A QUALITATIVE STUDY OF COLLABORATIVE RELATIONSHIPS ENABLING PHARMACEUTICAL CLINICAL TRIALS FOR ALZHEIMER'S DISEASE IN LOW- AND MIDDLE-INCOME COUNTRIES

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The Role of Collaborative Relationships in Enabling Pharmaceutical Clinical Trials for Alzheimer's Disease in Low- and Middle-Income Countries

Abstract

With no cure or disease-modifying treatment for Alzheimer's Disease (A.D.) and high-profile drug failures in recent clinical trials, there remains a global commitment to advancing dementia research and therapeutic innovation. As new clinical trials and research collaborations form, there is limited understanding of the factors that create or hinder equitable relationships between stakeholders that enable pharmaceutical-sponsored A.D. clinical trials and the opportunity to leverage clinical trials for expanded use in health system strengthening.

Part One of this thesis examines the potential for health system infrastructure strengthening in low- and middle-income countries (LMICs) through sponsored clinical research. It explores the motivations and influence of pharmaceutical companies in the context of the healthcare ecosystem, articulating their historical and present-day role in clinical trials as the primary funders of late-stage clinical research. Our research proposes that sponsored clinical research can be designed and positioned for greater value and impact to patients and health communities, providing treatments that are so desperately needed while supporting the patients and practitioners they aim to serve.

Part Two of this thesis summarizes a qualitative study on the collaborative relationships that enable pharmaceutical clinical trials for Alzheimer's disease in LMICs. This study used emergence-driven sampling with 19 participants representing four key stakeholders in the A.D. research and clinical trials ecosystem: 1) for-profit industry executives 2) researchers or key opinion leaders 3) government or regulatory leaders 4) members of non-profit organizations and

patient advocacy groups. In examining the collaborative practices that enable global clinical research for A.D., study participants elevated perspectives related to professional limitations in their work, which they described as operational barriers, culturalist claims about capability, and limited commercial opportunities. Participants also presented perspectives related to interpersonal behaviors related to fragile trust and creating and maintaining exclusivity. Taken together, these factors explain the lack of investment in LMICs for A.D. clinical trials and point to the inequalities present in this area of clinical research. Part Two concludes with a call to action to rectify the inequalities presented by managing the influential role of pharmaceutical companies and their commercial drivers as new research and clinical trial alliances are formed and passed on. A conscious and deliberate effort is required to create more equitable partnerships in A.D. clinical trials as the global demand for research expands.

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Part 1: Examination of Clinical Trial Research in Support of Health System Strengthening in Low- and Middle-Income Countries

Written in Autumn 2019

INTRODUCTION

"Are you interested in signing up to participate in a clinical trial?" This is a common question posed daily to patients at clinical research sites around the world. It is an invitation for volunteers to come forward and potentially receive a new, experimental drug under observation to help address a disease or pathology they are facing. The study's primary purpose is to prove the drug's efficacy, and with positive results, to scale the treatment to help similar patients. Most patients do not consider the benefit of participating in a clinical trial as a mechanism for strengthening the health system. Most ministries of health, regulators, pharmaceutical companies, and contract research organizations (CROs) are not thinking about clinical trials as a mechanism for health system strengthening. But as billions of dollars are invested in clinical research sites worldwide, are there potential secondary benefits to the local health communities that should be considered?

Clinical research has incredible value as it makes therapeutic innovation available for in vivo testing. Still, it is often downplayed for splashier headlines tied to the business of healthcare and the push for new drug approvals, drug costs, or bioethical questions. Clinical research tests emerging treatments and under-explored secondary benefits from clinical trials that support health system strengthening. In particular, low- and middle-income countries (LMICs) struggle to include non-communicable diseases, mental health, and aging care in their national health agendas. These countries could greatly benefit from additional operating resources to increase patient access, medical training, and diagnostic tools.

This paper aims to examine further the potential of health system infrastructure strengthening in LMICs through clinical research. Beginning with a brief history of pharmaceutical companies, this paper will explore their motivations and influence in the context of the healthcare ecosystem, articulating their role in clinical trials as the primary funders of late-stage clinical research. Then, by examining the history, context, and operations of pharmaceutical-funded clinical trials, this paper will propose that clinical research can be designed and positioned for greater value and impact to patients and health communities, providing treatments that are desperately needed while supporting the patients and practitioners they aim to serve.

ESTABLISHING THE MODERN CLINICAL TRIAL

Pharmaceutical companies are considered one of three primary players in the global healthcare ecosystem ("payer, provider, pharma"). Their function is to create and manufacture drug treatments that address the world's pathologies and ailments. Pharmaceutical companies are relatively new businesses in medicine, graduating from local chemist shoppes to European chemical companies, like Bayer, Sandoz, Ciba, and Hoechst. In the United States, the initial firms founded in the 19th and early 20th century included Eli Lilly, Abbott, Upjohn, Smith Kline, Squibb, and Wyeth, who created and sold natural products to customers. The birth of the modern pharmaceutical company came about in the 1940s, after World War II, due to post-war funding for developing penicillin and sulfa antibiotics and the rise in population growth, living standards, and unmet medical needs in North America and Western Europe (Malerba & Orsenigo, 2015).

Early pharmaceutical drug discovery was an exercise screening thousands of potential drug compounds in the hope of finding an effective treatment. While an inefficient process to generate drugs, the industry grew.

> "Despite the random nature of the process of drug discovery, innovation quickly became the name of the game. On the one hand, since very few effective drugs were in existence, the space for discovering new treatments and cures for most diseases was simply immense. On the other hand, the discovery of new drugs became a very profitable business, due to the growth of demand and – especially in the U.S. – to patent protection." (Malerba & Orsenigo, 2015)

If innovation was the goal, which would serve a public need, then the government's appropriate incentives would be to bring attention, time, and energy to achieving that goal. Patents were one of the incentives the United States government created. In 1946, the U.S. Patent Office granted a patent to streptomycin, overturning previous rulings that denied patentability to antibiotics, like penicillin, which they claimed were naturally occurring ingredients (Malerba & Orsenigo, 2015). Additionally, pharmaceuticals received special patent exceptions, qualifying for "product" patents compared to previously approved "process" patents (Malerba & Orsenigo, 2015). The U.S. Patent Office also was increasingly more restrictive, allowing for little or no imitation of the therapeutic by a rival generics company and exclusive national and international market dominance for the patent holder. Global demand, incentivized by patents, created the lucrative financial outlook that catalyzed the pharmaceutical industry's rapid growth between the 1940s and 1960s, known as pharma's "golden age" (Malerba & Orsenigo, 2015).

The modern clinical trial emerged in sequence with the growth of pharmaceuticals post-World War II in the 1950s and 1960s. A randomized-controlled trial (RCT), the most common

design for clinical trials, was not required until scientific communities and regulators observed the use of unproven, ineffective, and dangerous drugs that were not adequately tested before companies promoted their benefits. Yet, the U.S. Food and Drug Administration (FDA) lacked the necessary legislative and political support to strengthen drug efficacy and safety (Bothwell et al., 2020). With the drug safety crisis generated by the sedative thalidomide on maternal health, Senator Estes Kefauver gathered the necessary political support to pass the Kefauver-Harris amendments to the Federal Food, Drug, and Cosmetic Act in 1962, the legal mandate for the FDA to require drug manufacturers to provide "adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved" (FDA Conference on the Kefauver-Harris Drug Amendments and Proposed Regulations, 1963). This amendment introduced much-needed regulation. The amendment also set the expectation for trials with larger, placebo-controlled, randomized, and statistically-driven analyses (Greene & Podolsky, 2012).

