The Changing Geography of Clinical Research: A Critical Analysis of its Drivers

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Abstract

Research and development activities have become more and more internationalized with emerging economies playing an increasingly important role. This phenomenon is particularly debated in the pharmaceutical industry where (western-) pharmaceutical companies have started to offshore clinical research to –so called— *non-traditional* clinical research countries. This study empirically investigates the changing geography of clinical research between the years 2002 and 2012. Building on the concept of national innovative capacity (Furman *et al.*, 2002), we shed light on different drivers of countries' attractiveness as a location for clinical research including arguments related to the supply (cost)-side, the demand-side and the knowledge base. Our results challenge existing views on the extent of the phenomenon as well as the involvement of particular countries. Across *non-traditional countries*, the level of clinical research activities is driven by knowledge rather than cost arguments. Moreover, the rising strength of the knowledge base of *non-traditional countries* enables them to increasingly direct research in favor of local needs.

Keywords: International R&D, Knowledge Transfer, Offshoring, Pharmaceutical Industry

JEL-Classifications: F63; L65; O19; O32

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1 Introduction

The geographical distribution of several aspects of economic activity has changed tremendously in the last decades. Ideas, new products and technology are spreading faster than ever all over the world. Individuals in developing countries – formerly quite isolated – are more likely to have fast access to new (technological) developments and products. However, there is an ongoing controversy whether globalization increases prosperity for all humans or whether it exacerbates the split between rich and poor, even leading to the exploitation of the population and resources of less-privileged countries. This debate is particularly fueled in terms of the pharmaceutical industry.

Concurrently, it has been observed that emerging and developing economies play an increasingly important role in conducting clinical trials (e.g., Belforti *et al.*, 2010; Thiers *et al.*, 2008) although the economic and ethical consequences of this development are by no means clear and have been controversially debated (e.g., Lang and Siribaddana, 2012; Nundy and Gulhati, 2005). These new locations for clinical trials have been labelled as non-traditional countries. This terminology is based upon the until recently rather strong concentration of the industry's pre-clinical and clinical R&D activities in its "traditional centers" in North America, Western Europe, and a few other locations in the Asia-Pacific region, such as Japan, Australia, and New Zealand (Glickman *et al.*, 2009; Thiers *et al.*, 2008).

Interestingly, so far the evidence about the changing landscape of clinical research is mostly anecdotal, which has led to contradictory views about the involvement of particular countries, the underlying reasons for the phenomenon, and its consequences for the involved locations.

In this paper, our objective is to shed light on the involvement of non-traditional countries in clinical research activities. Thereby, we build on the national innovative capacity framework (Furman *et al.*, 2002) in order to examine the drivers of the involvement in clinical research activities across non-traditional countries. Following this concept, we consider supply-side arguments emphasizing lower costs, the increasing attractiveness of markets, as well as the rising knowledge base of countries and their impact on the number as well as the types of clinical trials performed in non-traditional

countries. By focusing on the country-level, we account for the importance of national institutions and differences in national innovative capacities (Henderson *et al.*, 1999). A comprehensive dataset of all registered clinical trials in the ClinicalTrials.gov database between January 2002 and December 2012, allows us to map internationalization patterns, identify stylized facts, and provide explanations for the observed developments.

Our findings suggest increasing clinical research activities in many non-traditional countries but with a large heterogeneity. While India is often named as the main destination for offshored clinical trials, the number of trials actually conducted in India increased only slightly. In contrast, the number of clinical trials performed in South Korea and China has accelerated. In terms of the drivers of this development related to countries' national innovative capacity, our analysis revealed that supply-related drivers have very limited explanatory power. The growth of clinical research activities in non-traditional countries is driven by knowledge intense phase 2 trials and not by data generating and cost-intense phase 3 trials.

Further, we extend the range of applications of the national innovative capacity framework by investigating the direction of R&D activities. More precisely, we map the similarity between non-traditional countries' clinical trial profiles and the US profile. We find no general pattern of convergence. Most interestingly, countries with a strong domestic science base—presumably spurred by learning from prior (offshored) trials— increasingly conduct clinical research corresponding to local health problems. In contrast, countries with more attractive domestic markets tend to be locations for clinical research focusing on disease areas with a global prevalence.

Our results challenge existing views and widely held beliefs among academics, policy makers, and industry experts concerning the changing geography of clinical trials. The results have important implications for the design of policies aiming at strengthening the national innovative capacity and at addressing the specific needs of host countries. Furthermore, our results call into question the relevance of cost related factors for the internationalization of R&D activities.

The remainder of the paper is structured as follows: Section 2 introduces the reader to the national innovative capacity literature and the drivers for changing global R&D particularly in pharmaceuticals. Section 3 describes the data, measures, and methods used in the empirical analysis. Section 4 provides the empirical analysis, and Section 5 concludes.

2 Arguments for the Changing Geography of Clinical Trials

In the past decades, R&D activities have become increasingly internationalized and have shifted towards emerging economies. In turn, emerging economies have become better connected to international networks in science and R&D (Cantner and Rake, 2014; Wagner and Leydesdorff, 2005). Nevertheless, there are remarkable differences among emerging economies. Some countries, particularly China and India, have become more embedded in international R&D activities than others (Thursby and Thursby, 2006; United Nations Conference on Trade and Development, 2005).

Differences in the involvement of particular countries in global R&D networks can be at least partly explained by differences in countries' national innovative capacity, i.e., their long-term ability to produce commercially relevant innovations (Hu and Mathews, 2005; Furman *et al.*, 2002; Porter and Stern, 2001). This literature highlights three main country-specific factors. First, differences among countries can be traced back to country-specific supply-side factors such as the innovation infrastructure related to the political environment, the stock of scientific and technological knowledge, as well as the availability of human capital and financial resources (e.g., Fagerberg and Srholec, 2008; Varsakelis, 2006). Secondly, domestic demand is an important factor shaping the rate and direction of innovation activities (Furman *et al.*, 2002; Porter and Stern, 2001). Thirdly, the strength of linkages between a country's common innovation infrastructure and its industrial clusters influence the extent to which its national innovative capacity can be translated into innovative outcomes. The absence of strong linkages within a country may lead to spillovers to other countries (Furman *et al.*, 2002). For emerging economies, these spillovers provide opportunities to enhance their national innovative capacity through the transfer of scientific and technological knowledge from developed economies (Liu and Buck, 2007).

We consider the concept of national innovative capacity to be useful for analyzing the changing geography of R&D activities for two reasons. Firstly, it describes a country's attractiveness as a location for offshored R&D activities depending on supply- and demand-side factors. Secondly, it can be transferred to our setting of trials-based research and the catch-up of emerging countries. Even though these countries may lag behind the scientific and technological frontier but benefit from linkages with advanced economies.

In the following, we outline supply-side, demand-side as well as arguments in terms of countries' knowledge bases as potential drivers of the changing geography of R&D activities in general and of clinical research activities in particular.[1]

2.1 Supply-side Arguments

With respect to supply-side factors, the realization of cost advantages through the internationalization of manufacturing can be seen as a role model for the geographical expansion of R&D activities to emerging economies, particularly for activities sensitive to R&D costs (Demirbag and Glaister, 2010; United Nations Conference on Trade and Development, 2005). One stream of literature argues that these cost advantages are strongly related to the availability of R&D inputs such as highly skilled science and engineering staff that have become increasingly scarce in developed countries. Thus, emerging economies with a large supply of human capital, particularly science and engineering talent, are attractive locations for offshored R&D activities (Lewin *et al.*, 2009; Manning *et al.*, 2008; Florida, 1997). Kumar (2001) reports that the availability of R&D personnel as well as the level of scientific and technological advancement improve the chances of a country of attracting R&D activities. Nonetheless, countries with a generally lower level of scientific and technological advancement may still become important providers of specific niche capabilities, e.g., specific scientific or technological knowledge (Thomson, 2013).

In the context of the pharmaceutical industry, supply-side arguments are associated with the emergence of another player in the value chain: research service providers. Since the mid-1980s, pharmaceutical companies contract out specific clinical research activities, particularly monitoring,

data management and other non-core activities, to specialized contract research organizations (CROs) which manage the key operational aspects of clinical trials (Howells *et al.*, 2008; Azoulay, 2004; Rettig, 2000). The involvement of CROs in clinical research allows pharmaceutical companies to adjust their organizational boundaries: They keep knowledge-intensive tasks, which are critical for a competitive advantage in-house, while outsourcing the coordination of data-intensive tasks (Azoulay, 2004).

It is widely noted and controversially debated, that pharmaceutical firms offshore clinical trials to non-traditional clinical trial countries in order to realize considerable cost advantages and access huge, well-trained, and often English speaking workforces (Ayalew, 2013; Haakonsson *et al.*, 2013; Petryna, 2009, 2007; Maiti and Raghavendra, 2007).[2] Moreover, non-traditional countries have developed a comprehensive research and health care infrastructure over time, including flagship facilities which are able to compete with their counterparts located in traditional countries (Crone, 2008; Maiti and Raghavendra, 2007). Another important aspect in the choice of clinical trial locations is the availability of a sufficient number of subjects willing to participate in clinical trials since the efficiency of clinical research depends largely on the number of enrolled subjects (Haakonsson *et al.*, 2013; Petryna, 2007). Non-traditional countries provide a high number of "treatment naïve" individuals who have not been treated with a particular drug or drug class before. Access to such individuals is very advantageous since it is less probable that there will be unintended interactions among different drugs. Moreover, uncontrolled factors which could potentially influence the study are reduced the probability that a drug candidate shows a statistically significant effectiveness increases (Petryna, 2009). Moreover, the comparatively high supply of trial subjects can reduce the cost of clinical research considerably and may influence the success of clinical trials in terms of the time needed for study completion (Petryna, 2009).

2.2 Demand-side Arguments

In contrast to supply-side arguments, a broad literature suggests that countries' attractiveness as locations for offshored R&D activities may be particularly shaped by the size of local demand.

Theoretical and empirical research on the subject matter suggests that the need to adapt products for local markets and local manufacturing may drive the location of R&D facilities abroad (Patel and Vega, 1999; Odagiri and Yasuda, 1996; Dunning, 1994; Håkanson and Nobel, 1993). Accordingly, countries with larger markets or fast growing markets may have advantages in attracting offshored R&D (Gassmann and Han, 2004). These demand-side patterns of R&D location may be of particular importance in the pharmaceutical industry where the rate and the direction of innovative activities are generally largely shaped by (potential) market size (Acemoglu and Linn, 2004).

Non-traditional trial countries became more attractive as markets for (western) pharmaceuticals since the steady economic growth in many of these countries has led to the emergence of broader high- and middle income classes. This development is accompanied by the development of health care provision, health insurance and potential demand for (western) pharmaceuticals (Epstein, 2007). Moreover, economic growth and increasing wealth have led to changes in local health problems caused by a different way of living and environmental impacts (Uusitalo *et al.*, 2003).

The global spread of many diseases, such as cancer, cardiovascular, and metabolic diseases, requires global clinical trials in order to account for different disease environments caused by geographical and economic factors and to ensure that benefits for the inhabitants of non-traditional clinical trial countries exist (Glickman *et al.*, 2009; Lanjouw, 2006; Kremer, 2002; Lanjouw and Cockburn, 2001). Besides the increasing market attractiveness of emerging countries, also for medications that address diseases with a worldwide prevalence, there is a need for clinical trials taking into account the specificities in the genetic constitution of local populations that can affect the safety and efficacy of medications (Wilson *et al.*, 2001; Evans and Relling, 1999).

2.3 Knowledge Base Arguments

While supply-side and demand-side factors mostly center around whether a country is attractive for offshored R&D activity, knowledge base arguments mainly consider the *internal* innovation capacity of a country. As such they focus on the point of view of a specific (emerging) country rather than the offshoring decision of a firm in a developed country. Countries may enhance their national innovative

capacity through a range of innovation-oriented policies and sustained investments, such as investments in their human capital (Furman and Hayes, 2004). Moreover, they can benefit from knowledge spillovers particularly if scientifically and technologically more advanced countries cannot fully translate their innovative capacity into innovative activities (Furman *et al.*, 2002; Liu and Buck, 2007). Prior studies suggest that particularly FDI and offshored R&D activities transfer skills and knowledge to host countries (e.g., Smarzynska Javorcik, 2004; van Pottelsberghe de la Potterie and Lichtenberg, 2001; Reddy, 1997). Host countries' innovative capacity may particularly benefit if learning is sufficiently easy, i.e., the geographical distance between local actors and multinational companies' R&D centers is sufficiently close to enable knowledge spillovers and host country actors pursue own R&D activities (Qu *et al.*, 2013; Hu *et al.*, 2005). Nevertheless, it cannot be taken for granted that host countries benefit from offshored R&D. Instead, literature on FDI spillovers suggests that particularly countries with a rather low GDP per capita and those with a rather high GDP per capita can benefit from spillovers. The same applies to institutional factors, like economic freedom, and science or technology indicators, like R&D expenditures and patenting (Meyer and Sinani, 2009).

From the perspective of the host countries, there are compelling learning arguments which increase their interest to insource clinical trials. Patients in emerging countries often suffer from diseases which differ from those prevalent in western countries. However, the rather small market size as well as a limited access to healthcare and health insurance has made it quite unattractive for (western) pharmaceutical companies to develop new pharmaceuticals addressing specific disease patterns prevalent in non-traditional countries (Chaudhuri, 2010; Yip and Mahal, 2008; Lanjouw and Cockburn, 2001). The number of new drugs against tropical diseases has been quite limited throughout the last decades and pharmaceutical innovation has not yet decreased the burden of disease in developing countries (Pecoul *et al.*, 1999; Lichtenberg, 2005).

Hence, such countries have a strong interest in developing a local knowledge base that enables its researchers to develop new medications or to improve and adjust existing medications for local needs. The offshoring of clinical trials provides an opportunity to enhance the national innovative

capacity through knowledge spillovers since particularly phase 1 and phase 2 trials focus on the generation of new knowledge through the development and the testing of hypotheses (Azoulay, 2004). In order to generate new knowledge, researchers often have to apply tacit knowledge from different disciplines (Cockburn and Henderson, 2001; Malterud, 2001). In such settings, knowledge transfer and learning occur predominantly through collaboration and joint clinical research activities between researchers embedded in professional networks that allow for the transfer of complex, tacit, and private knowledge, also enabling learning from peers (Reagans and McEvily, 2003; Uzzi and Lancaster, 2003). Since pharmaceutical R&D is characterized by substantial spillovers between projects, knowledge acquired through joint clinical research projects may be valuable in a wide range of subsequent projects (Cockburn and Henderson, 1996). Hence, the offshoring of clinical research raised expectations that non-traditional countries could enhance their national innovative capacity through an active participation of domestic scientists in clinical research projects originating in traditional countries. For example, the government of India relaxed the regulation of clinical trials in order to support domestic clinical research and participation in multinational trials in the hope of transforming the domestic pharmaceutical industry into an "innovative leader" (Pharmaceutical Research & Development Committee, 1999).

In contrast to expectations, however, it appeared difficult for non-traditional countries to reap the potential benefits from participating in clinical trials. While the enrollment of subjects from non-traditional countries increased in recent years, the involvement of researchers from those countries remained quite modest. Hoekman *et al.* (2012) show that authors from non-traditional countries are at best modestly involved in the production of scientific knowledge, particularly in industry-sponsored trials. This situation may limit the potential for learning and knowledge spillovers and contradict the expectations raised by local authorities. Additionally, the potential benefits from offshored clinical trials are limited by (western) pharmaceutical companies' preference to conduct data intensive trials that have a lower potential for knowledge spillovers and learning outside firm boundaries (Azoulay, 2004).

3 Clinical Trials Data

We used the ClinicalTrials.gov[3] database, a comprehensive registry of clinical trials maintained by the US National Library of Medicine at the National Institutes of Health, to obtain detailed information on clinical studies conducted in the US and 179 other countries. Different parties are involved in conducting clinical trials, each one with specific tasks and obligations. The (lead-)sponsor initiates and finances the clinical trial. The sponsor is most often involved in the trial design and data analysis but not necessarily in conducting it. Clinical trials are often performed in different types of facilities, commonly labeled as sites, including academic medical centers, private practices, community hospitals, or even dedicated, for-profit research centers (Azoulay, 2004). Particularly late phase clinical trials are often conducted in multiple facilities in different regions and countries at the same time in order to facilitate the enrollment of a sufficient number of subjects. If market approval in various parts of the world is targeted, the sponsors have to ensure that the sample population corresponds to the population in these markets in order to ensure the safety and efficacy of the drug candidate for different ethnic groups and different ways of living. Each facility follows a pre-defined protocol developed by the sponsor, the principal investigator, or by a contract research organization. The latter ones offer clinical trial management services such as assistance in developing the trial protocol, in selecting principal investigators and sites, in subject recruitment, as well as in analyzing and reporting the trial results (Rettig, 2000). Nevertheless, sponsors or principal investigators, i.e., the individuals who are responsible and accountable for conducting a specific clinical trial, are usually in charge of submitting the required information to the trial registry and keeping the information up to date.

The database provides detailed information on each clinical trial including its design, its sponsors, the facilities where it is conducted, and the disease or condition that it addresses as indicated by the Medical Subject Headings (MeSH). With MeSH the US National Library of Medicine provides a controlled vocabulary thesaurus for indexing scientific biomedical research, e.g., journal articles.[4] Clinical trials in our sample contain information on the corresponding MeSH terms to indicate which

conditions, diseases, treatments, or pathogens the trial addresses. MeSH terms are organized using an alphabetical as well as a hierarchical structure called trees. At the most general level, subject headings cover very broad terms such as “Neoplasms” that correspond to a 3-digit identification or tree number (e.g., C04 in case of “Neoplasms”). More specific subject headings are assigned to more detailed tree numbers, e.g., “Cysts” (C04.182) and “Bone Cysts” (C04.182.089). Each subject heading can be assigned to one or more tree numbers. In the case of “Bone Cysts” two tree numbers have been assigned, C04.182.089 and C05.116.070. The latter one indicates that bone cysts are a musculoskeletal, and particularly a bone disease. For each clinical trial in our dataset we assign tree numbers that correspond to the MeSH term.

The database includes investigational, observational and expanded access studies. In investigational studies, i.e., clinical trials in a narrow sense, the enrolled subjects receive none, one, or more diagnostic or therapeutic interventions according to the study protocol so that the effects of the interventions on their health outcomes can be evaluated. Subjects enrolled in observational studies may receive a particular intervention but they are not assigned to this intervention by the investigator. Expanded access refers to a FDA regulated process that allows for the provision of investigational new drugs to patients with serious diseases who are not eligible for clinical trials.

Mandatory registration of clinical trials has been extended since the establishment of ClinicalTrials.gov on February, 29, 2000. In March 2002 the FDA published guidelines explaining statutory requirements for information submissions and their implementation (Food and Drug Administration, 2002). Since then, studies addressing life-threatening diseases have to be registered in addition to trials funded by the US government. The Food and Drug Administration (2002, p.4) defines life-threatening as “diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted” and as “diseases or conditions with potentially fatal outcomes, where the endpoint of clinical trial analysis is survival”. The guidelines list the acquired immunodeficiency syndrome (AIDS) as well as all other stages of human immunodeficiency virus (HIV) infections, Alzheimer’s disease, angina pectoris, heart failure, and cancer as examples for life

threatening diseases. Moreover, chronic diseases such as inflammatory bowel disease, asthma, rheumatoid arthritis, diabetes mellitus, systemic lupus erythematosus, depression, and psychoses are described as being serious in the sense of the US clinical research legislation at least during some stages of the course of the diseases, or for certain populations.

The guidelines and laws dealing with clinical trial registration have been continuously updated and adjusted in recent years. Following today's legislation and with an exception for very early stage trials (phase 1), each clinical trial of drugs or biological products has to be registered if at least one trial site is located in the US, if drug candidates are manufactured in the US, or if the trial is conducted under an FDA investigational new drug application (US Public Law 110-85, 2007; Food and Drug Administration, 2004). Hence, registration does not depend on the country of origin of the sponsor but rather on the locations where the trial is conducted, the drug candidate is manufactured, or whether the US is the target market.[5] Registration of clinical trials at ClinicalTrials.gov may be subject to (manual) review in order to identify possible errors, deficiencies, or inconsistencies in the information provided by the responsible parties that were not detected by automatic checks during the submission process. Non-compliance with the rules of clinical trial registration can lead to public notice of non-compliance, loss of NIH funding, and civil monetary penalties of up to $ 10,000 per day until the violation has been corrected (US Public Law 110-85, 2007).[6]

In addition to these regulations and guidelines, the International Committee of Medical Journal Editors (ICMJE) has made clinical trial registration a pre-condition for publication in order to enable all interested stakeholders to explore the full range of clinical evidence (e.g., Angelis *et al.*, 2004). The ICMJE requires the registration of clinical trials in all phases of the drug development process, including the early ones, even though it does not require registering trials in any particular database (Wood, 2009). However, the registry has to meet some minimum requirements with respect to the accessibility, the information provided, opportunities to search the database, and the mechanism to ensure the validity of the data (e.g., Angelis *et al.*, 2004).

When ClinicalTrials.gov was established in the year 2000, it was not immediately clear for which trials registration was mandatory or optional. This issue had been considerably clarified by the 2002 FDA guidelines. Therefore, we exclude all trials that started before the year 2002 from our sample. The remaining sample encompasses 122,123 clinical trials that started between January 2002 and December 2012. For 112,194 of those clinical trials, we could identify whether they are conducted in facilities located in the United States or in one of the 179 "other" countries. In terms of "other" countries, 151 can be classified as non-traditional countries for conducting clinical trials. Following Thiers *et al.* (2008), non-traditional countries for clinical trials are those that are neither located in North America nor in Western Europe. Furthermore, Australia, Japan, and New Zealand can be seen as traditional clinical trial countries. The acceptance of data generated in clinical trial facilities and in clinical trials conducted outside the US is important for the approval of new pharmaceuticals. While the acceptance of data generated in traditional countries is without debate, trials conducted in non-traditional countries might be more controversial. The FDA accepts data in its approval process if it stems from adequate, well-controlled clinical trials that are conducted in compliance with the standards of good clinical practice and if the data are applicable to the US population (Khin *et al.*, 2013).

Most clinical trials are multi-center trials, i.e., they are conducted in different facilities and across different countries. We use information about the facilities of a trial to determine which countries are involved in a particular clinical trial by calculating the number of clinical trials per country using fractional counting of trials. Information on the lead sponsors of clinical trials is used to assign each lead sponsor to its country of origin. Since the database does not provide a unique identifier for sponsoring organizations and contains lots of different name variants of one and the same organization, we manually assigned the country of origin to all lead sponsors that were responsible for 4 or more clinical trials. More precisely, we assigned the country of origin to 3,567 lead sponsors that sponsor in sum 112,192 (91.87%) of the clinical trials in our sample. 9,931 clinical trials (8.13%) list a lead sponsor of a non-traditional country.

Our data contains clinical trials in all phases of the gradual clinical development process of new pharmaceuticals. Phase 0 trials include exploratory and microdose studies aiming at collecting early evidence whether the drug candidate acts in humans as anticipated in preclinical research. Phase 1 trials are usually conducted with healthy volunteers in order to assess the safety of a drug candidate and to identify the most frequent and most serious adverse events.[7] Furthermore, clinical trials in phase 1 are frequently conducted to get insights into how the drug candidate is metabolized and excreted. Phase 2 studies test drug candidates in humans who are affected by specific diseases or conditions to obtain preliminary data on a drug candidate's effectiveness. Trial subjects who receive the drug candidate can be compared with similar subjects who receive a pharmacologically inactive substance or with those receiving a different drug, mostly the standard of care. Safety evaluation continues and short-term adverse events are studied. Put differently, phase 2 clinical trials are used to study drug candidates in specific disease settings in order to obtain enough information concerning the efficacy in that particular case. Based on this information, sponsors of clinical trials have to decide whether or not to continue with phase 3 trials. Phase 3 trials employ larger sample sizes to evaluate the safety and efficacy within different populations and by using different dosages. Phase 4 studies are conducted after market approval to gather additional information concerning a drug's safety, efficacy and its optimal use. Hence, there are important differences between trial phases with respect to their importance for knowledge generation. While the generation and testing of hypotheses plays an important role in clinical research up to phase 2, trials from phase 3 onwards focus on the generation of empirical evidence proving the effectiveness of the drug candidate against a placebo or the existing standard of care. Consequently, we can assume that the importance of knowledge generation activities decreases relative to the progress of data generation activities and of the clinical research process (Azoulay, 2004).

In the dataset used in this study, 802 clinical trials are assigned to phase 0, 14,110 to phase 1, 21,893 to phase 2, 16,754 to phase 3, and 13,732 to phase 4. Moreover, for 47,273 clinical trials in our dataset information concerning the phase is missing while 7,559 are assigned to multiple phases.

4 Empirical Analysis

4.1 The Changing Geography of Clinical Trials over Time

In the following, we map the geography of trials over time in 11 non-traditional countries which can be found among the 30 countries with the highest number of weighted clinical trials.[8] We use the number of weighted clinical trials per country *i* (*Weighted Trials*$_{it}$), i.e., each trial is weighted by the number of countries it is performed in, to account for the contribution of a particular country in conducting a trial depending on the number of other countries involved. In doing so, we ensure that our results are neither driven by particular trials conducted in a large number of facilities in multiple countries, nor by trials that are exclusively conducted in one country.

We observe a general trend across countries that the number of clinical trials which started in a specific year has been rising over time, from approximately 3,900 in 2002 to more than 14,200 in the year 2012. While the United States is the leading country involved in 40 to 50% of clinical trials conducted globally, our analysis focusses on the development of clinical research activities in non-traditional clinical trial countries. China, South Korea, and Israel are the leading non-traditional countries. Their position can partly be explained by the strength of their domestic bio-pharmaceutical industry, the current or future importance of their markets, and governmental policies dedicated to the support of R&D investments as well as scientific and technological catch-up (Wang *et al.*, 2012; Liu *et al.*, 2011; Kroll *et al.*, 2008; Barki, 2005).

Figure 1 shows that the non-traditional among the leading clinical trial countries have been able to increase the total (weighted) number of clinical trials over time. Nevertheless, we observe considerable differences among these countries. Particularly China, South Korea, and Israel managed to steadily increase the number of clinical trials. In the year 2002, less than 32 trials started in Chinese facilities with this number rising to approximately 522 in 2012. Similar developments took place in South Korea, where the number of clinical trials increased from less than 11 to almost 478, and Israel where an increase from approximately 29 clinical trials in 2002 to almost 357 trials in 2012 can be observed.

Organizations based in Brazil and Taiwan have been able to increase their participation in international clinical trials considerably as well. However, these countries show a decline in the number of weighted clinical trials in recent years. Facilities located in India were also more frequently involved in clinical trials. After a considerable increase from approximately 9 trials in 2002 to slightly more than 100 trials in the year 2006, their number remains quite stable around 130 over time, with a slight decrease to approximately 119 clinical trials in the year 2012. The remaining non-traditional countries also show an increase which is followed by a rather stable number of trials in the last years of the observation period.

Insert Figure 1 about here

Next, we use regression models to explore the development of trials over time. The dependent variable, weighted clinical trials per country (*Weighted Trials*$_{it}$), is zero for a considerable number of cases and roughly continuously distributed over positive values. Since linear models do not fully account for this data structure, we use Tobit regression models with clustered standard errors on the country level. Since the objective of this study is to map the changing geography of clinical research, we use time (*T*) as an independent variable to test time effects. The year 2002 serves as the base year with *T*=1. We use the squared time period (T^2) in order to take non-linear relationships between time and the involvement of non-traditional countries in clinical activities into account.

Further, we account for country-specific supply-side factors and demand-side factors by using data provided by the World Bank. With respect to the supply-side we use the natural logarithm of countries' scientific and engineering journal articles as a proxy for countries' scientific basis (*SciTec Articles*$_{it}$). This variable refers to journal articles published in the fields of physics, biology, chemistry, mathematics, clinical medicine, biomedical research, engineering and technology, or earth and space sciences per year. Price and cost differences among countries are taken into account by using the GDP related purchasing power parity conversion factor, i.e., the number of a country's local currency

units required to buy the same amounts of goods and services in the corresponding country as one US dollar would buy in the US (*Price Level*$_{it}$).

With respect to the demand side, we use the natural logarithm of the total population as proxy for the size of a market (*Population*$_{it}$). According to the World Bank, *Population*$_{it}$ represents counts of all residents of a country regardless of legal status or citizenship except for refugees not permanently settled in the country of asylum. Furthermore, we use the natural logarithm of the GDP per capita (*GDP*$_{it}$) in current US dollars as well as the total of public and private health expenditures as a percentage of GDP (*Health Expenditures*$_{it}$) as further variables connected to the demand-side. Total health expenditures include the provision of preventive and curative health services, family planning activities, nutrition activities, and emergency aid designated for health.

Net inflows of foreign direct investments in billion US dollars (*Net FDI*$_{it}$) are used as a further control variable to account for the attractiveness of the economy and its involvement in international business activities.

Table 1, depicts several subsamples of trials: Model 1 reports results including all clinical trials, Model 2 represents the sub-set of trials sponsored by industry whereas Models 3 to 8 take into account the clinical phases. In line with the descriptive analyses, our regression analyses indicate that particularly the number of weighted phase 2 and phase 3 trials increase over time. In terms of the functional form, we detect an inverted u-shape relationship between time and the number of weighted clinical trials conducted in non-traditional countries. The number of weighted phase 2 and phase 3 clinical trials increased from 2002 to 2005 and shows a slight tendency to decrease thereafter. The size of the scientific basis of a country in terms of its scientific and engineering articles appears to be highly significantly correlated with the number of clinical trials in all subsamples. Hence, countries with a more sophisticated scientific basis are particularly equipped to conduct clinical trials. We do not find robust support for cost arguments influencing the number of clinical trials in non-traditional countries. Nevertheless, the price indicator is positively related to the overall number of weighted clinical trials as well as to the number of phase 2 and phase 3 trials. It is, however, not significantly

related to the number of industry sponsored trials indicating that cost-based arguments cannot fully explain the increasing global spread of clinical research activities.

Insert Table 1 about here

Variables related to the attractiveness of a country as a market for (western) pharmaceuticals are particularly correlated with the number of later stage trials and industry sponsored trials. More specifically, countries with a larger market, i.e., a larger population, a larger GDP per capita, or higher health expenditures as percentage of GDP, have a higher number of weighted total and industry sponsored phase 3 trials as well as a higher number of industry sponsored phase 2 trials. Net FDI inflows are positively related to the number of industry sponsored clinical trials and phase 3 trials. Lagged dependent variables are positively related to the number of clinical trials, suggesting some path dependency in their involvement in global clinical research. These results hold for the sample of traditionally country sponsored trials.[9]

Further, we use the share of a country in conducting clinical trials (*Share Country*$_{it}$) to analyze the changing relative importance of non-traditional countries. This variable is computed by dividing the number of weighted clinical trials in country *i* in a specific start year by the total number of all clinical trials conducted in traditional and non-traditional countries that started in that year.

