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Critical Analysis of the Confounding of Clinical Trials

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Critical Analysis of the Confounding of Clinical Trials

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I dedicate this to my Mom, Dad, and Brother. Thank you for always supporting my endeavors, ideas, and opinions. I love you.

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Chapter 1- Introduction

The realm of clinical research is one that is both profitable and evermore important to the wellness of society. Unfortunately, the combination of these two characteristics of clinical research has the potential to create conflicts of interest. The current design of clinical trials themselves may allow for profit-seeking behavior to confound the results of trials and make a particular drug seem more effective than it actually is. This issue leads to somewhat of a snowball effect in that subpar but costly drugs are approved by the FDA and end up in the medicine cabinets of patients across the country. The average patient is likely unaware of such direct exposure to corruptions in the healthcare market. Given that not all clinical trials are biased, those that have been confounded can and do have real and profound negative effects on one's health. The purpose of this paper is to provide a comprehensive analysis on the issues confounding clinical trials for those interested and those exposed unknowingly to medications produced through biased clinical trials.

As a standard procedure, the design of clinical trials randomizes the allocation of patients into different treatment groups. For example, a trial will normally have an active treatment and a control treatment to which patients are assigned through use of a randomization procedure. The worldwide medical community agrees on using the permuted block randomization procedure, making this particular procedure very familiar to investigators running trials. It is this familiarity with the randomization procedure that allow investigators to predict the next "random" patient allocation and therefore preferentially enroll patients in a given treatment group that constitutes selection bias [3]. The means by which an investigator decodes the randomization procedure is discussed explicitly in Chapter 3. Selection bias is more prevalent when trials are unmasked, meaning that the allocation history is revealed to the investigator. The reasons for compromising

a trial in this way could be financial incentives such as equity in pharmaceutical companies, patient sympathy for suffering patients assigned to placebo treatment groups, or even bribes from associated drug developing companies [9]. The other issue that exacerbates the confounding effects of selection bias is the inability to detect it. The current aim in clinical trial research is to innovate a mechanism to detect selection bias either during the trial or in the post-trial analysis of the data.

To provide a comprehensive overview of issues confounding clinical trials, Chapter 2 will discuss the parties involved in the research and development of medications and detail the individual responsibilities of each. However, the ambition of these individual entities often produces a conflict of interest especially when profits are involved [9]. Organizations and individuals such as insurance corporations, pharmaceutical companies (sponsors), pharmacy benefit managers, investigators (doctors/medical professionals) and most importantly patients, are all involved in carrying out clinical research and have definitive responsibilities they are required to follow for unbiased results. However, many rules are overlooked and biases go unrecorded causing the "good" in these institutions to be marred with unethical behavior and unreliable results [1]. After the completion of this section, the biases each entity, including investigators, can and do bring about in the clinical research process will be clear. It is sometimes not particularly obvious as to how selection bias can occur therefore the means of confounding trials by investigators is discussed in Chapter 3.

Chapter 4 will provide a critical analysis of the randomized clinical trial quality guidelines presented in the Consolidated Standards of Reporting Trials (CONSORT) Statement. This document serves to increase the accuracy and precision of results reporting of clinical trial results, however does not include repercussions for falsely recording data. Real trials where

biasing events have occurred and caused the confounding of trials continue to be published despite the existence of such guidelines. Some of these trials proceed further, in some cases to be fully published and accessible to the public, with no adequate consequences or repercussions. Even if there are consequences for biasing actions, they are not sufficient or efficient enough to ensure the protection of patients exposed to biased studies or the results of such studies. Critical analysis of these "guidelines," requires familiarity with current standards for the conduct of clinical trials in the Consolidated Standards of Reporting Trials (CONSORT) statement introduced in this chapter. Lastly, Chapter 5 will propose and detail a new selection bias detection mechanism entitled the rank correlation coefficient.

Chapter 2- Parties Involved in Clinical Trials

The overall healthcare market is organized into four different parties; drug manufacturers (medical/pharmaceutical companies), physicians/investigators, and patients, seen in the figure below.