What does clinical research look like today? The FDA defines clinical research as experiments or clinical trials designed to specifically answer questions related to a medical product (Commissioner, 2019). Drugs are tested in humans to ensure they are effective and safe based on early research and development (R&D) phases, primarily discovery and preclinical research. But this definition misses out on the impact of clinical research and what these studies offer the medical community; "clinical research provides financial and altruistic appeal: a successful [clinical trial] site will conduct a diversity of studies with commensurate compensation. The data generated (from trials conducted) could contribute to a regulatory agency submission for new drug approval. At the very least, a successful site will impact the drug development process." (Weeks-Rowe, 2018)

As much clinical preparation goes into developing a clinical trial and its related sites, just as much business acumen is also applied. Long before a clinical trial begins, R&D and commercial arms work side-by-side to see how potential therapeutic agents, known as "therapeutic assets," mature and advance in the R&D pipeline. Clinical trialists thoroughly plan for their primary objective: to determine if the proposed treatment is effective or not. Planning for a clinical trial will consider a wide range of aspects, at a global, national, and site level, including regulations, patient recruitment, patient demographics, physician and clinical team knowledge and expertise, access and quality of care, clinical operations, data collection and methods, supply chain, and many more. Most clinical trials are planned for five or more years in advance because of the numerous influences while tracking a potential therapeutic agent's ongoing development.

In looking at the complexities of clinical research, it is no surprise that R&D is the largest cost generator for most pharmaceuticals. Pharmaceuticals exist in a constant tension of enabling high-risk, high-reward R&D, and they must pump money into it to remain competitive and discover their next blockbuster drug. In a 2018 PwC study comparing the top 25 companies with the highest R&D expenditures globally, the pharmaceutical Celgene spent 46% of their revenue on R&D, and Roche, the Swiss pharmaceutical, invested $10.8 billion of their $40.1 billion in revenue on R&D (Braun, D. & Kramer, J., 2018). Clinical trials are the primary driver of these enormous R&D costs. A recent study on pharma R&D costs per clinical trial concluded that the total out-of-pocket cost per approved new drug is $1.4 billion. If fully capitalized, the total cost estimate is $2.6 billion (DiMasi et al., 2016). The authors summarized the continued growth of clinical trial costs as the following:

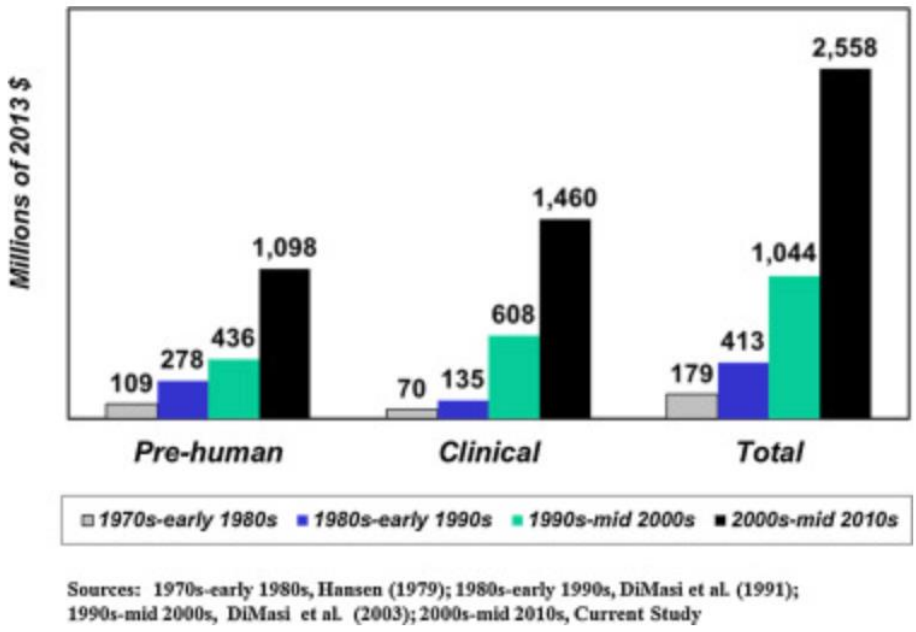

Figure 1: DiMasi et al., 2016

To afford to conduct a clinical trial, a pharmaceutical company cannot simply take out a massive loan because there is a high risk of the clinical trial failing – banks and profit-driven lenders do not want to take on that level of liability. Depending on the clinical area and the type of therapeutic agent, estimates suggest that, from basic research through FDA approval, the clinical success rate for a pharmaceutical asset hovers around 20%, not a strong likelihood of success (DiMasi et al., 2016). Therefore, pharmaceutical companies need to raise money from investors and create a business model that can attract billions of dollars for each trial and, more importantly, for continued R&D. While creating new medicines for patients is the driver of the industry, as businesses, pharmaceutical companies are challenged with maintaining their profit margins and fulfilling fiduciary requirements to their shareholders. Quite simply, in the current model, without funding from investors, clinical trials cannot exist. Therefore, today's modern pharmaceuticals are for-profit businesses, and as such, R&D and sales continue to be the primary cost and revenue drivers, respectively, of the pharmaceutical industry.

THE COMMERCIAL INFLUENCE ON R&D

Pharmaceuticals subscribe to a set of business norms around market demand, price optimization, and competition to attract investment, maintain profitability, and afford their continued R&D requirements. This market environment reflects much of what Max Weber described as the "iron cage of technical rationality," which traps people and systems into what many think of as efficient, rational, and pragmatic modes of order (Weber, 2009). In this sense, pharmaceuticals must have business models that generate profitable economic growth. To maintain this model, they must create the next generation of therapeutics through their R&D capabilities, execute global clinical trials, and enable market access and opportunities for global therapeutic expansion. In the current system, without this cycle, new drug treatments would not be available to anyone in the world. Thus, due to the business ecosystem that pharmaceuticals operate in, motivations and value drivers that do not ascribe to their market objectives (and those applied to them) become secondary. As Weber describes, with the values or market drivers set by capitalism, there is an inability to redefine or contain the capitalist impact on society. Pharmaceuticals cannot single-handedly transform the broken paradigm of global health but enable the continued frustration and pain of the healthcare model experienced today.

Since time is money and the pharmaceutical industry engages in global market competition, they are continually seeking new partners to optimize their clinical trial designs and operations to ensure their R&D funding is well spent. With all the moving pieces that enable clinical research, a new market arose around the increasing operational and regulatory requirements of randomized control and clinical trials. Contract Research Organizations (CROs) and Site Management Organizations (SMOs) quickly became commonplace partners in clinical trials in the late 1970s and early 1980s, with companies like Charles River Laboratories and

Huntingdon Life Sciences. With the ability to organize, recruit, and run clinical trials faster through these mechanisms than managing the process internally, pharmaceutical companies welcomed these new entrants. The accompanying industry around clinical trials emerged as a for-profit enterprise. Like pharmaceutical companies, CROs participate in the formal rationalization Weber describes as they provide a highly desired service that maximizes the value of R&D funding and reduces much of the stress and complexity of global clinical trials.