Figure 2 suggests that non-traditional countries have gained importance as locations for clinical trials, though their share is still low.[10] China, South Korea, and Israel started with a share of less than 1% in 2002 and increased to more than 3% in the case of China and South Korea and more than 2.5% in the case of Israel. Again, Taiwan and Brazil show a sharp decline in their share of weighted clinical trials due to the decrease in their number of weighted clinical trials in recent years. Initially, India can increase its share of clinical trials from 0.2% in 2002 to slightly more than 1% in 2007. Since then, the Indian share has decreased to 0.83%. This development, as well as the rather stable absolute number of weighted clinical trials, questions the importance of India as one of the main destinations for

clinical trial offshoring as reported in some parts of the (medical) literature (Gupta and Padhy, 2011; Drabu *et al.*, 2010; Cekola, 2007; Maiti and Raghavendra, 2007).

Insert Figure 2 about here

In addition, we use fractional logit regressions to analyze the share of countries in conducting weighted clinical trials (*Share Country*$_{it}$). Papke and Wooldridge (1996) propose models for fractional response if the dependent variable is bounded between 0 and 1 and is continuous within these boundaries. The proposed fractional response model ensures that the predicted values of the dependent variable are within the unit interval and do not require adjustments if the extreme values of the dependent variable, 0 or 1, are observed (Papke and Wooldridge, 1996). The proposed method uses quasi-maximum-likelihood estimation (QMLE) to obtain robust estimators of the conditional mean and satisfactory efficiency properties. In many economic applications the mean function takes the logistic form, a variant of the model that has been labeled fractional logit. We employ the fractional logit model with clustered standard errors on the country level.

Our fractional logit regressions in Table 2 indicate that non-traditional countries for clinical research have increased their share in clinical trials particularly in phase 2 and in industry-sponsored phase 3 trials. However, the results suggest that the share of non-traditional countries in these subsamples has decreased slightly since 2005. In line with our findings related to the weighted number of clinical trials per country, we find that a country's scientific basis is positively related to its share of clinical research across different phases. With the exceptions of total trials and phase 2 trials, price level factors are not associated with the share of clinical trials conducted in non-traditional countries. Demand related factors such as the population size, the GDP per capita, and health expenditures as percentage of GDP are related to the share of industry sponsored phase 3 trials. Net inflows of FDIs are negatively related to the share of a country in the samples of all trials, and in phase 3 trials irrespective of the type of sponsor. Lagged dependent variables are positively related to the share of

countries conducting clinical trials for all different specifications of the dependent variable. The results for the sample of clinical trials sponsored by traditional countries are largely in line with the results described above.

Insert

	(1)	(2)	(3)	(4)	(5)	(6)	
Sample	Full	Industry Sponsored	Phase 1	Phase 1 Industry Sponsored	Phase 2	Phase 2 Industry Sponsored	
Dependent Variable: Share Countryit							
T	0.1320	-0.0121	0.0660	0.8020*	0.2745***	0.3068**	0
	(0.0910)	(0.0802)	(0.1286)	(0.4603)	(0.0929)	(0.1232)	(0
T^2	-0.0170*	0.0010	-0.0003	-0.0436	-0.0230**	-0.0271**	-0
	(0.0092)	(0.0073)	(0.0116)	(0.0383)	(0.0092)	(0.0110)	(0
SciTec Articlesit	0.4526***	0.4829***	0.7485***	1.6062***	0.5649***	0.4968***	0
	(0.0690)	(0.1009)	(0.1845)	(0.4197)	(0.0935)	(0.1057)	(0
Price Levelit	0.8150*	0.2768	0.4148	0.2494	1.1038*	-0.0795	0
	(0.4849)	(0.5644)	(1.0149)	(1.4112)	(0.6500)	(0.5396)	(0
Populationit	0.1063	0.1619	-0.2069	-0.7876**	0.0423	0.0053	0
	(0.0927)	(0.1035)	(0.2161)	(0.3733)	(0.1144)	(0.1281)	(0
GDPit	-0.0301	0.2062*	-0.2736	-0.8934	-0.0661	0.0843	0
	(0.0998)	(0.1184)	(0.2647)	(0.5612)	(0.1411)	(0.1215)	(0
Health Expendituresit	0.0078	0.0211	-0.0274	-0.1594	-0.0142	0.0406	0
	(0.0389)	(0.0352)	(0.0923)	(0.1075)	(0.0436)	(0.0453)	(0
Net FDIit	-0.0057***	-0.0054***	-0.0034**	-0.0104**	-0.0038***	-0.0053**	-0
	(0.0011)	(0.0014)	(0.0016)	(0.0052)	(0.0012)	(0.0024)	(0
Share Countryit	98.4101***	180.9962***	119.6852***	50.9974	72.3819***	298.8294***	5
	(8.1512)	(59.9571)	(26.3361)	(70.8331)	(21.6600)	(37.9432)	(1
Constant	-12.1452***	-15.7663***	-7.1636	-0.7834	-12.1523***	-13.0159***	-1
	(1.7574)	(1.9538)	(4.4786)	(7.1337)	(2.3831)	(2.5110)	(2
N	566	566	566	566	566	566	5
AIC	29.4918	24.2312	25.7766	22.6661	28.4020	24.1526	3
BIC	72.8777	67.6171	69.1625	66.0520	71.7879	67.5386	7

Clustered standard errors in parentheses

* p<0.10, ** p<0.05, *** p<0.01

Dependent and lagged dependent variables are subset specific.

Table 2 about here

Overall, these findings suggest that at least some non-traditional trial countries have managed to narrow the gap to the leading countries in clinical research with respect to the absolute number as well as to the share of (weighted) clinical trials. These descriptive results are largely in line with the

findings presented by Thiers *et al.* (2008) who report that most non-traditional countries are small players but, as a group, host 17% of all active recruiting clinical trial facilities. The observed expansion of clinical trials in many non-traditional countries is in line with a decreasing share of the US whereas Western European countries have kept their share in terms of weighted clinical trials quite stable.

4.2 Overemphasis of Supply-Side Arguments: Limited Increase of Phase 3 Trials

Prior research supposes that clinical trial sponsors offshore trials that are predominantly conducted for data generation purposes as these are typically the most expensive ones (Rafols *et al.*, 2014; Howells *et al.*, 2008; Azoulay, 2004; DiMasi *et al.*, 2003). If this holds true, we would see that particularly phase 3 trials which need a high number of enrolled subjects are increasingly conducted in non-traditional countries where there is a high availability of treatment naïve subjects. Hence, we explore the relative frequency of different phases in the countries over time. In doing so, we calculate the share of a phase *j* in country *i* in a given year (*Share Phase* j_{it}). We calculate this variable by dividing the number of weighted clinical trials in a specific phase conducted in country *i* by the number of total weighted clinical trials performed in country *i*. All clinical trial counts and shares are calculated on a yearly basis in order to track changes over time.

Figure 3 depicts the share of (weighted) phase 3 trials as a percentage of all trials conducted in specific countries in a given start year.[11] Surprisingly, our analysis does not suggest that phase 3 trials are frequently conducted in non-traditional countries. In terms of China, the share of (weighted) phase 3 trials decreased from around 29% in 2002 to approximately 19% in 2012. Similar developments can be observed for South Korea, where the share decreased from approximately 50% to circa 15.5%, Israel showed a decrease from roughly 35% to approximately 10%, and India, which decreased from approximately 28% to 20%. These numbers are below the share of phase 3 clinical trials in all clinical trials in most traditional countries, which equaled 20 to 30%. As shown in Figure 4, the share of phase 3 trials among the industry sponsored trials usually exceeds the overall share of phase 3 trials but remains rather stable or even decreases over time for all non-traditional countries.[12] Even in Brazil, where approximately 60% of industry sponsored trials refer to phase 3,

the share remained rather stable since 2006. These results do not suggest that countries with considerable cost advantages, as compared to the US, show a relatively large increase in phase 3 clinical trials. Moreover, the development of the share of phase 3 clinical trials in these countries does not differ substantially from the development observed in countries that have a lower cost advantage to the US, such as Poland, Israel, or Taiwan. Russia might be an exception to some extent since the share of phase 3 clinical trials remains rather stable and showed an increase in recent years. This may have been driven by the relatively low cost of conducting clinical research, which equals around 40% of the US cost (Ayalew, 2013).

In contrast and quite surprisingly, most non-traditional countries increased the share of phase 1 and phase 2 clinical trials. In the case of China, the share of phase 1 trials rose from 7% in 2002 to approximately 11.5% in 2012 and the share of phase 2 trials increased from around 23.5% to 25.6%. Similarly, South Korea increased the share of phase 1 trials from 1% to approximately 15% and their share of phase 2 trials from almost 13% to 18%. India showed a growth of the share of phase 1 studies from 2% to more than 23% and a growth of phase 2 studies from 3% to 20%. In contrast, the share of phase 1 studies among the total clinical trials conducted in Israel remained rather constant with a value of 8.6% in 2002 and 7.5% in 2012. The share of phase 2 trials in Israel decreased from 27% to 13%. For most traditional countries the share of phase 1 trials is between 10% and 20% whereas the share of phase 2 trials varies around 20%. Overall, an increasing share of phase 1 and phase 2 trials can also be found for the trials sponsored by organizations from traditional countries and for industry sponsored trials.

The corresponding regression results suggest that particularly the share of phase 2 trials and industry sponsored phase 3 trials in non-traditional countries have been increasing over time. Again, we find an inverted u-shape relationship Model (3) and (4) in Table 3, indicating that the share of the corresponding trial type increased up to 2005 and has been decreasing thereafter. In addition, the results reveal that particularly a country's scientific basis is linked to its share of phase 2 trials irrespective of the type of sponsor. In contrast, cost or demand related factors have either no, e.g.,

price level and health expenditures or a negative association, e.g., population size, to the share of phase 2 trials in non-traditional countries. We find, however, a significant and positive relationship between the share of industry sponsored phase 3 trials and countries' health care expenditures.

Insert Figure 3 about here

Insert Figure 4 about here

Despite the slight increase in industry sponsored phase 3 trials over time, our results do not support the widely held notion that the shift of clinical research activities to non-traditional clinical research countries is mostly driven by cost arguments. Instead, our results indicate that non-traditional countries' scientific and technological knowledge bases support these countries in conducting knowledge-intense clinical trials.

Insert Table 3 about here

4.3 Convergence in Countries' Clinical Trial Profiles

In the following, we explore whether the clinical research profiles of non-traditional countries are showing an increasing similarity to the US profile, or whether these countries are addressing diseases which are rather country-specific. In Table 4, we present a detailed overview concerning the most frequently addressed disease areas based on 3-digit MeSH tree numbers in the main non-traditional countries. Surprisingly, a rather general MeSH tree number "Pathological Conditions, Signs and Symptoms" referring to "abnormal anatomical or physiological conditions and objective or subjective manifestations of disease, not classified as disease or syndrome" has been increasingly used to characterize clinical research in non-traditional countries. The increasing importance of this rather general category may partly explain the converging trend towards clinical research conducted in the

US for many countries. However,

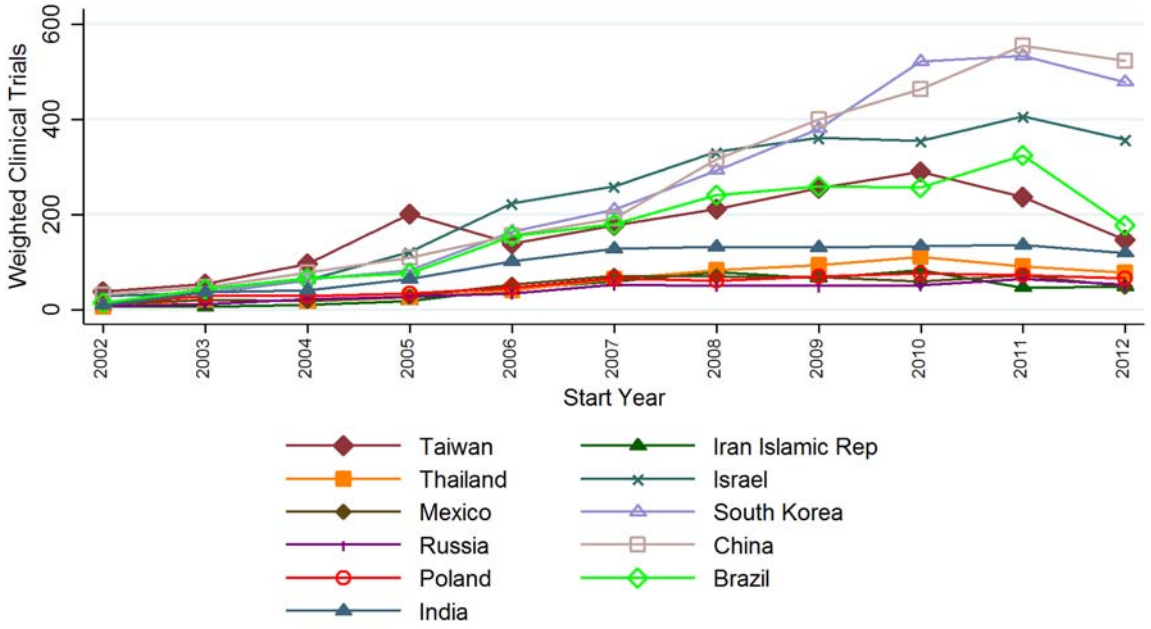

Figure 1: Number of Weighted Clinical Trials in Selected Non-Traditional Countries

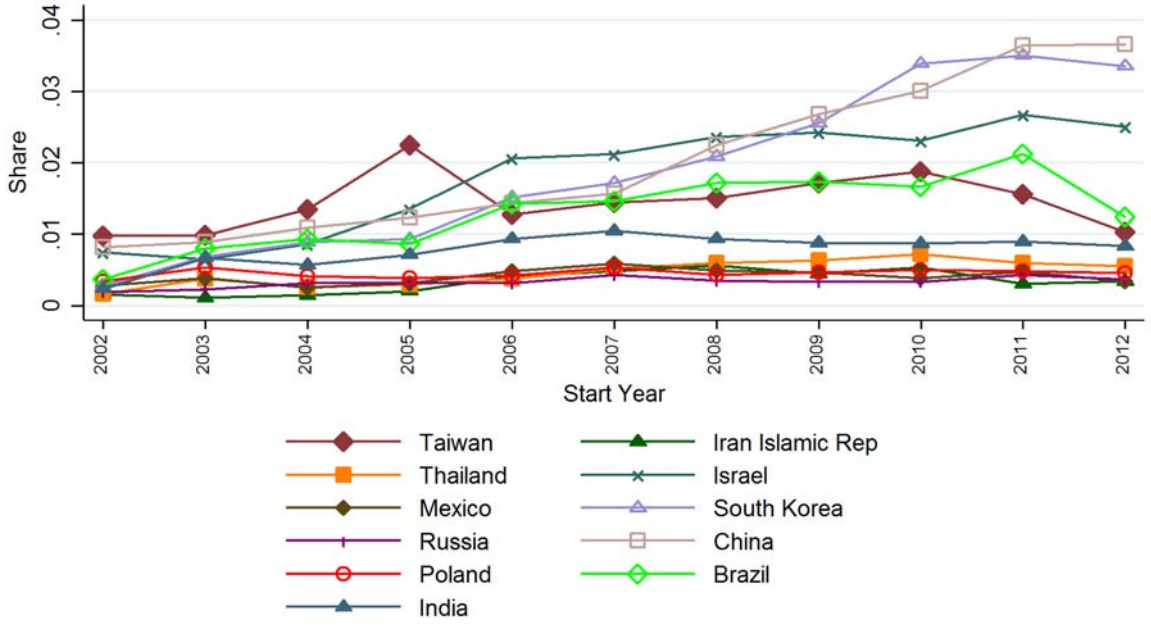

Figure 2: Share of Selected Non-Traditional Countries in Conducting Weighted Clinical Trials

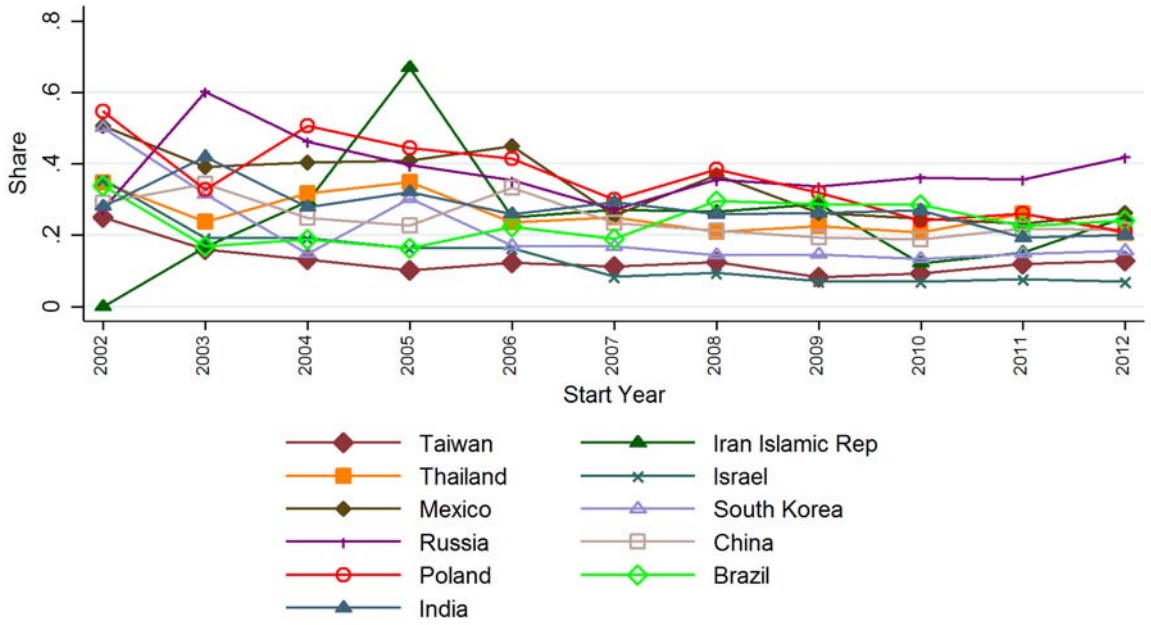

Figure 3: Share of Phase 3 Clinical Trials in Selected Non-Traditional Countries

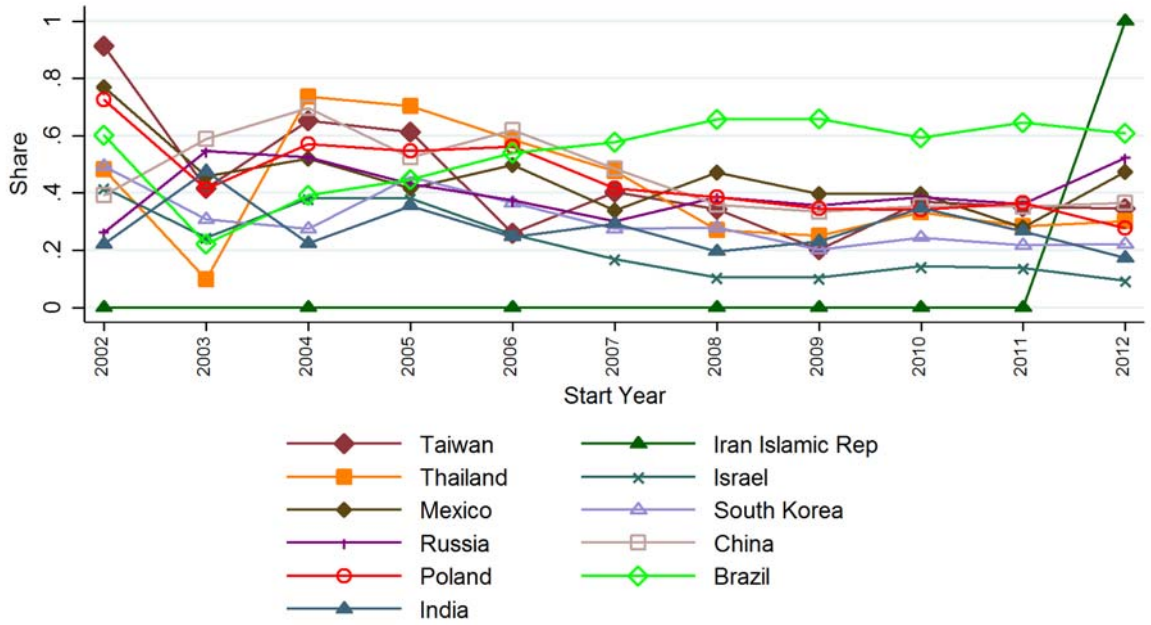

Figure 4: Share of Industry Sponsored Phase 3 Clinical Trials in Selected Non-Traditional Countries

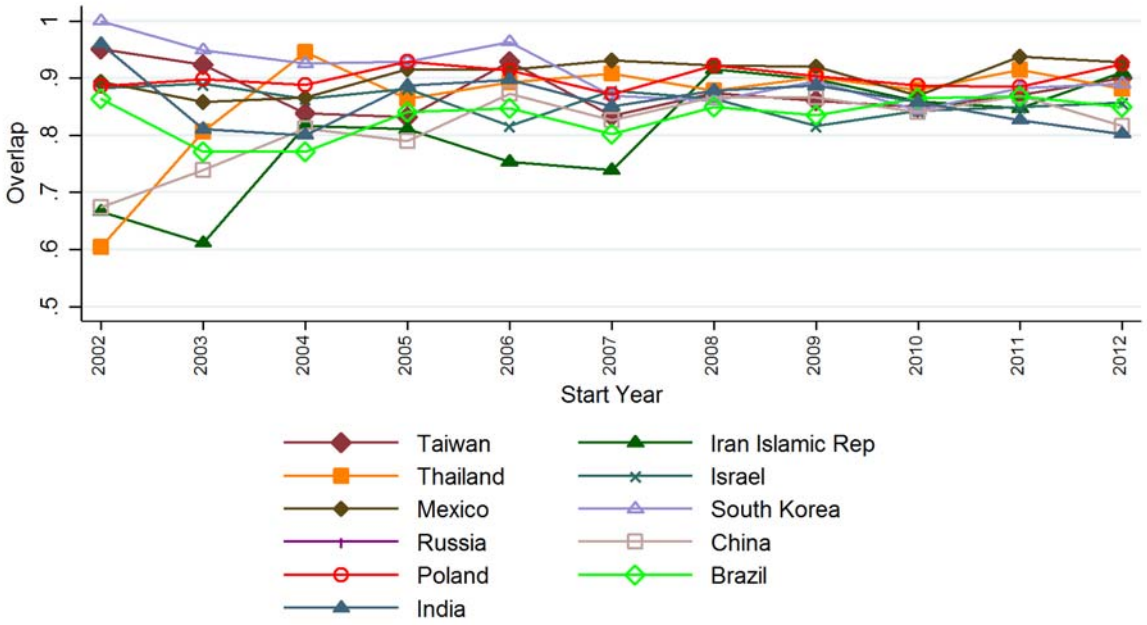

Figure 5: Development Overlap between the US and Selected Non-traditional Countries

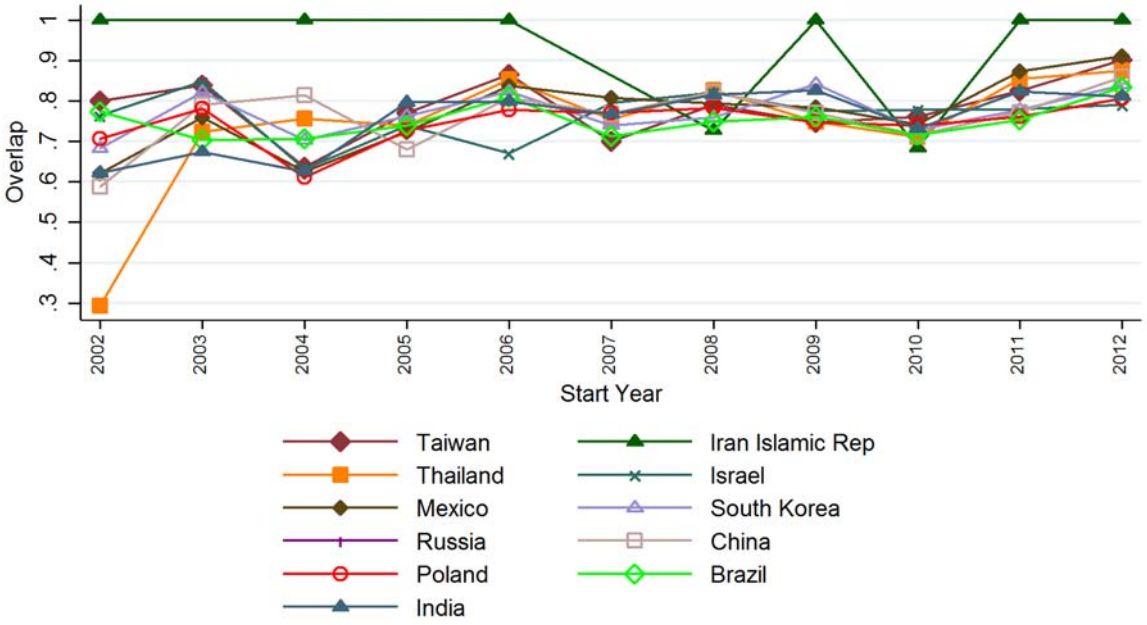

Figure 6: Overlap Share between the US and Selected Non-traditional Countries (only Industry Sponsored Clinical Trials) over time

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Sample	Full	Industry Sponsored	Phase 1	Phase 1 Industry Sponsored	Phase 2	Phase 2 Industry Sponsored	Phase 3	Phase 3 Industry Sponsored
Dependent Variable: Weighted Trialsit								
T	1.2138	0.5843	-0.4169	0.3822	0.9657**	0.3952*	0.5166*	0.6984***
	(0.7895)	(0.3818)	(0.4926)	(0.6347)	(0.4121)	(0.2055)	(0.2734)	(0.2028)
T^2	-0.1538*	-0.0636*	0.0771	0.0237	-0.0911**	-0.0334*	-0.0631**	-0.0812***
	(0.0843)	(0.0384)	(0.0497)	(0.0567)	(0.0410)	(0.0199)	(0.0267)	(0.0199)
SciTec Articlesit	0.7620**	0.5401***	1.2639***	1.5568**	0.9512***	0.4503***	0.4959***	0.3170**
	(0.3054)	(0.1804)	(0.3979)	(0.6173)	(0.2493)	(0.1188)	(0.1474)	(0.1280)
Price Levelit	4.5612**	2.1345	2.5622	0.6145	4.4004**	1.4255	2.3043**	0.6949
	(2.2574)	(1.6314)	(1.9309)	(2.7647)	(1.9879)	(0.8898)	(1.0119)	(0.7291)
Populationit	0.8946**	0.9567***	-0.0800	-0.1019	0.3482	0.2516*	0.6699***	0.6970***
	(0.3925)	(0.2858)	(0.3777)	(0.4465)	(0.2589)	(0.1427)	(0.2463)	(0.2244)
GDPit	0.3254	1.0744***	-0.7367*	0.2189	-0.3363	0.1912	0.1676	0.6322***
	(0.3630)	(0.2880)	(0.4280)	(0.5077)	(0.2675)	(0.1475)	(0.2224)	(0.2179)
Health Expendituresit	0.1790	0.2400**	-0.0092	0.0401	0.0846	0.0712	0.2353**	0.3019***
	(0.1365)	(0.0949)	(0.1250)	(0.1647)	(0.0917)	(0.0560)	(0.1094)	(0.0992)
Net FDIit	0.1149	0.0340	0.0167	0.0039	0.0508**	-0.0078	0.0564***	0.0266***
	(0.0784)	(0.0215)	(0.0118)	(0.0114)	(0.0201)	(0.0054)	(0.0177)	(0.0047)
Weighted Trialsit-1	1.1960***	1.0508***	1.1619***	0.9631***	1.0306***	1.0390***	0.9501***	0.8455***
	(0.0369)	(0.0520)	(0.1432)	(0.2345)	(0.0735)	(0.0852)	(0.0590)	(0.0739)
Constant	-26.5881***	-31.1400***	-4.3036	-16.9346**	-14.3206**	-11.0440***	-18.7191***	-21.9980***
	(9.8154)	(7.0839)	(8.1962)	(8.5684)	(6.0622)	(3.0852)	(6.0826)	(5.9239)
Sigma	7.8887***	4.0433***	3.8893***	3.8160***	4.1800***	1.8460***	3.1628***	2.0599***
	(1.2600)	(0.5897)	(0.6635)	(0.7961)	(0.7110)	(0.2053)	(0.5371)	(0.4008)
N	869	869	869	869	869	869	869	869
AIC	4759.6807	3078.4814	1563.2119	965.2903	2730.1018	1665.6218	2863.6265	2017.3375
BIC	4812.1215	3130.9222	1615.6527	1017.7311	2782.5426	1718.0626	2916.0673	2069.7783

Clustered standard errors in parentheses

* p<0.10, ** p<0.05, *** p<0.01

Dependent and lagged dependent variables are subset specific.

Table 1: Tobit Regressions for the Number of Weighted Clinical Trials in Non-Traditional Countries

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Sample	Full	Industry Sponsored	Phase 1	Phase 1 Industry Sponsored	Phase 2	Phase 2 Industry Sponsored	Phase 3	Phase 3 Industry Sponsored
Dependent Variable: Share Countryit								
T	0.1320	-0.0121	0.0660	0.8020*	0.2745***	0.3068**	0.1206	0.2162***
	(0.0910)	(0.0802)	(0.1286)	(0.4603)	(0.0929)	(0.1232)	(0.0905)	(0.0719)
T^2	-0.0170*	0.0010	-0.0003	-0.0436	-0.0230**	-0.0271**	-0.0114	-0.0214***
	(0.0092)	(0.0073)	(0.0116)	(0.0383)	(0.0092)	(0.0110)	(0.0084)	(0.0063)
SciTec Articlesit	0.4526***	0.4829***	0.7485***	1.6062***	0.5649***	0.4968***	0.4430***	0.4010***
	(0.0690)	(0.1009)	(0.1845)	(0.4197)	(0.0935)	(0.1057)	(0.0718)	(0.0922)
Price Levelit	0.8150*	0.2768	0.4148	0.2494	1.1038*	-0.0795	0.6768	-0.4880
	(0.4849)	(0.5644)	(1.0149)	(1.4112)	(0.6500)	(0.5396)	(0.4964)	(0.5356)
Populationit	0.1063	0.1619	-0.2069	-0.7876**	0.0423	0.0053	0.1446	0.2467**
	(0.0927)	(0.1035)	(0.2161)	(0.3733)	(0.1144)	(0.1281)	(0.0967)	(0.1166)
GDPit	-0.0301	0.2062*	-0.2736	-0.8934	-0.0661	0.0843	0.0054	0.3629***
	(0.0998)	(0.1184)	(0.2647)	(0.5612)	(0.1411)	(0.1215)	(0.1145)	(0.1163)
Health Expendituresit	0.0078	0.0211	-0.0274	-0.1594	-0.0142	0.0406	0.0266	0.0826**
	(0.0389)	(0.0352)	(0.0923)	(0.1075)	(0.0436)	(0.0453)	(0.0367)	(0.0401)
Net FDIit	-0.0057***	-0.0054***	-0.0034**	-0.0104**	-0.0038***	-0.0053**	-0.0056***	-0.0052***
	(0.0011)	(0.0014)	(0.0016)	(0.0052)	(0.0012)	(0.0024)	(0.0012)	(0.0017)
Share Countryit	98.4101***	180.9962***	119.6852***	50.9974	72.3819***	298.8294***	56.4029***	85.1716***
	(8.1512)	(59.9571)	(26.3361)	(70.8331)	(21.6600)	(37.9432)	(10.0107)	(20.1684)
Constant	-12.1452***	-15.7663***	-7.1636	-0.7834	-12.1523***	-13.0159***	-12.6658***	-17.6422***
	(1.7574)	(1.9538)	(4.4786)	(7.1337)	(2.3831)	(2.5110)	(2.0610)	(2.2320)
N	566	566	566	566	566	566	566	566
AIC	29.4918	24.2312	25.7766	22.6661	28.4020	24.1526	33.1890	28.3212
BIC	72.8777	67.6171	69.1625	66.0520	71.7879	67.5386	76.5749	71.7071

Clustered standard errors in parentheses

* p<0.10, ** p<0.05, *** p<0.01

Dependent and lagged dependent variables are subset specific.

