BENCHMARK REPORT ON THE PERFORMANCE OF THE NETHERLANDS IN CONDUCTING CLINICAL DRUG TRIALS

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Executive Summary

Introduction

An environment that facilitates research and attracts investment for drug research contributes to the health and wealth of a nation and will contribute to long term economic growth. Traditionally, the Netherlands has a major role in the conduct of clinical drug trials. Limited data is available on recent trends in worldwide participation of countries in clinical drug trials. The benchmark analysis described in the current report delineates the position of different regions and countries (with emphasis on the Netherlands) in conducting clinical drug research on the basis of the quantity and quality of scientific clinical drug trial publications.

Methodology

The number of scientific publications on clinical drug research over the period 1995-2007 indexed in PubMed and Thomson Scientific Web of Science was used as a proxy for quantitative clinical drug research activity. The international citation impact of these publications was used as a proxy measure for the qualitative clinical drug research output.

Results

Position of Europe compared to the rest of the world

Western Europe is leading in terms of crude publication output closely followed by North-America.

The publication output per capita is slightly lower in Europe compared to North-America.

A trend analysis over the period 1995-2007 shows a marked increase in quantitative publication output in Central and Eastern Europe as well as in Latin America.

North-America and Oceania exceed Western Europe in terms of the average number of citations that publications receive.

Position of the Netherlands compared to other EU countries

Within Europe, the Netherlands belongs to the top-5 countries in terms of absolute and per capita clinical drug research publications.

The Dutch average citation rates attenuated considerably over the period of analysis

Conclusion

Based on publication output as a proxy for the quantity of clinical drug research, the Netherlands is performing relatively well as compared to other European countries. However, the scientific visibility, quality, and impact of the conducted research has deteriorated over the last decade and needs proper attention in order to remain at the forefront of clinical drug research.

1 Introduction

Clinical drug research forms an essential part of a country's research and innovation agenda. In addition to other research, clinical research does not only produce new knowledge but it also translates into better ways to treat diseases and improved healthcare. Studies addressing the socio-economic effects of medical research have clearly shown high returns on investment for medical research.[1,2] A report from the UK Medical Research Council concluded that investment in medical research has improved the living standards and had a positive impact on long-term national productivity and economic growth.[3] Thus, an environment that facilitates research and attracts investment for drug research contributes to the health and wealth of a nation and will contribute to long run economic growth.

Traditionally, the Netherlands has a major role in the conduct of clinical trials. To guarantee a high participation level of the Netherlands in drug research in the future and to create a competitive knowledge based economy, we first need to establish how the Netherlands compared to Europe and the world is performing in conducting medical drug research. Second, we need to establish which factors are associated with its performance in order to find tools to sustain or improve the participation level of the Netherlands for the future.

To date there is no comprehensive database on all ongoing or finished clinical drug research worldwide and consequently systematic data on the position of countries in conducting these studies is lacking. The limited number of tools and difficulties to provide valid estimates has further hampered studies to precisely determine the comparative position of countries. This leads to different views and opinions on the comparative research productivity in different parts of the world.[4,5] The working group "Benchmarking the Netherlands in conducting clinical drug trials" aims to delineate the position of the Netherlands in conducting clinical drug trials.

To achieve this goal the working group will (i) assess and compare the number of publications arising from clinical drug trials among different countries or geographic regions, (ii) assess the participation of countries in clinical drug trials by determining the number of trials registered in clinical trial registries and submitted to the Dutch competent authority, (iii) conduct interviews with stakeholders to address bottlenecks and pitfalls in the conduct of clinical drug trials in the Netherlands. The present report benchmarks countries on the basis of the quantity and quality of scientific clinical drug trial publications. The results of the benchmark analysis based on clinical trial registries and trials submitted to competent authorities as well as the views of stakeholders on clinical drug research in the Netherlands will be presented in two additional reports.

2 Methods

2.1 Data sources

Clinical drug research is defined here as clinical research assessing efficacy and safety of small-molecule pharmaceuticals and adjuvants, biologics, and vaccines. The PubMed database was searched to identify all research-based publications on clinical drug trials in the period from 1995 until 2007. Publications are not instantly indexed in the PubMed or Thomson Scientific Web of Science database. Therefore it is not yet possible to benchmark the Dutch position based on its publications in 2008 and 2009. We searched for the medical subject heading (MESH) terms 'Clinical Trial' and ('Pharmaceutical Preparation', 'drug' or 'drugs'). Selected publication document types included *research publications, research notes, letters,* and *reviews*. After completing the query of the PubMed database, the gathered publications were matched with *Thomson Scientific Web of Science*-indexed publications (according to the name of first author, volume of journal, first page and year of publication) to obtain the full set of information on the country of origin of all authors. A publication was attributed to a geographical area (i.e. country or continent) if that area was included in an affiliate address of one of the authors. Hence, a publication was assigned to all geographical area listed in the author's address information.

2.2 Bibliometric indicators

Quantitative and qualitative indicators were used to describe international clinical drug research output. The number of medical drug trial publications was used as a proxy measure for the quantitative output of a country in clinical drug trials. Next to publication counts, we also report on citation counts. In order to obtain those citation counts we applied windows of four year in which publications are cited by other publications that are listed within the Thomson Scientific Web of Science database. For instance, the citation count for the period 1995-1998 counts the number of citations in the period 1995-1998 of articles that are published in the period 1995-1998. The citation rate, calculated as the ratio of the total number of citations that each country received over the total number of publications of that country was used as a measure of international scientific impact and as a proxy measure for the scientific relevance and quality of clinical drug trial output.

2.3 Associate factors

We also report on a couple of analyses we conducted to identify associate factors of drug clinical research publications. First of all a convergence analysis was conducted in which we try to establish a relationship between the publication output of countries and their relative growth in publication output. Clinical trials have traditionally been carried out in relatively wealthy locations, yet in recent years a shift towards non traditional research locations has been noted.[6,7] We therefore expected that countries with relatively few publications in the

first year of analysis (1995) tended to grow faster over the subsequent period (1995-2007). Second, we analyzed whether investments in Research and Development (R&D) are associated with drug clinical research publications. More specifically, we regressed the investments in pharmaceutical R&D by industry on the number of publications in each country and we also regressed the investments in clinical R&D by higher education on the number of publications in each country. Due to limited data availability we restricted these analyses to the group of countries that are either OECD member or a close partner of the OECD. Third, we checked the validity of the publication data by analyzing the relation between a country's publication output and the participation of countries in clinical drug trials as assessed by the number of clinical trials registered in www.clinicaltrials.gov.

