Which clinical trial study design will have the biggest impact and most relevant data when determining efficacy of an experimental cystic fibrosis medication.

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Decision Making in a Complex Environment
Final Project Report

Abstract

Cystic Fibrosis is a rare genetic disease with less than 200,000 new cases discovered every year. Cystic Fibrosis causes damage to the lungs as well as other organ systems. Specifically, this disease causes the production of abnormally thick mucus in the lungs and bronchioles that leads to complete blockages or partial occlusion of the bronchi, intestines, and pancreatic ducts. While this disease is considered rare, the development of a medication to treat the symptoms of cystic fibrosis is of high importance.

A major pharmaceutical company has developed a new experimental medication that is tended to treat symptomatic cystic fibrosis. The pharmaceutical company has selected the UPMC Division of Pulmonary Medicine to select and develop a study design that has the biggest impact and most relevant data in determining efficacy of the experimental medication. The UPMC Division of Pulmonary Medicine has narrowed the alternative trial designs to three different alternatives. These three alternatives consist of a Double Blind Randomized Control Trial, a Case Control Trial, and a Longitudinal Cohort Trial. Each trial design contains different benefits and short-falls in terms of types and quantity of data collected. The efficacy of the different alternatives with respect to the established sub-criteria and bottom-level criteria are examined in the following pages by means of a Benefits, Opportunities, Costs, and Risks model.

Alternatives

We specifically wanted to look at types of clinical trial designs that are most commonly used when determining efficacy of an experimental medication. When multiple factors, such as patient experience, patient compliance, data quality, and data quantity are all being considered, it is important to select a trial design that will give you the most usable data. Of the many different types of trial designs, three were selected.

Double Blind Randomized Control Trial

A double blind randomized control trial is a trial that is most commonly used in experimental medications. This clinical trial consists of enrolling a cohort of individuals that all carry the same genetic factor that causes cystic fibrosis. These individuals are then randomized to one of two treatment groups: the medication group, or the placebo group. The medication group will receive the experimental medication and their symptoms will be monitored. The placebo group will receive a dose of something that looks and tastes exactly like the experimental medication, but it is a deactivated substance that has no effect. The individual will be blinded to which treatment group that they are in. The important part of this type of trial is that the researchers are blinded as well. Study physicians are unaware which patient received which medication and therefore must treat all patients equally. This type of trial design greatly reduces biases as well as researcher influence within the trial. The downfall to this trial design is that it does not examine differing severities of the disease as well as long term effects.

Case Control Study

The next trial type that was selected was a case control trial. This type of trial looks at multiple cohorts of individuals with similar levels of lung function, but all carrying different genotypes of the same disease. This trial method would be best at looking at which genotype of the disease is most affected by the new experimental medication and why. This is beneficial because it allows researchers to pinpoint the cohort where the medication will have the most success in terms of treating symptoms. The downfall to this form of study is that the researchers are aware of which treatment groups are receiving the medication. Therefore this may lead to biases within the trial design. This type of trial also does not look at long term effects of the medication.