Table 2: Fractional Logit Regressions for the Share of Weighted Clinical Trials in Non-Traditional Countries

	(1)	(2)	(3)	(4)	(5)	(6)
Sample	Phase 1	Phase 1 Industry Sponsored	Phase 2	Phase 2 Industry Sponsored	Phase 3	Phase 3 Industry Sponsored
Dependent Variable: Share Phase j_{it}						
T	-0.3115	0.0332	0.4292***	0.3191*	0.1197	0.2801*
	(0.3397)	(0.3953)	(0.1627)	(0.1843)	(0.1394)	(0.1493)
T^2	0.0427	0.0170	-0.0381**	-0.0189	-0.0234*	-0.0396***
	(0.0321)	(0.0367)	(0.0159)	(0.0174)	(0.0135)	(0.0137)
SciTec Articlesit	0.1411	0.3677**	0.1578***	0.2243***	0.0004	-0.0341
	(0.1327)	(0.1829)	(0.0560)	(0.0758)	(0.0616)	(0.0718)
Price Levelit	0.4939	1.3587	-0.3974	0.7652	-0.2546	0.4812
	(0.9204)	(1.4733)	(0.5407)	(0.5171)	(0.5238)	(0.5781)
Populationit	-0.1954	-0.3225	-0.1445*	-0.2791***	-0.0292	-0.0218
	(0.1767)	(0.2236)	(0.0748)	(0.1079)	(0.0791)	(0.0950)
GDPit	-0.4504***	-0.4791	-0.1219	-0.5187***	0.0444	-0.1929
	(0.1725)	(0.2996)	(0.0950)	(0.1566)	(0.0876)	(0.1299)
Health Expendituresit	-0.0580	-0.1376	0.0174	-0.0118	0.0995**	0.0851*
	(0.0735)	(0.1108)	(0.0389)	(0.0581)	(0.0420)	(0.0471)
Net FDIit	0.0071	0.0044	-0.0003	-0.0030	0.0006	0.0050**
	(0.0056)	(0.0061)	(0.0025)	(0.0046)	(0.0024)	(0.0022)
Share Phase j_{it-1}	0.9945	2.7670**	0.5265*	0.5332	0.7717***	0.6708***
	(0.7525)	(1.2081)	(0.2727)	(0.3840)	(0.2094)	(0.2516)
Constant	3.5659	3.1678	0.0283	4.9311*	-1.3496	0.5364
	(3.9841)	(5.0979)	(1.6679)	(2.7290)	(1.6160)	(2.1419)
N	566	418	566	418	566	418
AIC	230.4934	139.1504	459.0778	368.2921	554.4061	443.1128
BIC	273.8793	179.5052	502.4637	408.6469	597.7921	483.4676

Clustered standard errors in parentheses

* p<0.10, ** p<0.05, *** p<0.01

Dependent and lagged dependent variables are subset specific.

Table 3: Fractional Logit Regressions for the Share of Clinical Trials in Specific Phases

Country	2002-2004	2010-2012
Brazil	***Pathological Conditions, Signs and Symptoms***; Cardiovascular Diseases; Respiratory Tract Diseases	***Pathological Conditions, Signs and Symptoms***; ***Cardiovascular Diseases***; Respiratory Tract Diseases
China	***Pathological Conditions, Signs and Symptoms***; Digestive System Diseases; ***Neoplasms***	***Neoplasms***; Digestive System Diseases; ***Pathological Conditions, Signs and Symptoms***
India	***Pathological Conditions, Signs and Symptoms***; ***Neoplasms***; Respiratory Tract Diseases	***Pathological Conditions, Signs and Symptoms***; Digestive System Diseases; Nutritional and Metabolic Diseases
Iran Islamic Rep.	Eye Diseases; Musculoskeletal Diseases; ***Pathological Conditions, Signs and Symptoms***	***Pathological Conditions, Signs and Symptoms***; Stomatognathic Diseases; ***Cardiovascular Diseases***
Israel	***Mental Disorders; Pathological Conditions, Signs and Symptoms***; Cardiovascular Diseases	***Pathological Conditions, Signs and Symptoms***; Nervous System Diseases; Mental Disorders
South Korea	***Neoplasms***; Digestive System Diseases; ***Mental Disorders***	***Neoplasms***; ***Pathological Conditions, Signs and Symptoms***; ***Cardiovascular Diseases***
Mexico	Nutritional and Metabolic Diseases; Endocrine System Diseases; ***Neoplasms***	***Pathological Conditions, Signs and Symptoms***; Nutritional and Metabolic Diseases; Respiratory Tract Diseases
Poland	Cardiovascular Diseases**; *Neoplasms***; Respiratory Tract Diseases	***Pathological Conditions, Signs and Symptoms***; ***Cardiovascular Diseases***; ***Neoplasms***
Russia	***Neoplasms***; ***Mental Disorders***; Cardiovascular Diseases	***Cardiovascular Diseases***; ***Pathological Conditions, Signs and Symptoms; Neoplasms***
Taiwan	***Neoplasms***; ***Pathological Conditions, Signs and Symptoms***; Cardiovascular Diseases	***Pathological Conditions, Signs and Symptoms***; ***Neoplasms***; ***Cardiovascular Diseases***
Thailand	Virus Diseases; Immune System Diseases; Eye Diseases	***Pathological Conditions, Signs and Symptoms***; Virus Diseases; Immune System Diseases
United States	***Neoplasms; Mental Disorders; Pathological Conditions, Signs and Symptoms***	***Neoplasms; Pathological Conditions, Signs and Symptoms; Cardiovascular Diseases***

Table 4 also suggests that non-traditional countries are able to address disease areas that are of particular importance in their local environment. In particular, infectious diseases as well as nutritional and metabolic diseases are among the most important causes of death in low and lower middle income countries (World Health Organization, 2014; Mathers *et al.*, 2009). Our results

indicate that countries like Brazil, India, Mexico, and Thailand emphasize these disease areas in their clinical research activities.

The World Health Organization (2014) points out that cardiovascular diseases, neoplasms/cancer and nervous system diseases such as Alzheimer's disease are the most important causes of death in high income countries. Table 3 shows that higher income countries among the non-traditional countries for clinical research conduct clinical research in these areas. Among the main non-traditional countries, Israel, South Korea, Poland, Russia, and Taiwan can be seen as higher income countries addressing these disease groups in their clinical research. China's classification as an "upper middle income" country by the World Bank may explain the importance of neoplasms in its clinical research to some extent.

In summary, our exploration indicates that non-traditional countries address MeSH tree numbers that are also addressed in the United States' clinical research more frequently. Thus, they are addressing diseases with either a worldwide prevalence or diseases with a particular importance for higher income countries. Nevertheless, some lower and middle income countries also manage to address disease areas that are important causes of death in their income group. Hence, at least to some extent, these countries address local health problems.

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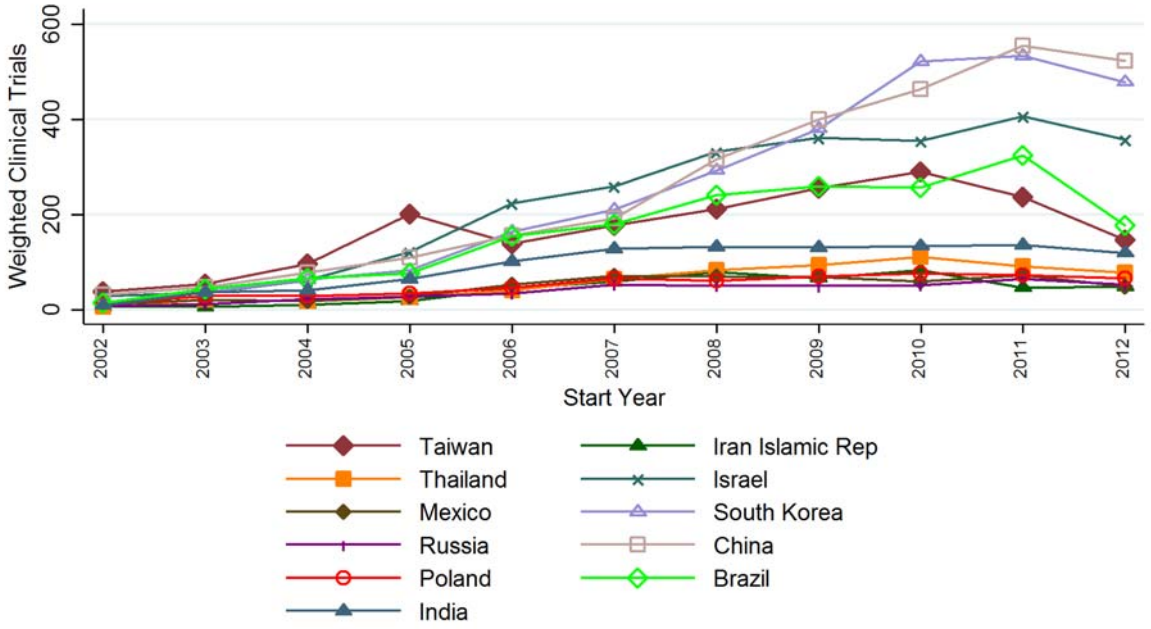


Figure 1: Number of Weighted Clinical Trials in Selected Non-Traditional Countries

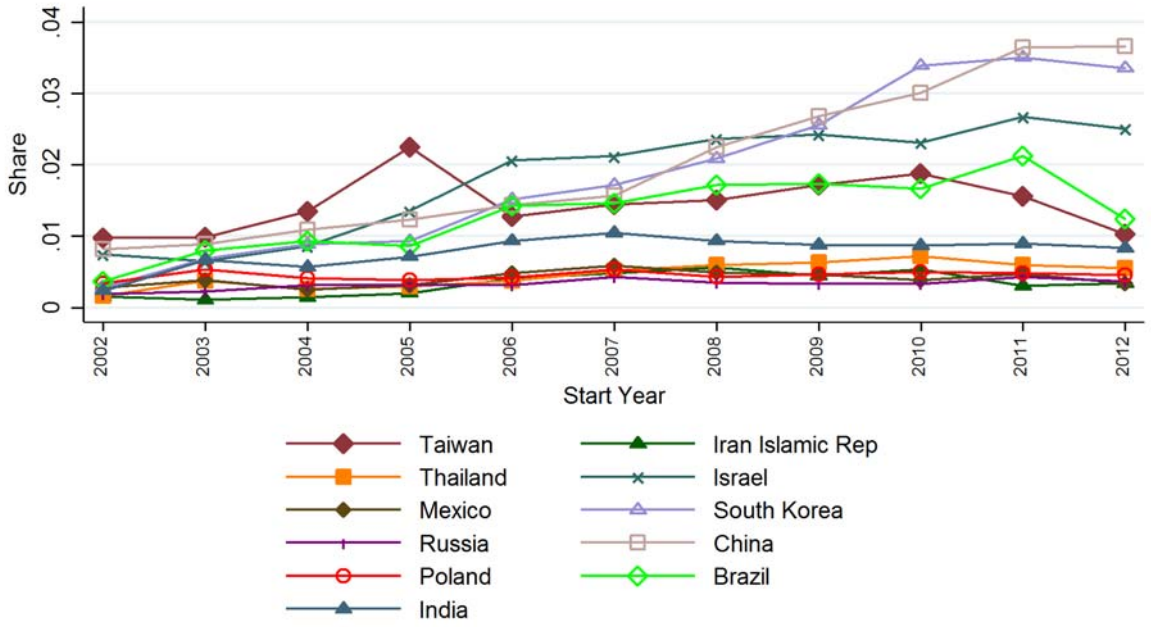


Figure 2: Share of Selected Non-Traditional Countries in Conducting Weighted Clinical Trials

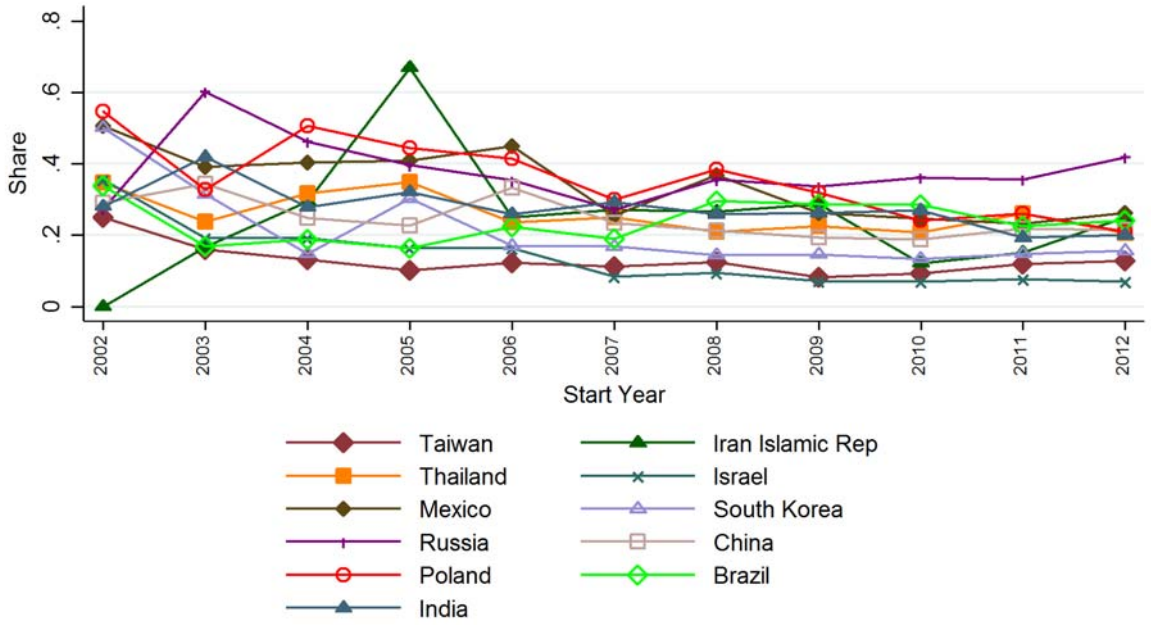


Figure 3: Share of Phase 3 Clinical Trials in Selected Non-Traditional Countries

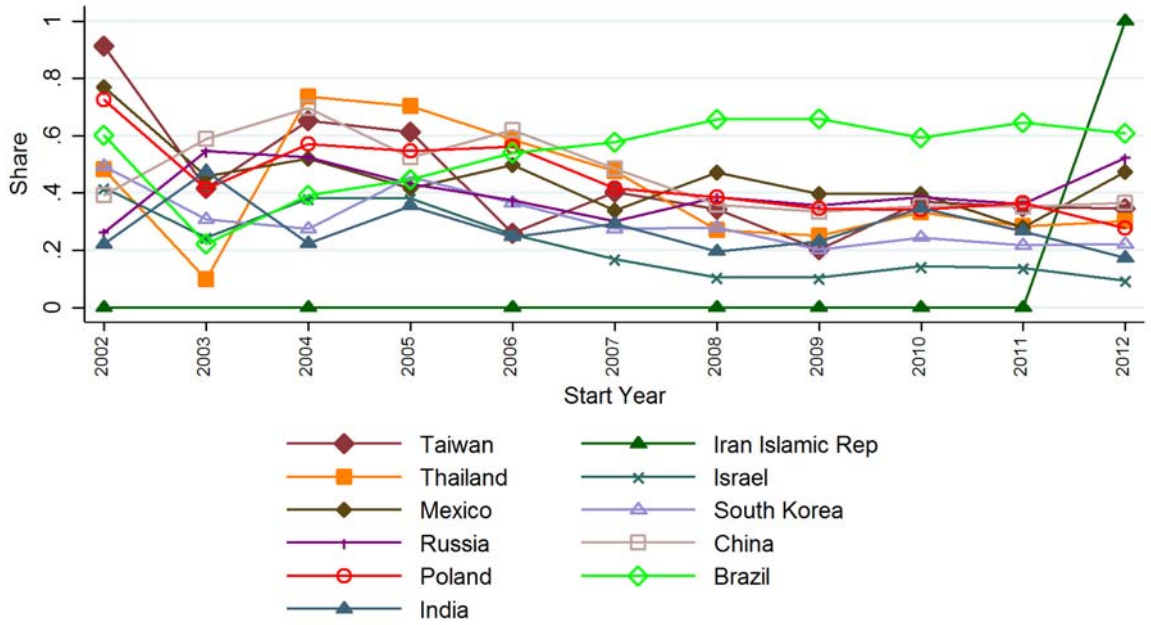


Figure 4: Share of Industry Sponsored Phase 3 Clinical Trials in Selected Non-Traditional Countries

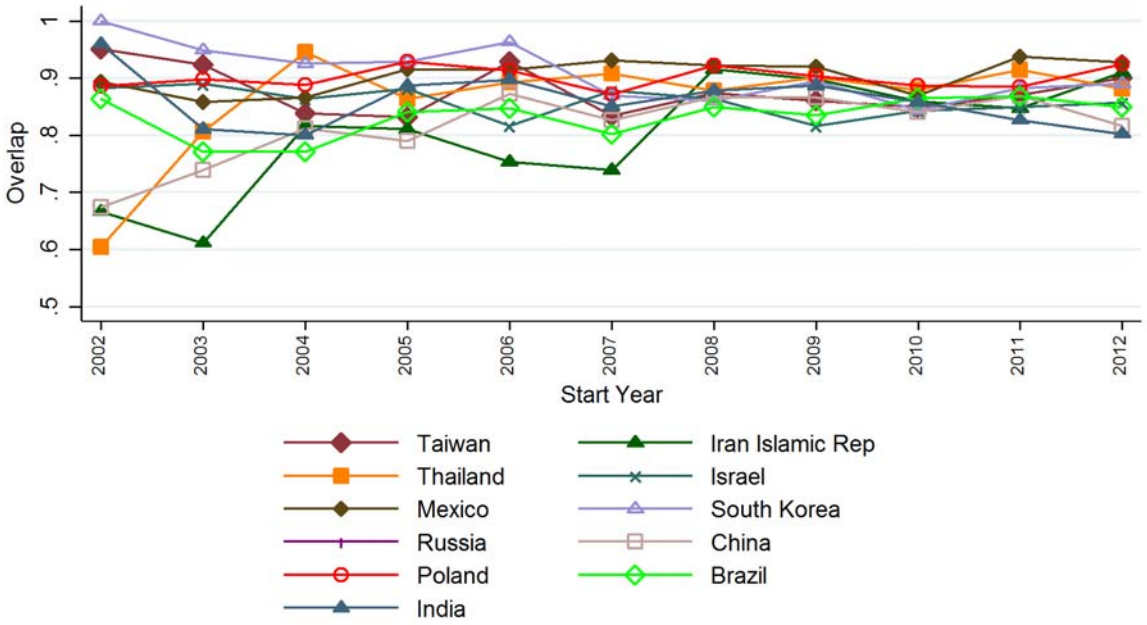


Figure 5: Development Overlap between the US and Selected Non-traditional Countries

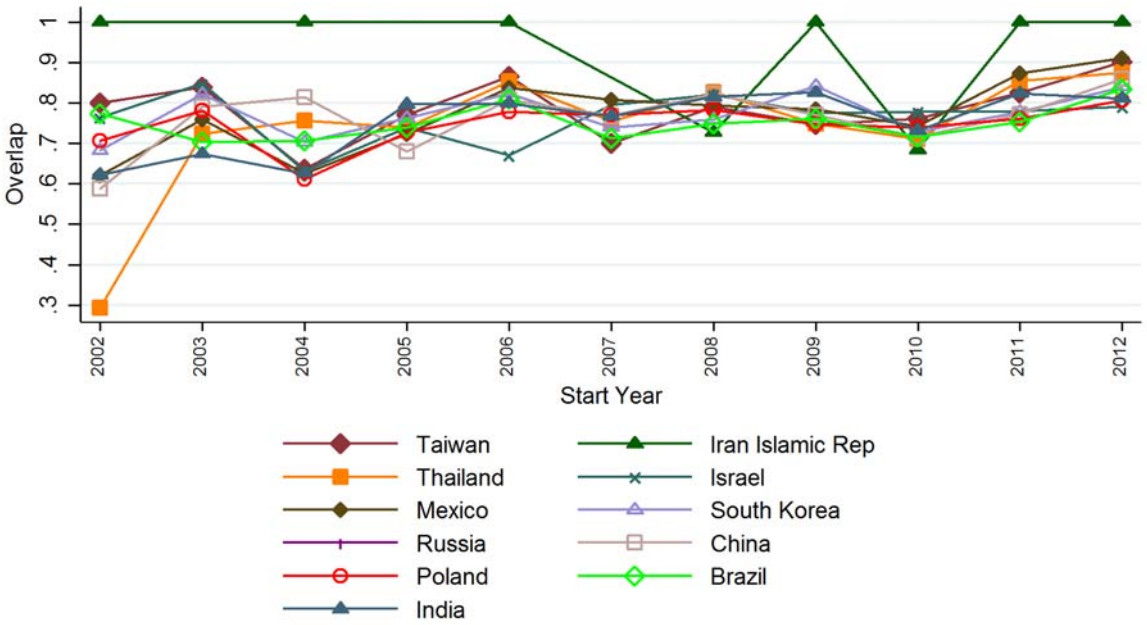


Figure 6: Overlap Share between the US and Selected Non-traditional Countries (only Industry Sponsored Clinical Trials) over time

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Sample	Full	Industry Sponsored	Phase 1	Phase 1 Industry Sponsored	Phase 2	Phase 2 Industry Sponsored	Phase 3	Phase 3 Industry Sponsored
Dependent Variable: Weighted Trialsit								
T	1.2138	0.5843	-0.4169	0.3822	0.9657**	0.3952*	0.5166*	0.6984***
	(0.7895)	(0.3818)	(0.4926)	(0.6347)	(0.4121)	(0.2055)	(0.2734)	(0.2028)
T^2	-0.1538*	-0.0636*	0.0771	0.0237	-0.0911**	-0.0334*	-0.0631**	-0.0812***
	(0.0843)	(0.0384)	(0.0497)	(0.0567)	(0.0410)	(0.0199)	(0.0267)	(0.0199)
SciTec Articlesit	0.7620**	0.5401***	1.2639***	1.5568**	0.9512***	0.4503***	0.4959***	0.3170**
	(0.3054)	(0.1804)	(0.3979)	(0.6173)	(0.2493)	(0.1188)	(0.1474)	(0.1280)
Price Levelit	4.5612**	2.1345	2.5622	0.6145	4.4004**	1.4255	2.3043**	0.6949
	(2.2574)	(1.6314)	(1.9309)	(2.7647)	(1.9879)	(0.8898)	(1.0119)	(0.7291)
Populationit	0.8946**	0.9567***	-0.0800	-0.1019	0.3482	0.2516*	0.6699***	0.6970***
	(0.3925)	(0.2858)	(0.3777)	(0.4465)	(0.2589)	(0.1427)	(0.2463)	(0.2244)
GDPit	0.3254	1.0744***	-0.7367*	0.2189	-0.3363	0.1912	0.1676	0.6322***
	(0.3630)	(0.2880)	(0.4280)	(0.5077)	(0.2675)	(0.1475)	(0.2224)	(0.2179)
Health Expendituresit	0.1790	0.2400**	-0.0092	0.0401	0.0846	0.0712	0.2353**	0.3019***
	(0.1365)	(0.0949)	(0.1250)	(0.1647)	(0.0917)	(0.0560)	(0.1094)	(0.0992)
Net FDIit	0.1149	0.0340	0.0167	0.0039	0.0508**	-0.0078	0.0564***	0.0266***
	(0.0784)	(0.0215)	(0.0118)	(0.0114)	(0.0201)	(0.0054)	(0.0177)	(0.0047)
Weighted Trialsit-1	1.1960***	1.0508***	1.1619***	0.9631***	1.0306***	1.0390***	0.9501***	0.8455***
	(0.0369)	(0.0520)	(0.1432)	(0.2345)	(0.0735)	(0.0852)	(0.0590)	(0.0739)
Constant	-26.5881***	-31.1400***	-4.3036	-16.9346**	-14.3206**	-11.0440***	-18.7191***	-21.9980***
	(9.8154)	(7.0839)	(8.1962)	(8.5684)	(6.0622)	(3.0852)	(6.0826)	(5.9239)
Sigma	7.8887***	4.0433***	3.8893***	3.8160***	4.1800***	1.8460***	3.1628***	2.0599***
	(1.2600)	(0.5897)	(0.6635)	(0.7961)	(0.7110)	(0.2053)	(0.5371)	(0.4008)
N	869	869	869	869	869	869	869	869
AIC	4759.6807	3078.4814	1563.2119	965.2903	2730.1018	1665.6218	2863.6265	2017.3375
BIC	4812.1215	3130.9222	1615.6527	1017.7311	2782.5426	1718.0626	2916.0673	2069.7783

Clustered standard errors in parentheses

* p<0.10, ** p<0.05, *** p<0.01

Dependent and lagged dependent variables are subset specific.

Table 1: Tobit Regressions for the Number of Weighted Clinical Trials in Non-Traditional Countries

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Sample	Full	Industry Sponsored	Phase 1	Phase 1 Industry Sponsored	Phase 2	Phase 2 Industry Sponsored	Phase 3	Phase 3 Industry Sponsored
Dependent Variable: Share Countryit								
T	0.1320	-0.0121	0.0660	0.8020*	0.2745***	0.3068**	0.1206	0.2162***
	(0.0910)	(0.0802)	(0.1286)	(0.4603)	(0.0929)	(0.1232)	(0.0905)	(0.0719)
T^2	-0.0170*	0.0010	-0.0003	-0.0436	-0.0230**	-0.0271**	-0.0114	-0.0214***
	(0.0092)	(0.0073)	(0.0116)	(0.0383)	(0.0092)	(0.0110)	(0.0084)	(0.0063)
SciTec Articlesit	0.4526***	0.4829***	0.7485***	1.6062***	0.5649***	0.4968***	0.4430***	0.4010***
	(0.0690)	(0.1009)	(0.1845)	(0.4197)	(0.0935)	(0.1057)	(0.0718)	(0.0922)
Price Levelit	0.8150*	0.2768	0.4148	0.2494	1.1038*	-0.0795	0.6768	-0.4880
	(0.4849)	(0.5644)	(1.0149)	(1.4112)	(0.6500)	(0.5396)	(0.4964)	(0.5356)
Populationit	0.1063	0.1619	-0.2069	-0.7876**	0.0423	0.0053	0.1446	0.2467**
	(0.0927)	(0.1035)	(0.2161)	(0.3733)	(0.1144)	(0.1281)	(0.0967)	(0.1166)
GDPit	-0.0301	0.2062*	-0.2736	-0.8934	-0.0661	0.0843	0.0054	0.3629***
	(0.0998)	(0.1184)	(0.2647)	(0.5612)	(0.1411)	(0.1215)	(0.1145)	(0.1163)
Health Expendituresit	0.0078	0.0211	-0.0274	-0.1594	-0.0142	0.0406	0.0266	0.0826**
	(0.0389)	(0.0352)	(0.0923)	(0.1075)	(0.0436)	(0.0453)	(0.0367)	(0.0401)
Net FDIit	-0.0057***	-0.0054***	-0.0034**	-0.0104**	-0.0038***	-0.0053**	-0.0056***	-0.0052***
	(0.0011)	(0.0014)	(0.0016)	(0.0052)	(0.0012)	(0.0024)	(0.0012)	(0.0017)
Share Countryit	98.4101***	180.9962***	119.6852***	50.9974	72.3819***	298.8294***	56.4029***	85.1716***
	(8.1512)	(59.9571)	(26.3361)	(70.8331)	(21.6600)	(37.9432)	(10.0107)	(20.1684)
Constant	-12.1452***	-15.7663***	-7.1636	-0.7834	-12.1523***	-13.0159***	-12.6658***	-17.6422***
	(1.7574)	(1.9538)	(4.4786)	(7.1337)	(2.3831)	(2.5110)	(2.0610)	(2.2320)
N	566	566	566	566	566	566	566	566
AIC	29.4918	24.2312	25.7766	22.6661	28.4020	24.1526	33.1890	28.3212
BIC	72.8777	67.6171	69.1625	66.0520	71.7879	67.5386	76.5749	71.7071

Clustered standard errors in parentheses

* p<0.10, ** p<0.05, *** p<0.01

Dependent and lagged dependent variables are subset specific.

Table 2: Fractional Logit Regressions for the Share of Weighted Clinical Trials in Non-Traditional Countries

	(1)	(2)	(3)	(4)	(5)	(6)
Sample	Phase 1	Phase 1 Industry Sponsored	Phase 2	Phase 2 Industry Sponsored	Phase 3	Phase 3 Industry Sponsored
Dependent Variable: Share Phase j_{it}						
T	-0.3115	0.0332	0.4292***	0.3191*	0.1197	0.2801*
	(0.3397)	(0.3953)	(0.1627)	(0.1843)	(0.1394)	(0.1493)
T^2	0.0427	0.0170	-0.0381**	-0.0189	-0.0234*	-0.0396***
	(0.0321)	(0.0367)	(0.0159)	(0.0174)	(0.0135)	(0.0137)
SciTec Articlesit	0.1411	0.3677**	0.1578***	0.2243***	0.0004	-0.0341
	(0.1327)	(0.1829)	(0.0560)	(0.0758)	(0.0616)	(0.0718)
Price Levelit	0.4939	1.3587	-0.3974	0.7652	-0.2546	0.4812
	(0.9204)	(1.4733)	(0.5407)	(0.5171)	(0.5238)	(0.5781)
Populationit	-0.1954	-0.3225	-0.1445*	-0.2791***	-0.0292	-0.0218
	(0.1767)	(0.2236)	(0.0748)	(0.1079)	(0.0791)	(0.0950)
GDPit	-0.4504***	-0.4791	-0.1219	-0.5187***	0.0444	-0.1929
	(0.1725)	(0.2996)	(0.0950)	(0.1566)	(0.0876)	(0.1299)
Health Expendituresit	-0.0580	-0.1376	0.0174	-0.0118	0.0995**	0.0851*
	(0.0735)	(0.1108)	(0.0389)	(0.0581)	(0.0420)	(0.0471)
Net FDIit	0.0071	0.0044	-0.0003	-0.0030	0.0006	0.0050**
	(0.0056)	(0.0061)	(0.0025)	(0.0046)	(0.0024)	(0.0022)
Share Phase j_{it-1}	0.9945	2.7670**	0.5265*	0.5332	0.7717***	0.6708***
	(0.7525)	(1.2081)	(0.2727)	(0.3840)	(0.2094)	(0.2516)
Constant	3.5659	3.1678	0.0283	4.9311*	-1.3496	0.5364
	(3.9841)	(5.0979)	(1.6679)	(2.7290)	(1.6160)	(2.1419)
N	566	418	566	418	566	418
AIC	230.4934	139.1504	459.0778	368.2921	554.4061	443.1128
BIC	273.8793	179.5052	502.4637	408.6469	597.7921	483.4676

Clustered standard errors in parentheses

* p<0.10, ** p<0.05, *** p<0.01

Dependent and lagged dependent variables are subset specific.