3 Results

3.1 Database

We indentified 283.493 clinical drug research publications in the Thomson Scientific Web of Science database for the period 1995-2007. The number of publications indexed by the Web of Science database has increased every year. This is in line with the general growth of the scientific literature. The total number of clinical drug research publications increased from 16.719 in 1995 to 28.291 in 2007.

3.2 Bibliometric Indicators

3.2.1 Position of Europe compared to the rest of the World

Figure 1 shows world maps of the publication output (upper-panel or A) and publication growth (lower-panel or B) per country. The countries that publish intensively are mainly located in Western Europe and North America. Yet, growth of publication output mainly occurs in non-traditional research locations including Central and Eastern European countries (e.g. Czech Republic, Romania and Estonia) and some Latin American and Asian countries (e.g. Brazil, China, South-Korea, Iran).

Western Europe - defined as the 15 countries that were EU member states during the entire period of analysis (1995-2007) including Switzerland, Norway and Iceland – consistently produced the largest number of clinical drug research publications over the period 1995-2007, closely followed by North America (Figure 2A). However, the per capita publication output of Western European drug clinical research publications is slightly lower than the per capita publication output of North America. More exactly, Western Europe produced 33.42 publications per million inhabitants in 2007, whereas North America generated 34.67 publications per million inhabitants in 2007 (Figure 2B). Of all world regions, the publication density is highest in Oceania (i.e. Australia and New Zealand) and increased more steeply since 2002 compared to other regions. The African continent generated the lowest number of publications.

A trend analysis of publication output based on Figure 2 reveals a 72% (absolute increase of 5.629 publications) increase in the Western European publication output over the period 1995-2007. Although Western Europe outpaces North America – with a growth rate of 62% (absolute increase of 4.448 publications) - in this respect, the observed Western European growth rates are not as high as those observed for other world regions. In particular, Latin America (222%; absolute increase of 696 publications) and Central and Eastern Europe (406%; absolute increase of 1.275 publications) show a marked relative increase in their number of publications. Despite this remarkable growth, absolute differences between those geographical regions and Western Europe remain considerable at the end of the observation period (Figure 2).

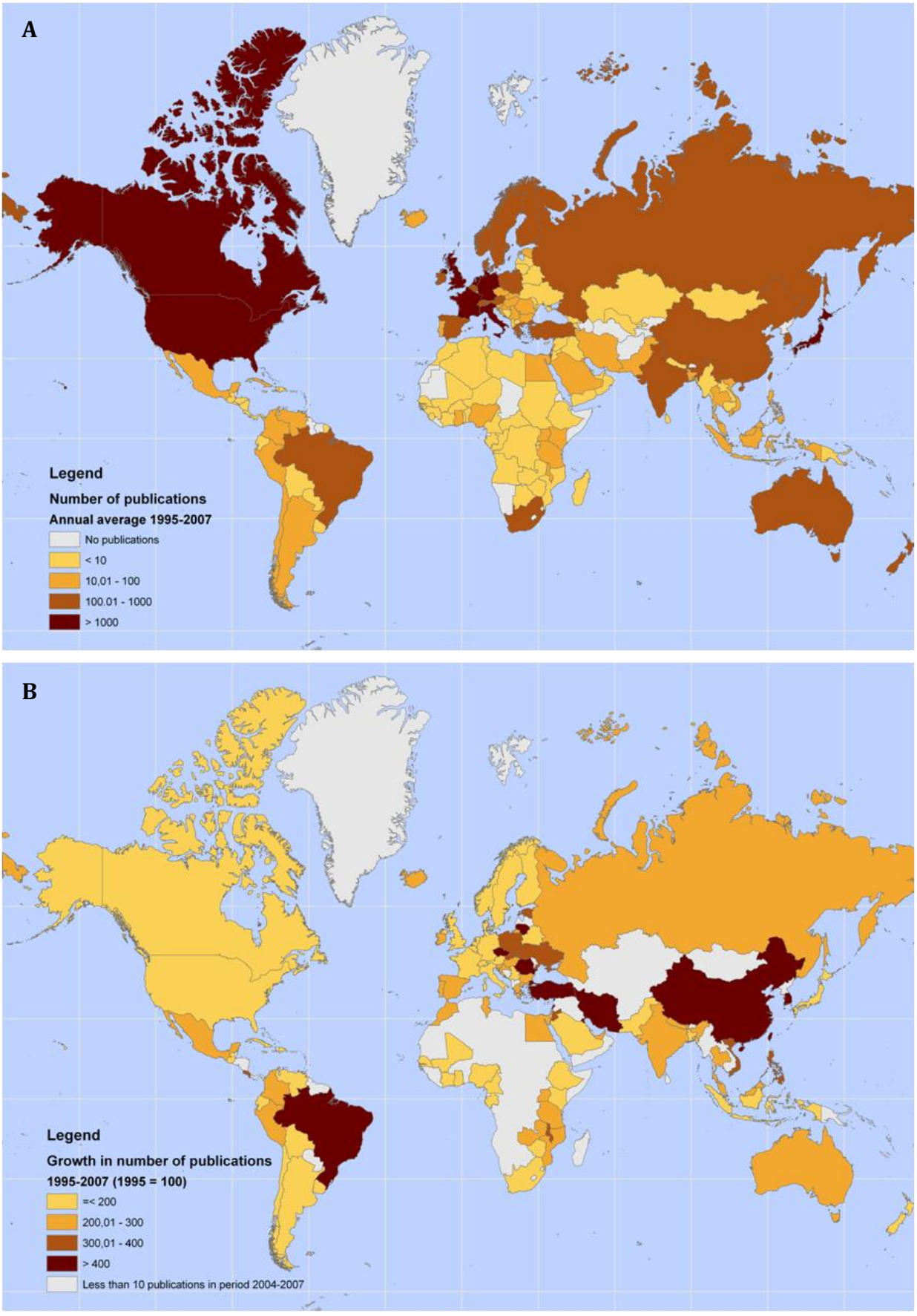

Figure 1: Publication output and publication growth. Upper panel (A): Annual average number of publications in the period 1995-2007. Lower panel (B): Growth in number of publications in the period 1995-2007. Four-year moving averages were used to control for yearly fluctuations.

