An Evaluation of Global Indicators as Surrogates for Clinical Research Capacity in the US, Poland, and Vietnam

An Evaluation of Global Indicators as Surrogates for Clinical Research Capacity in the US, Poland, and Vietnam

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Abstract

In the United States (US), the process for developing a new drug is a costly and lengthy endeavor. Study stakeholders would benefit from a novel methodology for identifying clinical trial site locations as a means to make the drug development process more expedient and more cost-effective. The aim of this study was to determine whether publicly available global indicator data could be used to evaluate the suitability of different countries for conducting human subject clinical trials. The US, Vietnam, and Poland were selected for this study as representative examples of regions with varying degrees of clinical trial framework robustness.

A set of nine dimensions was developed, representing important factors for conducting clinical trials, such as ethical oversight, human subject protections, and access to quality healthcare within a given country. Indicator data sets, from publicly available sources such as the World Health Organization, the World Bank, and the World Justice Project, were selected to align with each dimension. Novel indicators were created where alignment with existing, publicly available data was not possible. Publicly available indicator data aligned with four clinical trial infrastructure dimensions (Dimension 1, Dimension 5, Dimension 6, and Dimension 7), which were compared across 85 countries. These dimensions were also shown to correlate with the Human Development Index, a measure of human development based on life expectancy, years of schooling, and gross national income. A fifth dimension (Dimension 3) used clinical trial registry data and global burden of disease data to create a novel indicator related to research focus on

health needs/priorities for the US, Vietnam, and Poland. Novel indicators for the remaining dimensions were created based on a manual review of local regulations for the three countries of interest.

While the model developed for this study was too premature to fully comprehend the potential of using indicators derived from publicly available data to assess clinical research capacity, this study suggests that using these metrics could greatly aid in the decision-making process for clinical trial design. These methods could enable the identification of trial site locations far earlier than traditional methods, resulting in faster study startup, recruitment, and completion in regions with far lower study-related costs than the US or other developed nations – ultimately resulting in lower costs throughout the drug development process.

Acknowledgments

When I first began taking classes towards the Biotechnology ALM degree program, I was amazed at how quickly they flew by. Despite working full time in a demanding clinical research job that required frequent international travel, I still managed to stay on top of my responsibilities. It was not until I started down the thesis proposal development pathway that I lost momentum. Due in part to procrastination, as well as other life demands, I struggled to make regular progress as I moved through the process of performing my research.

I would like to thank my research directors, Katherine Arbour and Dr. Ron Knickerbocker, for their support and patience throughout this process. As I had questions about the scope of my research, whether my proposed methods were sound, or even about the thesis process itself, they were always willing to provide me with the insight and support I needed. I am truly grateful for their support.

I would also like to recognize and thank my wife, Carrie, for her support over the past several months as I have struggled to overcome this obstacle. I have never met anyone who believes in me as much as you, and I never would have been able to finish this without you.

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Chapter I.

Introduction

In the United States (US), the process for developing a new drug is a costly and lengthy endeavor. It takes 10-15 years to bring a new drug from the laboratory setting to market at an estimated cost of USD$500 million to USD$2.6 billion (Institute of Medicine (US) Forum on Drug Discovery, Development, and Translation, 2010; Collier, 2009; Adams & Brantner, 2006; DiMasi, Grabowski, & Hansen, 2016). Only five in 5,000 potential drug compounds successfully complete preclinical testing and make it into human trials, with approximately ten percent of those remaining actually making it through clinical testing to the pharmacy shelf (US FDA, 2015a). The process of demonstrating the safety and efficacy of a new drug in humans through clinical trials is critical to obtaining marketing approval from the United States Food and Drug Administration (FDA). Recent studies estimate that this stage of the drug development process alone takes approximately 6.7-7.5 years at a cost of up to USD$1.5 billion (DiMasi, Hansen, & Grabowski, 2003; Adams & Brantner, 2006; DiMasi et al., 2016).

In recent years the cost of drug development in the US has steadily increased, with one study estimating an annual increase in costs of close to 9% above inflation, with the growth rate of clinical costs being disproportionally higher than pre-clinical (DiMasi et al., 2016). The increase in development costs has resulted in some drug companies becoming more risk averse, focusing their efforts on improving drugs that are already on the market instead of developing novel therapies. Improving existing drugs requires larger studies with thousands of subjects in order to demonstrate a small, but statistically

significant, improvement (Collier, 2009; Sertkaya, Wong, Jessup, & Beleche, 2016). At the same time there has been a shift towards developing drugs to treat chronic and degenerative diseases rather than infectious diseases, which requires studies with lengthy follow-up periods to evaluate long-term outcomes (Sertkaya et al., 2016). The net result of these changes is that clinical trial protocols are becoming more complex, involving numerous endpoints, costly procedures and interventions, and frequent in-clinic assessments – all of which dramatically drive up study costs. With this rise in complexity comes a need for experienced investigators and support staff that can successfully execute the study and patients that are willing and able to meet the demands of participation (Collier, 2009; Getz, 2008; Sertkaya et al., 2016).

While the cost and complexity of trials have grown over the past few decades, the availability of qualified and experienced investigators and support staff has been on the decline in the US due in large part to a push to do more for less in an increasingly litigious and competitive environment (Getz, 2005). Many study centers are becoming more selective in the types of trials they are willing to conduct due to growing cost and complexity, while others are closing their doors entirely (Collier, 2009; Getz, 2010). Meanwhile, in other parts of the world, clinical research is becoming a major industry with plenty of qualified sites and potential study subjects. As study conduct standards and intellectual property (IP) protections continue to improve, developing nations that can offer shorter clinical development timelines and lower costs are becoming increasingly attractive to study sponsors (Glickman et al., 2009).

With the ever-increasing accessibility to information via the Internet, the barriers to a developing nation's ability to draft regulations and guidance documents that are on

par with those in the US have all but disappeared. Indeed, the International Council on Harmonisation (ICH) has published a large volume of guidance documents that have been adopted by the US, European Union (EU), and several other countries. Similarly, the FDA publishes all of its regulations, guidance documents, and a variety of training materials on its website for public use. However, there are a number of additional factors to consider when selecting a study site location beyond the mere presence of robust conduct standards. Economic stability, access to healthcare, and rights of citizens are just a few of the areas that must be evaluated before initiating a study that will take years to conduct, cost millions of dollars, and expose hundreds or thousands of people to an investigational product. Failing to perform an adequate regional assessment can have serious implications, from delaying the launch of a product to putting study participants' lives at risk. Despite the abundance of information available online, finding the *right* information to feed into the decision-making process is still a challenge.

One way to make sense of a large body of data is to create a composite indicator or index (CI) that provides a "big picture" interpretation of multiple sub-indicators that otherwise have no meaningful unit of measure (OECD, 2008). There are a number of publicly available international CIs and datasets that compare countries based on myriad factors that are relevant to conducting clinical research, such as human development, political instability, and perception of corruption, to name a few (Businesswire, 2009; Transparency International, 2017; UNDP, 2016b). Similarly, there are several reputable sources of country-specific regulations (or summaries), listings of countries voluntarily adopting harmonized standards, ethical oversight bodies, and other types of information that are not as easily represented in a numerical fashion. While CIs have been developed

for a variety of purposes, there do not appear to be any that are specific to conducting clinical research.

The Drug Development Process

In the US, the FDA breaks down the drug development process into five stages: Discovery/Concept, Preclinical Research, Clinical Research, FDA Review, and FDA Post-Market Safety Monitoring. A number of tests must be performed within each stage before moving on to the next, with the complexity and cost of testing exponentially increasing in each stage (Figure 1, below). During the first stage, the potential drug compound is tested in a lab setting to characterize properties such as absorption, mechanism of action (MoA), and the ideal route(s) of administration. During the preclinical research stage, testing moves from the bench into animals where preliminary safety is evaluated and the decision is made to discontinue development or to proceed into clinical testing in humans. The clinical research stage is broken up into three distinct phases, with phase I focusing on safety in less than 100 patients, phase II shifting to safety and preliminary efficacy in several hundreds of patients, and phase III evaluating both safety and efficacy compared to an already marketed drug or a placebo in thousands of patients.

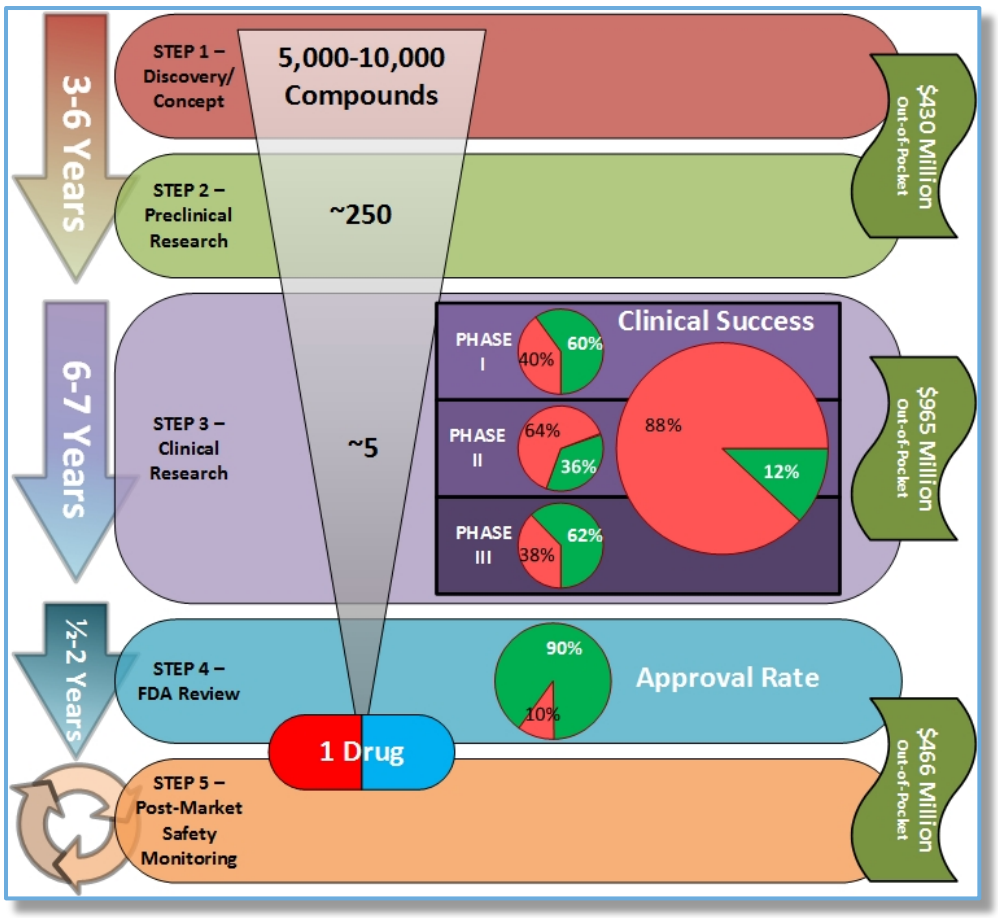


Figure 1 - The drug development process in the US

The process of bringing a novel drug candidate to market takes several years with significant costs at each stage of the process. The clinical stage is the most costly and time consuming. Only a small fraction of initial drug candidates actually make it to market. Adapted from:(PhaRMA, 2007; US FDA, 2015b; DiMasi et al., 2016)

The clinical research stage is the most costly and heavily regulated portion of the drug development process, which takes between 6.7-7.5 years at a cost of up to USD$1.5 billion (DiMasi et al., 2003; Adams & Brantner, 2006; DiMasi et al., 2016). It is also the riskiest stage. A recent study estimated the overall approval rate for a new compound that enters clinical testing to be less than 12%, which is almost half the success rate in the

same author's 2003 study (21.5%) (DiMasi et al., 2016). Once the clinical research stage is completed, the information gathered throughout all of the development stages is then submitted to the FDA for review. Following approval, the new drug is continuously evaluated to assess long-term safety in a larger group of patients than was included in the highly controlled clinical studies (US FDA, 2015b).

The entire drug development process takes 10-15 years at an estimated cost of USD$500 million to USD$2.6 billion (Institute of Medicine (US) Forum on Drug Discovery, Development, and Translation, 2010; Collier, 2009; Adams & Brantner, 2006; DiMasi et al., 2016). The development costs include those associated with successful drugs as well as the sunk costs for drug candidates that fail to make it to the market. In recent years the cost of drug development in the US has steadily increased, with one study estimating an annual increase in costs of close to 9% above inflation, with the growth rate of clinical costs being disproportionally higher than pre-clinical (DiMasi et al., 2016). Given the costs and timeframes associated with the clinical stage, any systemic improvements in efficiency could drastically reduce overall development costs. However, the clinical stage is also subject to the highest level of FDA regulation, so it is critical to balance regulatory risks with efficiency gains.

The US Food and Drug Administration

The origins of the FDA date back to the 1800s, when the agency's primary focus was to implement basic food and drug standards and inspect imported goods upon entry into the United States. Over the next century, the FDA's role evolved to ensure the accuracy of drug claims and to increase the level of recordkeeping necessary for narcotic drugs. By the mid 1900s, due in part to tragedies associated with products like Elixir

Sulfanilamide, Thalidomide, and a bad batch of the polio vaccine, there was a publicly recognized need for stronger drug regulations. With the passage of the Kefauver-Harris Drug Amendments in 1962, the FDA's authority had grown to the point that drug manufacturers were required to prove the safety and effectiveness of their drugs through well-controlled clinical trials prior to marketing them. It was at this point that the modern FDA's role as it is known today began to take shape (US FDA, 2014, 2016).

As the need for robust clinical trials grew, so too did the need for protecting the human subjects that were recruited to participate in them. Following the prosecution of Nazi war criminals for conducting medical experiments on unconsenting concentration camp prisoners, the Nuremberg Code was established in 1948 to make the voluntary consent of human subjects "essential," although not yet a legal requirement. This also introduced the concept of developing trials that requiring a favorable benefit-risk ratio (University of Missouri, 2009). In 1964, the World Medical Association (WMA) published the first version of the Declaration of Helsinki which served as a moral and ethical code of conduct for all physicians involved in conducting clinical research in human subjects – not just in the US, but around the globe. However, it was not until after the discovery that the deeply unethical Tuskegee Syphilis Study that began in 1934 was still ongoing in 1972 that any true ethical requirements were signed into law. In 1974, the passage of the National Research Act created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, which was charged with identifying and drafting guidance on the basic ethical principles that should underlie clinical research. The Commission did so in 1979 with the issuance of the Belmont Report, which established that three basic principles should be applied to clinical

research: respect for persons, beneficence, and justice (University of Missouri, 2009; US OHRP, 2009).

Today's regulations are essentially a conglomeration of the past century's legal and ethical advancements, many of which were implemented in response to large-scale health crises or tragedies, with the ultimate aim of protecting human subjects (US FDA, 2014, 2016). Despite the noble origins of these incremental changes, many of them were made hastily and their effectiveness was never evaluated (Fost & Levine, 2007). Furthermore, some have argued that the burdens imposed by regulations have actually had negative impacts on research outcomes and subject protection in the US (Califf et al., 2003; Ness, 2007). The FDA has long been criticized for its lack of transparency, lengthy review timelines, and labyrinthine regulations, but is working towards improving these deficiencies. Through efforts like the FDA Modernization Act of 1997, the ongoing FDA Transparency Initiative, and a 2011 executive order from President Barack Obama, the FDA is hoping to maintain the highest level of protection while taking the least burdensome approach on society (Barack Obama, 2011; US FDA, 1997, 2017a). While these initiatives are a step in the right direction, there are concerns that the regulatory behemoth will be unable to keep up with the technological advancements it is tasked with overseeing (Aylin Sertkaya, Anna Birkenbach, Ayesha Berlind, & John Eyraud, 2015). Countries that have been able to implement comparable regulatory oversight to the FDA without such cumbersome bureaucracy have become major players in clinical research, and many others are on their way.