Table 3: Fractional Logit Regressions for the Share of Clinical Trials in Specific Phases

Country	2002-2004	2010-2012
Brazil	***Pathological Conditions, Signs and Symptoms***; Cardiovascular Diseases; Respiratory Tract Diseases	***Pathological Conditions, Signs and Symptoms***; ***Cardiovascular Diseases***; Respiratory Tract Diseases
China	***Pathological Conditions, Signs and Symptoms***; Digestive System Diseases; ***Neoplasms***	***Neoplasms***; Digestive System Diseases; ***Pathological Conditions, Signs and Symptoms***
India	***Pathological Conditions, Signs and Symptoms***; ***Neoplasms***; Respiratory Tract Diseases	***Pathological Conditions, Signs and Symptoms***; Digestive System Diseases; Nutritional and Metabolic Diseases
Iran Islamic Rep.	Eye Diseases; Musculoskeletal Diseases; ***Pathological Conditions, Signs and Symptoms***	***Pathological Conditions, Signs and Symptoms***; Stomatognathic Diseases; ***Cardiovascular Diseases***
Israel	***Mental Disorders; Pathological Conditions, Signs and Symptoms***; Cardiovascular Diseases	***Pathological Conditions, Signs and Symptoms***; Nervous System Diseases; Mental Disorders
South Korea	***Neoplasms***; Digestive System Diseases; ***Mental Disorders***	***Neoplasms***; ***Pathological Conditions, Signs and Symptoms***; ***Cardiovascular Diseases***
Mexico	Nutritional and Metabolic Diseases; Endocrine System Diseases; ***Neoplasms***	***Pathological Conditions, Signs and Symptoms***; Nutritional and Metabolic Diseases; Respiratory Tract Diseases
Poland	Cardiovascular Diseases**; *Neoplasms***; Respiratory Tract Diseases	***Pathological Conditions, Signs and Symptoms***; ***Cardiovascular Diseases***; ***Neoplasms***
Russia	***Neoplasms***; ***Mental Disorders***; Cardiovascular Diseases	***Cardiovascular Diseases***; ***Pathological Conditions, Signs and Symptoms; Neoplasms***
Taiwan	***Neoplasms***; ***Pathological Conditions, Signs and Symptoms***; Cardiovascular Diseases	***Pathological Conditions, Signs and Symptoms***; ***Neoplasms***; ***Cardiovascular Diseases***
Thailand	Virus Diseases; Immune System Diseases; Eye Diseases	***Pathological Conditions, Signs and Symptoms***; Virus Diseases; Immune System Diseases
United States	***Neoplasms; Mental Disorders; Pathological Conditions, Signs and Symptoms***	***Neoplasms; Pathological Conditions, Signs and Symptoms; Cardiovascular Diseases***

Table 4 about here

We aim to further explore heterogeneity in the specialization of countries as well as similarity to the US as the dominant location for conducting clinical research, one of the largest markets for

pharmaceuticals worldwide and one of the leading countries in the field of biomedical research. In doing so, we use the Medical Subject Headings (MeSH) to analyze countries' specialization patterns in conducting clinical trials based on conditions, indications, treatments, and pathogens. We compare countries' specialization patterns by building upon prior work by Onal Vural *et al.* (2013) and Azoulay *et al.* (2006) who developed a measure of the scientific similarity between researchers based on the degree of overlap in keywords attached to their publications. In line with their work, our measure accounts for similarity in the clinical research profiles of a non-traditional country *i* and the US based on MeSH tree numbers:

$$Overlap_{i\ to\ US\ in\ t} = \frac{Count\ of\ overlapping\ MESH\ tree\ numbers}{Count\ of\ MeSH\ tree\ numbers\ associated\ with\ i}$$

We calculate the $Overlap_{i\ to\ US\ in\ t}$ on a yearly basis in order to track changes in countries' clinical research profiles over time. In doing so, we count the number of unique MeSH tree numbers that occur in clinical trials which are conducted in country *i* and which occur at the same time in clinical trials exclusively conducted in the US, i.e., all trial sites are located in the US. This count is divided by the total number of unique MeSH tree numbers found in clinical trials conducted in country *i*.

The overlap measure ranges from 0 to 1, with 0 indicating that no MeSH tree numbers addressed in country *i* overlap with MeSH tree numbers addressed in the US. An overlap measure equal to 1 stands for a complete overlap in MeSH tree numbers. Consequently, a low overlap measure indicates substantial differences in the conditions, indications, treatments, and pathogens addressed in clinical trials conducted in country *i* compared to the US, whereas a high overlap measure suggests a high level of similarity in the clinical research profiles of country *i* and the US. It should be noted that the measure is not symmetric but depends on the country chosen as a reference in the denominator. Moreover, and in contrast to other similarity measures, the overlap measure leads to meaningful results even if the benchmark country has a dominant position and conducts clinical trials related to most MeSH tree numbers.

In the following we provide an example for the calculation of the overlap measure. Suppose that clinical trials conducted in the US contain the different MeSH tree numbers; C04 (Neoplasms), C05 (Musculoskeletal Diseases), and C14 (Cardiovascular Diseases) whereas clinical trials conducted in country *i* report the MeSH tree numbers C03 (Parasitic Diseases) and C14. Hence, the number of overlapping MeSH tree numbers equals 1 (C14) and the count of country *i*'s MeSH tree numbers equals 2 so that the $Overlap_{i\,to\,US\,int} = 1/2$.

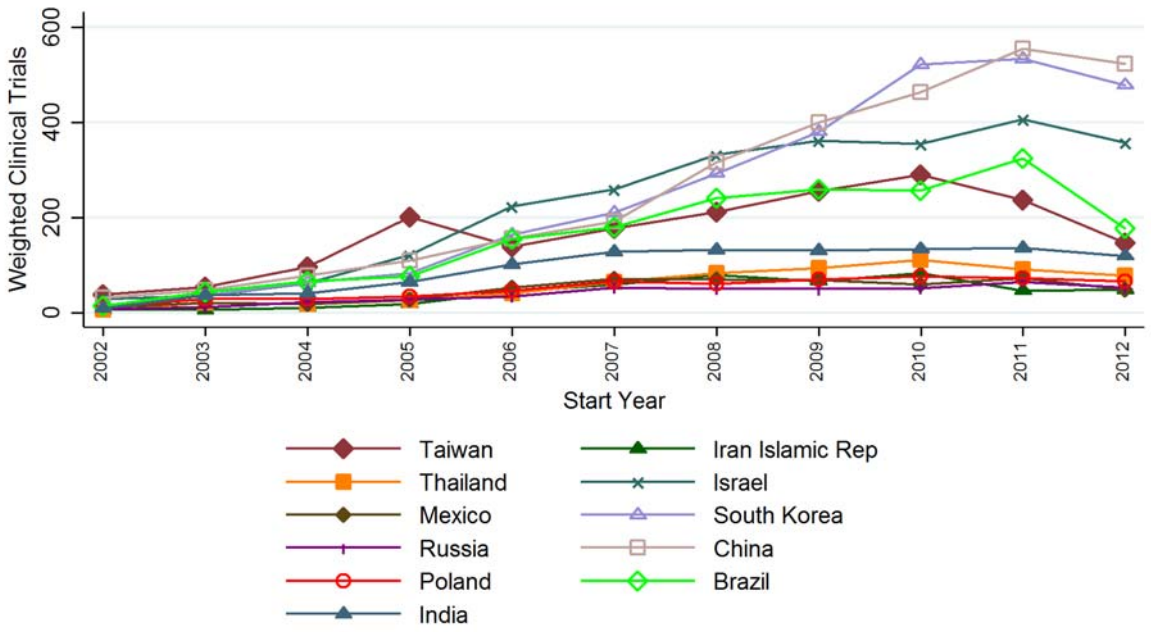
At first sight, Figure 5 suggests a general trend to convergence, but a closer look illustrates some differences in the development of the main non-traditional clinical trial countries' clinical research profiles and the clinical research profile of the US. While some countries increasingly conduct clinical trials that address conditions, indications, treatments, and pathogens that are addressed in clinical trials exclusively conducted in the US, other countries developed a clinical research profile that is less similar to the US' profile.

China, as the non-traditional country with the highest number of clinical trials, increased its overlap from 0.67 in 2002 to 0.87 in 2011, indicating that China's clinical research profile shows a growing similarity to the US profile. However, the overlap decreased again slightly to 0.82 in 2012. Several other countries show an increasing or rather stable similarity to the US profile particularly in the years after 2004, such as Brazil, Israel, Poland, Mexico, Poland, Russia, and Thailand. Remarkably, South Korea, which had exclusively addressed MeSH tree numbers that were also addressed in the US in 2002 decreased its overlap to 0.89 in 2012. Taiwan also shows a tendency to address more MeSH tree numbers that are not addressed in the US since its overlap decreased from approximately 0.95 in 2002 to approx. 0.9 in 2012. After an initial decrease from 0.96 in 2002 to 0.8 in 2004, India's clinical research profile became more similar to the US profile once more with an overlap of 0.9 in 2006. However, India has decreased its similarity to the US in subsequent years as indicated by an overlap of 0.8 in 2012.

Insert Figure 5 about here

The extent to which clinical trial profiles become more alike to the profile of the US may depend on the sponsors of clinical trials. Bio-pharmaceutical companies, particular those based in the traditional (western) industry centers, may prioritize clinical testing of drug candidates that address diseases or conditions with a worldwide prevalence and a high potential demand (in western markets), such as cancer, cardiovascular diseases, and nervous system diseases, e.g., those closely related to aging populations. Bio-pharmaceutical companies located in non-traditional countries may follow a rather similar strategy and address these worldwide diseases due to the larger market size as compared to diseases that are specific to their countries of origin or due to opportunities to develop generic drugs. On the contrary, non-traditional countries' governments and non-profit organizations may be interested in the development of treatments and new medications against local health problems, such as bacterial infections, virus or parasitic diseases that are rarely addressed by (western) bio-pharmaceutical companies. Moreover, local firms may have access to locally bounded knowledge which provides them with a unique competitive advantage in addressing country-specific diseases.

Concentrating on clinical trials that have been sponsored by the bio-pharmaceutical industry, the patterns presented in



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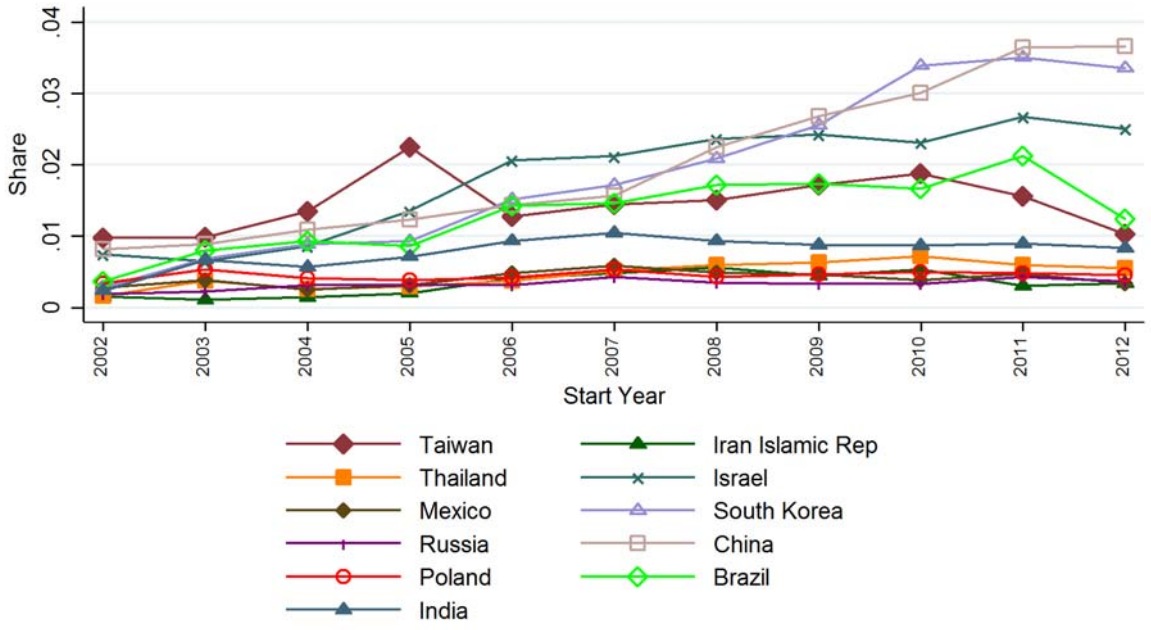

Figure 2: Share of Selected Non-Traditional Countries in Conducting Weighted Clinical Trials

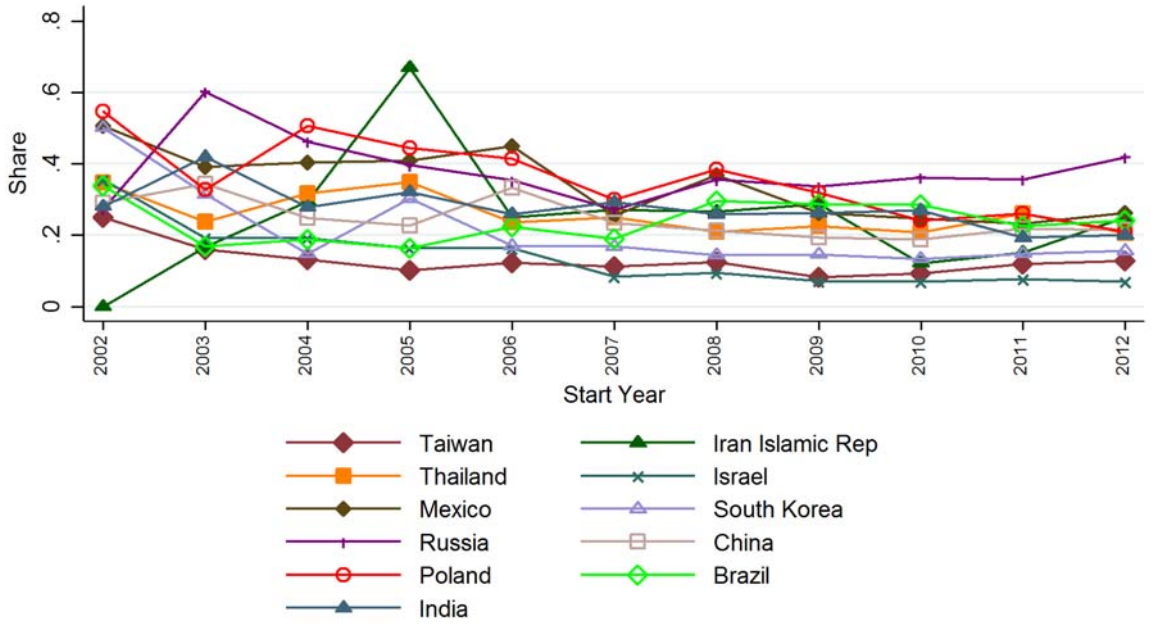

Figure 3: Share of Phase 3 Clinical Trials in Selected Non-Traditional Countries

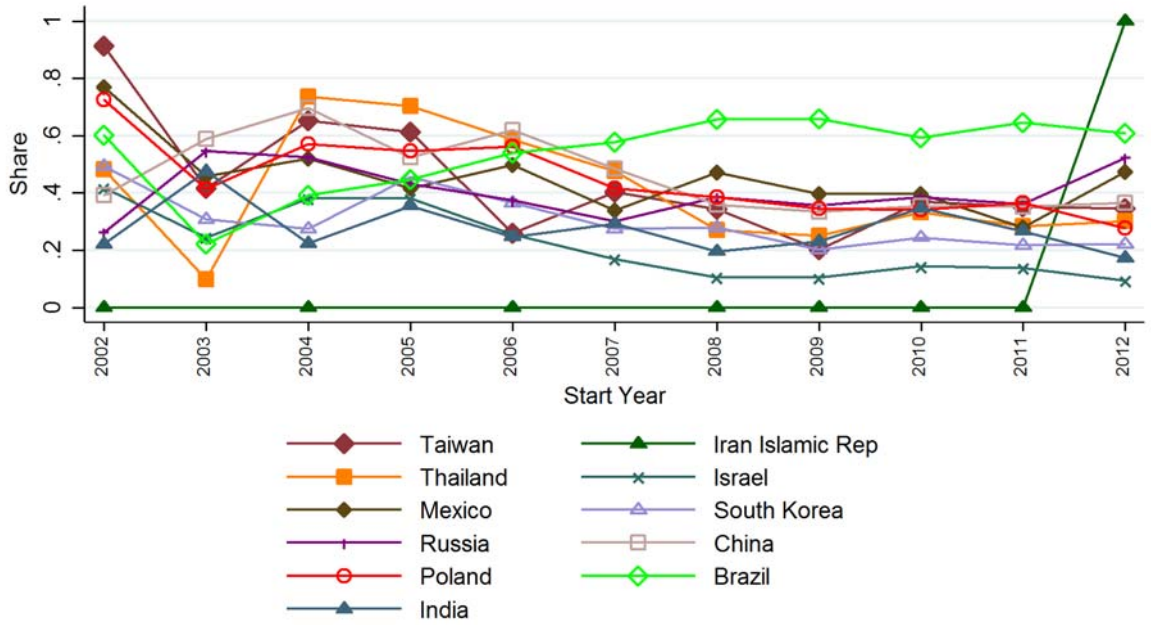

Figure 4: Share of Industry Sponsored Phase 3 Clinical Trials in Selected Non-Traditional Countries

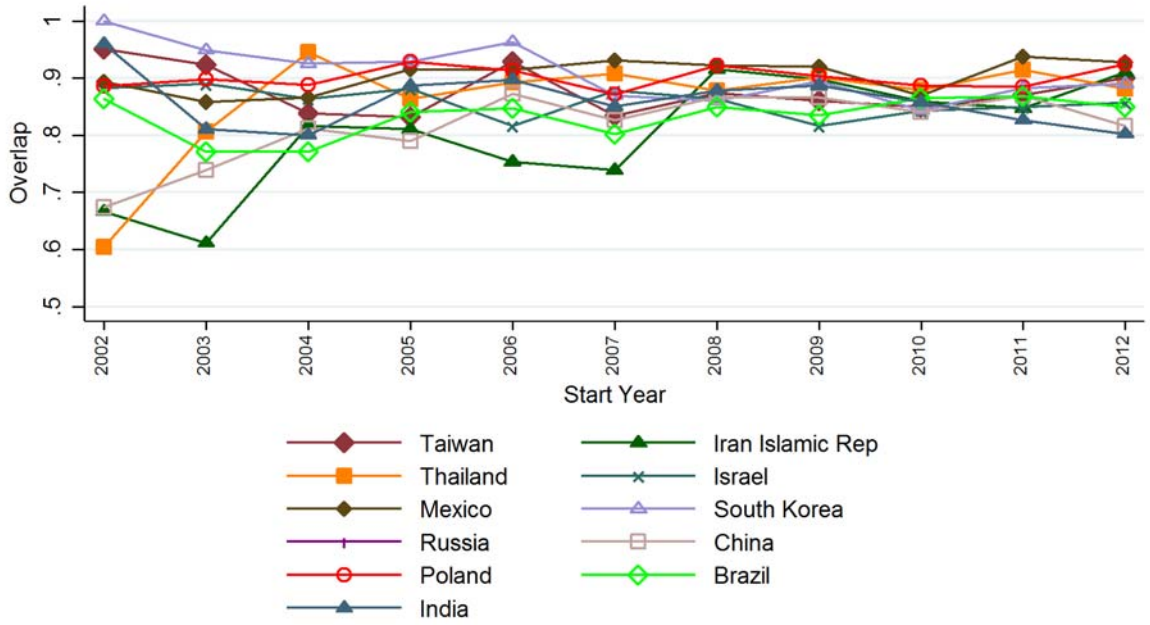

Figure 5: Development Overlap between the US and Selected Non-traditional Countries

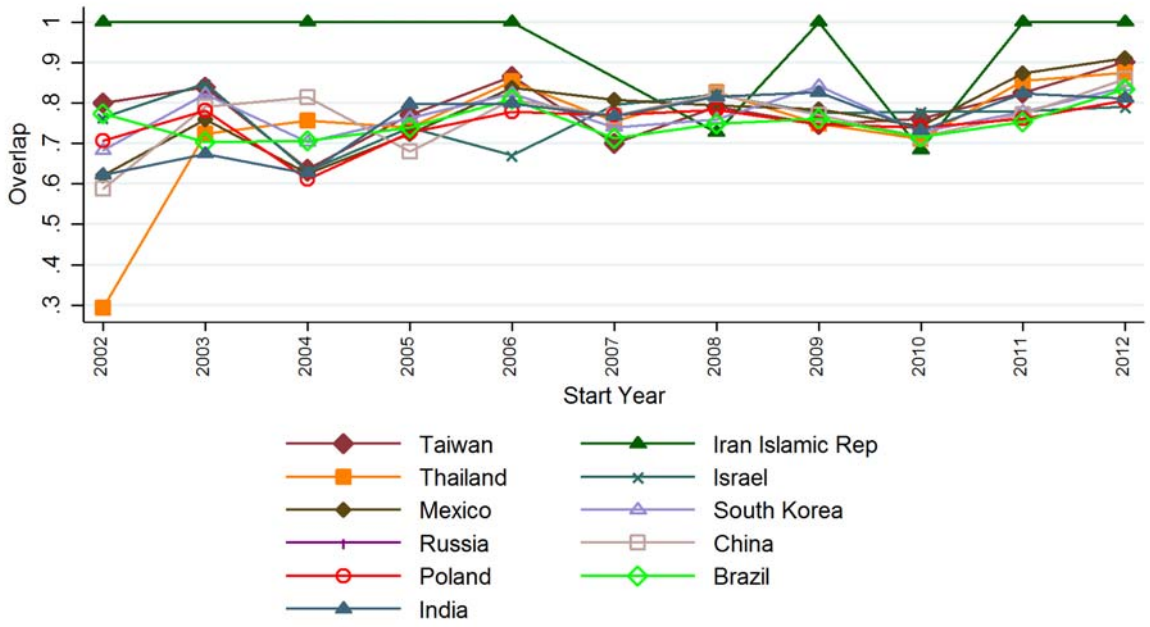

Figure 6 suggest that non-traditional countries' clinical research profiles converge to the profile of the US over time. Although industry sponsored trials show a higher initial level of dissimilarity in 2002, only minor differences in the overlap measure of industry sponsored and all clinical trials can be observed for the main non-traditional countries in 2012. The overlap measure referring to industry sponsored trials increased considerably for some countries, e.g., for China from 0.59 in 2002

to 0.86 in 2012, for India from 0.62 to 0.81, or South Korea from 0.68 to 0.84. For some other countries the decrease is more moderate e.g., Brazil's and Israel's overlap measure decreased from 0.77 in 2002 to 0.83 in 2012 and from 0.76 to 0.79 respectively. To some degree, Iran can be considered an exception since the country hosts only very few clinical trials sponsored by the bio-pharmaceutical industry.

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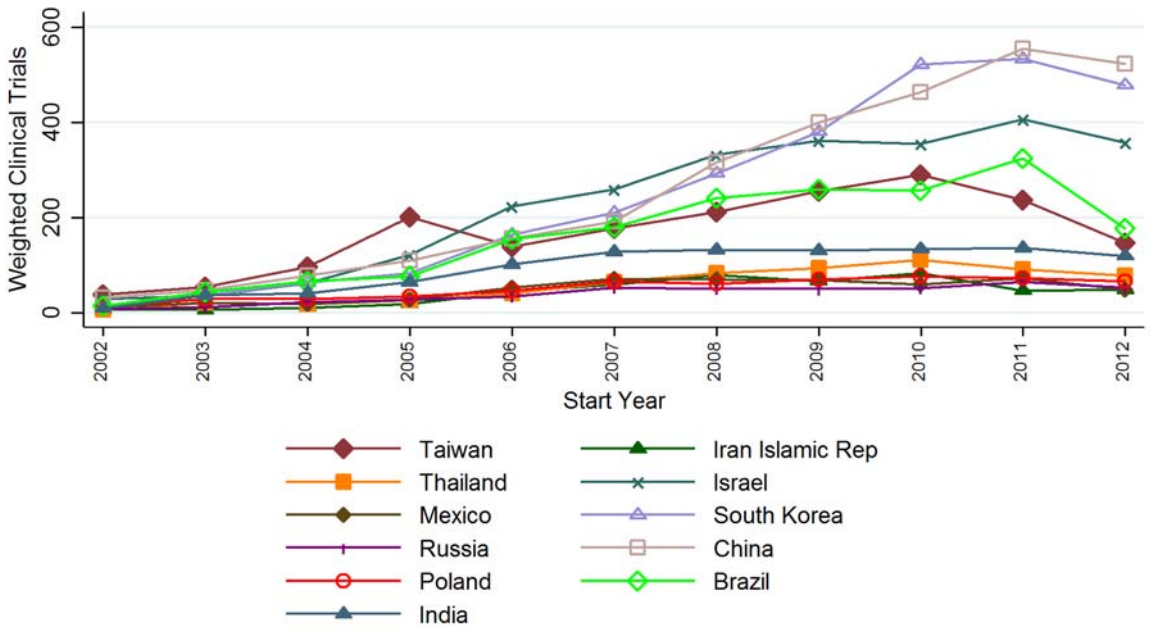

Figure 1: Number of Weighted Clinical Trials in Selected Non-Traditional Countries

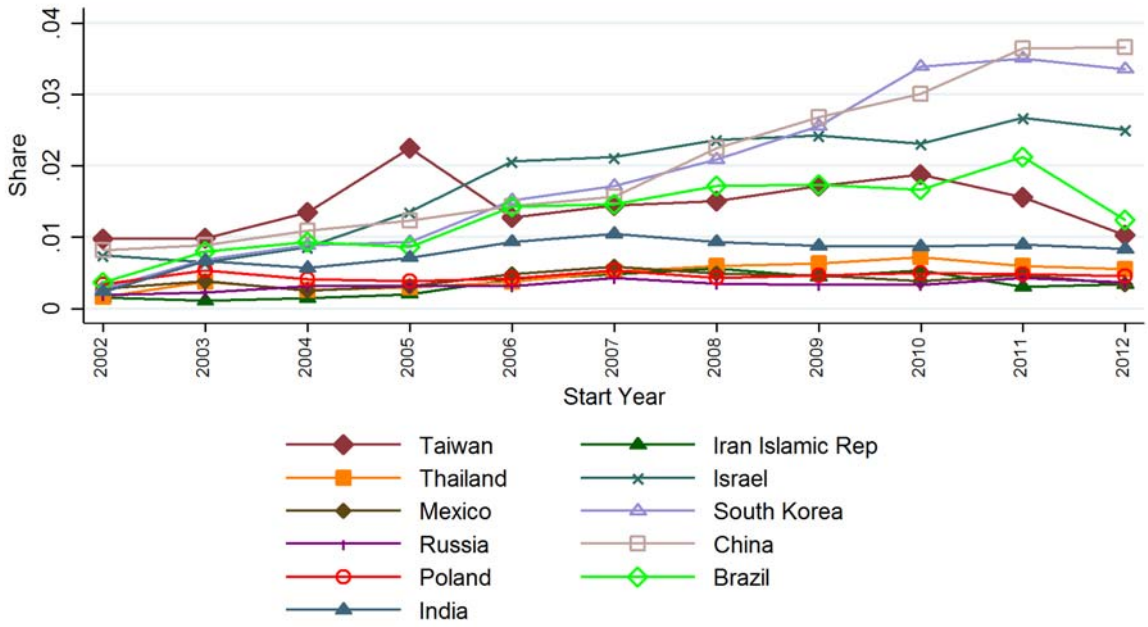

Figure 2: Share of Selected Non-Traditional Countries in Conducting Weighted Clinical Trials

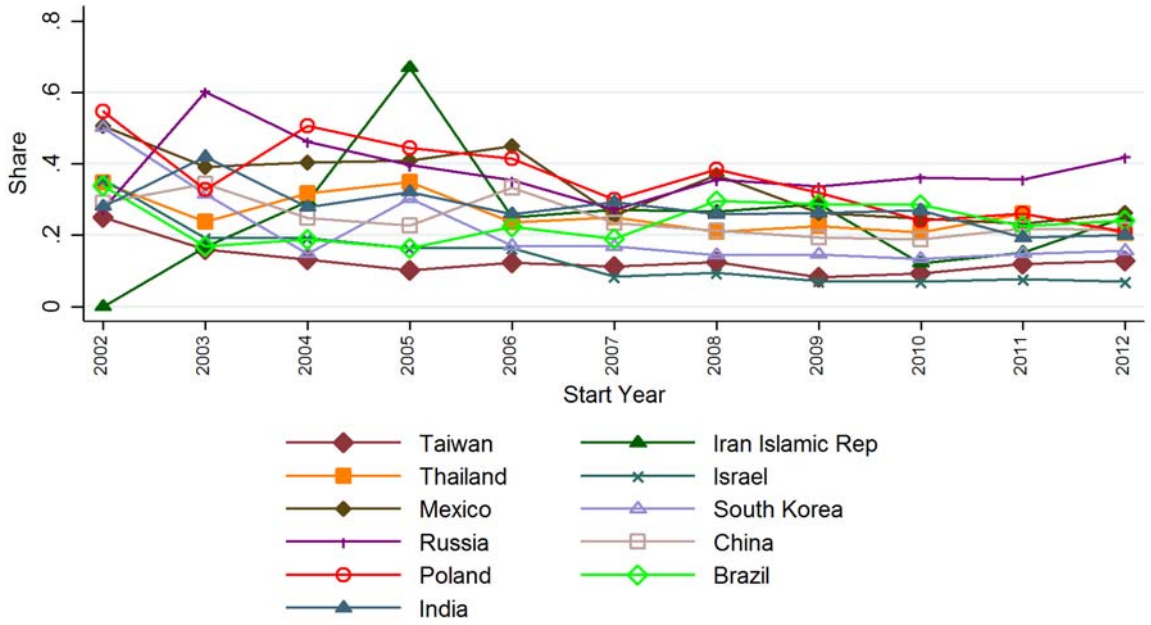

Figure 3: Share of Phase 3 Clinical Trials in Selected Non-Traditional Countries

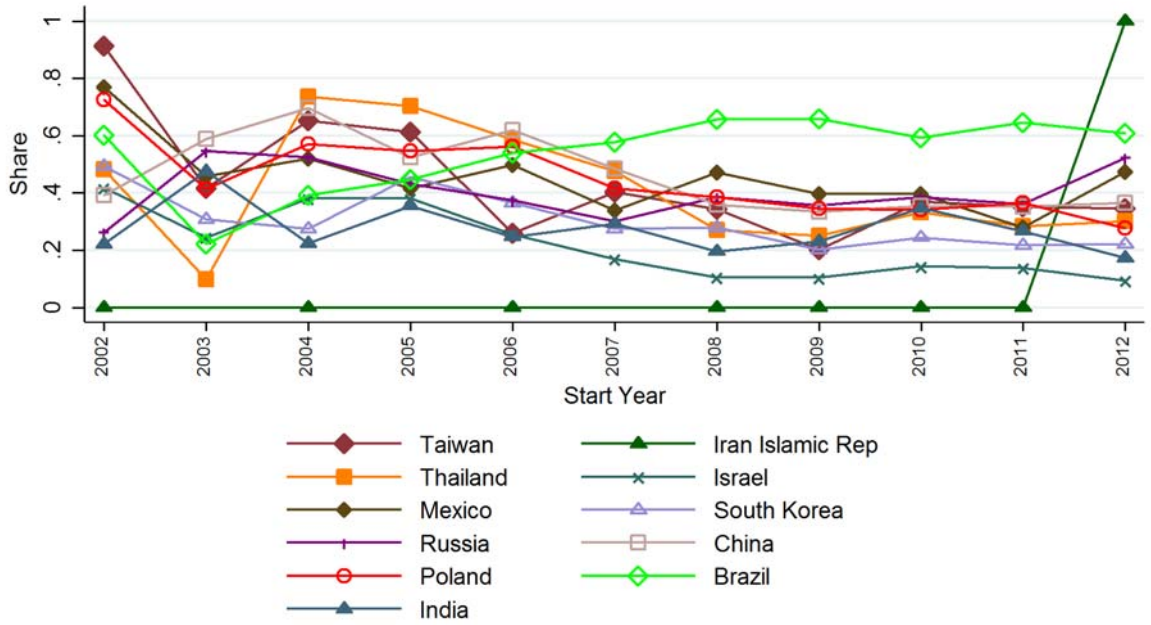

Figure 4: Share of Industry Sponsored Phase 3 Clinical Trials in Selected Non-Traditional Countries

