Evaluating the Barriers affecting Clinical Trial Proceedings using AHP analysis

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ABSTRACT

Purpose

The clinical trial industry is directly dealing with the prospects of wellbeing of the humans and hence any obstruction or barriers that affects the smooth conduct of clinical trials needs attention. The clinical trial progress studies have become of major importance in recent times owing to the pandemics like COVID-19 and the need for vaccine like never before. The main purpose of this study is to identify and prioritize the barriers affecting clinical trial proceedings so as to mitigate and minimize the risks and in turn reduce the overall cycle time for the completion of the trial proceedings.

Design

The evaluation is based on the AHP (analytical hierarchy process) framework. There are 6 barriers and 14 sub barriers that are listed and classified under the head barriers – behavioral, patient accrual, supply chain complexity, regulatory, financial and infrastructural barriers. These barriers were used as a criterion in the AHP and with the help of literature review and expert opinion the priority was devised. The selection of barriers was done based on the knowledge of clinical trials requirements and literature studies, while the weight assignment was made with the help of subject matter expert opinion.

Findings

Result shows that regulatory compliance was the highest-ranked barrier followed by the supply chain complexity, patient accrual, behavioral, financial and infrastructural barriers spread across the rankings. The priority list of the barriers can be considered while designing the clinical trial studies to have mitigations strategies at each stage of clinical trial and also have contingency planning that can avoid the redesigning of the clinical trials and in turn saves the cycle time of completion. This also gives an insight on the relative importance of these barriers.

Originality

The study analyses the potential barriers in the proceedings of the clinical trials and ranks these barriers as per their relative importance using AHP framework to help the clinical trial industry in reducing the timelines and better prepared for the foreseeable barriers as the trial progresses.

Keywords

Clinical Trials, Analytical Hierarchy Process (AHP), Barriers of clinical trials, Regulatory, Patient Physician relationship

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Introduction

Major expenditure of any pharmaceutical organization is in to Research & Development of innovative methods of treatments or diagnosis either through novel drugs or devices. Even before the people get the medications or it is launched in the market for general use there is a set of process that goes on to test the drug and get it approved by the relevant regulatory authorities before being launched into the market.This whole process of testing the drug for its dosage, effectiveness, side effects and safety is termed as the clinical trial. A clinical trial is an examination study led in people to address explicit inquiries concerning new treatments, immunizations or analytic methodology, or better approaches for utilizing known medicines.

The global clinical trials market size was valued at USD 46.8 billion as per the research conducted by the grand view research for the global clinical markets in 2019. Owing to the pandemic in the world, the rising need of vaccines and medications are only going to boost this figure further in 2020. This brings up an important aspect to be focused in the area of clinical trial studies about the barriers which are impacting this ever-growing segment of the pharmaceutical industry so that the cost involved can start returning in the form of revenues in a lesser period of time. The cost of developing a new product lies between 300 to 800 bn USD and the time to market for the drug is anywhere between 8 to 12 years (Liangrokapartand Raka, 2017).

There are generally three phases to the clinical trial after the indicative molecule is successfully developed in research:

- Phase 1: The Investigational New Drug (IND) undergoes the first phase of trial where; the way of administering & dosage determination is done. The pharmacokinetics and the pharmacogenetics of the drug is examined on 20-100 healthy patients. The length of the study is several months
- Phase 2: This phase deals with the efficacy of the drug is measured over a group of several 100 patients who are actually suffering from the indicative disease. The length of the study is several months to 2 years.
- Phase 3: The results of the phase 2 are confirmed in the phase 3 and possible adverse reactions are observed and recorded. This phase consists of more than ~3000 patients and is aimed at a larger audience. The length of the study is 1 to 4 years.

After successful completion of the three phase New Drug Application (NDA) is made to the relevant regulatory authority for approval. Followed by thisit also goes to the phase 4 post launch wherein a wide variety of audience is tested. Post Market Surveillance is also a part of the phase 4

studies. This structure of the trial might have minor modification depending upon the variabilities of the trials.

