

Inclusion of Subjects on Trials Not Meeting Criteria

Lauren E. Ey

Saint Joseph's University

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In the world of cancer research, clinical trials are the driving force in bringing new drugs to market. Clinical trials are a set of procedures in drug development that are conducted to allow safety and efficacy data to be collected. The purpose of the trial is to provide advancements in both health and medicine. Depending on where the drug is in its development process, clinical trials will be conducted in subjects to compare the new product with currently existing treatment or placebo. It is the subjects that are recruited for these trials and the data that is generated, that allow drugs to continue evolution through the phases of development. As each phase is completed successfully, another step of the process has been accomplished and another chance the drug has at coming to fruition. The number of compounds that progress through to Phase 3 pivotal trials are minimal, therefore producing scientifically sound and supportive data is vital to receiving drug approval.

Within this heavily regulated industry however, more scrutiny is being placed on trials and whether they are following true to design. The study protocol acts as the bible of the trial and includes the purpose, scientific rationale, objective, and design, as well as other additional study details. Furthermore, it also outlines the study's target population and specifies the eligibility criteria, which defines what makes an individual appropriate or not appropriate for participation in a study. Otherwise known as inclusion/exclusion criteria, this combined, defines the target population. When designing a protocol, researchers attempt to define all subjects to whom the study question may be applicable and identify factors that may present too great a risk for certain populations of participants. It is important to note, eligibility criteria are not guidelines, but rather requirements that must be followed to ensure and protect the safety of subjects entering the trial.

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In the clinical operations arena, we find all too often situations that arise, specifically within oncology trials, where a clinician at an investigative site has a potential patient presenting with a criterion that is different than what is outlined in the Investigational Review Board (IRB)/Ethics Committee (EC) approved protocol. For example, a subject according to the protocol must be > 18 years old; however they are two months shy of their 18 birthday. Or on the clinical side, a subject may have what is identified to be a very small bone metastasis at screening, and the protocol excludes bone metastasis for entry. These differences could be extremely minimal, but they deviate from what have been included in the protocol. Despite working in this highly regulated industry, investigators sometimes take it upon themselves to continue to enroll the subject in the trial, knowing that all documented criteria have not been met, for the simple fact that this subject has tried all other alternatives and sits before them knowing this is their last opportunity before death. For many of these subjects, time is of the essence as they are extremely sick; therefore the investigator feels they need to make a decision immediately. As Maria Merritt (2005) points out in her paper, *Moral Conflicts in Clinical Trials*, there is a struggle between an investigator decisions as it pertains to clinical trials:

“Many investigators who conduct clinical trials, a form of medical research with human subjects, face inevitable conflict between two moral duties. They have scientific duty: the duty to conduct any trial for which they are responsible so as to produce scientifically valid results in a timely manner, lest the participation of human subjects be in vain. They also have protective duty: the duty to protect human subjects’ medical wellbeing in the face of the medical burdens and risks of research participation. Both duties have wide scope in the context of clinical trials: they both govern an investigator’s conduct of a trial pervasively.”

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It is common practice for the investigator to call the Sponsor's Medical Monitor and ask for a waiver to allow the subject entry into the trial. As long as IRB approval is received prior to the subject enrolling, this is considered GCP-compliant, however there is still the question as to whether a subject should be entered into a trial when criteria has not been met. There is great ethical debate concerning what is the appropriate approach in handling a situation such as this, and whether protocol deviations should be allowable within a clinical trial. I will discuss in further detail through this paper the stakeholders involved and how one could interpret what could be morally acceptable through the eyes of a utilitarian and rights theory perspective, in addition to providing potential alternatives in order to help resolve this ethical debate.

There are a number of different stakeholders that have to be taken into account when determining who is affected by this ethical issue, including the following: the subject, the investigator, the sponsoring company, the IRB, the clinical research associate (CRA), FDA, and the payers. First and foremost, the subject is at the fore front of this issue. As stated previously, for many subjects attempting to enroll in an oncology clinical trial, this is their last option as all other attempts have failed. Furthermore, it is also the future subjects that could be affected by the outcome of the trial, and benefit from approval of the treatment. The investigator plays a key role as they take ownership for making the decision to include or exclude the subject. The sponsoring company is also involved as a stakeholder as they are affected by the decision made by the investigator, as well as forming their own decision on how to handle this situation. The IRB should be approving a protocol amendment to document this change, and is tasked with ensuring a protocol is safely designed. The CRA could be considered a stakeholder since they monitor the site to ensure the trial is being conducted according to GCPs. Finally, the payers are involved as they provide funding for a subject to participate. All of the stakeholders identified play a key role in health care delivery and making an ethical decision.