CROs typically support clinical trials through Phase I-III, where 70% of a drug's R&D costs are attributed (van Huijstee & Homedes, 2012). The global CRO market was valued at $38.4 billion in 2018 and projected to reach $91.0 billion by the end of 2026, creating a CAGR of 11.4% in the forecast period (2019-2026) (Contract Research Organization (CRO) Services Market Size by 2026, 2018). While there is no conclusive data on the cost per patient per trial available from CROs, recruiting one patient for a clinical trial can be between $2,000-$10,000, with higher fees as patient recruitment challenges increase. Regarding cancer research with CROs, "despite this high market penetrance and continued growth, details regarding the activities of CROs and their influence on research conduct have been poorly studied to date. For example, to our knowledge, there are currently no mechanisms with which to comparatively evaluate the quality, efficiency, competence and expertise, accuracy of data collection, and cost-effectiveness of CROs" (Roberts et al., 2016). This reality is critical because it underpins many of the healthcare challenges we face today. Pharmaceuticals, CROs, SMOs, and drug manufacturers are for-profit businesses, and there is limited transparency regarding how they manage clinical trial costs. These companies are motivated to create a margin from clinical trial design and R&D while completing clinical research as quickly as possible.

The business of a CRO hinges on the careful selection of global clinical trial sites, knowing the patient population, the healthcare economy, ethical considerations, regulatory landscape, and study operations. Today, clinical trial timelines can be delayed by 50% stemming from patient recruitment challenges, inexperienced staff, protocol violations, and low-quality data collection (Hurtado-Chong et al., 2017). Again, it is critical to acknowledge that the primary objective of a clinical trial funded by pharmaceuticals and supported by CROs is to determine a drug's efficacy. Therefore, both clinical and business factors influence site selection. It is not altruistic. There are multiple factors to consider to conduct a clinical trial, and there is no systematic evaluation method. Regarding site scouting, many pharmaceuticals and CROs require the following:

- Ease of access to a robust patient population that can be identified, screened and enrolled, and that will adhere to the study requirements.
- Trained clinical experts, including principal investigators (P.I.s) that can manage the clinical protocol, including data collection from patients and devices
- Operational staff that can manage study coordination, ensuring high-quality data collection, and engage with regulatory or ethical committees
- Historical participation in clinical research

In a meeting with a former pharmaceutical executive, they candidly described the approach to site selection as the following: "Epidemiological data is collected to identify where the greatest concentration of patients can be found, then we compare the regulatory landscapes, and only then do we start to look for KOLs (Key Opinion Leaders), P.I.s, and trial sites. The broader healthcare landscape is not even on the radar of the clinical leadership of pharmaceutical companies or CROs." As noted by this executive, the available patient population and the regulatory landscape

are the primary drivers in selecting a clinical trial site. The completion of the trial is the main objective.

BARRIERS TO THE EXPANSION OF CLINICAL TRIALS IN THE GLOBAL NORTH

Naturally, the increasing regulatory and operational complexity of the American healthcare system, complicated by the growing patient demand for clinical trials from pharmaceutical companies, encouraged CROs and SMOs to explore the potential of outsourcing clinical trials as a faster, more economical option in the late 1980s and early 1990s. Since then, these initial influences have only become more prominent and powerful. There are thousands of clinical trials that are launched each year globally in addition to ongoing studies. At the end of 2019, estimates claimed over 324,000 clinical trials underway around the world (*Trends, Charts, and Maps - ClinicalTrials.Gov*, 2019). As mandated through the Kefauver-Harris amendments to the Federal Food, Drug, and Cosmetic Act in 1962, trials require larger pools of eligible trial participants. As the number of trials increases year over year, the hunt for eligible participants intensifies as well.

Beyond the need for larger participant pools, the business influences of the pharmaceutical industry drive CROs to seek participants globally to support pharmaceutical market competition in countries where clinical trials can act as a foot-in-the-door to enable future drug sales. Even if pharmaceuticals and CROs wanted to use more Americans in their research, patients in the U.S. are already taking too many prescription drugs that would interfere with measuring the trial drug's effectiveness. The CDC estimates that 24% of Americans have taken three or more prescription drugs in the past 30 days (*FastStats*, 2019). Thus, with the participant

limitations in the U.S. and growing demands of the modern clinical trial for larger, purer patient populations, CROs must look for new patient populations to sample.

With the continued growth of outsourcing, potential trial sites or "host" countries shift their regulatory requirements to attract pharmaceuticals and CROs. By limiting the regulatory bureaucracy, LMICs can attract pharmaceuticals and CROs to their respective country and receive much-needed compensation for clinical trials. It is only natural that under-resourced countries welcome the opportunity to attract the billions of dollars that pharmaceuticals can inject into their countries' economies in the name of research. To further enable international clinical research, the International Conference on Harmonization (ICH) created a global standard for ensuring the quality, safety, and testing standards for clinical trials, which included the Good Clinical Practice guidelines, which launched institutional adoption review boards (IRBs) (Petryna et al., 2006). As long as studies are compliant with the ICH guidelines, the data generated from international clinical trials apply to FDA applications and patent submissions. This simplified data sharing supports efficiency and the continued streamlining of drug development and clinical research.

As noted above, the host country sets clinical trial regulations, so regulators must also act as a counterforce to protect vulnerable populations. Through advocacy and legal intervention, social protections ensure patient exploitation is minimal. However, governments and regulatory bodies are outmatched as they counter the rapid global clinical research expansion of pharmaceuticals and CROs. Alternatively, they also want to welcome the economic benefits of clinical research. This dual responsibility is conflicted, and therefore, it is ineffective and easily manipulated.

The market forces of pharmaceuticals and CROs and related counterforce of regulators tie to an example of one of Karl Polanyi's core concepts, double movement, where the market would expand continuously without a countermovement to check the market's expansion in an indefinite direction (Polanyi, 2001). "Precisely not because the economic but the social interests of different cross-sections of the population were threatened by the market, persons belonging to various economic strata unconsciously joined forces to meet the danger" (Polanyi, 2001). It is through this lens that clinical research is kept in check by effective regulatory requirements and oversight. Clinical trials are beneficial to a strong and influential but limited market, the pharmaceutical and healthcare industries, but patient safety and societal benefit apply to a wider constituency. Today, regulators in LMICs cannot withstand and manage their conflicted role, and they need to become a stronger counterforce to match the market force of pharma-funded clinical research.

The regulatory changes in the clinical trial landscape in India exemplify the double movement. After a series of high-profile clinical trial missteps around consent, subject safety, and quality of care, a series of stringent laws went into effect in 2013 that significantly impacted the launch and continued execution of clinical trials funded by the U.S. National Institute of Health (NIH) and pharmaceutical companies. In January 2013, The Ministry of Health and Family Welfare for India issued an amendment to the Drugs and Cosmetics Act, 1940 (Ministry of Health and Family Welfare, 2013). Issued by the Indian Ministry of Law, they outlined a final set of guidelines on patient compensation that now includes contentious clauses, like the need to provide compensation should an experimental drug fail to show therapeutic benefit (Barnes et al., 2018). These guidelines were withdrawn in 2016 but reintroduced in the Draft Rules of 2018 (Barnes et al., 2018). "The 2018 Draft Rules not only preserved the requirement that the sponsor

compensates trial participants for all injuries deemed related to a clinical trial under a broad list, but the 2018 Draft Rules also increased the burden on sponsors, even in excess of the existing regulations" (Barnes et al., 2018). The Indian government rallied to protect its people as trial participants in the most stringent way.