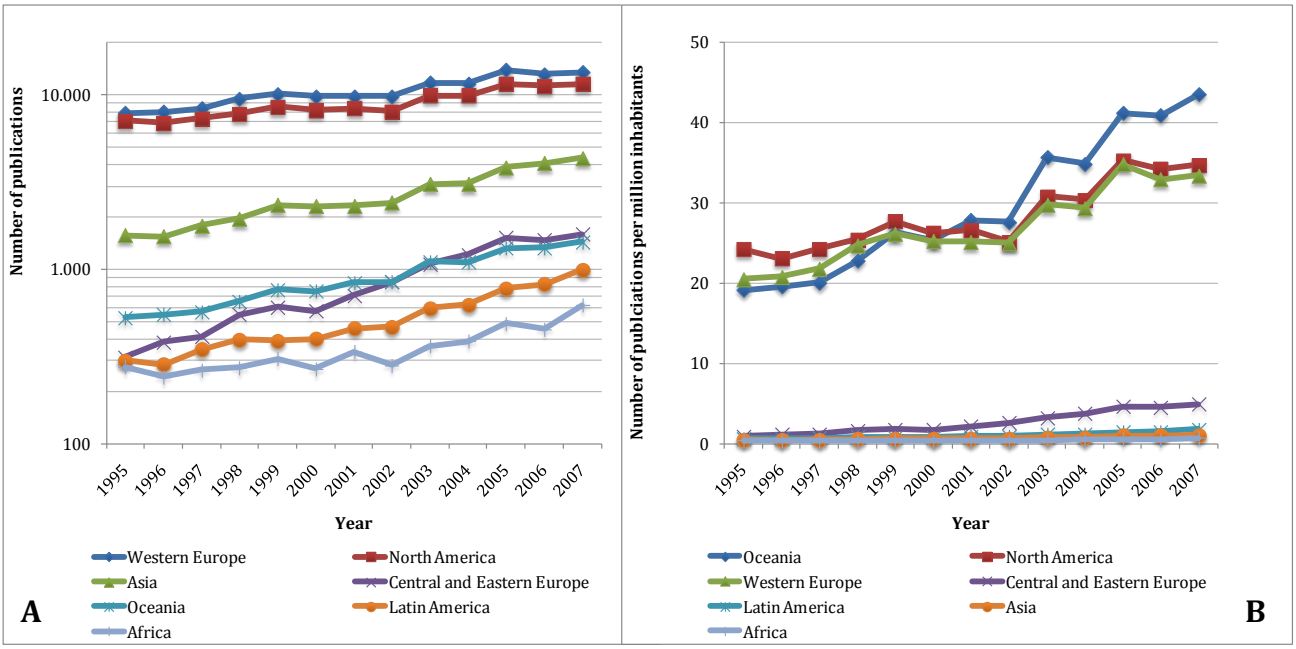

Figure 2: Publication output of geographical regions. (A) Trend in total publication output in the period 1995-2007 and (B) trend in total publication output per million in habitants in the period 1995-2007.
Western Europe consists of the EU-15 countries and Iceland, Norway and Switzerland. *Central and Eastern Europe* consists of other EU countries. *North-America* consists of the USA and Canada. *Asian* continent consists of: Japan, China, Korea, and neighbouring countries together with the Middle East. *Latin America* consists of Central and South America. *Oceania* consists of the following countries: Australia, New-Zealand and Philippines Islands.

The value of publications to the scientific community can be assessed in multiple ways. On a macro-scale however, citations to publications are a relevant marker for visibility and scientific impact. An analysis of average citation rates of publications (Figure 3) among world regions shows a rather different picture than the analysis of publication output (Figure 2). Publications originating from North America show the highest average citation rates, followed by Oceania. Western Europe only takes a third position in this respect and performs only slightly better than other world regions (with the exception of Asia) in terms of average citation rates per publication.

Based on a world map of the citation impact of countries (Figure 4), we observe that the scientific impact of clinical drug research is especially high for publications originating from a group of Central and Eastern European countries (e.g. Poland, Slovakia, Hungary, Romania).

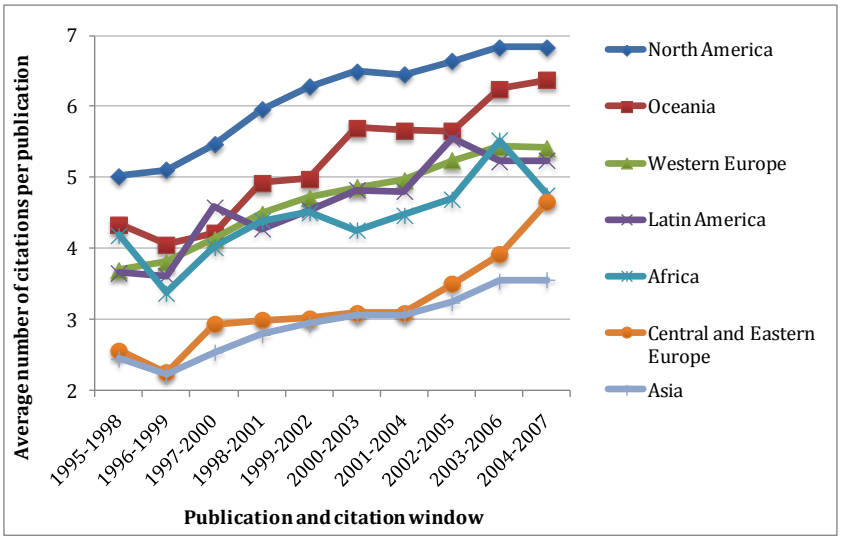

Figure 3: Citation rates of geographical regions. Average number of citations per publication excluding organizational self-citations

