%	161.9	3.2%	151.5	3.6%
% Change	14.6%		1.3%		6.9%			

Investment in R&D is increasing. But searches did not reveal any results for the company in terms of Clinical Trials, FDA premarket approval (PMA), EUDAMED or the EuroScan Database

2.7.15. ALLERGAN INC. (EUR)

Allergan, Inc. is a global healthcare engaged in the developing and commercializing pharmaceuticals, medical devices and over-the-counter products for the ophthalmic, neurological, medical aesthetics, medical dermatology, breast aesthetics, obesity intervention, urological and other specialty markets in more than 100 countries. The company operates through two business divisions: Specialty Pharmaceuticals and Medical Devices.

Table lviii: ALLERGAN INC. (EUR) Total R&D Investment

Mil USD	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	1,085.9	8.4%	616.9	7.2%	401.8	6.9%	227.7	6.9%
% Change	76%		53.5%		76.5%			

The company's commitment to R&D has increased massively since 2011, growing by over 375%. However, searches did not reveal any results for the company in terms of Clinical Trials, FDA premarket approval (PMA), EUDAMED or the EuroScan Database

2.7.16. ST. JUDE MEDICAL INC. (US)

St. Jude Medical, Inc. develops, manufactures and distributes cardiovascular medical devices for the global cardiac rhythm management, cardiovascular and atrial fibrillation therapy areas and neurostimulation medical devices for the management of chronic pain. It operates through two divisions: Cardiovascular and Ablation Technologies and Implantable Electronic Systems Division.

Table lix: ST. JUDE MEDICAL INC. (US) Total R&D Investment

Mil USD	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	692	12.6%	691	12.6%	676	12.3%	705.1	12.6%
% Change	0.1%		2.2%		-4.1%			

Investment in R&D has remained steady over the relevant period. Searches revealed results for the company in terms of FDA premarket approval (PMA). But they did not yield results for Clinical Trials,, EUDAMED or the EuroScan Database

Table lx: ST. JUDE MEDICAL INC. (US) PMA Medical Devices: CRDs*

Year of Approval	Product Name	Application
2014	CARDIOMEMS HF PRESSURE MEASUREMENT SYSTEM	Pulmonary hypertension

*http://www.accessdata.fda.gov/scripts/cdrh/devicesatfda/. For the search strategy, see the Appendix 2

2.8 Medical Devices Industry Output Data: Bibliometric Evidence

Output data for the top medical devices companies were gathered from the Web of Science database. Table lxi presents information on research outputs funded by the MD companies in the areas CRDs for 2009-13. The search was performed on Web of Science (see Appendix 7 for methodological details).

The search was performed under the bibliometric RESPI filter. It must be noted that the aliases/ spelling errors in naming the RFOs by WoS means that not all them may have been captured or that

other organizations may have accidentally also been captured due to the simplistic terms used. In cases where a company had only generic codes, the name was searched instead of the code. In RESPI and DIABE the funding data that were searched also include papers where the company was listed among the addresses; for the other NCDs (which are considered in other work packages) only the funding data were searched. It should also be noted that some of the companies also make pharmaceutical drugs and the counts of papers may include them.

With the exception of Novartis, which seems to dominate CRD research outputs, and is responsible for 79.4% of all scientific papers, we found limited scientific outputs for CRDs across the private sector.

Table lxi: Top Medical Devices Companies Bibliometric Output Data*

Company	Country	Code	Name of Alternative Code	Output Papers (RESPI)
Johnson & Johnson	US	JJJ-IP-US	Johnson & Johnson	**13**
		AZC-IN-US	Alza Corporation (SUBSID)	**0**
		CDM-IN-US	Codman (SUBSID)	**0**
		DPY-IN-UK	DePuy International Healthcare (SUBSID)	**0**
		ETC-SP-US	Ethicon Inc (SUBSID)	**0**
		ETH-IN-AU	Ethnor (SUBSID)	**0**
		JJJ-IP-US	Cougar Biotechnology (SUBSID)	**did not search**
		LFD-IN-US	LifeScan (SUBSID)	**0**
		MNP-IN-US	McNeil Pharmaceutical (SUBSID)	**0**
		SJV-BT-US	Scios (SUBSID)	**0**
		VIO-BT-BE	Virco (Tibotec) (SUBSID)	**0**
		X15-IN-US	Neutrogena Corporation (SUBSID)	**0**
		JNA-SP-AU	Janssen Pharmaceutical / Cilag (SUBSID)	**0**
		JNS-SP-BE	Janssen Pharmaceutica N V, Beerse (SUBSID)	**2**
		JNU-SP-UK	Janssen Pharmaceutical Ltd, Wantage, Oxon (SUBSID)	**0**
		CCR-IN-NL	Centocor (SUBSID)	**0**
		CLG-IN-BE	Cilag Biotech (SUBSID)	**0**
		ORJ-BT-US	Ortho Biotech / Division (SUBSID)	**0**
General Electric Co.	US	XXG-IN-US	General Electric Co.	**5**
Medtronic Inc	US	MDI-BT-US	Medtronic Inc	**2**

Covidien plc	IE	Y1B-BT-IE	Covidien plc	**2**
		Y15-IN-IE	Covidien plc	
		HUF-IN-IE	Covidien	**24**
Siemens AG	DE	SMN-IN-DE	Siemens AG	**11**
Baxter International Inc	US	BXT-IN-US	Baxter International Inc	**0**
		BXW-SP-BE	Baxter Medical A B, Bromma, Sweden (SUBSID)	**0**
		CLH-SN-UK	Clinitec, Nutrition Ltd (Baxter) (SUBSID)	**0**
		BAX-SP-UK	Baxter Healthcare Ltd, Newbury, Berks (SUBSID)	**0**
		BXR-SP-BE	Baxter R & D Europe, Nivelles (SUBSID)	**0**
Fresenius Medical Care AG & Co. KGAA	DE	XFN-IP-DE	Fresenius Medical Care AG & Co. KGAA	**2**
		FRS-SP-UK	Fresenius Ltd (FHC Holdings Ltd), Runcorn, Cheshire (SUBSID)	**0**
Koninklijke Philips NV	NL	PHG-IN-NL	Koninklijke Philips NV	**12**
Cardinal Health Inc.	US	X15-IN-US	Cardinal Health Inc.	**1**
		CJD-IN-US	Cordis (UK) Ltd, Brentford, Middx / Cardinal Health	**0**
Novartis AG (Alcon)	CH	NVP-IP-CH	Novartis AG	**334**
		ALC-IN-CH	Alcon Inc./Laboratories (SUBSID)	**3**
		CBP-FO-UK	Novartis Foundation (formerly Ciba Foundation), London	**0**
		CBG-IP-CH	CIBA-Geigy (SUBSID)	**0**
		CBJ-SP-US	Ciba (now 'Novartis') Corporation, Summit NJ	**0**
		CGP-SP-UK	CIBA-Geigy A G (Since 1996 'Novartis') , Basel, Switzerland	**0**
		NGY-SP-NL	Ciba - Geigy B V, Arnhem, Netherlands	**0**
		CIB-IP-JP	Japan: CIBA - Geigy Foundation, Takarazuka	**0**
		CRN-BT-US	Chiron Corporation (SUBSID)	**2**
		SDZ-IP-CH	Sandoz Pharmaceuticals (SUBSID)	**5**
Stryker Corp.	US	X1B-BT-US	Stryker Corp.	**0**
Becton, Dickinson and Co.	US	X1B-BT-US	Becton, Dickinson and Co.	**0**
		BDC-IN-US	Beckton, Dickinson (BD), Franklin Lakes, NJ	**0**

Boston Scientific Corp.	US	JBS-IN-US	Boston Scientific Corp.	**3**
Essilor Internati onal SA	FR	NO CODE	optical lenses	**Did not search**
Allergan Inc. (Actavis)	IE	ALL-IP-US	Allergan Inc. (Actavis)	**0**
		AVF-IP-US	Actavis Inc. / Aptalis	**1**
		AZG-SP-UK	Allergan Therapeutics Ltd (UK), High Wycombe, Bucks (SUBSID)	**0**
St. Jude Medical Inc.	US	NO CODE	CARDI	**Did not search**
TOTAL PAPERS (RESPI)				**422**

For the search strategy, see Appendix 7

2.9 Discussion and Conclusion: An Innovation Crisis?

The Medical Devices Industry provides a mixed picture in relation to investment in CRD research. Broadly, industry's commitment to R&D investment remained steady over the period and advancements were limited to individual companies. However, most companies in the sector had not developed any CRD relevant medical devices. Bibliometric output data confirms this assessment. Very few companies had produced research outputs in terms of scientific papers. Novartis was responsible for the overwhelming majority of papers (76%) with Covidien claiming a 5.7% share, Johnson and Johnson 3.0%, Koninklijke Philips NV 2.8% and Siemens 2.6%.

Considering the private sector as whole, investment in R&D remains a principal activity of both the pharmaceutical and medical devices industries. In the 1980s, analysts were confident that, throughout the 20th century, the industry had played a significant and indispensable role in the advancement of science through the production and publication of high quality research (Nairn and Rozek 1988, 139). However, the larger scientific paradigms under which R&D activities, particularly pharmaceuticals, are conducted has certainly undergone a tectonic shift. Back in the 1980s, industrial R&D was still about drug discovery on the basis of the old chemical paradigm, which reigned supreme throughout the 20th century. Under the chemical paradigm, drug discovery was about isolating the active ingredients of traditional remedies, serendipitous innovation and using discrete chemical substances to normalise biological processes (Drews 1998, Dutfield 2003, Allarakhia and Steven 2011). In this way, large pharmaceutical companies engaged in silo-chemistry, under which knowledge, new molecular entities (NMEs) and intellectual property was developed in house. In the 21st century, however, following the successful the mapping of the human genome, new pharmaceutical technologies are now created at the nexus of a number of intertwined disciplines: bio-pharmacology, chemistry, nanotechnology, and computational sciences (Allarakhia and Steven 2011, 105). Today, drug discovery is about managing complex information that derives from a variety of disciplines, all of which exist outside the walls of the traditional pharmaceutical firm. In the twenty-first century, large pharmaceutical companies are increasingly forming research consortia to manage and exploit new forms of data that have arisen from parallel advances in molecular biology, nanotechnology, super-computing, statistical analysis and data management (Allarakhia and Steven 2011, 105).

In the new millennium, analysts argue that, historically, the R&D process for drug discovery can be divided into three main epochs. The first epoch concerns the period of 1845-1945, in which little

new drug development occurred, and minimal research was conducted along predominantly raw and unrefined methods. The second epoch arrived with the outbreak of the Second World War and the large-scale development of penicillin. This epoch involved a chemical paradigm for drug discovery, which continued until about 1990, and was characterized by rapid rates of new drug development and introduction. Although the third epoch of biotechnological, or systems medicine had its origins in 1970s; it has only recently matured and superseded the chemical epoch, and is characterized by the use of the tools of genetic engineering in the production and discovery of new drugs (David Mowery, 1999).

With the changed research paradigm obliging companies both to explore a wide array of R&D trajectories, and also to utilise an increasing number of research methods, pharmaceutical companies are faced with new challenges regarding where and how knowledge is generated and protected (Orsenigo et al., 2001; Chiou et al 2011, 3-4). In the pharmaceutical sector, intellectual property rights and the search for competitive advantage are closely linked than in any other sector (Allarakhia and Steven 2011, 105). Today, the fact that drug discovery occurs outside the silo of individual pharmaceutical firms complicates IPR and increases the costs and risk associated with general investment in R&D (Reppy, 2008; Hoyle and Pries,2009; Allarakhia and Steven 2011, 105). Crafted under the old chemical model of drug discovery, IPR rights in the industry centre on the manufacture of chemical compositions of matter. And throughout the 20th century, industry defended its IP claims in relation to methods of synthesis, formulations, dosing, methods of treatment, and drug delivery systems (Allarakhia and Steven 2011, 106). But, as the model of drug discovery changed, industry has been forced to change its strategy, to re-evaluate the current patent system in order to accommodate new discovery processes and new categories of ‘‘biological’’ goods (Foray, 2004; Woodcock, 2010; Allarakhia and Steven 2011, 106).

The notion of a productivity crisis is an issue of some concern. In response to earlier analysts of the 1980s, analysts of the 21st century have asked, and with some justification, whether new models of drug discovery require new measures of industry productivity. In a changed environment for drug discovery, the ratio of R&D inputs to NME outputs may well be unreliable guide to productivity (Pammolli et al 2011, 428). With drug discovery involving manifold risks and uncertainties in terms of both knowledge generation and knowledge translation, several analysts are now suggesting that the quality of the outputs, in terms of the number of NMEs representing a therapeutic advance, is a much more relevant measure than of productivity than the absolute number of new drugs brought to market (Pammolli et al 2011, 428; Allarakhia and Steven 2011, 106; Light and Lexchin 2012, 1-2). Certainly, the suggestion has some merit. However, when analysts have applied the new measure to industry productivity, it has revealed a crisis of much more different and perhaps even more alarming nature. Where today’s analysts focus on innovation and quality rather than absolute numbers, they find that most NMEs provide only minor clinical advantages over existing treatments. Indeed, since the mid-1990s, an increasing number of independent reviews have found that about 85-90% of NMEs provided only few or no clinical advantages for patients at all (Light and Lexchin 2012, 1-2). Today, it seems that the real crisis across the pharmaceutical and biotechnology sector is about innovation, not productivity.

In the literature, analysts have associated this new notion of an innovation crisis with a number causes. For some, the crisis is the consequence of pharmaceutical companies attempting to control and regulate R&D costs associated with the new research paradigm. Analysts argue that companies are implementing sophisticated portfolio management techniques to smooth out new-drug outputs, to minimize financial risk, for the purpose of bringing order and predictability to the new “chaotic” model of scientific discovery (Munos and Chin 2011, 1). Commercial management of R&D investment, processes and output is a very recent development acorss the industry. Under the old chemical model of drug discovery, R&D divisions were ring fenced from the wider commercial initiatives of companies. Researchers were able to pursue drug discovery with greater freedom. As a consequence, they often produced therapies in disease areas in which companies had small

experience. Today, however, companies are attempting to join R&D divisions with market demand, instructing researchers to develop 'blockbuster drugs', which produce great more than $1 billion in returns per annum, that support wider marketing interests (Munos and Chin 2011, 1). But with the fact that most new drugs fail to constitute on advance on existing clinical therapies, some analysts fear that the industry is working on the basis of a 'hidden business model' which turns on the manufacture of scores of minor variant drugs, only some of which go on to become big "market blockbusters" (Light and Lexchin 2012, 2). The purpose of the hidden model is to smooth the highs and lows of the drug discovery process, which, otherwise, would produce scores of costly failures punctuated with a few high yielding successes, thereby scaring away investors looking for a capital safe havens. Under the hidden business model, sales from variants generate profits throughout the ups and downs of blockbusters coming off patents. Meanwhile, telling stories about an "innovation crisis" to politicians and the press serves as a wider "ploy", a clever industry "strategy to attract a range of government protections" from free market and generic competition (Light and Lexchin 2012, 1)

Others suggest that larger macro-strategic interests are responsible for the innovation crisis. In 2011, a former President of Pfizer Global Research and Development suggested that "the impact of mergers and acquisitions on R&D" were a less well documented contributor to the crisis (LaMattina 2011, 559). Mergers and acquisitions were usually accompanied by downsizing, integration and streamlining of R&D capabilities and infrastructure, resulting in the shutdown of many research facilities. The impact of mergers and acquisitions on the "R&D of the organizations involved has been devastating" (LaMattina 2011, 559) Largely, it has produced less competition and less aggregate investment. Cut backs have hit hard in areas like antibacterial drugs and neuroscience. These impacts, they claim, should be of major concern to patients, physicians and governments especially at a time when sufferers of NCDs like Alzheimer's disease and diabetes are in dire need of new treatments (LaMattina 2011, 560).

In a related way, other analysts associate the crisis with economic forces, whereby industry aims to maximise profit by protecting and expanding market share. Today, industry pursues health as a commodity which can be bought by those with the resources to pay. Accordingly, company interactions with its own researchers and outside clinicians are founded on a profit motive. In funding research, commercial motives control the study design and the use of comparators. Companies conduct seeding trials promote familiarity with new drugs for marketing purposes rather than knowledge creation (Macleod et al 2014, p. 104). They engage with clinicians for the purpose of offsetting the costs of high R&D investment by buying into the discoveries of other companies, exploiting them via marketing, brand recognition and instilling brand loyalty. For these reasons, analysts fear that the research pipeline for new drugs will soon run dry, leaving the public to the mercies of whatever illnesses befall them (Light and Lexchin 2012, 1).

3 Stakeholder Interviews: CRDs

Today, fewer EU citizens are contracting infectious and communicable diseases. Enjoying longer average life-spans, however, they are increasingly developing more debilitating non-communicable conditions that fall within the general category of CRDs. Broadly, CRDs involve a decline in lung function. They include major conditions like: chronic obstructive pulmonary disease (COPD), respiratory allergies, pulmonary hypertension, chronic bronchitis, asthma, emphysema and occupational lung diseases (Bousquet et al 2007, 216). Of these conditions, the two major and most common are asthma and COPD. For asthma, the decline can be temporary and associated with environmental stimulants. For conditions such as Cardio Pulmonary Obstruction Disorder (COPD), the decline can be permanent and associated with individual behavioral factors, like tobacco smoking. Both these conditions are largely preventable. In the developed MSs of the European Union, CRDs are typically associated with increased tobacco-use, obesity, socio-economic inequalities and limited access to healthcare resources (Yach et al 2004, 2617). And across Europe, policy-makers engaged in funding research for developing interventions and prevention strategies to mitigate the impact of CRDs before they require a public health response. In total, there are 118 Research Funding Organizations (RFOs) investing in CRD research. In Eastern Europe, all RFOs are government organizations, and third sector RFOs do not exist. In Western Europe, there is a greater number of charitable and voluntary sector RFOs. In all cases, however, few of these RFOs are devoted exclusively to CRD research, and the majority make research investments in other NCD disease areas.