The US Clinical Research Enterprise

In the US, industry sponsored clinical trials require a large amount of oversight and resources in order to be completed successfully. Most clinical studies need to be conducted under an FDA-approved Investigational New Drug (IND) application. Following approval by the FDA, the study protocol and various other study documents must then be approved by one or more Institutional Review Boards (IRBs) at the study sites that will recruit research subjects. Study sites typically include specialty clinical research centers, academic medical centers, and physician private practices – each of which may have a varying level of support staff and equipment to conduct protocol-required procedures. A given study may require only one study site, while others may require several dozen due to their complexity. If the study requires laboratory tests, radiological assessments, tissue sample processing, or other specialized testing, additional vendors may also need to be included in study conduct. A data management vendor may also be required to develop and maintain the database used to collect and analyze study data. To manage all of these various counterparts, a sponsor will often hire a Contract Research Organization (CRO) to oversee study activities at the site and vendor levels, and to ensure that study is conducted in accordance with the protocol and regulatory requirements.

In order to maintain compliance with an ever-changing regulatory landscape, not only drug manufacturers, but all parties involved with clinical research, have had to implement costly infrastructure. This applies to IRBs, CROs, clinical research specialty centers, academic medical centers, and others. Many clinical trials pose a high level of risk to research participants due to the novelty of the investigational therapy and potential

unknown side effects that may surface when the therapy is administered to a large number of people and/or for an extended period of time. It is therefore critical to ensure the highest level of protection for research participants in high-risk trials; however, the same level of scrutiny and oversight is often applied to studies that pose low or minimal risk as well. Whether due to a conservative interpretation of the regulations, having highly risk-averse leadership, intentionally profiting from additional administrative steps within a highly regulated environment, or some combination of the three, the process of conducting a clinical trial from start to finish in the US is often more drawn out and costly than necessary (Kramer, Smith, & Califf, 2012).

While the costs vary significantly depending on the therapeutic area of the drug, one study found the overall average cost per study to be approximately USD$3.8 million for phase I studies, USD$13.4 million for phase II studies, and USD$19.9 million for phase III studies (Figure 2, below). The mean cost of post-approval (phase IV) studies was found to be USD$19.5 million. The authors found that the sum of the IRB, vendor, and site costs (including 25% overhead) accounted for approximately 70% of the overall study costs. The leading cost drivers were found to be clinical procedures, administrative staff, site monitoring, site retention, and central laboratory costs (Aylin Sertkaya et al., 2015). Prior to receiving FDA approval, a given compound may require several studies within each clinical research phase in order to demonstrate its safety and efficacy. In contrast to the drug development costs discussed previously, these study costs reflect real expenditures to conduct individual studies and do not take into account the success or failure of the compound under investigation.

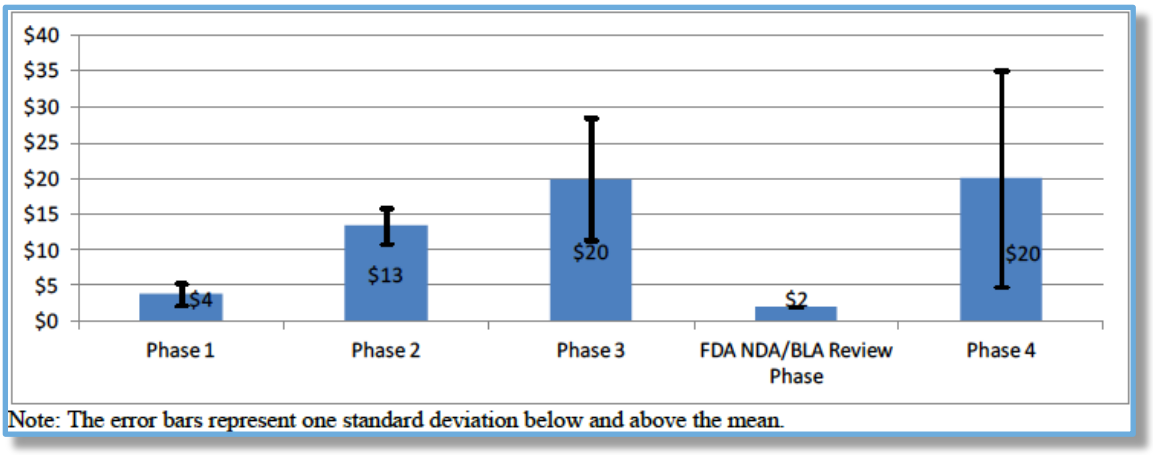


Figure 2 - Average per-study costs by phase (in USD$ millions) across therapeutic areas

From: (Aylin Sertkaya et al., 2015)

With so many players involved, even something like a minor amendment to a study protocol can result in hundreds of man-hours being dedicated to update related documents, data collection forms, and site-level documents. This is in addition to the protocol changes and updated documents needing to be reviewed and approved by one or more IRBs prior to staff being trained and the changes actually being implemented at study sites. With each man-hour corresponding to an hourly rate, it's easy to see how these incremental costs could add up. One study determined that, on average, each protocol amendment takes over two months to implement at a cost of approximately USD$453,932, with almost 60% of those costs being site fees (Getz, 2011). While protocol amendments may not always be avoidable, utilizing clinical sites in countries other than the US could drastically reduce associated costs. For instance, site costs in China, Poland, and India are approximately 50%, 39%, and 36% (respectively) of those in the US (Institute of Medicine (US) Forum on Drug Discovery, Development, and

Translation, 2010). Identifying clinical trial regions with appropriate regulatory and ethical oversight outside of the US can reduce the overall clinical development costs of a drug by hundreds of millions of dollars.

The Impact of the "Flattening" World

Advancements in technology during recent decades have changed the world in dramatic ways. The expansion of cell phone and wireless technology in particular has allowed developing nations to become as connected as the most developed nations almost overnight (Pew Research Center, 2015). The ability to communicate with others over long distances has evolved over the past few centuries, beginning with the development of the telegraph in the 1700s. In the late 1800s, the development of the telephone and telephone exchange allowed people over 50 miles away to speak to each other for the first time (Kempe & Garcke, 1911). Over the next century, through the development of costly infrastructure (e.g., telephone poles, wires, and exchange buildings), people in the developed world were able to communicate more and more easily.

The invention of the Internet and World Wide Web that relied on this wired infrastructure further set the developed world apart from those countries that didn't have the resources to keep up. However, in recent decades, as cell phones and wireless Internet have become more prevalent and affordable, people in developing nations have been able jump from relying on face-to-face or written communication to being able to talk, text, and tweet to each other without the need to follow the long development timeframe that it took to grow the technology. This "flattening" effect has had a dramatic influence on education, personal relationships, and the economy in developing nations (Pew Research Center, 2015).

As previously discussed, the development of drug manufacturing regulations, research standards, and human subject protections has also evolved over a long period of time in the developed world based on a number of global public health crises. In recent decades, as international trade has become increasingly commonplace, the need to harmonize these regulations has also grown. Since 1990, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) has been working to create a common set of technical guidelines and requirements for pharmaceutical development in the EU, Japan, and US (ICH, 2016). These guidelines, which are publicly available, provide a blueprint for implementing a regulatory infrastructure that is in-step with the largest markets in the world. As such, similar to adopting cell phones, a developing nation can adopt the ICH model and jump into the drug development industry, skipping the long regulatory development timeline. However, the mere presence of robust standards alone is not enough to make a country "qualified" to conduct clinical research.

The Benefits of a Data Rich Society

Historically, US drug companies conducted a majority of their studies in the US or a handful of Western European regions to gain approval, making the country selection process fairly easy. However, the global clinical research landscape is rapidly changing, and clinical research is now being conducted on every continent, including Antarctica (US National Library of Medicine, 2016). The decision for a pharmaceutical company to move a significant portion of its clinical research activities overseas is a complicated one, requiring careful appraisal of the country(ies) of interest. Economic stability, access to healthcare, and rights of citizens are just a few of the areas that must be evaluated before

initiating a study that will take years to conduct, cost millions of dollars, and expose hundreds or thousands of people to an investigational product. Failing to perform an adequate regional assessment can have serious implications, from delaying the launch of a product to putting study participants' lives at risk. Because there are so many global factors that are constantly in flux, it is becoming increasingly difficult to narrow down the list of potential clinical trial regions before performing an in-depth assessment.

In addition to publicly accessible regulations, guidance documents, and other valuable infrastructure related resources, there are hundreds of data repositories providing country comparisons on myriad public health factors, from adolescent health to incidence of Zika Virus, based on millions of individual data points. Much of this enormous body of data can be accessed directly or by viewing indicators that are focused on specific topics of interest. Another way to digest the information is by using Composite Indicators or indices (CIs), which provide a "big picture" interpretation of multiple sub-indicators that otherwise have no meaningful unit of measure (OECD, 2008). Examples of publicly accessible CIs include Transparency International's Corruption Perceptions Index, the United Nations' (UN) Human Development Index (HDI), and the World Health Organization's (WHO) Global Health Observatory (GHO) dashboard, which contain a number of individual and composite indicators (Transparency International, 2017; UNDP, 2016b; WHO, 2017). Despite the abundance of publicly available country-level information, finding the *right* data is not an easy task. For example, the WHO's Global Health Observatory (GHO) alone has over 1,000 individual indicators for the 194 WHO member states across over 30 different global health related themes (WHO, 2017). There

is currently no way to compare multiple countries based on publicly available indicators specific to clinical research.

Chapter II.

Research Methods

The goal of this study was to determine whether publicly available global indicators could be used to evaluate a country's suitability for conducting clinical trials. The research methods followed the basic steps outlined in Figure 3 (below), which are based on the OECD's *Handbook on Constructing Composite Indicators.* Each step is described in further detail within this section.

This study identified global indicators that are thought to align with each *dimension* – or important factor for conducting clinical trials – which were tested by comparing the global indicator data against in-depth assessments of these dimensions for the US, Vietnam, and Poland. These countries were selected for this study as representative examples of regions with varying degrees of clinical trial framework robustness: a "gold standard" country (the US), a developing nation that is in the early stages of implementing clinical research regulations (Vietnam), and one country that is in between the two ends of the spectrum (Poland). Poland was selected as the third country because it is a member of the European Union, but not as developed as other EU countries such as France, Germany, or Sweden.

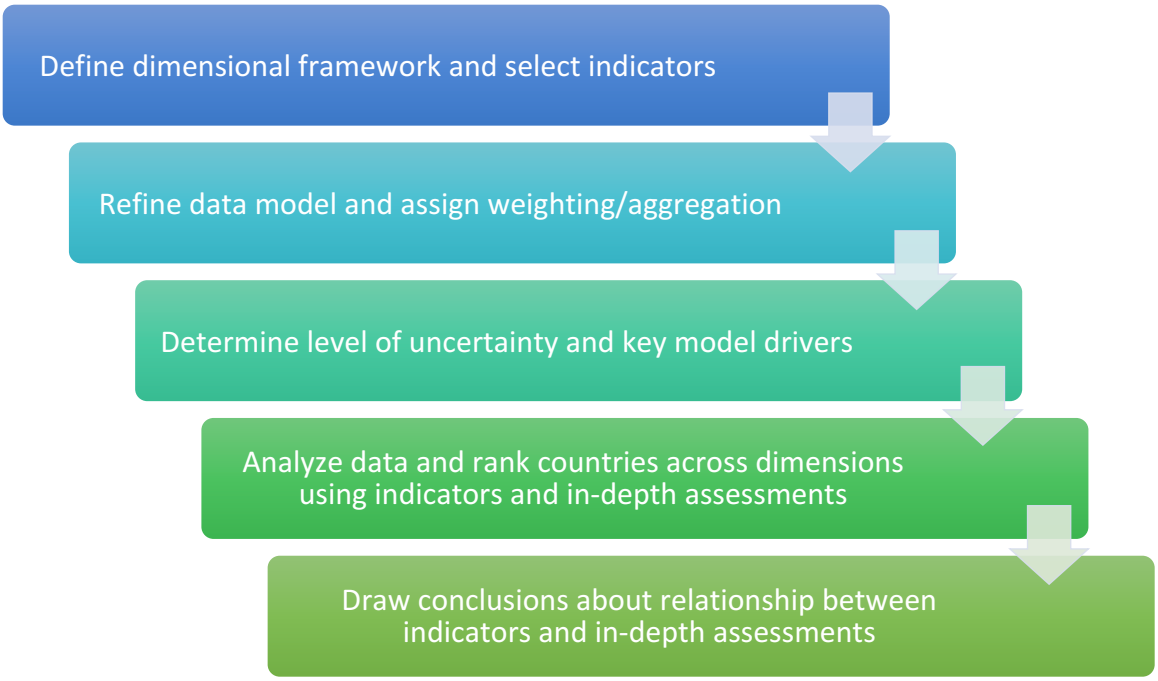


Figure 3 - Research flow diagram

This flow diagram summarizes the progression of steps needed to develop a composite indicator according to the OECD (OECD, 2008).

Define Dimensional Framework and Select Indicators

The clinical research infrastructure dimensional framework was developed in part using the CIOMS International Ethical Guidelines for Health-related Research Involving Humans (2016), which outlines the fundamental aspects that need to be considered for conducting clinical research. These guidelines were reviewed to identify elements of clinical research assigned specifically to governmental agencies and health authorities in order to focus on the highest level of oversight for each country. Among those aspects that can be evaluated at the country level are: 1) the requirements for human rights to be protected by law; 2) for there to be mandatory ethical oversight and review of study

protocols; 3) that in low resource settings, the research is in response to local health needs and priorities; 4) that the benefits and burdens of research are equitably distributed; and 5) that subjects have access to quality healthcare during and after participation (CIOMS, 2016). While the CIOMS guidelines include a number of other considerations specific to institutions, sponsors, investigators, and other stakeholders, these were excluded to keep the focus at the country level.

Additional factors that are important to conducting clinical trials for new drugs, from the sponsor's perspective, include: 6) the level of corruption within the country; 7) the country's adherence to international IP laws; 8) the cost of regulatory review of clinical trial protocols; and 9) the regulatory review timeframe for clinical trials. In contrast to dimensions 1-5, which are centered on the safeguards for study subjects, dimensions 6-9 focus on potential risks to study sponsors. Descriptions of each dimension are provided in Table 14 (Appendix 1).

Once the dimensional framework was defined, a search for corresponding global indicator repositories was conducted using Hollis+. The search strategy is outlined in Appendix 2. Three catalogs of global indicators were identified with a total of 391 indicator databases. The details of each database were reviewed and assessed based on their country coverage, update frequency, organization type, and area of focus. Indicator databases were excluded based on the following criteria:

- Country Coverage – databases that did not have global coverage, had a regional focus, or did not include all three of the countries of interest

- Update Frequency – databases that had an update frequency of more than 3 years, had not been updated since 2013, or had an infrequent or unknown update frequency
- Organization Type – organizations that did not have a global focus, and/or that were perceived to have a potential bias
- Area of Focus – databases focused on topics unrelated to the dimensional framework descriptions

According to the above criteria, 338 indicator databases were excluded. The remaining 53 databases were further evaluated against the descriptions of the clinical research infrastructure dimensions to determine appropriate matches for each. Of the 391 indicator databases identified, three were found to align with dimensions 1, 5, 6, and 7. A fourth database, the Human Development Index (HDI), was also found to align generally with these dimensions, and was included for comparison. Within each database were a number of different "factors" – composite indicators and individual indicators centered on a specific element of the database's larger focus[1]. These factors were further reviewed to identify specific measures aligned with each dimension whenever possible. If this was not possible, multiple factors were selected and combined. When no matching factors could be identified for a given dimension, a novel indicator was developed.

The three selected databases and five individual factors for dimensions 1, 5, 6, and 7 are presented in Table 1 (below). The rationale for selecting these is described in

[1] While the concepts are interchangeable, for clarity the term "factor" will refer to specific elements within a publicly available database, while the term "dimension" will refer to specific elements within the scope of this study.

detail in the following sections and in Appendices 2 and 3. Novel indicators were created for the remaining dimensions, as they were not found to correspond to any of the publicly available factors reviewed. These are also described in detail in the following sections and in Appendix 4.