According to Polyani's theory, social forces will keep economic or market forces in check; in return, "social protection [leads] to deep-seated institutional strain" (Polanyi, 2001). Both sides experience the strain created by social protection. Like regulators and governments, societal actors must act as enforcers, and it is also felt by the market players, like pharmaceuticals and CROs. They endeavor to deliver on their market value and business drivers. But since markets exist within societies, there is a critical tension that has to be resolved. This tension creates an opportunity for societal actors to ask something of "the market." In the case of clinical trials, it creates an opportunity for clinical trials to become more than just a study of a drug's efficacy but an opportunity to ensure broader societal benefit. According to Petryna et al.:

> "Clinical research attracts investments but also gives regulators in these countries a chance for their governments to exercise sovereignty as they see fit and to jockey for more say in the types of trials that are proposed. As trial environments solidify, so does this tension between public and private interests – a tension that does not necessarily stall trials but, rather, leads to continuous renegotiations over the application of the law, norms, investments, and operations." (Petryna, 2009)

The tension described in Polyani's double movement positions societal actors to leverage over yet effectively partner with industry.

MOVING TOWARDS RECOGNIZING DUAL BENEFIT

In an interview with Fitzhugh Mullan for *Health Affairs* in 2007, Paul Farmer said, "I believe that many transnational corporations really want to be involved in efforts to move global health equity forward. The important point is that it is our job to make sure they do it correctly. These companies can be significant contributors to health development in many important ways, including financing, production, distribution, and technology transfer." (Mullan, 2007) It is the job of regulatory bodies, like the Indian Ministry of Health and Family Welfare, to ensure that any partner, regardless of for-profit or non-profit status, is not causing harm but serving people and patients through the work. Why not leverage a clinical trial's benefits for greater strides in health system strengthening as pharmaceuticals, CROs, and clinical trials are already active participants in the healthcare ecosystem? Just as Farmer describes and the double movement theory instills, no singular healthcare-as-a-business force can dominate without a counterforce of strong regulatory oversight. Societal players, then, have the leverage to position clinical trials for more than just determining if a drug is effective or not.

Today, even without the use of societal leverage or regulatory enforcement, most pharmaceutical and healthcare industries are providing benefits to the global health ecosystem beyond what their business model demands. Oncology is a clinical area where pharmaceuticals support health system strengthening through clinical trials, but they continue to provide aid after the trial is complete and the drug is approved. For most oncology clinical trials, biomarker testing identified the patient's cancer pathology and determine enrollment eligibility in the clinical trial. With the advancements in precision medicine and targeted therapies, biomarker tests are now essential to determine what genes to target and inhibit. With 65% of the world's cancer patients, low-income countries have only 5% of the global cancer care resources. They

cannot afford the diagnostic infrastructure and tests required, let alone the treatment or trained staff to enable the standard of care (Farmer et al., 2010). As market-driven, for-profit businesses, pharmaceuticals are not obligated to enter any market that does not align with their aims. Yet, many pharmaceuticals are conducting clinical trials for innovative targeted cancer treatments in middle-income countries, introducing costly diagnostic tools, training clinical staff, and bringing potentially breakthrough medicines to patients that would not have access. For example, investments in precision medicine clinical trials treat non-small cell lung cancer with anaplastic lymphoma kinase (ALK) inhibitors. In speaking with a pharmaceutical executive, they explained the trial site investments they had to make to conduct the study. Then, once the drug was approved, they decided to expand their health system support further and pay for all biomarker tests because otherwise, no patient would receive ALK inhibitor treatments. While the pharmaceuticals' contribution does benefit their end aim of selling their treatments, pharmaceuticals are also making investments in health systems. It is not altruistic, but it is a benefit and an improvement in cancer care.

Imagine the potential benefit with more effective societal leverage for LMICs. Today, the indirect investments made in global healthcare systems from clinical trials are typically not tracked and rarely reported. However, follow-up studies on clinical trial infrastructure in Sub-Saharan Africa have captured data that demonstrate resource capacity creation, increased clinical knowledge, improved data collection, and provisioning of medical products, financing, and leadership skills (Asante et al., 2016). As compared to traditional claims around the value of horizontal and vertical approaches to capacity building in LMICs, with examples from Benton with HIV exceptionalism, the opportunity presented through clinical trials allows for funds to improve end-to-end Alzheimer's treatment and patient care while also elevating the overall

clinical practice (Benton, 2015). If governments, regulators, and policymakers saw the opportunity for increased, focused investment on driving health system strengthening through clinical trials, not at the detriment of pharmaceutical companies and CROs, but as a chance for a "win-win" and effective partnership, there is an incredible opportunity to bring patients the care they so desperately desire.

Through the work of Denburg, Rodriguez-Galindo, and Joffe, they validate the need to further explore the potential benefits of clinical trials as a mechanism for health system strengthening in low- and middle-income countries (Denburg et al., 2016). They, too, confirm that there is little data collected to support the claims of health system improvements and argue for a new perspective on clinical research. "Trial programs might come to be viewed not just as strategies for [the] development of new knowledge but also as mechanisms for evidence-based translation of existing knowledge into action" (Denburg et al., 2016). There are a critical need and opportunity for clinical trials to expand their value, showing not only drug efficacy but "the translation of existing knowledge into action" (Denburg et al., 2016). Beyond therapeutic exploration, clinical trials have the potential to bring existing, optimized, or better-tailored models of care into use in LMICs.

Could clinical trials include comprehensive strategies to deliver care and enable better use of proposed treatment? Denburg, Rodriguez-Galindo, and Joffee believe that they can. "Furthermore, by generating research evidence tailored to LMIC contexts, such research programs could mitigate the pitfalls of unexamined transfer of HIC treatment protocols to LMIC settings" (Denburg et al., 2016). As new therapies come to market, healthcare communities need to know how to incorporate them. What value is there in a drug treatment that requires essential infrastructure, just like the biomarkers and the ALK inhibitors for non-small lung cancer, if

healthcare systems cannot provide the necessary clinical support in conjunction with the treatment? Clinical trials can provide some of the required infrastructure and a roadmap to expand necessary diagnostic capabilities. While it is not the responsibility or aim of a pharmaceutical company to provide comprehensive care delivery, pharmaceuticals' investments can aid access and care to modern treatments.

Nevertheless, with any experimentation, there is always the risk of direct and indirect harm. History clearly shows that clinical research has not always respected personhood and bioethics, with flagrant crimes and well-known tragedies as depicted at the 1948 Nuremberg Trials and the Tuskegee syphilis experiments. While great strides in patient safety and oversight have been put in place to avoid such tragedies again, not all bioethical offenses are as vibrant and clear. There are parallel opportunities for harm or loss for all the identified areas of benefit from clinical research. With the increased medical knowledge and staff training, there is the likelihood of "brain drain" and the migration of trained clinical staff LMIC to high-income countries (HICs). There is the risk of an "empty choice" for patients who need consistent access to treatment or quality care that can only come through a clinical trial (Kingori, 2015). Indirect harm from clinical research can be as simple as yet another task on a clinician's "to-do" list, distracting the limited healthcare resources in LMICs from required patient care. While clinical trials offer advances, they also offer drawbacks. What is non-negotiable is that patient safety, choice, and equality should be protected at all times.

Yet, this jeopardizes the desperately needed therapeutics and innovation to treat the world's diseases by over-indexing on risk. The fallout from the Indian Ministry of Health and Family Welfare's strict regulatory stance has dropped the country's participation percentage in global clinical trials from 1.5% as of February 2017 to 1.2% as of February 2019 (Sharma,

2019). In their regulatory revisions, the Indian Ministry of Health adopted amendments that hold trial sponsors responsible for injuries regardless of fault (Barnes et al., 2018). Beyond potential accountability inaccuracies, the Ministry of Health ignores that the purpose of conducting clinical trials is, in part, to determine the efficacy and safety of the investigational treatment and side effects are possible (Barnes et al., 2018). With the pendulum on the side of allowing for little risk in the process of drug testing – something that certainly started as a protective measure for vulnerable populations – it is not surprising that pharmaceuticals and CROs would choose another country to collaborate with.