While accurate mapping of RFOs and their funding activities via surveys and bibliometrics can assist government in identifying the most fruitful approaches to making in NCD investments research; policy makers must also take account of the often strong visions and firm priorities of leaders in the field of CRD research. To this end, MAPPING_NCDs necessarily involves the conduct of semi-structured interviews as a means for eliciting the preferences and opinions of key CRD stakeholders. In this way, the project opens a dialogue with CRD researchers on the basis that qualitative interviews hold the potential to develop wider theory and hypothesis for both mapping CRD research funding, and also improving the relevance, efficiency and impact of CRD research investment (Wright et al 2014). To a some extent, new strategies and funding initiatives for CRD research must align with the scientific, clinical and economic priorities and interests of leaders in the field of CRD research. For this reason, the mapping of CRD research activities needs to consider stakeholder motivation and views for improving research investment strategies and outcomes for CRD.

Stakeholders are located at various points of the CRD research funding process. Typically, CRD funding originates from a variety of sources: national governments (European Union Member States), international organizations with regional or global reach (OECD, WHO Regional Office for Europe, World Bank, International Monetary Fund, United Nations), the private sector (pharmaceutical, biotechnology and medical device industry), charities (European Diabetes Foundation, Macmillan Cancer, World Cancer Research Fund), non-governmental organizations (United Nations Children's Fund, Global Fund to Fight AIDS, Tuberculosis and Malaria) and, importantly, supranational organizations (European Investment Bank, Council of Europe, The European Commission) as well as public-private partnerships (e.g. the Innovative Medicines Initiative). Stakeholders can either be directly associated with NCD research or involved in making research investments in NCD research. At both of these points, MAPPING _NCDs makes contact with stakeholders, seeking their views on both the current and future state of funding for CRD research.

As a research technique, semi-structured interviews provide opportunity to develop hypotheses about the future shape of CRD research funding. Enabling close collaboration between the

researchers and stakeholders, interviews allow stakeholders to describe their views of the current state of CRD research and to improve researcher's understandings of the key factors influencing the current and future shape of CRD research. They hold a capacity to answer the 'how' and 'why' of CRD research funding, allowing researchers to understand how funding activities are influenced by individuals and the contexts in which they are embedded (Baxter and Jack 2008, 556). Consequently, interviews have the potential to improve the quality of the wider mapping exercise by providing researchers with more complete understandings of causes and effects, enabling them to develop better ideas for future funding strategies that target more relevant factors. Ultimately, the purpose of the stakeholder interviews is to open a sophisticated and collaborative dialogue between decision makers and key personnel involved in the conduct of CRD research with a view to producing a more nuanced map of CRD research funding, and thereby heighten the potential for improving the state of CRD research funding in the future.

3.1 Methods

Stakeholders were purposively selected to reflect a range of factors including: expertise in CRD research, geographic location and expertise in awarding research funding. For all stakeholders, interview questions explored (1)current threads of research; (2) future research areas; (3) types of collaborations; (4) working with collaborators; (5) working with the private sector ; (6) types of funding organizations; (7) working with funding organizations; (8) future strategies for funding NCD research. Personnel were selected to reflect a range of geographical regions across the EU. The aim was to solicit views and experiences of people involved in both the conduct and funding of research across the EU area. In total, 14 interviews were conducted. All interviews were recorded and transcribed. Consent was gained for all interview subjects and their anonymity. Transcripts were typed verbatim, proof read and corrected, while notes and comments were collected and made into memos. Transcripts were analyzed on a thematic basis, with responses collated under the most common themes, and reported in the results section below. Examples from the analysis are included below to explain or illustrate key points. While retaining anonymity, the speakers have been identified by their order of interview in order to allow readers to distinguish different voices.

3.2 Results

Interviews with stakeholders revealed five major themes with regard to the future of research in the area of CRDs. There was a generalised recognition of the growing importance of stratified medicine, which several informants considered to be the future of research across the wider spectrum of NCDs. Other informants emphasised the importance of directing research towards tackling individual CRDs such as COPD and asthma. For COPD, informants stressed that the future was equally about non-clinical measures like smoking cessation, public health and health service delivery and also about relieving the symptoms of COPD via pharmaceutical treatments. For asthma, informants suggested there was a greater scope for developing innovative and game-changing pharmaceuticals than for COPD. Across the broader spectrum of CRDs, and indeed NCDs, Informants also suggested that there was a need to find new ways of working with private sector. Consistent with the academic literature, stakeholders emphasised that the model for drug discovery has changed and that pharmaceutical companies were less prepared to take risks in regard to allocating resources. Consequently, there was a need for academic institutions to pursue the basic science that pharmaceutical companies were no longer able to conduct for themselves. Other informants suggested that these new research requirements needed to fit within a wider strategic approach to the funding of NCD research that accommodated the both needs of researchers and the requirements of funders to demonstrate the effectiveness of their investments

3.2.1. Stratified Medicine

At the more generalized level, some informants insisted that the future for CRD research lay in relation to 'stratified medicine'. Sometimes called 'personalized medicine', stratified medicine involves the practice of subdividing patients into groups based on their responses to therapies or their risk profile for developing certain disease conditions. Ultimately, stratified medicine is using knowledge of patients and disease pathways to ensure that the right patients, receive the right types of medicine at the right times. Towards this end, it is also about early diagnosis and predicting the onset of disease using biological markers that divide patients in to groups for the purpose treating the disease much earlier. Informants suggested that "stratified medicine is definitely the future", that it was going to be the future "whether we like it or not". As a consequence, "we have got to make sure the respiratory community is properly connected with it" (13)

A stratified approach to CRD research was about understanding the role of epigenetic processes in the origins and onset of conditions like asthma and COPD, processes that "connect environment and genetics really." In these disease areas, informants explained that the practice of stratified medicine involved "developing new models to study respiratory disease by taking human cells, stem cells, expanding them in tissue culture and studying interactions with those cells in vitro, both in asthma, COPD and pulmonary fibrosis" (13) For the future, these practices would demand a more 'team orientated' approach to CRD research, which informants sometimes termed "big science" or "team science". Team science was about "bringing data together... being able to...integrate it." And it required CRD researchers to utilize skill sets that derived from outside the scientific disciplines, skills associated with other areas of industry "such as the computational and data analytic industries, not just the pharmaceutical industries". By employing the skills, stratified medicine held the potential to explain why "there is a lot of fall off", or a lot drugs "that are no longer as effective" upon their original manufacture (13). Attempting to connect CRD research with stratified medicine, some informants explained that organizations like "the European Respiratory Society," were forming "a new research agency in Europe where we can pool resources from across Europe to try and take greater advantage of the data and team science approach" (13)

These processes of teaming-up and pooling data were about creating "disease registers" or "biobanks" that consolidate "clinical trial data", which could "be analysed in large data sets...it is all about joining up really." With the ultimate aim being to deliver the right drug to the right patient and the right stage of development, teaming up or doing big science is about linking the disease, the patient and the treatment. With the mapping of the human genome, "it's getting much easier, we have got more and more genes which tell us whether we've got pre-disposition now." (5). For the future, "the big challenge now that our community is working with is how to integrate those data. (13) In terms of research, this creates the need to "capture the richness of the biological disease area and what we tended to do in the past is to concentrate on rather pure aspects of disease without looking at the wider implications of the disease in society ". In addition, stratified medicine provides human based tissues and cells and genes "to be able to show that linkage between the pathway and the disease." (13) It is about "capturing the gene through to the phenotype and the different stages" of the disease. Practicing big science CRD researchers were "forming these groups now.... very big cohorts, disease cohorts and COPD, bronchial asthma, interstitial pulmonary fibrosis, bronchiectasis, various other diseases... we haven't exploited them fully yet, and that is the challenge for the next five years. But they are in place now. (13)" Historically, the respiratory community have relied probably too much on industry to support them in trials and all this sort of stuff. But today, "the [CRD] community is having to reinvent itself." (13)

For CRD research, the future, some argued, would thus be "all about salami slicing complex disease around common pathways and identifying what those pathways are....and to be able to do that, we have got to be able to integrate these difference levels of information really." Some informants were adamant that the shift to stratified medicine was inevitable across the wider spectrum of NCDs. "If they want healthy aging, then they want to be able to predict who is heading for ill health, ten years,

fifteen years before it happens". (5) Stratified medicine "is the way medicine is going to be, you're going to be able to identify people at high risk long before they get the illness and there are some areas where we desperately need those genes." (5)

3.2.2. COPD

In terms of major CRD conditions such as asthma and COPD, informants suggested that future research areas would likely focus on stemming attacks that have the potential to result in hospitalisation or death. Typically, these hospitalisations were the result of respiratory infections associated with "the same viruses that for a healthy person gives them a common cold". At a disease level focus, the aim of researchers was to develop "better therapies to either prevent or, if we can't prevent, treat [infections] when they do occur" (12)

Beyond hospitalisation, future research for COPD would also likely focus on simple strategies of disease management, early diagnosis and smoking reduction. Indeed, the difficulty with COPD is that lung decline is irreversible and that lung functionality also declines naturally with age. COPD is about "an inevitable and prolonged decline due to premature aging." Unlike asthma and other CRDs, "the horse has already bolted with COPD". COPD is the consequence of "damage which has already occurred over years". Consequently, drugs that target "reversing inflammation or preventing the inflammatory process.... do it from thereon in."; and treatments for COPD are not going to improve damaged lungs. With COPD, lungs lose their elasticity, "they have lost their structure, you are not going to reverse that" (3). Certainly, asthma is a reversible process, "you would expect medication to reverse the process." But COPD is largely "an accelerated ageing of the lung and you can't reverse that." At best "you can improve it with some things, but those things don't work by reversing the pathological process. It makes COPD different" (3)

For these reasons, informants put much emphasis on "early diagnosis... because most patients with COPD have an opportunity missed many years before to make the correct diagnosis" (3). Informants even went so far as to suggest that "three quarters of the people with COPD have yet to be diagnosed". And, in some cases, they explained that these people were already suffering from the disease quite seriously. "Between 10% and 30% of patients who are admitted to hospital with an exacerbation of COPD" have never been diagnosed (3). In the main, these people have not been diagnosed because "diagnostic spirometry or case finding is not available." As one informant suggested, spirometry is a priority not for scientific research. Rather, it is a priority for "implementation research". It is "a fairly basic tool". Today, "you can't go to your G.P ... without getting your blood pressure taken or cholesterol or something, but very few of them will do speculative spirometry and case finding spirometry" (3).

Thus, the future for COPD research is not exclusively clinical. In the past, old models of care involve "reactive hospitals for unexpected emergencies," but today researchers are looking at "trying to link up primary and secondary care or primary and specialist care in a way that makes those distinctions less obvious" (3-2). For the future, the emphasis is on "chronic disease management...taking a symptom based approach" which involves a focus on key symptoms such as breathlessness and may have a relationship to other NCDs like CVD. (3) This strategy involves "giving patients control over their condition, getting their involvement in it, their health professionals around self-management and around chronic disease models which straddle acute care and long-term care". (3)

A problem with "COPD particularly" is that "people are seen of the victim of their own habits", specifically in relation to smoking. But this is often "grossly unfair for several reasons." Informants pointed out that "only about 15% of smokers will get COPD." There are degrees of vulnerability. It is not inevitable that smokers contract COPD . "Some people are particular vulnerable to cigarette smoking." (3) Furthermore, "smoking rates... are declining". And this fact is "not reflected in a reduction in the prevalence of COPD". Here, informants identified two reasons: one occupational exposures or... domestic exposures like passive smoking and through biomass fuel cooking" are

responsible for continued incidence of COPD; and two, the fact that "lung function declines with age anyway" has also ensured steady incidence rates for COPD. As people age, they "are developing COPD as a function of age and much more minor damage to their lungs from other agencies." In the past, a person aged 50 or 60 "would develop COPD predominantly through cigarette smoking." But today people are developing COPD in their "70's and 80's and developing COPD through a combination of mild noxious exposure, plus advancing age." Informants explained that the demographic profile of COPD is "changing so that is why the incidence hasn't really changed because of the ageing factor and ageing population" (3).

There is also much potential for research in the sociology of COPD. "Why is it that some people just sit at home and watch the T.V when they've got lung disease and others try and get on top of it?" (3-8) Scientists explained that non-clinical factors "taking pathophysiology into the sociological world", pursuing novel collaborations and extensions into other fields "may help explain a lot of the things that we don't know about" (3).

Others felt that the emphasis should shift "towards how you integrate the findings and service delivery and primary prevention and how you actually make it happen... all the way to rehabilitation and palliative care in cardiovascular disease" (10) Informant explained that "the health services and public health component has been seriously under-funded" (10). The emphasis is on "risk factors" and treatments, not necessarily "on public health and primary prevention on health services research." (10) Today, research was focussed on "medical treatment rather than thinking about what can we do to prevent, whether to actually prevent some people from taking up smoking" 10-2. Indeed, some maintained that "population level approaches are actually more effective than individual level approaches". The challenge lies in the implementation. For example, tobacco regulation necessarily excites the interest of the tobacco industry, and is also " an income source for governments" (10). Referring to the plain packaging issue, informants suggested that "Australia's currently the only country actually doing something about it... against tobacco industry interests" (10).

Overall, informants suggested that COPD was the CRD "which causes the most trouble economically." (3) Once a patient contracts the disease, the challenge is to slow down or prevent the progression of the disease. But once they have it, "acute attacks are by far the biggest problem. And they're a bigger problem in COPD than they are in asthma, in that people sit in hospital sometimes for weeks. They end up in intensive care. Once they've been in, they come in repeatedly. So, that's a big issue." (12) In western countries, the big public health issue is reducing smoking at a population level. (12) But there are also "other lifestyle factors which they can improve on, particularly around physical activity and alike and may be obesity if that is coexisting...if you wait until they're very symptomatic or they're going to hospital you are not going to achieve anything (3).

3.2.3. Asthma

Clinically, informants pointed out that significant scope remains for improving outcomes for asthma sufferers. Asthma is a temporary condition that involves a hypersensitivity to external stimulants. For asthma, "the basic problem is one of internal malfunction.... we are on the cusp of a lot of biological drugs for asthma like Metho and others. So there will be more expensive drugs coming for asthma, but probably not for COPD." (3) In the first place, the aim is always "to prevent asthma happening" (12). And asthma researchers are interested in helping lungs to develop tolerances to external stimulants. In this respect, the challenges are to identify both the external stimulants and the internal triggers that result in attacks. Informants pointed to the "potential for a huge improvement if you can find the key, potentially the airways can return to normal....become less responsive and less twitchy" (3). Once the attack occurs "then trying to cure it would be the next desire. And that comes down pretty much to the same thing" (12) In this respect researchers were

interested in “acute attacks of disease and what can you do about those.” For mild asthma, the condition is “relatively well-treated by drugs we have currently available but severe asthma is not. “ (12). And there are also fruitful areas of research around paediatric asthma, “linking allergy and asthma, especially around food allergy, peanut allergy... to try and understand how sensitisation can enhance asthma really” (13)

Interestingly, informants suggested that stratified medicine was also relevant to asthma research. Researchers are involved in projects that built “a handprint, a diagnostic handprint, of the different subtypes of severe asthma using progenomics, genomics, transcriptomics and so on.” 13-2. Here, the research challenge involves “developing team science within respiratory medicine, so that we have go the expertise to exploit these amazing interpretative datasets really” (13)

3.2.4. Working with the Private Sector

Informants were very much aware that the role of the pharmaceutical sector in NCD research was undergoing profound changes. As one suggested, “the pharmaceutical industry has shrunken so much and closed various places down, especially in our field....respiratory” (13). Generally, informants understood that bar for developing new drugs is higher “because the easy fruit have been picked. And it's the difficult things that are left”. In the past, “the industry had more money. They had less costs ...associated with drug development.” Today, clinical research “has got more and more expensive as the demands of the regulatory authorities have increased. So, there's simply less money in the coffers”. (12) Typically, informants identified two reasons for the shrinking of the industry. In the first place, the “patent cliff” in which some important drugs “used in asthma have come off patent and therefore profits into the companies are dramatically falling.” (13) And in the second place, the model of drug discover had changed. The old chemical paradigm had given way to “the stratified medicine approach”, the process of “catching up complex disease into disease related pathways and targeting those is where it is all going and industry is having to reinvent itself really, basically, to be able to deal with this.” (13). As a consequence, informants suggested that the industry “can't afford to do their own basic research and they're better off partnering with academic institutions and getting the basic research done in partnership with academic institutions. And some of them are very reasonable indeed about the intellectual property sharing.” (12)

The practice of stratified medicine would oblige the clinical academic community “to work much closer with industry than they have ever worked before”. And for some informants, working with the private sector was about a straight forward exercise of working within the established processes of private sector research. As one informant described: “I had an idea... based on the administration of this medication. So I approached the people from the company and I learned about the procedure.... they...have something like internal grant... so I applied....went through all the paper work...and at the end were successful so got the funding from them.” (1) Often, the private sector has more resources, they pointed out,. “if you are able to justify the costs you would get full funding.” Unlike public sector RFOs, pharma companies don’t say, “‘okay we will fund you the grant’, but only give you 60% because 100% will be too much. That is also one of the reasons why I would go to Pharma” (1)

Several informants also noted that drug companies were making less amounts of money available for basic research. Essentially, they thought that pharmaceutical companies were less willing to take risks. “Their readiness to spend money on basic research is diminished.” (12). One informant suggested that “at GSK” and also other companies, were “spending all their money developing yet another bronchodilator and yet another inhaled steroid, rather than looking at innovative approaches.” (12).

While there remained a potential for discovering game-changing drugs in relation to asthma, some informants even confided that the private sector may not be relevant to the treatment of some CRDs. For example, with COPD, the largest CRD, “inhaled treatment, the drug treatment is icing on

the cake. The things that do work, as I said to you at the beginning, are very basic things" (3). Informants thought that most pharmaceutical research is "aimed at market share, they're not…. they're all aimed at prompting the product. They are not about new science." (3) And particularly in terms of COPD, "it's not an area where you're going to find a cure because you can't reverse time." (3) As a consequence, "pharmaceutical research in that area has been focused on improving symptoms... improving on bronchodilators... taking them...now once a day because they have longer acting preparations, or they have different combinations of bronchodilators, or bronchodilators or inhaled steroids just around convenience or delivery side of things. So I'm not hopeful in COPD that anything will come out (3). For COPD, research is mostly about delivering care, "making sure that patients are diagnosed and reviewed, that they receive smoking cessation, active smoking cessation, that they get their flu immunisations and go to rehab." For the future, COPD research is "about organisation of care, not about new drugs... pharma hasn't come up with anything qualitatively new for COPD for twenty or thirty years" (3).