Table 1 - Databases and factors matched to dimensions 1, 5, 6, and 7

Dimension	Selected Factors	Source
Dimension 1 - Human Rights Protections	Worldwide Governance Indicators (WGI) database - Voice and Accountability factor	The World Bank
Dimension 5 - Access to Quality Healthcare	Sustainable Development Goals (SDG) 3.8.1 - Universal Health Coverage (UHC) Tracer Index factor	World Health Organization (WHO) Global Health Observatory (GHO)
	SDG 3.8.2 - Catastrophic Health Expenditure factor a) % of population with >10% expenditure on health b) % of population with >25% expenditure on health	
Dimension 6 - Control of Corruption	Worldwide Governance Indicators (WGI) database - Control of Corruption factor	The World Bank
Dimension 7 - Adherence to International IP Laws	Rule of Law database - Regulatory Enforcement factor	World Justice Project (WJP)

Dimension 1 – Human Rights Protections

As previously stated, a fundamental aspect of conducting clinical trials is ensuring that the rights of human subjects are protected. In the absence of a composite indicator focused specifically on study subject protections, it was believed that a high level of human rights protections for the general population might be an appropriate surrogate. The Voice and Accountability factor of the World Bank's WGI database was selected as a measure of human rights protections for several reasons. First, the description of the

factor aligns with that of Dimension 1 closely, stating that it captures the "perceptions of the extent to which a country's citizens are able to participate in selecting their government, as well as freedom of expression, freedom of association, and a free media" (Kaufmann & Kraay, 2017). Secondly, the WGI database has a longstanding history, dating back to 1996 when it was initially created. The data and methodology have been updated regularly since its inception in order to allow countries to be evaluated across the WGI's six different factors over time. Additionally, the Voice and Accountability factor comprises over 60 individual data points from 20 different sources, including Freedom House, Transparency International, and the Economist Intelligence Unit. Finally, the WGI methodology and source data are readily available to users through an interactive website.

Dimension 5 – Access to Quality Healthcare

Having access to quality healthcare is an important measure of a country's development, and a contributor to a high quality of life. Both the level of access to, and quality of, healthcare in a region are also important contributors to potential clinical research capacity. A quality healthcare system includes highly trained physicians and other health workers, as well as hospital facilities, all of which are important for conducting clinical trials. A concern with conducting clinical trials in low resource settings is the possibility of coercing patients into taking part in research due to a lack of other healthcare options. If patients have a high level of access to quality healthcare in a region, the risk of coercion may be lower. The UN's GHO database contains a large number of factors for a variety of topics related to healthcare around the globe.

One of the UN's Sustainable Development Goals (SDGs) is to ensure healthy lives and promote well-being for all, which includes moving towards ensuring universal health coverage (UHC) (United Nations, 2017). To measure UHC, the UN evaluates the coverage of essential health services and level of financial protection in separate factors: 1) The UHC Tracer Index, and 2) Catastrophic health expenditure. The UHC Tracer Index factor looks at four areas of health coverage: 1) Reproductive, maternal, newborn and child health; 2) Infectious disease control; 3) Non-communicable diseases; and 4) Service capacity and access. The WHO's definition of catastrophic health expenditure is "the proportion of population with large household expenditures on health as a share of total household expenditure or income," which includes two components with thresholds set at 10% and 25% (WHO, The World Bank, & International Bank for Reconstruction and Development, 2017). For this study, these factors were selected and combined to evaluate the level of access to quality healthcare.

Healthcare access and healthcare quality were initially going to be evaluated separately, but were ultimately combined into a single dimension due to a high degree of overlap between their respective factors.

Dimension 6 – Control of Corruption

The successful conduct of clinical research relies on a number of different parties working together in a coordinated, transparent, and unbiased nature that fosters trust. Corruption, whether in the form of favoritism, bribery, or otherwise, can erode that trust and put the completion of a clinical trial in jeopardy. This presents a business risk to the study sponsor, as well as a potential risk to the wellbeing of study subjects. The extent to which a country's corruption is controlled was measured using the Control of Corruption

factor of the WGI database. This factor “captures perceptions of the extent to which public power is exercised for private gain, including both petty and grand forms of corruption, as well as "capture" of the state by elites and private interests” (Kaufmann & Kraay, 2017). This description was found to align with that of Dimension 6. Furthermore, the same strengths previously outlined for the Voice and Accountability factor also apply to Control of Corruption.

Dimension 7 – Adherence to International IP Laws

Clinical study sponsors collaborate with investigators and institutions around the world to develop promising new therapies using cutting-edge technology. In the process, proprietary technologies and products are entrusted to researchers with the expectation that they will be only be used as intended for the conduct of a clinical trial, and that confidentiality will be maintained. The investment in conducting clinical trials is substantial, but necessary, to demonstrate the safety and efficacy of novel therapies. Study sponsors must ensure that their IP rights will be respected during and after the completion of research in the regions where the technology is researched and marketed. To measure adherence to international IP laws, the Regulatory Enforcement factor of the WJP’s Rule of Law Index was selected.

The Rule of Law Index was first developed in 2010, and has been updated annually since then. This index contains nine separate factors, including Constraints on Government Powers, Fundamental Rights, Absence of Corruption, Order & Security, as well as three factors focused on the carriage of justice itself. The Regulatory Enforcement factor of the Rule of Law Index “measures the extent to which regulations are effectively implemented and enforced without improper influence by public officials or private

interests… [which] also addresses whether the government respects the property rights of people and corporations" (World Justice Project, 2016). This definition was found to correspond with the description of Dimension 7.

Several factors of the Rule of Law Index were found to overlap with the factors selected from the WGI database, in particular, Fundamental Rights and Absence of Corruption. In addition, these factors are used as inputs to calculate the Voice and Accountability and Control of Corruption factors of the WGI. To avoid improper weighting due to duplicative source data, the Fundamental Rights and Absence of Corruption factors of the Rule of Law Index were excluded.

In summary, five individual factors were selected from three publicly available indicator databases to evaluate four of the dimensions in the model for this study (dimensions 1, 5, 6, and 7). An additional indicator database (the HDI) was also selected for comparison.

Refine Data Model and Assign Weighting/Aggregation

Once the publicly available factors were selected for each dimension, it was necessary to transform the data in order to facilitate comparisons. The first step in this process was to determine how to handle missing data. While the publicly available factors each had global coverage, they did not include all of the same regions. For simplicity, only countries with data for all factors were included in the analysis. Therefore, no imputation of missing data was necessary. Next, the scores for each factor were normalized using a simple ranking function in Microsoft Excel (RANK.AVG), which assigned each country a relative rank for each factor. The result comprised a complete data set for all four dimensions covering 85 countries. There are limitations to

these approaches, which are discussed in later sections. Since the focus of this preliminary research was to evaluate the suitability of three countries for conducting clinical research, the omission of countries with missing data and conversion of scores to ranks were not believed to have a significant impact on the results.

Prior to aggregating the data, a Principal Components Analysis (PCA) was performed to evaluate the underlying structure of the data using SPSS Version 24. As Table 2 (below) demonstrates, with the exception of >10% and >25% health expenditure, the factors for dimensions 1, 5, 6, and 7 were highly correlated with each other and the HDI. The two health expenditure factors were highly correlated with each other, but not with any of the other factors. A scree plot was generated to visually interpret the data (Figure 6, Appendix 5), which showed two principal components with eigenvalues >1.0 accounting for most of the variance in the model.

Table 2 - Correlation matrix for normalized (ranked) factor values

	Voice & Accnt.	UHC Tracer	>10% Hlth Expend.	>25% Hlth Expend.	Cntrl. Corrupt.	Reg. Enforce	HDI 2016
Voice & Accnt.	1.000	**.649**	.060	.064	**.775**	**.798**	**.501**
UHC Tracer		1.000	-.011	.009	**.718**	**.766**	**.573**
>10% Hlth Expend			1.000	**.925**	.114	.047	.030
>25% Hlth Expend				1.000	.129	.058	.066
Cntrl. Corrupt.					1.000	**.898**	**.524**
Reg. Enforce						1.000	**.571**
HDI 2016							1.000

Note: n=85. Bold values are statistically significant at p=0.002

To further explore the relationships between the factors and principal components a varimax rotation was performed on the data. Figure 4 (below) provides a visual representation of the rotated data showing tight clustering of the factors around the two principal components. The component loadings for the rotated data also supported the selection of two principal components, showing the two health expenditure factors to be highly related to Component 2, and the remaining factors to have a strong relationship to Component 1 (Table 23, Appendix 5). This demonstrates that the voice and accountability, UHC tracer, control of corruption, regulatory enforcement factors as well as the HDI are measuring similar phenomena. This is not surprising, as there is likely to be significant overlap between the elements and infrastructure that have a positive impact on these factors. Similarly, the two health expenditure factors are highly correlated because they are presenting two different thresholds of the same measure.

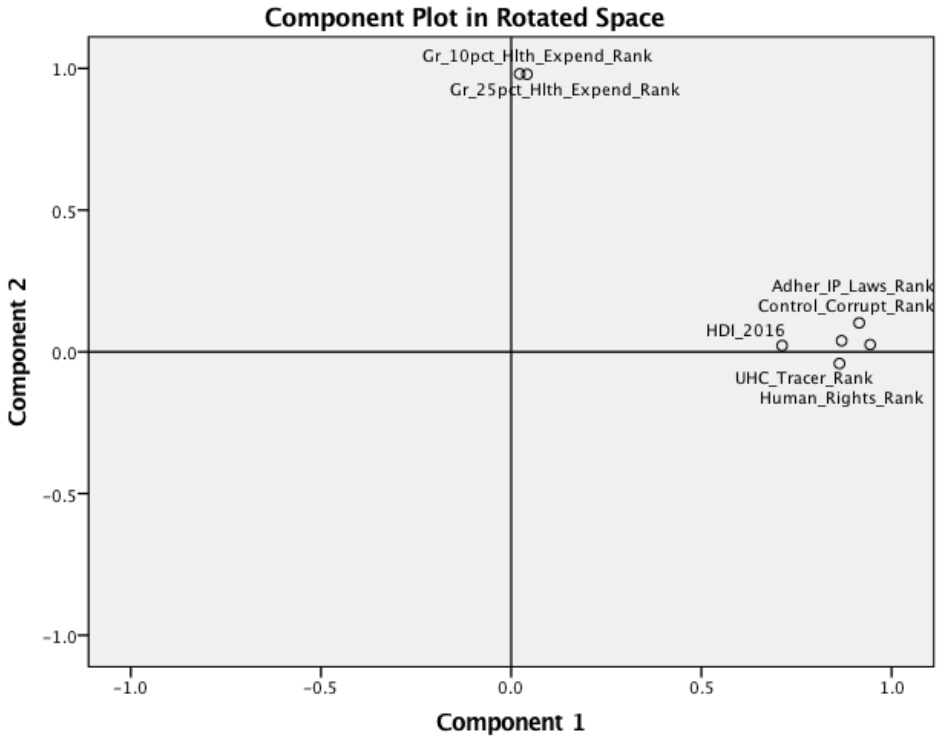


Figure 4 - Plot of rotated principal components

The two health expenditure factors are highly correlated with Component 2, while the remaining factors and HDI are correlated with Component 1

Publicly available factors were identified and selected for four of the clinical research infrastructure dimensions, with novel indicators being created for those remaining. A multivariate analysis showed that these factors measure two key dimensions. Because the publicly available factors had global coverage and the novel indicators were only based on the US, Vietnam, and Poland, it was decided that aggregating all of the dimensions into a single composite indicator would not be appropriate. Instead, the indicators for each dimension are presented separately for discussion and to provide a foundation for future research.

Dimension 5 was the only dimension found to align with multiple individual factors requiring aggregation. As the PCA demonstrated, the UHC tracer and health expenditure factors were strongly correlated with Components 1 and 2, respectively. This indicates that while the level of healthcare services covered in a given country may be related to other factors such as human rights, control of corruption, and regulatory enforcement, the ability to afford those healthcare services is not. A novel representation of healthcare coverage and access was created by aggregating both factors into one after normalizing each factor using a simple ranking function in Microsoft Excel (RANK.AVG). Both the UHC Tracer Index and Catastrophic Health Expenditure were assigned equal weighting. Because Catastrophic Health Expenditure was measured using a >10% and a >25% threshold, these two values were first combined using the AVERAGE function in Microsoft Excel. The resulting Catastrophic Health Expenditure value was then aggregated with the UHC Tracer Index value using the same function to create a single composite indicator for Dimension 5.

Determine Level of Uncertainty and Key Model Drivers

A key step in developing a composite indicator is to perform sensitivity and uncertainty analyses to evaluate the robustness of the underlying model, and to understand how variations in the model output can be explained by the model assumptions and various inputs (OECD, 2008). As previously mentioned, this study stopped short of aggregating the indicators for each dimension into a single composite indicator. Therefore, sensitivity and uncertainty analyses were not necessary. If future research further aggregates these dimensions into a single composite indicator, sensitivity and uncertainty analyses should be performed.

Novel Indicator Development

Novel indicators were developed for dimensions 2, 3, 8, and 9 (Table 14, Appendix 1), which were not found to correspond with any publicly available global indicator databases. To create the novel indicators, the descriptions of each dimension were considered in the context of the types of data or information that were available. These novel indicators required manual calculation and were only created for the US, Vietnam, and Poland. As a result, they were analyzed separately from the dimensions containing data from 85 countries. A novel indicator was not created for Dimension 4, which is explained below.

Dimension 2 – Ethical Oversight and Review

Dimension 2 asserts that a clinical trial must be reviewed by an independent ethics committee, and that this should be a legal requirement in the country where the research will be conducted. To translate this dimension into a measurable indicator, a checklist was created based on the requirements for IRBs/IECs in the ICH's Guideline for Good Clinical Practice (ICH GCP). The ICH GCP is an internationally recognized set of clinical study conduct requirements that ensure the protection of human subjects as well as the credibility of clinical trial data (ICH, 1996). The clinical trial regulations for each country were reviewed against the checklist and scored as the percentage of the requirements that were met. Because the ICH GCP requirements represent a minimum threshold, anything less than 100% compliance represented inadequate ethical oversight requirements. The checklist is provided in Figure 7 (Appendix 6).

The CIOMS guidelines used to define the clinical research infrastructure dimensional framework also provides details on the requirements for ethical oversight

and review. The ICH GCP requirements were chosen instead of the CIOMS guidelines, however, because they are more prescriptive. Furthermore, the ICH GCP document is what is frequently cited in regulations pertaining to clinical research.

Dimension 3 – Research Focus on Local Health Needs/ Priorities

Dimension 3 states that it is essential for research to be responsive to the health needs of the community where the research will be conducted, especially in low-resource settings. While no publicly available indicators were found to align with this dimension directly, a novel indicator was created using publicly available data from the Global Burden of Disease (GBD) and clinicaltrials.gov databases. The GBD database is managed by the Institute for Health Metrics and Evaluation (IHME), and provides annual data on the causes of death and disability across the globe (IHME, 2018). The clinicaltrials.gov database is a repository of publicly registered clinical trials and is managed by the US National Library of Medicine. Study sponsors are legally obligated to register their studies on clinicaltrials.gov if their interventional drug trials are being conducted in the US, if their studies are being conducted under a US FDA Investigational New Drug application (IND), and/or if their studies involve a product manufactured in the US (US National Library of Medicine, 2017a). Local health needs of the US, Vietnam, and Poland were assessed alongside research priorities by comparing the leading causes of death and disability to the leading clinical trial topics in each of the three regions.

The indicator value for Dimension 3 was calculated based on the percentage of the top 10 causes of death and disability (2016 GBD values) that were represented in the top 25 clinical trial topics in each region. To determine the leading clinical research

topics in each region, a search was conducted on clinicaltrials.gov to find all interventional studies with start dates between January 1, 2015 and December 31, 2016 for the US, Vietnam, and Poland (separately), excluding studies recruiting healthy volunteers. The results were then refined using the "by topic" tab on the web page and sorting the conditions in descending order by the number of studies focused on each. The coding terms used to list medical conditions in the GBD and clinicaltrials.gov databases were different, so a manual comparison was performed to calculate the percentage for the indicator. Each of the 10 leading causes of death and disability corresponding with one or more of the top 25 clinical research topics received a score of 1. If a cause did not correspond with a study topic a score of 0 was assigned. The sum was then divided by 10 and multiplied by 100 to give a percentage. Additional details on the dimension calculations are provided in Appendix 4.

