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PROMOTING NOVEL DRUG INNOVATION WHILE PROTECTING THE WELFARE OF CLINICAL TRIAL SUBJECTS

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ABSTRACT
The clinical trials are an important characteristic of the new drug discovery and development process since required to show that new medications are safe and effective in humans. The numerous agendas of the many parties leave the possibility for numerous conflicts of interest inside the process. It is not unexpected to find allegations of and confirmed incidents of ethical infractions connected to clinical study conduct in the news. The previous literature on the protection of human participants in clinical trials focuses on the consequences of ethical violations, then moves on to specific methods, such as informed consent or monitoring, to prevent such violations from happening again.

KEYWORDS: Ethical Conduct, Game Theory, Systemic Uncertainty, Endogenous Uncertainty, Clinical Trial.

1. INTRODUCTION

Medicines play a critical role in promoting health and well-being. A medicine, on an individual level, either helps to avoid certain illnesses or serves as a treatment to alleviate the suffering of those who are afflicted with specific illnesses. Individual's sickness prevention and treatment indications wider population of healthy people, who can later become more productive members of society. Countries with more access to medicines that are in high demand locally may profit economically from a more productive populace.[1] Pharma companies must pursue approval from each country's government to market their drugs within the country; hence access to medicines is normally gained at the country level. This approval process begins in the preclinical stages of drug research and continues until the medicine is ready. Clinical trials are an important aspect of the drug discovery and development process, and part of the process that exposes human subjects to the greatest dangers when new medications are tested. Any incident that could cause harm to the clinical trial subject is considered a risk. Thus, the dangers to which clinical trial subjects are exposed are not limited to the physical hazards of being exposed to experimental items; there are also a variety of social, economic, and psychological costs that clinical trial volunteers may be forced to undergo.[2] Governments frequently face the exertion of ensuring that human subjects in clinical trials are sufficiently protected. In this context, the terms ethics and ethical conduct, as used in this review paper, refer only to the concepts specified as necessary for the protection of human participants of research in international recommendations for the protection of human subjects in clinical trials. The word ethical concern refers to concerns regarding insufficient protection of human participants in clinical trial studies, as used in this paper. As they relate to these concepts, this paper focuses on governance rules and tactics for optimizing subject protection while allowing clinical trials to take place.

The governance or the regulatory authorities of clinical trials operates at three different levels

(i) Several organizations set standards for the ethical conduct of clinical studies on a global scale. These include- a) the World Medical Association's Declaration of Helsinki, which establishes "ethical principles for medical research involving human persons and b) the International Conference on Harmonisation's (ICH) Good Clinical Practices standards, which "describes the necessities for conducting clinical research involving human, duties and expectations of all participants in the conduct of clinical trials and the Council for International Organizations of Medical Sciences (CIOMS) publications, which provide recent conversations on the ethics of human subjects research.[3]

(ii)At least 113 countries have endorsed some arrangement of laws, regulations, and guidelines governing human subject research on a national level.
(iii)Each pharmaceutical, contract research organization (CRO), and ethical committee (EC) functions under a set of policies, procedures, and/or guidelines at the institutional level.[4]

Despite this multi-level approach to clinical trial administration, the current system of clinical trial governance has flaws, as evidenced by instances of ethical infractions that have happened around the world. For decades, traditional clinical trial markets such as North America and Western Europe have faced ethical difficulties related to clinical study conduct. Though the development of supervisory procedures in these markets has helped to reduce ethical infractions, they nevertheless happen.[5,6,7,8] These are some examples of violations: In the 1940s, convicts at the Stateville Penitentiary in Illinois "were infected with malaria and treated with experimental medications that often had nasty adverse effects," according to a US military-sponsored research operation. ii) A UK government-approved phase 1 clinical trial undertaken by which was found to lack scientific integrity, improperly qualified physician investigators, and failed to arrange for timely medical treatment of the volunteers and iii) In India, in 2009-2010, research involving the delivery of the human papillomavirus (HPV) vaccine to 2,300 girls from "poor and disadvantaged social groups" was carried out without acceptable scientific reason or informed permission.[9]