And furthermore, in terms of COPD, researchers, particularly non-clinical CRD researchers, were reluctant to become involved with the private sector. "I just felt like it was important to me to maintain my virginity. I could have gotten a lot of money and made a lot of money, personally, doing it. But... I mean I get attacked all the time by tobacco interests and other bad guys. And being able to say I've never taken a penny from these people. Yes, I know them. They're friends of mine. I talk to them. We have some common interests. I help them sometimes. But there's never been any formal monetary relationship. I think it protects the credibility of our work." (7)

However, some argued that the lack of industry risk-tolerance created a new role for academics. Companies are "still looking for new approaches", but "generally pretty poorly, I would say. They follow the literature. But if you went to anybody at GSK and asked them detail on the sort of work I'm doing or any other academic, they wouldn't be able to give you detail" (12). In short, there was a need for new types of collaborations. In the past, collaborations were often ad-hoc and sporadic. "Sometimes you meet them at congresses and sit down and chat and give them some ideas. And they might then decide to put some money into your work because they find it interesting. But it often... it also changes with personnel. You often have a relationship with a person in a company. And when that person moves on, you've then got to build a new relationship with new teams. So, it's a constantly moving ball-game" (12).

Others, however, pursued more unique collaborations. As one informant remarked: "we made a discovery about why viruses trigger asthma attacks and patented that." On the basis of this discovery, the university based scientists formed their own company to tempt the interest of larger pharmaceutical companies. It "wasn't a fashionable thing to do in those days I have to tell you." Fortunately, the experiment worked: "the agent we were going to administer had a lot of the safety toxicology already done on it... so all we had to do was adapt it for inhalation. So I and two of my colleagues formed the company, got some seed funding and then launched it on the alternative investment market.... and it has done really well." (13) The academics out-licenced the clinical development of the agent to a large pharma company "for $230 million to [deleted]...it worked really well... now we are bringing forward three new products...back into the company from [university] to further develop them" (13). The process demonstrates that the conduct of "high quality basic bimolecular science in a university setting" can eventually turn "into something where patients are going to benefit at the end of the day". For informants, these were useful partnerships in which academics could use their expertise and also allow others to uses theirs. The partnership was not "just selling it off to big companies", but developing the hard science, and increasing its value, "and then passing it on to those that can best develop it" (13). Informants explained that pharmaceutical companies were also useful in "giving some seed funding because they were interested in the idea, but also helped us with the legal and patent side of it all, which sometimes academia does not do very well." (13)

3.2.5. Funding Future CRD Research

Overall, informants suggested that RFOs could take advantage of these developments largely through the pursuit of a "broad portfolio" of research. In other words, RFOs needed to develop a research pipeline in which they consolidated "some quick wins.. translation in the next five years...gets into the clinic, everybody's happy, everyone can see where the money is going". In addition, RFOs also needed to develop a pipeline of "underpinning research that funds the translational work that will be taking place in five, ten, fifteen, twenty years' time" (9). Ultimately, informants suggested that "politicians like five year cycles," which often fitted nicely with their electoral mandate. "It makes sense for them to have these quick wins" (9). Scientifically, however, "you've got to think longer term than that". And in developing the longer term, "you've then got to think" (9)

3.3 Discussion and Conclusion

Perhaps the most striking themes to emerge from the stakeholder interviews were the significant emphasis several informants place on stratified medicine, and the consequent changes to collaborations between industry and academic researchers. Certainly, analysis of the academic literature in relation to shifting methods of working in the private sector confirms that the pharmaceutical industry is in the grip of major systemic changes. In response to the rapidly changing environment, both the literature and our informants suggests that industry has implemented conservative management practices for the purpose of increasingly the predictability of drug discovery and the sustainability of returns on capital investment in R&D. For example, sources in the literature argue that investments in R&D produce NMEs that are, at best, only marginally better than existing therapies, thereby stifling innovation and amplifying a sense of crisis across the industry (Munos and Chin 2011, 1). And for the future, sources in the literature fear that unless industry ceases to pursue "safe" risk-averse management strategies, unless it adopts more collaborative approaches to knowledge creation and costs sharing, few breakthroughs will reach patients and sufferers of disease (Munos and Chin 2011, 1). Indeed, these sources counsel that sustainability and risk aversion did not characterise the breadth of vision shown by the industry's early pioneers. Figures like Eli Lilly, the literature argues, thrived on tumult and disruption. Successfully developing so-called 'wonder drugs' like insulin, figures like Lily did not aim to support the company's other prosperous product lines in dubious tonics and elixirs. They did not engage in risk assessment, they held no concerns for brand recognition, and no anxieties about market share. Lilly immediately recognised the medical importance of the new drug, and trusted his scientists to rise to the challenge of mastering its implementation in clinical practice (Munos and Chin 2011, 1). In the twenty first century, however, the entrepreneurial model is gone. Consistent with the views of stakeholders, the literature suggests that industry must find new means by which to respond to unmet need, particularly in the area of NCDs.

In pursuing this new mode of drug discover, there may be significant scope for new types of collaborations between academics and industry, with each taking advantage of the other's major skill sets. As informants suggest, academics may need to pursue the raw science of drug discovery through the analysis of big data sets. Upon making breakthroughs, academics may need to secure patents, explore the launch of IPOs, which could function as the scientific plankton for the development of new pharmaceutical technologies. Both industry and university based academics may also need to gain more experience in negotiating mutually amicable IP rights, with academics recognizing the skills of industry in relation to the clinical development of NMEs. Certainly, key informants have described useful collaborations with industry along these lines which have ultimately ensured that suffers gain access to innovative pharmaceutical treatments.

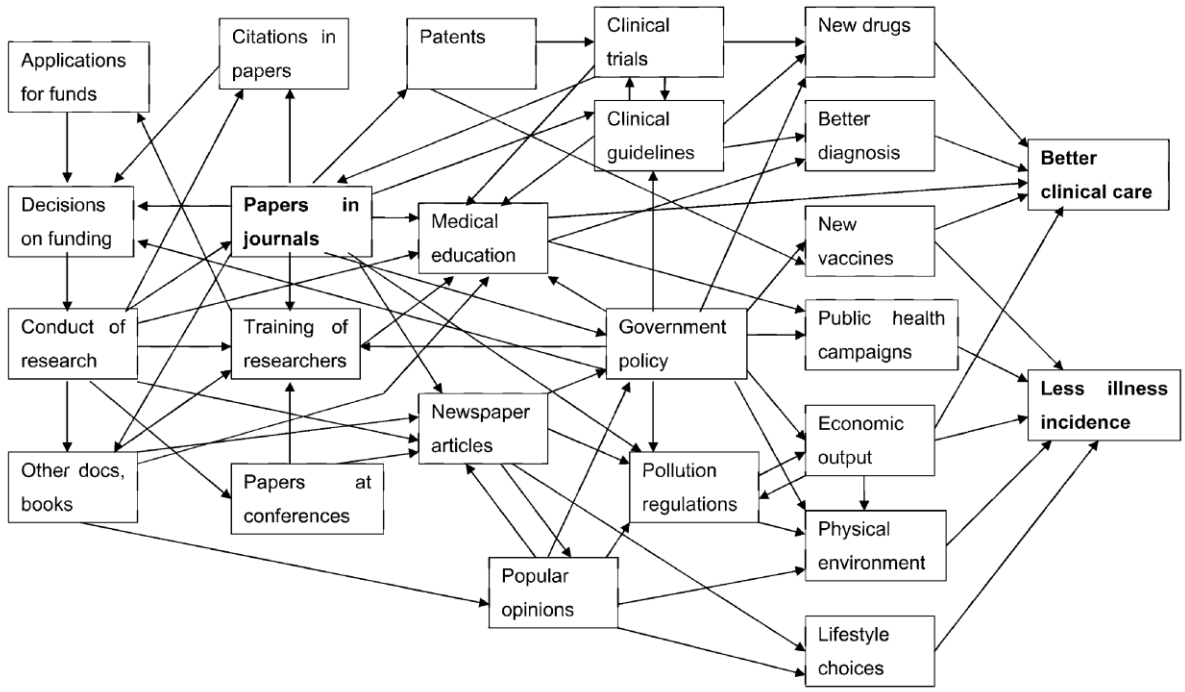
4 Bibliometrics: Impact of CRD Research Funding

A key goal of MAPPING_NCDs is to establish the impact of funding investment across five key NCD areas: cardiovascular disease, chronic respiratory diseases, diabetes, cancer and mental health. In this aim, MAPPING_NCD moves beyond the state of the art in the research area by pursuing bibliometric mapping and analysis of the volume of research outputs in the EU and MSs relevant to these disease categories. Bibliometrics establishes the impact of funding investments by mapping and analyzing of the volume, citations, funding sources, influence on clinical guidelines and newspaper stories of research papers and reviews in the Web of Science (WoS) published in EU MSs during the last ten years (2002-12). Where funded research produces scientific papers, funding is considered to have had 'impact'. Bibliometrics identifies specific impacts associated with individual research papers through citations in other relevant papers. Bibliometrics also checks funding acknowledgments in relevant scientific papers. It considers the extent to which they have provided the evidence base for clinical guidelines relevant to various NCDs. And, it also considers the extent to which they are cited in stories about NCD research in newspapers and the broadcast media in MS. In this way, the impact of the paper is associated with the relative values that papers achieve against these measures.

4.1 What is Research Impact?

Measuring the impact of research is a complex task. Often, health improvements depend on a host of different research discoveries, which are made at different times and in different places. The pathway from the conduct and publication of research to better health is usually indirect. In addition, the results of research contribute to better health in different ways, from the improved diagnosis and treatment of patients to the prevention of illness or the reduction incidence. Figure vi: Links between research and healthcare improvement details the manifold linkages between research funding and health impacts.

Figure vi: Links between research and healthcare improvement



Among these many nodes and linkages, 'government policy' occupies a central position and has a several linkages to other nodes. Moreover, the 'reduction of illness incidence' also depends on a

large number of inputs, including: environmental pollution, individual health behaviours, wealth, education and the effectiveness of public health campaigns. Thus, it can be observed that research impacts upon all these nodes, many of which are not specific to individual disease areas. Similarly, different types of research can also deliver advances in individual disease areas. And for these reasons, the norms for measuring both the effectiveness of research and its quality can also differ.

Nevertheless, all of these nodes are inter-connected. And at connection points, hard evidence of research impact necessarily accumulates. In the main, the evidence of research impact manifests itself in the paper trails that flow between one node and another. For example, research funding produces research, which produces papers in scientific journals, which in turn lead to citations in other journals, decision making influence, policy, media stories and even the allocation of additional research grants. Tracking and analyzing these paper trails, using them as a proxy for research impact, is the fundamental business of bibliometic research.

In this section of the paper, we utilize bibliometric methods to analyses data that accumulates at five of these nodes along the many paths to research impact for CRDs. These nodes are :

- Scientific research papers
- Funding sources (decisions on funding)
- Citations
- The evidence base of clinical guidelines;
- The stories in newspapers and the research papers that they cite.

4.2 Scientific Research Papers: CRDs

The first means by which bibliometric analysis establishes funding impacts is by the number of published scientific papers. This section of the report details the number of downloads papers for CRDs whose details are in the Web of Science (WoS) from 31 European countries (the 28 EU Member States, plus Iceland, Norway and Switzerland) in the 12 years 2002-13. To this end, bibliometric analysis utilizes two overlapping databases, the Science Citation Index Expanded (SCI) and also the Social Sciences Citation Index (SSCI), for the provision of knowledge on socio-economic impact and behavioral interventions associated with CRDs.

The report identifies by means of a “filter” whose precision and recall was determined by means of experts in the subject area marking sets of papers as relevant or not. Filters were developed for each of the five disease areas:

- Cancer research (oncology): ONCOL
- Cardiovascular research, including stroke: CARDI
- Diabetes research: DIABE
- Mental disorders research: MENTH, and
- Respiratory disease research: RESPI

Details for each filter were written to five Excel spreadsheets for analysis, which are explained in each of the five relevant Critical Appraisal documents. The main analyses were of country outputs, their research levels (from clinical to basic) and for some subject areas, the type of research or disease. Each filter was applied to the Web of Science for the Science Citation Index (extended) – SCI – and for the Social Sciences Citation Index(SSCI), for the twelve years 2002-13, and articles and reviews only were identified. The papers were also limited to those with at least one address in one or more of the following 31 countries – the 28 Member States of the European Union plus Iceland, Norway and Switzerland. Table 2 lists the countries with their digraph ISO codes.

Table lxii: List of 31 countries used to limit the downloaded papers

ISO	*Country*	ISO	*Country*	ISO	*Country*	ISO	*Country*
AT	*Austria*	**EE**	*Estonia*	**IS**	*Iceland*	**PL**	*Poland*
BE	*Belgium*	**ES**	*Spain*	**IT**	*Italy*	**PT**	*Portugal*
BG	*Bulgaria*	**FI**	*Finland*	**LT**	*Lithuania*	**RO**	*Romania*
CH	*Switzerland*	**FR**	*France*	**LU**	*Luxembourg*	**SE**	*Sweden*
CY	*Cyprus*	**GR**	*Greece*	**LV**	*Latvia*	**SI**	*Slovenia*
CZ	*Czech Rep.*	**HR**	*Croatia*	**MT**	*Malta*	**SK**	*Slovakia*
DE	*Germany*	**HU**	*Hungary*	**NL**	*Netherlands*	**UK**	*United Kingdom*
DK	*Denmark*	**IE**	*Ireland*	**NO**	*Norway*		

The “full record”, which includes all addresses, e-mails and funding details (where given) were then downloaded to a series of 12 “year” files, 500 papers at a time. These were then processed by a special macro to produce one combined Excel spreadsheet.

Each paper in the combined sheet was given an individual index number, and the following parameters were recorded:

- Names of all authors, in the format SMITH-AB
- Paper title
- Source (journal name, year, volume, issue, pages)
- Journal name
- Document type (article or review)
- Addresses (all in upper case, separated by a forward slash). Note: in the WoS UK papers are attributed separately to ENGLAND, WALES, SCOTLAND or NORTH-IRELAND.
- Country of publication
- Year of publication
- Month of publication (for most papers where the date of the journal was given)
- Language (almost all were in English)
- E-mail address(es) of corresponding author, sometimes others
- Funders, FU (for late 2008 papers and subsequently)
- Funding acknowledgement text, FX
- Composite list of authors and their individual addresses (from 2008)
- Authors’ full names (where given), in the format Wilhelm, Hans; Wanke, Isabel; Hirche, Herbert (this allows the sex of most of the authors to be determined)
- Whether in the SCI or SSCI only

Although most papers in the WoS have their chosen keywords and formal abstracts, these were not recorded in the main spreadsheet as they would have made it far too cumbersome. From the paper title, a macro was applied to determine if the paper could be classed as “clinical “ or “basic” or “both”, according to the presence of one or more words on two lists (see Lewison and Paraje, 2004). The research level of the journal in which the paper was published was also determined from a master list, based on the same scheme; clinical journals were classed as RL = 1 and basic ones as RL = 4, and ones in between were given an RL value as a decimal number between 1.0 and 4.0. These RL values were determined for groups of five years, 2000-04, 2005-09 and 2010-14.

In order to measure the impact of CRDs, a specialized RESPI filter was created. The RESPI filter, like the filters for other disease areas, consists of two main parts: a list of specialist journals and another list of title words. In terms of definition and subject area, the filter was discussed with a leading expert in the field, Professor Tariq Sethi of Guy's Hospital, King's College London. Following these discussions, the filter was created to include the major non-infectious respiratory diseases, such as allergic rhinitis, asthma, chronic obstructive pulmonary/respiratory disease, cystic fibrosis, and emphysema. However, it was also contrcuted to include the effects of infection if the primary problem was one of pulmonary insufficiency (e.g., for environmental or genetic reasons).

CRD is one of the smaller NCD research areas. By comparison with other disease areas, the RESPI filter was short and listed four specialist journals and eight title words or phrases. As expected, it generated the smallest of the five NCD files, with just 18822 papers, of which 188 were in the SSCI only (1.0%). The calibration gave values for precision, p = 0.939 and recall, r = 0.884.

Table lxiii: Outputs and Parameters of the five NCDs by size

Subject	World output*	EUR31 output*	% world	% BIOMED
BIOMED	6075502	2442063	40	
ONCOL	748724	282055	38	11.5
CARDI	508611	211507	42	8.7
MENTH	349027	138666	40	5.7
DIABE	103792	40550	35	1.7
RESPI	33629	18822	56	0.8

**indicates the number of research papers published in the disease area*

RESPI research was divided into the six main disease areas, which are listed in Table lxiv with the numbers of papers in each, and the percentages of the total that these represented.

Table lxiv: CRDs categories against Scientific Papers (2002-13).

Subject	Code	Papers	Percent
Allergic rhinitis	ALR	869	4.8
Asthma	AST	7534	41.3
Bronchiectasis	BRO	197	1.1
Chronic obstructive pulmonary disease	COP	4445	24.4
Cystic fibrosis	CYF	3137	17.2
Emphysema	EMP	446	2.5
Total		**18222**	

As the figure above indicates, the disease areas are very unequal, with asthma representing over 40% of the total, and bronchiectasis barely 1%. The research was very clinical, and no disease area had papers with RL > 2.0.

The RESPI files also enabled analysis of world and European outputs, year by year, for CRD research papers. The following table provides access to the comparative results.

Table lxv: EUR31 outputs RESPI papers WoS (2002-2013), integer and fractional counts

	RESPI					RESPI/BIOMED%	
Year	**World**	**EUR31 Int**	**EUR31 frac**	**EUR %**	**Int'l %**	**World**	**EUR31**
2002	2104	1202	1128	57.1	6.2	0.57	0.76
2003	2123	1253	1150	59.0	8.2	0.55	0.77
2004	2177	1222	1122	56.1	8.2	0.54	0.72
2005	2429	1401	1273	57.7	9.1	0.57	0.79
2006	2635	1401	1280	53.2	8.6	0.59	0.76
2007	2771	1537	1399	55.5	9.0	0.57	0.78
2008	2889	1537	1384	53.2	10.0	0.55	0.73
2009	2990	1654	1479	55.3	10.6	0.55	0.76
2010	3108	1730	1546	55.7	10.6	0.54	0.77
2011	3293	1889	1646	57.4	12.9	0.54	0.80
2012	3482	1897	1663	54.5	12.3	0.54	0.76
2013	3628	2099	1838	57.9	12.4	0.55	0.82

By comparison with the other NCD results, RESPI shows a much greater European presence, averaging 56%, which is much higher than the percentages for the other four (38% for ONCOL, 42% for CARDI, 40% for DIABE and 35% for MENTH). The internationalism was initially lower than in the other NCDs, but has caught up and even surpassed some of them. But RESPI is a very small subject area, and even in Europe only averages 0.8% of the papers in biomedicine overall.