It is important to note that the WHO's International Clinical Trial Registry Platform (ICTRP) was initially selected to identify the leading clinical research topics in the US, Vietnam, and Poland. The ICTRP is a repository of publicly registered interventional clinical trials that captures trial information from a number of primary and partner registries from around the world (WHO, 2018b). Because the ICTRP contains records from several global registries, it was believed to be an ideal source for clinical trial information. However, after analyzing the ICTRP data, several inconsistencies were identified that pertained to coding conditions and interventions under study, trial phases, date formats, among others. For this reason, clinicaltrials.gov was selected instead. While clinicaltrials.gov may not be a comprehensive source of clinical trial information, it was

considered sufficient for the current study. Future research should explore other global registry platforms for comparison.

Dimension 4 – Equitable Distribution of Research Benefit and Burden

Dimension 4 dictates that the benefits and burdens of clinical research must be equitably distributed among the various groups within the region where the research is being conducted. After considering potential data sources for Dimension 4, it was decided that this dimension would need to be assessed at the study level, rather than at the country level. Furthermore, the requirement for ethical oversight and review at the country level (Dimension 2) should also include an assessment of the equitable distribution of research benefits and burdens at the study level. As a result, Dimension 4 was excluded from further analysis.

Dimensions 8 and 9 – Regulatory Review Cost and Timeframe

Dimensions 8 and 9 state that the cost of regulatory review should not be disproportionate to the level of effort required, and that regulatory review should be performed in a timely manner, respectively. A search was performed for publicly available metrics on average regulatory review costs and cycle times by country; however, none were found. Instead, a manual review of the regulations in each region was performed to determine the fees and review timeframes required for clinical trial initiation. In the absence of published information, the regulatory agencies were contacted directly. Because clinical trial approval typically requires both regulatory and EC review prior to initiation, fees and timeframes for both were considered. Indicator 8 consists of a combination of the regulatory authority review fee and EC review fee for a

typical phase III interventional drug trial in US Dollars, with currency conversion rates as of January 15, 2018. A typical phase III trial might include several dozen sites and require multiple revisions at the regulatory and/or IRB/IEC review level. However, for simplicity, the cost in this study is based on the assumption that a single site is used in each country, and that the trial is reviewed and approved without needing modifications. Indicator 9 shares the same assumptions, and is the sum of the published review timeframes for each of the steps from initial regulatory and IRB/IEC submission to final regulatory and IRB/IEC approval, given in calendar days.

Aside from regulatory and IRB/IEC review, there are a number of other steps required to initiate a clinical trial that add significant cost and time to the process. Perhaps the most prominent example of this is the budget negotiation and contracting process, which can add several weeks to the study startup process. Continuing review, annual reporting, and protocol amendments can also add substantial delays and expense to a clinical trial. While these are no doubt relevant activities, for the sake of simplicity this dimension was limited to initial regulatory and IRB/IEC review.

Chapter III.

Results

Table 3 (below) presents the relative country rankings expected for each dimension for the US, Vietnam, and Poland.

Table 3 - Expected outcomes by dimension and country

Dimension	Rank		
	US	Vietnam	Poland
1) Human rights protections	1	3	2
2) Ethical oversight and review	1	3	2
3) Research focus on local health needs/priorities	1	2	3
4) Equitable distribution of research benefit and burden	1	3	2
5) Access to quality healthcare*	1	3	2
6) Control of corruption	1	3	2
7) Adherence to international IP laws	1	3	2
8) Cost of Regulatory Review	1	3	2
9) Regulatory Review Timeframe	1	3	2

**There were initially two separate healthcare dimensions, one for access, and one for quality. However, due to the amount of overlap in corresponding indicators they were combined.*

Dimensions with Publicly Available Data

As described in Chapter II, publicly available indicators were selected for four of the clinical trial infrastructure dimensions: Dimension 1 - Human Rights Protections, Dimension 5 - Access to Quality Healthcare, Dimension 6 - Control of Corruption, and Dimension 7 - Adherence to International IP Laws. The relative rankings for the US, Vietnam, and Poland are presented in Table 4 (below). The global rankings for all 85

countries included in this study are provided in Table 24 (Appendix 7). Each dimension is described in detail in the following sections.

Table 4 - Relative rankings for dimensions with publicly available data

Dimension	Rank (relative)		
	USA	Vietnam	Poland
1) Human Rights Protections	1	3	2
5) Access to Quality Healthcare	1	3	2
6) Control of Corruption	1	3	2
7) Adherence to International IP Laws	1	3	2

Dimension 1 - Human Rights Protections

As previously mentioned, the Voice and Accountability factor of the WGI database was selected as a measure of human rights protections for the overall population. In order to make cross-country comparisons with other publicly available data sources, only 85 of the 200 countries in the WGI database were included in this analysis. After removing countries without complete data sets, the global rankings for the USA, Vietnam, and Poland were 15, 83, and 22, respectively. These rankings were in line with the predicted relative rankings for the three regions; however, Vietnam's rank of 83 out of 85 was lower than expected. To further examine this finding, the ranks for the Voice and Accountability factor of the WGI database were reviewed over time from 2006-2016 (Table 5, below), which showed a stable trend. These findings were also compared with the rankings relative to the same 85 countries in the HDI database, which were also stable (Table 6, below).

The HDI uses life expectancy, years of schooling, and gross national income to rank countries on human development (UNDP, 2016a). The underlying data sources that

the HDI and Voice and Accountability composite indicators are based on differ significantly, which is one reason why the rankings in each are different. Vietnam ranked much higher in the HDI than in the Voice and Accountability rank.

Table 5 - WGI Voice and Accountability rank over time

Country	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
USA	12	14	13	14	12	12	11	14	16	15	15
Vietnam	83	82	82	82	82	82	82	82	82	82	83
Poland	24	24	22	19	20	20	16	19	15	18	22

Adapted from: ("WGI 2017 Interactive > Home," n.d.)

Table 6 - HDI rank over time

Country	2010	2011	2012	2013	2014	2015
USA	4	5	5	5	6	6
Vietnam	59	59	59	59	59	59
Poland	20	20	20	20	20	20

Adapted from: (UNDP, 2016b)

A number of things could contribute to Vietnam's low ranking on Voice and Accountability. First, it is possible that the exclusion of countries with incomplete data across all publicly available data sources could have resulted in the disproportionate removal of lower income countries that would have ranked below Vietnam on this measure. Similarly, not all variables used to calculate the Voice and Accountability factor were representative of all of the regions included. This could have resulted in non-representative variables having a disproportionate impact on the overall factor score. Another contributing element to the perception that people of Vietnam have a low level of Voice and Accountability could be that Vietnam is a communist nation. This could have a dramatic impact on the contributing variables that assess freedom of elections,

transparency of government, satisfaction of democracy, and other government-related factors. It is also interesting to note that China, the only other communist nation of the 85 countries compared, ranked last for Voice and Accountability.

Vietnam first implemented regulations for conducting clinical trials in 2007 and has issued revisions and guidance documents in the years since then. The present Vietnamese regulations and guidance documents closely resemble those of developed regions, such as the US and the EU, and include safeguards for clinical trial subjects. This topic is discussed in additional detail in subsequent sections. The discrepancy between Vietnam's low Voice and Accountability rank and the fact that Vietnam's regulations include safeguards and rights for clinical trial subjects may signify that this composite indicator alone may be an inadequate measure of trial subject human rights. The mere presence of safeguards for trial subjects in Vietnam's regulations, however, does not guarantee that these safeguards will be enforced in practice. It would be worthwhile to develop a questionnaire for study investigators and study subjects to obtain a more precise measure of the perception of human rights protections specific to clinical trials. Future research should also explore how the inclusion and exclusion of individual variables from the Voice and Accountability indicator may affect the composite score.

Dimension 5 - Access to Quality Healthcare

Access to quality healthcare was assessed by creating an aggregate of the UCH Tracer Index and Catastrophic Health Expenditure factors from the WHO's GHO. For access to quality healthcare, the US ranked 8, Vietnam ranked 69.5, and Poland ranked 43.5. These values were in agreement with the predicted relative ranks. The data indicate that of the three regions of interest, the US has the highest level of healthcare capacity

and lowest level of catastrophic health expenditure relative to household expenditure or income, followed by Poland, then Vietnam. These findings were also compared with the rankings relative to the same 85 countries in the HDI, which were somewhat similar (Table 7, below). Interestingly, Poland ranked much higher in the HDI than in the access to quality healthcare indicator. One explanation for this may be that despite having a relatively high GNI (which has a positive influence on the HDI), Poland also has high catastrophic health expenditures (which negatively impacts access to quality healthcare).

Table 7 - HDI rank out of 85 countries and GNI

Country	Access to Quality Healthcare Rank	HDI Rank	Gross National Income (GNI) Per Capita*
USA	8	6	$53,245
Vietnam	69.5	59	$5,335
Poland	43.5	20	$24,117

**Gross national income (GNI) per capita: Aggregate income of an economy generated by its production and its ownership of factors of production, less the incomes paid for the use of factors of production owned by the rest of the world, converted to international dollars using PPP rates, divided by midyear population. Adapted from: (UNDP, 2016b)*

To account for the vast general differences between the US, Vietnam, and Poland, the data was further explored to compare these countries to the ranks of other similar countries based on income and geography. According to the WHO, the US and Poland are both High Income Countries (HIC), while Vietnam is considered a Lower-Middle Income Country (LMIC) (United Nations, 2017). Table 8 (below) presents the data for Dimension 5 by income group. Among the 25 HIC countries, the US ranks above the mean. Conversely, Poland is more than three standard deviations below the mean, ranking only above Chile and tying with Portugal. Vietnam's rank is lower than the mean

of the LMIC regions, but still within the standard deviation. Looking at this data by geographic region instead of income group (Table 25, Appendix 8), Poland and Vietnam rank below the means of their respective geographical regions, but are both within the standard deviations.

Table 8 - Dimension 5 - Access to Quality Healthcare by income group

Income Group	n	Mean	St. Dev.
HIC	25	14.24	9.23
UMIC	10	51.96	21.47
LMIC	23	57.26	15.51
LIC	27	57.90	15.28

**Income group represents 2016 values*

The finding that Poland ranked substantially lower than other HIC countries may indicate that it has lower quality healthcare than other HIC regions, that health expenditure is higher than other HIC regions, or perhaps a combination of these two. As a result, Poland may not be an ideal location to conduct clinical research. At minimum, additional safeguards should be in place to minimize any potential coercion for subjects to take part in clinical research due to a lack of affordable healthcare. This also highlights a potential area of concern where a study sponsor should conduct deeper site selection research before deciding to proceed with study sites located in Poland.

As previously discussed, the UHC Tracer Index was found to be correlated with all of the publicly available factors that were selected for this study, with the exception of Catastrophic Health Expenditure. Furthermore, it has also been shown to be correlated with other health and development related measures, including life expectancy, under-5 mortality rate, and the HDI (WHO et al., 2017). This is not surprising, as elements that

contribute to developing a healthcare infrastructure are likely to overlap with other infrastructure-related indicators. The existence of a healthcare infrastructure, however, does not necessarily guarantee equal access to those services, which is why this dimension combined the Catastrophic Health Expenditure and UHC Tracer Index factors. While the combination of these two factors should provide a leveling effect for countries with relatively high healthcare quality and income, it is possible that this indicator will not be as accurate in regions with lower healthcare quality and income. In these regions there may not be enough income to pay for healthcare services, or there may not even be sufficient healthcare services available to spend money on.

Dimension 6 – Control of Corruption

The successful conduct of clinical research relies heavily on trust, transparency, and cooperation among the large number of stakeholders involved. This trust can be eroded by the presence of corruption. The extent to which corruption is controlled within a given country was measured using the Control of Corruption factor of the WGI database. For this measure, the US, Vietnam, and Poland ranked 12, 51, and 19, respectively, which was in agreement with the expected values. Looking at this data in the context of income groups (Table 9, below), the ranks for the US and Poland are close to the mean for HIC countries. Vietnam ranked slightly higher than the mean of the LMIC income group. Comparing the rankings to geographic locations (Table 26, Appendix 8), Poland scored slightly higher than the European mean, while Vietnam's rank nearly met the mean Control of Corruption score for Asia.

Table 9 - Dimension 6 - Control of Corruption by income group

Income Group*	n	Mean	St. Dev.
HIC	25	14.36	9.27
UMIC	10	46.70	17.72
LMIC	23	61.26	15.83
LIC	27	62.60	18.37

**Income group represents 2016 values*

These results are based on the well-established methods developed by the World Bank for the WGI database, which provide a measure of the perceptions of how well corruption is controlled within a given country based on a variety of sources. These methods, however, do not provide a minimum threshold below which control of corruption is considered inadequate for conducting clinical research. This dimension may be useful in guiding the selection of a potential country for conducting a clinical trial from a group of similar countries where other minimum safeguards have been ensured. Future research should further explore the concept of establishing a minimum threshold for corruption control, as it may greatly strengthen the World Bank's methodology. It may also be useful to combine this dimension with a novel measure of corruption perceptions specific to clinical research from the standpoint of the sponsor, investigator, and perhaps subject.

Dimension 7 – Adherence to International IP Laws

In addition to ensuring that corruption is controlled within a prospective clinical study site location, study sponsors must also ensure sure there is a high level of respect for international IP laws. To evaluate this dimension, the WJP's Rule of Law factor on Regulatory Enforcement was used. For Adherence to International IP Laws, the US

ranked 14, Poland 21, and Vietnam ranked 65.5, which was in line with the expected relative rankings. Compared to the HIC group as a whole (Table 10, below), the US and Poland ranked slightly higher and slightly lower than the mean, respectively. Conversely, Vietnam ranked over a standard deviation lower than the mean of the LMIC group, which may indicate an area of concern for conducting clinical research. When comparing the results to the geographical regions (Table 27, Appendix 8), however, Vietnam still scored lower than the mean for Asia, but was within the standard deviation. Poland's rank for Dimension 7 was slightly higher than the mean for Europe.

Table 10 - Dimension 7 - Adherence to International IP Laws by income group

Income Group*	n	Mean	St. Dev.
HIC	25	15.04	11.02
UMIC	10	69.30	14.83
LMIC	23	43.35	15.85
LIC	27	61.54	16.85

**Income group represents 2016 values*

This dimension uses the methodology developed by the WJP for the Rule of Law Index, focusing on the Regulatory Enforcement factor. Like Dimension 6, this provides a useful comparison of countries, but does not specify a threshold to determine whether or not a country's adherence to international IP laws is acceptable. Future research should explore whether it is possible to establish such a threshold as it may increase the value and significance of the WJP's methodology.

Dimensions with Novel Indicators

When publicly available indicators could not be identified for a dimension, a novel indicator was created. Novel indicators were created for Dimension 2 - Ethical Oversight and Review, Dimension 3 – Research Focus on Health Needs/Priorities, Dimension 8 – Cost of Regulatory Review, and Dimension 9 – Regulatory Review Timeframe. The expected outcomes for each dimension are included in Table 3 (above). As previously discussed, no indicator was created for Dimension 4 – Equitable Distribution of Research Benefit and Burden.

Dimension 2 - Ethical Oversight and Review

The ability to provide independent ethical oversight and review of clinical trials in a country is one of the most important elements of clinical trial infrastructure development. To assess each country's compliance with the ICH GCP requirements, a checklist (Figure 7, Appendix 6) was used to determine which core IRB/IEC-related requirements were captured in the country's legal framework. The scorecard and results for the US, Vietnam, and Poland are presented in Figure 8 (Appendix 9). Because each of the items in the checklist is considered a requirement, a score of less than 100% indicates inadequate ethical oversight and review. Based on these findings, only the US meets all of the requirements. The Polish regulations were found to lack details on the steps the EC should take when reviewing non-therapeutic trials as well as protocols indicating that prior consent of subjects or their legally authorized representatives is not possible. Vietnam's regulations were found to have the same deficiencies, in addition to deficiencies related to reviewing subject payments to ensure there are no issues of undue

influence or coercion, requiring that only members participating in the IRB/IEC review and discussion should be allowed to vote, and providing an avenue for expedited review.

It is not possible to summarize the true adequacy of a country's regulations in a single metric for such a complex issue. The aim of this dimension was to provide a snapshot of the ethical oversight regulations in place for a given country as a means to quickly rule out countries that are premature. In contrast to the previously discussed dimensions, this one was intended to serve as a minimum threshold to aid in decision-making. Section 3 of the ICH GCP was used to develop the checklist for this dimension because it is the part of the globally recognized standard focused on the responsibilities, composition, functions, operations, procedures, and recordkeeping requirements for IRBs/IECs (ICH, 1996). The finding that Vietnam's regulations did not meet all of the elements included in the checklist was not surprising, as this country is still in the process of refining its clinical research regulations. However, the finding that Poland's regulations were not in step with the ICH guideline was unexpected. As part of the EU, Poland's regulations should reflect harmonization with this guidance.