Such a stringent stance also has economic consequences. Barnes et al. highlight in their assessment of the rapidly changing clinical trial regulatory landscape in India that:

> "It is difficult to avoid the conclusion that some of the harsher regulatory reforms harmed the clinical enterprise throughout India, resulting in fewer trials of new, experimental therapeutic products and shutting off the availability of experimental products to persons in India, who would have accessed them through a clinical trial. Declining pharmaceutical investment in India would be regrettable in light of India's enormous potential as a location for clinical trials and, more importantly, because it would hinder the Indian population's access to novel, innovative investigational therapies that may meet unmet medical needs. Promoting and bolstering clinical trials activity in India would also be a boon to the Indian economy, spurring many jobs such as those in research, clinical data management, biostatistics, and I.T. services" (Barnes et al., 2018).

Since the initial amendment in 2013, India is continually refining its regulatory pathways and requirements for pharmaceuticals, medical devices, and CROs. The country continues to explore how best to balance the welcomed innovation that clinical trials offer and their people's safety.

As of 2018, the Draft Rules still do not clarify the initial amendment's most critical points, and clinical trial investments continue to wane (Barnes et al., 2018).

Finally, one component often overlooked in clinical trials' contentious evaluation is the healthcare ecosystem's interpersonal dynamics. As Farmer stated, many corporations desire more conscientious capitalism and support the global health movement (Mullan, 2007). However, pharmaceuticals and CROs are rarely considered partners in the global health landscape, and they are frequently villainized. It is not without merit that such stigma is assigned, as noted above, with the bioethical challenges of clinical research; however, there is a clear risk of limiting access to much-needed therapeutics and R&D innovation to treat global disease when one partner in the healthcare ecosystem is dismissed or underappreciated. In speaking with a former pharmaceutical executive, they said, "Pharmaceuticals companies are human, and they function like any other relationship. If you do something nice and your partner's response is 'why didn't you do more?', the lack of appreciation is a disincentive. Why try if you can never win?" Healthcare is about partnership and finding sustainable solutions that lead to equitable, enduring patient care. While not all healthcare ecosystem players have the same roles or objectives, it is critical to find ways of working that are beneficial to all, which is the foundation for long-lasting health system strengthening.

Clinical trials are the foundation of therapeutic R&D, enabling new treatments to reach patients in need worldwide. However, remembering that pharmaceuticals and CROs are businesses with particular interests is critical in understanding their behavior, motivating change, and building win-win partnerships. Certain clinical areas, like non-communicable diseases, mental health, and dementia, are rarely funded by the ministries of health of LMICs. They lack the financial and resource capacity to invest in these critical areas of patient care. The presence

of pharmaceutical companies and CROs in this space is an opportunity to expand medical care in these areas and build local infrastructure and capacity that can go far beyond a clinical trial. This leaves us with an important question: What partnership model with industry sponsors on clinical trials will create more value to patients and strengthen healthcare communities in LMICs?

Part 2: A Qualitative Study of Collaborative Relationships Enabling Pharmaceutical Clinical Trials for Alzheimer's Disease in Low- and Middle-Income Countries

Abstract

Background: With no cure or disease-modifying treatment for Alzheimer's Disease (A.D.) and high-profile drug failures in recent clinical trials, there remains a global commitment to advancing dementia research and therapeutic innovation. As new clinical trials and research collaborations form, there is limited understanding of the factors that create or hinder equitable relationships between stakeholders that enable pharmaceutical-sponsored A.D. clinical trials.

Methods: We conducted a qualitative study using emergence-driven sampling with 19 participants completing 1:1 semi-structured interviews through video conferencing during the COVID-19 pandemic. Study participants represented four key stakeholders in the A.D. research and clinical trials ecosystem: 1) for-profit industry executives, 2) researchers or key opinion leaders, 3) government or regulatory leaders, 4) members of non-profit organizations and patient advocacy groups. Each interview examined the evaluation process and criteria when selecting and comparing potential clinical trial sites, resource and stakeholder identification for A.D. clinical trials, the formation of collaborative relationships to enable A.D. clinical trials, and multi-stakeholder relationship development and maintenance of collaborations. The research team completed an inductive analysis to identify cross-cutting patterns and themes that described the key factors that enable pharmaceutical-sponsored A.D. clinical trials.

Results: In examining the collaborative practices that enable global clinical research for A.D., participants elevated perspectives related to professional limitations in their work, which they

described as operational barriers, claims about capability, and limited commercial opportunities. Participants also presented perspectives related to interpersonal behaviors related to fragile trust and creating and maintaining exclusivity. Taken together, these factors explain the lack of investment in LMICs for A.D. clinical trials and point to the inequalities present in this area of clinical research.

Conclusion: It is important to rectify the inequalities presented in our research by managing the influential role of pharmaceutical companies and their commercial drivers as new research and clinical trial alliances are formed and passed on. A conscious and deliberate effort is required to create more equitable partnerships in A.D. clinical trials as the global demand for research expands.

Keywords
Alzheimer's disease, Dementia, Clinical Trials, Low-and Middle-Income Countries, Collaboration Models, Pharmaceutical Companies, Researchers

Introduction

The World Health Organization (WHO) estimates that around 50 million people worldwide have dementia, with 60% of the patient population living in low- and middle-income countries (LMICs) (World Health Organization, 2018). They project the worldwide prevalence to reach 82 million by 2030 and 152 million by 2050 (ibid, 2018). The WHO findings estimate that 60% of all dementia cases are Alzheimer's disease (A.D.) (2018). Over the next 20 years, Alzheimer's Disease International predicts a 77% increase in the southern Latin American cone (e.g., Argentina and Chile) and 489% increase in the developed Asia Pacific countries. These figures compare with projected 117% growth in East Asia, 107% increase in South Asia, 134 to 146% increase in the rest of Latin America, and 125% in North Africa and the Middle East. (ADI/Bupa report, 2013).

Clinical trials are underway to combat this disease, and as of 2020, clinicaltrials.gov tracked 121 unique dementia therapeutics in development; however, 30% of Phase 3 and 61% of Phase 2 trials include sites only in North America (Cummings et al., 2020). The exclusion of LMICs is notable in light of the increasing prevalence of A.D. in those regions, and researchers have specifically identified a significant lack of clinical trial research in Latin America and Africa (Prince et al., 2009).

With no cure or disease-modifying treatment for A.D. and recent high-profile drug failures in clinical research, there remains a continued commitment to dementia research and therapeutic innovation. With the formation of collaborations like the 10/66 dementia research group, Global Alzheimer's Platform (GAP), European Prevention of Alzheimer's Dementia Consortium (EPAD), the Dementia Discovery Fund, and the Davos Alzheimer's Collaborative (DAC), new working groups continue to sponsor more research. Yet, even with multi-

stakeholder engagement and participation in support of clinical trial research, 61% of Phase 3 trials are sponsored by biopharmaceutical companies, positioning their commercial priorities at the forefront of A.D. research (Cummings et al., 2020).

What remains unclear are the factors that create or hinder collaborative relationships between stakeholders that enable pharmaceutical-sponsored A.D. clinical trials. Beyond feasibility studies and site selection protocols commonly conducted by pharmaceutical companies or contract research organizations (CROs) in preparation for a clinical trial, there is little research on the priorities of the different stakeholders supporting the launch of a pharmaceutical-sponsored A.D. drug trial. Noting the continuation and expansion of Alzheimer's disease clinical trials and the projected patient demand in the coming decades, we conducted a qualitative study of four different stakeholder groups within the A.D. clinical trials community to understand their approach to collaboration and factors that enhance or reduce their value. We conducted an emergence-driven qualitative study of 19 global leaders in A.D. clinical trials to address these questions.

