

UNCERTAINTY PRINCIPLE VERSUS CLINICAL EQUIPOISE IN CLINICAL TRIALS IN SUB –SAHARAN AFRICA: ARE THEY REALLY TENABLE?

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Abstract

The argument for ‘evidence based medical practice’ is compelling and the ideal protocol of randomized controlled studies to obtain higher level evidence is equally sound. However, some peculiarities of African countries make the conduct of standard control trials difficult and raise some serious ethical questions over claims of good trial practices. It may be difficult to apply the uncertainty principle or clinical equipoise as moral underpins for randomization in clinical trials in Africa. A ‘social contract’ argument may be a useful alternative.

Key words: Clinical trials, Sub Saharan Africa

Introduction

‘Evidence based medicine’ can be argued to be a justified renaissance in medical practice. The principle of best ‘evidence’ acquisition demands randomization of patients to alternative treatment modalities or comparison of known versus new/proposed treatment modalities.¹ One ethical issue is how to justify placing a candidate in one treatment modality and not the other, since by default; any patient wants the best treatment. Various arguments have been used for these placements. These arguments may not hold true African regions. Can they be modified or do we need another moral standpoint as a justification?

The ethical arguments for randomization

Two principles are now used as moral underpin for randomizing patients into trial arms and the one applied really depends on whether you are in Europe or America. These principles are; ‘The Uncertainty principle’² and ‘Equipoise’.² The former claims that we do not know the ‘best’ treatment for the illness, that we genuinely believe that the patient is fit for both the trial and known treatment and that we are

confident in these believes. The central rationale being that if the best treatment is “unknown” then people contribute to posterity at no cost (e.g. ‘the best treatment’) to themselves. ‘Equipoise’ refers to regarding two treatments as equal in prospect. Equipoise may be ‘clinical’ or ‘patient’². Clinical equipoise may be ‘Collective’ where the profession at large is equally balanced or ‘Individual’ where the researcher accepts such a position. Patient’s equipoise is better presented than defined, and is observed when a group of patients are well informed of the benefits and risks of alternative treatment modalities and patients that chose any modality as are so treated but those undecided are said to be in ‘equipoise’ and randomized into the study. These principles are themselves conjectural and are still debated.³ While the uncertainty principle is favored in Europe, equipoise appears to be the American option. Can these principles operate in Africa? What could be the moral underpin for randomization of patients into trial arms in this region of the world?

The defects in “equipoise or uncertainty” in Africa

It can be argued that a primary quality of doctor-patient relationship is “Trust”. This implies a patient’s

confidence in the reliability of the doctor and imposes a duty of benevolent concern for the interests and welfare of the patient (altruism) while respecting the patient's right and capacity to self determination. Medicine has no room for utilitarianism (i.e. end justifies the means) nor paternalism (like making decisions for competent patients).⁴

In most of Africa the 'best' treatment is often not available and /or unaffordable.⁵ The routine practice of the clinician may often be 'the available' treatment. In such circumstance the 'uncertainty principle' may be difficult to evoke as the clinician is reasonably certain there is a better treatment. Also, most trial candidate drugs are fresh from the discovery-production pipeline and are by definition costly. This implies that the prospect of contributing to 'posterity' in the context of the patient's environment is remote (and even more so in chronic illnesses). The justification for pushing an 'uncertainty' agenda in these situations is to rationalize that the patient may at least benefit from the free trial drugs: this is classic 'utilitarianism' with underlying 'paternalism' and therefore betrays 'trust'. Thus the 'uncertainty principle' could be difficult to justify in Africa.

Given the uncertainty of the 'uncertainty principle' in Africa, equipoise may be the available 'justification' for randomization. An immediate problem is the patient's autonomy which places 'patient equipoise' superior to 'collective and/or individual' clinical equipoise.⁶ It can be argued that patient's equipoise is the true equipoise of clinical trials because clinical equipoise demands beneficence. This requires 'justified true belief' which may only be claimed without the risk of betraying patients' trust after the study. Patient's equipoise requires that the patient is sufficiently competent and informed to make decisions. Most patients in Africa reflect the high level of illiteracy. This is clouded by cultural taboos and role allocations that often place decision making to others like husband, community leaders and religious leaders. Detailed information to patients in such a context may mean 'informed scaring of patients'⁷(an 'unphysician' approach) while decision by others simply imply 'surrogate' equipoise.

Advocacy for "Social contract" in clinical trials in Africa

Africans must take treatments and this implies that clinical trials must be conducted. What then, could be the moral underpin for randomization? A solution could be to apply the "Social contract"² argument which pursues that individuals agree to relinquish some of their natural liberties in a civil society for

collective advantage. This may be patronizing if proposed in the context of 'the human race' but may be tenable if obvious gains to the immediate society are contracted. These may include guaranteed supply of subsidized test and treatment(s) and obvious relevance of the trial to the test community's disease pattern. Clinical trial design may have to be restrictive to less risky types like 'sequential trials'² where outcome are continuously monitored and the trials terminated according to predetermined stopping rule and 'crossover studies.'² This ensures that all patients benefit from the available and proven treatment modality. Zelen's design² may be particularly useful in surgical trials because it compares standard versus novel methods. It randomizes patients before seeking consents and only needs consent from the trial group.

The basic principles of patient randomization into clinical trials in Africa are difficult to implement. Meanwhile, while the need for standard conduct of clinical trials anywhere cannot be argued, the realities of Africa may compromise such trials. Perhaps subtle modifications of trial protocols that do not compromise the integrity of the patient may be useful in this region.

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