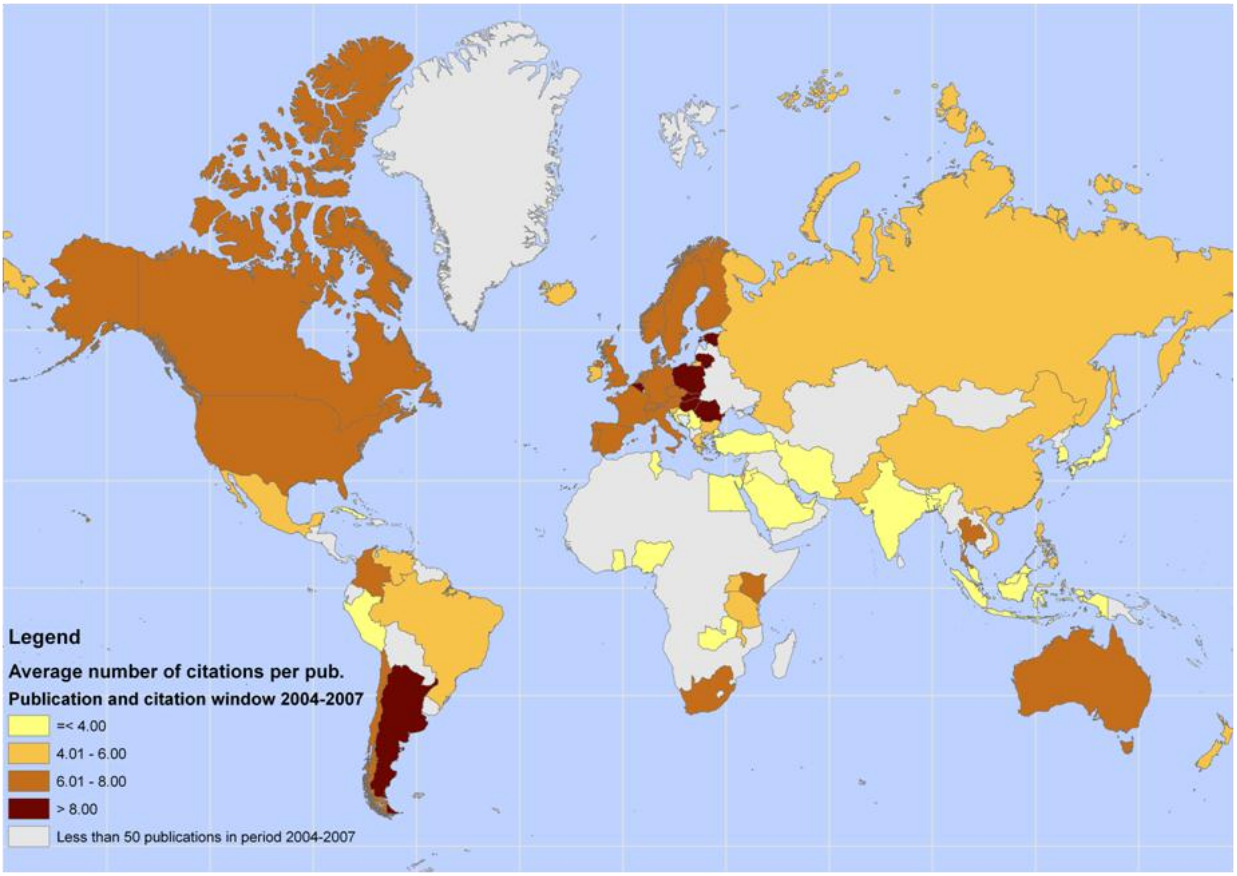

Figure 4: Average number of citations per publication. The publication and citation window 2004-2007 was used as dataset for this figure.

This conclusion still holds when controlling for the fact that Central and Eastern European countries tend to specialize in cardiovascular research publications which receive on average more citations per publications than publications from other fields. This conclusion is also supported by Figure 3, which shows a steep increase in the citation rate of Central and Eastern European countries, especially in later years of analysis. The impact of Western European and North American countries tend to be above average but is not among the highest.

Another way to assess the scientific value of publications is the number of articles published in highly cited scientific journals. We therefore looked at the geographical distribution of publications in six selected top-journals (i.e. American Journal of Medicine, Annals of Internal

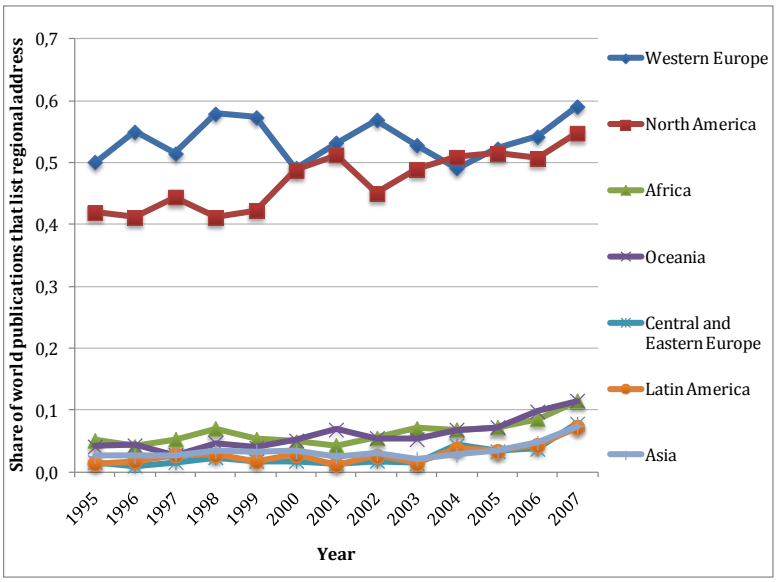

Figure 5: Publication output in selected top journals. Share of publications that list an address in geographical region.

Medicine, British Medical Journal, Journal of the American Medical Association (JAMA), Lancet, New England Journal of Medicine). The percentage of publications that contain at least one Western European address increased from 50% to 59% over the period 1995-2007 (Figure 5). With the exception of 2004, this is the highest share of all geographical regions, although North America follows closely.

In Figure 6 we decompose the publication output into seven research areas: cardiovascular, endocrinology, infectious diseases, nervous system, nephrology, oncology and pulmonology. The Western European publication profile (2004-2007) is very similar to the World's distribution of publication output over research areas. In other words, the publication output of Western Europe does not show a specialization in a particular research area. A marked difference is observed in Africa which seems to be specialized in infectious diseases research.

