Title 1: Randomized controlled trials, the gold standard with?

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Aim

"Randomized controlled trials appear to annoy human nature - if properly conducted, indeed they should." - Schultz 1995

Randomized Controlled Trials (RCTs) is by a majority of the medical community considered as the "gold standard" for medical research. This essay is aiming to see if RCTs also are ethically sound.

Introduction

A randomized control trial (RCT), sometimes also refered to as a randomized clinical trial or a randomized controlled trial, is a commonly used study design in clinical trials. A fundamental idea of the design is to group the patients prior to the study into (most commonly) two the random selection of patients into these groups are the "randomized controlled" part. The patients are then treated according to their group. Typically one group receives a novel treatment, and the outcome of the group is compared to a "status quo treatment". Another typical example is comparing the treatment to a group given a placebo. If the two groups of patients are equal, the effect of the better drug should reveal itself.

The idea is not new, the history of RCTs begins in the 18th century, during the age of sail. Long voyages and monotenous food-supply on navy vessels resulted in a heinos condition, costing an estimated 2 million lives between 1500 to 1800, scurvy. Documentation of the symptoms of scurvy dates back to Hippocrates, and symptoms of a scurvy-like disease was recorded by the ancient egyptians some 3500 years ago. A cure however, had eluded man for centuries [1] This changed in 1747, when James Lind, a Scottish physician, proved that sailors drinking citrus was spared for the disease. The detail that separates Lind from the others, is that instead of setting out to prove that a specific remedy helped, he carefully selected 12 patients, gave two and two different treatments, and watched the outcome. Patients were selected for the group to be is homogeneous as possible in respect to severity of disease, diet etc. The common diet in itself is interesting "...water gruel sweetened with sugar...fresh mutton broth...boiled

[1] Some honorable mentions goes to Jaques Cartier who learned to drink water boiled with Eastern White Cedar, Sir Richard Hawkins who recomended orange and lemon juice, and John Woodall that recommended fresh fruits in general

biscuit with sugars" and "barley and raisins, rice and currents, sago and wine and the like" [**?**]. Two patients took "elixir vitriol" thrice a day, two others got vinegar, two got cider, two got an "electory recommended by the surgeon general", two got seawater (!) and the last two got two lemons and one lime each day. All patients apart from the two citrus-consumers (and to a lesser extent the cider-drinkers) deteoriated and Lind concluded that citrus was the best remedy. These weeks in the ultimo of May 1747 changed medicine.

Today, in and around the medical community, such a design is the gold standard. It is the study design said to be the design of which all other designs should try to replicate. A search for "Clinical" and "Randomized Controlled Trial" as a publication type in the database of US National Library of Medicine (PUBMED) gave on the 20. of June 2017 308 669 results, numbers gradually increasing since XX Another role of RCTs is that they are gate-keepers of new drugs, which has to pas one (or sometimes several) RCTs to become avaliable on the market. For being such a large and leading part of the medical field, the ethical considerations should also stand to great scrutiny. A full covering of the ethical concerns of RCTs is beyond the scope of a meager essay. I will focus my discussion on XX concerns, first "The dilemma of the physician-scientist", secondly I will highlight a problem with

Now is a good time to introduce some kind of practical situations, grounding our discussion in some borderline real-life situations. A physician is conducting a trial, testing a new form of monoclonal antibodies to treat an especially nasty type of cancer. The new treatment is though to have mild side effects, as shown in a small prior cohort of cancer patients, compared to the standard treatment (several rounds of chemotherapy). Now a RCT is planned and executed, with 50 patients receiving the new treatment and 50 patients receiving the standard treatment. All patients signed a written form of consent and were randomized into each group according to established good practises. As we will make ourself omniscient for the sake of argument, lets assume that the new treatment is *vastly* better than the standard treatment, both in curing and increase the quality of life of the patients.

The first aspect I want consider, is the person conducting the RCT. She has a dilemma. Lets assume that she is a physician, she would then be a "physician-scientist", a termed coined by Hellman and Hellman [cite]. The term is rather apt, although a bit unmusical describing two roles that are difficult to reconcile. The physician connects deeply with the patient. As Hellmann and Hellmann cites Leon Kass: "the physician must produce unswervingly the virtues of loyalty and fidelity to his patient." It is simple to argue that this relationship should (and to a large extent also is) mandated primarily by deontological ethics. The physician feel a *moral* obligation to help her patients. Close (some might argue closer) is the concept of *virtue ethics*. Beuchamp and Childress, cited in the paper "A virtue ethics approach to moral dilemmas in medicine", named five virtues applicable to the medical practitioner: Trustworthiness, integrity, discernment, compassion and conscientiousness. The physician that adheres to these five virtues should fulfill the common notion of a "good doctor". Either if the main rationale stems from virtue or moral obligation, the physician should do what is best for her patient. This extends naturally to all patients, and even though the physicians time and energy are limited resources, the "good doctor" would either disperse her time across all patients or refer the patients to another (good) doctor.

Now, the other of the dual roles of our physician comes into play, the scientist of the "physician-scientist". I have used the word "patient" but I could just as well have used the term "research subject" to further separate the "care from the experiment". It would be naive and a bit simple to say that the scientist disregard the well being of the

patients. On the contrary, the felt responsibility towards *future* patients is potentially quite strong, with compassion and the intent to do no harm. Although it is also natural to describe the scientific effort also in terms of deontological and virtue ethics, we are now moving to a realm where consequence-ethics is arguably more natural. A smaller group (the research subjects) are sacrificing themselves for some "greater good", the potential of a better cure. This is text-book utilitarianism.It is then tempting to accept RCTs based on consequencialism alone.