The results for the individual European countries are shown in figure below. The UK has the highest output, more than twice as high as the second country, France, which is publishing almost twice as much as expected, as are Sweden and the Netherlands. On the other hand, Austria is publishing very little, and Germany, Norway and Switzerland are doing barely half of what might be expected from their wealth.

Table lxvi: EUR31 RESPI Outputs SCI and SSCI, integer and fractional counts (2002-13)*

Country	Int ct	Frac ct	% int	AAPG		Country	Int ct	Frac ct	% int	AAPG
UK	5537	3924	29.1	3.1		**AT**	263	140	46.9	0.9
FR	2387	1870	21.7	0.1		**HU**	158	109	31.0	5.1
IT	2372	1847	22.1	4.1		**CZ**	131	77	41.4	7.5
DE	2474	1701	31.2	3.1		**HR**	88	77	13.0	12.5

NL	2065	1447	29.9	5.4		**RO**	85	61	28.0	19.2
ES	1742	1351	22.4	7.8		**SK**	64	45	28.9	17.6
SE	1407	886	37.1	3.0		**SI**	58	43	25.2	30.6
BE	990	617	37.7	6.3		**IS**	89	33	63.2	5.7
DK	792	487	38.5	8.8		**LT**	39	27	31.9	9.5
PL	580	454	21.7	13.2		**BG**	33	17	48.7	19.2
GR	510	383	25.0	10.1		**EE**	45	12	74.1	2.5
CH	695	353	49.2	4.1		**CY**	16	8	49.7	11.4
FI	489	342	30.1	1.9		**MT**	13	6	51.3	5.4
NO	458	267	41.6	7.0		**LV**	6	4	29.2	20.9
PT	225	164	26.9	19.4		**LU**	3	1	66.7	2.7
IE	239	155	35.3	13.5						

**For the percent foreign contribution and the annual growth rate. The countries are ranked by their fractional count outputs.*

In order to break the data down into individual CRDs across EU MSs, the RESPI filter was divided into five specific diseases, which were coded as follows:

- Allergic rhinitis, coded ALRH
- Asthma, coded ASTH
- Chronic Obstructive Pulmonary Disease, coded COPD
- Cystic Fibrosis (Mucoviscidosis), coded CYFI
- Emphysema, coded EMPH.

The table below lists the numbers of papers relevant to each disease against the 31 European MSs.

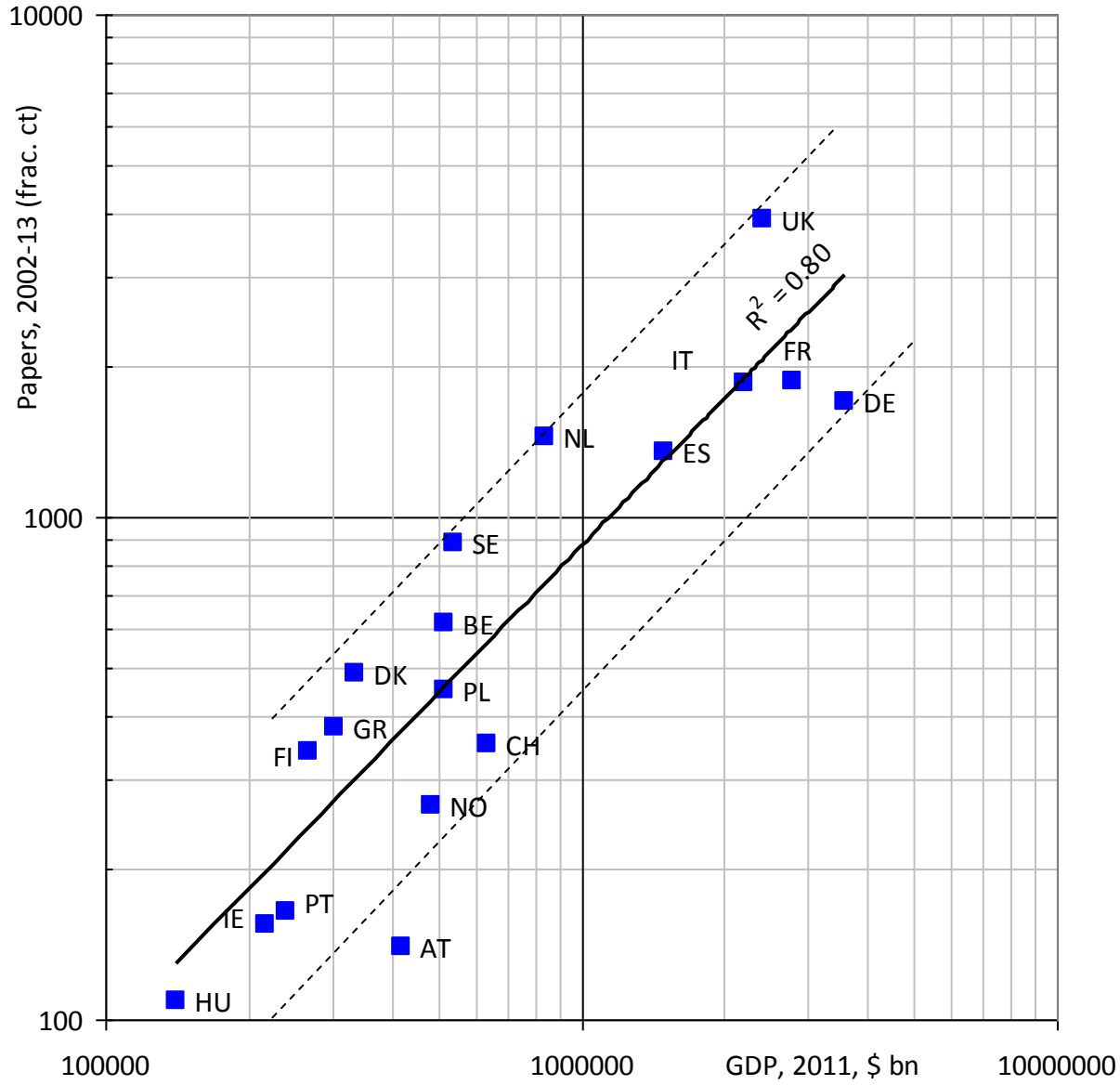
Table lxvii: Papers in 5 RESPI disease areas for Euro31 countries (2002-13)

ISO	ALRH	ASTH	COPD	CYFI	EMPH	RESPI		ISO	ALRH	ASTH	COPD	CYFI	EMPH	RESPI
UK	108	1752	1070	914	77.1	3924		**AT**	10.1	64.1	38.7	21.2	7.1	140
FR	82.1	852	320	556	53.0	1870		**HU**	13.7	65.5	16.0	10.4	2.7	109
IT	166	750	564	361	77.3	1847		**CZ**	4.9	34.9	10.8	28.9	1.5	77
DE	123	693	365	414	79.3	1701		**HR**	4.1	48.0	21.4	2.0	0.0	77
NL	34.0	645	591	163	48.7	1447		**RO**	3.7	28.7	24.4	6.4	1.0	61
ES	79.3	512	586	143	35.5	1351		**SK**	5.3	16.7	19.5	2.8	0.0	45
SE	86.4	508	217	76	25.0	886		**SI**	0.0	24.1	20.5	2.7	0.0	43
BE	43.9	220	158	163	29.4	617		**IS**	0.5	19.3	12.4	0.5	0.0	33
DK	22.9	227	154	90	12.0	487		**LT**	2.2	15.9	11.0	1.6	0.0	27
PL	38.0	299	78.4	56.3	1.0	454		**BG**	1.2	10.4	4.2	2.2	0.0	17

GR	17.5	169	166	35.6	7.3	383		**EE**	1.8	5.2	3.3	0.1	0.3	12
CH	18.0	141	96.2	80.7	13.6	353		**CY**	1.0	6.0	0.0	0.0	2.0	8
FI	20.2	264	58.0	4.3	7.6	342		**MT**	0.0	6.3	0.0	0.0	0.0	6
NO	5.4	138	109	15.6	2.9	267		**LV**	0.0	0.2	4.0	0.0	0.0	4
PT	7.4	79.1	27.0	50.9	5.0	164		**LU**	0.0	0.8	0.3	0.0	0.0	1
IE	6.6	29.7	24.5	90.1	3.4	155		**EUR**	***858***	***7279***	***4585***	***3214***	***478***	***16248***

National impacts of funding investment, in terms of research papers from each European country, are compared with national GDP in order to reveal which countries are contributing the most to each subject area, with some outliers being noted. Most of the papers were at the clinical end of the spectrum, and in most NCDs had become more so over the 12 years of the study.

Figure vii: Plot of RESPI paper output (2002-13)* against GDP for 18 European countries**



**For countries with fractional counts above 100 papers. ** Note: BG, CY, CZ, EE, HR, IS, LT, LU, LV, MT, RO, SI and SK omitted. Dashed lines show values x 2 or x 0.5 relative to power trend-line.*

The research level of the RESPI papers tended to increase slightly (i.e., become more basic) over time, and the papers were noticeably more clinical than the average for the journals in which they were published. This rose from 1.72 to 1.82; not a big rise but in the other NCD areas the journals tended to become more clinical with time.

Data were also obtained on the burden of disease in each of the 31 European countries and in the group as a whole. These data have been taken from the WHO Global Burden of Disease study for 2010.

Comparing results against the 2010 WHO data on the burden of disease, bibliometrics analysis has the potential to identify where resources are being usefully invested, and where savings might be made by deploying resources elsewhere. Conversely, where fewer papers are published in high burden areas, it also holds the potential to identify evidence of a research gap. Bibliometrics can also identify potentialities for international collaboration: countries with smaller scientific output

usually have a greater need to seek partners abroad. Here, bibliometrics can identify MS that collaborate less with other MSs in a given subject area than would be expected, which can be interpreted to suggest the need for the deployment of additional means to encourage such partnerships. Using this approach, bibliometrics provides an indication of the potential shortfalls, excesses and potential for synergies in terms of NCD research funding.

Table lxviii: % DALYs for Euro31 MSs Asthma, COPD and other lung diseases (2010)

	ASTH	COPD	Other	RESPI			ASTH	COPD	Other	RESPI
UK	1.81	4.19	1.07	7.07		**BG**	0.40	3.47	0.64	4.52
CH	1.29	4.46	0.88	6.64		**DE**	1.05	2.94	0.48	4.47
DK	1.13	4.75	0.56	6.43		**IT**	0.98	2.64	0.55	4.17
IE	1.65	3.31	0.81	5.77		**HU**	0.46	3.43	0.28	4.16
BE	0.94	3.88	0.80	5.62		**FR**	1.46	2.10	0.59	4.15
GR	0.63	2.88	2.09	5.61		**PL**	0.85	2.71	0.41	3.97
CY	1.57	2.31	1.52	5.40		**SI**	0.63	2.82	0.42	3.87
NL	0.93	3.88	0.53	5.34		**HR**	0.58	2.88	0.33	3.79
PT	1.61	2.26	1.25	5.12		**CZ**	0.44	2.67	0.37	3.48
NO	1.27	3.32	0.46	5.05		**FI**	1.10	1.97	0.40	3.48
SE	1.56	2.93	0.52	5.01		**RO**	0.62	2.42	0.22	3.25
AT	0.90	3.51	0.39	4.80		**SK**	0.68	2.13	0.38	3.20
ES	0.83	2.65	1.30	4.77		**LT**	0.37	2.01	0.24	2.62
IS	1.37	2.70	0.57	4.64		**LV**	0.43	1.42	0.27	2.11
LU	0.88	3.10	0.61	4.59		**EE**	0.53	1.21	0.23	1.97
MT	1.09	2.78	0.67	4.55						

The range of values is fairly narrow, but it is clear that the UK tops the list. The three small Baltic countries suffer the least from these diseases.

Finally, figure below indicates the relative commitment of the leading 18 European MSs to these five disease areas based on GDP and burden of disease, with Green representing a high commitment, yellow a medium level commitment and pink a low commitment.

Table lxix: Research commitment 5 RESPI diseases 18* European countries (2002-13)**

	ALRH	ASTH	COPD	CYFI	EMPH			ALRH	ASTH	COPD	CYFI	EMPH
UK	0.51	0.99	0.97	1.20	0.67		**PL**	1.56	1.46	0.61	0.64	0.08
FR	0.82	1.01	0.61	1.53	0.97		**GR**	0.85	0.98	1.53	0.48	0.65
IT	1.67	0.90	1.08	1.00	1.44		**CH**	0.95	0.88	0.96	1.17	1.32
DE	1.34	0.90	0.76	1.25	1.60		**FI**	1.10	1.72	0.60	0.06	0.77

NL	0.44	0.99	1.45	0.58	1.16		**NO**	0.38	1.15	1.45	0.30	0.38
ES	1.09	0.84	1.54	0.54	0.90		**PT**	0.84	1.07	0.58	1.59	1.04
SE	1.82	1.27	0.87	0.44	0.97		**IE**	0.80	0.43	0.56	2.99	0.75
BE	1.33	0.79	0.91	1.36	1.64		**AT**	1.35	1.02	0.98	0.78	1.74
DK	0.88	1.03	1.12	0.95	0.85		**HU**	2.34	1.33	0.52	0.49	0.83

** with at least 100 RESPI papers **compared to outputs in RESPI overall. Values > 2 tinted bright green; values > 1.41 tinted pale green; values < 0.71 tinted gold; values < 0.5 tinted pink.*

4.3 Funding Sources

The funding of research is recognised as an important source of information for its evaluation (Lewison & Dawson, 1998; Lewison & Devey, 1999; Lewison & van Rooyen, 1999; Lewison, Grant & Jansen, 2001; Roe et al., 2010; Rigby, 2013). At its simplest, the acknowledgement of a funding source on a paper indicates that an agency, usually an external one, has reviewed the research project and judged that it is worthy of support. Multiple funding sources would indicate that the project has found favour in several places.

In the past, the recording of the funding sources on a paper was a labour-intensive task as each paper needed to be inspected individually, usually in a big library. It was, however, worthwhile if the work could serve to provide many different funding bodies with a tally of papers that they had supported. This was the principle behind the creation of the Wellcome Trust's Research Outputs Database (Jeschin et al, 1995; Dawson et al., 1998; Webster, 2005). This covered all UK biomedical papers over the 14 years, 1988-2001, and was based on the papers in the Science Citation Index on CD-ROM, which was purchased from the Institute for Scientific Information in Philadelphia (now Thomson Reuters) and operated under license from them. The data were made available to members of the "ROD club", who paid a graduated annual fee and in return received a list of their papers, together with access to consultancy advice.

Since the introduction of the Science Citation Index , the facilities available for searching and for retrieving data have been steadily enhanced. During 2008, Thomson Reuters started to provide details of funding for individual papers – quite likely stimulated by the earlier existence of the ROD! There are two individually searchable fields, FO = funding organization and FT = funding text. The FO field lists the names of the acknowledged funders and FT gives the full text of the acknowledgement, including recognition of individuals who have helped with the research. For some funding bodies, the FO field also lists the grant numbers, although they are often absent and have not been considered in this analysis.

Authors of papers record their funding acknowledgements in a wide variety of ways. Many papers had multiple funding acknowledgements[3]. In order to determine the funding sources for RESPI and the four other disease areas, it was therefore decided to use a coding system, with four parts:

- a trigraph (three character) code designating the individual funding body;
- a single letter code showing the form of support (no longer used);
- a digraph (two character) code designating the sector and sub-sector of the funder;
- and another digraph showing the country of the funder based on the ISO codes.

[3] There are also acknowledgements to individuals who have provided help or advice. These are not considered further in this report.

The trigraphs were designed to be easily memorable, *e.g.*, MRC = UK Medical Research Council; BHF = British Heart Foundation, although it turned out that there were so many different funders of UK research papers that many had to be given odd combinations of letters[4].

It also became apparent that some papers did not carry an acknowledgement because they had been supported internally – in a government lab (such as one supported by a research council or Government department), by a collecting charity, or by a commercial company. So the decision was made to include these "implicit" acknowledgements along with the "explicit" ones in the acknowledgement paragraph to form a composite acknowledgement[5].

In principle, the research described in all published papers has to be paid for in some way. In practice, however, there are many papers (especially ones describing clinical work) that do not contain any formal acknowledgement.

In any case, most of their authors would be academics or medical personnel working in a hospital or clinic, supported by general university funds or by salary support from the health service. But such support would not be peer-reviewed, and so such papers would perhaps be of a lower standard. For these reasons, it did not seem appropriate to record this nominal support, and the ROD was set up to record such papers as "unfunded", and the hospital or university or research institute address was not given a code. However, if a specific acknowledgement appeared to a university or department, or to a hospital, then it was presumed that some system of grants was in place and the contribution of the employing organisation WAS recorded with a code. This gave rise to three sub-sectors of the private-non-profit sector, namely HT = hospital trustees, MI = academic[6] and NP = other non-profit. The other two were CH = collecting charity and FO = endowed foundation.

The methodology used to extract funding information for papers whose details were downloaded from the Web of Science (WoS) was the same across the five disease areas. The basic principle used was to assign a three-part code to each funding body, with a three-letter code to identify it uniquely, a two-character code to identify the sector and sub-sector, and another two-character code to identify the ISO designation. Codes were assigned to each funding body listed in the FO = funding organization section of the WoS, subject to redaction if they were mentioned in a conflict of interest statement only as having paid for unrelated work. Codes were also assigned where there was an acknowledgement implicit from one (or more) of the addresses - a government department or agency, the laboratory of a collecting charity, or of an industrial company.

Once codes were assigned to each funding body, they were collected and written to two thesauruses for future use. The spreadsheet of papers was then completed with the explicit and implicit codes by means of a special macro, which also combined the codes into a single column. Another macro determined the division of funders by main sector for each European country (own government including local and regional authorities; own private-non-profit (PNP), industry, international, and other). These were doubly fractionated: to allow for the fractional presence of the target country on each paper, and to allow for the total number of funders on a paper.

