



Ethical issues in competing clinical trials

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ABSTRACT

The proliferation of clinical trials in the last decade and the relatively limited number of experienced clinical trial sites in comparison has created in some sites an environment of clinical trial abundance. As clinical trial protocols typically restrict patients from concurrent clinical trial participation, and patients may be eligible for more than one trial at any given time, selecting the best trial for an individual patient requires evaluation of not only the merits of the individual trials but also patient preferences. This article highlights some potential ethical issues which should be considered when clinical trials are raised as a treatment option and when patients are eligible for more than one trial at the time of evaluation.

1. Introduction

The clinical trial landscape has evolved. The growing proliferation of trials, investigating an increasing number of potentially promising novel disease therapies and health interventions, has grown disproportionately to the number of experienced clinical research centers. As of June 2017, there were close to 250,000 studies listed in [clintrials.gov](http://clinicaltrials.gov) (of which over 42,000 were listed as recruiting), representing a seven-fold increase compared to 2007 when approximately 35,000 studies were listed (Source <https://clinicaltrials.gov>). This registration has been a regulatory requirement since 2007 in accordance with Section 801 of the US Food and Drug Administration Amendments Act for certain clinical trials of drugs, biologics or devices and is also required by the International Committee of Medical Journal Editors (ICMJE) as a condition for publication.

This has created in some centers, an environment of clinical trial abundance. Eligibility criteria for clinical trials may be sufficiently broad that patients may qualify for several trials at a given point in time, and even in instances where inclusion criteria are relatively restrictive, a patient may meet the eligibility criteria for more than a single trial. This poses a relatively new dilemma for clinical investigators, ethics committees and patients.

1.1. Competing Clinical Trials and Current Approaches

While in some contexts, clinical trials are much less abundant such

as in orphan diseases, these will not be discussed here. The following discussion is also prefaced on the assumption that a decision has already been made to consider clinical trials offering interventions as potential treatment options, and this represents a very specific segment of patients in clinical practice (i.e. those who have diseases for which investigational treatments are available, who are treated at, or referred to participating trial centers and who would be eligible for, and consider an investigational treatment for their disease). When more than one clinical trial investigating experimental treatment options exists concurrently, with partial or total overlap of patients for inclusion within the same institution, this has been referred to as competing clinical trials [1]. This creates a need to strategically assess the available trials with invested stakeholders including treating physicians, research investigators, institutions, funding agencies, ethics committees and should arguably also include patients, and caregivers.

Protocols generally restrict enrolling patients in more than one clinical trial at a time because determination of clinical efficacy and safety of a treatment cannot be established in a straightforward manner if not studied in isolation from other concurrently administered investigational therapies. In some cases, it may be possible for patients to be enrolled in more than one clinical trial at a time, a situation referred to as “co-enrollment” into concurrent trials, which is conceivably possible and potentially advisable if the protocols in question permit it, patient safety is in no way compromised, and if appropriate measures are taken to ensure statistical and scientific integrity, and ethical soundness [2]. In cases where it is not ethical, practical or safe to enroll

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eligible patients into multiple clinical trials, the foreseeable issue, and the focus of this article, becomes how to approach which patients, for which trials.

From the point at which it is decided that clinical trial options should be considered, current approaches range from full disclosure of all available trials, to a paternalistic approach where physicians select the preferred trial(s) to present to their patients based on factors such as individual patient risks or co-morbid history, potential of the investigational treatment to have therapeutic benefit, study requirements, or random approaches [3,4]. There are other strategies, which may appear somewhat arbitrary, such as prioritization of studies based on remaining time for recruitment, ‘first come first served’ basis where the first approved study at an institution will take priority for enrolling eligible patients, or alternating eligible patients from one study to another [3,4]. Proposals have been made for institutional policies that prioritize recruitment for some trials over others in the interest of minimizing the number of studies that do not complete enrollment as ethical justification that limits patient exposure to unnecessary harms or burden [5].