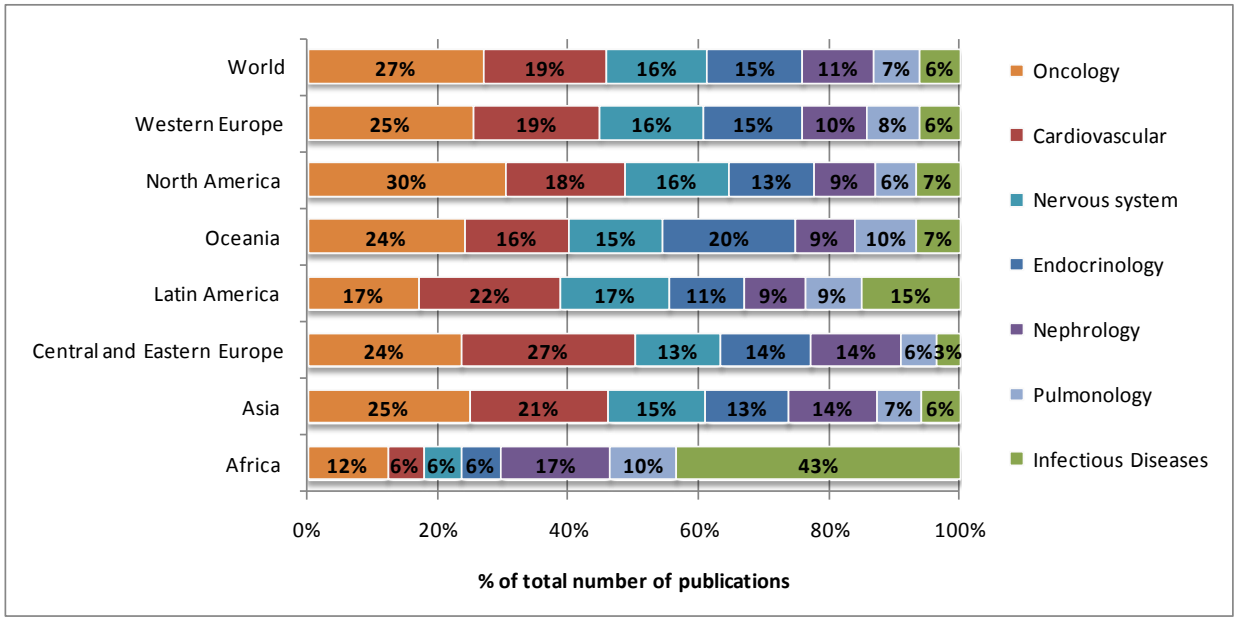

Figure 6: Distribution of publications over research areas for the period 2004-2007. Labels within bars indicate the share of the respective research area in the total sum of publications of the seven research areas.

3.2.2 Position of the Netherlands compared to other EU countries

When focusing on the publication output of a group of selected European countries[1], we observe wide variations. In absolute terms United Kingdom, Germany and Italy dominate (Figure 7A). The Netherlands competes with France for the fourth position when looking at the total number of clinical drug research publications. In terms of publications per capita, the Netherlands also holds a stable fourth position behind Denmark, Switzerland and Sweden (Figure 7B). European countries that show a marked increase in publication output are Czech Republic (616%), Poland (392%) and Greece (325%). The Netherlands has a growth rate of 112% and performs in this respect relatively well in comparison to their main competitors such as Denmark (82%), Switzerland (109%), Sweden (63%) and France (81%).

[1] The largest countries in terms of total publication output are included.

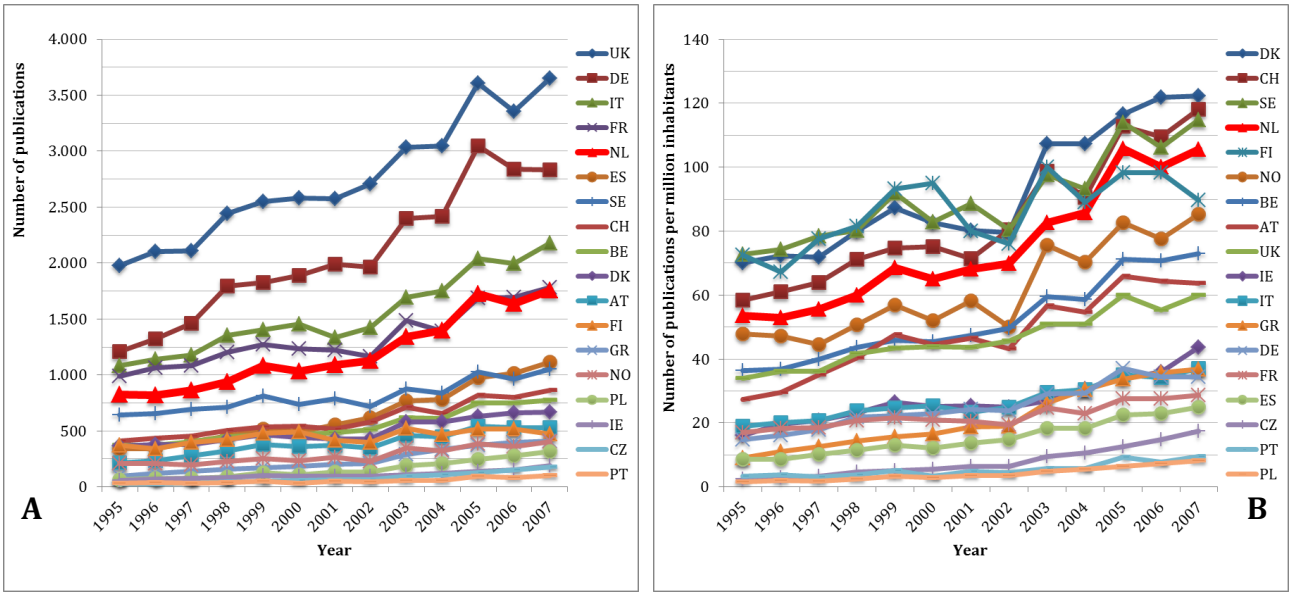

Figure 7: Publication output for selected European countries. (A) Trend in total publication output in the period 1995-2007 and (B) trend in total publication output per million inhabitants in the period 1995-2007.

Abbreviations: AT, Austria; BE, Belgium; CH, Switzerland; CZ, Czech Republic; DE, Germany; DK, Denmark; ES, Spain; FI, Finland: FR, France; GR, Greece; HU, Hungary; IE, Ireland; IT, Italy; NL, Netherlands; NO; Norway; PL, Poland; PT, Portugal; SE, Sweden; SI, Slovenia; SK, Slovakia; UK, United Kingdom.

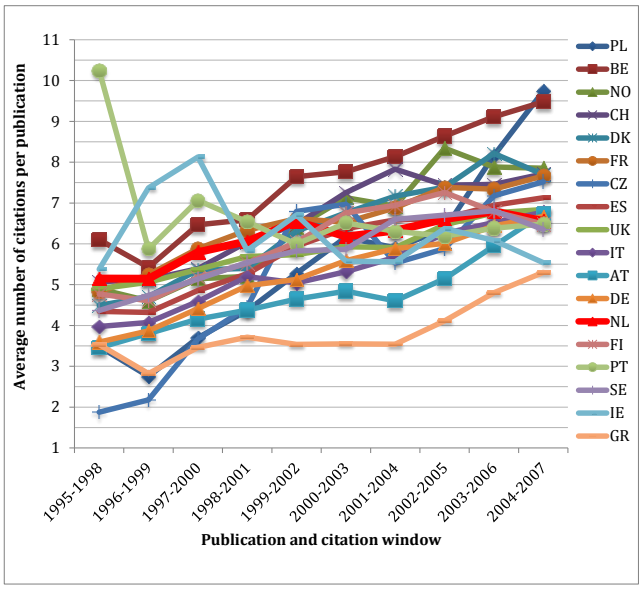

Figure 8: Citation impact for selected European countries. Average number of citations per publication in four year time intervals in the period 1995-2007. Abbreviations are lister in legend Figure 7.