The commercial sector was divided up into five sub-sectors, with companies divided into three: pharmaceutical, biotech and industrial. The first and third of these were further divided into independent and subsidiary. The purpose was to distinguish between the research activities of UK subsidiaries of large multi-national companies which might be relatively independent of the parent,

[4] Initially, every UK research funder was given an individual trigraph in order to cater for the possibility that it would become a ROD member, although membership seldom rose above 30.
[5] Several of the ROD members maintained their own labs and also gave external research grants and this system allowed them to compare their respective outputs.
[6] This term was used because many universities and colleges are both endowed with capital and are still collecting money (*e.g.*, from their alumni).

e.g., the Merck Neuroscience Park in Harlow, which did its own research and also gave funding to universities. However there were many takeovers of small biotech (and not so small pharma) companies and it seemed appropriate to regard the takeover as a way in which the new parent company would thereby gain the intellectual property of the new acquisition. This meant that many of the commercial codes became out-of-date. This had two consequences for the analysis of funding sources. First, the country of a company was effectively undefined, and second, the sub-sector could change when a biotech company had brought a new drug to market and had so become a pharma company.

The public sector was divided into three sub-sectors: government department (controlled by ministers), government agency (nominally independent of ministerial directives) and local authorities (including regions, counties and cities). They were given sectoral codes: GD, GA and LA, respectively. Although the latter form of support hardly exists in the UK, it is becoming increasingly common in several continental European countries (Länder in Germany, régions in France, provinces in Spain) and also in North America (provinces in Canada and states in the USA) and in Australia (states and territories). Most of these regions have been given their own trigraphs, although some smaller regions have generic codes, see below.

Because of international collaboration on biomedical research papers, many of the UK papers covered in the ROD also had foreign partners and acknowledgements to foreign funding sources. The thesaurus soon began to run out of trigraph codes, and we started to use "generic" codes for the smaller organisations (in terms of their biomedical research spend). These consisted of a single letter (X, Y or Z) followed by one digit (to designate the country) and another to designate the sector and sub-sector. Individual countries that supported a lot of biomedical research were given their own digraph (e.g, X1 = USA); others were given one that showed their continent. There is, of course, some redundancy as the country and sector/sub-sector are also given by the second and third digraphs, but these are needed for the main analyses. For example, X1B-BT-US indicates a US biotechnology company in two ways. Generic codes for the UK were not used initially, but have been introduced to cater for the large number of new British funding bodies, and codes UK1, UK2 etc. are employed.

Table lxx: Digraphs for countries with generic codes and designated sector or sub-sector

Digits 1 & 2	ISO	Country		Digit 3	Code	Category
X0	NL	Netherlands		1	CH	Charity
X1	US	USA		2	FO	Foundation
X2	DE	Germany		3	GD/GA	Government
X3	JP	Japan		4	HT	Hosp. Trustees
X4	SE	Sweden		5	IN	Industry (non-pharma)
X5	NZ	New Zealand		6	IP	Pharma industry
X6	CA	Canada		7	LA	Local/regional authority
X7	FR	France		8	MI	Mixed (i.e., academic)
X8	ZA	South Africa		9	NP	Non-profit (e.g., professional body)

X9	IT	Italy		B	BT	Biotech company
Y0	BR	Brazil		Z0	EU	Europe
Y1	IE	Ireland		Z1	CN	China
Y2	CH	Switzerland		Z2	HU	Hungary
Y3	DK	Denmark		Z3	AT	Austria
Y4	NO	Norway		Z4	HK	Hong Kong
Y5	ES	Spain		Z5	AU	Australia
Y6	FI	Finland		Z6	XX	not known
Y7	BE	Belgium		Z7	AF	Africa
Y8	IL	Israel		Z8	AS	Asia
Y9	IN	India		Z9	LA	Latin America

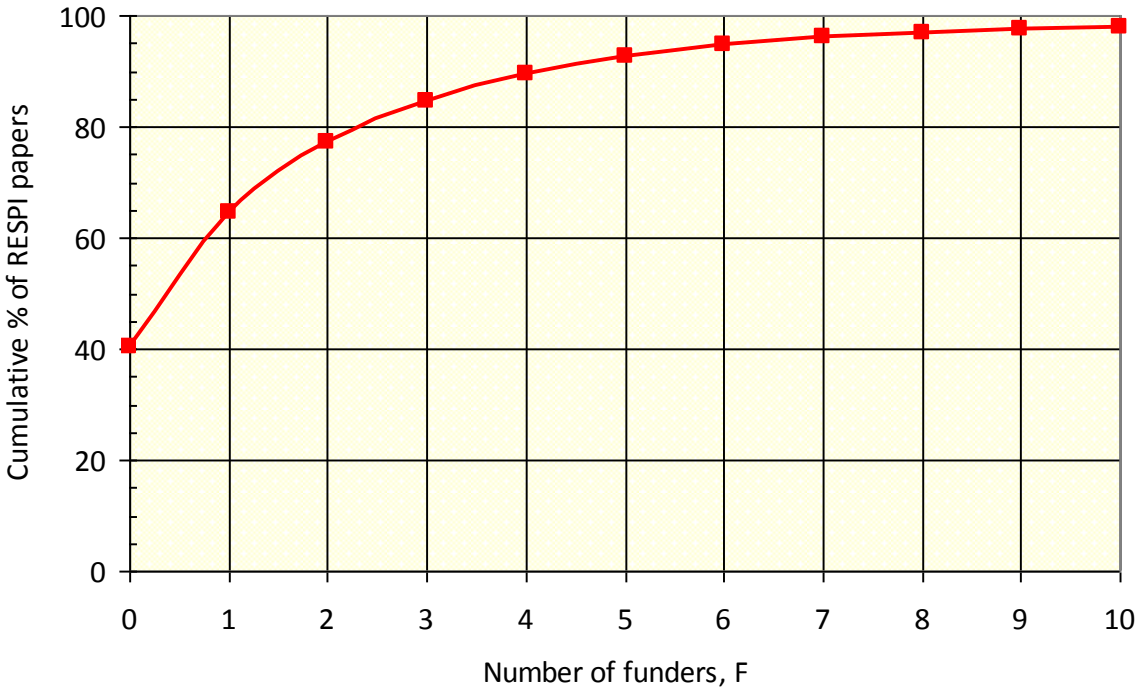
The code "Z4" for Hong Kong is still used, although the country digraph of CN for China shows that this is now part of the People's Republic.

These trigraphs, and the associated sectoral and country codes, were assembled into a large thesaurus of funding bodies. The thesaurus is structured so that the different names and formats given to a funding body (and in some cases its dependent agencies, bodies or companies) are all listed to facilitate the allocation of codes. At the time of writing, there were 17,485 entries and 10,045 (out of a possible 17,576) individual letter trigraphs. This suggests that there is still plenty of opportunity for new codes, but it is often difficult to find appropriate letter combinations for new organisations with many funded papers. These are appearing in continental European countries as work on the project develops, because the thesaurus was originally developed mainly for UK funding bodies.

4.4 RESPI: Funding Sources

RESPI is the smallest of the five NCDs in terms of numbers of papers, with diabetes (DIABE), the second smallest. CRDs was the first of the five to be analysed in accordance with the methodology described above. The file consisted of 18,822 papers, of which 9269 were published during the last five years, 2009-13. Of these, 775 or 8.4% had a conflict of interest statement, and needed to be examined individually in order to check the funding bodies listed in the FU column of the spreadsheet, and redact them if necessary. Some papers originally crediting funding bodies were found not to be funded explicitly, and others had the number sharply reduced; a very few should have had additional funders credited. After the redaction, 5451 papers had one or more funders (59%) and the remaining 41% had none. This redaction process was very labour-intensive, and involved the removal of approximately half the commercial funding credits listed in the WoS FO field. Figure viii shows the percentages of papers with given numbers of funders or more.

Figure viii: Cumulative percentage of RESPI papers with different numbers of funders (2009-13)



The average number of acknowledged funders per paper varied from over four for papers from Luxembourg, Estonia and Iceland to less than 0.5 for papers from Croatia and Slovenia.

Among the countries with a fractional count of papers of at least 100 (numbering 15 out of 31), those from Finland and Sweden attracted most funders, and fewer than one in five had no acknowledgements. These papers also had the most support from private-non-profit sources: 48% for Finland and 39% for Sweden. In 10 of the 15 countries, private-non-profit (PNP) sources out-numbered those using public moneys. Industry provided about 13% of funders on average, and international sources, 3.5% – notably the European Commission.

Funding also varied with the subject matter and type of the research, with asthma and COPD receiving the most funding attention and bronchiectasis the least. Clinical papers were less likely to be funded than basic ones. Papers with more authors tended to have more funding bodies, and that (for the 2009 papers for which five-year citation counts were available) the number of citations was positively correlated with the number of funders. For example, "unfunded" papers received only 11 cites on average, papers with 3 to 5 funders averaged 25 cites and papers with 11 or more funders averaged 38 cites.

By way of comparison, DIABE funding gave rather similar results, with data for each of 14 subject areas. However, the diabetes papers attracted more funding than the respiratory disease ones, and only 31% had no specific funding (cf. 41%). The average paper had 2.5 funders compared with only 1.8 for the RESPI ones. We noticed that the later papers (2012-13) acknowledged more funders than the earlier ones (2009-10): in DIABE the mean rose from 2.1 to 2 .8, and in RESPI from 1.5 to 2.1.

The literature clearly shows that more funders are positively correlated with publication in higher impact journals, and with receipt of more citations in a given time window, even when other possible confounding factors are taken into account by means of multiple regression analysis (Roe et al., 2010). We have found that an important confounding factor is the research level of the paper (clinical or basic), see Lewison and Paraje (2004). Basic papers tend to receive more funding and receive more citations than clinical ones. This may put clinicians at a disadvantage when they apply for research grants.

Another important factor in the European context is that researchers in some countries may have many more potential sources of support than others. In particular, the pharma industry is more prominent in Western Europe, and there are also many more charities and endowed foundations. In addition, there may be more governmental and regional sources, as we have observed in Belgium, France, Germany, Italy, Spain and Sweden. The countries of Eastern Europe have been freed from the centralised system of government support for research for nearly 25 years, but we have not so far observed significant numbers of private-non-profit organisations that sponsor biomedical research in these countries.

The first analysis was in terms of the mean number of funders per country, and there was a big variation, with the Scandinavian countries having the most and (of the major countries) Poland and Greece the least. The number of funders has been calculated on a fractional count basis. The analysis by main sector, using fractional counts of sectors for each paper and fractional country counts, is shown in Figure ix.

Figure ix: Fractional counts for each paper by country (2009-13)

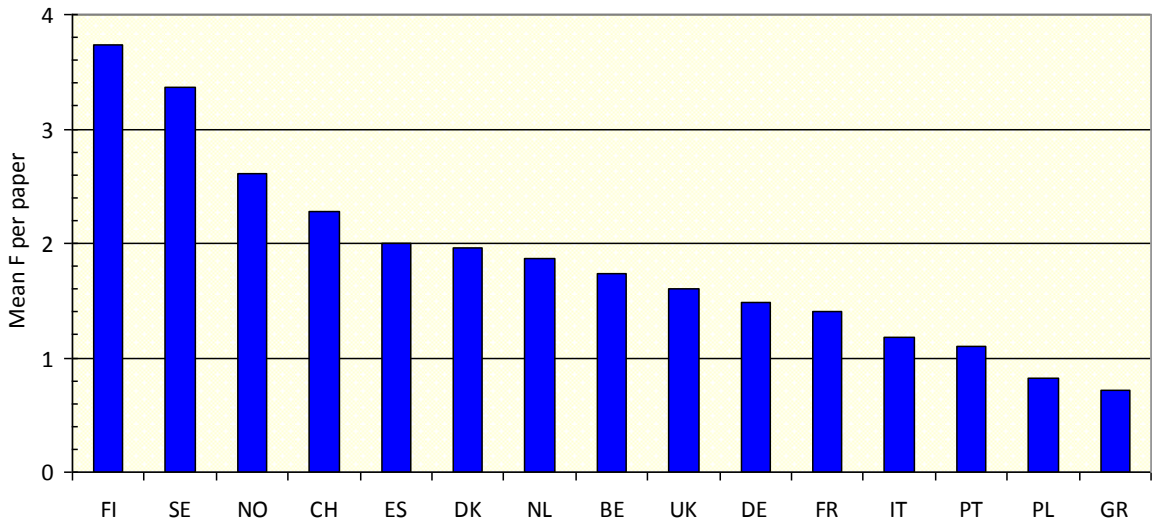
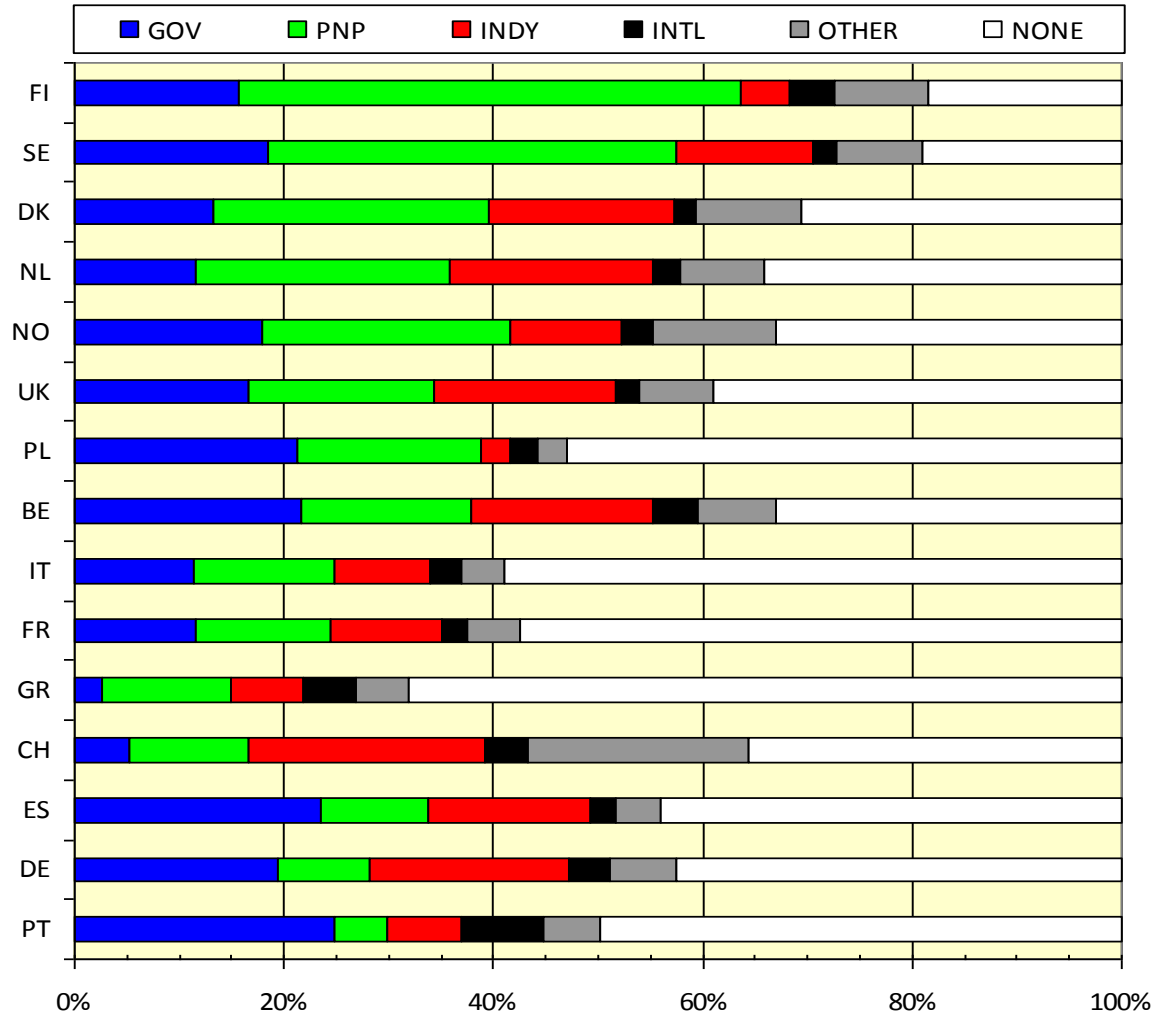


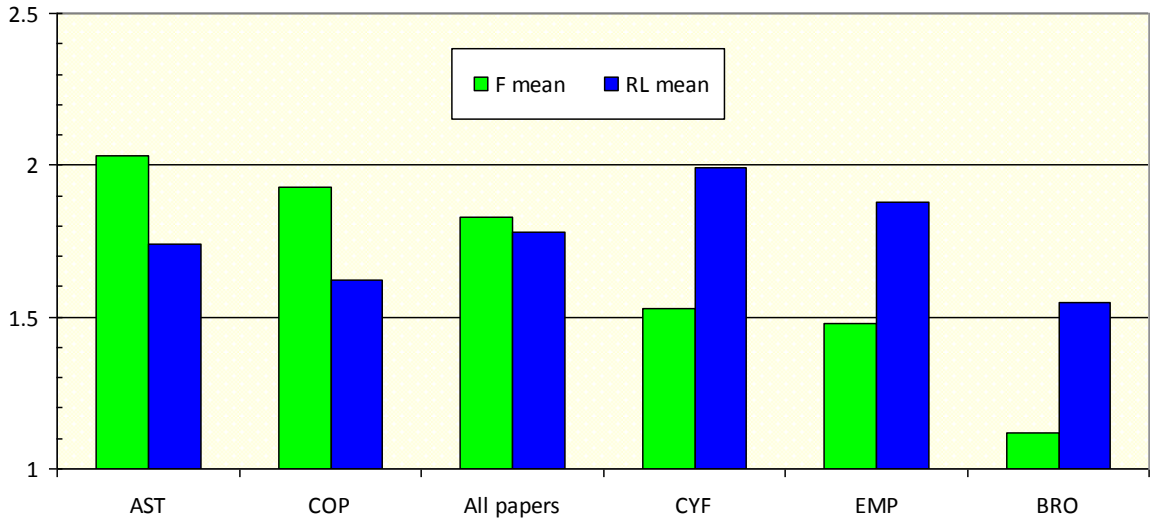
Figure x: Mean number of funders* per RESPI papers (2009-13)**



**for countries with at least 100 papers ** The countries are ranked by the percentage of private-non-profit funded papers.*

The RESPI database was divided up by five disease areas: asthma (AST), bronchiectasis (BRO), chronic obstructive pulmonary disease (COPD, COP), cystic fibrosis (CYF) and emphysema (EMP). Figure xi shows the numbers of funders and the mean research level of the papers in each area. Cystic fibrosis is the most basic, followed by emphysema, but asthma, followed by COPD, receives the most funding (in terms of numbers of funders per paper).

