The Equitable Inclusion of All Populations Into Clinical Trials From a Distributive Justice Perspective. *By Colin L. Soskolne, PhD*

A meaningful clinical trial is one which is developed to answer the question of the relative merits of a proposed new way of treating a particular clinical condition or disease process. We must be sure, as scientists, that when the clinical trial "experiment" is over, we have a valid reference point against which we can evaluate the success of our trial. We must be able to compare what we have discovered concerning the outcome of, say, a new drug designed to intervene in the natural course of a disease process, with the effect of either an old drug, or of no drug at all used to treat or prevent the onset of the particular disease of concern. The question then becomes: *What is the effect of the new mode of treatment (or, prevention) when compared to either the former mode of treatment (or, prevention) or to no treatment at all?*

In any scientific experiment of this type we must ensure that we have not only an experimental arm (e.g., a new drug whose effect we are trying to determine through rigorous scientific enquiry), but also a control. The latter serves as the baseline against which new attempts at treatment (or of prevention) can be evaluated.

Good science requires judicious application of resources to address important public health concerns. Sampling is usually an efficient and effective strategy. However, representative random sampling is optimal because it permits conclusions that can be generalized to a larger number of people outside of the study itself. The term Randomized Controlled Trial (RCT) is the generic form of trial, representing the most powerful of all epidemiologic study designs. The experimental treatment is ideally administered in a double-blind fashion, where neither the participant nor the experimenter is aware of what drug (active ingredient or placebo) that the participant has been assigned. This helps to reduce the likelihood of bias.

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Scientific Validity, Values and Ethical Conduct

In thinking about fairness (i.e., equity) when considering whom to include in any type of clinical trial, we must remember that we are engaged in a scientific experiment to which we must remain true. Without being true to our science, with its associated methods and approaches in the pursuit of truth (i.e., the pursuit of valid findings), we certainly cannot be true to the patients and people that we serve and hence to those in whose best interests we are working.

Without being true to the rigors of the scientific method, no good is done for any person, or group of people that we, as scientists, are attempting to serve and in whose interests we work. Good science means conducting ethically replicable and systematic work to advance knowledge one step at a time. So, what then are some of the rigors about which we must be concerned?

Science operates in a value-laden word. Whereas we like to think of science as an objective pursuit – a value-free or value-neutral enterprise – the instrument of science, namely the scientist, is not value-free. Our social context ingrains in each of us biases that influence not only the way we behave, but also the way we think about problems. Consequently, from the very questions that are tackled, to the manner in which they are formulated and addressed, there are both conscious and sub-conscious biases and interests at play that can confound our attempts at objective science. To help control bias in epidemiologic research: (a) the peer review process exists for research proposals and publications; and (b) ethics guidelines exist to help thoughtful scientists to maintain, among other things, their integrity.

General ethical considerations in experimentation with human beings require that we "respect the autonomy of each person (i.e., the individual's right to self-determination", "do good (i.e., beneficence)", and "do no harm" (i.e., *primum non nocere*, or non-maleficence). These are the three of the four principles foundational to the conduct of ethical biomedical research, of which the clinical trial is but one of many different research approaches. The fourth principle is that of "distributive justice", requiring the fair and equitable distribution of resources to all without discrimination. It is the latter principle that is the focus of this essay.

However, it is important to recognize that no one of the above four principles can be addressed in isolation. In fact, all four principles are in a constant state of tension, with trade-offs needing to be made. In the United States, recognizing the trade-offs is one of the tasks of the Institutional Review Board (IRB). These Boards are composed of a broad range of scientific, philosophical, religious and lay competence. Their responsibility is to be accountable for (a) maintaining both individual and community rights to privacy, and (b) ensuring that the research being proposed conforms to normative standards considered within the context of local values, all within the broader social and legal environment.

One example worth noting about distributive justice pertains to clinical trails of AIDS and HIV vaccines in the 1980s. Large Pharma had conducted trials where design efficiency and cost would be optimal – in Africa. However, once the vaccine might have been available, the local African population would not have been able to afford access to it. The unacceptable concern that put a stop to such research came from the distributive justice argument that those who take the risks (through participation in any such trial) should also be able to derive the benefits from such a drug had it come to market.

Defining our Purpose and Our Terms

For clinical trials, the scientific method requires that we define our areas of concern very specifically. So, we must ask, for

instance: *What is the disease of concern? What kind of person is affected (e.g., young, old, male, female, black, white, rich, poor, and so on)? Who are we trying to help with any potential new therapy? Will we be causing more good than harm? Are people's rights being respected?*

But, in the real world, life usually presents to us not simple dichotomies of extremes (e.g., black and white, good and harm), but rather with many shades of grey. This makes the design of clinical trials all the more of a challenge.