The objective of this study is to categorize the potential barriers in clinical trial studies and prioritize them as per their impact. The barriers are known to everybody only when it occurs in a particular stage of clinical trial studies and till then it becomes too late to avoid or mitigate the barrier, hence knowing it before hand at least keeps them ready to reduce the impact if not totally overcome the barriers. This will also help in reducing the cycle time of trial completion and in turns saves the cascading effect of extending the trial, cost of extension and other uncertainties in the value chain due to the extension.

Literature Review

To make sure about the efficacy of the drug, it is important to have an effective randomization design of the trial with a cordial approval and relation of the patient and the doctor.(Wendy S, 1994) This brings up an important point of the behavioral factors of both the doctors and the patients which forms the starting point even before initiating the clinical trial studies.The behavioral factors do take into consideration the risk apprehensions by the patient, the interaction with the physician, the physician attitude towards the patient explaining about the trial, patient eligibility and cost reimbursement difficulties by the patient. Nonenrolment of qualified patients in clinical preliminaries can be because of doctor or patient variables. Doctors frequently choose not to get some information about preliminary cooperation because of institutional or center time/repayment imperatives, treatment inclination, or different reasons (Unger, J.M. et al., 2019). According to (Tanner, A et al., 2013) one of the important factors also resides in the type of population being addressed, rural or urban. Especially in rural, it was found that distrust and fear or misperceptions about the Clinical trials is very prominent. Patient accrual become a crucial starting point to understand the effectiveness of clinical trial. Accrual means the number of subjects who are actively involved in the clinical trial or have already completed the trial. This points to an issue that must be addressed when evaluating clinical trial barriers; given limited resource availability, expending time and effort on studies that do not accrue is clearly nonvalue added(Diltsand Sandler, 2006). The patient accrual is majorly dependent on the behavioral aspects discussed above but more so it is also governed by the eligibility criteria for the indicative trials. The trials are meant to be conducted on patients with certain pre decided criteria and hence for certain disorders which are very rare in nature it is tough to have a good rate of patient enrollment. A huge imbalance between the age imbalance between the population which is intended to disease and population over which the trial is conducted can also be a big barrier in effective results(Ludmir E. B., et al., 2019) . The consent forms and documents fail also contribute to this accrual rate because they fail to document the contribution to medical knowledge and how this becomes an opportunity to help others through participation in investigational studies (Cassileth B., et al, 1982). The barriers to the participation of trials are also subjective to the demographics and socioeconomic conditions (Unger J. M., et al., 2016)

Once the trial is in pace the success of the trial depends a lot on the supply of the clinical materials necessary for the studies. Thus, the complexity of the supply chain in the clinical trial industry also forms an important barrier in smooth conduct of the trials. The commercial supply chain is different from clinical because of the time horizon where the commercial supply chain never officially terminates but the clinical supply chain it terminates once the trials are done and the residual materials have to be discarded(Ye Chenet al., 2012).Unlike the commercial markets where the demand is being created, forecasted and based on that the supply planning is done, clinical supply planning is based on the design of the clinical trial including the geographies, number of patients enrolled, the type of supply (centralised or decentralised) etc. Hence the supply planning although constant but has more complexity because of the nature of the raw material, drug and its shelf life, failure of enrolment, cease of trials in between etc. Hence the flow of clinical trial is dependent a lot on the complexity of the supply & distribution network.

The complexity in supply chain also leads to a heavy investment either in technology or process excellence to solve the issues. Rather the investment starts right from the research and development costs which requires the maximum investment to the market launch. Whether it is a new investigational drug or variations in the existing drug the investment is only going to increase with huge number of trials to identify statistically significant results. Such large number of trials leads to regulatory compliance, administrative burden and high overall cost of trials. Thus, there are these multiple factors which contribute to the expenditure in the clinical trials – large number of patients, long timeframes, recruitment efforts, data collection, administrative compliance, regulatory compliance and other trial components(Beleche T et al., 2016). Such large investment limits the number of sponsors that can successfully conduct the clinical trials.

The clinical trial is highly bound by the regulatory framework since it deals with a large variety of patients across the geographies for varied investigational drugs for a particular indication. These frameworks are intended to ensure the patient’s safety but also shouldn’t become a bottleneck. The multinational clinical trial processes are aimed at reaching a larger population to demonstrate effectiveness in a range of population. The changes or additional directives brought in by the regulatory bodies across the border stagnates the clinical trials or might lead to restrict the trial procedures within a specific boundaries (Berge E. et al., 2015). This contributes as an important barrier in the clinical trial studies throughout the lifecycle of clinical trial.