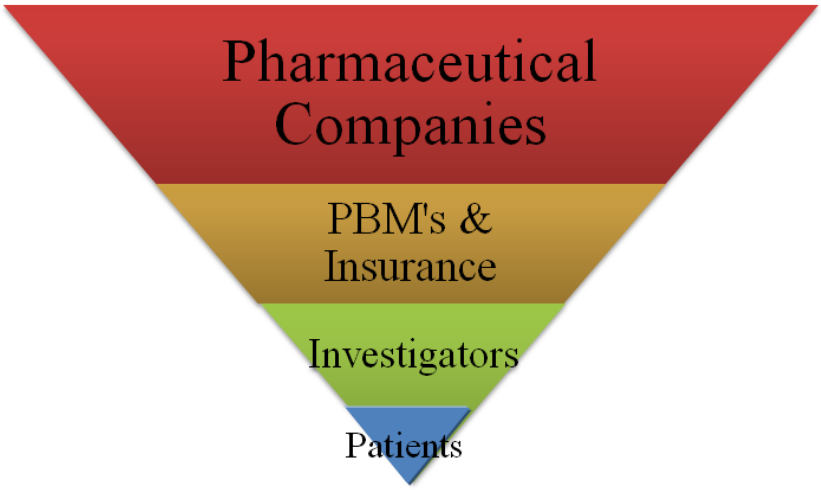

Figure 1. Organization of Entities Involved in RCTs.

The first and largest player in clinical trials is the *for-profit* medical companies. A for-profit corporation bases production and investment in its own economic interests and in the interest of shareholders who receive dividends. The "responsibilities" of medical companies are to research, organize, fund and run clinical trials on new drugs and devices to sell, that are expected to improve health [9]. Examples of companies such as these are Johnson and Johnson, AstraZeneca, Merck, and Novartis. The research conducted by pharmaceutical companies is mistakenly assumed accurate and unbiased. Much concern with the conflict of interest between providing viable clinical trial results and the financial incentive to make large profit margins has called great attention to these companies' roles in the healthcare sector. This ill-incentivized market sometimes causes pharmaceutical companies to confound trials, making a drug appear to

be better than it may actually be, to then bring it to market and begin making profits at a lower overhead cost to the company.

In recent times, the more questionable medical entity that is also large and profit-driven is the pharmacy benefit manager (PBM). The responsibility of the PBM is to act as an intermediary between insurance companies and drug inventors and manufacturers as seen in the figure below [12].