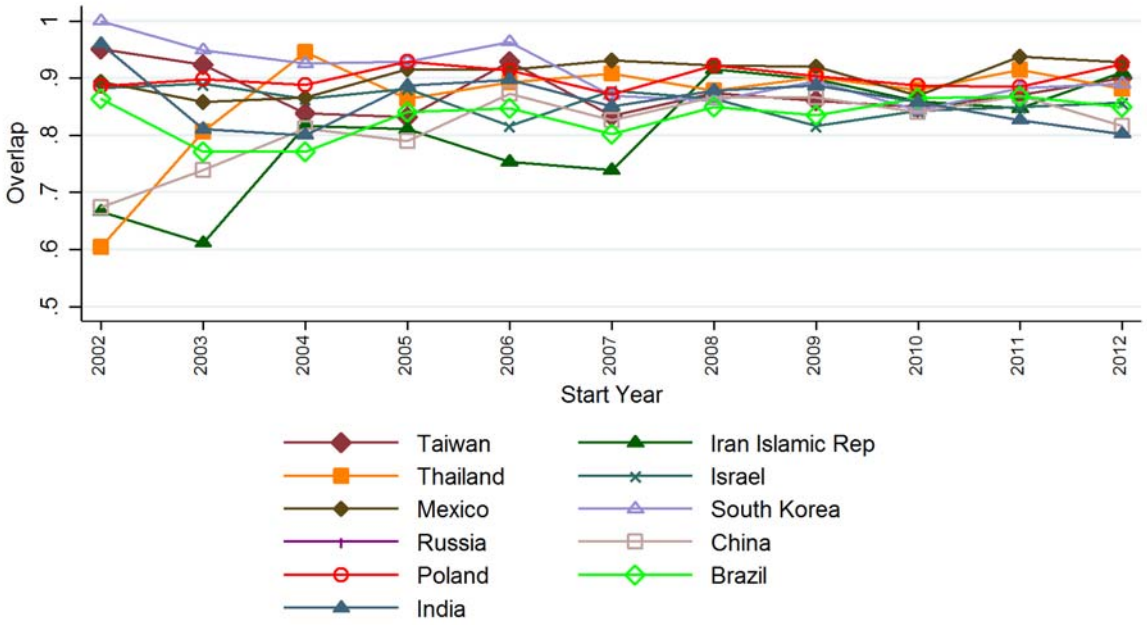

Figure 5: Development Overlap between the US and Selected Non-traditional Countries

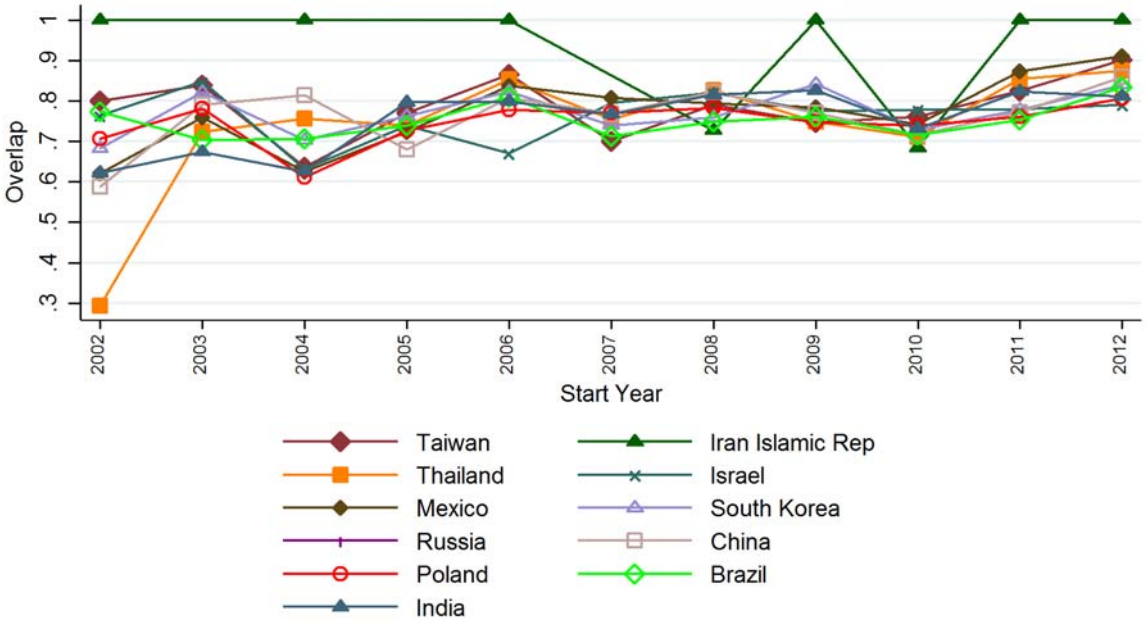

Figure 6 about here

The results of the fractional logit regressions investigating whether the overlap between the US and non-traditional clinical trial countries' MeSH tree numbers changed over time are presented in Table

5. The exploration of several subsamples of clinical trials depending on sponsor and trial characteristics reveals nuanced patterns of development. We do not find support for a changing overlap over time in the full sample. However, the overlap to the US changes particularly for industry sponsored trials. More specifically, we find a u-shaped relationship between the time *T* and the overlap of non-traditional countries clinical research profiles to the US profile for all industry sponsored trials as well as for phase 3 industry sponsored trials. While the similarity to the US decreased for the sample of industry sponsored trials until 2006 or 2007 and increased thereafter again, it decreased in case of industry sponsored phase 3 trials until 2009 and showed an increase thereafter. Contrary to these results, we find an inverted u-shaped relationship between *T* and the overlap for phase 1 industry sponsored trials, suggesting that in this category clinical trial profiles initially become more similar before turning more diverse in the period including and after 2005. For the subsample of phase 3 clinical trials we find a linearly decreasing similarity over time. Countries with a high population and a high GDP per capita, as indicators for market attractiveness, show a higher overlap for phase 3 trials and industry sponsored phase 3 trials. In addition, GDP per capita is positively related to the overlap in the full sample and in the sample of industry sponsored trials. The number of countries' scientific articles is negatively related to the overlap measure for phase 3 and industry sponsored phase 3 trials while the price level indicator is negatively associated with the overlap for industry sponsored trials and phase 2 industry sponsored trials.

Our regression analysis points to a rather limited convergence of non-traditional countries clinical research profiles to the profile of the US based on MeSH tree numbers.[13] With respect to knowledge transfer arguments, non-traditional countries might have learnt through the increasing number of trials they have hosted over time to address conditions, diseases, treatments, or pathogens that are of local importance, at least in phase 3 projects. Particularly, countries with a strong scientific base are able to conduct late stage clinical research activities that do not correspond to US clinical trials. These developments towards a more independent clinical research profile are to some extent

counterbalanced by variables related to market size and attractiveness that stimulate clinical research activities similar those conducted in the US.

The results for clinical trials sponsored by organizations based in traditional countries are rather similar to those discussed above.

Insert Table 5 about here

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5 Discussion and Conclusions

There seems to be a broad consensus that clinical trials are globally migrating. However, the so far scant empirical attention has led to contradicting views in terms of the involved countries and the underlying reasons for the globalization of clinical research. Building on the concept of national innovative capacity (Furman *et al.*, 2002), we explored the changing geographical patterns of clinical research activities and its drivers based on a comprehensive dataset of clinical trials registered in the years from 2002 to 2012.

Our empirical analyses suggest that non-traditional countries are often increasingly involved not only in data-intense but also in knowledge-intense clinical research activities irrespective of the type of sponsor. Particularly the leading non-traditional countries, e.g., China, South Korea, and Israel, increased the absolute number of trials as well as their share in global clinical trials, while the dominant position of the US has been (slightly) weakened. Some countries, such as India, that are often named as important locations for clinical trials, are not involved as much as anecdotal evidence has suggested (Glickman *et al.*, 2009).

So far, the mounting involvement of non-traditional countries in offshored R&D activities is widely attributed to cost reductions and efficiency improvements in data generation trials (Gupta and Padhy, 2011; Glickman et al., 2009). Contrary to this widely held belief, our results do not indicate that cost differences are the main reason for the involvement of non-traditional countries in clinical research. Beyond the specific setting of the geography of clinical research, this result questions to some extent the importance of cost advantages for R&D offshoring in general (Demirbag and

Glaister, 2010; Farrell, 2005). Instead, our findings reveal that non-traditional countries' scientific and technological knowledge bases tend to drive the amount of clinical trials performed in these countries. This result supports the view that host countries' knowledge base as well as the availability of science and engineering talent determines countries' attractiveness for offshored R&D services (Lewin et al., 2009; Manning et al., 2008).

Furthermore, our empirical results suggest that differences in countries' national innovative capacity lead to considerable variation in the direction of their R&D activities in terms of whether their fields of research are locally or globally relevant. On the one hand, for knowledge intense, early stage trials we find a tendency that non-traditional countries are increasingly addressing disease areas that are conducted at the same time in the US. On the other hand, non-traditional countries have been able to increasingly address local health problems in late stage clinical research. An advanced science and technology base enables non-traditional countries to benefit from offshored R&D activities through knowledge spillovers and knowledge transfer (Hu *et al.*, 2005) and to perform clinical research activities that correspond to local health problems.

In addition, and consistent with the literature (Gassmann and Han, 2004), our findings indicate that, across non-traditional countries, demand side factors support the involvement in late stage clinical trials which have a rather limited potential for knowledge spillovers and transfer. More attractive markets support clinical research activities directed towards global rather than local health problems. The consequences for the inhabitants of non-traditional countries are, however, ambiguous. On the one hand, they may benefit from the improved safety and efficacy due to drug development that takes local specificities into account (Kremer, 2002). On the other hand, the negligence of local health problems in (western) pharmaceutical R&D may continue.

These results are highly relevant and have important implications for innovation and pharma-economics scholars as they provide insights into the extent of internationalization of clinical research and the involvement of particular countries. They go beyond many existing studies by challenging widely shared beliefs claiming that predominantly data intense development activities are relocated

to non-traditional countries due to cost advantages. Instead, our results suggest that knowledge-intense development activities are also increasingly conducted in non-traditional countries.

For policy makers in non-traditional countries, our study suggests that investments into countries' science and technology base support their attractiveness for knowledge-intense trials that are associated with a higher potential for knowledge transfer and learning, thus supporting the development of the domestic bio-pharmaceutical industry. At the same time, these investments enable countries to address local health problems, at least in late stage clinical research.

For practitioners in the bio-pharmaceutical industry, the paper provides a detailed description of the changing geography of clinical research and its drivers that can be helpful for future decisions about the location of clinical trials.

We see our exploratory analysis as the first step of a broader research agenda to deepen our understanding of the involvement of non-traditional countries in international R&D activities, the drivers of this development, and its consequences, particularly but not exclusively with respect to clinical research activities. Firstly, the mechanisms of knowledge spillovers and knowledge transfer through offshored R&D activities such as clinical trials need to be thoroughly examined. Secondly, there is a lack of empirical investigations evaluating the consequences of offshored R&D activities for serving the needs of non-traditional countries and their populations such as the availability, safety, and efficacy of new or improved medications. Thirdly, we need a detailed understanding of whether offshored development activities, such as late stage clinical trials, can stimulate the development of the domestic knowledge base and support R&D activities with a domestic relevance.

Acknowledgements

We thank the editors and two anonymous reviewers, Anne Assmus, Patrick Figge, Timothy Quigley, Joachim Schnurbus, the participants of the 15th International Joseph A. Schumpeter Society Conference in Jena, Germany, as well as the participants of the Workshop "What Do We Know and What Should We Know about International Knowledge Sourcing?" in Catania, Italy, particularly Grazia

Santangelo, for stimulating discussions and valuable suggestions. Thomas Dengler and Manuel Donaubauer provided competent research assistance.

Appendix

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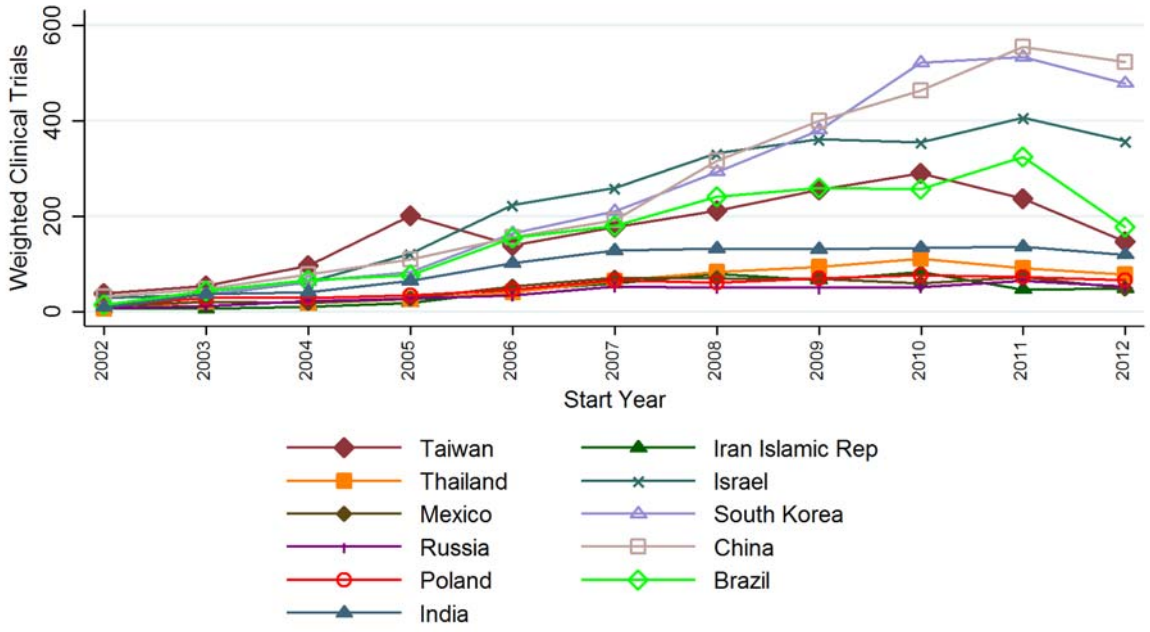

Figure 1: Number of Weighted Clinical Trials in Selected Non-Traditional Countries

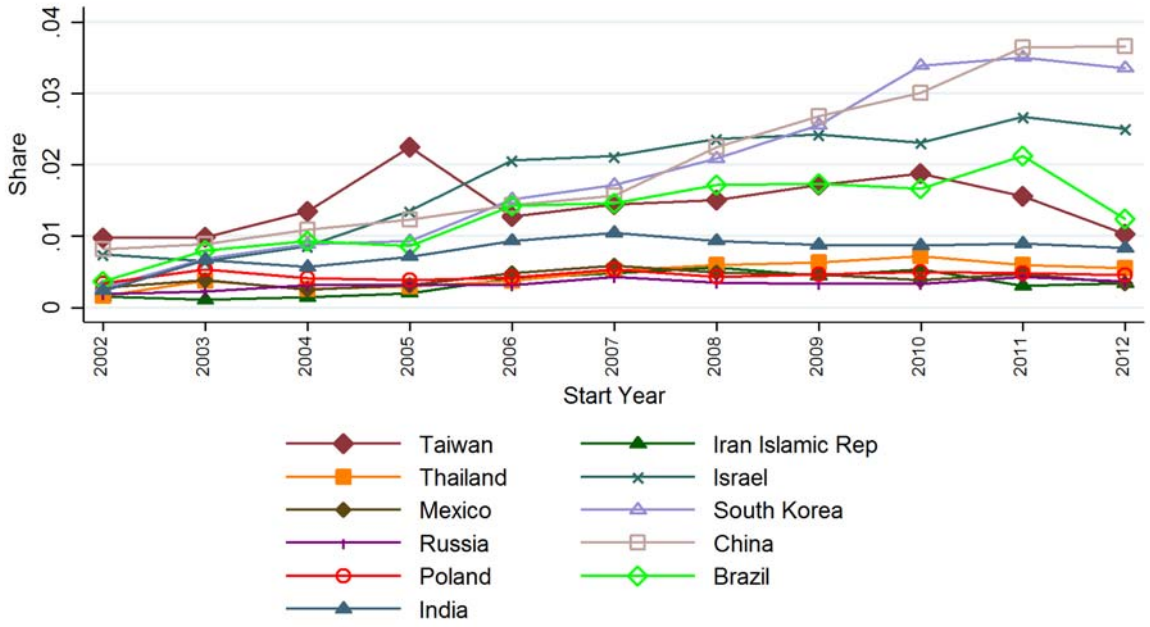

Figure 2: Share of Selected Non-Traditional Countries in Conducting Weighted Clinical Trials

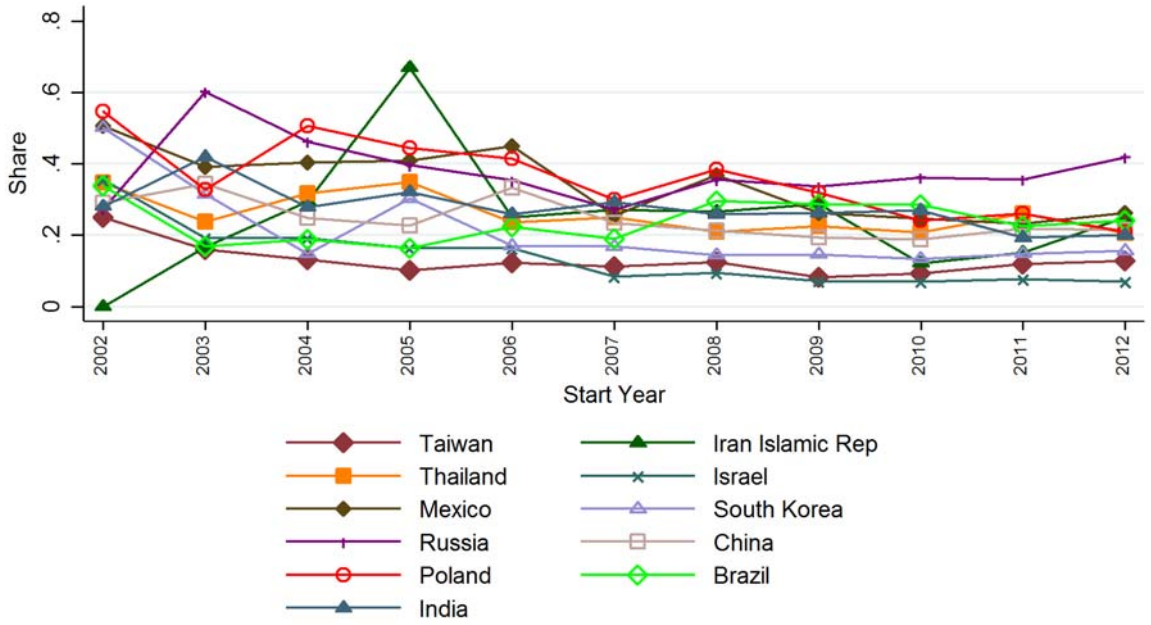

Figure 3: Share of Phase 3 Clinical Trials in Selected Non-Traditional Countries

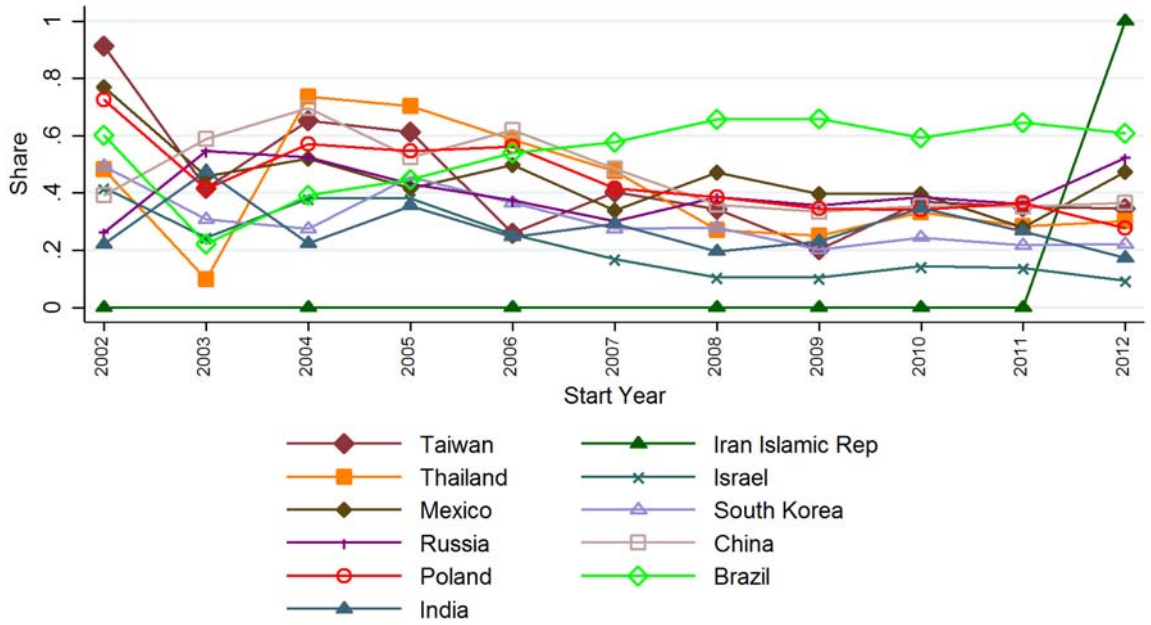

Figure 4: Share of Industry Sponsored Phase 3 Clinical Trials in Selected Non-Traditional Countries

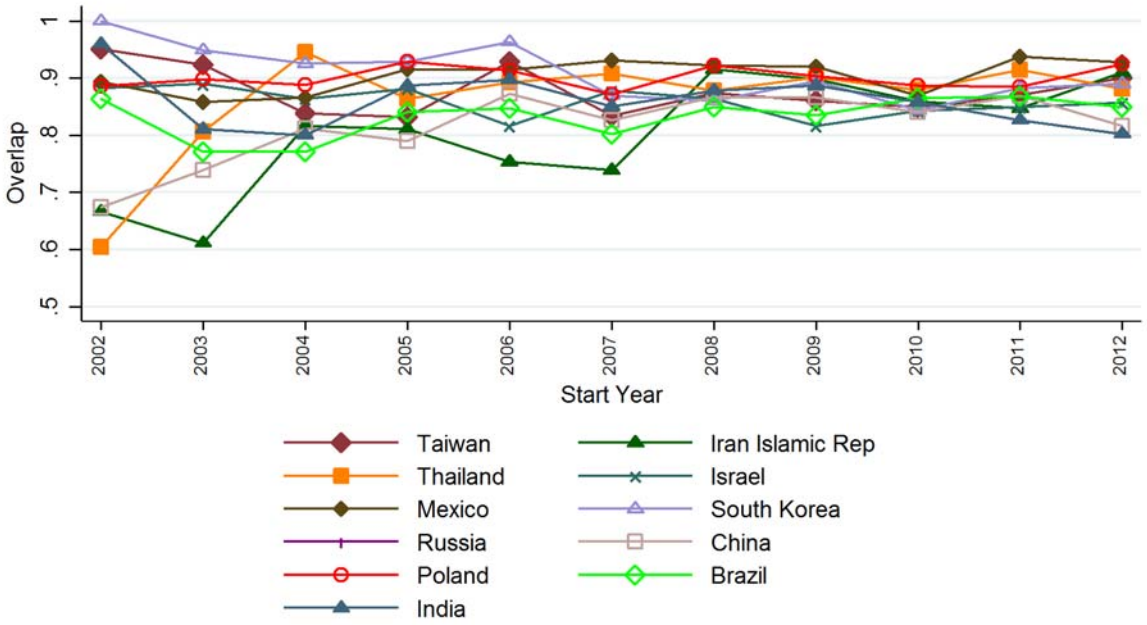

Figure 5: Development Overlap between the US and Selected Non-traditional Countries

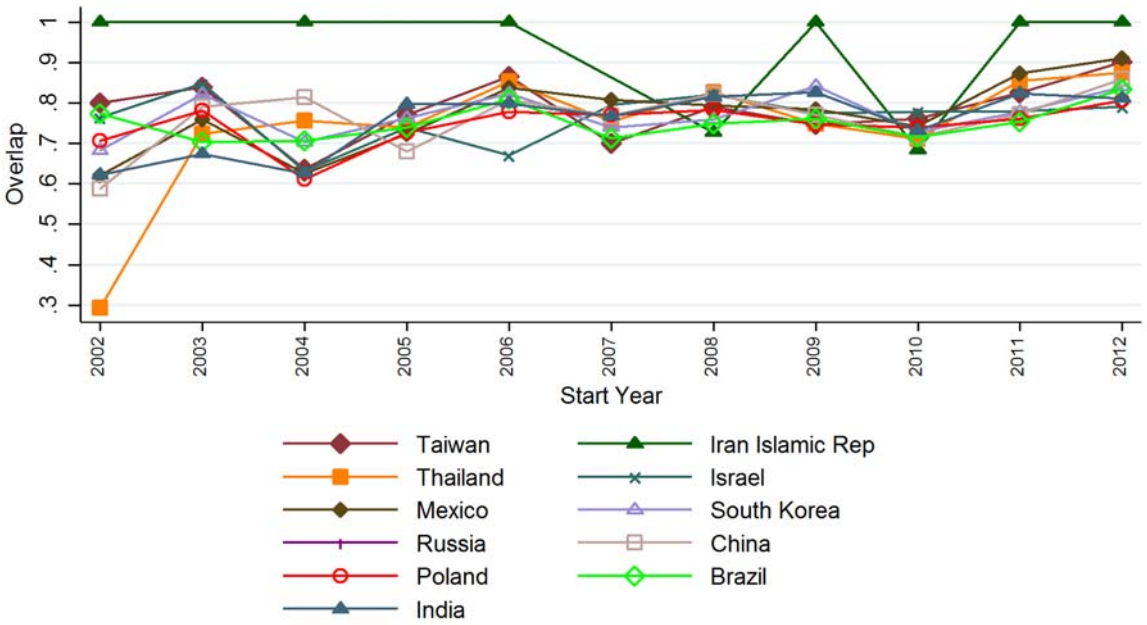

Figure 6: Overlap Share between the US and Selected Non-traditional Countries (only Industry Sponsored Clinical Trials) over time

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Sample	Full	Industry Sponsored	Phase 1	Phase 1 Industry Sponsored	Phase 2	Phase 2 Industry Sponsored	Phase 3	Phase 3 Industry Sponsored
Dependent Variable: Weighted Trials$_{it}$								
T	1.2138	0.5843	-0.4169	0.3822	0.9657**	0.3952*	0.5166*	0.6984***
	(0.7895)	(0.3818)	(0.4926)	(0.6347)	(0.4121)	(0.2055)	(0.2734)	(0.2028)
T^2	-0.1538*	-0.0636*	0.0771	0.0237	-0.0911**	-0.0334*	-0.0631**	-0.0812***
	(0.0843)	(0.0384)	(0.0497)	(0.0567)	(0.0410)	(0.0199)	(0.0267)	(0.0199)
SciTec Articles$_{it}$	0.7620**	0.5401***	1.2639***	1.5568**	0.9512***	0.4503***	0.4959***	0.3170**
	(0.3054)	(0.1804)	(0.3979)	(0.6173)	(0.2493)	(0.1188)	(0.1474)	(0.1280)
Price Level$_{it}$	4.5612**	2.1345	2.5622	0.6145	4.4004**	1.4255	2.3043**	0.6949
	(2.2574)	(1.6314)	(1.9309)	(2.7647)	(1.9879)	(0.8898)	(1.0119)	(0.7291)
Population$_{it}$	0.8946**	0.9567***	-0.0800	-0.1019	0.3482	0.2516*	0.6699***	0.6970***
	(0.3925)	(0.2858)	(0.3777)	(0.4465)	(0.2589)	(0.1427)	(0.2463)	(0.2244)
GDP$_{it}$	0.3254	1.0744***	-0.7367*	0.2189	-0.3363	0.1912	0.1676	0.6322***
	(0.3630)	(0.2880)	(0.4280)	(0.5077)	(0.2675)	(0.1475)	(0.2224)	(0.2179)
Health Expenditures$_{it}$	0.1790	0.2400**	-0.0092	0.0401	0.0846	0.0712	0.2353**	0.3019***
	(0.1365)	(0.0949)	(0.1250)	(0.1647)	(0.0917)	(0.0560)	(0.1094)	(0.0992)
Net FDI$_{it}$	0.1149	0.0340	0.0167	0.0039	0.0508**	-0.0078	0.0564***	0.0266***
	(0.0784)	(0.0215)	(0.0118)	(0.0114)	(0.0201)	(0.0054)	(0.0177)	(0.0047)
Weighted Trials$_{it-1}$	1.1960***	1.0508***	1.1619***	0.9631***	1.0306***	1.0390***	0.9501***	0.8455***
	(0.0369)	(0.0520)	(0.1432)	(0.2345)	(0.0735)	(0.0852)	(0.0590)	(0.0739)
Constant	-26.5881***	-31.1400***	-4.3036	-16.9346**	-14.3206**	-11.0440***	-18.7191***	-21.9980***
	(9.8154)	(7.0839)	(8.1962)	(8.5684)	(6.0622)	(3.0852)	(6.0826)	(5.9239)
Sigma	7.8887***	4.0433***	3.8893***	3.8160***	4.1800***	1.8460***	3.1628***	2.0599***
	(1.2600)	(0.5897)	(0.6635)	(0.7961)	(0.7110)	(0.2053)	(0.5371)	(0.4008)
N	869	869	869	869	869	869	869	869
AIC	4759.6807	3078.4814	1563.2119	965.2903	2730.1018	1665.6218	2863.6265	2017.3375
BIC	4812.1215	3130.9222	1615.6527	1017.7311	2782.5426	1718.0626	2916.0673	2069.7783

Clustered standard errors in parentheses

* p<0.10, ** p<0.05, *** p<0.01

Dependent and lagged dependent variables are subset specific.