Figure xi: Mean number of funders per paper (F) and mean research level (RL)*



*a scale from 1 = clinical to 4 = basic research for all RESPI papers 2009-13.

Overall, papers in clinical journals tend to give fewer funding acknowledgements than ones in basic journals. This also holds true for papers with clinical title words compared with ones containing basic title words

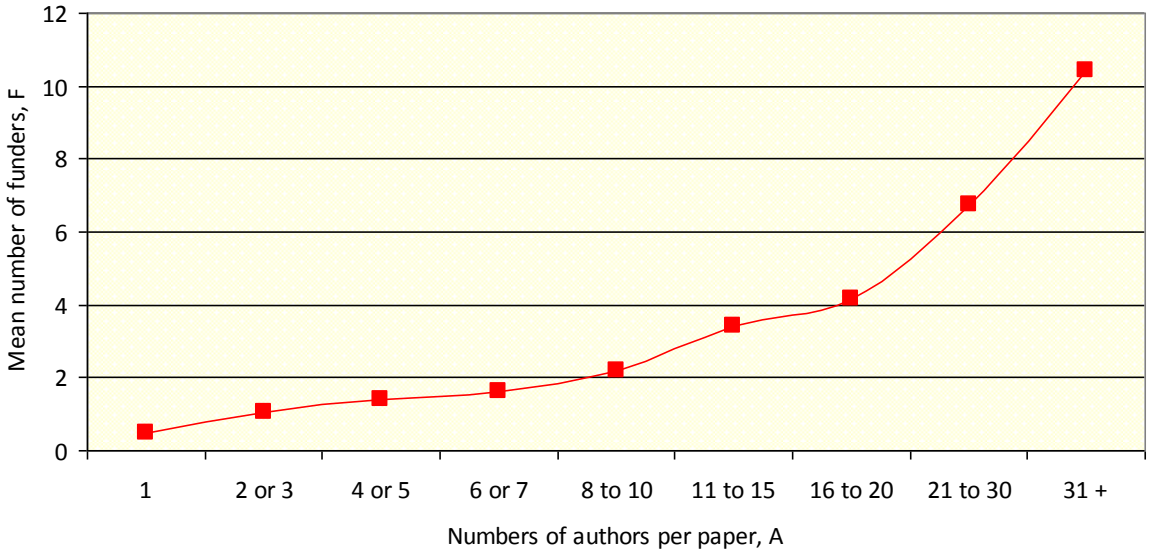
Table lxxi: Numbers of funding bodies per paper for RESPI papers (2009-13)*

RL (J)	F	N	F = 0	% fund		Title words	F	N	F = 0	% fund
1.0 to 1.5	1.36	4487	2284	49.1		Clinical not basic	1.06	1051	593	43.6
1.5 to 2.0	1.92	2023	734	63.7		All clinical	1.14	1168	633	45.8
2.0 to 2.5	2.53	1155	348	69.9		Clinical and basic	1.81	117	40	65.8
2.5 to 3.0	2.33	815	212	74.0		All basic	2.11	255	81	68.2
3.0 to 3 .5	2.62	480	106	77.9		Basic not clinical	2.36	138	41	70.3
3.5 to 4 .0	3.24	281	36	87.2						

** in journals of different RL (RL 1 is clinical; RL4 is basic) and containing clinical and/or basic title words. N = total number of papers in each group; F = 0 is number with no funding acknowledgements.*

It is not surprising that the average number of funders per paper rises with the number of authors, A, as the additional authors may be expected to be able to tap extra funding sources, and papers with many authors are likely to be international and attract funding from different countries, but nevertheless the correlation is striking.

Figure xii: Mean number of funding bodies per paper for RESPI papers (2009-13.)

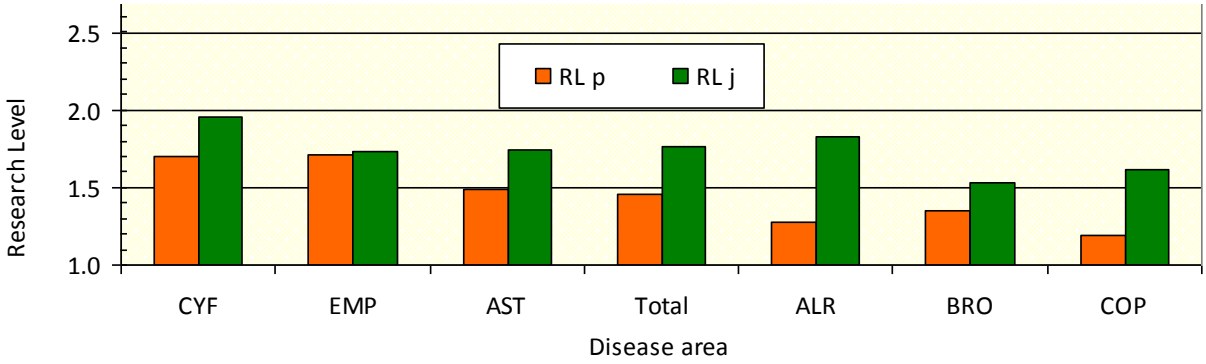


4.5 Citations of Research Papers

Bibliometric analysis uses citation scores to measure of the impact of research papers. For most NCDs, European research was better cited than the world average, although there was much variation between countries. Interestingly, there was generally poor correlation between the burden from particular diseases and the amount of research. In this case, there may be grounds for re-balancing some national research portfolios.

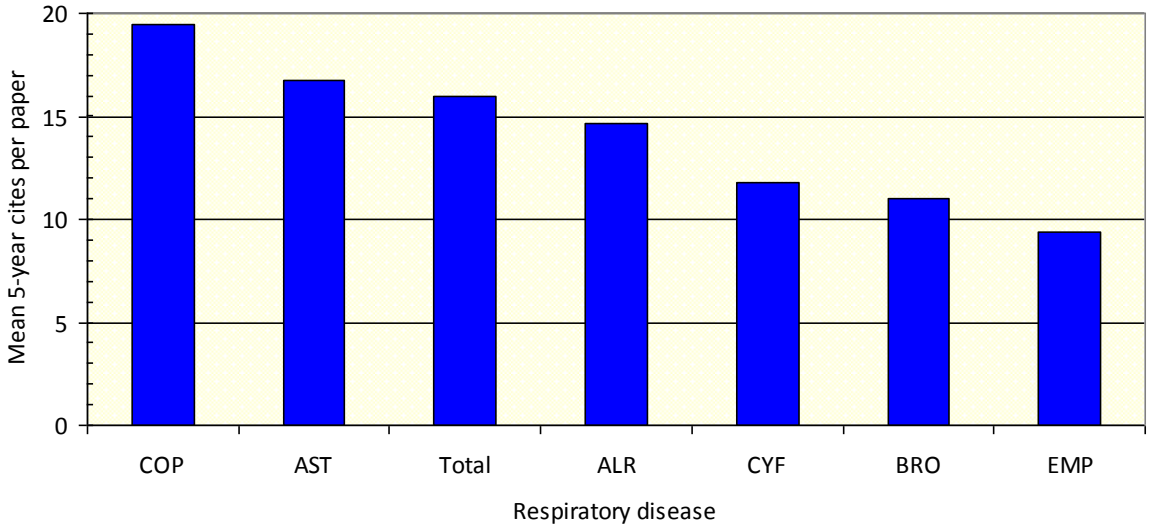
There was again a big difference between the disease areas in terms of their propensity to attract citations, with a two-to-one variation between chronic obstructive pulmonary disease (COPD) and emphysema, see Figure viii. This was in part because of the size of the researcher cohort (*i.e.*, the number of papers), for which the correlation with ACI was $r^2 = 0.49$.

Figure xiii: Mean research level of RESPI papers and journals*



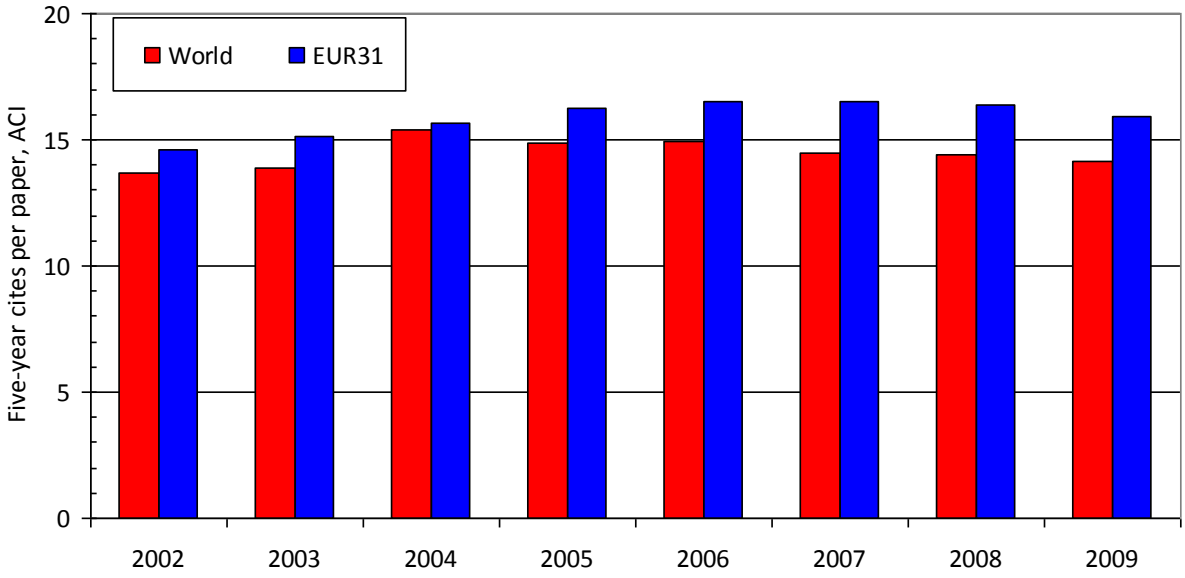
** RL = 1.0 is clinical observation; RL = 4.0 is basic research.*

Figure xiv: Mean five-year cites for RESPI papers in six disease areas (2002-09)



The citation scores (five-year cite scores, ACI) for the world and for the EUR31 countries are given in the figure below for the eight years, 2002-09.

Figure xv: RESPI Mean Citation Scores world and EUR31 (2002-9)*



**world (red) and for EUR31 (blue) papers*

Below, the table shows the citation scores (ACI) for individual countries and also the numbers of papers whose citations put them in the top 5% of the cohort in terms of citations, for which the qualifying numbers were 52 cites.

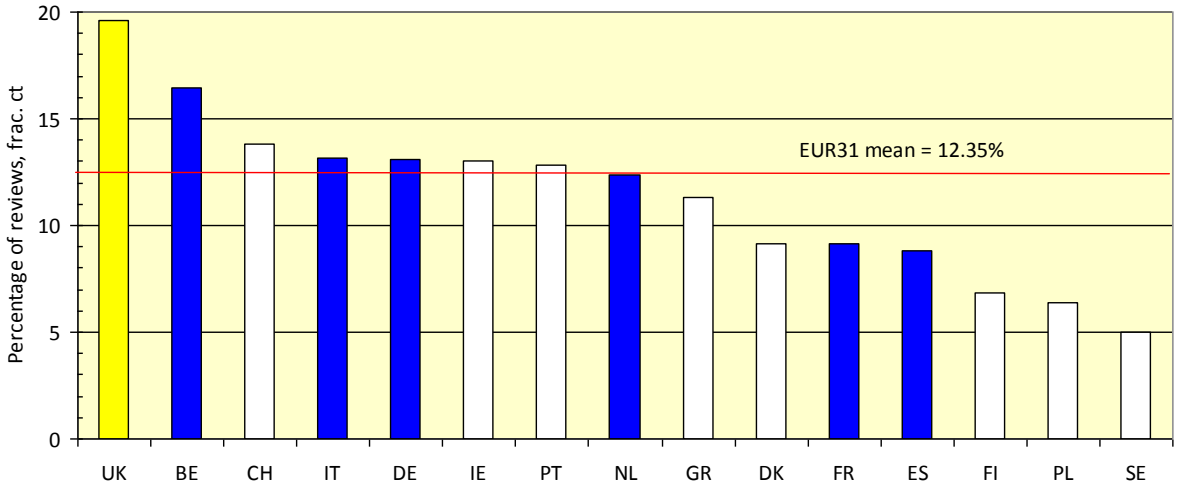
Table lxxii: Citation performance of 18 EUR31 countries in RESPI (2002-09) *

ISO	**ACI**	**Top 5%**	**%**		**ISO**	**ACI**	**Top 5%**	**%**		ISO	**ACI**	**Top 5%**	**%**
UK	19.6	176.4	7.28		**NO**	14.7	5.4	3.80		FI	14.1	5.6	2.44

BE	18.2	24.8	6.74		**ES**	12.2	23.7	3.12		GR	10.1	3.6	1.65
DK	18.3	15.3	6.04		**IT**	12.9	35.1	3.08		HU	11.3	1.0	1.65
NL	17.9	45.1	5.32		**IE**	11.9	2.0	2.97		PL	8.5	3.9	1.59
CH	16.0	9.6	4.64		**FR**	9.8	34.9	2.80		AT	11.4	1.2	1.27
DE	13.9	43.9	4.04		**SE**	13.7	13.8	2.55		PT	8.3	0.3	0.33

** with at least 50 citable papers, ranked by the percent with 52 or more cites in the five years following publication (ACI) (Top 5%) rather than the mean value*

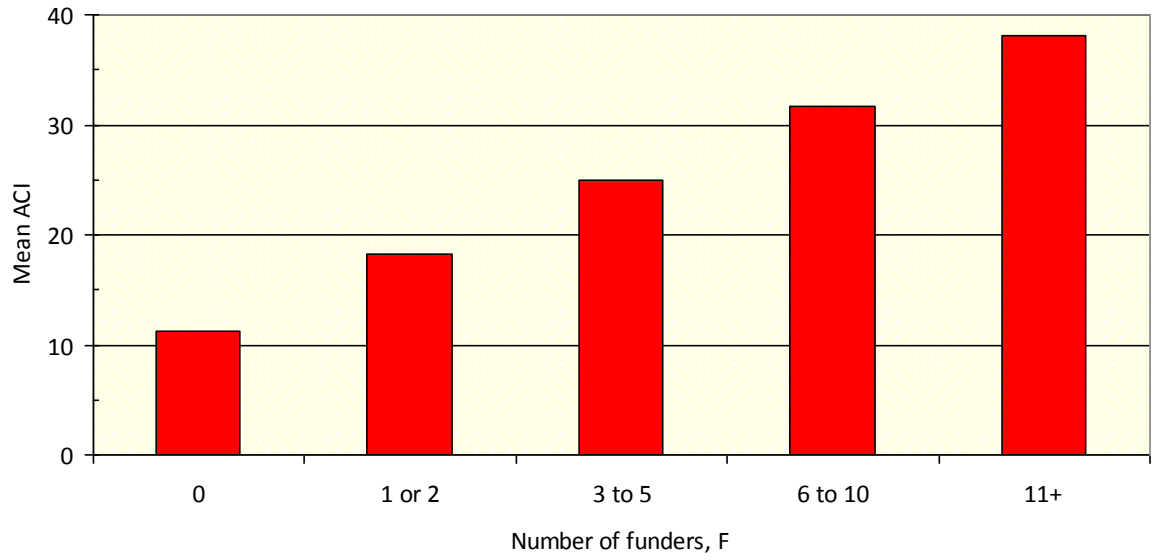
Figure xvi: % of reviews among RESPI papers from 15 European countries*



**with at least 20 reviews in the WoS in 2002-13. Yellow bar: > 300 reviews; blue bars: > 100 reviews.*

Consistent with the analysis presented above, we found that, for 2009 papers, the numbers of funding bodies correlated positively with the mean citation score, see Figure xvii. The increase in actual citation impact (ACI) for papers with many funding acknowledgements is very clear, and the relationship will be expected to hold even when account is taken of factors such as the papers tending to be basic and having more authors (Lewison & Dawson, 1998; Roe *et al.*, 2010).

Figure xvii: Mean five-year citation count (ACI) RESPI papers (2009)*



*with different numbers of funding acknowledgements

The average number of acknowledged funders per paper varied from over four for papers from Luxembourg, Estonia and Iceland to less than 0.5 for papers from Croatia and Slovenia.

Among the countries with a fractional count of papers of at least 100 (numbering 15 out of 31), those from Finland and Sweden attracted most funders, and fewer than one in five had no acknowledgements. These papers also had the most support from private-non-profit sources: 48% for Finland and 39% for Sweden. In 10 of the 15 countries, private-non-profit (PNP) sources out-numbered those using public moneys. Industry provided about 13% of funders on average, and international sources, 3.5% – notably the European Commission.

Funding also varied with the subject matter and type of the research, with asthma and COPD receiving the most funding attention and bronchiectasis the least. Clinical papers were less likely to be funded than basic ones. We observed that papers with more authors tended to have more funding bodies, and that (for the 2009 papers for which five-year citation counts were available) the number of citations was positively correlated with the number of funders. For example, "unfunded" papers received only 11 cites on average, papers with 3 to 5 funders averaged 25 cites and papers with 11 or more funders averaged 38 cites.

4.6 Clinical Guidelines

This measure of impact has been used previously both to evaluate the research being cited, and to describe the evidence base for recommendations regarding clinical practice. However, the mere presence of such guidelines is no guarantee that they will be effective at improving healthcare (Schrader et al., 2006). The first study, on a small scale, examined the cited papers on a sample of 15 UK clinical guidelines (Grant et al., 2000). It found that they were very clinical and that UK research was over-cited by 2.5 times. A subsequent study of 43 cancer clinical guidelines in the UK (Lewison et al., 2008) reached similar conclusions, and showed that they could also be used as a means to evaluate research in other countries, for example six Swedish universities. This work was subsequently updated (Pallari and Lewison, 2014) and showed that surgery featured strongly among the cited references (over 25% of the total). It also showed a big variation in whether a country's papers were over- or under-cited relative to its presence in cancer research. Thus UK research was over-cited by almost four, Danish, Dutch and Swedish research by more than two, but that from the "accession" Member States (Poland, Czech Republic and Romania) by half or less.

We investigated the clinical guidelines currently available in the different European Member States in order to extend the work to other countries. Although many countries had a set of national guidelines, some had regional ones as well, and there were yet others published by European societies of professionals in various branches of medicine. We even learned that in Sweden, each of the 21 counties had their own clinical guidelines. Clearly, it would have been impossible for us to collect the references on all of these, and so we decided to limit the study to national guidelines.