"Clinical trials are progressively occurring on a worldwide scale as corporate and government sponsors in wealthier countries relocate trials to less wealthy countries," adding to the intricacy of clinical trial regulation. Clinical trials have globalized in current years, with a focus on rising markets such as Asia, Latin America, and Eastern Europe.[10] Clinical trials are being introduced to these expanding countries at a much faster rate than local governments' abilities to establish and execute efficient oversight procedures. As a result, these markets have a larger chance of ethical infractions than traditional markets.[11,12] Human subjects in clinical trials face difficulties in emerging markets due to a number of factors, including a lack of a well-established regulatory oversight system, a lack of well-established and experienced ethical committees, and "differences in education, economic and social status, and health-care systems," all of which "put the rights of research participants in jeopardy."[13]

2. MATERIALS AND METHODS

The present study is, a unique mixture of two qualitative research methods: inductive reasoning and game theory. "Inductive reasoning is a type of reasoning in which the buildings are designed to provide strong suggestion for the conclusion's truth. It refers to reasoning that takes specific data and applies it to a broader generalization that is thought to be reasonable" Preston.[14]

"Game theory is a decision-making theory, Game theory is a paradigm for "... analyzing circumstances of interactive decision making" in "situations involving multiple decision-makers with varied aims, in which each decision has an impact on the outcome for all the decision-makers." Based on these definitions, this thesis assumes that the clinical trial process necessitates the participation of several actors in cooperative decision-making, which has an impact on each player's agenda. The government, the pharmaceutical business and the ethicist are the primary participants.

A conceptual framework to analyze clinical trial governance by combining specific information from literature and documentary review with notions from game theory relevant to interactive decision-making. The framework is based on basic game-theoretic notions to identify and characterize the types of uncertainties that these participants confront throughout clinical trial implementation.

Case studies of clinical trial regulatory oversight in the United States (US) and India, as well as industry player obligations and views, are then used to evaluate the paradigm. Existing US and Indian regulations are evaluated using the conceptual framework. The two regulatory monitoring systems are then subjected to empirical examinations. Using publicly available data from the US regulatory oversight system, the compliance of various participants with standards for human subject protection in clinical trials is analysed. The Indian regulatory supervision system is evaluated using information acquired through interviews with industry professionals. Industry players' responsibilities are evaluated using the same approach as the global framework guidelines for conducting ethical clinical studies. Furthermore, data acquired from interviews with industry representatives are used to assess industry actors' perceptions of their responsibilities for the protection of human subjects. All of this is then used to develop knowledge of each decision maker's potential policy and strategy outcomes, as well as their impact on the overall balance of innovation and welfare.

3. Development of a Framework

3.1 Game Theory

Game theory is the study of "conflict and cooperation between intelligent logical decision-makers"[15], and it's used by academics to "construct interdependent decision-making".[16] It uses arithmetic to simulate "how individuals interact and make decisions... on the idea that each person's action has an impact on the well-being of all other players in the game".[17]

3.2 Establishing the need for a framework

An integrated strategy is essential to understand the interdependencies among the multiple parties involved in

the clinical trial process, as well as to determine how best to build integrated strategies for social benefit. To do this, a framework for comprehending and evaluating clinical trial governance is needed, one that considers the interdependencies of the many decision-makers.

3.3 Sequential Game

According to the definition[18], a sequential game is one in which "only one player moves at a time and each player knows every action of the players who came before him at every moment." Participants in any sequential game with imperfect information face the difficulty of incomplete information. In a sequential game with asymmetric information, one or more players retain secret knowledge. "By private information, we mean knowledge about game settings that is only available to a select group of participants. It is not necessary for private information to be exact; probabilistic beliefs could be employed instead. When one or more players in a sequential game have access to confidential information, the game is said to be "sequential it is called an asymmetric game".[19]

3.4 The Players

Clinical trials are a crucial aspect of the drug development process, as indicated in the introduction to this thesis. A significant number of people are involved in the pharmaceutical development process. However, because this thesis focuses on clinical trials, the players in this section are limited to those who are active in the clinical trial process. As a result, players involved in early stages of drug development, such as animal testing and preclinical testing, as well as post-trial marketing and commercialization, are excluded. The government, the pharmaceutical business, the sponsor, and the contract research organization are all involved in the study process. The ethics commission (EC) or an institutional review board (IRB), civil society, and human subjects.