Table 1: Tobit Regressions for the Number of Weighted Clinical Trials in Non-Traditional Countries

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Sample	Full	Industry Sponsored	Phase 1	Phase 1 Industry Sponsored	Phase 2	Phase 2 Industry Sponsored	Phase 3	Phase 3 Industry Sponsored
Dependent Variable: Share Country$_{it}$								
T	0.1320	-0.0121	0.0660	0.8020*	0.2745***	0.3068**	0.1206	0.2162***
	(0.0910)	(0.0802)	(0.1286)	(0.4603)	(0.0929)	(0.1232)	(0.0905)	(0.0719)
T^2	-0.0170*	0.0010	-0.0003	-0.0436	-0.0230**	-0.0271**	-0.0114	-0.0214***
	(0.0092)	(0.0073)	(0.0116)	(0.0383)	(0.0092)	(0.0110)	(0.0084)	(0.0063)
SciTec Articles$_{it}$	0.4526***	0.4829***	0.7485***	1.6062***	0.5649***	0.4968***	0.4430***	0.4010***
	(0.0690)	(0.1009)	(0.1845)	(0.4197)	(0.0935)	(0.1057)	(0.0718)	(0.0922)
Price Level$_{it}$	0.8150*	0.2768	0.4148	0.2494	1.1038*	-0.0795	0.6768	-0.4880
	(0.4849)	(0.5644)	(1.0149)	(1.4112)	(0.6500)	(0.5396)	(0.4964)	(0.5356)
Population$_{it}$	0.1063	0.1619	-0.2069	-0.7876**	0.0423	0.0053	0.1446	0.2467**
	(0.0927)	(0.1035)	(0.2161)	(0.3733)	(0.1144)	(0.1281)	(0.0967)	(0.1166)
GDP$_{it}$	-0.0301	0.2062*	-0.2736	-0.8934	-0.0661	0.0843	0.0054	0.3629***
	(0.0998)	(0.1184)	(0.2647)	(0.5612)	(0.1411)	(0.1215)	(0.1145)	(0.1163)
Health Expenditures$_{it}$	0.0078	0.0211	-0.0274	-0.1594	-0.0142	0.0406	0.0266	0.0826**
	(0.0389)	(0.0352)	(0.0923)	(0.1075)	(0.0436)	(0.0453)	(0.0367)	(0.0401)
Net FDI$_{it}$	-0.0057***	-0.0054***	-0.0034**	-0.0104**	-0.0038***	-0.0053**	-0.0056***	-0.0052***
	(0.0011)	(0.0014)	(0.0016)	(0.0052)	(0.0012)	(0.0024)	(0.0012)	(0.0017)
Share Country$_{it}$	98.4101***	180.9962***	119.6852***	50.9974	72.3819***	298.8294***	56.4029***	85.1716***
	(8.1512)	(59.9571)	(26.3361)	(70.8331)	(21.6600)	(37.9432)	(10.0107)	(20.1684)
Constant	-12.1452***	-15.7663***	-7.1636	-0.7834	-12.1523***	-13.0159***	-12.6658***	-17.6422***
	(1.7574)	(1.9538)	(4.4786)	(7.1337)	(2.3831)	(2.5110)	(2.0610)	(2.2320)
N	566	566	566	566	566	566	566	566
AIC	29.4918	24.2312	25.7766	22.6661	28.4020	24.1526	33.1890	28.3212
BIC	72.8777	67.6171	69.1625	66.0520	71.7879	67.5386	76.5749	71.7071

Clustered standard errors in parentheses

* p<0.10, ** p<0.05, *** p<0.01

Dependent and lagged dependent variables are subset specific.

Table 2: Fractional Logit Regressions for the Share of Weighted Clinical Trials in Non-Traditional Countries

	(1)	(2)	(3)	(4)	(5)	(6)
Sample	Phase 1	Phase 1 Industry Sponsored	Phase 2	Phase 2 Industry Sponsored	Phase 3	Phase 3 Industry Sponsored
Dependent Variable: Share Phase j_{it}						
T	-0.3115	0.0332	0.4292***	0.3191*	0.1197	0.2801*
	(0.3397)	(0.3953)	(0.1627)	(0.1843)	(0.1394)	(0.1493)
T^2	0.0427	0.0170	-0.0381**	-0.0189	-0.0234*	-0.0396***
	(0.0321)	(0.0367)	(0.0159)	(0.0174)	(0.0135)	(0.0137)
SciTec $Articles_{it}$	0.1411	0.3677**	0.1578***	0.2243***	0.0004	-0.0341
	(0.1327)	(0.1829)	(0.0560)	(0.0758)	(0.0616)	(0.0718)
Price $Level_{it}$	0.4939	1.3587	-0.3974	0.7652	-0.2546	0.4812
	(0.9204)	(1.4733)	(0.5407)	(0.5171)	(0.5238)	(0.5781)
$Population_{it}$	-0.1954	-0.3225	-0.1445*	-0.2791***	-0.0292	-0.0218
	(0.1767)	(0.2236)	(0.0748)	(0.1079)	(0.0791)	(0.0950)
GDP_{it}	-0.4504***	-0.4791	-0.1219	-0.5187***	0.0444	-0.1929
	(0.1725)	(0.2996)	(0.0950)	(0.1566)	(0.0876)	(0.1299)
Health $Expenditures_{it}$	-0.0580	-0.1376	0.0174	-0.0118	0.0995**	0.0851*
	(0.0735)	(0.1108)	(0.0389)	(0.0581)	(0.0420)	(0.0471)
Net FDI_{it}	0.0071	0.0044	-0.0003	-0.0030	0.0006	0.0050**
	(0.0056)	(0.0061)	(0.0025)	(0.0046)	(0.0024)	(0.0022)
Share Phase j_{it-1}	0.9945	2.7670**	0.5265*	0.5332	0.7717***	0.6708***
	(0.7525)	(1.2081)	(0.2727)	(0.3840)	(0.2094)	(0.2516)
Constant	3.5659	3.1678	0.0283	4.9311*	-1.3496	0.5364
	(3.9841)	(5.0979)	(1.6679)	(2.7290)	(1.6160)	(2.1419)
N	566	418	566	418	566	418
AIC	230.4934	139.1504	459.0778	368.2921	554.4061	443.1128
BIC	273.8793	179.5052	502.4637	408.6469	597.7921	483.4676

Clustered standard errors in parentheses

* p<0.10, ** p<0.05, *** p<0.01

Dependent and lagged dependent variables are subset specific.

Table 3: Fractional Logit Regressions for the Share of Clinical Trials in Specific Phases

Country	2002-2004	2010-2012
Brazil	***Pathological Conditions, Signs and Symptoms***; Cardiovascular Diseases; Respiratory Tract Diseases	***Pathological Conditions, Signs and Symptoms***; ***Cardiovascular Diseases***; Respiratory Tract Diseases
China	***Pathological Conditions, Signs and Symptoms***; Digestive System Diseases; ***Neoplasms***	***Neoplasms***; Digestive System Diseases; ***Pathological Conditions, Signs and Symptoms***
India	***Pathological Conditions, Signs and Symptoms***; ***Neoplasms***; Respiratory Tract Diseases	***Pathological Conditions, Signs and Symptoms***; Digestive System Diseases; Nutritional and Metabolic Diseases
Iran Islamic Rep.	Eye Diseases; Musculoskeletal Diseases; ***Pathological Conditions, Signs and Symptoms***	***Pathological Conditions, Signs and Symptoms***; Stomatognathic Diseases; ***Cardiovascular Diseases***
Israel	***Mental Disorders; Pathological Conditions, Signs and Symptoms***; Cardiovascular Diseases	***Pathological Conditions, Signs and Symptoms***; Nervous System Diseases; Mental Disorders
South Korea	***Neoplasms***; Digestive System Diseases; ***Mental Disorders***	***Neoplasms***; ***Pathological Conditions, Signs and Symptoms***; ***Cardiovascular Diseases***
Mexico	Nutritional and Metabolic Diseases; Endocrine System Diseases; ***Neoplasms***	***Pathological Conditions, Signs and Symptoms***; Nutritional and Metabolic Diseases; Respiratory Tract Diseases
Poland	Cardiovascular Diseases**; *Neoplasms***; Respiratory Tract Diseases	***Pathological Conditions, Signs and Symptoms***; ***Cardiovascular Diseases***; ***Neoplasms***
Russia	***Neoplasms***; ***Mental Disorders***; Cardiovascular Diseases	***Cardiovascular Diseases***; ***Pathological Conditions, Signs and Symptoms; Neoplasms***
Taiwan	***Neoplasms***; ***Pathological Conditions, Signs and Symptoms***; Cardiovascular Diseases	***Pathological Conditions, Signs and Symptoms***; ***Neoplasms***; ***Cardiovascular Diseases***
Thailand	Virus Diseases; Immune System Diseases; Eye Diseases	***Pathological Conditions, Signs and Symptoms***; Virus Diseases; Immune System Diseases
United States	***Neoplasms; Mental Disorders; Pathological Conditions, Signs and Symptoms***	***Neoplasms; Pathological Conditions, Signs and Symptoms; Cardiovascular Diseases***

Table 4: Most Frequently Addressed Disease Areas in Selected Non-traditional Countries

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Sample	Full	Industry Sponsored	Phase 1	Phase 1 Industry Sponsored	Phase 2	Phase 2 Industry Sponsored	Phase 3	Phase 3 Industry Sponsored
Dependent Variable: $Overlap_{i\ to\ US\ in\ t}$								
T	0.1063	-0.2867**	0.3210	1.8540***	0.2067	0.2877	-0.2948*	-0.3613**
	(0.1884)	(0.1463)	(0.5409)	(0.6661)	(0.2664)	(0.2053)	(0.1620)	(0.1477)
T^2	-0.0063	0.0257*	-0.0264	-0.1545***	-0.0188	-0.0263	0.0175	0.0238*
	(0.0184)	(0.0135)	(0.0486)	(0.0582)	(0.0245)	(0.0195)	(0.0149)	(0.0137)
$SciTec\ Articles_{it}$	0.0330	-0.0651	0.2788	0.1779	0.1517	0.1224	-0.1606***	-0.1598***
	(0.0678)	(0.0632)	(0.1801)	(0.1545)	(0.1064)	(0.0796)	(0.0549)	(0.0422)
$Price\ Level_{it}$	-0.2909	-1.5060**	-1.1911	-1.3068	-1.3983	-1.8819**	-0.1743	-0.6552
	(0.5895)	(0.7425)	(1.6123)	(1.7368)	(0.9504)	(0.9419)	(0.5506)	(0.4522)
$Population_{it}$	-0.1083	0.0658	-0.4533**	-0.2097	-0.0260	-0.0533	0.2021***	0.1158*
	(0.1081)	(0.0845)	(0.2071)	(0.2204)	(0.1373)	(0.0973)	(0.0759)	(0.0678)
GDP_{it}	0.1650*	0.5268***	-0.3053	-0.1694	0.2913	0.2894	0.4048***	0.3679**
	(0.0991)	(0.1370)	(0.3216)	(0.4051)	(0.1980)	(0.2407)	(0.0960)	(0.1479)
$Health\ Expenditures_{it}$	0.0033	0.0845	0.0418	0.1532	0.0558	0.1182*	0.0167	0.0393
	(0.0463)	(0.0555)	(0.0811)	(0.1318)	(0.0658)	(0.0639)	(0.0436)	(0.0325)
$Net\ FDI_{it}$	-0.0001	0.0011	-0.0010	-0.0059	-0.0011	-0.0016	-0.0019	0.0008
	(0.0021)	(0.0022)	(0.0033)	(0.0039)	(0.0035)	(0.0022)	(0.0021)	(0.0022)
$Overlap_{i\ to\ US\ in\ t-1}$	2.1861***	0.7849**	1.1382**	-0.8088	0.6143*	0.7720***	0.9838***	1.0886***
	(0.3608)	(0.3824)	(0.5105)	(0.6296)	(0.3306)	(0.2640)	(0.3048)	(0.3223)
Constant	0.2256	-3.4773*	8.4545*	0.0027	-2.3387	-2.7197	-4.7425***	-3.2344*
	(2.1116)	(1.9874)	(4.6766)	(8.0475)	(3.2573)	(2.8827)	(1.5368)	(1.8295)
N	556	414	133	82	314	259	409	333
AIC	324.6233	331.2875	125.7455	91.9782	282.0538	263.9782	398.0347	340.4711
BIC	367.8310	371.5461	154.6489	116.0454	319.5477	299.5465	438.1718	378.5525

Clustered standard errors in parentheses

* p<0.10, ** p<0.05, *** p<0.01

Dependent and lagged dependent variables are subset specific.

Table 5: Fractional Logit Regressions for Non-traditional Countries Profiles' Overlap to the US

	Country	All Trials	Phase 1	Phase 2	Phase 3	Country Type
1	US	59,921.38	12,274.36	17,399.21	6,597.01	Traditional
2	Canada	6,500.78	828.17	1,588.96	1,252.34	Traditional
3	Germany	5,351.99	768.77	1,299.15	1,053.79	Traditional
4	France	5,144.44	427.42	1,095.56	1,102.27	Traditional
5	United Kingdom	3,978.65	858.17	928.24	660.24	Traditional
6	China	2,970.51	298.44	641.73	650.11	Non-Traditional
7	South Korea	2,840.04	327.21	587.65	448.51	Non-Traditional
8	Israel	2,760.17	288.75	482.03	273.74	Non-Traditional
9	Italy	2,577.80	140.75	678.57	650.42	Traditional
10	Denmark	2,306.52	140.56	331.18	249.86	Traditional
11	Netherlands	2,192.11	294.53	401.29	376.58	Traditional
12	Japan	2,084.91	449.20	516.13	707.00	Traditional
13	Spain	1,974.53	180.54	531.19	387.72	Traditional
14	Taiwan	1,946.67	118.19	265.71	227.12	Non-Traditional
15	Brazil	1,915.50	146.27	286.56	475.19	Non-Traditional
16	Belgium	1,636.33	303.29	395.63	261.07	Traditional
17	Switzerland	1,550.15	188.24	295.63	203.32	Traditional
18	Australia	1,344.03	285.01	366.70	296.53	Traditional
19	Sweden	1,313.11	174.00	252.45	190.57	Traditional
20	Norway	1,143.54	78.04	205.38	149.73	Traditional
21	India	1,093.10	217.35	212.80	283.87	Non-Traditional
22	Austria	1,040.74	90.62	226.22	196.93	Traditional
23	Finland	672.59	53.73	119.45	126.74	Traditional
24	Thailand	657.74	49.49	133.96	158.38	Non-Traditional
25	Poland	590.49	42.38	164.71	194.06	Non-Traditional
26	Mexico	545.05	57.68	153.70	169.56	Non-Traditional
27	Singapore	533.01	158.08	113.76	67.10	Non-Traditional
28	Iran Islamic Rep.	484.35	81.00	177.50	117.22	Non-Traditional
29	Greece	484.07	18.32	107.43	86.82	Non-Traditional
30	Russia	436.43	35.67	144.31	159.22	Non-Traditional

Table 6 about here

Insert

	(1)	(2)	(3)	(4)	(5)	(6)	(7)
(1) T	1.0000						
(2) SciTec Articles$_{it}$	0.0498	1.0000					
(3) Price Level$_{it}$	0.0844**	0.1896***	1.0000				
(4) Population$_{it}$	0.0288	0.5649***	-0.0330	1.0000			
(5) GDP$_{it}$	0.1985***	0.3683***	0.6762***	-0.3488***	1.0000		
(6) Health Expenditures$_{it}$	0.1251***	0.0112	-0.0131	-0.1221***	-0.0477	1.0000	
(7) Net FDI$_{it}$	0.1084***	0.4656***	0.0159	0.3432***	0.1995***	-0.0495	1.0000

* p<0.05, ** p<0.01, *** p<0.001

Although some correlation may seem quite high, variance inflation factors do not suggest multicollinearity.

Table 7 about here

Insert

	Sample	N	Mean	SD	Min.	Max.
Weighted Trials$_{it}$	Full	1661	13.4719	48.7690	0.0000	553.6893
Weighted Trials$_{it}$	Industry Sponsored	1661	4.4469	13.6722	0.0000	164.4452
Weighted Trials$_{it}$	Phase 1	1661	1.3007	5.6466	0.0000	75.2583
Weighted Trials$_{it}$	Phase 1 Industry Sponsored	1661	0.6461	3.5663	0.0000	63.5472
Weighted Trials$_{it}$	Phase 2	1661	2.7738	9.8228	0.0000	142.6488
Weighted Trials$_{it}$	Phase 2 Industry Sponsored	1661	1.0803	3.2332	0.0000	34.4322
Weighted Trials$_{it}$	Phase 3	1661	2.8828	8.8544	0.0000	120.7325
Weighted Trials$_{it}$	Phase 3 Industry Sponsored	1661	1.5836	4.6172	0.0000	50.2564
Share Country$_{it}$	Full	1172	0.0016	0.0041	0.0000	0.0366
Share Country$_{it}$	Industry Sponsored	1172	0.0005	0.0012	0.0000	0.0108
Share Country$_{it}$	Phase 1	1172	0.0009	0.0029	0.0000	0.0329
Share Country$_{it}$	Phase 1 Industry Sponsored	1172	0.0004	0.0018	0.0000	0.0282
Share Country$_{it}$	Phase 2	1172	0.0013	0.0036	0.0000	0.0443
Share Country$_{it}$	Phase 2 Industry Sponsored	1172	0.0005	0.0012	0.0000	0.0099
Share Country$_{it}$	Phase 3	1172	0.0022	0.0052	0.0000	0.0577
Share Country$_{it}$	Phase 3 Industry Sponsored	1172	0.0012	0.0027	0.0000	0.0240
Share Phase 1 $_{it}$	Phase 1	1172	0.0635	0.1444	0.0000	1.0000
Share Phase 1 $_{it}$	Phase 1 Industry Sponsored	872	0.0559	0.1426	0.0000	1.0000
Share Phase 2 $_{it}$	Phase 2	872	0.1933	0.2365	0.0000	1.0000
Share Phase 2 $_{it}$	Phase 2 Industry Sponsored	872	0.2368	0.2805	0.0000	1.0000
Share Phase 3 $_{it}$	Phase 3	872	0.2968	0.2992	0.0000	1.0000
Share Phase 3 $_{it}$	Phase 3 Industry Sponsored	872	0.4158	0.3335	0.0000	1.0000
Overlap$_{i \text{ to US in t}}$	Full	1155	0.8747	0.1969	0.0000	1.0000
Overlap$_{i \text{ to US in t}}$	Industry Sponsored	867	0.7680	0.2484	0.0000	1.0000
Overlap$_{i \text{ to US in t}}$	Phase 1	428	0.7576	0.3150	0.0000	1.0000

$Overlap_{i \text{ to US in t}}$	Phase 1 Industry Sponsored	272	0.6457	0.3318	0.0000	1.0000
$Overlap_{i \text{ to US in t}}$	Phase 2	734	0.7478	0.3010	0.0000	1.0000
$Overlap_{i \text{ to US in t}}$	Phase 2 Industry Sponsored	570	0.6510	0.3040	0.0000	1.0000
$Overlap_{i \text{ to US in t}}$	Phase 3	874	0.6137	0.2914	0.0000	1.0000
$Overlap_{i \text{ to US in t}}$	Phase 3 Industry Sponsored	704	0.4786	0.2829	0.0000	1.0000
T	Full	1661	6.0000	3.1632	1.0000	11.0000
$SciTec\ Articles_{it}$	Full	1083	4.3973	2.4329	-2.3026	11.2121
$Price\ Level_{it}$	Full	1452	0.4884	1.1368	0.1410	43.1612
$Population_{it}$	Full	1595	15.8390	1.8273	10.3937	21.0239
GDP_{it}	Full	1504	7.8857	1.4605	4.6823	12.1751
$Health\ Expenditures_{it}$	Full	1360	6.0086	2.2787	1.1215	22.1866
$Net\ FDI_{it}$	Full	1486	4.5875	16.7515	-20.9335	280.0720

Table 8 about here

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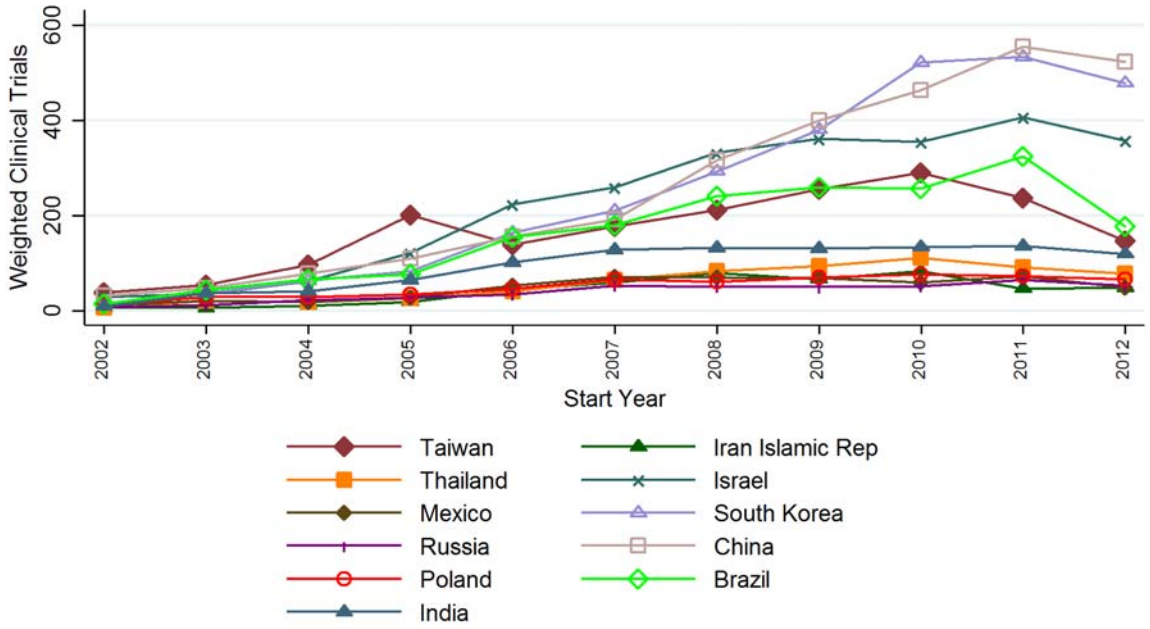

Figure 1: Number of Weighted Clinical Trials in Selected Non-Traditional Countries

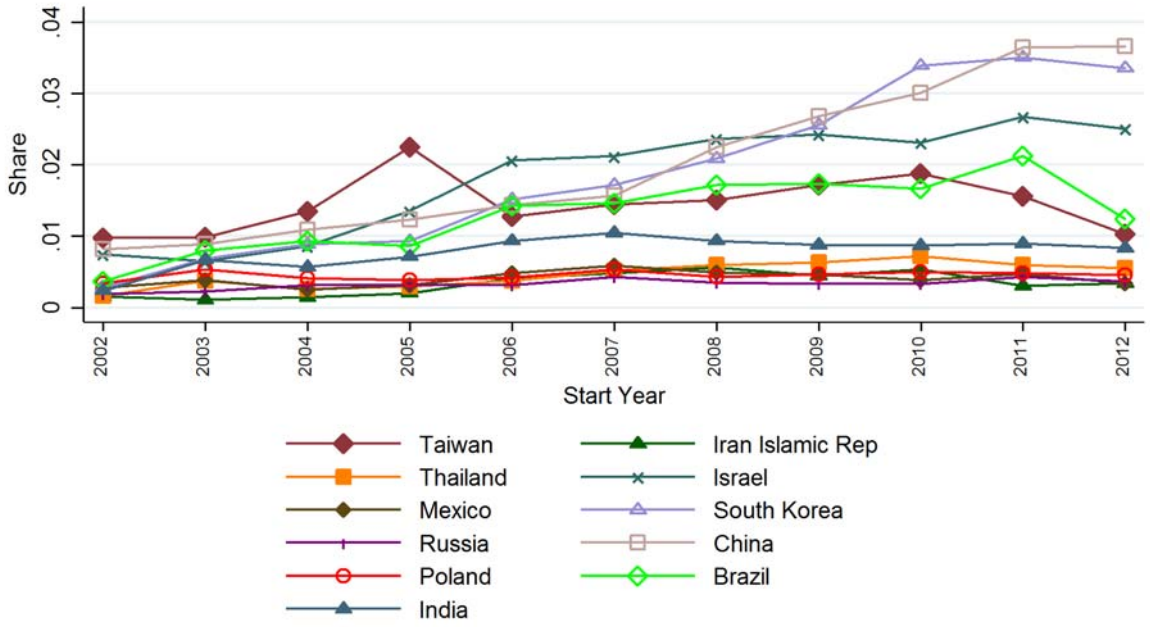

Figure 2: Share of Selected Non-Traditional Countries in Conducting Weighted Clinical Trials

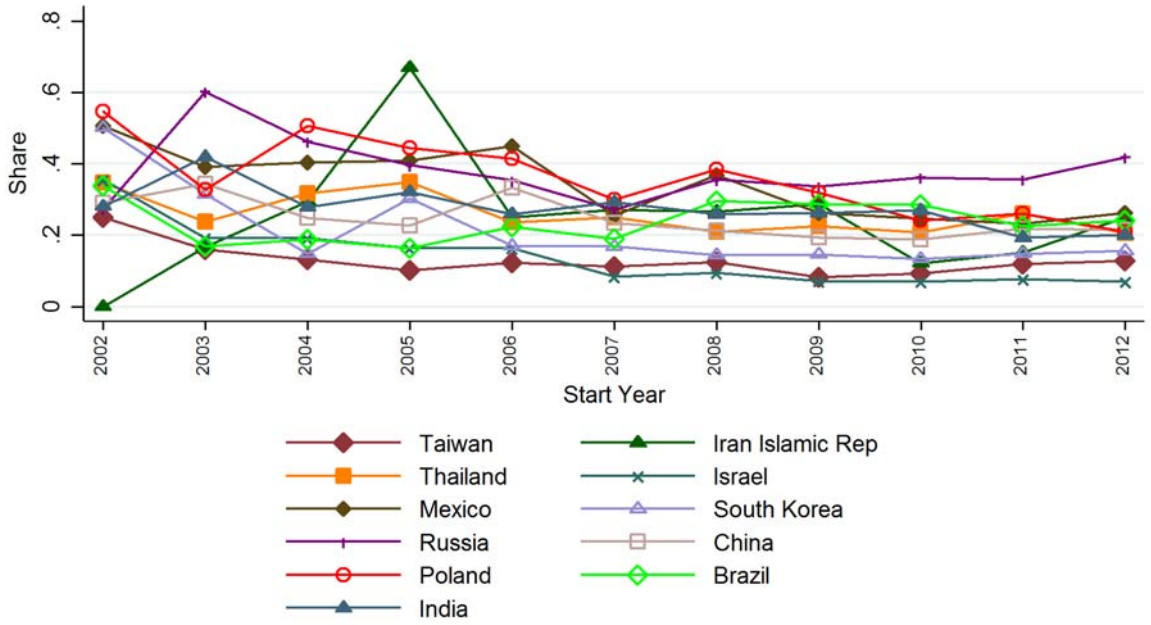

Figure 3: Share of Phase 3 Clinical Trials in Selected Non-Traditional Countries

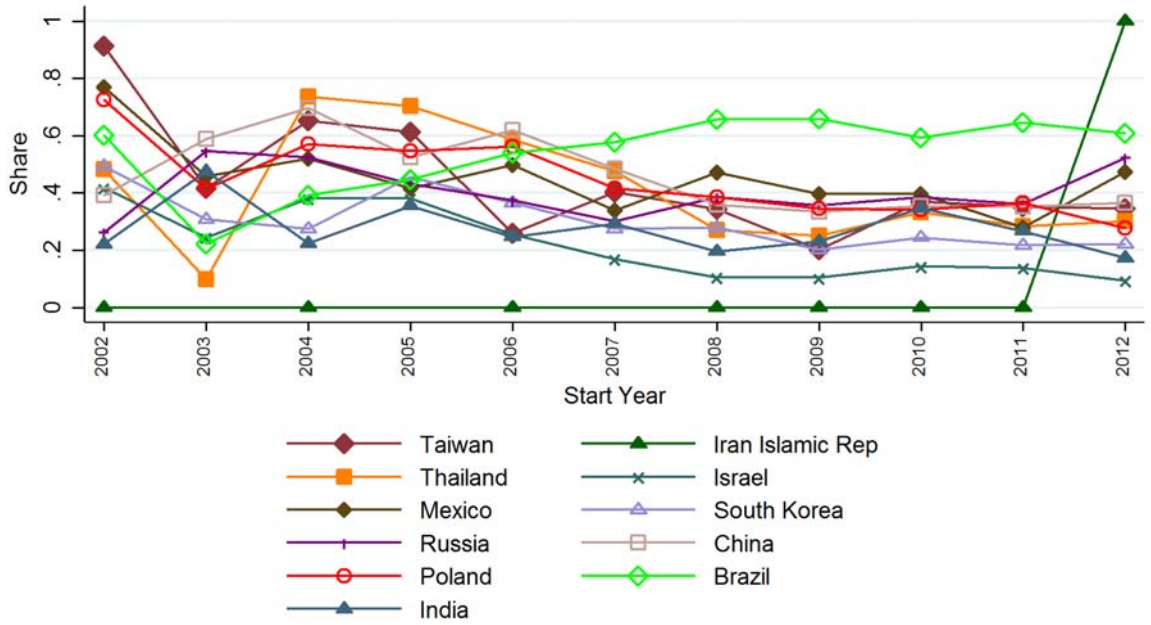

Figure 4: Share of Industry Sponsored Phase 3 Clinical Trials in Selected Non-Traditional Countries