Clinical trials are not possible without the necessary infrastructure available to conduct the studies. By infrastructure here it means the right academic or institutional setup which offer the services for preparing the design of the clinical studies and executing. These infrastructures are important as it becomes one of the central points which can utilized to perform all the regulatory works, monitoring, connecting all the investigational network/ These institutions would also have the necessary technologies, competencies, tools and expertise to handle the center. Not all the geographical locations are capable to

have the public funding which can drive this kind of centers. So, unless there are some organizations sponsoring the trial, it becomes difficult to carry out and sustain the studies.From the technology standpoint as well, there are various barriers which obstructs the use of these technologies in innovating the clinical trials. One such is Patient facing technologies as explained (Polhemus, A. M. et al., 2019) which includes eConsent forms to engage patients, enabling decentralised trials, data collection and management etc. The adoption of these technologies is not smooth and hence becomes a barrier in conduct of smooth clinical trials.

Analytic Hierarchy Process AHP is a process to analyze the factors and barriers in decision making and analysingthem. AHP methodology was first developed by Thomas L. Saaty in the 1970s and people have modified that based on their goals since then. AHP connects all the levels of hierarchy and this helps in identifying how one factor affecta the other one.Figure 1 dictates all the barriers categorised in individual heads as explained above with respect to a common goal of prioritizing these barriers. The first layer is the main criteria and the subsequent are the sub criteria.