3.5 Systemic Uncertainty

A sequential game with systemic uncertainty is being developed because the rules of a sequential game are theoretically confined to the order of play and the reward structure of the game. In real-world circumstances, such as clinical trials, however, vague systemic criteria may decide the outcomes. When it comes to conflict resolution, for example, there may be no rules or multiple rules. As stated in the introduction to this thesis, the clinical trial procedure is governed at three levels: International recommendations, which have a high expectation of compliance but lack enforcement capacity; national regulations; and pharmaceutical firm, CRO, and ethics institutional norms and processes and ethics committee. There is systemic uncertainty as a result of the multiple layers of governance in a clinical investigation.

National and international regulatory agencies address the same problems in different ways. Differences in institutional policies and procedures could also exist. As a result, there may be a lack of or several rules, creating a decision issue. These are examples of "systemic uncertainty," as I call them. An example of systemic uncertainty in the clinical trial process is the lack of rules connected to concerns about treatment costs and harm compensation.

3.6 Endogenous Uncertainty

Due to defective or incomplete knowledge, one or more of the players is unclear about the past or future moves of any of the players and/or their characteristics (e.g. resources, beliefs, and objectives).

Endogenous uncertainty leads to two types of strategic issues, both of which have been studied in economics

1. "Player A confronts a moral hazard problem from player B if he is unsure about a past or future (unpreventable) move by player B that lowers his payoffs. To put it another way, player B has the ability to make a decision that is not visible or controllable to player A but has the potential to lower player A's payoffs. This is frequently referred to as the "hidden actions" issue.[20]
2. "If player B knows information that is unknown to player A but has the ability to influence the game outcomes of player A's strategy, player A faces an adverse selection dilemma from player B. The 'hidden information dilemma' is another name for it.[21]

3.7 Principal-Agent Model

Adverse selection, moral hazard, and corruption are three endogenous uncertainties that can emerge in the context of **'principal-agent** models. "In the principal-agent paradigm, the principal's compensation is contingent on the agent's action." Before the contract is implemented, the principal, on the other hand, has no notion what activities the agent would engage in. Nonetheless, the principal must make an incentive offer to the agent before the contract can be completed. Depending on the incentive offered, the agent decides whether or not to join the contract, and once signed, the agent evaluates which behaviours will maximize his or her reward. As a result, the principle must agree to an incentive before learning about the agent's actions, which will have a direct impact on the principle's return.[22] A conflict of interest arises when a principal hires an agent to perform specific duties that are in the best interest of the principle but may be costly or not in the best interest of the agent. A principal must establish an incentive system that motivates the agent to align its behaviour with the principal's objectives even after the contract has been completed. Due to information asymmetry, the principal is uninformed of the agent's intentions and skills to properly implement the contract.

3.8 Expert Interviews

To validate the concerns identified from documentary and literature analysis, we conducted semi-structured

interviews with representatives of the United States and Indian government; global pharmaceutical companies with a presence in India; contract research organizations with a presence in India; and Indian researchers and civil society.

Interview Methodology

This interview study involved the use of qualitative semi-structured interviews. The final number of interviews was determined as the study progressed, depending on when saturation was reached and no new challenges or barriers were identified. I concluded the study with a total of thirteen interviews. When interview studies are conducted to gain "content validity," as is the case in my work, "the suitable sample size is a function of the aim of the study and the complexity, range, and distribution of experiences or views of interest, rather to the statistical parameters used in quantitative research." They go on to use two studies to back up their claims. Interview 13 provided a new belief, while 14 interviews revealed saturation.