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From a utilitarian point of view, the course of action of enrolling this subject into the study is not maximizing the overall good for the greatest number of individuals. As John J. McCall points out in his paper, *A General Introduction to Moral Theory*, utilitarianism “takes the objective of morality, general human welfare, and argues that the most straightforward understanding of that is captured by a principle which urges us to do what is necessary to produce the greatest net collective well-being”(p.6). Considering the likely consequences of this action, the overall risk is much greater than the benefit. When identifying the benefits that result from enrolling a subject, one could argue that similar to sales, the clinical project team has timelines and forecasts that have to be met. By allowing ineligible subjects into the trial, this is a sure way to enroll the trial quicker, resulting in potentially getting a drug to market quicker. The subject and the investigator are also directly satisfied as the subject will now have access to potentially novel therapy. The subject could be perceived to have benefited as they are being provided with a course of treatment that would otherwise be inaccessible. It could be considered altruistic in nature to permit this subject into the trial; however the trial is being exposed to potential jeopardy, resulting in the risk being greater than the benefit. By allowing subjects on trial who do not meet criteria, the sponsor is deviating from the protocol design and defined treatment population, and allowing their own interests to be put above the protocol’s intent, therefore not keeping the greater good in mind. The investigator is putting the prospective subject at risk, as their criteria differ from the IRB/EC approved patient population that was meant to be eligible for enrollment. Therefore, this action could result in affecting the safety and efficacy of the data as the study was designed for a different subject population. At the conclusion of the study, the sponsor risks the FDA determining that the intended population was not essentially treated as the protocol was designed, and could require exclusion of these subjects from the efficacy analysis. From a utilitarian point of view, the benefit to the greater common

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good is to not allow subjects who do not meet eligibility criteria to be placed on study. By doing so, this will prevent any chances of jeopardizing validity of the data that could result in a promising drug being kept from market, thus sacrificing happiness of others. We must be reminded that the primary purpose of clinical research is to improve future therapy by collecting sound data to prove more effective ways to treat, prevent, or diagnose disease, which in turn benefits future subjects, not necessarily the subject. With that said, by allowing a subject on trial who does not meet criteria, we could potentially prevent good data from being collected and risk the drug from being approved, consequently affecting the satisfaction of those affected and minimizing the greater benefit.

A potential alternative to this matter is for pharmaceutical companies to implement expanded access programs, which allows use of an investigational drug outside of the clinical trial for those subjects who do not meet eligibility criteria. This would permit therapy to be given safely to the subject who the investigator felt would benefit from the treatment, however was not eligible for the clinical trial. Expanded access programs do take additional time and money to implement, on top of what has already been invested in their clinical programs; therefore they are not always conducted by pharmaceutical companies in parallel to their trials. While it is not as simplistic as it sounds, it can be an alternative if companies would implement these sorts of programs to allow subject's access to drug, that they otherwise would not be eligible to receive. Furthermore, if an expanded access program is not already in place by the sponsor, an investigator has the option to file a single patient IND to the FDA requesting that an individual be allowed access to drug on a compassionate use basis (American Cancer Society, 2011). The FDA can grant acceptance and the subject would then be given investigational product. It should be noted that this process does take time, as a separate Informed Consent Form would be created and submitted. Additionally, the FDA requires time to review the IND and

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grant acceptance, which delays the subject from receiving treatment. If we analyze these alternatives from a utilitarian perspective, one can argue that both alternatives put the greater good in mind. Despite a delay in receiving FDA approval, the subject is still provided with drug that could potentially save their life, while the sponsor does not compromise data as the investigator refrained from enrolling the subject into the trial. Overall, the greater benefit is maximized with these alternatives. With that said, investigators quite frequently do not have the option of having an expanded access program for their subject, which leaves them in a situation described above, where they want to do what is in their immediate power, in order to provide comfort and benefit to their subjects.