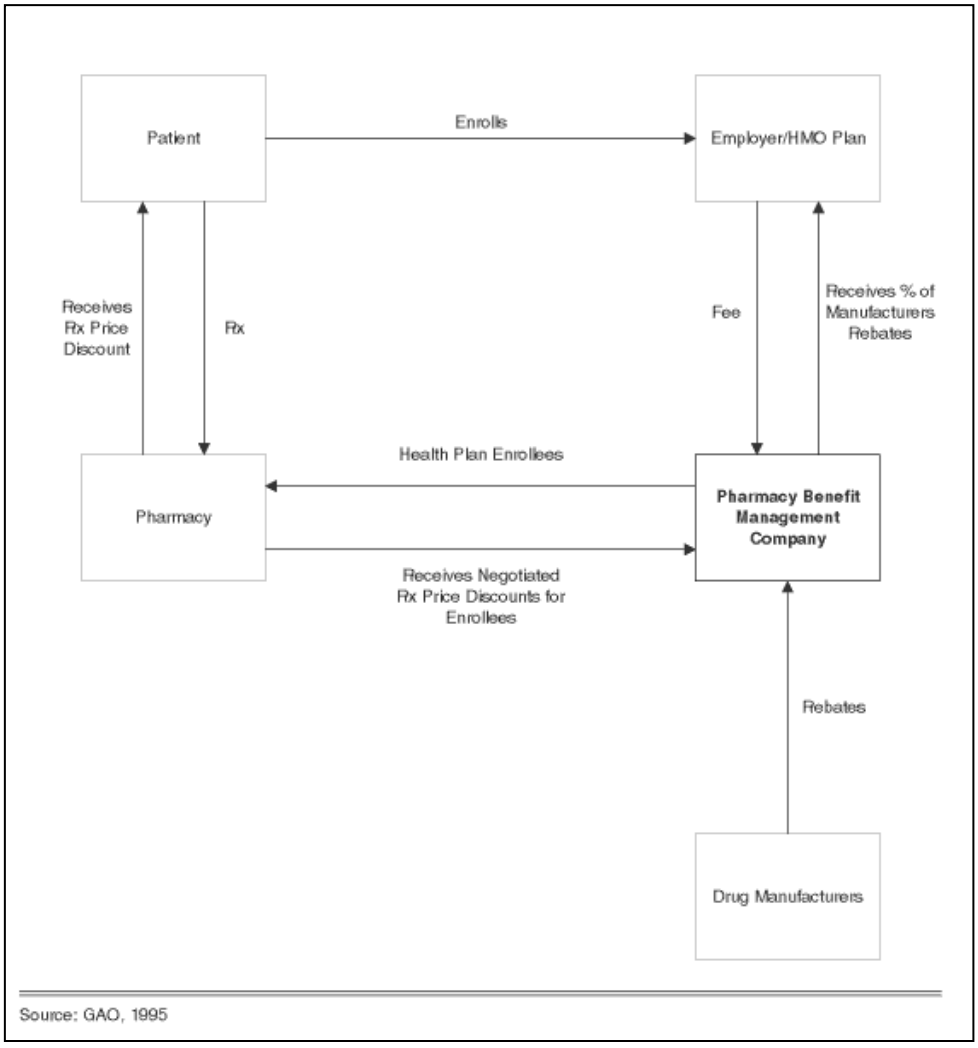

Figure 2. Organization of the Pharmacy Benefit Market [12].

The main goal of the PBM industry the negotiation of lower prices for drugs and devices in order to curb the rising costs of healthcare in the United States. PBMs also determine "drug formularies" which list the medications or devices that should be covered by different insurance policies available for patients [9]. The establishment of the PBM market was originally in the interest of patients; however, the information produced through negotiations and developing drug formularies has become marketable data. Many drug manufacturers who have produced and "passed" a product are turning to Pubs to conduct statistical analyses to determine how a particular drug is performing on the market. The ownership of such data and ability to run statistical analyses has proved to be very profitable for PBM's on top of the profits gained from being an intermediary entity between insurance and pharmaceutical companies. Again, a conflict of interest exists since Pubs are benefitting financially to misrepresent the results of the statistical analyses of the product on the market in order to retain the pharmaceutical companies business. Under pressure from pharmaceutical companies and possibly under-the-table financial incentives, a PBM would much rather use the collected data to further increase profits by making a drug appear better than it really is than to lose relations with well-known pharmaceutical companies. Another interesting facet of this relationship is the new trend in the purchasing of PBM companies by large drug manufacturers therefore increasing the likelihood of a conflict of interest, for example, the merging of UnitedHealth and Optum Rx.

Doctors participating in a clinical trial, commonly referred to as investigators, are responsible for administering drugs and monitoring enrolled patients. These direct interactions with patients, through enrollment, testing, and interpretation of results, have the potential for investigators to introduce bias to a study. Although the pharmaceutical companies do not always explicitly employ investigators, there is still much interaction and communication between the

two parties during the process of a clinical trial. This opens channels through which biases can occur, keeping in mind the incentives pharmaceutical companies have to falsify data in clinical trials. Although the majority of physicians are facilitating clinical trials to foster the development of new and improved drugs, some are vulnerable to financial briberies offered by pharmaceutical companies to alter the results of a clinical trial.

Lastly, but most importantly, the patients and those who are not enrolled in clinical trials are affected by the decisions of the various entities in the healthcare industry through the development of expensive and ineffective drugs. However, contrary to the economics of the goods or financial markets, a consumer of healthcare products lacks the medical knowledge to make appropriate decisions about their health or prescriptions. Patients rely on doctors to provide their best advice and knowledge and generally have no basis to question a doctor's prescriptions, therefore conceding the power of decision of the consumer to those qualified to prescribe treatment. Since the doctor has incentives other than patient health, another level of complexity is added to the prescription of medications, enrollment in clinical trials, and bias creating behavior. Overall, patients can be harmed by the medications and devices created in biased trials, therefore making the issue of confounded clinical trials of the utmost importance.

Chapter 3- Means of Confounding by Investigators

Randomized clinical trials (RCTs) have become the standard in testing new and old medications or treatment regiments in the medical field. An RCT has four main components: a control, statistical analysis of results, level of concealment, and randomization of treatment assignment [8]. Much like any scientific study, a control group must also exist in order to compare the effects of the active treatment against a baseline. In order to compare these two groups, summary statistics are performed to determine the effectiveness and statistical significance of the trial results. Prior to the beginning of a clinical trial, the level of concealment must also be determined. The concealment level refers to the amount of information regarding the trial provided to investigators involved and patients enrolled in the trial. For example, if the level of concealment is low, the investigator may be told the allocation of patients therefore allowing the investigator to know whether the patient was assigned to the active or control treatment group. This type of information exposure could lead to a self-fulfilling bias in that the investigators' expected results alter the true results of the trial by recording only those responses that support the expectation of the investigators. The majority of trials that are confounded via "selection bias" are those that lack concealment and reveal the history of patient allocations to investigators.