Given that the purpose of my interviews was to determine the strengths and limitations, as well as the problems, of clinical trial oversight in India at the time of the interviews, I set initial sample size of 13, with a pre-determined stopping criterion of three if any new ideas or thoughts emerged after the first 13 interviews. After the tenth interview, no new themes appeared, indicating that saturation had been attained at ten samples.

we invited a few US specialists to get a more objective internal and foreign viewpoint, as well as to check if there are any first perception disparities within and beyond India. However, the vast majority of the participants were from India. Among the 13 people interviewed were.

- 4 Indian government officials
- 3 Indian researchers, one of whom is also a member of Indian civil society, and the other two work for the Indian government 1 Indian ethics committee member
- 2 Indian civil society representative
- 4 representatives from the pharmaceutical business in India

3.9 Snowball sampling

The Snowball sampling technique has a lot of advantages for research that want to reach out to hard-to-reach or hidden populations. Snowball sampling can be used to contact a target demographic in a 'informal' manner. The most common method for conducting qualitative research, primarily through interviews, is to use snowball sampling.

Interviewees were reached via email and LinkedIn invitations, and they were asked to provide more contacts from the various groups of persons being questioned. The conversations took place over the phone. I used a guidance in the form of a pre-written interview script. Following that, individual responses were used to generate follow-up questions. First, the interviewers were asked open-ended questions to determine India's top three strengths and shortcomings as a clinical trial market. They were then asked to judge the efficiency and openness of CDSCO's approval and safety monitoring procedures on a five-point scale, as well as the efficacy, qualifications, and transparency of the Indian ethics committees with whom they had contact on a five-point scale. Following these ratings, the respondent was asked a series of open-ended questions about potential roadblocks to the implementation of upcoming revisions to the Drugs and Cosmetics Rules.

4. STRENGTHS AND WEAKNESSES OF INDIA AS A CLINICAL TRIAL MARKET

One of the top three advantages of India as a clinical trial market, according to 85 percent of respondents, is the large number of treatment-naive people. The availability of infrastructure and qualified investigators was the second most generally noted strength, as indicated by 62 percent of respondents. With 31% of responders identifying it, low cost was the third most commonly reported strength.

According to 77 percent of respondents, India's regulatory framework is the country's most critical shortcoming as a clinical trial market. The second most common fault was reported by 62 percent of respondents as a lack of understanding and education. The social imbalance was the third most prevalent flaw cited, with 38 percent of respondents expressing ethical issues.

4.1 Effective Oversight

There are four criteria for effective oversight that allow for an acceptable risk/benefit ratio in the design and conduct of a clinical trial: I sound research design to produce valid data, which necessitates adequate scientific review by the regulatory agency approving the trial's conduct; ii) adequate ethics committee oversight to protect human trial subjects; iii) adequate clinical trial monitoring; and iv) adequate clinical trial reporting.

Transparency in the regulatory oversight process is critical because it allows all stakeholders to understand the decisions being made as well as the effectiveness of the process. On their public websites, the respective authorities of each nation have published their policies and procedures for conducting a clinical study.

4.2 Endogenous and Systemic Uncertainties

Another point of comparison is how the regulatory bodies in the two nations handle endogenous and systemic uncertainty that different parties face. Based on the comparison, the following findings were reached: I The US regulations impose requirements related to some endogenous uncertainties that are not addressed in the Indian regulations, but they do not include mechanisms for addressing the uncertainties or converting them into calculable risks; thus, the US and Indian regulations are

comparable in terms of their ability to address endogenous uncertainties; ii) the Indian regulations do not include mechanisms for addressing endogenous uncertainties or converting them into calculable risks; thus, the US and Indian regulations are comparable in terms of their ability to address endogenous uncertainties, therefore, the US and Indian regulations are comparable in terms of their ability to address endogenous uncertainties.