In the case of both Vietnam and Poland, it is possible that the selection of regulations included in the review was incomplete due to a lack of familiarity with the legislative structure in each region. Similarly, because much of the review relied on the use of unofficial translations, it is possible that the deficient sections were in fact adequate, but mistranslated. The fact that Poland is currently conducting hundreds of clinical trials is evidence that this dimension is inadequate, rather than the other way around. The ICH GCP provides a solid foundation for assessing regulatory adequacy, especially for developing nations; however, it may be beneficial to include additional best

practices to the checklist to help differentiate more developed regions. Future research should also consider working with local stakeholders familiar with the legal framework within their country to complete the checklist. This could help avoid potential confusion and incomplete regulatory review.

Dimension 3 - Research Focus on Health Needs/ Priorities

To determine the extent to which ongoing clinical research activities are focused on local health needs/priorities, the leading causes of death and disability in each country were compared with the conditions being studied by publicly registered clinical trials. Table 11 (below) presents the percentage of the top 10 causes of death and disability represented in the top 25 conditions under study in the US, Vietnam, and Poland. Additional details on the results for this dimension are contained in Appendix 10. It was expected that the US would rank highest in this dimension, followed by Vietnam, then Poland. The assumption was that as a wealthy developed nation, the US would have a number of companies competing to develop treatments for the leading causes of death and disability. Conversely, as a developed nation on the lower end of the same income group as the US, Poland was expected to have the largest number of clinical trials focused on the health needs of wealthier nations. Vietnam was expected to have a larger number of studies focused on local health needs/priorities than Poland, as it is a developing nation that is not as established as a clinical trial proving ground. It was expected that the trials in Vietnam would be largely in response to communicable diseases.

Table 11 - Scores and ranks for Dimension 3 - Research Focus on Health Needs/ Priorities

	US	Vietnam	Poland
Score	100%	50%	50%
Rank	1	2	2

Interestingly, none of the regions had any communicable diseases among the leading causes of death and disability (Figure 5, below). The leading research topic in Vietnam, however, was communicable diseases, representing 41% of the total number of studies being performed. In total, 11 (44%) of the top 25 study topics in Vietnam were focused on some type of infection or other communicable disease. Two of the top 25 study topics in the US also focused on communicable diseases and infections, representing approximately 6% of the total number of studies being performed. Based on these findings, comparing the leading causes of death and disability to the research topics with the largest *number* of studies may be an inadequate measure of research focus on health needs/priorities. Focusing on the size of clinical trials instead of, or in addition to, the number of trials focused on a given topic may be more appropriate.

	US	Vietnam	Poland
1	Ischemic Heart Disease	Cerebrovascular Disease	Ischemic Heart Disease
2	Low Back & Neck Pain	Ischemic Heart Disease	Low Back & Neck Pain
3	Drug Use Disorders	Road Injuries	Cerebrovascular Disease
4	Lung Cancer	Low Back & Neck Pain	Falls
5	COPD	Sense Organ Diseases	Lung Cancer
6	Diabetes	Lung Cancer	Sense Organ Diseases
7	Skin Diseases	Diabetes	Migraine
8	Cerebrovascular Diseases	Skin Diseases	Road Injuries
9	Depressive Disorder	COPD	Diabetes
10	Road Injuries	Congenital Defects	Self-Harm

Figure 5 - Leading causes of death and disability in 2016 with overlap

Conditions are highlighted to indicate overlap between regions: a) blue indicates overlap across all three regions; b) orange indicates overlap between the US and Vietnam; and c) green indicates overlap between Vietnam and Poland. Adapted from: (IHME, 2017)

It is also interesting to note that the leading causes of death and disability were found to be quite similar across all three regions, overlapping by 60%. Among the remaining causes, the US and Vietnam shared two, while Poland and Vietnam shared one. Despite the high level of overlap for conditions and diseases among the three regions, there was only 24% overlap for the top 25 research topics. It is also interesting to note that there does not appear to be a relationship between the ranks of the death and disability causes and the ranks of the conditions under study. Had the calculation for this indicator been based on the top 10 conditions under study (instead of the top 25), the US, Vietnam, and Poland would have received scores of 60%, 30%, and 20%, respectively.

One possible explanation for this disagreement could be that the search for the leading study topics was based on study start dates in 2015 and 2016. If the same leading causes of death and disability were present prior to 2015, studies that were already

underway could have been missed in the search. Another possibility is that the clinicaltrials.gov database does not contain a full listing of the studies being conducted in Vietnam and Poland. Differences in the medical coding terms used in the GBD and clinicaltrials.gov databases could have also contributed to a mismatch of terms in the two rankings. Future research should investigate the possibility of using a global trial register such as the ICTRP and processing the coding terms into a common language that could be compared with the GBD and other databases. It may also be useful to consider GBD and clinical research trends over time to better understand how research responds to local health needs.

Dimension 8 - Cost of Regulatory Review

The cost of regulatory and IRB/IEC review and approval of a clinical trial is small in comparison to the overall cost of a study, but not insignificant. It can be an especially important consideration for smaller companies trying to bring their first drug to market. In the US, Vietnam, and Poland, most interventional drug trials require review and approval by a regulatory authority and an IRB/IEC prior to beginning recruitment. A publicly available database of regulatory review costs could not be identified, so a manual review of regulations was performed in each country. Vietnam does not publish the regulatory or IEC fees for reviewing clinical trials publicly, so the Ministry of Health was contacted directly via email; however, no response was received. The costs that could be obtained for each type of review are presented in Table 12 (below).

Table 12 - Regulatory and IRB/IEC review costs (USD$)

	US	Vietnam	Poland
Regulatory Review	0	UNK	$2,354
IRB/IEC Review	$3,304*	UNK	$2,439*
TOTAL	$3,304	UNK	$4,708
Rank	1	-	2

**Estimated costs. Individual IRB/IEC fees vary by institution.*
Costs assume regulatory review and a full panel IRB review at a single study site for a phase III interventional drug trial.
Exchange rates from January 15, 2018 were used to convert costs to USD.

Albeit incomplete, these results indicate that the cost of regulatory and IRB/IEC review for a phase III study involving a single site is lower in the US compared to Poland. In both countries, however, each additional site that is added to a study would require an additional IRB/IEC review and corresponding fee. If the study included ten sites the resulting costs for the US and Poland would be USD$33,040 and USD$26,744, respectively, slightly favoring Poland. It is important to note that the US is currently undergoing a shift towards using centralized IRBs for multicenter studies in order to increase review efficiency and decrease costs. Many local site or institutional IRBs in the US still insist on performing a cursory review of study materials even when a centralized IRB is used, which comes with an associated fee. For simplicity, this study assumed that local IRB/IEC review was mandatory. As previously mentioned, additional study costs related to the start-up and conduct were also omitted for simplicity.

In both the US and Poland, ethical review is typically performed by an institution-affiliated IRB/IEC for each study site included in the trial. One small difference in Poland is that one site must be designated as the coordinating or lead site, which results in the associated IEC having slightly more responsibility. There are approximately 50 different

IECs in Poland and several hundred IRBs within the US, each of which has its own fee schedule. The European Network of Research Ethics Committees (EUREC) states that the average review fee for Polish IECs is approximately 2,000 EUR (USD$2,439) (EUREC, 2018). To obtain an estimated IRB review fee for the US, an informal Google search was conducted with the search terms "IRB review fees, clinical trials." The first 10 IRB websites in the search results were visited to obtain fees for full panel reviews, which were then used to calculate the average in Table 12. The full listing of IRB fees are presented in Table 31 (Appendix 11).

The aim of this dimension was to provide an indicator for regulatory review costs in the context of evaluating clinical research capacity at the country level. While there are other potential measures of more significant clinical trial costs, such as procedure costs, monitoring costs, and others related to study execution at the trial level, these are believed to be beyond the scope of this study. Given the scarcity of regulatory and ethical review cost data, and the fact that it represents such a small portion of the overall clinical trial cost, it may not be as important as other factors like regulatory review timelines for evaluating clinical research capacity. Future studies may be able to omit this dimension entirely without a significant impact to the overall results.

Dimension 9 - Regulatory Review Timeframe

As previously described, prior to beginning a clinical trial, it is necessary to obtain both regulatory and IRB/IEC approval. In the US, this process starts with submitting an NDA to the FDA for review. Next, the protocol and other study materials are submitted to one or more IRBs for review. The process in Poland is very similar to that in the US, with the FDA being replaced by the Office for Registration of Medicinal

Products, Medical Devices and Biocidal Products (URPL). Vietnam's review process contains many of the same elements as the US and Poland, but with a few additional review steps in conducted by Vietnam's regulatory body, the Ministry of Health (MOH). Similar to Dimension 8, no publicly available indicators were identified for regulatory review timeframes for the US, Poland, and Vietnam. In the absence of historical review cycle times, a manual review of applicable clinical trial regulations was performed to identify the published review timeframes. For this dimension, the regulatory review timeframe was defined as the time from initial submission of clinical trial materials until final approval from the regulatory authority and IRB/IEC. The regulatory review timeframe results are presented in Table 13 (below).

Table 13 - Dimension 9 - Regulatory Review Timeframe (in calendar days)

	US	Vietnam	Poland
Regulatory Review	30	60	60
IRB/IEC Review	variable	45	60
Parallel Review?	Yes	Yes	Yes
TOTAL (days)	30+	60	60
Rank	-	1	1

Based on the published regulatory and IRB/IEC review timeframes in the applicable regulations in the three regions of interest, it appears that regulatory and ethical review should be completed within 60 days of submission for both Vietnam and Poland. In the US there is no published timeframe for IRB review, so a total review timeframe could not be calculated. While the published review timeframes provide interesting discussion points, they are of little value for making meaningful comparisons across countries regarding their capacity to conduct clinical research. In the US and

Poland, once the regulatory review timeframe has elapsed, tacit approval can be assumed; however, formal approval from an IRB/IEC is still necessary to begin a trial. Standardized metrics are also needed to evaluate regulatory review timeframes in a meaningful way. The CTTI has also recognized this issue, and began working to establish standard metrics for study startup activities with the goal of driving improvement in efficiency (CTTI, 2016).

One study conducted by CTTI members found that the median time from the submission of study materials to the site to the time of the IRB decision was 48 days (range 0-794) for all types of sites and studies in the US. When looking at different types of sites, the researchers found that private practice sites had the quickest median cycle time at 36 days (range 0-498), while hospital-based sites had the longest at 109 days (range 0-621) (Abbott et al., 2013). It was noted, however, that this study suffered from large amounts of missing and inconsistent data. Despite the CTTIs initiative to establish study startup metrics dating back to 2010, there is little evidence of progress today. Future research should continue to work towards establishing such metrics so that clinical research can be conducted in a more efficient manner.

Chapter IV.

Discussion

The aim of this study was to determine whether publicly available global indicator data could be used to evaluate the suitability of different countries for conducting human subject clinical trials. The hypothesis was that it would be possible to identify key indicators that closely relate to foundational clinical research requirements, such as ethical oversight, human subject protections, and access to healthcare within a given country, and that these indicators could serve as surrogates. This hypothesis was partially supported, with publicly available indicator data being found to align with four dimensions (Dimension 1, Dimension 5, Dimension 6, and Dimension 7) across 85 countries. These dimensions were also shown to correlate with the HDI, which is a measure of human development based on life expectancy, years of schooling, and GNI. A fifth dimension (Dimension 3) used clinical trial registry data and GBD data to create a novel indicator related to research focus on health needs/priorities.

The remaining three dimensions required the manual review of clinical trial regulations to determine the relative ranks of the US, Vietnam, and Poland (Dimension 2, Dimension 8, and Dimension 9). Dimension 2 was calculated by completing a checklist based on the IRB/IEC requirements contained within the ICH GCP. Dimensions 8 and 9 were also calculated by manually reviewing clinical trial regulations in order to compare regulatory review costs and timeframes. While more oblique than the others, these final two dimensions highlighted a pressing need for standardized metrics that has previously been identified by others, such as the CTTI. The model created for this study is too premature to stand on its own as a tool for evaluating a country's suitability for

conducting clinical research, but it provides a solid foundation on which to build future research. If the novel dimensions that were created could be populated with data from the other 82 regions contained in Dimensions 1, 5, 6, and 7, it would be possible to perform additional statistical analyses to understand how they relate to each other. From there, a dashboard could be created to allow for a simple comparison of different countries.

A key component of this study was to use new and existing composite indicators to measure the complex topic of clinical research infrastructure indirectly to aid in the process of study site selection. Synthesizing a complex concept into a more digestible measure is a strength of composite indicators; however, a major criticism is that they oversimplify such complex phenomena and lead decision makers to take action based on an incomplete picture of a situation (OECD, 2008). Indeed, the model created in this study is intended to aid in decision-making, and thus is potentially susceptible to such misuse. It is important to note that the intent of this model is to guide the very early stages of study site selection, rather than replace the more in-depth country and site level reviews that are necessary to ensure that the appropriate clinical research infrastructure and safeguards are in place. Unless some sort of formalized country-level accreditation system is created, sponsors and CROs will continue to be tasked with assessing clinical research infrastructure and safeguards for the foreseeable future.

Using any sort of global data to make cross-country comparisons comes with several inherent limitations. For instance, many of the data sources used in this study rely on surveys to measure local perceptions of factors like human rights, control of corruption, trust in government officials, and overall satisfaction with life. When translating these surveys to dozens of different languages there is a risk that at least some

of the questions will be interpreted differently. Similarly, the local context of a given dimension may be very different among disparate regions, resulting in scoring discrepancies. The WHO's Catastrophic Health Expenditure factor used to calculate Dimension 5, for example, defines health expenditure as either the percentage of *income* or *expenditure* used to pay for healthcare. Furthermore, with respect to making comparisons between the rich and poor, the 2016 report on health coverage states: "whether catastrophic spending incidence is higher among the poor or rich likely depends in part on (a) whether living standards are measured using consumption or income, and (b) any deduction is made from income or consumption for expenditure on necessities " (WHO et al., 2017). This illustrates that even within a well-defined framework, there can be differences in interpretation and measurement. As a result, it is important to use caution when drawing conclusions about differences and similarities between different regions.

When making comparisons between countries from different geographies or socioeconomic levels, it is important to consider how each respective country compares to its peers. For the dimensions in the current study that were based on publicly available data, the US, Vietnam, and Poland were compared with each other and with other regions within their respective UN geographies and WHO income groups in order to better understand how they rank globally. A significant limitation to this study was that this level of comparison could not be performed for the dimensions for which novel indicators were developed. Future research should involve gathering global data for the novel indicators in order to make these same types of comparisons. The underlying methodology for all of the dimensions should be further refined through collaboration

with stakeholders at the local and sponsor levels, in tandem with further statistical analysis. The process of refining the dimension methodology will also create benchmarks that can be used for future comparison.

The current study showed that the four dimensions with publicly available data were measuring phenomena along two different dimensions, or principal components; however, it is expected that if the dimensions with novel indicators had sufficient data to be included in a multivariate analysis using PCA, additional principal components would emerge. This would be important, as it would demonstrate that the model has sufficient breadth to measure unrelated phenomena that are relevant to clinical research. If only two or three principal components were identified in a full dataset with all of the dimensions, it may indicate that the model has too narrow a focus. The lack of a universal set of rules for developing composite indicators can be seen as both a strength and a weakness. The level of interpretation required of the developer allows the flexibility to explore the relationships of seemingly abstract topics. On the other hand, it can also result in inaccurate conclusions.

As previously discussed, a number of factors are involved in the selection of study sites. There are strategic commercial reasons for conducting studies in one region or another that need to be determined at the sponsor level. Contract Research Organizations have close relationships with study sites, and have built proprietary databases containing procedure costs, recruitment projections, and site performance metrics based on historical data. The purpose of this study was not to recreate or replace the tools that currently exist, but to consider site selection from a new perspective. Instead of relying on historical data from prior studies, a model was created using publicly available and novel indicators to

present a picture of clinical research capacity. By using regularly updated indicators from sources like the WHO, WJP, and the World Bank, it was anticipated that rapidly developing countries capable of conducting clinical trials could be identified earlier than by using traditional methods.