The last and most important aspect of an RCT is the random assignment of patients to treatment groups. The most effective method of randomization is heavily debated; however, the scientific community has explicitly agreed on the utilization of a common randomization procedure entitled "permuted block procedure". The details of this procedure are outside the scope of this paper but are very important when considering the validity of a clinical trial [11].

The confounding of trials seems near impossible when randomization and history concealment are enforced; however, because trials involve humans, there is a great margin for error where information can be exposed and prediction can occur. These errors can lead to selection bias in two forms: direct or indirect selection bias [4]. *Direct selection bias* occurs when the allocation sequence is supposedly randomly determined, like the flipping of a coin, but the coin is flipped until the preferred outcome is reached [4]. Therefore, the investigator preferentially determines the allocation of the patient, cancelling the randomness associated with flipping a coin to determine the sequence that can lead to misleading results. On the other hand, *indirect selection bias* occurs when an investigator does not directly affect the random allocation sequence, but rather the physical allocation of the patient into a particular treatment group [4]. For example, the allocation sequence is pre-determined before the start of the trial and adhered to for the endurance of the trial. However, if an investigator prefers to enroll a patient because the patient is expected to respond well to the active treatment, the investigator will defer the enrollment of this patient until the probability of the patient ending up in the desired treatment group is highly likely. If this continues to occur, a treatment may appear to be more effective than it actually is because of the higher response rate of patients preferentially enrolled in the desired treatment group. This will most definitely lead to a confounded clinical trial and invalid results.

The ethical responsibility of investigators is another topic that is introduced when discussing selection bias. A physician is responsible for administering and monitoring the patients enrolled in a study. Generally, the doctors are already familiar with a patient's health situation prior to the start of the study. One ethical dilemma investigators face is whether to disobey the randomized assignment and assign a very ill patient to an active treatment group.

The physician places these patients in a group study that may not at all benefit the patients' health but is a required action for the validity of a study. Therefore, sympathy for patients by the physician becomes an influential factor as to whether or not the doctor will corrupt the trial and cause selection bias. Whether the influence is internal in the form of sympathy or external, such as financial incentives from pharmaceutical companies, investigators tend to act in a manner that is likely to produce bias and potentially confound the results of a trial.

The means by which selection bias is created occurs mostly through investigators familiarity with a particular randomization procedure. Familiarity of a procedure like the permuted blocks for example, allows for "excessive prediction", making preferential patient enrollment much easier and more successful, giving reason for the discovery and implementation of a new and unfamiliar randomization procedure. Not only will a new procedure protect randomization from excessive selection bias, but it will also be above average simply by virtue of being different due to the lack of familiarity investigators will have with new procedures. Although researchers know selection bias occurs even in RCTs, there is still not an adequate way to detect it. The rank correlation coefficient technique presented in Chapter 5 will provide a new possible way to detect and, therefore, prevent selection bias to ensure the validity of a randomized clinical trial.

Chapter 4- Quality Guidelines: The CONSORT Statement

Considering the great importance of the validity of randomized clinical trials, it would be correct to assume there are some means of regulation in the testing and reporting of data prior to FDA submission. Although there is not federal regulation, rather a document entitled the Consolidated Standards of Reporting Trials (CONSORT) Statement comprised of particular "guidelines" aimed at increasing and ensuring the validity of RCTs. The CONSORT Statement originated in 1996 and was revised once in 2001 and again in 2010 with the expectation of improving clinical trial quality [10]. The entity that has the ability to require RCTs to adhere to the CONSORT Statement is journals that edit and publish scientific studies. However, the decision of the journal to follow these guidelines is optional and the requirements are somewhat superficial, for example the idea that the title must simply state that the study is randomized (Figure 3). The CONSORT Statement is organized into a checklist describing the requirements of each section of a study for publication as seen in below (Figure 3) [2].

