QUESTION 1

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Question 1(a)

Describe the ethical issues in placebo control trials and explain how they might be overcome by design modifications.

Answer 1(a) (800 Words)

In a placebo-controlled trial, patients are randomly assigned to either the test treatment or a 'placebo control'[5]. A 'placebo' is a treatment that appears identical to the test treatment, but does not contain its active element[5]. This, however, does not mean that those in the placebo-controlled group are necessarily untreated[5]. A placebo is necessary for blinding, so placebo-controlled trials are almost always double blind, and in fact some trials that are not placebo-controlled include a placebo to aid in blinding[5]. Placebo-controlled trials are generally superiority trials, where a difference in outcome between the two groups is the measure of treatment effect[5]. They have the ability to control "for all potential influences on the actual or apparent course of the disease other than those arising from the pharmacologic action of the test drug" (ICH-10, 2000)[5] by facilitating blinding, randomisation, and the inclusion of a group who receive an inert treatment[5].

If no effective treatment is known for a given condition, then there is often no ethical issue with utilising a placebo controlled trial[2;5]. Ethical issues may arise when there exists an effective treatment which is known to prevent serious harm, such as death or irreversible morbidity[5]. If patients are fully informed of the available treatments and the consequences of delaying treatment, and no serious harm can befall the patient by being on the placebo, then a placebo-controlled trial is generally considered ethical[5]. This is true even if the patient would experience discomfort as a result of being on the placebo[5]. Other ethical issues may arise if patient's conditions can worsen if they are on the placebo for too long[5].

To deal with these ethical issues one can employ design modifications[5]. A three-arm trial utilises both active and placebo controls, meaning that the number of patients on the placebo is reduced, and it is possible to improve this even further by making the active groups larger than the placebo groups[5]. It also has many methodological benefits[5]. It does not address the issue of the length of time patients are on the placebo. Three-arm trials are considered the gold standard in placebo-controlled trials[8]. An example is Adrion et al. (2016) who investigate betahistine treatment for Menieres disease[1].

An alternative design is an add-on trial, in which the placebo is actually a standard treatment, and the test treatment is assessed in patients already receiving the standard treatment[5]. Thus, patients are always receiving the best-known treatment, alleviating that ethical issue. It also allows for patients who would otherwise be caused serious harm to be included, and allows for long-term studies. There are, however, some methodological issues with this type of study that limit the situations in which it can be applied, such as only looking at the combination treatment, and not the mono-therapy[5]. An example is Lind et al. (2015) which adds Liraglutide to daily insulin injections[7].

Replacement design is a variation on add-on design, in which the placebo or test treatment is added at random to the standard treatment, and then the standard treatment is withdrawn, usually by tapering[5]. One then observes the ability of each treatment group to maintain the patients baseline, thus it is particularly useful for chronic diseases[5]. This obviously cannot be used with those at serious risk, but it can give information on mono-therapy while avoiding withdrawal symptoms and revival of symptoms in a wash-out period[5]. An example is Ducharme (2002), a systematic review which describes studies tapering doses of inhaled glucocorticoids to investigate the monotherapy of Anti-leukotrienes[4].

A limited placebo period is also a design modification[5]. At the beginning of a trial every patient is on a placebo, and after a short period they are each randomly assigned to either an

active-control or the test treatment, and continue without a placebo group[5]. This is useful when long-term placebo treatment is unethical[5], though it still cannot include patients at risk of serious harm, and has the methodological issue of only being able to study short-term effects[5]. An example is Hoksrud et al. (2011) which switches all control patients to the active treatment after 4 months[6].

An adaptation of this is a randomised withdrawal trial, in which every patient begins the trial on an active treatment, and at a specified time, each patient is randomly assigned to either stay on an active treatment, or switch to a placebo[5]. This addresses the ethical issue of patients spending a long time on the placebo, and allows for long-term effects to be investigated[5]. An example is Tandon et al. (2016)[9]. The time spent on the placebo can be improved even further when used in conjunction with early escape, allowing patients to switch back to an active treatment if their condition worsens[5].