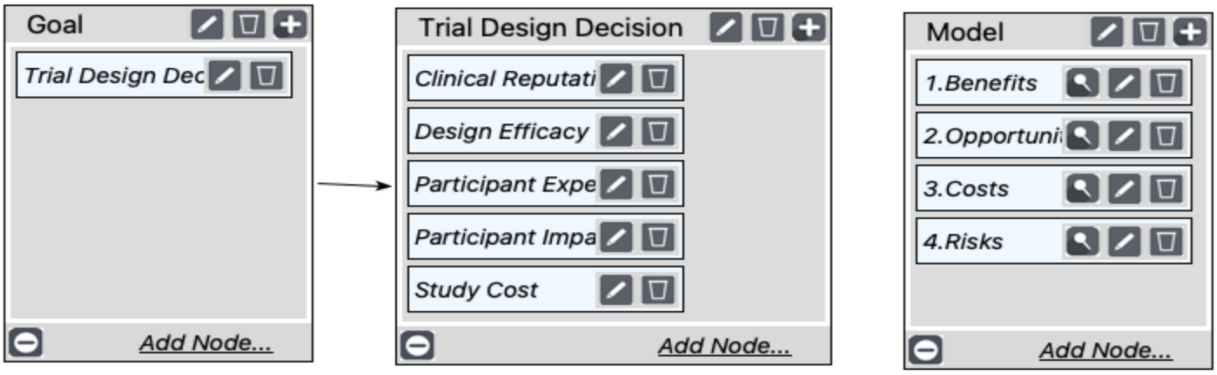
Longitudinal Cohort Study

The final trial design selected was a longitudinal cohort study. This type of trial places individuals into cohorts based on differing levels of severity of symptoms within the same genotype. This trial typically includes a large sample of individuals and examines the effect of the medication

over a long period of time. Having a large sample increases reproducibility of results, but also leads to mass quantities of data collected which requires more resources to sort through it all. Also, recruiting large quantities of individuals to participate and following them for an extended period of time requires a lot of resources to maintain. Sometimes, requiring individuals to be active participants for multiple years makes communication and patient follow up extremely difficult.

Methods

A BOCR analysis was created in super decisions to compare our alternatives with respect to the established strategic and bottom level criteria. The main network model can be seen below.



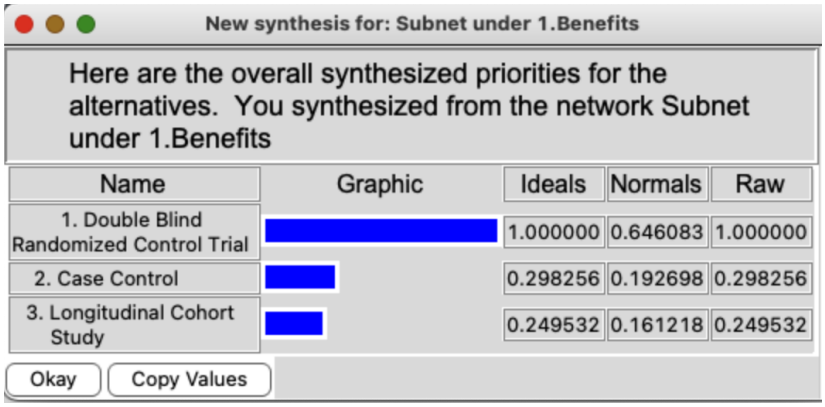
Benefits Subnetwork

1. Biases
    a. Participant Knowledge: The participant having knowledge of whether they received the actual study medication or not can lead to increased bias in the trial.
    b. Placebo Effect: Sometimes when there is a treatment and a placebo group, individuals who received the placebo may believe they received the actual medication and may actually start to believe that it is having an effect.
    c. Researcher Influence: If the research knows what medication the individual received, that may influence their treatment decisions.

d. Researcher Knowledge: If the research has knowledge of what medication the individual received, they may subconsciously lead to bias within the trial.

2. Comparability
    a. Data Quality: Having high quality data leads to reproducibility and comparability.
    b. Existing Trial Similarities: Drawing similarities to existing trial designs will lead to higher comparability.
    c. Trial Criteria/Population: Selecting the proper population is important depending on the trial type.
3. Funding
    a. Companies Preference: The pharmaceutical company provides funding to carry out the research. If they have a preference on trial design it will influence the decision.
    b. Grant Types: The type of grant given will affect the allowance of the duration of the research trial.
    c. Resource Allocation: The clinical center is given the task of allocating resources within the clinical trial to ensure reproducible results.