While many of the objectives of this study were achieved, the model that was developed is still too premature to perform a comprehensive assessment of clinical research capacity. This study sought to establish a minimum threshold for key components vital to the protection of human subjects (Dimension 2) alongside other performance based indicators (Dimensions 8 and 9). Future research should further explore the combination of minimum infrastructure thresholds with performance metrics. Creating a model that could filter out countries based on pre-defined thresholds would allow powerful comparisons to be made among a more focused group of countries and allow rapid identification of potential study site regions. This process, combined with traditional in-depth regional and site assessments could result in faster study startup, recruitment, and completion in regions with far lower study-related costs than the US or other developed nations. The end result could result in savings of tens of millions of dollars throughout the drug development process.

Appendix 1.

Clinical research infrastructure dimensional framework

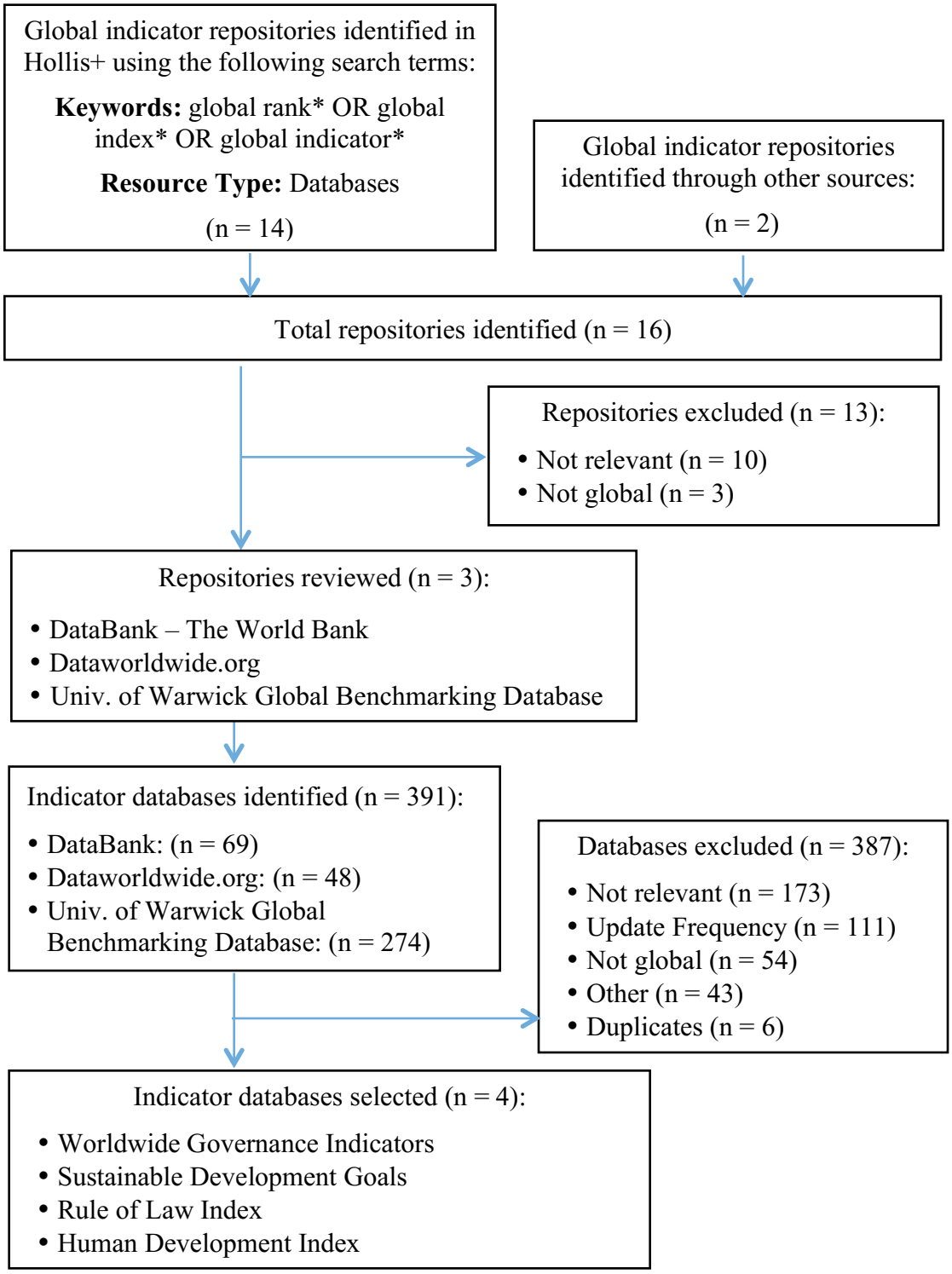
Table 14 – Clinical research infrastructure dimensional framework

Dimension	Description
Dimension 1 - Human Rights Protections	All research with humans must be carried out in ways that show respect and concern for the rights and welfare of individual participants and the communities in which research is carried out. A high level of human rights protections for the general population may correspond with protections for clinical trial subjects.
Dimension 2 - Ethical Oversight and Review	Clinical research involving human subjects must be reviewed ethically and scientifically by a competent and independent research ethics committee. This should be a legal requirement in any host country where research is going to be performed.
Dimension 3 - Research Focus on Local Health Needs/Priorities	Especially in low-resource settings, it is essential that research is responsive to the health needs of the community where the research will be conducted.
Dimension 4 - Equitable Distribution of Research Benefit and Burden	It is essential that the benefits and burdens of clinical research are equitably distributed among the groups, communities, and individuals invited to participate without discrimination based on gender, social or economic position, convenience, or otherwise.
Dimension 5 - Access to Quality Healthcare	It is essential that research participants' health needs are met during, and if necessary, following the completion of research. The obligation to care for those health needs ultimately lies with the researcher and sponsor, however, it is impractical to expect researchers and sponsors to take on the role of the host country's health system. Providing healthcare services in low-resource settings can also create ethical issues. Therefore, prior to conducting research in a region, it is important that there is sufficient infrastructure for the general population of the region to have access to quality healthcare.
Dimension 6 - Control of Corruption	Clinical research requires the cooperation of sponsors, researchers, health authorities, and government agencies without bias. This requires transparency and for corruption to be minimized.

Dimension 7 - Adherence to International IP Laws	Study sponsors invest millions of dollars into developing new health technologies, which must be vetted through clinical investigations. They should be able to expect that their IP rights will be respected in the regions where the technology is researched/sold, both during and after the completion of research.
Dimension 8 - Cost of Regulatory Review	Conducting clinical trials in a region requires local regulatory and ethical review. The costs associated with these mandatory reviews should not be disproportionate to the level of effort involved in performing the reviews.
Dimension 9 - Regulatory Review Timeframe	Conducting clinical trials in a region requires local regulatory and ethical review. There should be sufficient resources dedicated to these reviews within a country to allow for timely review.

Appendix 2.

Global Indicator Search Strategy



Appendix 3.

Descriptions of Publicly Available Indicators

Table 15 - Dimension 1 Indicator Details

Dimension 1 - Human Rights Protections	
Description	All research with humans must be carried out in ways that show respect and concern for the rights and welfare of individual participants and the communities in which research is carried out. A high level of human rights protections for the general population may correspond with protections for clinical trial subjects.
Normalization Details	Data was normalized by performing a simple ranking of the data for the 85 countries included in the analysis using the RANK.AVG function in Microsoft Excel
Aggregation Details	N/A - Indicator data is from a single composite indicator
Other Notes	In the absence of an indicator specific to study subject rights protections, an indicator on human rights protections in general was selected as a surrogate. The Voice and Accountability dimension of the Worldwide Governance Indicators was felt to capture a number of elements central to human rights.
Base Indicator Details	
Name/ Topic	Voice and Accountability - from Worldwide Governance Indicators
Source	http://info.worldbank.org/governance/wgi/index.aspx#home
Description /Rationale	Voice and accountability captures perceptions of the extent to which a country's citizens are able to participate in selecting their government, as well as freedom of expression, freedom of association, and a free media.
Background on Source	The WGI are composite governance indicators based on over 30 underlying data sources. These data sources are rescaled and combined to create the six aggregate indicators using a statistical methodology known as an unobserved components model. A key feature of the methodology is that it generates margins of error for each governance estimate. These margins of error need to be taken into account when making comparisons across countries and over time.
Data Type Representation	Score from 0-1 with higher values representing better outcomes.
Data Sources	The WGI project relies exclusively on perceptions-based governance data sources. The data sources include surveys of firms and households, as well as the subjective assessments of a variety of commercial business information providers, non-governmental organizations, and a number of multilateral organizations and other public-sector bodies

Method of Measurement	Various
Method of Estimation	Unobserved Components Model
Frequency of data updates	Annual since 2002
Data Collection Start	1996

Base indicator details were obtained from the documentation section of the WGI database website (World Bank, 2017).

Table 16 - Dimension 5 Indicator Details

Dimension 5 - Access to Quality Healthcare	
Description	It is essential that research participants' health needs are met during, and if necessary, following the completion of research. The obligation to care for those health needs ultimately lies with the researcher and sponsor, however, it is impractical to expect researchers and sponsors to take on the role of the host country's health system. Providing healthcare services in low-resource settings can also create ethical issues. Therefore, prior to conducting research in a region, it is important that there is sufficient infrastructure for the general population of the region to have access to quality healthcare.
Normalization	Data was normalized for each base indicator by performing a simple ranking of the data for the 85 countries included in the analysis using the RANK.AVG function in Microsoft Excel
Aggregation Details	The normalized data (ranks) of the two 5.2 base indicators were aggregated using the AVERAGE function in Microsoft Excel for each country. The resulting aggregated 5.2 values were then aggregated with the normalized data (ranks) of the 5.1 base indicator using the AVERAGE function in Microsoft Excel to create a single aggregated value for each country.
Other Notes	None
Base Indicator 5.1 Details	
Name/ Topic	Universal Health Coverage (UHC) Service Coverage Index
Source	http://apps.who.int/gho/cabinet/uhc.jsp
Description /Rationale	Coverage of essential health services (defined as the average coverage of essential services based on tracer interventions that include reproductive, maternal, newborn and child health, infectious diseases, noncommunicable diseases and service capacity and access, among the general and the most disadvantaged population)
Background on Source	The GHO data repository is WHO's gateway to health-related statistics for its 194 Member States. It provides access to over 1000 indicators on priority health topics including mortality and burden of diseases, the Millennium Development Goals (child nutrition, child health, maternal and reproductive health, immunization, HIV/AIDS, tuberculosis, malaria, neglected diseases, water and sanitation), non communicable diseases and risk factors, epidemic-prone diseases, health systems, environmental health, violence and injuries, equity among others.
Data Type Representation	Percentage
Data Sources	As a measure of SDG indicator 3.8.1, the UHC service coverage index combines 16 tracer indicators of service coverage into a single summary measure. Currently, only SDG baselines values for 2015 have been estimated.

Method of Measurement	For each country, the most recent value for each tracer indicators is taken from WHO or other UN global databases. Primary data sources vary across the 16 tracer indicators, but include household surveys, administrative data and facility surveys.	
Method of Estimation	The index is computed using geometric means of the tracer indicators. Values greater than or equal to 80 are presented as >=80 as the index does not provide fine resolution at high values; 80 should not be considered a target.	
Frequency of data updates	1-5 years	
Data Collection Start	Unknown	
Other Notes	Method of estimation of global and regional aggregates: A population-weighted average of UHC service coverage index values across countries.	
Base Indicator 5.2 Details		
Name/ Topic	Population with household expenditures on health greater than 10% of total household expenditure or income (SDG indicator 3.8.2)	Population with household expenditures on health greater than 25% of total household expenditure or income (SDG indicator 3.8.2)
Source	http://apps.who.int/gho/cabinet/uhc.jsp	
Description /Rationale	Health expenditures are likely to expose households to financial hardship in particular when they exceed a pre-defined threshold of a household's ability to pay. When this happens they are characterized as being catastrophic. To fully understand progress towards UHC within the SDG monitoring framework, SDG indicator 3.8.2 should be monitored jointly with SDG indicator 3.8.1 on coverage of essential health services.	
Background on Source	The GHO data repository is WHO's gateway to health-related statistics for its 194 Member States. It provides access to over 1000 indicators on priority health topics including mortality and burden of diseases, the Millennium Development Goals (child nutrition, child health, maternal and reproductive health, immunization, HIV/AIDS, tuberculosis, malaria, neglected diseases, water and sanitation), non communicable diseases and risk factors, epidemic-prone diseases, health systems, environmental health, violence and injuries, equity among others.	
Data Type Representation	Percentage	
Data Sources	Preferred data sources: Household budget surveys Household income and expenditure surveys	

	Household socioeconomic and living standards surveys Other possible data sources: Health surveys with a module on household expenditures
Method of Measurement	See below
Method of Estimation	Within the SDG monitoring framework (SDG indicator 3.8.2), the proportion of the population facing catastrophic expenditures is measured as the population weighted average of the number of households with "large household expenditures on health" as a share of total household expenditure or income (household's budget). Large is defined as health expenditures exceeding 10% or 25% total household expenditure or income. Household's sample weight multiplied by the household size is used to obtain representative numbers per person. If the sample is self-weighting then only the household size is used as the weight. Household expenditures on health are defined as formal and informal payments made at the time of getting any type of care (promotive, curative, rehabilitative, palliative or long term care) provided by any type of provider. These payments include the part not covered by a third party such as the government, health insurance fund or private insurance but exclude insurance premiums as well as any reimbursement by a third party.
Frequency of data updates	Every 1–5 years depending on implementation of population-based household expenditure surveys led by national statistics offices
Data Collection Start	Unknown
Other Notes	Other approaches can be used to monitor catastrophic health spending. These approaches relate health expenditures (out-of-pocket payments) to income or consumption less a deduction for necessities.

Base indicator details were obtained from the GHO Indicator Metadata Registry (WHO, 2018a)

Table 17 - Dimension 6 Indicator Details

Dimension 6 - Control of Corruption	
Description	Clinical research requires the cooperation of sponsors, researchers, health authorities, and government agencies without bias. This requires transparency and for corruption to be minimized.
Normalization Details	Data was normalized by performing a simple ranking of the data for the 85 countries included in the analysis using the RANK.AVG function in Microsoft Excel
Aggregation Details	N/A - Indicator data is from a single composite indicator
Other Notes	The Control of Corruption dimension of the Worldwide Governance Indicators was felt to capture a number of elements central to corruption that might be encountered in conducting clinical research.
Base Indicator Details	
Name/ Topic	Control of Corruption - from Worldwide Governance Indicators
Source	http://info.worldbank.org/governance/wgi/index.aspx#home
Description /Rationale	Control of corruption captures perceptions of the extent to which public power is exercised for private gain, including both petty and grand forms of corruption, as well as "capture" of the state by elites and private interests.
Background on Source	The WGI are composite governance indicators based on over 30 underlying data sources. These data sources are rescaled and combined to create the six aggregate indicators using a statistical methodology known as an unobserved components model. A key feature of the methodology is that it generates margins of error for each governance estimate. These margins of error need to be taken into account when making comparisons across countries and over time.
Data Type Representation	Score from 0-1 with higher values representing better outcomes.
Data Sources	The WGI project relies exclusively on perceptions-based governance data sources. The data sources include surveys of firms and households, as well as the subjective assessments of a variety of commercial business information providers, non-governmental organizations, and a number of multilateral organizations and other public-sector bodies
Method of Measurement	Various
Method of Estimation	Unobserved Components Model
Frequency of data updates	Annual since 2002
Data Collection Start	1996

Base indicator details were obtained from the documentation section of the WGI database website (World Bank, 2017).