Consolidation of Standards for Reporting Trials—CONSORT[3,4]

Heading	Subheading	Descriptor	Was It Reported?	On What Page No.?
Title		Identify the study as a randomized trial.[7]		
Abstract		Use a structured format.[8,9]		
Introduction		State prospectively defined hypothesis, clinical objectives, and planned subgroup or covariate analyses.[10]		
Methods				
	Protocol	Describe Planned study population, together with inclusion/exclusion criteria. Planned interventions and their timing. Primary and secondary outcome measure(s) and the minimum important difference(s), and indicate how the target sample size was projected.[2,11] Rationale and methods for statistical analyses, detailing main comparative analyses and whether they were completed on an intention-to-treat basis.[12,13] Prospectively defined stopping rules (if warranted).[14]		
	Assignment	Describe Unit of randomization (eg, individual, cluster, geographic).[15] Method used to generate the allocation schedule.[16] Method of allocation concealment and timing of assignment.[17] Method to separate the generator from the executor of assignment.[17,18]		
	Masking (Blinding)	Describe mechanism (eg, capsules, tablets); similarity of treatment characteristics (eg, appearance, taste); allocation schedule control (location of code during trial and when broken); and evidence for successful blinding among participants, person doing intervention, outcome assessors, and data analysts.[19,20]		
Results				
	Participant Flow and Follow-up	Provide a trial profile (Figure) summarizing participant flow, numbers and timing of randomization assignment, interventions, and measurements for each randomized group.[3,21]		
	Analysis	State estimated effect of intervention on primary and secondary outcome measures, including a point estimate and measure of precision (confidence interval).[22,23] State results in absolute numbers when feasible (eg, 10/20, not 50%). Present summary data and appropriate descriptive and inferential statistics in sufficient detail to permit alternative analyses and replication.[24] Describe prognostic variables by treatment group and any attempt to adjust for them.[25] Describe protocol deviations from the study as planned, together with the reasons.		
Comment		State specific interpretation of study findings, including sources of bias and imprecision (internal validity) and discussion of external validity, including appropriate quantitative measures when possible. State general interpretation of the data in light of the totality of the available evidence.		

Figure 3. Original CONSORT Statement Protocol, 1996 [2].

The main components of the statement that protect against selection bias are the reporting of randomization, allocation sequence, and masking or blinding mechanism (Figure 3).

A meta-analysis was performed in 2014 to study the extent of adherence to the requirements of the CONSORT Statement in RCTs performed in adult traumatic brain injury (TBI) [10]. Of the papers published on TBI those in 1976- 2001 versus those from 2002-2010 and 2011-2013, spanning the periods of each revision, exhibit continual improvement in compliance with the CONSORT Statement [10]. In addition, it proves that each revision was effective in increasing the reliability of the TBI RCTs within each period. Although the TBI meta-analysis yields a promising trend in the improvement of RCTs, it is apparent that the reporting in other areas of medical research is “still not at an acceptable level” [10]. It is claimed

that studies continue to lack effective allocation concealment in experimental design and disclosure of the randomization scheme implementation; two factors that are vital in ensuring the quality of a clinical trial [10]. Although The CONSORT Statement and its successive revisions appear to be improving the validity of some clinical trials, other trials completely disregard these standard guidelines and proceed to publications in journals that do not require CONSORT Statement adherence. There are no incentives to follow these rules or repercussions for ignoring them, allowing for the publication of biased clinical trial results. Without consequences for the attempt to publish flawed medical studies, real humans will continue to suffer from the issue of selection bias and confounded clinical trials.

Chapter 5- Rank Correlation Coefficient

Due to the implications of excessive selection bias, the detection of its presence can protect the validity of a clinical trial. The rank correlation coefficient technique, described in this chapter, has the potential to detect selection bias and the extent thereof in post-trial analysis if the allocation sequence is predetermined. Depending on the randomization procedure chosen and the allocation probabilities[1] assigned, an investigator bent on forecasting allocations can attempt to rank his/her probability of guessing the future treatment assignments correctly based on the conditional probabilities of the treatment assignment history. This is a ranking system where the investigator ranks, for example, the next four allocations from 1, where guessing correctly is most likely (high predictability), to a rank of 4 where guessing correctly is least likely (low predictability). These ranks are *expected* ranks because the actual treatment assignments have yet to be revealed to the investigator. The investigator can calculate these expected ranks of future treatment assignments and use this ranking to decode the allocation sequence to manipulate the assignment of patients.