Synthesis of Benefits

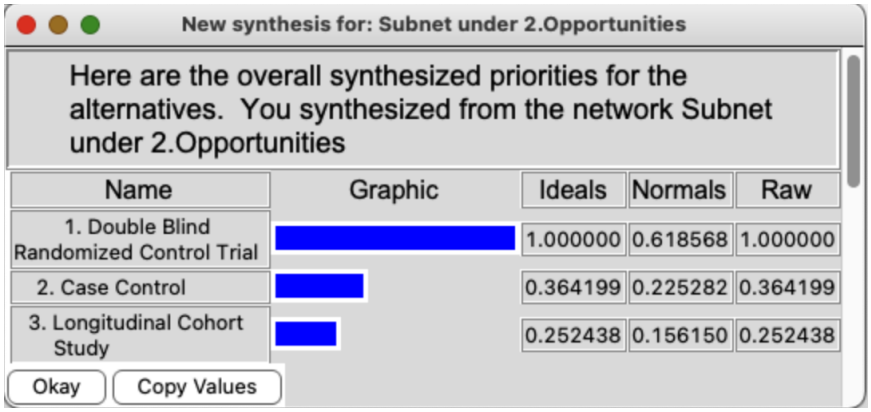


According to the synthesis of the overall benefits, a double blind randomized control trial is significantly better than both of the other alternatives in terms of the overall benefits. The next

highest ranking alternative is a case control study. We believe the double blind randomized control trial ranked so high because it has the best chance of eliminating bias on both the researcher and participant sides.

Opportunities Subnetwork

1. Comparability
    a. Clinical Outcomes: Knowing how well the medication treats symptoms of cystic fibrosis is very important.
    b. Future Publications: Proper trial design and execution will lead to future publications of research findings.
    c. Reproducibility: Reproducibility is key in collecting high quality data that can be used to bring the experimental medication to market.
    d. Reputation of Center: Proper trial design and execution can either make or break a clinical center's reputation.
2. Data Quantity
    a. Population Forecasting: It is important to make sure that you are gathering data from an area with a high population of people of interest.
    b. Predictability of Future Results: Higher quantity of data can lead to predictability of future results.
    c. Study Power: Having a larger quantity of data means that there is a higher chance of gathering some data that is of high importance.

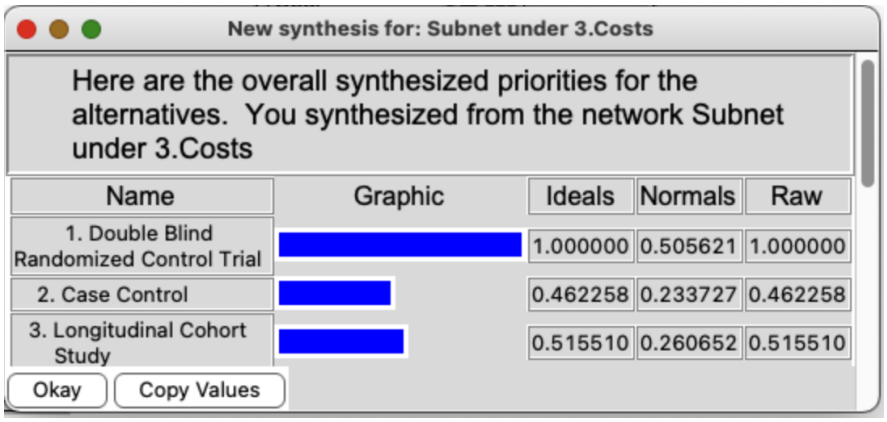


According to the synthesis of the subnet under Opportunities, the double blind randomized control trial ranks the highest in terms of long term benefits. This makes sense because a double blind study is a way for researchers to directly see the effect of the medication on a treatment group compared to a similar group that is not receiving the medication.

Costs Subnetwork

1. Biases
    a. Data Quality: Having higher quality data will reduce bias within the study trial.
    b. Impact of Results: The level of bias within the clinical trial will have an impact on the results and decrease reproducibility.
    c. Participant Perceived Outcomes: The participant having an idea of what medication they received may lead to short term bias.
2. Compliance
    a. Distribution: Distribution of study resources among participants is important in maintaining participant compliance.
    b. Legal Implications: Maintaining health and safety guidelines is very important to maintain a successful research design.
    c. Manufacturer Stipulation: If the manufacturer of the medication states that
3. Follow-Up

a. Number of Visits: The higher the number of study visits there are, the less likely it will be for patients to continue to return.
b. Patient Appointment Compliance: Patient showing up for their appointments and being willing to complete all study tasks.
c. Retention Rates: A higher retention rate leads to an increase in the quality of the data.
d. Side Effects: Side effects of the experimental medication can lead to a decreased likelihood of approval.