Methods

Study Design and Setting

This qualitative study used emergence-driven sampling to select information-rich participants for individual interviews intentionally. Data was collected between May 2020 through October 2020 from 19 participants. The study was completed remotely via video conference call due to COVID-19 travel limitations.

Approach to Sampling

This study used all 19 participants selected from emergence-driven sampling to build the participant sample (Patton, 2015). The research team introduced participants to the study based on contacts or leads; this network effect is critical. This study depends on identifying participants primarily through peer validation and industry/market awareness of expertise. The first author identified the initial study participants through her professional network. After concluding 1:1 semi-structured interviews with qualified participants, the first author sought recommendations for additional prospective participants for the study to enable further emergence-driven sampling. Based on the participant's guidance, the first author approached prospective participants about their interest in the study. Sampling continued until the research team recognized that participants were making similar comments, no new themes emerged, and there was a robust understanding of all themes.

Study Participants

All study participants (see Table 1) were required to be active in Alzheimer's disease research, as defined as participants that are, currently or within the past two years, responsible for enabling a particular aspect of Alzheimer's disease clinical trials, ranging from clinical trial design to patient recruitment to regulatory approvals, etc. Additionally, all participants had exposure to supporting Alzheimer's disease clinical trials in low- and middle-income countries (LMICs). Participants had at least one example of an Alzheimer's disease clinical trial that they supported in LMICs in the past five years. Study participants reflected four key stakeholders in the dementia research and clinical trials ecosystem: 1) for-profit industry executives (e.g., pharmaceutical companies, biotech, contract research organizations) 2) researchers or key opinion leaders (KOLs) 3) government or regulatory leaders 4) members of non-profit

organizations and patient and advocacy group. As this is a global field with global roles, many participants work and live in multiple locations. It was important for our participant data collection to capture the countries they professionally engage with (see Table 1).

Data Collection

Data was collected through individual qualitative interviews that leveraged a semi-structured interview guide. Each participant group had a different semi-structured interview guide to reflect the nature of their work in enabling sponsored Alzheimer's disease clinical trials research. However, every interview guide included the following core topics: 1) evaluation process and criteria when selecting and comparing potential clinical trials and related sites 2) resource and stakeholder identification for Alzheimer's disease clinical trials 3) the formation of collaborative relationships to enable Alzheimer's disease clinical trials 4) multi-stakeholder relationship development and maintenance of collaborations.

The goal of the 1:1 interviews was to elicit data on the individual experiences of the various stakeholders across the global Alzheimer's disease research community that enable clinical trials. Each participant was interviewed once between May 2020 and October 2020, and all interviews were conducted virtually via video conference, allowing participants to select a location that reflected their privacy needs. Only audio was recorded from the meeting for transcription purposes. The first author conducted the interviews in English, with one exception when a translator was requested, and each interview lasted approximately 45 minutes. After completing each interview, interview recordings were transcribed verbatim, including interviewer questions and participant responses.

The research met the exemption criteria under regulations established by the Harvard Faculty of Medicine and the Office of Regulatory Affairs and Research Compliance in April

2020. The Harvard Medical School Department of Global Health and Social Medicine faculty provided oversight of the research. Written, informed, and verbal consent was obtained from all participants.

Data analysis

The research team used inductive analysis and a grounded theory approach for the study's data analysis to identify possible categories, themes, and patterns around the relationships and collaboration models that enable Alzheimer's disease clinical trials (Corbin, 2008). Following a complete review of A.H.'s data, a subset of the data was open coded by A.H., examining and naming key themes tied to the observed phenomena. Another member of the research term, H.G., reviewed the codes and discussed discrepancies before drafting the codebook. Building on the open coding exercise, a codebook was drafted by A.H., reviewed and revised by H.G., and approved for application to the data. The codebook was hosted in the qualitative analytics tool, Dedoose, to tag data points, organize the codes to the related participant interviews and quotations, and iterate and develop categories. The research team used an inductive analysis to produce cross-cutting patterns and themes to elevate new findings from participant interviews and data coding. A.H. conducted weekly reviews of the data with H.G. on the iterative coding and categorization exercises. Synthesis drove the interpretation, helping generate significance and hypotheses about the data and behaviors observed with continued reviews involving all of the research team (A.H., H.G., S.K., L.H.) until finalized.

Results

Study Participants

Study participants from the for-profit sector and researchers and KOLs had an equal number of participants (7), whereas regulatory and non-profit representation was limited to 5%

and 21%, respectively. Each group had representation from LMICs, and more than half of the participants were female. Due to this work's international nature, study participants are stationed around the world and work across multiple geographies. Their present location does not necessarily reflect the geography they work in (see Table 1).

Table 1: Summary of Participant Descriptors

Participant Count (19)	Group 1 – *For-profit industry*	7
	Group 2 – *Researchers, KOL*	7
	Group 3 – *Regulatory or government*	1
	Group 4 – *Non-profit, multi-lateral*	4
Gender	● Male: 7 ● Female: 12	
Current Country Location of Participants	● Argentina ● China ● Cuba ● India ● Mexico ● Japan ● Kenya ● UK ● USA	
Countries Referenced in Data Collection	● Argentina ● Brazil ● Canada ● Chile ● China ● Cuba ● Dominican Republic ● Germany ● Hungary ● India ● Indonesia ● Mexico ● Japan ● Kenya ● Russia ● Sri Lanka ● Sweden ● Taiwan ● Thailand ● Uruguay ● UK ● USA	

Descriptive Categories

In examining the global Alzheimer's disease clinical research community's collaborative experiences, key themes emerged related to professional limitations described as operational barriers, culturalist claims about capability, and limited commercial opportunities. Participant dialogues also highlighted interpersonal behaviors through themes related to fragile trust and creating and maintaining exclusivity.

Operational Barriers

Participants across multiple disciplines frequently acknowledged that LMICs are not given an equal opportunity to participate in Alzheimer's disease clinical trials compared to their peers in the global north. Some participants reported tangible limitations like limited infrastructure, regulatory barriers, or resource or skillset deficits as the primary drivers for exclusion. Pharmaceutical company leaders and CROs positioned these limitations as addressable but a problem for other stakeholders like the ministry of health, other levels of government, or researchers in the dementia community to resolve with the LMICs.

> *"And I think it's biased, because of this lack of an infrastructure in places and this feeling like, if we go there, we'll lose money and we won't be able to do [a clinical trial] as efficiently if we do [a clinical trial] here in a higher income country, where we can get the work done." – Global Pharmaceutical, Participant 16*

> *"One is the complexity of the Alzheimer's disease and the level of resources that the disease required to do a clinical trial, like having neuroimaging, having CSF studies, having all that kind of stuff. So, my general perception is that it, I mean, when you have like a different part, where you could take it to the country, to a lower middle income, test the product, and get results, we're willing to do it because you are saving costs. But if you have to invest in that country, to create the resources and do the clinical trial, then you see that companies tend to be more like, let's hold off and think a different way." P.I./Researcher, Participant 3*

Culturalist Claims About Capability

Study participants from pharmaceutical companies made arguments around limited research capabilities in LMICs as a primary factor for their infrequent selection of LMICs for Alzheimer's disease clinical trials. However, culturalist influences were also presented as participants stated their concerns about local cultures based on geography, limited awareness of research capabilities in LMICs, and the inconvenience of collaborating with LMICs as contributing factors. Participants shared how these factors unfairly paint willing contributors to A.D. research, and the culturalist influences weaken the primary claim of limited research capabilities in LMICs. The culturalist undercurrent reveals the decision-making within pharmaceutical companies and CROs as they determine where to invest their resources for an Alzheimer's disease clinical trial. Industry participants had fewer actionable ideas on how to address these cultural perceptions.