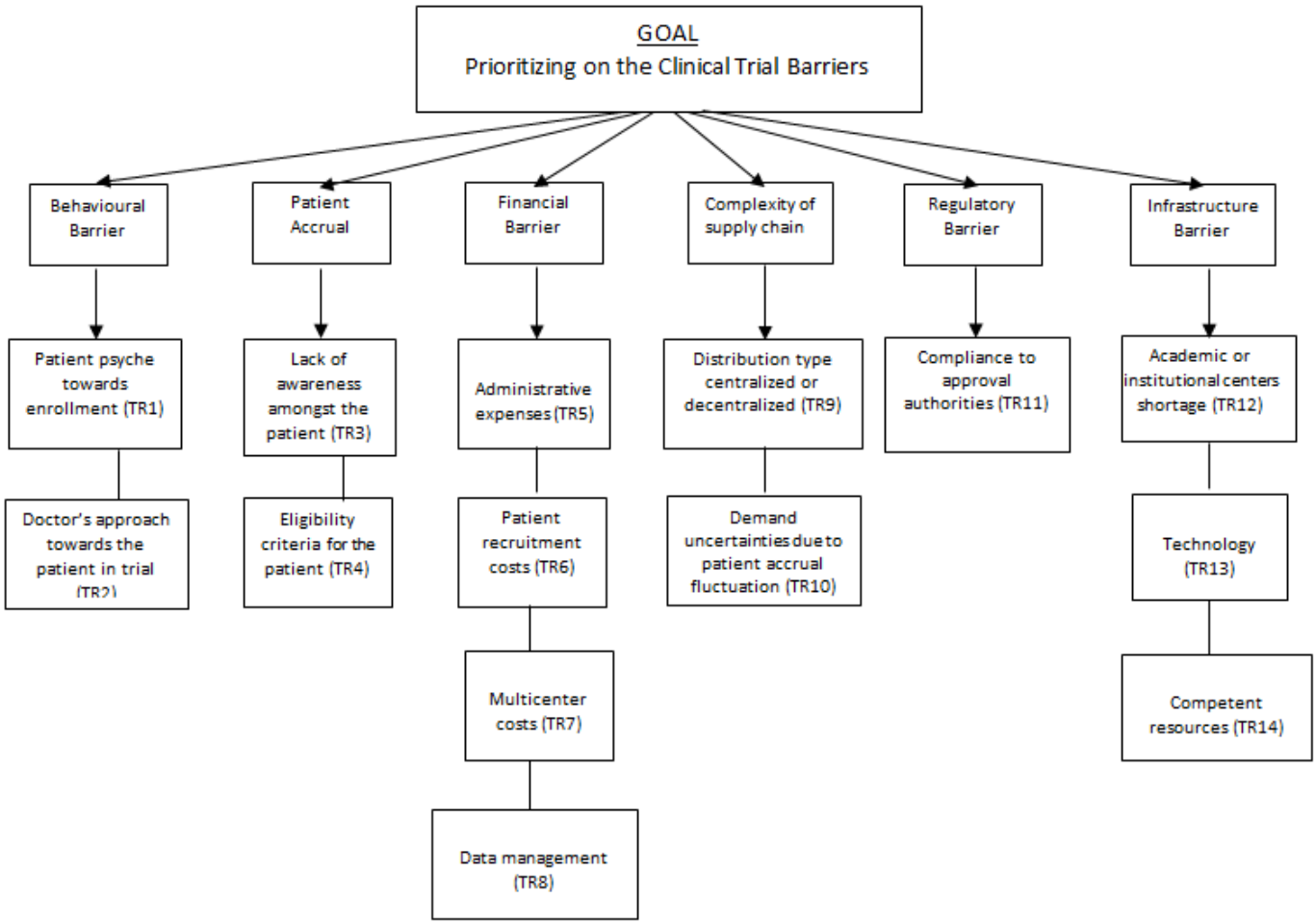

Figure 1. Barriers in clinical trials(Author's Compilation)

Methodology

In AHP, first step is to set the goal or the problem statement, followed by identifying the important factors affecting the problem statement and this can be in a hierarchal representation. This will help in quantitative as well as qualitative analysis. The third step is to do a pair-wise comparisonand providing weightage to each comparison (Liangrokapart and Raka, 2017).The fourth step is to check the consistency of score. Next step is to calculate the weights for each pairwise comparison and the last step is ranking and decision making.

3.1 Step1: Setting the goal and then selecting appropriate barriers for the analysis.

The goal is to prioritize the potential clinical trial barriers. The appropriate barrier selection was done based on the literature review and process understanding from the experts. The barriers were clustered under the 7 heads accordingly their nature and hence becomes easy to prioritize.

3.2 Step2: Pairwise-Comparison matrix

Table 1 shows the pair-wise comparison matrix of the barriers with respect to the goal and its importance is indicated by the numbers relative to the other. The transverse values are the reciprocals of these values and are defined by aij = 1/aji.Data was developed based on the self-study and expert opinions. Decision was based on the fundamental scale of AHP as described below:

1.0 = Equally important, 1.5 = Slightly more important, 2.0 = Moderately more important, 2.5 = Highly important and 3.0 = Extremely important

Each barrier is weighted against the other to understand the relative comparison and importance to prioritize the rankings.

Table 1: Pairwise comparison matrix for the barriers of clinical trial proceedings

	TR1	TR2	TR3	TR4	TR5	TR6	TR7	TR8	TR9	TR10	TR11	TR12	TR13	TR14
TR1	1.00	1.33	1.00	0.67	0.67	0.67	1.33	2.00	0.80	0.80	0.57	1.00	1.00	1.00
TR2	0.75	1.00	2.00	0.50	0.50	0.50	0.67	0.83	0.67	0.67	0.50	0.80	1.33	0.67
TR3	1.00	0.50	1.00	0.67	0.67	0.50	0.50	0.80	0.67	0.50	0.57	0.80	1.25	1.00
TR4	1.50	2.00	1.50	1.00	1.00	1.00	2.00	1.33	1.00	0.80	0.67	1.00	2.00	2.00
TR5	1.50	2.00	1.50	1.00	1.00	0.57	1.00	0.80	0.80	0.57	0.67	1.00	1.00	1.00
TR6	1.50	2.00	2.00	1.00	1.75	1.00	1.33	0.80	0.67	0.57	0.67	0.67	1.00	1.00
TR7	0.75	1.50	2.00	0.50	1.00	0.75	1.00	0.80	0.67	0.80	0.67	1.00	1.00	1.00
TR8	0.50	1.20	1.25	0.75	1.25	1.25	1.25	1.00	0.67	0.57	0.67	0.80	0.80	1.00
TR9	1.25	1.50	1.50	1.00	1.25	1.50	1.50	1.50	1.00	1.00	0.80	1.00	1.33	1.33
TR10	1.25	1.50	2.00	1.25	1.75	1.75	1.25	1.75	1.00	1.00	0.80	1.33	1.33	2.00
TR11	1.75	2.00	1.75	1.50	1.50	1.50	1.50	1.50	1.25	1.25	1.00	2.00	2.00	1.33
TR12	1.00	1.25	1.25	1.00	1.00	1.50	1.00	1.25	1.00	0.75	0.50	1.00	1.33	1.33
TR13	1.00	0.75	0.80	0.50	1.00	1.00	1.00	1.25	0.75	0.75	0.50	0.75	1.00	0.80
TR14	1.00	1.50	1.00	0.50	1.00	1.00	1.00	1.00	0.75	0.50	0.75	0.75	1.25	1.00