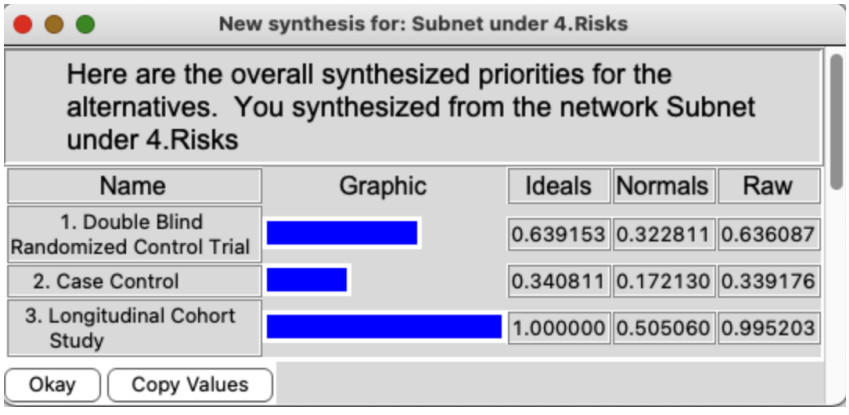
According to the synthesis of Costs in the short term, a double blind randomized control trial is the most costly and requires the most resources. This makes sense because more research personnel are needed for this type of study than any other. The next most costly alternative is the longitudinal study. This requires extended funding to maintain the study duration.

Risks Subnetwork

1. Compliance
    a. FDA Approval: A study design that gives the best results will lead to the highest potential of FDA approval.
    b. Medication Efficacy: The effectiveness of the medication to treat the symptoms of cystic fibrosis are being examined in the long term.
2. Duration

a. Add on Phases: Continuously adding new phases to the existing study will increase the duration of the study.
b. Data Cleaning: The longer the trial lasts, the more unusable data will be collected which needs cleaned or sorted.
c. Data Relevance: With an extended study duration, it is important to continuously make sure that the data you are collecting is relevant and usable.
d. Participant Fallout: The longer the study duration, the more likely it is that study participants will drop out of the study.
e. Side Effects: Increased study duration will lead to better knowledge and understanding of the medications side effects.

3. Funding
    a. Company Funding: Maintaining a successful trial is important to get continued funding from the pharmaceutical company that is funding the research.
    b. Company Resource Allocation: The company must allocate resources appropriately to the different aspects of the study.
    c. Funding Terms: If the grants that are allocated to the research center have specific terms in which they must be spent, that will influence how the center decides on a trial method.

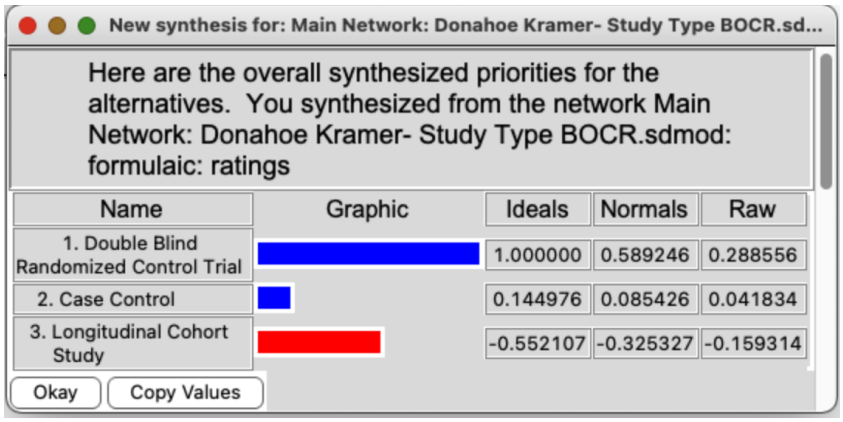


According to the synthesis of the results of the long term risk involved in the research trial, the Longitudinal cohort study is the riskiest. This makes sense because an increased duration of the study trial associated with a longitudinal trial increases the risk of participant fallout. The next riskiest is the double blind randomized control trial.