The scientific method used in clinical trials research falls within the domain of clinical epidemiology. What is clinical epidemiology? The "clinical" portion refers to what takes place to maintain and improve patient care; the "epidemiology" portion refers to a branch of applied science that is concerned with assessments made on the population level. It is here that we are concerned with the need to carefully define the population of concern so that we may address the issue of distributive justice.

By "population of concern" we refer to those groups, or classes of people that have certain attributes or conditions, and in whose interests we are working to maintain and/or improve their health and well-being. So, implicit in this is the selection of eligible people from a defined group (population) of people who we then will ask to volunteer their participation in a clinical trial. Unless we have carefully identified and randomized patients or participants that are eligible for our trial, we cannot know how to generalize our research findings. Any inference made from a poorly designed experiment would be of little value and could likely be of harm to people, even to those beyond the trial.

Selecting Trial Groups

Epidemiologists study diseases where they occur. So, if diseases do not occur in men, we will not study men. If diseases occur in the young, they ought to be studied among the young. If diseases occur among the indigent, then they should be studied there, all so that conclusions of relevance can be reached. Further, it is of questionable value to study a new drug in one demographic group, and then infer that the same drug at the same dosage will have equally beneficial effects in other demographic groups.

Recognizing these points, however, we also must acknowledge that research, as with most other endeavors, is resource-constrained. We thus have to optimize our research designs. This is where our individual biases can heavily influence our decisions. For instance, the vested interests of stakeholders can severely influence the nature of our scientific question (e.g., HIV-AIDS research gained significant amounts of funding in North America after pressure from at-risk population groups was exercised). If it is the interests of a business venture to discover for profit a new way of controlling a particular disease, then that business will drive the research agenda. Access to affordable drugs becomes the challenge after such ventures in the so-called free market.

As will be seen in ethics guidelines for epidemiologists, to ensure that research is community relevant, community engagement/involvement in a steering committee will help to provide insight into the disease to be investigated. This can also help in accrual to trial, and in translation (from bench to practice). Engaging the "population of concern" in the research process in this manner may also enhance distributive justice, as the population affected is more informed because of their inclusion in the research process.

The statistical design of a trial is critical to valid conclusions. In this regard, statistical power and sample size considerations feed directly into questions of the cost of trials. It is critical to conduct feasibility studies so that we may enhance trial design. Further, the findings of all studies should be disseminated through a carefully constructed communication plan that should form part of the ethics review for any proposed trial.

Should a drug not studied in pregnant women be taken by pregnant women? What about concern for the fetus? What about dosages in infants, children, and adolescents? Would these be the same as that of adults among whom a trial was conducted? And, among adults of child-bearing age? Could a new drug have effects on fertility and semen quality? Would dosages applicable among poorly nourished segments of the population be the same as those in better nourished segments of the population? And, what about geriatric populations? And, what about phenotypically different members of society? Would the same dose among whites be applicable to blacks; to males as to females; and to the rich as to the poor?

The principle of distributive justice requires that the trials be conducted with all groups to whom the treatment may apply. Each of these questions outline above touch upon the challenges we face in ensuring distributive justice. Although there are no simple answers to these complex questions, there are avenues we can pursue to ensure they are considered.

Conclusions and Recommendations

Each trial needs to be designed to answer a specific question. Namely, the target group needs to be defined in advance and the nature of the question needs to be specifically articulated as this will have direct bearing on the trail design selected. Regarding distributive justice, the issue of paramount importance is the definition of the "population of concern." This definition will help guide the development of the research protocol and ensure that the participants' demographics are consistent with the target population.

So, if the epidemiologist is to design a study in the cancer prevention area, thinking of the type of prevention being undertaken would be important (see Table 1).

The literature contains nothing on the broad topic of the ethical dimensions of clinical trials at the primary, secondary and tertiary levels of prevention. Therefore, it could be of great benefit if such work were commissioned to help establish normative guidelines to better stimulate appropriate research in each of these broad areas.

At the end of the day, concern about what we determine through trials (namely, safety and efficacy) versus what we determine through Phase 4 studies where effectiveness is the concern; that is, concern about the outcome once the drug is commercially available and no longer under the direction of a controlled trial.●

Table 1. Levels of Prevention and Clinical Trials

Primary Prevention	Secondary Prevention	Tertiary Prevention
Trials designed to intervene among people with, say, cancer risk profiles: the objective is to eliminate exposures that could trigger mutagenesis or carcinogenesis (e.g., in occupational settings)	Identify genetic markers, or biomarkers, or even early clinical diagnosis and clinical manifestation (e.g., a breast lump; a skin lesion; a persistent cough) to arrest the process through drugs prior to serious manifestations that could be chronic and life threatening	Surgical and adjuvant chemo therapies, or even natural remedies to rehabilitate to ensure maximal quality of both function and life

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