(TR1 = Patient psyche towards enrollment, TR2 = Doctor's approach towards the patient, TR3 = Lack of awareness amongst the patient, TR4 = Eligibility criteria for the patient, TR5 = administrative expense, TR6 = Patient recruitment cost, TR7 = Multicenter costs, TR8 = Data management costs, TR9 = Distribution type centralized or decentralized, TR10 = Demand uncertainties due to patient accrual fluctuation, TR11 = Compliance to approval authorities, TR12 = Academic or institutional centers shortage, TR13 = Technology, TR14 = Competent resources)

3.3 Step 3: Normalized Matrixand Priority Vector

Normalizing the matrix by taking the column sum of pairwise comparison matrix and divide each cell value by its column sum. Then take the sum row wise of this normalized matrix, this column is Normalized Inputs (Priority Vectors) which is denoted by PV. Based on this PV the ranking of the barriers is done as shown in the Table 2 & 3below.

	TR1	TR2	TR3	CR4	TR4	TR5	TR6	TR7	TR8	TR9	TR10	TR11	TR12	TR13	Total
TR1	0.063	0.067	0.049	0.056	0.043	0.046	0.082	0.120	0.068	0.076	0.061	0.072	0.057	0.061	0.92
TR2	0.048	0.050	0.097	0.042	0.033	0.035	0.041	0.050	0.057	0.063	0.054	0.058	0.076	0.040	0.74
TR3	0.063	0.025	0.049	0.056	0.043	0.035	0.031	0.048	0.057	0.047	0.061	0.058	0.071	0.061	0.71
TR4	0.095	0.100	0.073	0.085	0.065	0.069	0.122	0.080	0.086	0.076	0.071	0.072	0.113	0.121	1.23
TR5	0.095	0.100	0.073	0.085	0.065	0.039	0.061	0.048	0.068	0.054	0.071	0.072	0.057	0.061	0.95
TR6	0.095	0.100	0.097	0.085	0.114	0.069	0.082	0.048	0.057	0.054	0.071	0.048	0.057	0.061	1.04
TR7	0.048	0.075	0.097	0.042	0.065	0.052	0.061	0.048	0.057	0.076	0.071	0.072	0.057	0.061	0.88
TR8	0.032	0.060	0.061	0.063	0.082	0.086	0.077	0.060	0.057	0.054	0.071	0.058	0.045	0.061	0.87
TR9	0.079	0.075	0.073	0.085	0.082	0.104	0.092	0.090	0.086	0.095	0.086	0.072	0.076	0.081	1.17
TR10	0.079	0.075	0.097	0.106	0.114	0.121	0.077	0.105	0.086	0.095	0.086	0.096	0.076	0.121	1.33
TR11	0.111	0.100	0.085	0.127	0.098	0.104	0.092	0.090	0.107	0.119	0.107	0.144	0.113	0.081	1.48
TR12	0.063	0.062	0.061	0.085	0.065	0.104	0.061	0.075	0.086	0.071	0.054	0.072	0.076	0.081	1.02
TR13	0.063	0.037	0.039	0.042	0.065	0.069	0.061	0.075	0.064	0.071	0.054	0.054	0.057	0.049	0.80
TR14	0.063	0.075	0.049	0.042	0.065	0.069	0.061	0.060	0.064	0.047	0.080	0.054	0.071	0.061	0.86