Ratings Priorities:

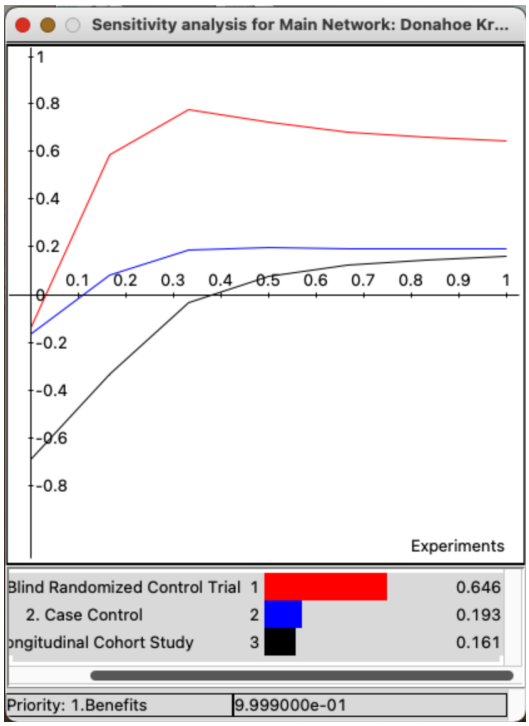
Alternatives	Priorities	Totals	Clinical Reputation (0.0771)	Design Efficacy (0.5676)	Participant Experi... (0.1986)	Participant Impact (0.1190)	Study Cost (0.0376)
1.Benefits	0.3384	0.8051	Medium	Excellent	Average	Above Average	Hi
2.Opportunities	0.2655	0.6317	High	Above Average	Average	Above Average	Hi
3.Costs	0.1740	0.4140	Low	Average	Above Average	Average	Hi
4.Risks	0.2221	0.5285	High	Average	Excellent	Above Average	Med

Main Network Synthesis:

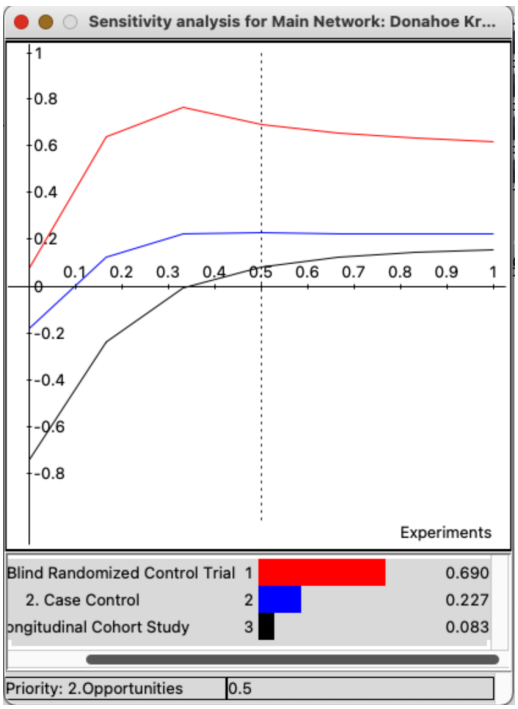


The overall model has the double blind randomized control trial selected as being the best possible clinical trial to use to begin researching the new experimental cystic fibrosis medication. This makes sense compared to the BOCR model rankings with the double blind randomized control study ranking highest on B and O and towards the middle in C and R. This is consistent with the type of research trial that would be used in medical research to begin human testing on a new experimental medication. Case control and longitudinal cohort studies are both effective means to study efficacy of a medication in different ways but the double blind randomized control trial has the most power to directly observe the efficacy of the medication to treat symptomatic cystic fibrosis.