> *"If you mentioned that you did a study in Eastern Europe [referring to therapeutic area experts], automatically, their eyes will roll, or if you say that China is going to be involved, 'Oh well, China, they're going to pull the study results down.' And there's this automatic insinuation that I think, particularly for Russia, Eastern Europe, China, there's this sort of intellectual snobbery that actually I really don't think is fair." Global Pharmaceutical, Participant 5*

> *"There are not any clinical trials sites that have been either invested in or risen out of the organic infrastructure and pick a country Mexico, Kenya, Namibia. Kazakhstan, they just don't exist, or because I am intellectually honest, there is an uninformed prejudice against some countries. Because if you talk to [person], for example, and look at international data, Poland, Russia, Istanbul, I mean, Turkey, Egypt are all countries that appear to have really good researchers, but big pharma, at least in neurology…and the way they were trained, shy away from those countries because they have a, I think, perhaps uninformed view of their ability to perform trials well." Non-profit, Participant 10*

Alternatively, research participants from LMICs expressed frustration at the for-profit industry perception that they could not deliver high-quality work for a clinical trial. They shared

how they believed their talent, ways of working, and research sites possessed the equivalent value as those found in the global north.

> *"I'm from Latin America. I recognize that our country is a developing country, but we work in the same kind of, in the same level. We like to work in the same level of other a part of the world. We are very strict with the work we have; for example, for Alzheimer's disease, we perform care, we have a PET scan, we perform a lumbar puncture." Clinical Researcher, Participant 6*

Limited Commercial Activity

As commercialization is a key driver of pharmaceutical-sponsored research and clinical trial activity, participants reported speed to market, regulatory approval, prospective sales, and marketing as influences on dementia clinical trials. Sponsors will make exceptions to include or exclude countries and related markets in clinical trials as a part of their planning for future sales.

> *"Finally, it comes down to dollars and cents, unfortunately. And so, for some of the bigger markets like China, right, it is a huge market for commercialization. So, regardless of what regulatory barriers they are, what healthcare system barriers that are, pharma companies want to go in there because if not, they will lose on, you know, $10 billion markets as an example, right." CRO, Participant 4*

Participants shared that LMICs are not as profitable as countries in the global north. They cannot compete to satisfy pharmaceutical companies' commercial drivers as dementia often lacks government funding and prioritization within the health concerns of LMICs. With limited potential for sales revenue, pharmaceutical participants reported that LMICs have fewer opportunities to participate in dementia clinical trials since pharmaceutical companies aim to conduct research in countries where the data generated can be leveraged for regulatory purposes as they aim to sell their prospective new therapeutic. Participants cited limited engagement with LMICs, including the participation of KOLs and leadership, patient recruitment, and use of their clinical trial sites, further stressing that dementia clinical trials do not reflect the needs of the global patient population they aim to serve.

"But I think I sort of, you know, I've had a discussion with one pharma company where I was sort of saying, 'Yeah, are you thinking about trialing this thing in low-and middle-income countries?' They were like, 'Well, that's not really our market,' because they don't see that they're going to be able to sell anything." Global Pharmaceutical, Participant 16

"In Kenya, still, we are [at] the initial stages of understanding what dementia really is…Now on clinical trials, we've never had an opportunity to participate in any clinical trial in Kenya….I think it is a good thing to put them on the clinical trials so that we can understand does it make a difference and what changes we will notice with these people. So, with the clinical trials, we've not had an opportunity to be part of any of the clinical trials." Non-profit, Participant 7

A Fragile Trust

All participants highlighted that developing working relationships for Alzheimer's disease clinical trials is complex, with multiple stakeholders having overlapping, competing, or misaligned interests, but no clinical trial can happen without partnerships and collaboration. Participants positioned that the foundation for effective partnerships begins with finding mutual interests or a shared value proposition - an awareness that "we want the same things" from a dementia clinical trial. Participants cited win-win examples of basic or early-stage research by KOLs or P.I.s contributing to pharmaceutical companies' awareness and regulatory alignment between researchers, advocacy, and private sector parties.

"And the [pharmaceutical] company said, 'As well as clearly wanting our funding, what else can we bring to the table for you?' And so, they tend to ask what you want of them. They clearly come because they're really interested in the [dementia research] project. And absolutely always, they see the benefits of entering into a partnership because of what you have. So, they already know in their mind how they would want to use what you are trying to develop. Otherwise, they probably won't come to the table. I mean, everybody has a little bit of a philanthropic aspect to them, but they won't tend to come to the table with in-kind support and funding if they're not interested in what you've got. So, if you can interest them in what you're trying to develop and you can tell them how this will benefit them. Then they tend to be a lot more willing to partner." Non-Profit, Participant 2

However, participants also reported heavy skepticism regarding their clinical trial partners, particularly in the relationships between for-profit and public organizations. Seeds of distrust are planted by one or both parties when there is inconsistency in their communication, interim data, and outcomes or when individual benefit limits the broader shared interest, like conflicts around intellectual property, funding, or publication. Participants reported continuing with the collaboration, but they expressed having a heightened and lingering distrust of their colleagues.

> *"I left [a multi-lateral program]. And I worked for one year with them, and we never managed to come to an agreement on these clear terms, you know, for the contracts, because it's not possible because every sponsor has their own language, and every academic institution has their own language. And so, bringing up five sponsors to align, plus five academics and big institutions to align, when it is governmental institutions like this or huge companies, it was not very easy, but we discussed it, and perhaps I think it was still beneficial because everybody got more aware of the pain, and especially the academics." Global Pharmaceutical, Participant 1*

Creating and Maintaining Exclusivity

With the high cost and increasing complexity of executing global clinical trials for potential dementia therapeutics, pharmaceutical companies, as the primary sponsor and funder for this work, are responsible for creating a comprehensive study that generates the required data for their drug considered for regulatory approval. Pharmaceutical participants highlighted that, because of the amount of financial and scientific risk involved with dementia clinical trials, pharmaceutical companies will often work with established partners, including former colleagues and their referral networks, or working at clinical trial sites in nearby countries with similar cultural norms and language.

> *"It's really interesting, actually. I don't know. I wonder if you look at just the closest to you. I wonder if you look at the closest to you and the people that you tend to work with a lot. And so certainly from my experience in pharma, EEA European countries are the next ones you work with them, you tend to collaborate a lot." Non-Profit, Participant 2*

This tendency was also acknowledged across other participant groups. Research participants highlighted that pharmaceutical companies repeatedly use the same academic partners and their associated resources for their dementia clinical trials. For-profit participants named the same CROs for dementia clinical trials. Participants also mentioned that these same parties and their associates attend the same series of conferences, join dementia-related working groups, and form strategic projects, which often do not have representation from LMICs. Together, these like-minded leaders validate one another, forming an exclusive but informal "club," which limits their collaboration network, reinforces their ways of working and perspectives, and builds greater comfort and familiarity.