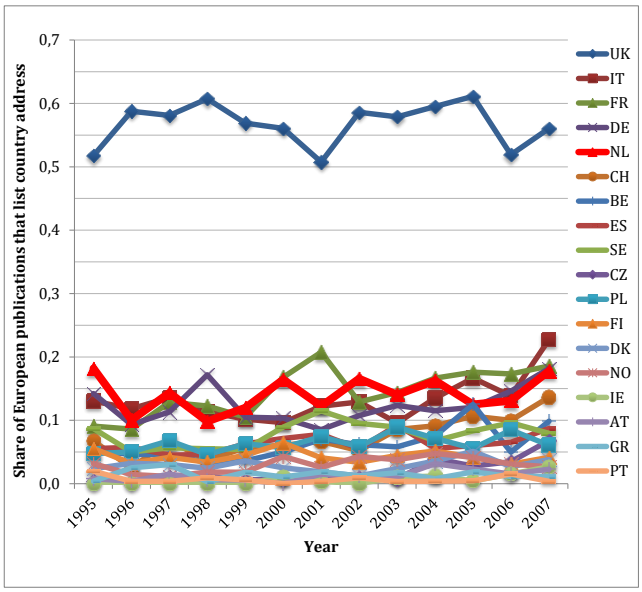

Figure 9: Share of publications in six selected top journals. Trend in share of publications for selected European countries in the period 1995-2007. The total number of publications is the total for EU27. Abbreviations are listed in legend Figure 7.

The citation scores of Dutch clinical drug research in comparison to its European competitors is shown in Figure 8. The data illustrate that the Netherlands is not doing very well in terms of citation impact. More specifically, the Netherlands ranks only 13th out of 18 selected European countries in the period 2004-2007. During the nineties this relative position was much higher and we can therefore conclude that the relative visibility of Dutch clinical drug research in the scientific literature has deteriorated considerably. Figure 9 shows a better picture for the Netherlands in that the share of publications in highly cited research journals arising (partly)

from the Netherlands belongs to the top 3 in Europe. Clearly, the UK outpaces all EU countries which is likely the consequence of the "home advantage" since the British Medical Journal and the Lancet are UK based journals.[8]

In terms of specialization profile, the Netherlands does not show marked deviations from either the overall distribution of research areas or the distribution of research areas within the 27 member states of the European Union (Figure 10). Medical drug research in oncology is slightly overrepresented in the Netherlands, whereas research into infectious diseases is slightly underrepresented.

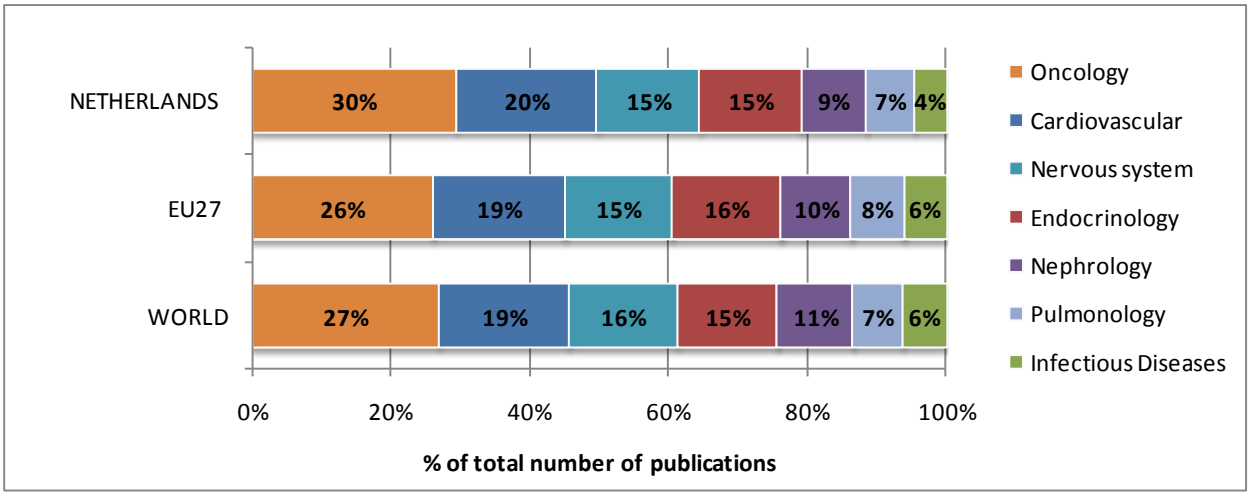

Figure 10: Distribution of publications over research areas for the period 2004-2007. Labels within bars indicate the share of the respective research area in the total sum of publications of the seven research areas.

3.3 Associate factors

To examine how the relative position of the Netherlands in clinical drug research is changing and to indentify factors that are associated with publication output we conducted three regression analyses. In Figure 10 we relate the publication output of countries in 1995 with their relative growth over the period 1995-2007. In Figure 1 we already observed that geographic regions with relative low publication output in 1995 (e.g. Central and Eastern Europe, Latin America) tend to grow relatively fast. Indeed, in a convergence analysis we also observe a significant negative relationship (R^2=0.49, P<0.001). This suggests that countries with relatively low publication output in 1995 tend to grow faster in the subsequent period than countries with a relatively high publication output. The position of the Netherlands in Figure 10 is slightly above the regression line, indicating that the growth of publication output is slightly higher than could be expected on the base of its publication output in 1995.

Figure 11 and Figure 12 reveal that the publication output of a country is associated with pharmaceutical R&D investments of industry (R^2=0.63, P<0.001) and especially with the R&D investments in medical higher education (R^2=0.80, P<0.001). Additional investments in

Research and Development are highly likely to result in more publication output. It should be noted however that these associations do not directly imply causality.

Finally, Figure 13 relates the publication output of countries in 2006-2007 to the registration of clinical trials in www.clinicaltrials.gov. We selected all registered trials on drugs and/or biologicals that started in the year 2005-2006. Based on this information, we find a striking correlation between the participation of countries in clinical trials as registered in www.clinicaltrials.gov and subsequent publication output of countries (R^2=0.83, P<0.001). This suggests that publication output can be considered a reliable indicator of worldwide clinical trial activity.