Table 18 - Dimension 7 Indicator Details

Dimension 7 - Adherence to International IP Laws	
Description	Study sponsors invest millions of dollars into developing new health technologies, which must be vetted through clinical investigations. They should be able to expect that their IP rights will be respected in the regions where the technology is researched/sold, both during and after the completion of research.
Normalization Details	Data was normalized by performing a simple ranking of the data for the 85 countries included in the analysis using the RANK.AVG function in Microsoft Excel
Aggregation Details	N/A - Indicator data is from a single composite indicator
Other Notes	None
Base Indicator Details	
Name/ Topic	World Justice Project Rule of Law Index - Factor 6 - Regulatory Enforcement
Source	http://data.worldjusticeproject.org/
Description /Rationale	Factor 6 - Regulatory Enforcement measures the extent to which regulations are effectively implemented and enforced without improper influence by public officials or private interests. It also includes whether administrative proceedings are conducted in a timely manner without unreasonable delays and whether due process is respected in administrative proceedings. This factor also addresses whether the government respects the property rights of people and corporations.
Background on Source	The World Justice Project (WJP) is an independent, multidisciplinary organization working to advance the rule of law around the world. The rule of law provides the foundation for communities of peace, opportunity, and equity – underpinning development, accountable government, and respect for fundamental rights.
Data Type Representation	Score from 0-1 with higher values representing better outcomes.
Data Sources	See below
Method of Measurement	The scores and rankings of the 44 sub-factors (factors 1 through 8) draw from two data sources collected by the World Justice Project in each country: 1) a general population poll (GPP) conducted by leading local polling companies using a representative sample of 1,000 respondents in the three largest cities, and 2) qualified respondents' questionnaires (QRQs) consisting of closed-ended questions completed by in-country practitioners and academics with expertise in civil and commercial law, criminal justice, labor law, and public health. Taken together, these two data sources provide up-to-date firsthand information from a large number of people on their experiences and

	perceptions concerning their dealings with the government, the police, and the courts, as well as the openness and accountability of the state, the extent of corruption, and the magnitude of common crimes to which the general public is exposed.
Method of Estimation	These data are processed, normalized on a 0 to 1 scale, and aggregated from the variable level all the way up to the dimension level for each country, and then to an overall score and ranking using the data map and weights reported in the "Methodology" section of the WJP Rule of Law Index website. Finally, these scores are validated and cross-checked against qualitative and quantitative third-party sources to identify possible mistakes or inconsistencies within the data.
Frequency of data updates	Annual
Data Collection Start	2010

Base indicator details were obtained from the World Justice Project Rule of Law Index Report 2016 (World Justice Project, 2016)

Appendix 4.

Descriptions of Novel Indicators

Table 19 - Indicator description for Dimension 2

	Dimension 2 - Ethical Oversight and Review
Source	Manual review of country regulations
Description /Rationale	Percentage of 26 ICH GCP requirements met in local regulations.
Background on Source	Official English translations were used when possible, followed by unofficial English translations. Where no English translations were available Google translate was used
Data Type Representation	Percentage
Data Sources	Manual review of: **US** - 21 CFR 312, 21 CFR 50, 21 CFR 56, 21 CFR 314 **Vietnam** - Decision No: 799/Q -BYT on the issuance of Guideline on "Good Clinical Practice" Law No. 105/2016 / QH13 - Law on Pharmacy Decision No.: 460 /QD - BYT On the promulgation of Regulations on organization and operation of Ethical Evaluation Committee in biomedical research of Ministry of Health, period 2012 - 2017 Decision No: 111 /QĐ - BYT On promulgation of Regulation on Organization and Operation of Council of Ethics in Biomedical Research at grass-root level **Poland** - Art 37m of the Pharmaceutical Law 2001 (en)/ Dz.U. 2008 nr 45 poz. 271 (pl) Order of the Minister of Health 2 May 2012 (Dz.U. 2012 poz.491) OJ 2012 item 489 Regulation of the Minister of Health of May 2, 2012 regarding Good Clinical Practice European Network of Research Ethics Committees (EUREC)
Method of Measurement	Percentage of 26 ICH E6 requirements met in local regulations.

(Order of the Minister of Health, 2012; Polish Ministry of Health, 2012a, 2012b; US FDA, 2017d, 2017b, p. 21, 2017c, p. 21, 2017e; Vietnam Ministry of Health, 2008, 2012, 2013)

Table 20 - Indicator description for Dimension 3

	Dimension 3 - Research Focus on Local Health Needs/Priorities
Source	Manual search of clinicaltrials.gov and GBD databases
Description /Rationale	Percentage of top 10 causes of death and disability with corresponding study topics in top 25 interventional clinical trial topics.
Background on Source	clinicaltrials.gov searches were performed for the US, Vietnam, and Poland (separately) for interventional trials with start dates from 01/01/2015 to 12/31/2016, excluding trials that accepted healthy volunteers. Results were then sorted to reveal the top 25 conditions being studied. The 2016 GBD report country profiles were reviewed to identify the top 10 leading causes of death and disability in the US, Vietnam, and Poland.
Data Type Representation	Percentage
Data Sources	Manual searches of: IHME GBD database, clinicaltrials.gov
Method of Measurement	Percentage of top 10 causes of death and disability with corresponding study topics.

(IHME, 2018; US National Library of Medicine, 2017b)

Table 21 - Indicator description for Dimension 8

	Dimension 8 - Cost of regulatory review
Description /Rationale	Cost (in USD$) of regulatory authority and ethical review of clinical trial materials.
Background on Source	Assumes minimum number of EC reviews needed to start study and that no revisions are needed. Cost taken from text of regulations and/or correspondence with regional regulatory bodies.
Data Type Representation	USD$
Data Sources	Manual review of: **US** - 21 CFR 312 **Vietnam** - Decision No: 799/Q -BYT on the issuance of Guideline on "Good Clinical Practice" **Poland** - Art 37m of the Pharmaceutical Law 2001 (en)/ Dz.U. 2008 nr 45 poz. 271 (pl) Order of the Minister of Health 2 May 2012 (Dz.U. 2012 poz.491) European Network of Research Ethics Committees (EUREC)
Method of Measurement	Sum of regulatory and ethical review fees converted to USD$ (if necessary) as of January 15, 2018

(EUREC, 2018; Order of the Minister of Health, 2012; US FDA, 2017d; Vietnam Ministry of Health, 2008)

Table 22 - Indicator description for Dimension 9

	Dimension 9 - Regulatory review timeframe
Description /Rationale	Maximum time (in days) needed for regulatory and ethical review of clinical trial materials.
Background on Source	Assumes minimum number of EC reviews needed to start study and that no revisions are needed. Timing taken from text of regulations.
Data Type Representation	Calendar Days
Data Sources	Manual review of: **US** - 21 CFR 312 **Vietnam** - Decision No: 799/Q -BYT on the issuance of Guideline on "Good Clinical Practice" **Poland** - Art 37m of the Pharmaceutical Law 2001 (en)/ Dz.U. 2008 nr 45 poz. 271 (pl) Order of the Minister of Health 2 May 2012 (Dz.U. 2012 poz.491)
Method of Measurement	Sum of stated review times for regulatory and ethical reviews

(EUREC, 2018; Order of the Minister of Health, 2012; US FDA, 2017d; Vietnam Ministry of Health, 2008)

Appendix 5.

Additional data from principal component analysis

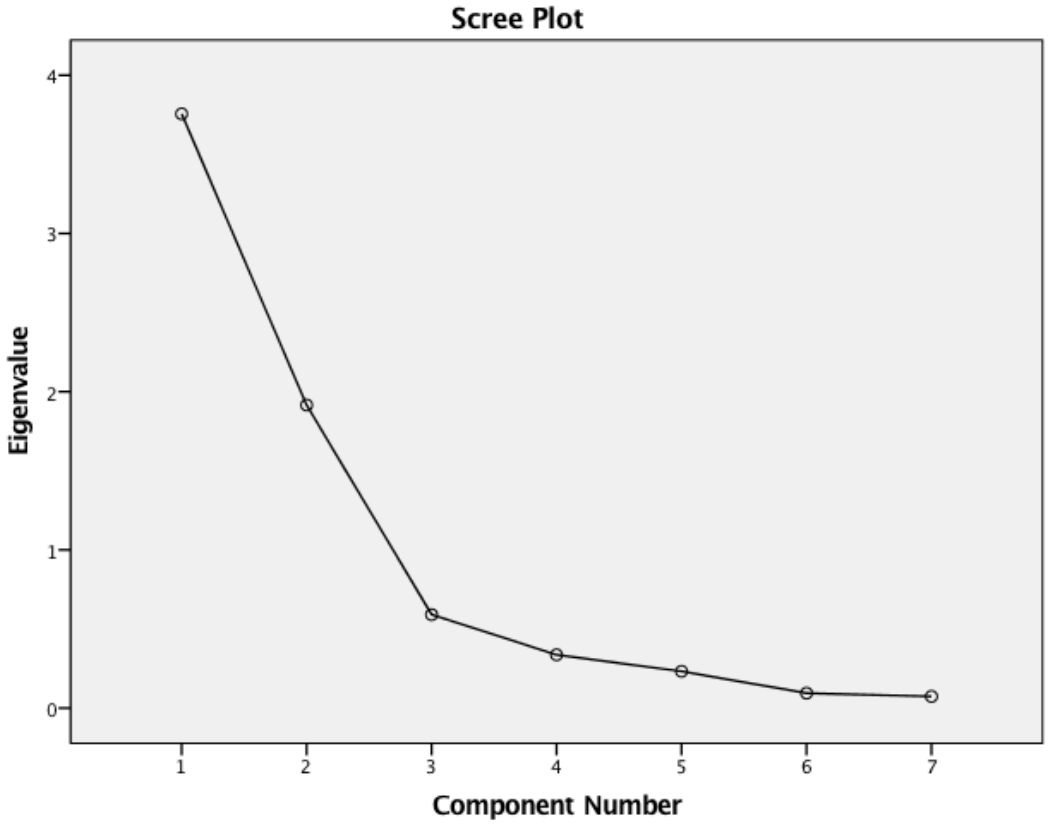


Figure 6 – Scree plot for normalized factor values

The first two components were considered principal components and account for a majority of the variance in the model. The remaining components with Eigenvalues of <1.0 were excluded.

Table 23 - Component loadings for rotated normalized factor values

	Component	
	1	2
Voice & Accnt.	**.869**	.039
UHC Tracer	**.863**	-.041
>10% Health Expend	.022	**.981**
>25% Health Expend	.042	**.980**
Cntrl. Corrupt.	**.915**	.102
Reg. Enforcement	**.944**	.026
HDI 2016	**.712**	.022
Extraction Method: Principal Component Analysis. Rotation Method: Varimax with Kaiser-Normalization.		
Rotation Converged in 3 iterations.		

Values >.500 represent a moderate to high loading; the bold values for each factor demonstrates the strength of the relationship to the respective components.

Appendix 6.

Checklist for Dimension 2 – Ethical Oversight and Review

Item	Responsibilities	YES	NO
1	An IRB/IEC should safeguard the rights, safety, and well-being of all trial subjects. Special attention should be paid to trials that may include vulnerable subjects.		
2	The IRB/IEC should obtain the following documents: - trial protocol(s)/amendment(s), - written informed consent form(s) and consent form updates that the investigator proposes for use in the trial, - subject recruitment procedures (e.g., advertisements), - written information to be provided to subjects, - Investigator's Brochure (IB), - available safety information, - information about payments and compensation available to subjects, - the investigator's current curriculum vitae and/or other documentation evidencing qualifications, - and any other documents that the IRB/IEC may need to fulfil its responsibilities.		
3	The IRB/IEC should review a proposed clinical trial within a reasonable time and document its views in writing, clearly identifying the trial, the documents reviewed and the dates for the following: - approval/favourable opinion; - modifications required prior to its approval/favourable opinion; - disapproval / negative opinion; and - termination/suspension of any prior approval/favourable opinion.		
4	The IRB/IEC should consider the qualifications of the investigator for the proposed trial, as documented by a current curriculum vitae and/or by any other relevant documentation the IRB/IEC requests.		
5	The IRB/IEC should conduct continuing review of each ongoing trial at intervals appropriate to the degree of risk to human subjects, but at least once per year.		
6	When a non-therapeutic trial is to be carried out with the consent of the subject's legally acceptable representative (see 4.8.12, 4.8.14), the IRB/IEC should determine that the proposed protocol and/or other document(s) adequately addresses relevant ethical concerns and meets applicable regulatory requirements for such trials.		

7	Where the protocol indicates that prior consent of the trial subject or the subject's legally acceptable representative is not possible (see 4.8.15), the IRB/IEC should determine that the proposed protocol and/or other document(s) adequately addresses relevant ethical concerns and meets applicable regulatory requirements for such trials (i.e., in emergency situations).		
8	The IRB/IEC should review both the amount and method of payment to subjects to assure that neither presents problems of coercion or undue influence on the trial subjects. Payments to a subject should be prorated and not wholly contingent on completion of the trial by the subject.		
9	The IRB/IEC should ensure that information regarding payment to subjects, including the methods, amounts, and schedule of payment to trial subjects, is set forth in the written informed consent form and any other written information to be provided to subjects. The way payment will be prorated should be specified.		
	Composition, Functions and Operations		
10	The IRB/IEC should consist of a reasonable number of members, who collectively have the qualifications and experience to review and evaluate the science, medical aspects, and ethics of the proposed trial. It is recommended that the IRB/IEC should include: (a) At least five members. (b) At least one member whose primary area of interest is in a nonscientific area. (c) At least one member who is independent of the institution/trial site.		
11	Only those IRB/IEC members who are independent of the investigator and the sponsor of the trial should vote/provide opinion on a trial-related matter.		
12	A list of IRB/IEC members and their qualifications should be maintained		
13	The IRB/IEC should perform its functions according to written operating procedures, should maintain written records of its activities and minutes of its meetings, and should comply with GCP and with the applicable regulatory requirement(s).		
14	An IRB/IEC should make its decisions at announced meetings at which at least a quorum, as stipulated in its written operating procedures, is present.		
15	Only members who participate in the IRB/IEC review and discussion should vote/provide their opinion and/or advise.		
16	The investigator may provide information on any aspect of the trial, but should not participate in the deliberations of the IRB/IEC or in the vote/opinion of the IRB/IEC.		
	Procedures		
The IRB/IEC should establish, document in writing, and follow its procedures, which should include:			
17	3.3.1 Determining its composition (names and qualifications of the members) and the authority under which it is established.		
18	3.3.2 Scheduling, notifying its members of, and conducting its meetings.		

19	3.3.3 Conducting initial and continuing review of trials		
20	3.3.4 Determining the frequency of continuing review, as appropriate.		
21	3.3.5 Providing, according to the applicable regulatory requirements, expedited review and approval/favourable opinion of minor change(s) in ongoing trials that have the approval/favourable opinion of the IRB/IEC.		
22	3.3.6 Specifying that no subject should be admitted to a trial before the IRB/IEC issues its written approval/favourable opinion of the trial.		
23	3.3.7 Specifying that no deviations from, or changes of, the protocol should be initiated without prior written IRB/IEC approval/favourable opinion of an appropriate amendment, except when necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change of monitor(s), telephone number(s)) (see 4.5.2).		
24	3.3.8 Specifying that the investigator should promptly report to the IRB/IEC: (a) Deviations from, or changes of, the protocol to eliminate immediate hazards to the trial subjects (see 3.3.7, 4.5.2, 4.5.4). (b) Changes increasing the risk to subjects and/or affecting significantly the conduct of the trial (see 4.10.2). (c) All adverse drug reactions (ADRs) that are both serious and unexpected. (d) New information that may affect adversely the safety of the subjects or the conduct of the trial.		
25	3.3.9 Ensuring that the IRB/IEC promptly notify in writing the investigator/institution concerning: (a) Its trial-related decisions/opinions. (b) The reasons for its decisions/opinions. (c) Procedures for appeal of its decisions/opinions.		
	Records		
26	The IRB/IEC should retain all relevant records (e.g., written procedures, membership lists, lists of occupations/affiliations of members, submitted documents, minutes of meetings, and correspondence) for a period of at least 3-years after completion of the trial and make them available upon request from the regulatory authority(ies).		
	TOTAL		

Figure 7 - Checklist for Dimension 2 – Ethical Oversight and Review

Adapted from Section 3 of ICH GCP (ICH, 1996)

Appendix 7.