For example, a study exists where the active treatment (T) and the control or placebo treatment (G) patients are randomly assigned to each treatment group depending on the randomization procedure that produces the treatment assignment sequence for this particular trial. Preceding the n^{th} treatment assignment the investigator can calculate the probability of treatment T based on the randomization scheme and the past treatment history[2] for each future patient. Although he/she can calculate the probability of T, the investigator does not perfectly

[1] Allocation probabilities: the likelihood of a patient ending up in one treatment group over the other. Can be 50/50 or any other set of probabilities depending on which randomization procedure chosen for the study.

[2] Treatment history refers to the previous treatment assignments, T or G that patients have received.

know the probabilities of T the n_{+1}, n_{+2}, or n_{+3} for patients yet to be treated. The investigator can then assign ranks for the consecutive three patients' conditional probabilities of T. After the allocation sequence and treatment assignment are revealed, one can calculate the actual ranks assigned for each T or G treatment. Using the Spearman rank correlation coefficient equation the correlation between the investigators expected rankings and the actual ranks could be quantified [13]. Generally, the correlation result will be within a range of -1 to +1. The closer the coefficient is to +1, the more successful the investigator was at determining how his/her current guesses compared to his/her future guesses, therefore indicating the presence of selection bias.

When a procedure involves ranking, it is likely that rank ties will surface. There is a specific methodology to solving the tie problem in a ranking system called the "mid-rank method" [7]. For example, an investigator would first rank a series of four probabilities for which he/she would assign four ranks and then order those ranks from top to bottom rank. Assume that the top rank, rank one, is the most predictable probability and the second rank is less predictable than the first, however more predictable than the third and fourth rank. If say ranks three and four are tied, meaning they have the same probability and are equally predictable, they would be assigned a rank of 3.5, the average of 3 and 4 [7]. This method would also work in a scenario where there are multiple ties. For instance, within a five rank allocation, the first rank has a higher predictability than the other four, that all happen to have equal probabilities, results in a four-way tie. Adhering to the mid-rank method, the averaging of the four remaining ranks: 2, 3, 4, and 5 equals 3.5, therefore these ranks would all be denoted with a 3.5 ranking, reflecting the equal probabilities of the last four ranks.

The current mechanisms designed to detect selection bias define bias by the amount of "excessive" guessing that occurs when investigators believe a high probability of guessing

correctly exists. However, this is technically not reflective of the true definition of selection bias because investigators may be guessing excessively, but it is assumed that they do not know when that probability of guessing is heightened to ensure success. Simply because an investigator believes he/she can guess correctly today depends on the probabilities of guessing in the future. Should the investigator guess now and take the chance at possibly a lower probability of being correct, rather than waiting for a higher likelihood of correct guessing in the future? The advantage of employing the rank correlation coefficient method is demonstrated by the detection of patterns of the investigators ability to predict when guessing will most likely be correct in the future. Although this procedure is merely a proposal, the implementation of such methods is expected to detect and therefore reduce the presence of selection bias in RCTs.

Chapter 6- Conclusion

Although many clinical trials succeed in bringing safe and beneficial drugs and devices to the healthcare market, it is important to understand that biasing activity occurs and has the ability to confound a clinical trial. In healthcare, it is highly unlikely that a patient has the knowledge about one's health situation to question whether a prescribed medication is a biologically active product or rather a pill of ground horse hooves. This fact alone allows for the discovery of loopholes, which are then taken advantage of through unethical, profit-seeking behavior of pharmaceutical companies, investigators, and others involved in confounding a clinical trial. It is shocking to most that a physician would intentionally confound a trial, but when financial or sympathetic incentives are involved, as they sometimes are, investigator behavior changes as do the trial results at the discretion of a few individuals. The lack of strict and punishing regulation for attempting to publish flawed medical research reinforces the desire to cheat the system, despite the efforts brought forth by the CONSORT Statement.

Regardless of the ineffectiveness of preventative measures against selection bias, implementing a successful detection mechanism such as the rank correlation coefficient can improve the validity of results gathered from a randomized clinical trial. It is unknown to most the doings of drug manufacturers in clinical trials however, through exposing this injustice, it is the hope that a lesser number of harmful or ineffective drugs will reach the market, therefore preventing the negative consequences of selection bias from harming innocent patients.

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