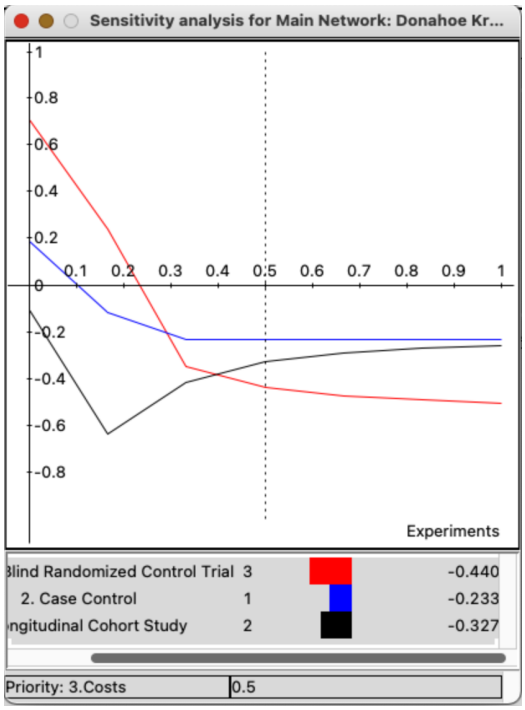
Sensitivity Analysis



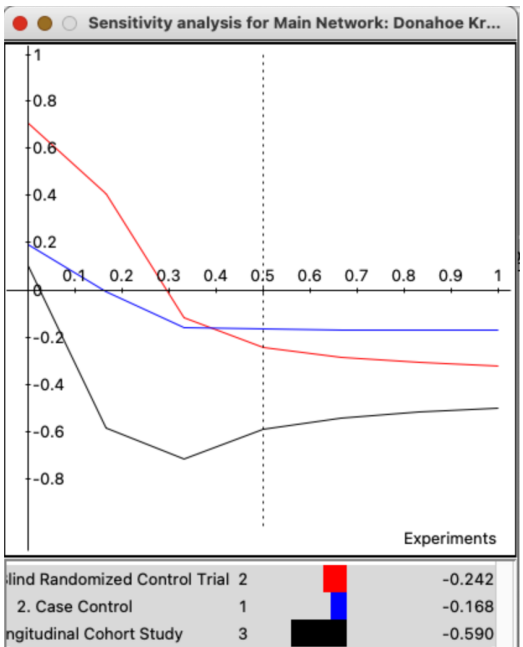
Regarding the Benefits in the BOCR model, the Double Blind randomized control trial ranked significantly higher than both the case control trial and the longitudinal cohort study.



Regarding the Opportunities in the BOCR model, the double blind randomized control trial once again ranked significantly higher than both the case control trial and the longitudinal cohort study.



Regarding the Costs in the BOCR model, a rank reversal can be observed. With the double blind randomized control trial beginning as the most costly, and then transitioning to the least costly as time continues.