However, in my opinion it is far from straight forward, to illustrate: Consequencialism relies on the consequences of actions. But, when does the consequence arise? Immediately after the action? A lot of actions are merely chains of events, where one "action" blends into another "action". When the chain of actions becomes long, the influence of each action becomes smaller, and the endpoints on the chain becomes rather arbitrarily. Where does the chain end? To illustrate we might do a more elaborate though experiment: A researcher in Brazil is doing a large RTC on patients suffering from our aforementioned nasty cancer. A parallel study is also conducted in Mexico, and is starting to recruit patients when the Brazilian study is well under way. Now, the patients in the Brazilian study are having bad side-effects of the new drug, and the study is cancelled. The Mexican physician-scientist is also cancelling his experiment, feeling that it is unethical to risk the well being of the patients. The cancellations are ethically sound, sparing the patients harm from the seemingly worse treatment. But, in the land of Brutopia, a Brutopian physician-scientist does a trial anyway, driven by her own ideas and relaxed regulations. The trial goes very well in favor for the new therapy, with strong positive response when compared to the previous therapy. Some years of research down the line, it becomes clear that the reason for the severe side-effects in the Brazilians were due to a rare gene shared by many Brazilians, but almost none Brutopians. The lessons learned from the Brutopians were shared to the rest of the world community and appropriate patients (lacking the Brazilian gene) were treated and suffering in the world was reduced. Now, the Mexican physician-scientist did the ethical right thing, both in light of moral ethics and consequencialism. But in hindsight, so did the Brutopian, although unjustified at the time it is according to consequencialism retrospective ethically sound. Further more, this argumentation could be used to justify fluke experiments if it could be pointed to other fluke experiments retrospectively shown themselves to yield good (and ethically sound) results.

One could argue that such a scenario is highly unlikely and quite "artificial" and contrived. But I would argue that it showcases a problem with "pure" consequencialism, knowing *when* and *where* to stop and calculate the tally of positive and negative consequences is notoriously difficult. The very least we must accept, is that our chain of actions and consequences can be broken down in small incremental steps, and each step yields a sum of "good" consequences. Only then is RCTs (or any kind of clinical trials for that matter) justified.

The outcome of the experiment is unknown for the physician-scientist, it is unknown for the patient and it is unknown for the whole medical community. Given that the new treatment is fully ineffective, having no treatment ability, we have introduced a lot of suffering, with no benefit. Conversely, if the treatment is enormously more effective than the current treatment, we introduce suffering by not offering the treatment to the patients in the control arm. Either way, suffering in the form of sub-optimal treatment is inevitable, it is a fundamental pre-requisite for the trial to have meaning. The afore-mentioned physician-scientist dilemma now comes full force. In order to gather medical evidence, the "good doctor" must become less of a good doctor for some of her patients, and fulfilling the role of

both physician and scientist becomes difficult. It is evident that continuing a trial where (perhaps for unforeseeable reasons) a large amount of suffering has been introduced is unethical. In a utilitarian view this is fairly unproblematic given the payoff in the end, but it goes at the expenses of the integrity of the patients as moral subjects.

A solution to this dilemma is not evident. One possible angle of attack, is to have a clinical trial lead fifty-fifty by a physician and a scientist. This might create more problems than solutions, the internal struggle becomes an external. We could remove the physician from the equation entirely, if we argue strong enough that the patients are merely research subjects. In practice this could back-fire, a d

A mandatory requirement in almost all clinical trials are a written consent from the patients. The process of obtaining written consent is in a large number of countries formalized and tightly regulated through review boards and ethical committees. The consent must also be "informed", meaning that the patients must have an understanding of what the risk and benefits are. The written consent should remove some of the problems encountered previously. The patients *knows* that they risk harm from the treatment and they *know* that they help to increase the knowledge about the disease. And they are perfectly *fine* with that, they have, after all, given their written consent. It is the ultimate get-out of jail-free card for the scientist. There are obvious problems with it though. If we consider the written consent as both necessary and sufficient, we exclude treatment designs on subjects that are not considered to be able to give consent, like children and the severe mentally handicapped.

If the patients wants to sacrifice themselves on the scientific alter, we should let them. There are some problems with this as well. The validity of written consent relies on the factor the patients have understood the full consequences of their signing. This extends understanding the stress and unpleasantness associated with the "extra" non-beneficial interventions (e.g. blood drawing and sitting still for hours in a scanner). A more fundamental, and problematic concern is that the patients do not understand that they are *not* treated but experimented on. This notion has its own term "therapeutic misconception", coined by Applebaum in the early eighties. The patient believes he gets the best treatment. This is not however because the patient is stupid. Consider for

Are the patients first and foremost patients or are they research-subjects?

Should we remove the medical doctors from the trial? Introduce the "good enough doctor".

I have used the terms "better" and "worse" treatments when comparing two treatments being tested. Implicit I have though of the "better" treatment as the more effective (making the patients free from their illness). However, we could include a number of parameters making a treatment "better" or "worse". One is side-effects, if two treatments are equally effective, but one of the treatments result in severe side effects, the other could be thought of as "better". It is not evident however, what the individual patient consider as a more severe side effects. If one treatment results in severe dis figuration, and another (equally effective) side effect results in prolonged fatigue, some patients would prefer one that another might not prefer. Should we, in a state of true equipoise (if there are such a thing) let the patients decide which treatment to take, based on their preference in regards to side effects? One is likely to say that this introduces bias in the randomization process. If some clinically relevant parameter is associated with the aversion for a certain side-effect this can indeed be damaging for the integrity of the randomization. However, *some* level of "non-randomization" is a large part of

An important aspect in an RCTs is something called "power", or "statistical power". One conducts an analysis before the RCT start and calculates the needed participants in the study to reveal an effect. The results from an "underpowered" RCT should be considered "scientifically worthless" (Halpern citing Altmann). To call them