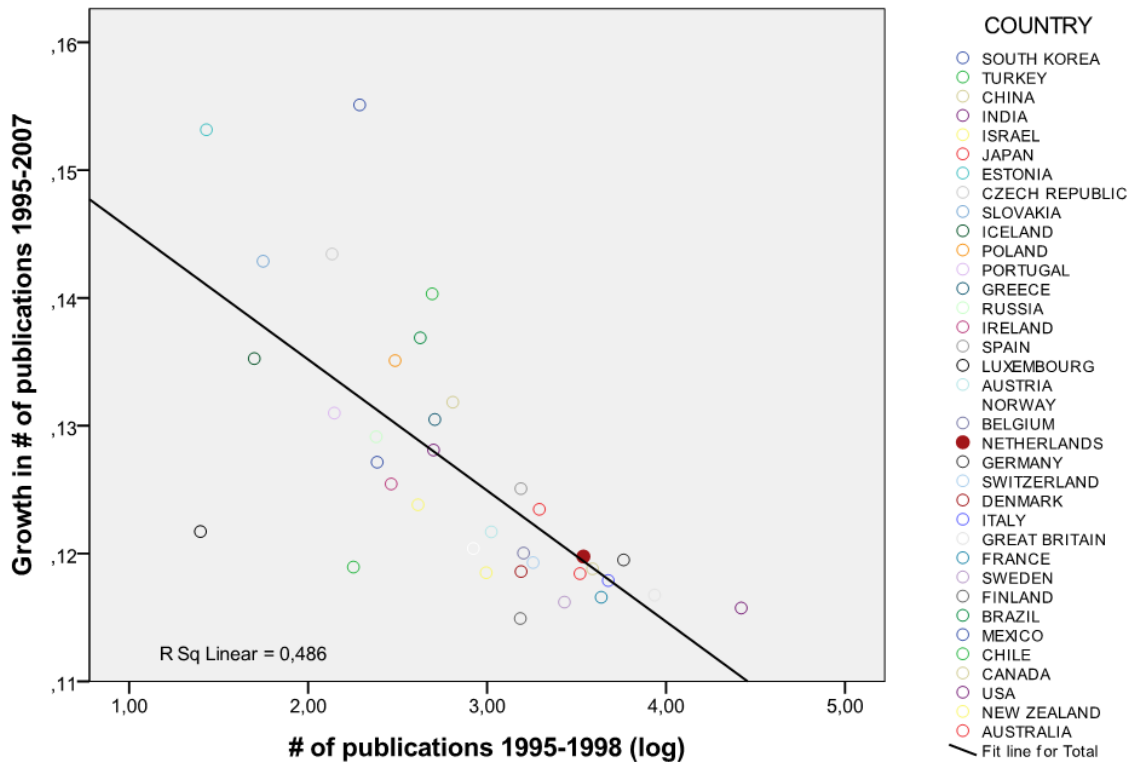

Figure 10: Convergence analysis for OECD countries. X-axis: logarithm of total number of publications in the period 1995-1998. Y-axis: growth in number of publication in the period 1995-2007: $(1/t(\log(Y)) / \log(Y_{t-1})$.

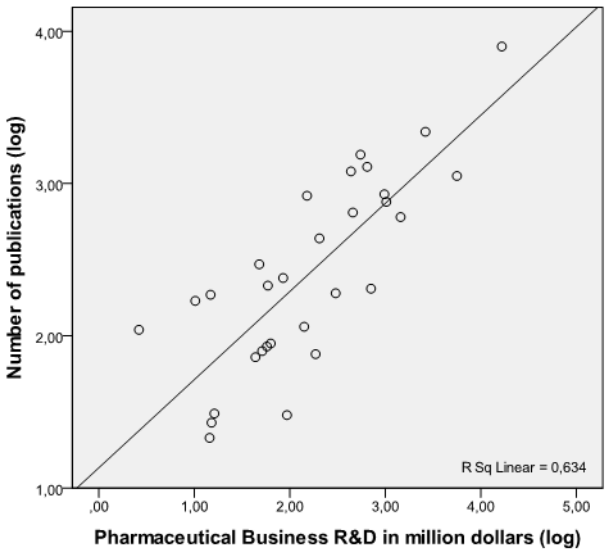

Figure 11: Relation between business investments in pharmaceutical research and development and the number of publications for available years.

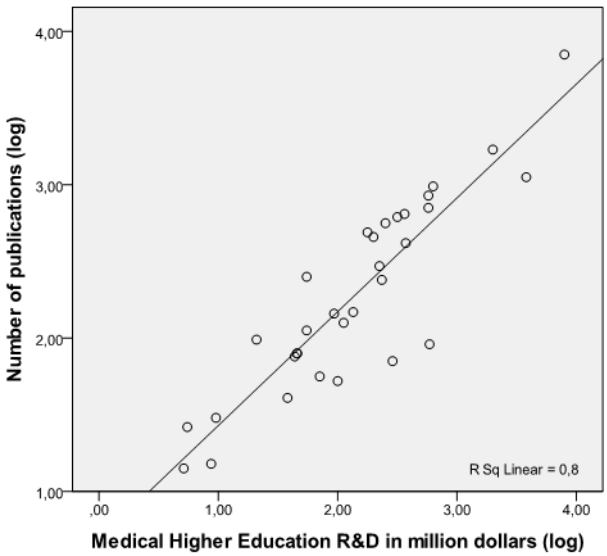

Figure 12: Relation between research and development investments in medical higher education and the number of publications for available years.