4.3 Policy Implications and Recommendations

This research yields a set of policy recommendations aimed at three levels of decision-makers in the drug development process: I global governance organisations; ii) specific country governments; and iii) clinical trial institutions, such as sponsors, contract research organisations, and ethics committees.

5. International Requirements

The Declaration of Helsinki and ICH Good Clinical Practice, the two most generally referenced worldwide ethical guidelines for the conduct of clinical trials, do not adequately explain the obligations of industry stakeholders, as discovered in Chapter 6. These two documents, on the other hand, remain the cornerstones for assigning ethical duty to all parties, including those in the sector.[23,24,25] Only physicians are expected to observe the Declaration of Helsinki, which has a limited scope. The ICH GCP already has the structure in place to expand on these commitments because it now separates the document into the duties and obligations of ethical committees, investigators, and sponsors. Furthermore, because both industry and government are represented on the ICH, it already has access to both perspectives. Thus, they may be able to make global recommendations for all stakeholders using tools developed by ICH participants in this thesis, such as the framework and policy and strategy alternatives, with the ultimate societal good of balancing welfare and innovation as the preferable outcome.

5.1 Government Policies

Because of the impact of local socioeconomic realities on ethical dilemmas, international ethical standards are insufficient in and of themselves, as detailed in chapters 1-5. As a result, local laws and norms are critical in improving the welfare of the local subject population as well as bringing novel drugs to the market. Clinical trials are governed by a combination of legally binding regulations and ethical principles published by regulatory bodies. "A regulatory system capable of making publicly defensible decisions that are always in the public interest is required." Governments should, it is said that, It is recommended that governments, particularly those in emerging markets where local actors are still learning the intricacies of the trial process, make every effort to distinguish between enforceable legislation and ethical recommendations, as well as the consequences of non-compliance with each. Additionally, the regulatory agencies can use tools such as the framework and policy and strategy options presented in this thesis to determine the best combination of regulatory requirements and ethical guidelines to promote within their local context.

5.2 Institutional (Sponsor, CRO and Ethics Committee) Policies and Procedures

Among these are the pharmaceutical sponsor, the contract research organisation, and the ethics committee. The thesis indicates that integrated clinical trial governance solutions are required for effective clinical trial governance that balances welfare and innovation. The chapters on the United States and India both close with a proposal for governments to find an effective strategy to achieve this within their respective local settings without constructing new hurdles to innovation. Prior to implementation, institutional policies and procedures must be certified, as well as baseline accreditation standards for each institution's human subject protection programme. The need for a well-established relationship structure among clinical trial stakeholders is not mentioned in the current literature.

Suggestions for Future Research

This review paper could lay the groundwork for future research targeted at balancing clinical trial participants' demands with the requirement for innovation. In addition, the paradigm provided in this thesis can be utilised to undertake future research in order to examine the current and evolving oversight systems of traditional and emerging markets in their different local settings, as well as to identify any oversight flaws. Second, policy and strategy alternatives, as well as their positions on the social welfare or social problem spectra, might be utilised to suggest solutions to any gaps found. Third, game theory scholars can utilise this thesis to build game models that look at how the rules of the game for a single market or the global clinical trial process might be adjusted to create a better balance between welfare and innovation at the market or global level. Finally, researchers might use the framework and policy suggestions to examine and evaluate the balance between welfare and innovation in the development of other pharmaceutical products including medical devices and diagnostics.

6. CONCLUSION

To summarize, current research on clinical trial ethics focuses on one part of the equation: subject welfare maximization. This thesis takes a broader perspective, allowing for both the maximization of subject welfare and the need for drug research innovation to be addressed. The findings of this review paper can assist all decision-makers involved in clinical trial governance, including the pharmaceutical sponsor, the contract research organization (CRO), the ethics committee, and the government, in developing regulations, policies, and procedures that maximize subject protection while remaining an impediment to innovation Finally, the thesis offers researchers tools for assessing clinical trial governance, as well as practitioners' tools for developing

integrated strategies for maximizing subject welfare while driving innovation.

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