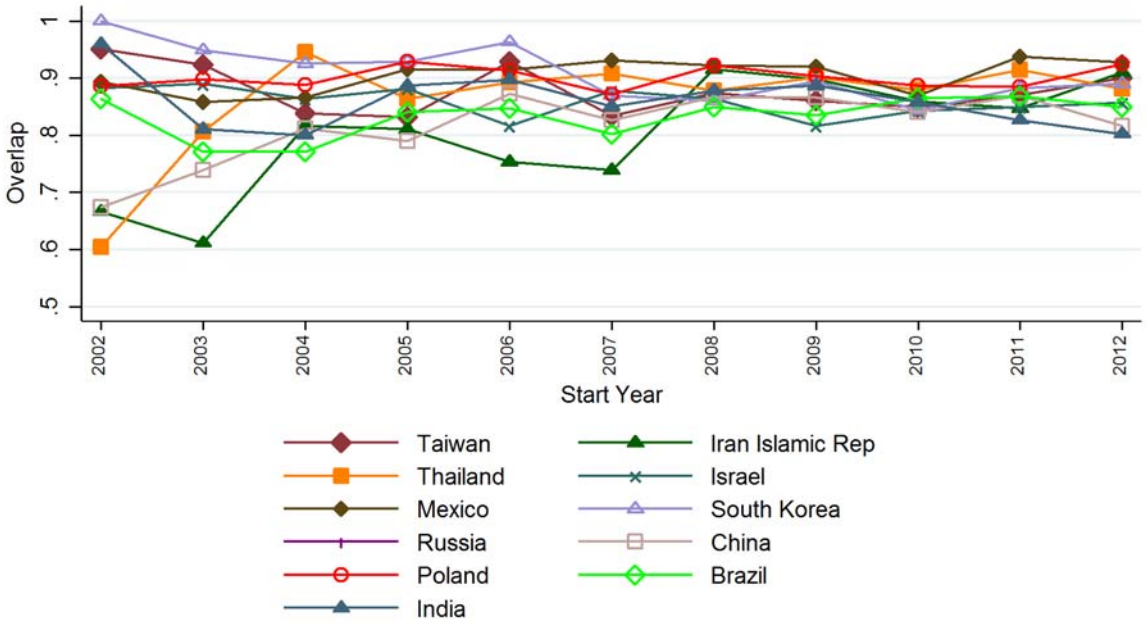

Figure 5: Development Overlap between the US and Selected Non-traditional Countries

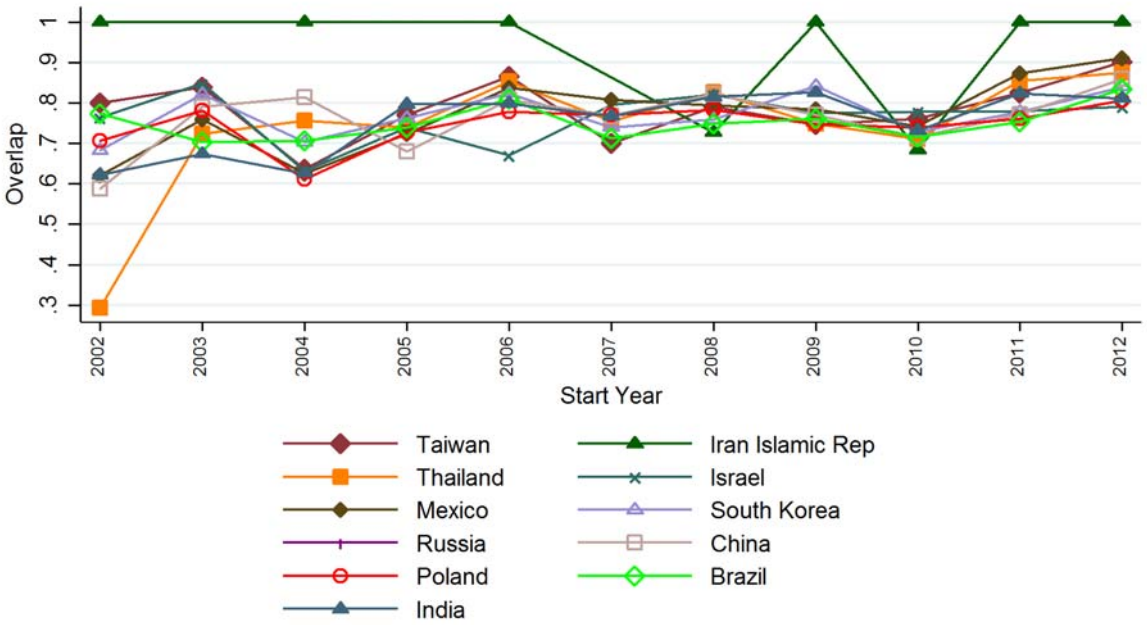

Figure 6: Overlap Share between the US and Selected Non-traditional Countries (only Industry Sponsored Clinical Trials) over time

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Sample	Full	Industry Sponsored	Phase 1	Phase 1 Industry Sponsored	Phase 2	Phase 2 Industry Sponsored	Phase 3	Phase 3 Industry Sponsored
Dependent Variable: Weighted Trials$_{it}$								
T	1.2138	0.5843	-0.4169	0.3822	0.9657**	0.3952*	0.5166*	0.6984***
	(0.7895)	(0.3818)	(0.4926)	(0.6347)	(0.4121)	(0.2055)	(0.2734)	(0.2028)
T^2	-0.1538*	-0.0636*	0.0771	0.0237	-0.0911**	-0.0334*	-0.0631**	-0.0812***
	(0.0843)	(0.0384)	(0.0497)	(0.0567)	(0.0410)	(0.0199)	(0.0267)	(0.0199)
SciTec Articles$_{it}$	0.7620**	0.5401***	1.2639***	1.5568**	0.9512***	0.4503***	0.4959***	0.3170**
	(0.3054)	(0.1804)	(0.3979)	(0.6173)	(0.2493)	(0.1188)	(0.1474)	(0.1280)
Price Level$_{it}$	4.5612**	2.1345	2.5622	0.6145	4.4004**	1.4255	2.3043**	0.6949
	(2.2574)	(1.6314)	(1.9309)	(2.7647)	(1.9879)	(0.8898)	(1.0119)	(0.7291)
Population$_{it}$	0.8946**	0.9567***	-0.0800	-0.1019	0.3482	0.2516*	0.6699***	0.6970***
	(0.3925)	(0.2858)	(0.3777)	(0.4465)	(0.2589)	(0.1427)	(0.2463)	(0.2244)
GDP$_{it}$	0.3254	1.0744***	-0.7367*	0.2189	-0.3363	0.1912	0.1676	0.6322***
	(0.3630)	(0.2880)	(0.4280)	(0.5077)	(0.2675)	(0.1475)	(0.2224)	(0.2179)
Health Expenditures$_{it}$	0.1790	0.2400**	-0.0092	0.0401	0.0846	0.0712	0.2353**	0.3019***
	(0.1365)	(0.0949)	(0.1250)	(0.1647)	(0.0917)	(0.0560)	(0.1094)	(0.0992)
Net FDI$_{it}$	0.1149	0.0340	0.0167	0.0039	0.0508**	-0.0078	0.0564***	0.0266***
	(0.0784)	(0.0215)	(0.0118)	(0.0114)	(0.0201)	(0.0054)	(0.0177)	(0.0047)
Weighted Trials$_{it-1}$	1.1960***	1.0508***	1.1619***	0.9631***	1.0306***	1.0390***	0.9501***	0.8455***
	(0.0369)	(0.0520)	(0.1432)	(0.2345)	(0.0735)	(0.0852)	(0.0590)	(0.0739)
Constant	-26.5881***	-31.1400***	-4.3036	-16.9346**	-14.3206**	-11.0440***	-18.7191***	-21.9980***
	(9.8154)	(7.0839)	(8.1962)	(8.5684)	(6.0622)	(3.0852)	(6.0826)	(5.9239)
Sigma	7.8887***	4.0433***	3.8893***	3.8160***	4.1800***	1.8460***	3.1628***	2.0599***
	(1.2600)	(0.5897)	(0.6635)	(0.7961)	(0.7110)	(0.2053)	(0.5371)	(0.4008)
N	869	869	869	869	869	869	869	869
AIC	4759.6807	3078.4814	1563.2119	965.2903	2730.1018	1665.6218	2863.6265	2017.3375
BIC	4812.1215	3130.9222	1615.6527	1017.7311	2782.5426	1718.0626	2916.0673	2069.7783

Clustered standard errors in parentheses

* p<0.10, ** p<0.05, *** p<0.01

Dependent and lagged dependent variables are subset specific.

Table 1: Tobit Regressions for the Number of Weighted Clinical Trials in Non-Traditional Countries

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Sample	Full	Industry Sponsored	Phase 1	Phase 1 Industry Sponsored	Phase 2	Phase 2 Industry Sponsored	Phase 3	Phase 3 Industry Sponsored
Dependent Variable: Share Country$_{it}$								
T	0.1320	-0.0121	0.0660	0.8020*	0.2745***	0.3068**	0.1206	0.2162***
	(0.0910)	(0.0802)	(0.1286)	(0.4603)	(0.0929)	(0.1232)	(0.0905)	(0.0719)
T^2	-0.0170*	0.0010	-0.0003	-0.0436	-0.0230**	-0.0271**	-0.0114	-0.0214***
	(0.0092)	(0.0073)	(0.0116)	(0.0383)	(0.0092)	(0.0110)	(0.0084)	(0.0063)
SciTec Articles$_{it}$	0.4526***	0.4829***	0.7485***	1.6062***	0.5649***	0.4968***	0.4430***	0.4010***
	(0.0690)	(0.1009)	(0.1845)	(0.4197)	(0.0935)	(0.1057)	(0.0718)	(0.0922)
Price Level$_{it}$	0.8150*	0.2768	0.4148	0.2494	1.1038*	-0.0795	0.6768	-0.4880
	(0.4849)	(0.5644)	(1.0149)	(1.4112)	(0.6500)	(0.5396)	(0.4964)	(0.5356)
Population$_{it}$	0.1063	0.1619	-0.2069	-0.7876**	0.0423	0.0053	0.1446	0.2467**
	(0.0927)	(0.1035)	(0.2161)	(0.3733)	(0.1144)	(0.1281)	(0.0967)	(0.1166)
GDP$_{it}$	-0.0301	0.2062*	-0.2736	-0.8934	-0.0661	0.0843	0.0054	0.3629***
	(0.0998)	(0.1184)	(0.2647)	(0.5612)	(0.1411)	(0.1215)	(0.1145)	(0.1163)
Health Expenditures$_{it}$	0.0078	0.0211	-0.0274	-0.1594	-0.0142	0.0406	0.0266	0.0826**
	(0.0389)	(0.0352)	(0.0923)	(0.1075)	(0.0436)	(0.0453)	(0.0367)	(0.0401)
Net FDI$_{it}$	-0.0057***	-0.0054***	-0.0034**	-0.0104**	-0.0038***	-0.0053**	-0.0056***	-0.0052***
	(0.0011)	(0.0014)	(0.0016)	(0.0052)	(0.0012)	(0.0024)	(0.0012)	(0.0017)
Share Country$_{it}$	98.4101***	180.9962***	119.6852***	50.9974	72.3819***	298.8294***	56.4029***	85.1716***
	(8.1512)	(59.9571)	(26.3361)	(70.8331)	(21.6600)	(37.9432)	(10.0107)	(20.1684)
Constant	-12.1452***	-15.7663***	-7.1636	-0.7834	-12.1523***	-13.0159***	-12.6658***	-17.6422***
	(1.7574)	(1.9538)	(4.4786)	(7.1337)	(2.3831)	(2.5110)	(2.0610)	(2.2320)
N	566	566	566	566	566	566	566	566
AIC	29.4918	24.2312	25.7766	22.6661	28.4020	24.1526	33.1890	28.3212
BIC	72.8777	67.6171	69.1625	66.0520	71.7879	67.5386	76.5749	71.7071

Clustered standard errors in parentheses

* p<0.10, ** p<0.05, *** p<0.01

Dependent and lagged dependent variables are subset specific.

Table 2: Fractional Logit Regressions for the Share of Weighted Clinical Trials in Non-Traditional Countries

	(1)	(2)	(3)	(4)	(5)	(6)
Sample	Phase 1	Phase 1 Industry Sponsored	Phase 2	Phase 2 Industry Sponsored	Phase 3	Phase 3 Industry Sponsored
Dependent Variable: Share Phase j_{it}						
T	-0.3115	0.0332	0.4292***	0.3191*	0.1197	0.2801*
	(0.3397)	(0.3953)	(0.1627)	(0.1843)	(0.1394)	(0.1493)
T^2	0.0427	0.0170	-0.0381**	-0.0189	-0.0234*	-0.0396***
	(0.0321)	(0.0367)	(0.0159)	(0.0174)	(0.0135)	(0.0137)
SciTec Articles$_{it}$	0.1411	0.3677**	0.1578***	0.2243***	0.0004	-0.0341
	(0.1327)	(0.1829)	(0.0560)	(0.0758)	(0.0616)	(0.0718)
Price Level$_{it}$	0.4939	1.3587	-0.3974	0.7652	-0.2546	0.4812
	(0.9204)	(1.4733)	(0.5407)	(0.5171)	(0.5238)	(0.5781)
Population$_{it}$	-0.1954	-0.3225	-0.1445*	-0.2791***	-0.0292	-0.0218
	(0.1767)	(0.2236)	(0.0748)	(0.1079)	(0.0791)	(0.0950)
GDP$_{it}$	-0.4504***	-0.4791	-0.1219	-0.5187***	0.0444	-0.1929
	(0.1725)	(0.2996)	(0.0950)	(0.1566)	(0.0876)	(0.1299)
Health Expenditures$_{it}$	-0.0580	-0.1376	0.0174	-0.0118	0.0995**	0.0851*
	(0.0735)	(0.1108)	(0.0389)	(0.0581)	(0.0420)	(0.0471)
Net FDI$_{it}$	0.0071	0.0044	-0.0003	-0.0030	0.0006	0.0050**
	(0.0056)	(0.0061)	(0.0025)	(0.0046)	(0.0024)	(0.0022)
Share Phase j_{it-1}	0.9945	2.7670**	0.5265*	0.5332	0.7717***	0.6708***
	(0.7525)	(1.2081)	(0.2727)	(0.3840)	(0.2094)	(0.2516)
Constant	3.5659	3.1678	0.0283	4.9311*	-1.3496	0.5364
	(3.9841)	(5.0979)	(1.6679)	(2.7290)	(1.6160)	(2.1419)
N	566	418	566	418	566	418
AIC	230.4934	139.1504	459.0778	368.2921	554.4061	443.1128
BIC	273.8793	179.5052	502.4637	408.6469	597.7921	483.4676

Clustered standard errors in parentheses

* p<0.10, ** p<0.05, *** p<0.01

Dependent and lagged dependent variables are subset specific.

Table 3: Fractional Logit Regressions for the Share of Clinical Trials in Specific Phases

Country	2002-2004	2010-2012
Brazil	***Pathological Conditions, Signs and Symptoms***; Cardiovascular Diseases; Respiratory Tract Diseases	***Pathological Conditions, Signs and Symptoms***; ***Cardiovascular Diseases***; Respiratory Tract Diseases
China	***Pathological Conditions, Signs and Symptoms***; Digestive System Diseases; ***Neoplasms***	***Neoplasms***; Digestive System Diseases; ***Pathological Conditions, Signs and Symptoms***
India	***Pathological Conditions, Signs and Symptoms***; ***Neoplasms***; Respiratory Tract Diseases	***Pathological Conditions, Signs and Symptoms***; Digestive System Diseases; Nutritional and Metabolic Diseases
Iran Islamic Rep.	Eye Diseases; Musculoskeletal Diseases; ***Pathological Conditions, Signs and Symptoms***	***Pathological Conditions, Signs and Symptoms***; Stomatognathic Diseases; ***Cardiovascular Diseases***
Israel	***Mental Disorders; Pathological Conditions, Signs and Symptoms***; Cardiovascular Diseases	***Pathological Conditions, Signs and Symptoms***; Nervous System Diseases; Mental Disorders
South Korea	***Neoplasms***; Digestive System Diseases; ***Mental Disorders***	***Neoplasms***; ***Pathological Conditions, Signs and Symptoms***; ***Cardiovascular Diseases***
Mexico	Nutritional and Metabolic Diseases; Endocrine System Diseases; ***Neoplasms***	***Pathological Conditions, Signs and Symptoms***; Nutritional and Metabolic Diseases; Respiratory Tract Diseases
Poland	Cardiovascular Diseases**; *Neoplasms***; Respiratory Tract Diseases	***Pathological Conditions, Signs and Symptoms***; ***Cardiovascular Diseases***; ***Neoplasms***
Russia	***Neoplasms***; ***Mental Disorders***; Cardiovascular Diseases	***Cardiovascular Diseases***; ***Pathological Conditions, Signs and Symptoms; Neoplasms***
Taiwan	***Neoplasms***; ***Pathological Conditions, Signs and Symptoms***; Cardiovascular Diseases	***Pathological Conditions, Signs and Symptoms***; ***Neoplasms***; ***Cardiovascular Diseases***
Thailand	Virus Diseases; Immune System Diseases; Eye Diseases	***Pathological Conditions, Signs and Symptoms***; Virus Diseases; Immune System Diseases
United States	***Neoplasms; Mental Disorders; Pathological Conditions, Signs and Symptoms***	***Neoplasms; Pathological Conditions, Signs and Symptoms; Cardiovascular Diseases***

Table 4: Most Frequently Addressed Disease Areas in Selected Non-traditional Countries

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Sample	Full	Industry Sponsored	Phase 1	Phase 1 Industry Sponsored	Phase 2	Phase 2 Industry Sponsored	Phase 3	Phase 3 Industry Sponsored
Dependent Variable: $Overlap_{i\ to\ US\ in\ t}$								
T	0.1063	-0.2867**	0.3210	1.8540***	0.2067	0.2877	-0.2948*	-0.3613**
	(0.1884)	(0.1463)	(0.5409)	(0.6661)	(0.2664)	(0.2053)	(0.1620)	(0.1477)
T^2	-0.0063	0.0257*	-0.0264	-0.1545***	-0.0188	-0.0263	0.0175	0.0238*
	(0.0184)	(0.0135)	(0.0486)	(0.0582)	(0.0245)	(0.0195)	(0.0149)	(0.0137)
$SciTec\ Articles_{it}$	0.0330	-0.0651	0.2788	0.1779	0.1517	0.1224	-0.1606***	-0.1598***
	(0.0678)	(0.0632)	(0.1801)	(0.1545)	(0.1064)	(0.0796)	(0.0549)	(0.0422)
$Price\ Level_{it}$	-0.2909	-1.5060**	-1.1911	-1.3068	-1.3983	-1.8819**	-0.1743	-0.6552
	(0.5895)	(0.7425)	(1.6123)	(1.7368)	(0.9504)	(0.9419)	(0.5506)	(0.4522)
$Population_{it}$	-0.1083	0.0658	-0.4533**	-0.2097	-0.0260	-0.0533	0.2021***	0.1158*
	(0.1081)	(0.0845)	(0.2071)	(0.2204)	(0.1373)	(0.0973)	(0.0759)	(0.0678)
GDP_{it}	0.1650*	0.5268***	-0.3053	-0.1694	0.2913	0.2894	0.4048***	0.3679**
	(0.0991)	(0.1370)	(0.3216)	(0.4051)	(0.1980)	(0.2407)	(0.0960)	(0.1479)
$Health\ Expenditures_{it}$	0.0033	0.0845	0.0418	0.1532	0.0558	0.1182*	0.0167	0.0393
	(0.0463)	(0.0555)	(0.0811)	(0.1318)	(0.0658)	(0.0639)	(0.0436)	(0.0325)
$Net\ FDI_{it}$	-0.0001	0.0011	-0.0010	-0.0059	-0.0011	-0.0016	-0.0019	0.0008
	(0.0021)	(0.0022)	(0.0033)	(0.0039)	(0.0035)	(0.0022)	(0.0021)	(0.0022)
$Overlap_{i\ to\ US\ in\ t-1}$	2.1861***	0.7849**	1.1382**	-0.8088	0.6143*	0.7720***	0.9838***	1.0886***
	(0.3608)	(0.3824)	(0.5105)	(0.6296)	(0.3306)	(0.2640)	(0.3048)	(0.3223)
Constant	0.2256	-3.4773*	8.4545*	0.0027	-2.3387	-2.7197	-4.7425***	-3.2344*
	(2.1116)	(1.9874)	(4.6766)	(8.0475)	(3.2573)	(2.8827)	(1.5368)	(1.8295)
N	556	414	133	82	314	259	409	333
AIC	324.6233	331.2875	125.7455	91.9782	282.0538	263.9782	398.0347	340.4711
BIC	367.8310	371.5461	154.6489	116.0454	319.5477	299.5465	438.1718	378.5525

Clustered standard errors in parentheses

* p<0.10, ** p<0.05, *** p<0.01

Dependent and lagged dependent variables are subset specific.

Table 5: Fractional Logit Regressions for Non-traditional Countries Profiles' Overlap to the US

	Country	All Trials	Phase 1	Phase 2	Phase 3	Country Type
1	US	59,921.38	12,274.36	17,399.21	6,597.01	Traditional
2	Canada	6,500.78	828.17	1,588.96	1,252.34	Traditional
3	Germany	5,351.99	768.77	1,299.15	1,053.79	Traditional
4	France	5,144.44	427.42	1,095.56	1,102.27	Traditional
5	United Kingdom	3,978.65	858.17	928.24	660.24	Traditional
6	China	2,970.51	298.44	641.73	650.11	Non-Traditional
7	South Korea	2,840.04	327.21	587.65	448.51	Non-Traditional
8	Israel	2,760.17	288.75	482.03	273.74	Non-Traditional
9	Italy	2,577.80	140.75	678.57	650.42	Traditional
10	Denmark	2,306.52	140.56	331.18	249.86	Traditional
11	Netherlands	2,192.11	294.53	401.29	376.58	Traditional
12	Japan	2,084.91	449.20	516.13	707.00	Traditional
13	Spain	1,974.53	180.54	531.19	387.72	Traditional
14	Taiwan	1,946.67	118.19	265.71	227.12	Non-Traditional
15	Brazil	1,915.50	146.27	286.56	475.19	Non-Traditional
16	Belgium	1,636.33	303.29	395.63	261.07	Traditional
17	Switzerland	1,550.15	188.24	295.63	203.32	Traditional
18	Australia	1,344.03	285.01	366.70	296.53	Traditional
19	Sweden	1,313.11	174.00	252.45	190.57	Traditional
20	Norway	1,143.54	78.04	205.38	149.73	Traditional
21	India	1,093.10	217.35	212.80	283.87	Non-Traditional
22	Austria	1,040.74	90.62	226.22	196.93	Traditional
23	Finland	672.59	53.73	119.45	126.74	Traditional
24	Thailand	657.74	49.49	133.96	158.38	Non-Traditional
25	Poland	590.49	42.38	164.71	194.06	Non-Traditional
26	Mexico	545.05	57.68	153.70	169.56	Non-Traditional
27	Singapore	533.01	158.08	113.76	67.10	Non-Traditional
28	Iran Islamic Rep.	484.35	81.00	177.50	117.22	Non-Traditional
29	Greece	484.07	18.32	107.43	86.82	Non-Traditional
30	Russia	436.43	35.67	144.31	159.22	Non-Traditional

Table 6: Accumulated Clinical Trials per Country (2002 -2012)
(Clinical trial counts are weighted by the number of involved countries)

	(1)	(2)	(3)	(4)	(5)	(6)	(7)
(1) T	1.0000						
(2) SciTec Articles$_{it}$	0.0498	1.0000					
(3) Price Level$_{it}$	0.0844**	0.1896***	1.0000				
(4) Population$_{it}$	0.0288	0.5649***	-0.0330	1.0000			
(5) GDP$_{it}$	0.1985***	0.3683***	0.6762***	-0.3488***	1.0000		
(6) Health Expenditures$_{it}$	0.1251***	0.0112	-0.0131	-0.1221***	-0.0477	1.0000	
(7) Net FDI$_{it}$	0.1084***	0.4656***	0.0159	0.3432***	0.1995***	-0.0495	1.0000

* p<0.05, ** p<0.01, *** p<0.001

Although some correlation may seem quite high, variance inflation factors do not suggest multicollinearity.

Table 7: Correlations

	Sample	N	Mean	SD	Min.	Max.
Weighted Trials$_{it}$	Full	1661	13.4719	48.7690	0.0000	553.6893
Weighted Trials$_{it}$	Industry Sponsored	1661	4.4469	13.6722	0.0000	164.4452
Weighted Trials$_{it}$	Phase 1	1661	1.3007	5.6466	0.0000	75.2583
Weighted Trials$_{it}$	Phase 1 Industry Sponsored	1661	0.6461	3.5663	0.0000	63.5472
Weighted Trials$_{it}$	Phase 2	1661	2.7738	9.8228	0.0000	142.6488
Weighted Trials$_{it}$	Phase 2 Industry Sponsored	1661	1.0803	3.2332	0.0000	34.4322
Weighted Trials$_{it}$	Phase 3	1661	2.8828	8.8544	0.0000	120.7325
Weighted Trials$_{it}$	Phase 3 Industry Sponsored	1661	1.5836	4.6172	0.0000	50.2564
Share Country$_{it}$	Full	1172	0.0016	0.0041	0.0000	0.0366
Share Country$_{it}$	Industry Sponsored	1172	0.0005	0.0012	0.0000	0.0108
Share Country$_{it}$	Phase 1	1172	0.0009	0.0029	0.0000	0.0329
Share Country$_{it}$	Phase 1 Industry Sponsored	1172	0.0004	0.0018	0.0000	0.0282
Share Country$_{it}$	Phase 2	1172	0.0013	0.0036	0.0000	0.0443
Share Country$_{it}$	Phase 2 Industry Sponsored	1172	0.0005	0.0012	0.0000	0.0099
Share Country$_{it}$	Phase 3	1172	0.0022	0.0052	0.0000	0.0577
Share Country$_{it}$	Phase 3 Industry Sponsored	1172	0.0012	0.0027	0.0000	0.0240
Share Phase 1 $_{it}$	Phase 1	1172	0.0635	0.1444	0.0000	1.0000
Share Phase 1 $_{it}$	Phase 1 Industry Sponsored	872	0.0559	0.1426	0.0000	1.0000
Share Phase 2 $_{it}$	Phase 2	872	0.1933	0.2365	0.0000	1.0000
Share Phase 2 $_{it}$	Phase 2 Industry Sponsored	872	0.2368	0.2805	0.0000	1.0000
Share Phase 3 $_{it}$	Phase 3	872	0.2968	0.2992	0.0000	1.0000
Share Phase 3 $_{it}$	Phase 3 Industry Sponsored	872	0.4158	0.3335	0.0000	1.0000
Overlap$_{i \text{ to US in t}}$	Full	1155	0.8747	0.1969	0.0000	1.0000
Overlap$_{i \text{ to US in t}}$	Industry Sponsored	867	0.7680	0.2484	0.0000	1.0000
Overlap$_{i \text{ to US in t}}$	Phase 1	428	0.7576	0.3150	0.0000	1.0000
Overlap$_{i \text{ to US in t}}$	Phase 1 Industry Sponsored	272	0.6457	0.3318	0.0000	1.0000
Overlap$_{i \text{ to US in t}}$	Phase 2	734	0.7478	0.3010	0.0000	1.0000
Overlap$_{i \text{ to US in t}}$	Phase 2 Industry Sponsored	570	0.6510	0.3040	0.0000	1.0000
Overlap$_{i \text{ to US in t}}$	Phase 3	874	0.6137	0.2914	0.0000	1.0000
Overlap$_{i \text{ to US in t}}$	Phase 3 Industry Sponsored	704	0.4786	0.2829	0.0000	1.0000
T	Full	1661	6.0000	3.1632	1.0000	11.0000
SciTec Articles$_{it}$	Full	1083	4.3973	2.4329	-2.3026	11.2121
Price Level$_{it}$	Full	1452	0.4884	1.1368	0.1410	43.1612
Population$_{it}$	Full	1595	15.8390	1.8273	10.3937	21.0239
GDP$_{it}$	Full	1504	7.8857	1.4605	4.6823	12.1751
Health Expenditures$_{it}$	Full	1360	6.0086	2.2787	1.1215	22.1866
Net FDI$_{it}$	Full	1486	4.5875	16.7515	-20.9335	280.0720

Table 8: Summary Statistics

[1] Beyond these arguments discussed below, international agreements like the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) and memberships in international organizations such as the World Trade Organization (WTO) led to the introduction of product patents for pharmaceutical products providing the industry standard protection mechanism against imitation of drug candidates under development which can be seen as an enabling factor for offshoring of (clinical) research activities (Kyle and McGahan, 2012).

[2] As described in Section 1, non-traditional countries are those locations that have until recently not been involved in the industry's pre-clinical and clinical R&D activities (Glickman *et al.*, 2009; Thiers *et al.*, 2008).

[3] http://clinicaltrials.gov/ct2/home

[4] https://www.nlm.nih.gov/pubs/factsheets/mesh.html

[5] As compared to other databases, e.g., the WHO Trial Registration Data Set, a meta-registry offered by the World Health Organization, ClinicalTrials.gov offers very detailed information concerning the facilities where the trial is actually conducted. However, the database does not cover all clinical trials that are conducted worldwide. In particular, it may not cover trials that are not conducted in the US testing drug candidates that are not manufactured in the US without an intention by the sponsor to get market approval in the US. Based on registration requirements in ClinicalTrials.gov database we expect that the database offers a reliable but conservative estimate of the role of non-traditional countries in global clinical research.

[6] It is important to note that most studies criticizing the completeness of the data reported in ClinicalTrials.gov focus their critics not on registration of data but on whether results of clinical trials are made available through the database or in scientific publications (e.g., Prayle et al., 2012). This study, however, does not take the clinical trial results and their reporting into account.

[7] Clinical trials addressing cancer are a notable exception. Due to the severe and harmful side-effects of cancer drugs phase 1 trials are conducted with patients that are affected by the disease (Azoulay, 2004).