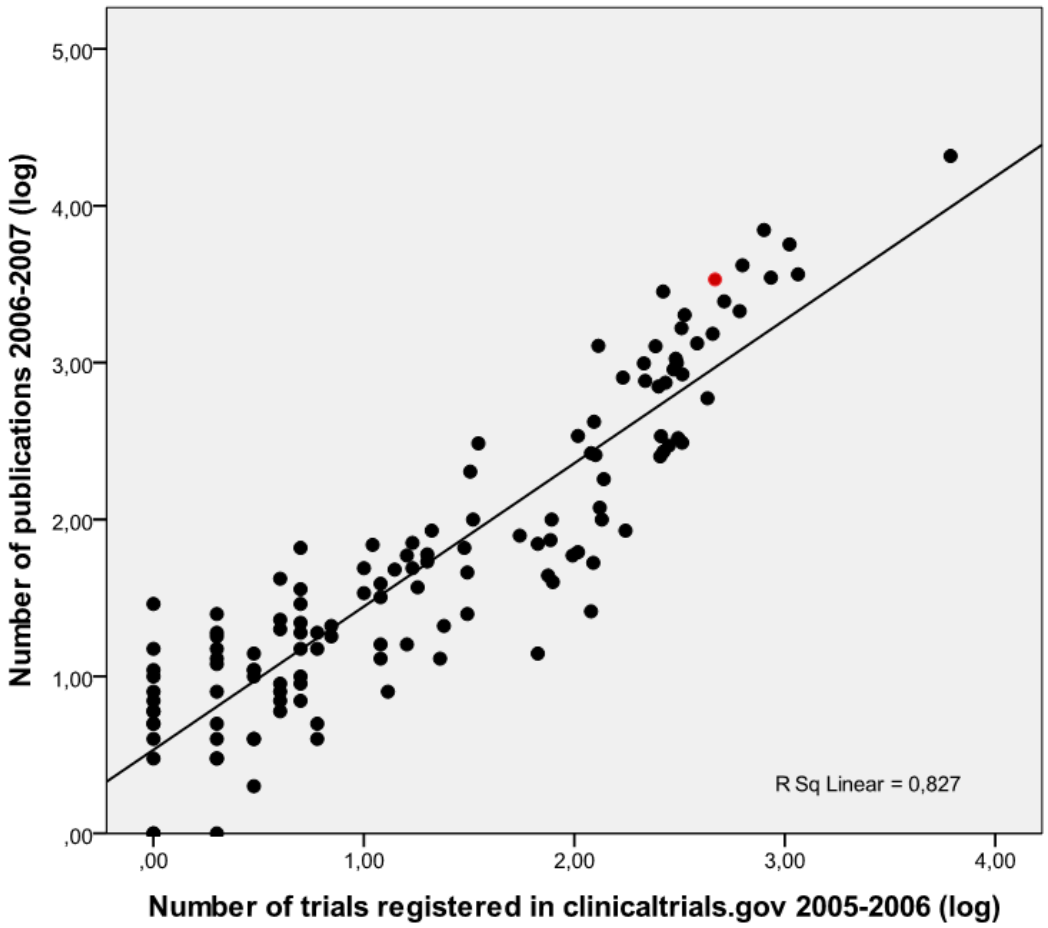

Figure 13: Relation between number of trials registered in www.clinicaltrials.gov in the period 2005-2006 and publication output in the period 2006-2007. the Netherlands is indicated by the red dot.

4 Discussion

This study was conducted to evaluate the position of Europe and the Netherlands in conducting clinical drug research. The main conclusions holds that Western Europe and the Netherlands are performing relatively well in terms of quantitative publication output, but their relative position in terms of qualitative citation rates has deteriorated considerably over the last decade.

Western Europe is still leading in terms of crude publication output and consistently shows a high publication output per capita. However, the USA and Oceania far exceed Western Europe in terms of the average number of citations that publications receive. Looking at the trend in citation rates, we also observe that Western Europe is losing ground in comparison to regions that are catching-up rapidly (e.g. Central and Eastern Europe, Latin America).

Within Europe, the Netherlands is one of the leading countries in terms of absolute and per capita medical drug research publications. Yet, the Dutch average citation rates deteriorated considerably over the period of analysis. This is convincingly illustrated by a drop in country ranking of almost ten positions in the last decade. Whereas, the Netherlands was one of the top-performers in 1995, it is currently performing below European average. This suggests an increasing quality difference in research visibility, reception and impact of the published results of Dutch clinical drug research and strongly suggests that the Netherlands is losing ground vis á vis their main competitors.

Different tools are available to benchmark countries in their clinical trial performance. Using scientific publication as a proxy for clinical trial activity is one method. The use of scientific publications has the advantage that they contain a wealth of information for long time periods and many countries. They also provide insight into the disciplinary portfolios in different countries. The disadvantage is that papers may have authors from different countries and that the study may be carried out in another country than the authors' country of origin. To ensure the validity of our publication based data, we related the publication output to the number of trials registered in clinical trial databases. For this purpose we used the www.clinicaltrials.gov database. We used data from 2005-2006 from the www.clinicaltrials.gov website and publication data over the period 2006-2007 because a lag-time exists between the conduct and reporting date of a trial. Intriguingly, we found a marked correlation between the publication output and participation of a country in clinical drug trials. This suggests that publication output can be considered a reliable indicator for the publication output.

What initiatives should be taken to improve or sustain clinical trial performance? Country specific factors associated with publication output were Research and Development expenditure of pharmaceutical companies and R&D expenditures of medical higher education

institutes. Given the strong associations between R&D and publication output it is likely that spending may partly explain why the United States produces more publications per capita and higher impact publications than Western Europe. A comprehensive analysis of funding has shown that the USA spends for instance, almost twice as much as Europe relative to GDP on medical research than Europe[3] and as a result it has been proposed that the present level of funding for medical research across Europe should be increased to keep in track with the United States.

An increase in funding seems a "sine qua non" to improve clinical trial performance, but is not enough in itself. Strengthening and harmonizing the legislative and regulatory framework seems important as well in this respect, since it has significant impact on the efficiency, costs, and duration of clinical trial conduct. Within the EU an important step to harmonize the legislative and regulatory framework was taken with the finalization of the EUCTD in 2005 and subsequent country implementation in the subsequent two years. The aim of the Directive was to harmonize clinical research practice within EU and align Europe with international standards in order to facilitate clinical drug research.[9] However, after implementation, several reports warned for the increase in red tape and demonstrated that, if anything, the EUCTD did not reduce the duration to initiate a clinical trial.[10,11,12] The consequences of the EUCTD on clinical research within the EU should therefore not be negated and further harmonization of clinical research practices within Europe is crucial to remain at the forefront of clinical drug research. The EUCTD is currently under revision.[13,14,15] It is anticipated that the revised EUCTD includes the concerns of the different stakeholders, such as reducing the bureaucracy and workload, harmonizing the interpretation of rules to avoid confusion, and streamlining the ethical process of gaining approval.[16]

Our data do not support these warnings of suppression of clinical drug research activity in Europe since 2005. This is likely the consequence of the time lag between the execution of a trial and publication. Many trials that were initiated in 2005 or 2006 were not yet published in 2007. Due to the fact that not all trials are indexed instantly in PubMed or Thomson Scientific Web of Science database, we were not able to benchmark countries based on their publications in 2008 or 2009. Drug trials published during these years have likely included trials that are initiated after implementation of the EUCTD. It is therefore expected that future benchmark studies provide more insight of the implementation of the EUCTD on clinical drug trial publication output.

Increasing European-wide research collaboration with the inclusion of actors from different institutional domains seems necessary as well.[6,7] From a European perspective, medical drug research is rather fragmented along national lines. The current state limits possibilities for cost-savings on research infrastructure and training, curtails cross-fertilization opportunities between public and private actors and may result in costly duplications of research efforts.

Efforts to stimulate collaboration and the sharing of results such as set out in the EC Green Paper should therefore be stimulated.[3]

Based on publication output as a proxy for the quantity of clinical research, the Netherlands is performing relatively well compared to other European countries. However, the decreasing scientific visibility and quality of the conducted research is worrying. Clinical research is an essential activity for science and for developing knowledge on diseases and their treatments. In order to remain at the forefront of clinical drug research, it remains therefore critical to keep on monitoring clinical trial activity and to update practices accordingly.

5 References

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