In the earlier studies on UK guidelines, the identification of the references with papers processed for the Web of Science involved much labour as each one had to be sought individually. It would not have been practical in the scope of this project to continue in this way for guidelines for the other NCDs and for all the other European countries, but we were able to semi-automate the process by means of a visual basic macro, written by Dr Philip Roe of Evaluametrics Ltd. This worked as follows: first, the references section of a guideline in PDF format were copied and pasted to an Excel spreadsheet; second, these were slightly tidied by removal of page numbers, document running heads, etc; and thirdly, the macro was then operated, and it generated sets of search statements, eight at a time, ready for copying and pasting into the search panel of the WoS. An example is given below:

((AU=(Anderson AND Pottier AND Strachan) AND TI=concurrent AND SO=(T*) AND PY=1992) OR (AU=(Heaney AND Conway AND Kelly AND Johnston AND English AND Stevenson) AND TI=Predictors

AND SO=(T*) AND PY=2003) OR (AU=(Martin AND McLennan AND Landau AND Phelan) AND TI=childhood AND SO=(B*) AND PY=1980) OR (AU=Roorda,R AND TI=adolescence AND SO=(T*) AND PY=1996) OR (AU=(Remes AND Pekkanen AND Remes AND Salonen AND Korppi) AND TI=hyperresponsiveness AND SO=(T*) AND PY=2002) OR (AU=(Brouwer AND Roorda AND Brand) AND TI=spirometry AND SO=(E*) AND PY=2006) OR (AU=(Pellegrino AND Viegi AND Brusasco AND Crapo AND Burgos AND Casaburi) AND TI=Interpretative AND SO=(E*) AND PY=2005) OR (AU=(Dundas AND Chan AND Bridge AND McKenzie) AND TI=bronchodilator AND SO=(T*) AND PY=2005))

The limit of eight individual papers was set so as to keep within the limits for the number of terms allowed by the WoS. Author names (AU) up to six in number were given without initials as sometimes they were given incorrectly by the guideline although if there was only one author the first initial was given. [In the WoS, Jones or Jones,A will find papers by Jones, AT but Jones,PR will NOT find papers by Jones, PRT.] The title word (TI) was selected to be the longest in the paper title. The journal name (source, SO) was given by just its initial letter as the guidelines usually gave an abbreviated name and this would have needed to be substituted by its full name, which would have had to be researched and entered into the macro. Finally, the publication year (PY) was given for completeness.

This process worked well, and even though the search statements needed to be inspected individually (to remove author names with non-Roman characters which are not recognized by the WoS and to delete any punctuation marks attached to title words), it was possible to identify and download over 860 references from one guideline in about 3 1/2 hours. The macro also listed references that did not satisfy its specific requirements so that any errors could be corrected manually and the macro then run again.

4.7 Clinical Guidelines: CRDS

This guideline was the Scottish Inter-collegiate Guidelines Network guideline on the management of asthma (no. 141). This was one of only three UK guidelines on respiratory diseases, the other two being from the National Institute for health and Care Excellence (NICE) – number 101 on chronic obstructive pulmonary disease (COPD) and number 163 on idiopathic pulmonary disease. The three clinical guidelines cited a total of 1179 papers in the WoS, and their cumulative distribution with age is shown in Figure xviii.

Figure xviii: Cumulative time distribution of references on three UK clinical guidelines for CRDs

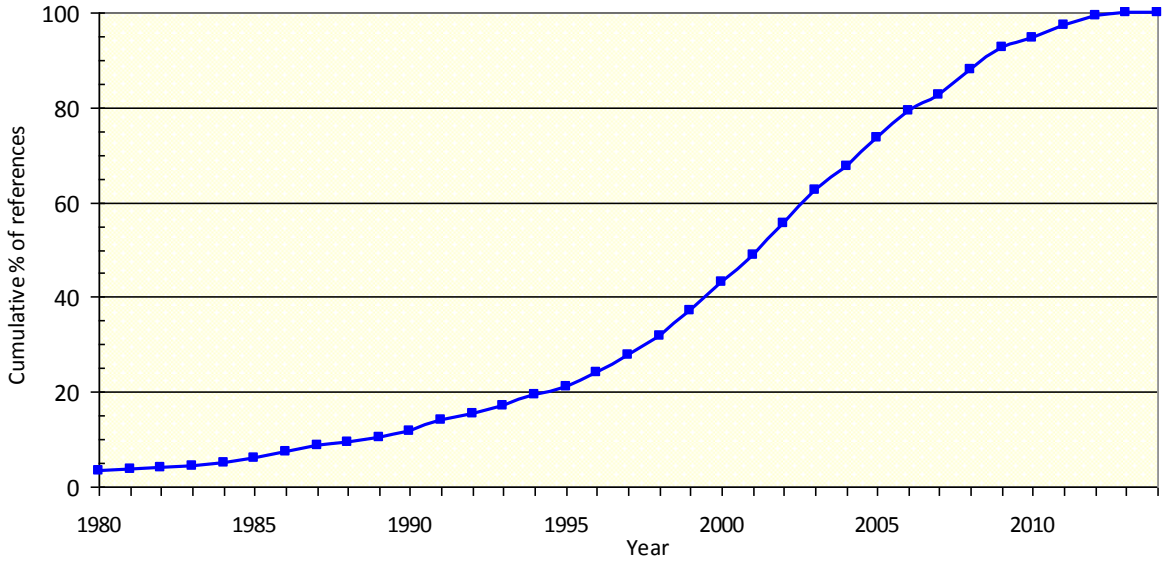
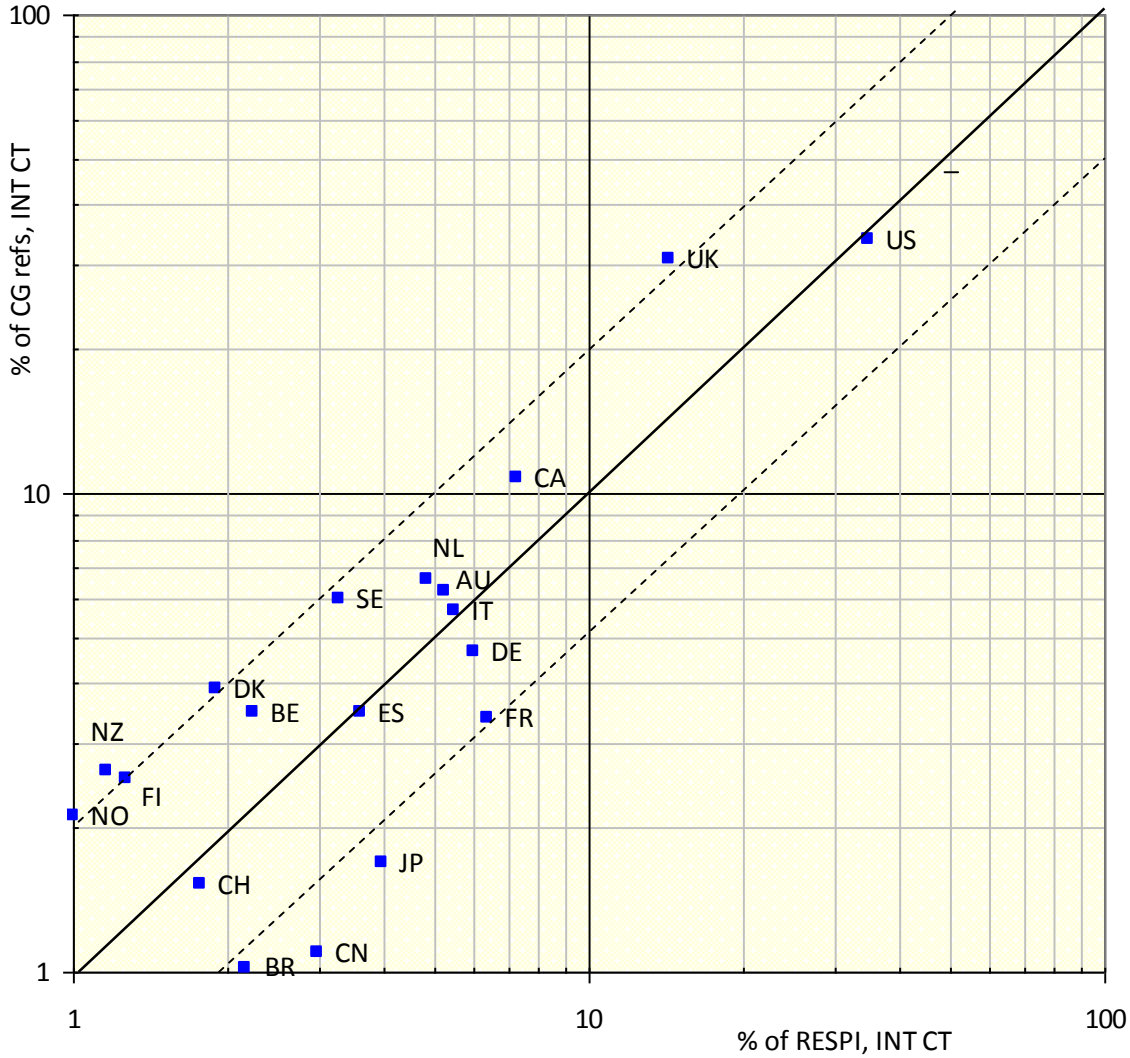


Table lxxiii shows the distribution by country, on the basis of integer counts, for the cited references plotted against the percentage presence of each country in respiratory disease research in the 18 years, 1997-2014, which account for three quarters of the cited papers. [See Table 9, below, for their ISO codes.] The UK, together with New Zealand and the five Nordic countries, are over-cited by a factor of two (the spot for Iceland is not shown, but the citation ratio is 2.4). On the other hand, Japan, China and Brazil are all under-cited by a factor of two or more, and South Korea and Taiwan by more than that. Within the UK, Scotland shows to advantage, particularly on the SIGN references where it is over-cited by 2.4 times, but only x 2 on the NICE guideline references. The cited papers are very clinical, as expected, with a research level (RL) based on their individual titles of 1.05 on a scale running from clinical observation = 1.0 to basic research = 4.0.

Table lxxiii: Digraph ISO codes for 20 countries for comparison between papers cited on clinical guidelines and presence in CRD research.

Country	ISO	Country	ISO	Country	ISO	Country	ISO
Australia	AU	Denmark	DK	Italy	IT	Spain	ES
Belgium	BE	Finland	FI	Japan	JP	Sweden	SE
Brazil	BR	France	FR	Netherlands	NL	Switzerland	CH
Canada	CA	Germany	DE	New Zealand	NZ	United Kingdom	UK
China (P.R.)	CN	Israel	IL	Norway	NO	United States	US

Figure xix: The distribution by country* of the references cited by three UK CRD clinical guidelines, plotted against the countries' presence in CRD research for (1997-2014)**



*based on integer counts of papers. **The two dotted lines are drawn a factor of two above and below the line of equivalence.

4.8 Newspaper Stories

There is abundant evidence that politicians are unduly sensitive to stories in the media. Some of these are based on individual cases, in which it is reported that named patients do not have access to particular means of therapy (expensive drugs, for example). Ministers react by making special provision for them, but this can distort the overall health-care system as with the Cancer Drugs Fund in the UK (Thornton, 2011; Knapton, 2014). Senior officials can use the stories to bring news of research to their ministers; most will not have the time to read the literature extensively and need help to learn about interesting developments. The same is true for health-care administrators in hospitals and clinics, who may learn about new methods of health-care delivery that offer potential cost savings. Medical personnel will also benefit, though the media can also provide misinformation that can cause doctors to misdiagnose (Schmidt *et al.*, 2014). They can also influence researchers, and there is evidence that media coverage increases modestly the numbers of citations (Phillips *et al.*, 1991; Lewison *et al.*, 2008). The print media may even be a source in their own right (Hicks & Wang, 2013). The biggest influence may be on ordinary people, and could assist the public to

choose healthier life styles (Nishtar *et al*., 2004; Caburnay *et al*., 2008; Hellyer & Haddock-Fraser, 2011), including enrolment for vaccinations (Olufowote, 2011; Robbins, Pang & Leask, 2012), although sensational press coverage of supposed links between MMR (measles, mumps, rubella) vaccination and autism has had a negative effect (Holton *et al*., 2012).

They may also add to the political pressure for public investment in medical research, particularly if own-country papers are well-cited. In some countries, commentators on the significance of the research often come from medical research charities, which thereby gain exposure (Lewison et al., 2012). Print newspapers are in decline in many countries, but many have a strong web presence and are still important despite the growing influence of social websites such as Twitter and Facebook.

This part of the project was intended to show the effects of European NCD research on six groups of people:

- politicians and other decision-makers;
- senior officials and advisers;
- health-care administrators;
- medical personnel (doctors, other professionals);
- researchers;
- the general public.

It embarked on an ambitious programme of study on the coverage of research in the five NCDs during the 12-year period, 2002-13, in a large number of European newspapers. Some of these have their own searchable websites; others can be searched through full-text databases such as Factiva ©Dow Jones, to which KCL subscribes.

The results of this element of the project span the five NCD disease areas. For this reason, they will be reported in the Bibliometrics Work Package of Mapping NCDS.

4.9 Discussion and Conclusion

Measuring the impact research investments is a complex task because pathway from the conduct and publication of research to better health is usually indirect. Indeed, health improvements stem from a wide variety of interrelated research discoveries, made at different times and in different places. Other factors such as environmental pollution, individual health behaviors, wealth, education and public health campaigns also have an important bearing on the incidence of illness and further complicate the task of measuring research impact For this reason, research impacts are evident at a variety of nodes along the pathway, many of which are not specific to individual disease areas. Bibliometrics has the capacity to quantitative measure impact at several of these nodes, including: scientific research papers, funding sources (decisions on funding), citations, evidence base of clinical guidelines; and newspapers stories regarding research papers.

In terms of the number of published scientific papers, CRDs generated the smallest of the five results for NCDs, with just 18822 papers, of which 188 were in the SSCI only (1.0%). However, by comparison with the other NCDs, published research for CRDs shows a much greater European presence, averaging 56%, which is much higher than the percentages for the other four NCD areas (38% for ONCOL, 42% for CARDI, 40% for DIABE and 35% for MENTH). But, even in Europe, CRDs is a very small subject area, averaging only 0.8% of the papers in biomedicine overall. In terms of individual European countries, the UK published the most research regarding CRDs, more than twice the amount than France, the second leading EU MS, which itself publishes almost twice as much CRD research as expected, and similarly with Sweden and the Netherlands. As expected, UK based research had greater level of impact than research in other European MSs. Indeed, UK research was

over-cited by 2.5 times. The UK, together with New Zealand and the five Nordic countries, are over-cited by a factor of two (the spot for Iceland is not shown, but the citation ratio is 2.4). On the other hand, Japan, China and Brazil are all under-cited by a factor of two or more, and South Korea and Taiwan by more than that.

Within the area of CRDs, the individual disease conditions, such as asthma and COPD, are uequally represented, with asthma accounting for over 40% of the total number of published papers, and bronchiectasis barely 1%. In the UK and France, and also across the EU, most scientific papers are published in relation to asthma rather than COPD and other CRDs. In terms of funding, asthma, followed by COPD, receives the most funding (in terms of numbers of funders per paper). There was a large difference between the disease areas in terms of their propensity to attract citations, with a two-to-one variation between chronic obstructive pulmonary disease (COPD) and emphysema. Funding also varied with the subject matter and type of the research, with asthma and COPD receiving the most funding attention and bronchiectasis the least. Clinical papers were less likely to be funded than basic ones. We observed that papers with more authors tended to have more funding bodies

As for most NCDs, European research was better cited than the world average, although there was much variation between countries. Interestingly, there was generally poor correlation between the burden from particular CRDs and the amount of research published. Based on the levels of disease burden reported in the GBD study, the UK and France demonstrated a medium level of commitment to CRDs. Across the EU in general, MSs demonstrated a medium to high level of commitment to research for asthma and COPD. In this regard, there may be grounds for re-balancing some national research portfolios.

5 Conclusion

According to the Global Burden of Disease study, CRDs are the fifth leading cause of lost DALYs across Europe in terms of NCDs (5%). Breaking down the category into its major diseases, COPD is the largest cause of lost DALYs (30.2%) by comparison with asthma (1.21%). In the past few years, research investment in CRDs has grown. In terms of project aims, most CRD research has focused on the development of new drugs and therapies. In respiratory medicine, drugs are becoming increasingly important. The use of antibodies and antagonists to block and change disease mechanisms, oncogenes and metabolic pathways is relevant to key disease types like Asthma, COPD, pulmonary fibrosis, and pulmonary hypertension.

The European pharmaceutical sector has five companies in among the world's top ten pharmaceutical firms. The research pipeline for the top 10 European pharmaceutical companies suggests that firms seem to specialize in certain NCD categories. For example, pipeline data shows that SANOFI-AVENTIS, preferring to focus on other areas, does not have any CRD relevant molecules under development; other firms like GSK, however, are developing several. Overall, the European pharmaceutical sector has increased its commitment to R&D over the past four years. GSK is the only top 10 company to record a shrinking commitment to research investment. Some companies, like AstraZeneca, have recorded a massive increase in R&D spending. But most companies have recorded progressive of steady increases. By contrast, US levels of investment in R&D have been more mixed.

Interviews with stakeholders revealed several major themes with regard to the future of research in the area of CRDs. There was a recognition of the growing importance of stratified medicine, which several informants considered to be the future of research across the wider spectrum of NCDs. There was a need to find new ways of working with private sector. And there was a need to accommodate new research requirements within a wider strategic approach to the funding of NCD research which considered the needs of researchers for autonomy and the requirements of funders to demonstrate the effectiveness of their investments. In terms of the effectiveness of research investment, CRD funding demonstrates a significant European presence. And average 56% of paper published for CRDs are of European origin, which is much higher than the percentages for the other four (38% for ONCOL, 42% for CARDI, 40% for DIABE and 35% for MENTH). The internationalism was initially lower than in the other NCDs, but has caught up and even surpassed some of them.