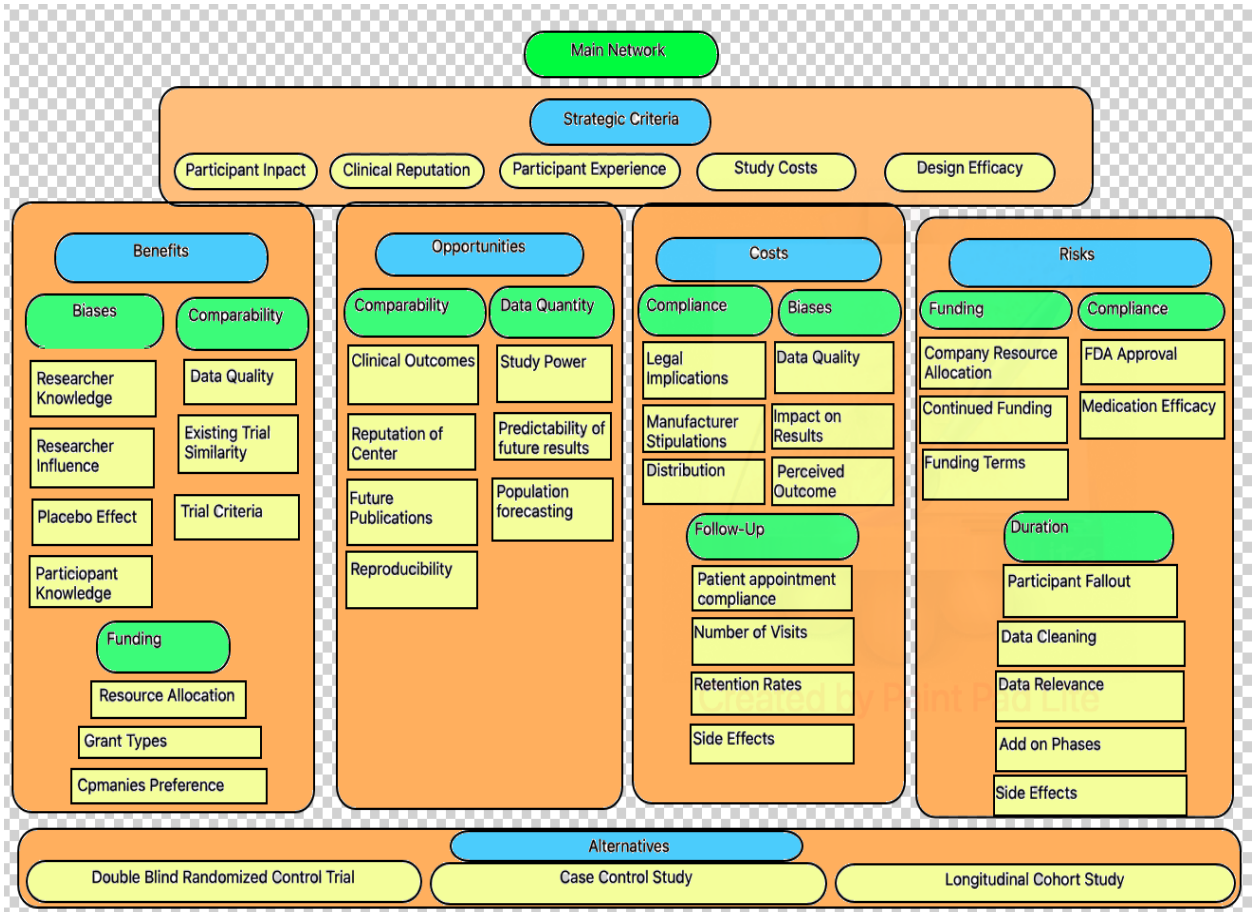


Finally, regarding the Risks in the BOCR model, another rank reversal can be observed. The double blind randomized control trial began as the most risky and later transitioned into the second riskiest of the three alternatives. With the longitudinal cohort study remaining the riskiest trial throughout the duration.

Conclusion

In conclusion, using BOCR, as well as AHP and ratings models, we can confirm that the double blind randomized control trial is the best alternative in carrying out clinical research on this experimental medication. This data shows that these models are effective means of quantifying qualitative data to use software to make an educated decision. As predicted, all of the individual steps of the model creation led to the same conclusion of the double blind randomized control trial being the best possible alternative in terms of studying the efficacy of the new medication while also collecting usable and reproducible data.

Complete Model


Main Network
Strategic Criteria
Participant Inpact
Clinical Reputation
Participant Experience
Study Costs
Design Efficacy
Benefits
Biases
Comparability
Researcher Knowledge
Researcher Influence
Placebo Effect
Particiopant Knowledge
Data Quality
Existing Trial Similarity
Trial Criteria
Funding
Resource Allocation
Grant Types
Cpmanies Preference
Opportunities
Comparability
Data Quantity
Clinical Outcomes
Reputation of Center
Future Publications
Reproducibility
Study Power
Predictability of future results
Population forecasting
Costs
Compliance
Biases
Legal Implications
Manufacturer Stipulations
Distribution
Data Quality
Impact on Results
Perceived Outcome
Follow-Up
Patient appointment compliance
Number of Visits
Retention Rates
Side Effects
Risks
Funding
Compliance
Company Resource Allocation
Continued Funding
Funding Terms
FDA Approval
Medication Efficacy
Duration
Participant Fallout
Data Cleaning
Data Relevance
Add on Phases
Side Effects
Alternatives
Double Blind Randomized Control Trial
Case Control Study
Longitudinal Cohort Study