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# Flaws in Current Clinical Trial Design: Need for Intermediate Markers

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The gold standard for the approval of drugs for use in humans is by demonstrating a benefit in clinical trials. This system seems to have worked very well for most drugs on the market today. However the outcomes of recent trials and the ongoing notices from the Food and Drug Administration (FDA) about the cardiovascular risk posed by already approved medications, calls for the research community to pause and re-think the processes involved in clinical trials. Clinical trials are conducted over a long period of time at an enormous cost to the funding agencies and when the outcomes unfortunately are negative takes a big toll on participants. The length of these trials also contributes to the high cost of medications once approved and produces skeptics in communities where individuals have been harmed by the clinical trial process reducing community participation in subsequent clinical trials.

Most cardiovascular medications developed target a single cardiovascular risk factor during its development and as long as this agent shows improvement in this single cardiovascular risk factor in initial phases of the drug development process, it is assumed that this improvement in this single cardiovascular risk factor would translate into an improvement in cardiovascular events. The ILLUMINATE [1], AIM HIGH and ACCORD [2] trials among others have unfortunately showed that this assumption may be wrong. Despite the improvement in high density lipoprotein levels in both ILLUMINATE and AIM HIGH trial, trocetrapid in the ILLUMINATE trial actually caused harm and niacin in the AIM HIGH trial showed a neutral effect on cardiovascular events compared with placebo. These risk factors and medications interact within the human body to produce an effect. In addition, the drug may also have off-target effects that may results in an overall deleterious effect on the cardiovascular system. Thus the net effect of the improvement a single cardiovascular risk factor, its interaction with other factors and the off-target effect of the intervention in question may be an overall negative outcome on the cardiovascular system and therefore harm participants during the trial process or later on when the drug has already been approved by the FDA and has been on the market for a while. The Rofecoxib (Vioxx) fiasco [3] and the ongoing varenicline (Chantix) [4] episode that is currently playing out are examples of the need to evaluate the off-target effects of even non cardiovascular interventions on the cardiovascular system. There is therefore the need for very active research to identify an intermediate marker, which can be easily measured with minimal or no additional discomfort or risk to participants, reproducible and sensitive enough to respond to a relatively short duration of a participant's exposure to therapy. This intermediate marker should therefore be a global cardiovascular risk marker that captures cardiovascular risk over and beyond all the traditional cardiovascular risk factors combined.

Assessing this global cardiovascular risk early in clinical trials, preferable before the initiation of an intervention and then reassessing this same marker 6 months out in these individuals should give the investigators a sense of the potential direction of the main findings of the trial. This would also aid the Drug Safety and Management Board (DSMB) in making decisions regarding early termination of a harmful intervention or a neutral intervention. This has cost saving implications for funding agencies and would minimize or reduce harm to participants.

A global cardiovascular risk marker would also help explain the findings of these trials. For example even though torcetrapid improved HDL levels it was shown in subsequent research by Connelly et al. [5] that it impairs endothelial function (a measure of global cardiovascular risk) explaining why the increase in HDL levels did not translate into improvement in cardiovascular events. Similarly Warnholtz et al. [6] showed that niacin(ER) does not improve endothelial function. This also provides an explanation for the neutral effect of niacin(ER) in the AIM HIGH study. These findings and others were made either after the trials or whilst the trial was well underway and even though it provides an explanation for the primary outcomes of these trials, it would have been more useful if had been used to signal the DSMB's of a potential harmful/ neutral effects of these medications and therefore aid in the early termination of the trials, reducing the cost of the trials and also saving lives.

The National Institute of Health (NIH), pharmaceutical companies and researchers should focus on identifying a marker solely for this purpose and aim at implementing it for a short duration in all clinical trials to assess the effects of these therapies on global cardiovascular risk. This would provide an additional push for DSMB's to either stop or prolong a given clinical trial and thus save money and lives.

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