The UK has the highest output in terms of CRD papers, more than twice as high as the second country, France. The UK is publishing almost twice as much as expected, as are Sweden and the Netherlands. On the other hand, Austria is publishing very little, and Germany, Norway and Switzerland are doing barely half of what might be expected considering their levels of GDP. Papers from Finland and Sweden attracted most funders, and fewer than one in five papers for CRD had no acknowledgements. These papers also had the most support from private-non-profit sources: 48% for Finland and 39% for Sweden. In 10 of the 15 countries, private-non-profit (PNP) sources out-numbered those using public moneys. Industry provided about 13% of funders on average, and international sources, 3.5% – notably the European Commission.

Levels of funding also varied with the subject matter and type of the research, with asthma and COPD receiving the most funding attention and bronchiectasis the least. Clinical papers were less likely to be funded than basic ones. Papers with more authors tended to have more funding bodies, and that (for the 2009 papers for which five-year citation counts were available) the number of citations was positively correlated with the number of funders.

6 References

Allarakhia, Minna and Steven Walsh (2011) “Managing knowledge assets under conditions of radical change: The case of the Pharmaceutical industry”, Technovation 31: 105–117.

Chiou, Jing-Yuan, Laura Magazzini, Fabio Pammolli, Massimo Riccaboni (2011) “The Value of Failure in Pharmaceutical R&D”, 4th ZEW Conference on Economics of Innovation and Patenting, Mannheim, May 19-20, 2011.

Cockburn, Iain M. (2007) “Is the Pharmaceutical Industry in a Productivity Crisis?” in Josh Lerner and Scott Stern (eds.) Innovation Policy and the Economy, Volume 7, Massachusetts: MIT Press. pp. 1 - 32

Drews, J. (1998) In Quest of Tomorrow’s Medicine . New York: Springer-Verlag.

Dutfield, G. (2003) Intellectual Property Rights and the Life Sciences Industries: A Twentieth Century History. Burlington: Ashgate Publishing Limited,.

[EFPI] The European Federation of Pharmaceutical Industries (2014) he Pharmaceutical Industry in Figures-Key Data 2014. Brussells: EFPI available online at http://www.efpia.eu/uploads/Figures_2014_Final.pdf

Foray, D. (2004) The Economics of Knowledge. Cambridge: MIT Press.

Hoyle, K. and Pries,F. (2009) “Repeat commercializers, the habitual entrepreneurs of the university–industry technology transfer”, Technovation 29: 682–689.

Koenig, Michael E.D. (1983) “A bibliometric analysis of pharmaceutical research”, Research Policy 12: 15-36

Lewison, G & Paraje, G (2004) The classification of biomedical journals by research level. *Scientometrics*,60(2) , 145-157.

Lewison G (2009) The percentage of reviews in research output: a simple measure of research esteem. *Research Evaluation*, 18 (1), 25-37.

Light, Donald W. Joel R Lexchin (2012) “Pharmaceutical research and development: what do we get for all that money?” BMJ 344: e4348.

Macleod, Malcolm R., Susan Michie, Ian Roberts, Ulrich Dirnagl, Iain Chalmers, John P A Ioannidis, Rustam Al-Shahi Salman, An-Wen Chan, Paul Glasziou (2014) “Biomedical research: increasing value, reducing waste”, The Lancet 383: 101-104

Murray, CJL, Ezzati, M, Flaxman, AD, Lim, S, Lozano, R, Michaud, C et.al. (2012) GBD 2010: design, definitions and metrics *The Lancet*, 380 (9859) 2063-2066.

Munos, Bernard H. and William W. Chin (2011) “How to Revive Breakthrough Innovation in the Pharmaceutical Industry”, Science Translation Medicine 3 (89): 1- 3

Narin, Francis and Richard P. Rozek (1988) Bibliometric Analysis of the U.S. pharmaceutical industry research performance”, Research Policy 17: 139-154.

Orsenigo, L., Pammolli, F. and Riccaboni, M. (2001) "Technological Change and Network Dynamics: Lessons from the Pharmaceutical Industry", Research Policy 30(3): 485–508.Hernández, Héctor, Alexander Tübke, Fernando Hervás, Antonio Vezzani, Mafini Dosso, Sara Amoroso, Nicola Grassano (2014) EU R&D SCOREBOARD: The 2014 EU Industrial R&D Investment Scoreboard. Brussels: European Commission. Available online at: http://iri.jrc.ec.europa.eu/scoreboard14.html

Pammolli, Fabio, Laura Magazzini, Massimo Riccaboni (2011) "The productivity crisis in pharmaceutical R&D", Nature Reviews 10: 428-438

[PHRMA] Pharmaceutical Research and Manufacturers of America (2015) "The Biopharmaceutical Industry: Creating Research, Progress and Hope", online at: http://www.phrma.org/about/biopharmaceutical_sector (accessed 29.05.2015)

Reppy, J., (2008) "A biomedical military–industrial complex?", Technovation 28(12): 802–811.

Rajendram R, Lewison G and Preedy VR (2006) World-wide alcohol-related research and the disease burden *Alcohol and Alcoholism* 41 (1), 99-106

Shaw JE, Sicree RA and Zimmel PZ (2009) Global estimates of the prevalence of diabetes for 32010 and 2030. *Diabetes Research and Cliical Practice*, 87 (1), 4-14.

Woodcock, J. (2010) "Precompetitive research: a new prescription for drug development?", Clinical Pharmacology and Therapeutics 87(5): 521–523.

Wright, John S.F., Paul G. Dempster, Justin Keen, Pauline Allen And Andrew Hutchings (2014) "How Should we Evaluate the Impacts of Policy? The case of Payment by Results and the 18 Week Patient Pathway in English Hospitals, Policy Studies, 35(1): 59-78.

Appendix 1

Table lxxiv: Purpose Sample Rlevant EU RFOs

NAME	TYPE OF RFO
AUSTRIA	
1. Christian Doppler Forschungsgesellschaft - Christian Doppler Research Association	Private no profit
2. Fonds zur Förderung der wissenschaftlichen Forschung - Austrian Science Fund (FWF)	Private no profit
3. Wiener Wissenschafts- Forshungs und Technologiesfonds - Vienna Science and Technology Funds (WWFT)	Public Institution
BELGIUM	
4. Fonds Wetenschappelijk Onderzoek - Research Foundation Flanders (FWO)	Private
5. Koning Bouwdewijn Stichting - King Baudouin Foundation	Private no profit
ESTONIA	
6. Eesti Teadusagentuur - Estonian Research Council	Public Institution
FINLAND	
7. Suomen Akatemia - Academy of Finland	Public Institution
FRANCE	
8. ANR- Agence National de la recherce – National Research agency	Public
9. Fonds de dotation recherche en santé respiratoire - Fund for respiratory research	Other
10. Institut national de la santé et de la recherche médicale - French National Institute of Medical Research (INSERM)	Public Institution
11. Ministère des Affaires sociales, de la Santé et des Droits des femmes - Ministry of Social affairs, Health and Women rights	Public Institution
GERMANY	
12. Deutsche Forschungsgemeinschaft - German Research Foundation (DFG)	Other
13. DLR Projektträger - Project Management Agency in DLR (DLR-PT)	Private
14. Helmut Horten Stiftung - Helmut Horten Foundation	Private no profit
15. Bundesministerium für Bildung und Forschung- Federal ministry of Education and research(BMBF)	Public
HUNGARY	
16. Hungarian Scientific Research Fund	Public Institution
INTERNATIONAL/EUROPEAN	
17. European Commission (EC)	Public Institution
18. European Federation of Allergy and Airways Diseases Patients' Association (EFA)	Private no profit
19. European Lung Foundation	Private no profit
20. European Research Council (ERC)	Public Institution
21. European Respiratory Society (ERS)	Private no profit
ITALY	
22. Fondazione Cassa di Risparmio di Lucca - Foundation of Bank of Lucca	Private no profit
23. Fondazione Cassa di Risparmio di Puglia - Foundation of Bank of Puglia	Private no profit
24. Fondazione del Monte di Bologna e Ravenna - Foundation of Bank of Bologna and Ravenna	Private no profit

25. Fondazione Roma - Foundation of Rome	Private no profit
26. Ministry of Health(Finalized research to the Regional Agency for health services)	Public Institution
27. Ministry of Health (Finalized research to Institute for Prevention and Safety at Work.)	Public Institution
28. Ministry of Education, University and Research (MIUR)	Public Institution
29. Ministry of Health (Co-financing for finalized research)	Public Institution
30. Ministry of Health (Finalized research to The Health Institute)	Public Institution
31. Ministry of Health (Finalized research to Regions)	Public Institution
32. Ministry of Health (Finalized research to the Institutes of care and recovery (IRCCS)	Public Institution
33. Ministry of Health (Young researcher funds)	Public Institution
34. Regione Emilia Romagna - Emilia Romagna Region	Public Institution
IRELAND	
35. Asthma Ireland	Private no-profit
36. Health Research Board	Public Institution
37. Irish Research Council	Public Institution
LATVIA	
38. Study and Research Administration, Ministry of Education and Science Latvia	Public Institution
LITHUANIA	
39. Research Council of Lithuania	Public Institution
NETHERLAND	
40. Dutch Technology Foundation (STW)	Public Institution
41. Lung Foundation Netherlands	Private no profit
NORWAY	
42. The Research Council of Norway	Public Institution
PORTUGAL	
43. Fundaco para ciencia e a tecnologia – Fundation for Science and technology	Public Institution
POLAND	
44. National Centre for Research and Development	Public Institution
45. National Science Centre	Public Institution
SLOVAKIA	
46. Agency to support research and development	
47. Ministry of Health	Public Institution
48. Slovak Academy of Science	Public Institution
49. Vedecká grantová agentúra Ministerstva školstva- Scientific Grant Agency of the Ministry of Education (VEGA)	Public Institution
SPAIN	
50. Consejería de Sanidad. Comunidad de Castilla León - Castilla y Leon Regional Government Health Department	Public Institution
51. Centro para el Desarrollo Tecnológico Industrial - Centre for Industrial Technological Development (CDTI)	Public Institution
52. Departament Salud Generalitat de Catalunya - Department of Health of Catalonia	Public Institution
53. Consellería de Sanitat. Generalitat Valenciana - Department of Health of Valencia	Public Institution
54. Departamento de Salud. Gobierno de Navarra. - Department of Health Navarre Government	Public Institution
55. Departamento de Salud del Gobierno Vasco- Department of Health of the Vasque Government	Public Institution

56. Fundación BBVA - Foundation BBVA	Private
57. Fundación para el fomento en Asturias de la investigación científica aplicada a la tecnología - Foundation for Promotion of Applied Scientific Research in Technology. Biosanitary Research Unit (FICYT)	Private
58. Fundación Mapfre - Foundation Mapfre	Private
59. Fundación Mateu Orfila - Foundation Mateu Orfila	Private
60. Fundación Mutua Madrileña - Foundation Mutua Madrileña	Private
61. Fundación Canaria de Investigación y Salud - Foundation of Research and Health of the Canary autonomous region (FUNCIS)	Public Institution
62. Instituto de Salud Carlos III - Institute of Health Carlos III (ISCIII)	Public Institution
63. Ministerio de Economía y Competitividad - Ministry of Economy and Competitiveness	Public Institution
64. Consellería de Economía e Industria. Xunta de Galicia - Regional Ministry of Economy and Industry of Galicia	Public Institution
65. Consejería de Economía, Innovación, Ciencia y Empleo. Junta de Andalucía - Regional Ministry of Economy, Innovation, Science and Employment of Andalusia	Public Institution
66. Consejería de Igualdad, Salud y Políticas Sociales. Junta de Andalucía - Regional Ministry of Health and Social Politics of Andalusia	Public Institution
67. Consejeria de Sanidad y Asuntos Sociales de Castilla La Mancha - Regional Ministry of Health and Social Politics of Castilla La Mancha	Public Institution
68. Consejería de Salud y Politica Social. Extremadura - Regional Ministry of Health and Social Politics of Extremadura	Public Institution
69. Sociedad Española de Neumología y Cirugía Torácica (SEPAR)	Public Institution
70. Conselleria de Sanidade. Xunta de Galicia. Investigacion e innovacion sanitaria - Regional Ministry of Health of Galicia	Public Institution
71. Consejería de Sanidad. Madrid - Regional Ministry of Health of Madrid	Public Institution
72. Departamento de Sanidad, Bienestar Social y Familia. Gobierno de Aragon - Regional Ministry of Health, Social Politics and Family of the Aragon Government	Public Institution
73. Fundación Séneca. Agencia de ciencia y tecnología. Región de Murcia - Seneca Foundation. Agency for Science and Tecnology of Murcia	Public Institution
74. Foundation Fundación La Marató de TV3 - The Marato of TV3	Private non profit
SWITZERLAND	
75. Swiss National Science Foundation	Public Institution
UNITED KINGDOM	
76. Asthma UK	Private no profit
77. British Lung Foundation	Private no profit
78. Chief Scientist Office Scottish Government Health Directorates support research through NHS Research Scotland	Public Institution
79. Health Science Scotland	Public Institution
80. Medical Research Council (MRC)	Public Institution
81. Wellcome Trust	Private no profit

Appendix 2

Table lxxv: Purposive Sample Search Words

List of Search Words	
COPD	Pulmonary hypertension
Chronic obstructive pulmonary diseases	Emphysema
Asthma	Lung
Non-communicable	Air
Cystic Fibrosis	Smoking
Bronchitis	Nitric Oxide synthese

Appendix 3

Search strategy for MDs' clinical trials from www.clinicaltrials.gov

The search was performed according to top MD companies.

Search strategy:

1. Interventions: device
2. Sponsor (lead):
    - Johnson & Johnson
    - General Electric Co.
    - Medtronic Inc
    - Siemens AG
    - Baxter International Inc
    - Fresenius Medical Care AG & Co. KGAA
    - Koninklijke Philips NV
    - Cardinal Health Inc.
    - Novartis AG (Alcon)
    - Covidien plc
    - Stryker Corp.
    - Becton, Dickinson and Co.
    - Boston Scientific Corp.
    - Essilor International SA
    - Allergan Inc. (Actavis)
    - St. Jude Medical Inc.

Only ongoing/completed clinical trials between 2011 and 2015 have been considered. Moreover only MDs for non-communicable diseases have been included.

We excluded terminated clinical trials and those with unknown/not verified status.

Appendix 4

Search strategy for PMA (Premarket Approval) of medical devices at FDA

Premarket approval (PMA) is the FDA process of scientific and regulatory review to evaluate the safety and effectiveness of Class III medical devices. Due to the level of risk associated with Class III devices, FDA has determined that a PMA is needed in order to obtain marketing clearance. PMA is the most stringent type of device marketing application required by FDA.

The search was performed according to indication in the five NCD areas (cancer, respiratory disease, cardiovascular disease, diabetes, mental health) and not according to top MD companies.

Search strategy:

3. Date: 01/01/2011 – current date (June 2015)
4. Keywords:

- ONCOL:
  - cancer
- CARDI:
  - cardiovascular
  - stroke
- DIABE:
  - diabetes
- RESPI:
  - respiratory
  - pulmonary
  - pneumonia
  - pharyngitis
  - rhinitis
  - bronchitis
  - asthma
  - allergy
  - COPD
  - emphysema
  - lung
  - apnea
- MENTH:
  - mental
  - depression
  - schizophrenia
  - dementia
  - alzheimer
  - brain
  - pain
  - epilepsy
  - addiction
  - smoke/smoking
  - behavior/behavioral

- anxiety
- eating disorder
- sleep

Appendix 5

Search strategy for de novo medical devices at FDA

The FDA added the de novo classification option as an alternate pathway to classify novel devices of low to moderate risk that had automatically been placed in Class III after receiving a "not substantially equivalent" (NSE) determination in response to a premarket notification [510(k)] submission. Devices that are classified through the de novo process may be marketed and used as predicates for future 510(k) submissions.

The search was performed first according to top MD companies, but we did not find any result. The search strategy adopted was the following:

1. Decision date: 01/01/2011 – current date (June 2015)
2. Requester name:
    - Johnson & Johnson
    - General Electric Co.
    - Medtronic Inc
    - Covidien plc
    - Siemens AG
    - Baxter International Inc
    - Fresenius Medical Care AG & Co. KGAA
    - Koninklijke Philips NV
    - Cardinal Health Inc.
    - Novartis AG (Alcon)
    - Stryker Corp.
    - Becton, Dickinson and Co.
    - Boston Scientific Corp.
    - Essilor International SA
    - Allergan Inc. (Actavis)
    - St. Jude Medical Inc.

Then, we performed a second search using as filter only the decision date (from 01/01/2011 to June 2015). We included only MDs for non-communicable diseases and MDs which have not received 510(k) clearance yet.

Appendix 6

Search strategy for EuroScan medical devices

The search was performed according to indication in the five NCD areas (cancer, respiratory disease, cardiovascular disease, diabetes, mental health) and not according to top MD companies.

Search strategy:

1. Technology–type: device
2. Specialty:
    - ONCOL: Oncology & radiotherapy
    - CARDI: Cardiovascular disease & vascular surgery
    - DIABE: Endocrine, nutritional and metabolic
    - RESPI: Respiratory disease & thoracic surgery
    - MENTH: Mental health, addiction & learning difficulties

Only MDs approved between 2011 and 2015 have been considered.

Appendix 7

Search strategy for top MD companies research outputs

The search was performed on Web of Science database. As ONCOL, MENTH and CARDI have yet to be coded, specific search terms were used to filter the RFOs. It must be noted that the aliases/ spelling errors in naming the RFOs by WoS means that not all them may have been captured or that other organizations may have accidentally also been captured due to the simplistic terms used. In cases where a company had only generic codes, the name was searched instead of the code. In RESPI and DIABE the funding data that were searched also include papers where the company was listed among the addresses; for the three other NCDs only the funding data were searched. It has to be noted that some of the companies also make pharmaceutical drugs and the counts of papers may include them.

Appendix 8

Table lxxvi: Semi Structured Interview Questionnaire

Name: **Organization:** **Date:**
Past and Existing Funding Strategies and Programmes for CRDs: ➢ Can you describe some of the impacts of these programmes and strategies ➢ In what ways have the impacts been positive? ➢ In what ways have the impacts been negative?
The Challenges for the Future: ➢ Can you describe some of the challenges for future CRDs research? ➢ Can you describe some of the funding challenges for CRDs research?
Recommendations for Future EC Activity on CRD: ➢ How would you describe the current research gaps for CRDs ➢ How would you describe the future priorities for CRDs research funding ➢ How can the EC position itself to address the gaps and priorities? ➢ What do you think the EU should be doing with regard to CRDs funding and research?
Any other Relevant Information: ➢ Can you recommend any other key stake holder to who we should speak?