Other placebo-controlled design modifications include additional doses or factorial designs, but it is not obvious how they can alleviate the ethical issues[5].

Question 1(b)

Describe the methodological issues in active control trials and outline how they might be overcome by design modifications.

Answer 1(b) (800 Words)

In an active control trial, patients are randomly assigned to either the test treatment or an active control[5]. The active control is often the current, historically established, standard treatment for the illness[5]. Usually they aim to be double-blind trials, though this is not always possible[5].

Active control trials can have one of two distinct aims, then can either aim to show superiority of the test treatment over the active-control treatment, or non-inferiority or equivalence of the two treatments[5]. In either case it is critical to consider whether the trial demonstrates assay sensitivity; the ability to distinguish an effective treatment from a less effective or ineffective treatment (ICH-10, 2000)[5]. If a superiority trial lacks assay sensitivity, then it will fail to show the test treatment is superior and fail to conclude efficacy of the test treatment[5]. If one of the treatments is shown to be superior then the trial had assay sensitivity[5]. If a non-inferiority trail lacks assay sensitivity, then it may find an inferior treatment to be non-inferior, and falsely conclude efficacy[5]. Non-inferiority trails, however, generally do not have such direct internal evidence of assay sensitivity as superiority trials[5].

Randomised and blinded active control trials generally minimise subject and investigator bias, however since all subjects are getting an active treatment, for partially subjective evaluations this could result in a decrease in observed treatment differences and increase the chances that the results of the trial are not representative[5]. It should also be noted that non-inferiority trials can require very large sample sizes, since the differences in treatment effect will be small, as will the non-inferiority margins[5]. Large sample sizes are also needed for superiority active-control trials, since the difference between the test treatment and control will always be less than that between the test treatment and a placebo[5].

To deal with these methodological issues one can employ design modifications. A three-arm trial utilises both active and placebo controls, allowing it to measure effect size (test vs. placebo), and compare the test treatment with the active control where assay sensitivity is established by comparing the active-control with the placebo[5]. This also addresses the issue of bias as there would be a chance to not be on an active treatment. Since there are less people in each group however, this may lead to an increase in the necessary sample size, however, making the active group larger than the placebo group could improve the precision and bring it partly back down. Three-arm trials are considered the gold standard[8]. An example is Bensdorp et al. (2015) which provides evidence that two test treatments were non-inferior to a standard treatment[3].

An alternative design modification is a limited placebo period, in which the trial begins with all patients on a placebo, they are then randomly switched to either the active control or test treatment [5]. This is useful for establishing assay sensitivity (at least for short term effects) when long-term placebos are not acceptable [5]. This however does not address the issue of bias or sample size, and as noted may only establish assay sensitivity for the short term. An example is Hoksrud et al. (2011) which switches all control patients to the active treatment after 4 months [6].

Randomised withdrawal is another possible design modification, in which patients begin by being randomly assigned to either the active control treatment or the test treatment [5]. At a specified time, patients will be randomly assigned to the placebo, and stop receiving active treatment, or to remain on their current treatment [5]. Any change after the switch demonstrates an effect of treatment, and thus assay sensitivity [5]. This improves on the limited placebo period trial by allowing the study of long-term effectiveness [5]. Again, this does not improve on the necessary sample size, but would still require less than a three-arm trial, but would not improve bias as much. There are also other issues that need to be considered with this study such as withdrawal effects [5]. An example is Tandon et al. (2016) in which patients who maintained clinical stability were randomly assigned to either placebo or lurasidone for an additional 28 weeks [9].

Additional doses design, where multiple fixed doses of the test treatment are considered, is also a possible modification [5]. It allows assessment of dose response and fair comparison of treatments [5]. It will not address the issue of bias, as all patients will still be on active treatment (unless a placebo is included) and may even increase the necessary sample size, but it may aid in establishing assay sensitivity in both superiority and non-inferiority trials [5].

Other active-controlled design modifications include early-escape or factorial designs, but it is not obvious how they can alleviate the methodological issues [5]. When a non-inferiority active control study cannot be carried out, or would be too difficult to interpret, one could use an add-on study, which is a placebo-control study [5].

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