Table 2: Normalized Matrix

Table 3: Barrier ranking as per Priority vector

Barrier	Priority vector	Rank
Compliance to approval authorities	0.099	1
Demand uncertainties due to patient accrual fluctuation	0.089	2
Eligibility criteria for patients	0.082	3
Distribution type centralised or decentralised	0.078	4
Patient recruitment expense	0.069	5
Academic or institutional centres shortage	0.068	6
Administrative Expense	0.063	7
Patient's psyche towards enrolment	0.061	8
Multicentre expense	0.059	9
Data Management expense	0.058	10
Competent resource	0.058	11
Technology	0.053	12
Doctor's approach towards patient	0.050	13
Lack of awareness amongst the patient	0.047	14

3.4 Step 4: Next step is to check the consistency of scores, and for this we have to find following things:

- Calculate the consistency measure.

In excel consistency measure can be calculated by using the formula MMULT(), here we are multiplying each column of the pair wise comparison matrix by the corresponding weight and then divide by the sum of the row entries by the corresponding weight i.e., priority vector.

- Calculate the consistency index (CI).

Take the average of the outcomes of the pervious step and name it as Lambda n, n is the number of factors

CI = ((Lambda n) – n) / (n – 1)

In the study presented here the CI comes out to be 0.0245

- RI is the randomness index and for n=14 RI is 1.57
- Calculate the consistency ratio

CR = (CI/RI)

If CR is equal to or less than 0.1 then it is acceptable, the consistency is there in the scores provided.

For our studies with 14 barriers the Consistency Ratio CR comes out to be 0.0156, which being less than 0.1 indicates and validates the consistency of the scores given to the barriers.

Result

Figure 1 shows the main barriers and the sub barriers which are found to be contributing factors for creating roadblocks in conducting the clinical trials. The goal of using AHP is to come to a decision about prioritizing the major barriers which can be considered as significant out of the 14 listed in the figure after carefully examining the process, expert opinion and research study through articles. As shown in the table 3 the barriers are ranked using the AHP method and regulatory compliance turns out to be the biggest barrier in successful conduct of the clinical trials. This is also supported by the fact that the changes in the regulations of multiple nations across the globe can halt the trials which are ongoing for many years. Followed by it are the supply chain complexities viz Demand uncertainties (Rank-2) and the distribution strategy (Rank-4), these two are also a major hindrance for any clinical trial studies. As explained earlier they are linked to a number of factors again which points to the patients pulling out of the ongoing trial or more patient accrual is necessary which leads to the uncertainties at demand planning. Ultimately if the planning fails the trial will face difficulties in the downstream phase. The eligibility criteria barrier (Rank-2) for clinical trial becomes significant for the trial because unless the desired volunteer or patients are not available the trail results won't be effective to prove the indications. The patients undergoing trail treatment form the sample, the results for which are extrapolated for a large mass. Hence it becomes an important barrier if the right sample of eligible patients are not available.

The successive barriers starting from rank 5 are under the criteria of cost barriers and the infrastructure barriers which forms an obstruction to the clinical trial at different stage of its lifecycle to smaller or larger extent. The order of their rankings is: Patient recruitment expense, Academic or institutional centers shortages, Administrative Expenses, Patient's psyche towards enrollment, Multicenter expenses, Data Management expense, Competent resources,

Technology, Doctor's approach towards patient and Lack of awareness amongst the patient

Conclusion and Future Scope

The contribution of this study is to provide a holistic picture of the barriers that can affect the clinical trial and also prioritizing them using the AHP methodology. For ease of comprehending the barrier, expert opinion along with the literature review and clinical trial understanding has helped to a larger extent. The AHP computations identified the barriers and ranked them appropriately so that proper mitigation or forecasting strategies can be utilized to have a smooth conduct of the clinical trial within the stipulated timeline and reduced rework costs. The same framework of AHP can be utilized to add a number of other barriers which are specific to a geography, organization or indicative drug. The goals, criteria and the sub criteria might change as per the mentioned subjectivity and applied further investigative studies can be accomplished.

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