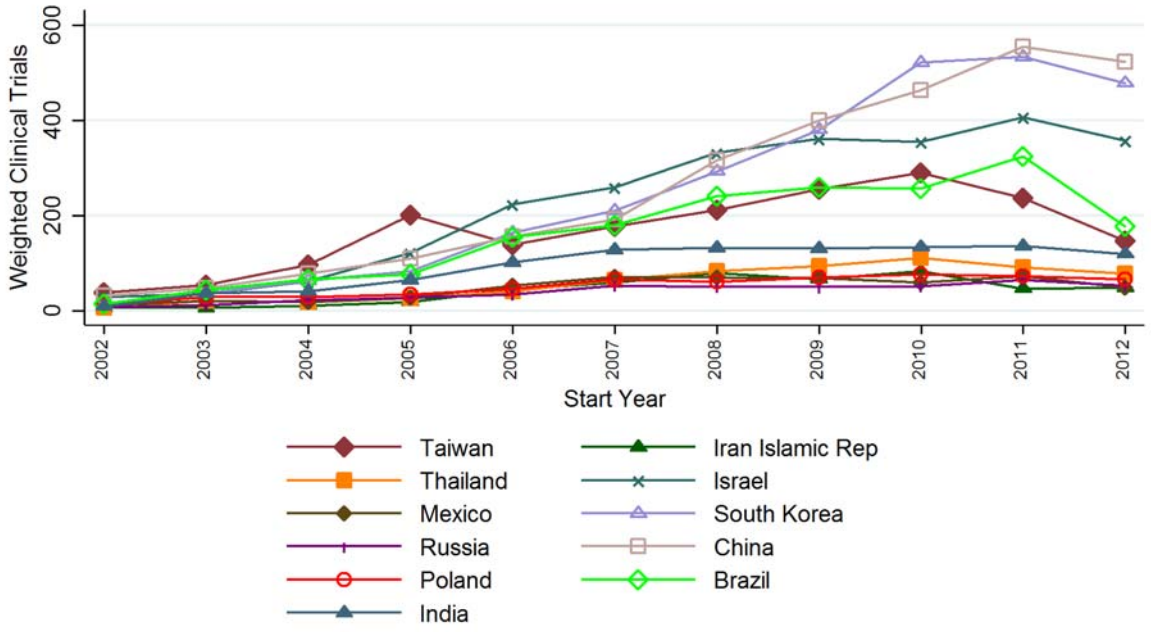

Figure 1: Number of Weighted Clinical Trials in Selected Non-Traditional Countries

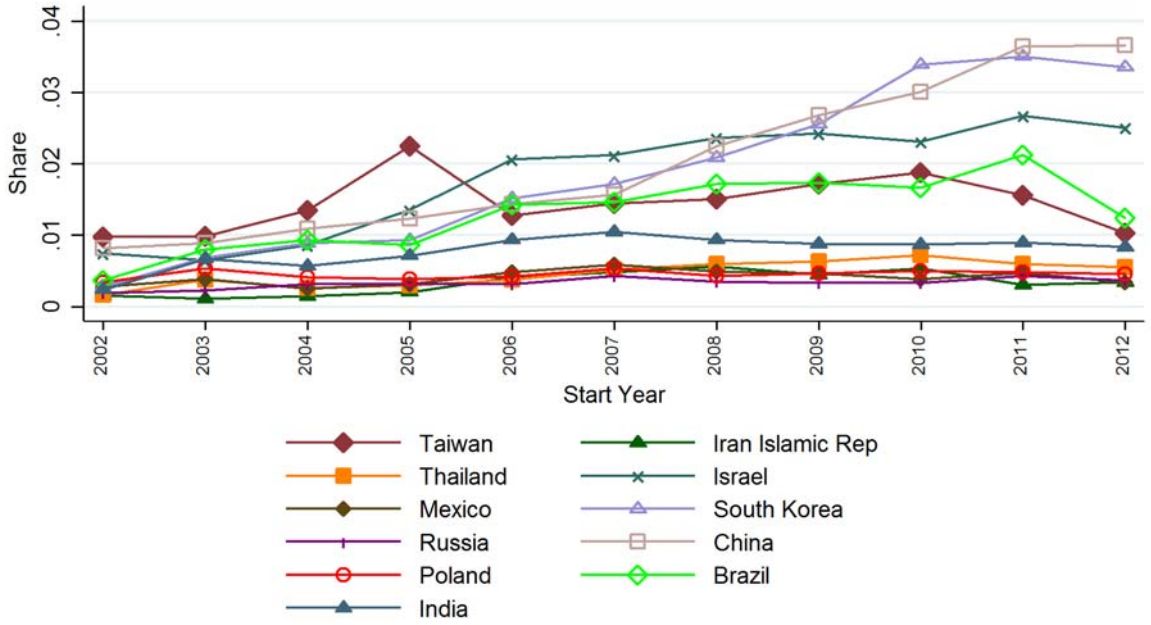

Figure 2: Share of Selected Non-Traditional Countries in Conducting Weighted Clinical Trials

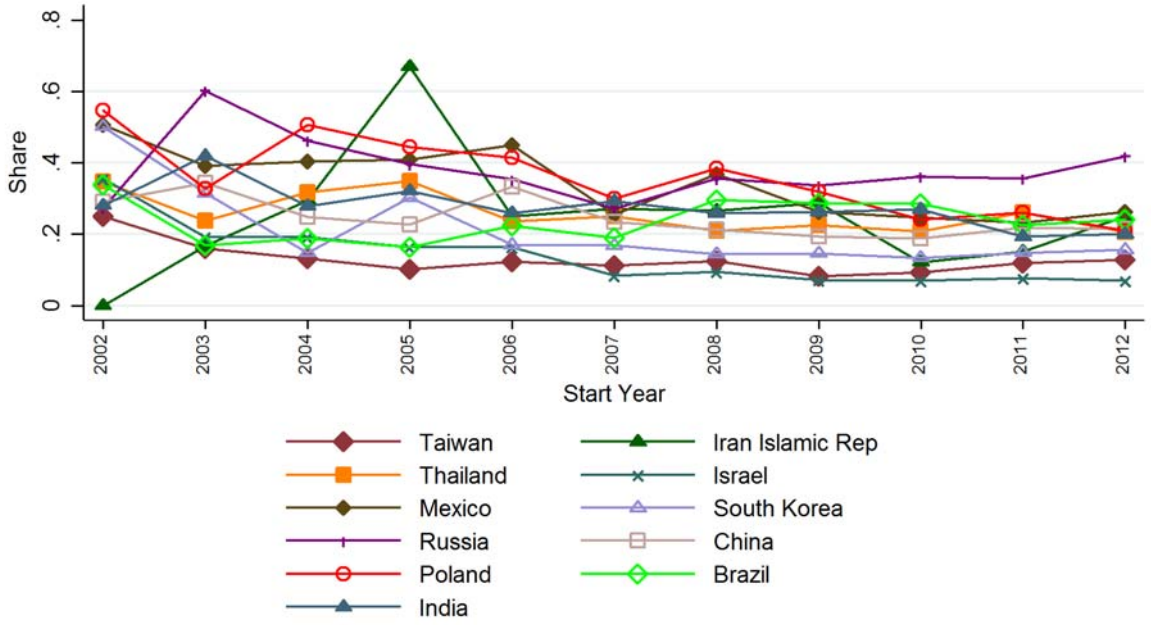

Figure 3: Share of Phase 3 Clinical Trials in Selected Non-Traditional Countries

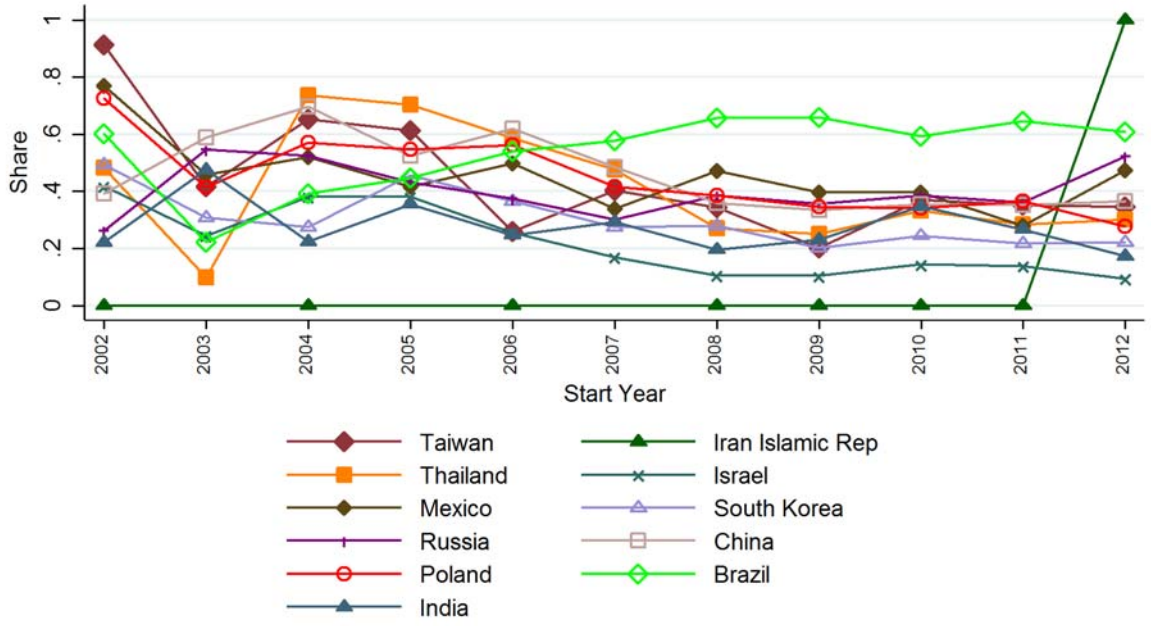

Figure 4: Share of Industry Sponsored Phase 3 Clinical Trials in Selected Non-Traditional Countries

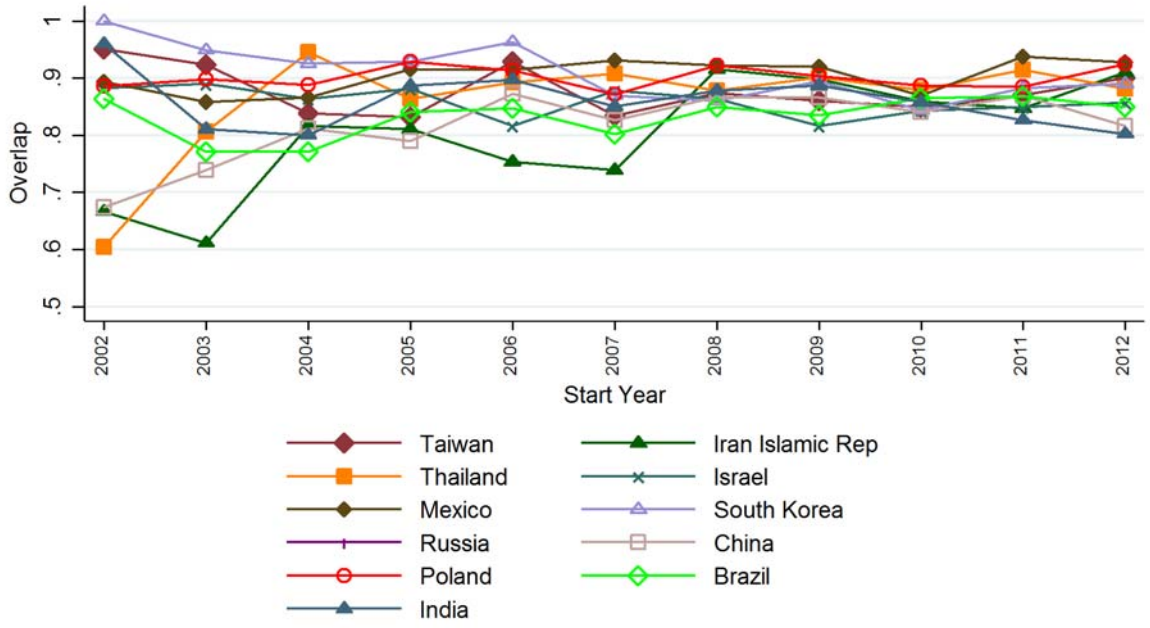

Figure 5: Development Overlap between the US and Selected Non-traditional Countries

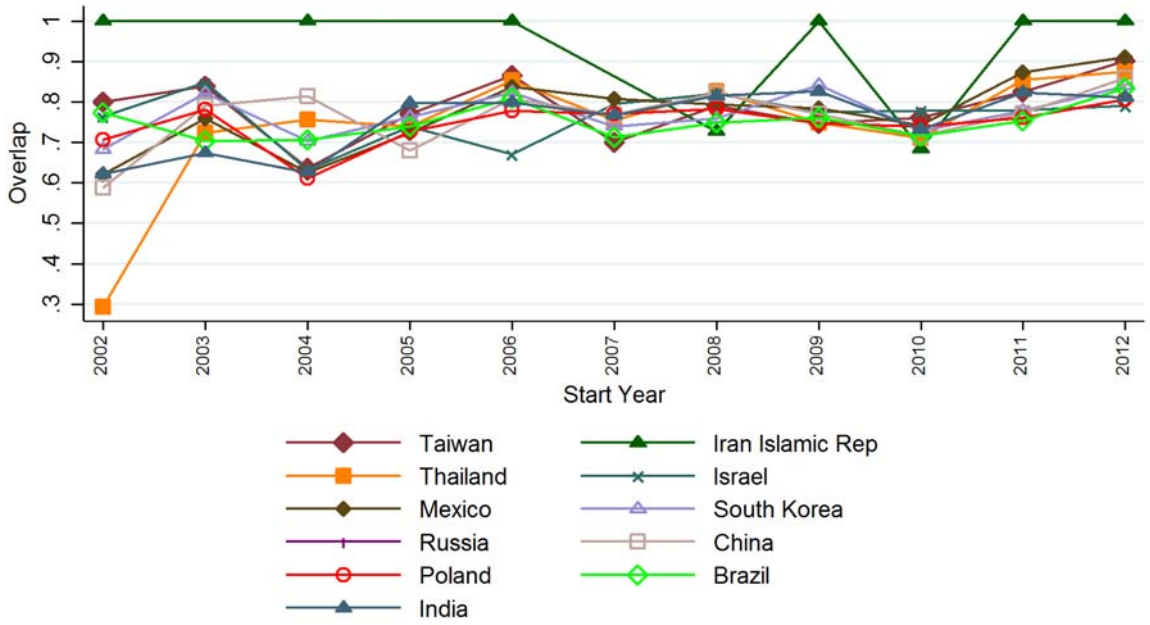

Figure 6: Overlap Share between the US and Selected Non-traditional Countries (only Industry Sponsored Clinical Trials) over time

	(1)	(2)	(3)	(4)	(5)	(6)

Sample	Full	Industry Sponsored	Phase 1	Phase 1 Industry Sponsored	Phase 2	Phase 2 Industry Sponsored
Dependent Variable: Weighted Trials$_{it}$						
T	1.2138	0.5843	-0.4169	0.3822	0.9657**	0.3952*
	(0.7895)	(0.3818)	(0.4926)	(0.6347)	(0.4121)	(0.2055)
T^2	-0.1538*	-0.0636*	0.0771	0.0237	-0.0911**	-0.0334*
	(0.0843)	(0.0384)	(0.0497)	(0.0567)	(0.0410)	(0.0199)
SciTec Articles$_{it}$	0.7620**	0.5401***	1.2639***	1.5568**	0.9512***	0.4503***
	(0.3054)	(0.1804)	(0.3979)	(0.6173)	(0.2493)	(0.1188)
Price Level$_{it}$	4.5612**	2.1345	2.5622	0.6145	4.4004**	1.4255
	(2.2574)	(1.6314)	(1.9309)	(2.7647)	(1.9879)	(0.8898)
Population$_{it}$	0.8946**	0.9567***	-0.0800	-0.1019	0.3482	0.2516*
	(0.3925)	(0.2858)	(0.3777)	(0.4465)	(0.2589)	(0.1427)
GDP$_{it}$	0.3254	1.0744***	-0.7367*	0.2189	-0.3363	0.1912
	(0.3630)	(0.2880)	(0.4280)	(0.5077)	(0.2675)	(0.1475)
Health Expenditures$_{it}$	0.1790	0.2400**	-0.0092	0.0401	0.0846	0.0712
	(0.1365)	(0.0949)	(0.1250)	(0.1647)	(0.0917)	(0.0560)
Net FDI$_{it}$	0.1149	0.0340	0.0167	0.0039	0.0508**	-0.0078
	(0.0784)	(0.0215)	(0.0118)	(0.0114)	(0.0201)	(0.0054)
Weighted Trials$_{it-1}$	1.1960***	1.0508***	1.1619***	0.9631***	1.0306***	1.0390***
	(0.0369)	(0.0520)	(0.1432)	(0.2345)	(0.0735)	(0.0852)
Constant	-26.5881***	-31.1400***	-4.3036	-16.9346**	-14.3206**	-11.0440***
	(9.8154)	(7.0839)	(8.1962)	(8.5684)	(6.0622)	(3.0852)
Sigma	7.8887***	4.0433***	3.8893***	3.8160***	4.1800***	1.8460***
	(1.2600)	(0.5897)	(0.6635)	(0.7961)	(0.7110)	(0.2053)
N	869	869	869	869	869	869
AIC	4759.6807	3078.4814	1563.2119	965.2903	2730.1018	1665.6218
BIC	4812.1215	3130.9222	1615.6527	1017.7311	2782.5426	1718.0626

Clustered standard errors in parentheses

* p<0.10, ** p<0.05, *** p<0.01

Dependent and lagged dependent variables are subset specific.

Table 1: Tobit Regressions for the Number of Weighted Clinical Trials in Non-Traditional Countries

	(1)	(2)	(3)	(4)	(5)	(6)
Sample	Full	Industry Sponsored	Phase 1	Phase 1 Industry Sponsored	Phase 2	Phase 2 Industry Sponsored
Dependent Variable: Share Country$_{it}$						
T	0.1320	-0.0121	0.0660	0.8020*	0.2745***	0.3068**
	(0.0910)	(0.0802)	(0.1286)	(0.4603)	(0.0929)	(0.1232)
T^2	-0.0170*	0.0010	-0.0003	-0.0436	-0.0230**	-0.0271**
	(0.0092)	(0.0073)	(0.0116)	(0.0383)	(0.0092)	(0.0110)
SciTec Articles$_{it}$	0.4526***	0.4829***	0.7485***	1.6062***	0.5649***	0.4968***
	(0.0690)	(0.1009)	(0.1845)	(0.4197)	(0.0935)	(0.1057)
Price Level$_{it}$	0.8150*	0.2768	0.4148	0.2494	1.1038*	-0.0795
	(0.4849)	(0.5644)	(1.0149)	(1.4112)	(0.6500)	(0.5396)
Population$_{it}$	0.1063	0.1619	-0.2069	-0.7876**	0.0423	0.0053
	(0.0927)	(0.1035)	(0.2161)	(0.3733)	(0.1144)	(0.1281)

GDP_{it}	-0.0301	0.2062*	-0.2736	-0.8934	-0.0661	0.0843	0
	(0.0998)	(0.1184)	(0.2647)	(0.5612)	(0.1411)	(0.1215)	(0
Health $Expenditures_{it}$	0.0078	0.0211	-0.0274	-0.1594	-0.0142	0.0406	0
	(0.0389)	(0.0352)	(0.0923)	(0.1075)	(0.0436)	(0.0453)	(0
Net FDI_{it}	-0.0057***	-0.0054***	-0.0034**	-0.0104**	-0.0038***	-0.0053**	-0
	(0.0011)	(0.0014)	(0.0016)	(0.0052)	(0.0012)	(0.0024)	(0
Share $Country_{it}$	98.4101***	180.9962***	119.6852***	50.9974	72.3819***	298.8294***	5
	(8.1512)	(59.9571)	(26.3361)	(70.8331)	(21.6600)	(37.9432)	(1
Constant	-12.1452***	-15.7663***	-7.1636	-0.7834	-12.1523***	-13.0159***	-1
	(1.7574)	(1.9538)	(4.4786)	(7.1337)	(2.3831)	(2.5110)	(2
N	566	566	566	566	566	566	5
AIC	29.4918	24.2312	25.7766	22.6661	28.4020	24.1526	3
BIC	72.8777	67.6171	69.1625	66.0520	71.7879	67.5386	7

Clustered standard errors in parentheses

* p<0.10, ** p<0.05, *** p<0.01

Dependent and lagged dependent variables are subset specific.

Table 2: Fractional Logit Regressions for the Share of Weighted Clinical Trials in Non-Traditional Countries

	(1)	(2)	(3)	(4)	(5)	(6)
Sample	Phase 1	Phase 1 Industry Sponsored	Phase 2	Phase 2 Industry Sponsored	Phase 3	Phase 3 Industry Sponsored
Dependent Variable: Share Phase j_{it}						
T	-0.3115	0.0332	0.4292***	0.3191*	0.1197	0.2801*
	(0.3397)	(0.3953)	(0.1627)	(0.1843)	(0.1394)	(0.1493)
T^2	0.0427	0.0170	-0.0381**	-0.0189	-0.0234*	-0.0396***
	(0.0321)	(0.0367)	(0.0159)	(0.0174)	(0.0135)	(0.0137)
SciTec $Articles_{it}$	0.1411	0.3677**	0.1578***	0.2243***	0.0004	-0.0341
	(0.1327)	(0.1829)	(0.0560)	(0.0758)	(0.0616)	(0.0718)
Price $Level_{it}$	0.4939	1.3587	-0.3974	0.7652	-0.2546	0.4812
	(0.9204)	(1.4733)	(0.5407)	(0.5171)	(0.5238)	(0.5781)
$Population_{it}$	-0.1954	-0.3225	-0.1445*	-0.2791***	-0.0292	-0.0218
	(0.1767)	(0.2236)	(0.0748)	(0.1079)	(0.0791)	(0.0950)
GDP_{it}	-0.4504***	-0.4791	-0.1219	-0.5187***	0.0444	-0.1929
	(0.1725)	(0.2996)	(0.0950)	(0.1566)	(0.0876)	(0.1299)
Health $Expenditures_{it}$	-0.0580	-0.1376	0.0174	-0.0118	0.0995**	0.0851*
	(0.0735)	(0.1108)	(0.0389)	(0.0581)	(0.0420)	(0.0471)
Net FDI_{it}	0.0071	0.0044	-0.0003	-0.0030	0.0006	0.0050**
	(0.0056)	(0.0061)	(0.0025)	(0.0046)	(0.0024)	(0.0022)
Share Phase j_{it-1}	0.9945	2.7670**	0.5265*	0.5332	0.7717***	0.6708***
	(0.7525)	(1.2081)	(0.2727)	(0.3840)	(0.2094)	(0.2516)
Constant	3.5659	3.1678	0.0283	4.9311*	-1.3496	0.5364
	(3.9841)	(5.0979)	(1.6679)	(2.7290)	(1.6160)	(2.1419)
N	566	418	566	418	566	418

AIC	230.4934	139.1504	459.0778	368.2921	554.4061	443.1128
BIC	273.8793	179.5052	502.4637	408.6469	597.7921	483.4676

Clustered standard errors in parentheses

* p<0.10, ** p<0.05, *** p<0.01

Dependent and lagged dependent variables are subset specific.

Table 3: Fractional Logit Regressions for the Share of Clinical Trials in Specific Phases

Country	2002-2004	2010-2012
Brazil	***Pathological Conditions, Signs and Symptoms***; Cardiovascular Diseases; Respiratory Tract Diseases	***Pathological Conditions, Signs and Symptoms***; ***Cardiovascular Diseases***; Respiratory Tract Diseases
China	***Pathological Conditions, Signs and Symptoms***; Digestive System Diseases; ***Neoplasms***	***Neoplasms***; Digestive System Diseases; ***Pathological Conditions, Signs and Symptoms***
India	***Pathological Conditions, Signs and Symptoms***; ***Neoplasms***; Respiratory Tract Diseases	***Pathological Conditions, Signs and Symptoms***; Digestive System Diseases; Nutritional and Metabolic Diseases
Iran Islamic Rep.	Eye Diseases; Musculoskeletal Diseases; ***Pathological Conditions, Signs and Symptoms***	***Pathological Conditions, Signs and Symptoms***; Stomatognathic Diseases; ***Cardiovascular Diseases***
Israel	***Mental Disorders; Pathological Conditions, Signs and Symptoms***; Cardiovascular Diseases	***Pathological Conditions, Signs and Symptoms***; Nervous System Diseases; Mental Disorders
South Korea	***Neoplasms***; Digestive System Diseases; ***Mental Disorders***	***Neoplasms***; ***Pathological Conditions, Signs and Symptoms***; ***Cardiovascular Diseases***
Mexico	Nutritional and Metabolic Diseases; Endocrine System Diseases; ***Neoplasms***	***Pathological Conditions, Signs and Symptoms***; Nutritional and Metabolic Diseases; Respiratory Tract Diseases
Poland	Cardiovascular Diseases**; *Neoplasms***; Respiratory Tract Diseases	***Pathological Conditions, Signs and Symptoms***; ***Cardiovascular Diseases***; ***Neoplasms***
Russia	***Neoplasms***; ***Mental Disorders***; Cardiovascular Diseases	***Cardiovascular Diseases***; ***Pathological Conditions, Signs and Symptoms; Neoplasms***
Taiwan	***Neoplasms***; ***Pathological Conditions, Signs and Symptoms***; Cardiovascular Diseases	***Pathological Conditions, Signs and Symptoms***; ***Neoplasms***; ***Cardiovascular Diseases***

Thailand	Virus Diseases; Immune System Diseases; Eye Diseases	***Pathological Conditions, Signs and Symptoms***; Virus Diseases; Immune System Diseases
United States	***Neoplasms; Mental Disorders; Pathological Conditions, Signs and Symptoms***	***Neoplasms; Pathological Conditions, Signs and Symptoms; Cardiovascular Diseases***

Table 4: Most Frequently Addressed Disease Areas in Selected Non-traditional Countries

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	
Sample	Full	Industry Sponsored	Phase 1	Phase 1 Industry Sponsored	Phase 2	Phase 2 Industry Sponsored	Phase 3	Ph Ind Spo
Dependent Variable: $Overlap_{i\ to\ US\ in\ t}$								
T	0.1063	-0.2867**	0.3210	1.8540***	0.2067	0.2877	-0.2948*	-0.36
	(0.1884)	(0.1463)	(0.5409)	(0.6661)	(0.2664)	(0.2053)	(0.1620)	(0.14
T^2	-0.0063	0.0257*	-0.0264	-0.1545***	-0.0188	-0.0263	0.0175	0.02
	(0.0184)	(0.0135)	(0.0486)	(0.0582)	(0.0245)	(0.0195)	(0.0149)	(0.01
$SciTec\ Articles_{it}$	0.0330	-0.0651	0.2788	0.1779	0.1517	0.1224	-0.1606***	-0.15
	(0.0678)	(0.0632)	(0.1801)	(0.1545)	(0.1064)	(0.0796)	(0.0549)	(0.04
$Price\ Level_{it}$	-0.2909	-1.5060**	-1.1911	-1.3068	-1.3983	-1.8819**	-0.1743	-0.65
	(0.5895)	(0.7425)	(1.6123)	(1.7368)	(0.9504)	(0.9419)	(0.5506)	(0.45
$Population_{it}$	-0.1083	0.0658	-0.4533**	-0.2097	-0.0260	-0.0533	0.2021***	0.11
	(0.1081)	(0.0845)	(0.2071)	(0.2204)	(0.1373)	(0.0973)	(0.0759)	(0.06
GDP_{it}	0.1650*	0.5268***	-0.3053	-0.1694	0.2913	0.2894	0.4048***	0.36
	(0.0991)	(0.1370)	(0.3216)	(0.4051)	(0.1980)	(0.2407)	(0.0960)	(0.14
$Health\ Expenditures_{it}$	0.0033	0.0845	0.0418	0.1532	0.0558	0.1182*	0.0167	0.03
	(0.0463)	(0.0555)	(0.0811)	(0.1318)	(0.0658)	(0.0639)	(0.0436)	(0.03
$Net\ FDI_{it}$	-0.0001	0.0011	-0.0010	-0.0059	-0.0011	-0.0016	-0.0019	0.00
	(0.0021)	(0.0022)	(0.0033)	(0.0039)	(0.0035)	(0.0022)	(0.0021)	(0.00
$Overlap_{i\ to\ US\ in\ t-1}$	2.1861***	0.7849**	1.1382**	-0.8088	0.6143*	0.7720***	0.9838***	1.08
	(0.3608)	(0.3824)	(0.5105)	(0.6296)	(0.3306)	(0.2640)	(0.3048)	(0.32
Constant	0.2256	-3.4773*	8.4545*	0.0027	-2.3387	-2.7197	-4.7425***	-3.23
	(2.1116)	(1.9874)	(4.6766)	(8.0475)	(3.2573)	(2.8827)	(1.5368)	(1.82
N	556	414	133	82	314	259	409	333
AIC	324.6233	331.2875	125.7455	91.9782	282.0538	263.9782	398.0347	340.
BIC	367.8310	371.5461	154.6489	116.0454	319.5477	299.5465	438.1718	378.

Clustered standard errors in parentheses

* p<0.10, ** p<0.05, *** p<0.01

Dependent and lagged dependent variables are subset specific.

Table 5: Fractional Logit Regressions for Non-traditional Countries Profiles' Overlap to the US

Country	All Trials	Phase 1	Phase 2	Phase 3	Country Type

1	US	59,921.38	12,274.36	17,399.21	6,597.01	Traditional
2	Canada	6,500.78	828.17	1,588.96	1,252.34	Traditional
3	Germany	5,351.99	768.77	1,299.15	1,053.79	Traditional
4	France	5,144.44	427.42	1,095.56	1,102.27	Traditional
5	United Kingdom	3,978.65	858.17	928.24	660.24	Traditional
6	China	2,970.51	298.44	641.73	650.11	Non-Traditional
7	South Korea	2,840.04	327.21	587.65	448.51	Non-Traditional
8	Israel	2,760.17	288.75	482.03	273.74	Non-Traditional
9	Italy	2,577.80	140.75	678.57	650.42	Traditional
10	Denmark	2,306.52	140.56	331.18	249.86	Traditional
11	Netherlands	2,192.11	294.53	401.29	376.58	Traditional
12	Japan	2,084.91	449.20	516.13	707.00	Traditional
13	Spain	1,974.53	180.54	531.19	387.72	Traditional
14	Taiwan	1,946.67	118.19	265.71	227.12	Non-Traditional
15	Brazil	1,915.50	146.27	286.56	475.19	Non-Traditional
16	Belgium	1,636.33	303.29	395.63	261.07	Traditional
17	Switzerland	1,550.15	188.24	295.63	203.32	Traditional
18	Australia	1,344.03	285.01	366.70	296.53	Traditional
19	Sweden	1,313.11	174.00	252.45	190.57	Traditional
20	Norway	1,143.54	78.04	205.38	149.73	Traditional
21	India	1,093.10	217.35	212.80	283.87	Non-Traditional
22	Austria	1,040.74	90.62	226.22	196.93	Traditional
23	Finland	672.59	53.73	119.45	126.74	Traditional
24	Thailand	657.74	49.49	133.96	158.38	Non-Traditional
25	Poland	590.49	42.38	164.71	194.06	Non-Traditional
26	Mexico	545.05	57.68	153.70	169.56	Non-Traditional
27	Singapore	533.01	158.08	113.76	67.10	Non-Traditional
28	Iran Islamic Rep.	484.35	81.00	177.50	117.22	Non-Traditional
29	Greece	484.07	18.32	107.43	86.82	Non-Traditional
30	Russia	436.43	35.67	144.31	159.22	Non-Traditional

Table 6 in the Appendix provides an overview of countries conducting the highest number of weighted clinical trials throughout our period of observation. We did not include Singapore and Greece in the descriptive analysis since these two countries may be rather similar to traditional countries for clinical research.

[9] These results are robust to the inclusion of WHO Regions as well as World Bank income groups as additional control variables.

[10] The observed increase in the share for the different countries is in line with a decreasing share of the US from around 50% in 2002 to less than 40% in 2012. However, the US remain the dominating country in clinical research. The share of other leading traditional trial locations, i.e., countries particularly located in Western Europe, rests quite stable between 2% (United Kingdom) and 5 % (Canada).

[11] Consequently, a decreasing share of phase 3 trials in a country implies that the country conducts more trials in other phases.

[12] Iran is to some extent an exception because only very few industry sponsored trials are conducted in Iran.

[13] It should be noted that our database accounts for a rather conservative estimation of the amount of clinical trials addressing disease areas with a local prevalence since these trials may not necessarily be registered in ClinicalTrials.gov.