> *"I think it's a club. It is a club. You're in the club, you're fine, and you publish in some circles. And all you have to do is open Alzheimer's and dementia [journals]; it's the same names. I go to JPAD, the journal of, I don't know what… one of those journals, it's the same honest, the whole issue with the same names, the entire issue… I don't know how other fields work. I've only since I started working in XXXXXXX, I've always worked in the field, but they have the impression that it's been, so you had to align to succeed in a way, but then even to get funded. You see, it's almost like you need to add some names if you want to get funded." Researcher, Participant 14*

Through these conscious and subconscious behaviors, "the club" creates a legacy that ensures their ways of working continue through their labs, colleagues, and protégés in future clinical trials. Newcomers to the dementia research community from LMICs may attempt to participate in upcoming clinical trials. However, they do not have equal footing and the opportunity to engage in trials in a meaningful way like their well-connected peers.

> *"XXXXX is organized every year, two research roundtables and in the research roundtable, you have the public, you have the sponsors, you have the academics, you have the non-profit organizations, and you have FDA, and perhaps a representative from ENA. And so, I think it's a very, very useful meeting because you really tackle all the scientific issues in a small group, from every company, you are allowed only to have four people, from every sponsor company. So, it's a very small thing with like, say 60 people*

and 50 to 60 people, so you are in a room, and you can really communicate with people." Global Pharmaceutical, Participant 1

Discussion

Based on the data from our study, there are various operational, social, financial, and professional limitations that, together, result in excluding low- and middle-income countries (LMICs) from Alzheimer's disease clinical trials. Missing infrastructure, limited clinical research training, and a lack of funding are examples of major operational barriers that limit LMICs from participating in Alzheimer's disease clinical trials and fulfilling study requirements. Biases compound these limitations against LMICs, rooted in exclusivity, misperceptions around trust, and a limited understanding of a prospective LMIC partner's capabilities. But ultimately, if there is a limited market opportunity in LMICs, the commercial drivers that heavily influence Alzheimer's disease clinical trials will direct the research to countries with greater financial resources and, ultimately, greater capacity to purchase the "pharmaceutical asset" after successful trials. The limitations found in this research are only a sampling of the many influences that contribute to the fixed and recurrent behaviors that keep Alzheimer's disease clinical trials focused on the global north.

Through this work, it was noted that a highly selective and trusted network of individuals and organizations, functioning as an axis of power, is at the core of enabling Alzheimer's disease clinical trials. This network is insular and self-protected with established participants and their protégés, reinforcing existing relationships and connecting to those within the established inner circle (Braun, 2018). Through these networking behaviors, trust is inherited as colleagues within the network connect and reconnect based on prior positive collaborations as a means of reducing uncertainty and risk (Plotnikova & Rake, 2014). There are known venues and conferences for

engagement, primarily hosted in countries located in the global north, where the relevance and importance of clinical investigators and research sites are reconfirmed (Petryna, 2009). The network continually moves inward, further curating participants to ultimately establish which individuals matter within the dementia research community and which do not, empowering the views, ways of working, and needs of the select few.

The governance of this network is managed by the pharmaceutical companies that sponsor Alzheimer's disease clinical trials. As pharmaceutical companies have the greatest ease of access to significant funding, their money allocation enables the execution of Alzheimer's disease clinical trials (Petryna, 2009). The ecosystem that participates in dementia clinical trials feeds off this primary resource, curating their activities, perspectives, and results to satisfy the pharmaceutical sponsor (Lundh et al., 2017). The motivation to satisfy the pharmaceutical companies' priorities limits the quality and access to care that clinical trials and innovative therapeutics could and should provide to communities and individuals who participate in the trials (Healy, 2012). Researchers and health communities in LMICs are excluded as they cannot deliver the transactions pharmaceutical companies require to get their drug to market.

Pharmaceutical sponsors enable the manufacturing and delivery of therapeutics through their supply chain and marketing capabilities; they orchestrate the ultimate endpoint, providing an approved treatment to a patient. This results in their chosen role as manager, orchestrating the various stakeholders or "gatekeepers" in and out of their direct control to achieve their endpoint. Our data demonstrates, building on the work of Applbaum, how pharmaceutical companies align stakeholders with united goals, pulling disparate views together to create a perceived collaboration and consensus that ultimately converts gatekeepers to compliant facilitators (Applbaum, 2009). Following Applbaum, in the Alzheimer's disease research community, the

curation of clinical trial researchers by pharmaceutical companies shortens the conversion of this set of gatekeepers as they have prior relationships and familiarity that can be leveraged to streamline decision making within the trial design and implementation. Again, the insular network is the key to enabling faster alignment and consensus, reducing the time to conduct a clinical trial and moving towards key decision points that enable the maker of an Alzheimer's disease therapeutic to seek regulatory approval to go to market.

In this managerial role, pharmaceutical companies also select which individuals or organizations qualify as gatekeepers. To align with their commercial endpoint, pharmaceutical companies partner with leading researchers who can also influence prescribers and "seed" clinical trials in the interest of future sales (Kessler et al., 1994). With the priority of market access and sales, our data validate that LMICs are not viewed as lucrative partners or gatekeepers that warrant pharmaceutical companies' attention and respect. Furthermore, market access is limited for a new drug with LMICs, but reoccurring sales are also limited. Pharmaceutical companies seek markets that will perpetually need their drugs; pharmaceutical therapeutics, supported by market access and sales teams, aims to treat illness and disease and perpetuate the continued management and treatment of health risks (Dumit, 2012; Greene, 2006). Many LMICs do not currently reflect this expectation nor the market for ongoing treatment compared to the global north.

Taken together, the data highlights powerful forces at work in the selection of clinical trial sites, trial participants, and beneficiaries. By revealing how the dementia community and the selected network of participants come together, this data highlights how pharmaceutical companies, as the primary influencer, align global research participants to support their single-minded objective for the community to achieve - the pursuit of a financial return. Profitability is

essential to continue to fund and advance R&D within the selected network that leads the global dementia community. It is a shared burden and shared benefit for the selected network to pursue. With limited funding and the continued challenges of therapeutic failure, there is limited willingness to expand the network to new, unproven clinical trial partners in LMICs.

This research has a few notable limitations. First, emergence-driven sampling enabled access into the Alzheimer's disease research and clinical trials community, but the network effect that built our sample population also skewed the participating sample. Nevertheless, this sampling method is participant-directed and reflects their professional connections, which delivers on this work's aims. Second, the study sample size lacks country representation in examining Alzheimer's disease clinical trials globally. This hinders equitable and nuanced representation, as the diversity of healthcare challenges and Alzheimer's disease clinical trials are unique and local.

Additionally, all interviews were conducted in English - a second language for many participants. The nuance of explaining relationship developments could have been limited due to language. Finally, the first author is an active member of the global Alzheimer's disease research community, and to apply an emergence-driven sampling method, and her network was used to identify the initial participants in the study, skewing the participant sample. However, without leveraging her network, assess to this study population would not have been possible.

Conclusion

Our research captures the ingrained beliefs, attitudes, and actions of the key stakeholders that enable Alzheimer's disease clinical trials to function in a transactional manner. We demonstrate the prominent influence of the pharmaceutical industry's near-term commercial

goals as a force within the dementia community and a limitation to viewing trials as a form of social good and engagement with communities. Our findings highlight the exclusive, insular network that streamlines Alzheimer's disease clinical trials and limits opportunities for new ways of working and for participation from LMICs. In recognition of these current behaviors, it is important to rectify the inequalities in A.D. collaboration models by managing pharmaceutical companies' influential role, and their commercial drivers as new research and clinical trial alliances are formed and passed on. A conscious and deliberate effort is required to create more equitable partnerships in Alzheimer's disease clinical trials as the global demand for research expands.

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