Global data for dimensions 1, 5, 6, and 7

Table 24 - Global data for Dimensions 1, 5, 6, and 7

Region Details			Dimension 1	Dimension 5	Dimension 6	Dimension 7
Country/ Territory	UN region name	Income Group in 2016	Human Rights	Access to Quality Healthcare	Control of Corruption	Adherence to Intern. IP Laws
Afghanistan	Asia	LIC	76.00	62.00	85.00	81.00
Australia	Oceania	HIC	8.00	12.50	8.00	6.50
Austria	Europe	HIC	9.00	20.00	10.00	8.00
Bangladesh	Asia	LMIC	68.00	83.00	70.00	74.50
Belarus	Europe	UMIC	82.00	14.00	43.00	35.00
Belgium	Europe	HIC	6.00	21.00	9.00	12.00
Bolivia	LAC	LMIC	48.00	76.00	63.00	65.50
Bosnia and Herzegovina	Europe	UMIC	55.00	54.50	55.00	44.00
Botswana	Africa	UMIC	34.00	53.00	17.00	24.00
Brazil	LAC	UMIC	31.00	74.50	54.00	32.50
Bulgaria	Europe	UMIC	33.00	56.00	38.00	39.00
Burkina Faso	Africa	LIC	45.00	54.50	35.00	59.50
Cameroon	Africa	LMIC	75.00	80.00	84.00	78.00
Canada	North America	HIC	5.00	4.00	5.00	9.50
Chile	LAC	HIC	21.00	64.00	15.00	19.00
China	Asia	UMIC	85.00	77.00	41.00	59.50
Colombia	LAC	UMIC	44.00	74.50	47.00	36.50
Costa Rica	LAC	UMIC	14.00	31.00	20.00	17.50
Côte d'Ivoire	Africa	LMIC	60.00	81.50	59.00	48.50
Croatia	Europe	HIC	29.00	22.00	26.00	44.00
Czech Republic	Europe	HIC	17.00	2.00	23.00	16.00
Denmark	Europe	HIC	4.00	12.50	2.00	3.00
Dominican Republic	LAC	UMIC	42.00	66.50	69.00	71.00
Ecuador	LAC	UMIC	58.00	57.00	61.00	55.50
Egypt, Arab Rep.	Africa	LMIC	79.00	79.00	60.00	84.00
Estonia	Europe	HIC	11.00	30.00	14.00	11.00

Ethiopia	Africa	LIC	84.00	48.00	53.00	85.00
Finland	Europe	HIC	3.00	15.00	1.00	5.00
Georgia	Asia	UMIC	40.00	69.50	21.00	21.00
Germany	Europe	HIC	7.00	3.00	7.00	3.00
Ghana	Africa	LMIC	26.00	51.00	39.00	29.00
Greece	Europe	HIC	24.00	35.00	33.00	29.00
Guatemala	LAC	LMIC	63.00	36.00	66.00	76.00
Honduras	LAC	LMIC	64.00	49.00	62.00	71.00
Hungary	Europe	HIC	37.00	11.00	28.00	39.00
India	Asia	LMIC	35.00	84.00	44.00	55.50
Indonesia	Asia	LMIC	43.00	60.00	49.00	39.00
Iran, Islamic Rep.	Asia	UMIC	81.00	59.00	65.00	44.00
Italy	Europe	HIC	18.00	18.00	30.00	26.50
Jamaica	LAC	UMIC	23.00	38.50	37.00	32.50
Japan	Asia	HIC	19.00	24.00	11.00	6.50
Jordan	Asia	UMIC	74.00	33.00	25.00	25.00
Kazakhstan	Asia	UMIC	80.00	7.00	71.00	44.00
Kenya	Africa	LMIC	54.00	63.00	77.00	65.50
Korea, Rep.	Asia	HIC	27.00	41.00	24.00	13.00
Kyrgyz Republic	Asia	LMIC	66.00	26.50	83.00	78.00
Lebanon	Asia	UMIC	67.00	66.50	80.00	71.00
Liberia	Africa	LIC	51.00	71.00	64.00	71.00
Macedonia, FYR	Europe	UMIC	57.00	41.00	45.00	51.50
Madagascar	Africa	LIC	59.00	41.00	78.00	78.00
Malawi	Africa	LIC	46.00	28.00	67.00	59.50
Malaysia	Asia	UMIC	65.00	5.00	27.00	51.50
Mexico	LAC	UMIC	50.00	37.00	68.00	62.50
Moldova	Europe	LMIC	49.00	68.00	79.00	71.00
Mongolia	Asia	LMIC	32.00	19.00	57.00	51.50
Morocco	Africa	LMIC	71.00	73.00	36.00	32.50
Nicaragua	LAC	LMIC	69.00	81.50	76.00	55.50
Nigeria	Africa	LMIC	61.00	85.00	81.00	65.50
Norway	Europe	HIC	1.00	9.00	4.00	1.00
Pakistan	Asia	LMIC	72.00	45.00	74.00	83.00
Panama	LAC	UMIC	28.00	32.00	56.00	36.50
Peru	LAC	UMIC	39.00	58.00	48.00	44.00
Poland	Europe	HIC	22.00	43.50	19.00	21.00
Portugal	Europe	HIC	13.00	43.50	16.00	23.00
Romania	Europe	UMIC	30.00	50.00	31.00	26.50
Russian Federation	Europe	UMIC	78.00	29.00	75.00	51.50

Senegal	Africa	LIC	36.00	38.50	32.00	29.00
Serbia	Europe	UMIC	41.00	46.00	46.00	55.50
Sierra Leone	Africa	LIC	53.00	65.00	72.00	82.00
Slovenia	Europe	HIC	20.00	6.00	18.00	21.00
South Africa	Africa	UMIC	25.00	26.50	29.00	32.50
Spain	Europe	HIC	16.00	16.00	22.00	17.50
Sri Lanka	Asia	LMIC	52.00	17.00	42.00	44.00
Sweden	Europe	HIC	2.00	10.00	3.00	3.00
Tanzania	Africa	LIC	56.00	78.00	58.00	68.00
Thailand	Asia	UMIC	77.00	52.00	52.00	44.00
Tunisia	Africa	LMIC	38.00	61.00	34.00	48.50
Turkey	Asia	UMIC	70.00	25.00	40.00	62.50
Uganda	Africa	LIC	73.00	72.00	82.00	80.00
Ukraine	Europe	LMIC	47.00	47.00	73.00	74.50
United Kingdom	Europe	HIC	10.00	1.00	6.00	9.50
United States	North America	HIC	15.00	8.00	12.00	14.00
Uruguay	LAC	HIC	12.00	34.00	13.00	15.00
Vietnam	Asia	LMIC	83.00	69.50	51.00	65.50
Zambia	Africa	LMIC	62.00	23.00	50.00	59.50

Appendix 8.

Additional results by geographic region for dimensions with publicly available data

Table 25 - Dimension 5 - Access to Quality Healthcare by geographic region

UN Region	n	Mean	St. Dev.
Africa	20	58.60	19.53
Asia	20	46.25	25.37
Europe	27	26.81	19.02
LAC	15	53.97	18.23
North America	2*	6.00	2.83
Oceania	1*	12.50	N/A

**Number of countries within region too small for meaningful comparison*

Table 26 - Dimension 6 - Control of Corruption by geographic region

UN Region	n	Mean	St. Dev.
Africa	20	55.35	20.46
Asia	20	50.60	22.22
Europe	27	28.00	22.65
LAC	15	50.33	20.31
North America	2*	8.50	4.95
Oceania	1*	8.00	N/A

**Number of countries within region too small for meaningful comparison*

Table 27 - Dimension 7 - Adherence to International IP Laws by geographic region

UN Region	n	Mean	St. Dev.
Africa	20	58.98	20.46
Asia	20	50.70	22.22
Europe	27	27.44	21.00
LAC	15	46.03	20.76
North America	2*	11.75	3.18
Oceania	1*	6.50	N/A

**Number of countries within region too small for meaningful comparison*

Appendix 9.

Scorecard and ranks for Dimension 2 – Ethical Oversight and Review

Item	USA	Vietnam	Poland
	Responsibilities		
1	X	X	X
2	X	X	X
3	X	X	X
4	X	X	X
5	X	X	X
6	X	O	O
7	X	O	O
8	X	O	X
9	X	X	X
	Composition, Functions and Operations		
10	X	X	X
11	X	X	X
12	X	X	X
13	X	X	X
14	X	X	X
15	X	O	X
16	X	X	X
	Procedures		
17	X	X	X
18	X	X	X
19	X	X	X
20	X	X	X
21	X	O	X
22	X	X	X
23	X	X	X
24	X	X	X
25	X	X	X
	Records		
26	X	X	X
Score	**100%**	**81%**	**92%**
Rank	**1**	**3**	**2**

Figure 8 - Scorecard and ranks for Dimension 2 - Ethical Oversight and Review

Each numbered item corresponds to the checklist for Dimension 2 (Figure 7, Appendix 6), based on the ICH GCP section pertaining to IRBs/IECs. An "X" indicates that the requirements for the item were met, while an "O" indicates they were not. The score for each country is the percent of the 26 items that met the requirements.

Appendix 10.

Additional Data for Dimension 3 – Research Focus on Health Needs/ Priorities

	USA	Vietnam	Poland
1	Ischemic Heart Disease (b)	Cerebrovascular Disease (b)	Ischemic Heart Disease (b)
2	Low Back & Neck Pain (b)	Ischemic Heart Disease (b)	Low Back & Neck Pain (b)
3	Drug Use Disorders (b)	Road Injuries (c)	Cerebrovascular Disease (b)
4	Lung Cancer (b)	Low Back & Neck Pain (b)	Falls (c)
5	COPD (b)	Sense Organ Diseases (b)	Lung Cancer (b)
6	Diabetes (b)	Lung Cancer (b)	Sense Organ Diseases (b)
7	Skin Diseases (b)	Diabetes (b)	Migraine (b)
8	Cerebrovascular Disease (b)	Skin Diseases (b)	Road Injuries (c)
9	Depressive Disorder (b)	COPD (b)	Diabetes (b)
10	Road Injuries (c)	Congenital Defects (b)	Self-Harm (c)

Figure 9 - Leading causes of death and disability in 2016

Conditions with corresponding clinical trial topics are highlighted in green. Causes of death and disability include a) Communicable, maternal, neonatal, and nutritional diseases; b) Non-communicable diseases; and c) Injuries. Adapted from: (IHME, 2017)

Table 28 - Leading clinical trial topics in the US

Search Parameters:		
Country	US	
Study Type	Interventional	
Accepts Healthy Volunteers?	No	
Start Date	01/01/2015 to 12/31/2016	
Funding Source	Any	
Search Results:		
# of Studies	13,337	
# of Conditions	2,827	
Top 25 Conditions being studied:		
Conditions	**# of Studies**	**% of Studies**
Neoplasms by Histologic Type	1,676	13%
Mental Disorders	1,298	10%
Psychotic Disorders	1,295	10%

Immune System Diseases	1,268	10%
Digestive System Diseases	1,027	8%
Gastrointestinal Diseases	1,027	8%
Respiratory Tract Diseases	1,019	8%
Central Nervous System Diseases	965	7%
Skin Diseases	952	7%
Carcinoma	933	7%
Neurologic Manifestations	874	7%
Syndrome	860	6%
Brain Diseases	840	6%
Endocrine System Diseases	829	6%
Communicable Diseases	828	6%
Infection	828	6%
Pain	817	6%
Vascular Diseases	817	6%
Metabolic Diseases	792	6%
Neoplasms, Glandular and Epithelial	788	6%
Lung Diseases	763	6%
Musculoskeletal Diseases	617	5%
Wounds and Injuries	584	4%
Urogenital Neoplasms	548	4%
Diabetes Mellitus	546	4%

Results from: (US National Library of Medicine, 2018b). Conditions corresponding with leading causes of death and disability are highlighted in green.

Table 29 - Leading clinical trial topics in Vietnam

Search Parameters:		
Country	Vietnam	
Study Type	Interventional	
Accepts Healthy Volunteers?	No	
Start Date	01/01/2015 to 12/31/2016	
Funding Source	Any	
Search Results:		
# of Studies	70	
# of Conditions	225	
Top 25 Conditions being studied:		
Conditions	**# of Studies**	**% of Studies**
Communicable Diseases	29	41%
Infection	29	41%

Respiratory Tract Diseases	15	21%
RNA Virus Infections	12	17%
Virus Diseases	12	17%
Lung Diseases	10	14%
Central Nervous System Diseases	9	13%
Bacterial Infections	8	11%
Gram-Positive Bacterial Infections	8	11%
Parasitic Diseases	8	11%
Genital Diseases, Male	7	10%
Immune System Diseases	7	10%
Malaria	7	10%
Protozoan Infections	7	10%
Acquired Immunodeficiency Syndrome	6	9%
Central Nervous System Infections	6	9%
Genital Diseases, Female	6	9%
HIV Infections	6	9%
Infertility	6	9%
Respiratory Tract Infections	6	9%
Carcinoma	5	7%
Neurologic Manifestations	5	7%
Pregnancy Complications	5	7%
Syndrome	5	7%
Brain Diseases	4	6%

Results from: (US National Library of Medicine, 2018c). Conditions corresponding with leading causes of death and disability are highlighted in green.

Table 30 - Leading clinical trial topics in Poland

Search Parameters:		
Country	Poland	
Study Type	Interventional	
Accepts Healthy Volunteers?	No	
Start Date	01/01/2015 to 12/31/2016	
Funding Source	Any	
Search Results:		
# of Studies	771	
# of Conditions	843	
Top 25 Conditions being studied:		
Conditions	**# of Studies**	**% of Studies**

Immune System Diseases	172	22%
Neoplasms by Histologic Type	108	14%
Musculoskeletal Diseases	101	13%
Autoimmune Diseases	96	12%
Respiratory Tract Diseases	96	12%
Digestive System Diseases	92	12%
Gastrointestinal Diseases	92	12%
Joint Diseases	87	11%
Lung Diseases	87	11%
Arthritis	84	11%
Skin Diseases	76	10%
Connective Tissue Diseases	72	9%
Carcinoma	70	9%
Collagen Diseases	65	8%
Rheumatic Diseases	65	8%
Intestinal Diseases	57	7%
Central Nervous System Diseases	55	7%
Endocrine System Diseases	52	7%
Brain Diseases	50	6%
Heart Diseases	50	6%
Arthritis, Rheumatoid	49	6%
Gastroenteritis	46	6%
Metabolic Diseases	46	6%
Neoplasms, Glandular and Epithelial	46	6%
Vascular Diseases	46	6%

Results from: (US National Library of Medicine, 2018a). Conditions corresponding with leading causes of death and disability are highlighted in green.

Appendix 11.

US IRB Full Panel Review Fees

Table 31 - US IRB full panel review fees (in USD)

IRB Institution	IRB URL	Full Panel Review Fee
University of California, Irvine	https://research.uci.edu/compliance/human-research-protections/researchers/irb-fees.html	$2,200
Northwestern University	https://irb.northwestern.edu/about/fees	$5,000
Yale	https://your.yale.edu/sites/default/files/irb_fee_schedule_august_3_20151.pdf	$3,000
University of California, San Francisco	https://irb.ucsf.edu/irb-review-fees	$2,700
University of Illinois	http://research.uic.edu/irb/investigators-research-staff/irb-fees	$2,900
Georgetown University	https://ora.georgetown.edu/irb/fees	$4,500
Johns Hopkins University	https://www.hopkinsmedicine.org/institutional_review_board/about/fees.html	$2,500
University of California, Davis	http://research.ucdavis.edu/policiescompliance/irb-admin/researchers/fees/	$3,400
Boston University	http://www.bumc.bu.edu/irb/bumcirb/charges-for-irb-review/	$3,894
Philadelphia University & Thomas Jefferson University	http://www.jefferson.edu/university/human_research/irb-reference-documents/fee_schedule.html	$2,950
	Average	**$3,304**
	St. Dev.	**$899**
	Median	**$2,975**
	Min	**$2,200**
	Max	**$5,000**

Taken from: (Boston University IRB, 2017; Georgetown University, 2017; Johns Hopkins University IRB, 2018; Northwestern University, Office for Research, 2018; Philadelphia University + Thomas Jefferson University - Thomas Jefferson University, 2018; UC Davis, 2009; UC Irvine, 2017, 2017; UCSF Institutional Review Board, 2017; Yale IRB, 2015)

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