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 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. In this essay I will try to highlight some aspects of RCTs in general, describing and dealing with concepts such as equipose, blinding, written concent and so on. I will then discuss these elements of RCTs as well as RCTs in general within

[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

the most common ethical frame works, first and foremost utilitarism and deontology. Lastly I will try to sum up with some concluding remarks.

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 human subject. 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: 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 apparent 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 ineveble, it is a fundamental pre-requisite for the trial to have meaning. The afore-mentioned physician-scientist dilemma now reveal itself. 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 unforseeable 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

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

Should we remove the medical doctors from the trial?

The patients themself - are they just means to justify our ends?

Written consent - yes, but do the patients know that?

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 a lot 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.

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