From a rights theory point of view, the argument seems to be similar of that from the utilitarian perspective. It can be seen that by deviating from the protocol, the sponsor and investigator are violating the protocol in ways that affect the rights, welfare and well-being of study subjects. At first glance though, one would argue that the subject's right to life, which could be interpreted as entry into the trial, should triumph all other rights as this is a basic right, one that is essential for treating people with dignity and respect. However, we must realize that the subject's right to life could be jeopardized by entering the study, as the safety and risks of the treatment have not been defined for that subject, and are largely unknown. Therefore, the subject's right to safety and well-being should be what is most important in making this decision and their right to life is influenced by such. It is the stakeholder's right to ensure that safety is met in the study. Safety is a derivative right that is instrumentally valuable because of the good it promotes. The IRB's responsibility and role in a clinical trial is to ensure they are providing an independent assessment of the risks/benefits of the study. The IRB is required to make certain determinations during protocol review, including a determination that "risks to subjects are minimized: (i) by using procedures which are consistent with sound research design and

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which do not unnecessarily expose subjects to risk” (U.S FDA, 2011). Protocol deviations do not necessarily allow the risk/benefit to the subject to be evaluated as the research was not designed to allow this specific subject. Overall, the subject’s right to their safety and well-being is the driving force behind making the decision not to enroll a subject in a clinical trial that does not meet criteria.

If we assess the same alternatives described previously, that of an expanded access program or compassionate use setting for the subject, we find a similar outcome when evaluating from a rights theory perspective. When an investigator chooses to file a single patient IND with the FDA, the risk of safety is still largely unknown, and could potentially outweigh the benefit to the subject. The option of having an expanded access program available to investigators is ideal for situations such as this, where the sponsor and FDA have approved the program, and it runs parallel to the clinical trial. This would cause less harm to the subject as the population receiving the investigational product through expanded access program would have already been defined by the sponsor and the FDA, and would be similar to that of the clinical trial. This would provide the maximal benefit to the subject as it would minimize the risk and supply the subject with study drug. Furthermore, sponsors would avoid compromising the data from their clinical trials as these subjects would not be enrolled by the investigators.

In summary, the decision to enroll a subject into a trial when they do not meet eligibility criteria is one that is ethically charged. I believe that the investigators are truly taken the subjects safety and well-being into account when enrolling them into the trial, but in reality this may not be the appropriate thing to do as the risk will likely outweigh the benefit. Many times the investigators believe the deviation is safe for the subject; however the question that remains unanswered is whether if enrolling that subject, would or would not have influence on the

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scientific integrity of the trial data. Looking through the eyes of both the utilitarian and rights theory perspectives, both point to the direction that the subject should not be enrolled. In both circumstances, the risk/benefit ratio and the rights of those involved, all conclude that the results are unknown and more harm can be caused enrolling the subject than not. In today's world, we know that protocols are being amended quite frequently to change criteria so it may be less conservative than the study was originally designed, but when looking into this issue a bit deeper, it is something that does have a great moral debate associated with it. Unfortunately, the decision goes back to the principle that the primary purpose of clinical research is to improve therapy for future subjects, therefore collection of strong, good data is key in order to prove more effective ways to diagnose, treat, or prevent disease. Hence, providing benefit to subjects on the trial could be considered secondary. As I had previously discussed, if expanded access programs are implemented by sponsors, this would result in less protocol deviations and avoid compromising of data, however these programs are not always realistic and are generally unavailable, as they too have financial requirements associated. Therefore, investigators find themselves in the same situation when it comes to deciding if a subject should or should not be enrolled. As easy as the decision appears to be, it is a bit harder for an investigator who is confronted on a daily basis with a subject sitting in their office, suffering from end stage cancer, and of which all treatment options have failed. This could be their last hope at any potential for quality of life and prolongment of death, and the investigator's judgment of risk could be clouded with the simple fact that this human being may benefit from the treatment.

References:

American Cancer Society (2011, June). Compassionate Drug Use. Retrieved from <http://www.cancer.org/Treatment/TreatmentsandSideEffects/ClinicalTrials/compassionate-drug-use>

McCall, John J. *A General Introduction to Moral Theory*.

Merritt, Maria. (2005). Moral Conflict in Clinical Trials. 1.

U.S Food and Drug Administration (2011, August). CFR - Code of Federal Regulations Title 21. Retrieved from <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/CFRSearch.cfm?fr=56.111>