In some exceptional situations where clinical trials are considered the most promising of available treatment options, it may result in a demand for participation exceeding the number of available spots, shifting the focus from a primary aim to protect patients from harms to ensuring equitable access to limited therapies [6]. In these instances when the balance between protection and entitlement becomes more heavily weighted in the direction of entitlement, recommendations have been proposed to ensure fair access, such as enrolling the sickest patients first followed by random selection [6].

The decisions around optimal patient enrolment strategies in the increasingly common environment of competing clinical trials is fraught with challenges [1], and potential conflicts of interest should be openly addressed to help guide clinical investigators and their staff to consider the ethical ramifications of certain approaches over others. Compensation, personal interests, collegial or political pressures may result in sacrificing patient best interests for those of the investigator or institution, and the risk of such biases may further be amplified when the treating physician is also a principal or sub-investigator for one or more of the competing trials under consideration.

This is an issue which neither falls under legal nor regulatory purview. Physician investigators do not have a legal responsibility to inform patients of all clinical trial options when discussing treatment options with patients, and treatment options that are only available within an investigational research context do not legally have to be disclosed at all [1,7]. Regulatory bodies evaluate each clinical trial application independently and may provide regulatory approval for investigational sites to conduct the research but they do not mandate which patients should be approached for a given study (only that those who are entered meet the eligibility criteria), much less how the situation of competing clinical trials should be managed.

Nevertheless, the ethical issues are apparent. From the point at which clinical trials are identified as a viable treatment option, withholding information precludes full disclosure of all available options and consequently true informed consent. While clinical equipoise establishes that there is genuine uncertainty of potential benefit to be obtained from clinical trial participation, it also maintains that potential benefit cannot be reasonably ruled out. In the extreme case, this could result in denied access to therapeutic options which may hold promise. This potentially divisive issue has not been extensively addressed to this point by ethics committee policies. Since studies are rarely submitted for ethics review at the same time, ethics boards typically review merits and risks of individual studies rather than multiple studies contemporaneously. In many cases, there may be no obligation to ensure that there is a comprehensive strategy in place to best manage patient enrollment if all protocols are approved at a single research center, although research ethics policies may advise distribution of specific populations across multiple centers. The central

question becomes whether there should be ethical guidance for managing such situations. As the primary responsibility of research ethics committees is to assess potential risks and harms, protect research participants and endorse high ethical standards in health research, the issue of competing trials should arguably fall under their scope of responsibility and a framework for providing consolidated periodic review of competing research is perhaps warranted.

2. Discussion

With the currently limited involvement of research ethics committees on this issue, investigators must use their best judgment, reach collegial consensus independently, or when need arises, find other sources of mediation, for example with the support of hospital or departmental administrators to guide the process to be adopted.

The basic tenets to ensure ethical treatment of human subjects who volunteer to participate in clinical trials are met through the foundational concepts of respect for persons, beneficence, and justice [8,9]. Respect includes allowing patients to have the autonomy to choose which, if any, study they decide to participate in based on their individual beliefs and values, the right to decline, and opportunity to withdraw without loss of any potential benefits. Beneficence entails putting the welfare of the patient before all other goals including the research objectives, or investigator interests, and ensuring that actions and choices do not inflict harm on patients. Justice refers to the fair treatment of patients and equitable distribution of benefits and harms.

Trials differ in important aspects, including investigational treatments and their associated efficacy and safety profiles as well as trial schedules and burden. While there may be practical considerations such as geographical proximity of the patient to the centre, length of the study, number of visits or availability of study site resources, that should be considered, neither physicians nor ethics committees should in isolation make decisions about which studies should be presented to patients based on assumed risk profiles or perceived burden as these are only meaningful if individual patient perspectives and preferences are considered. A patient may not necessarily prefer the study with fewer visits, or they may choose the study with the highest potential risk if they perceive these are outweighed by the potential benefits in their individual circumstances.

Furthermore, for potential clinical trial participants, equitable treatment can only be achieved at a given time point if all potentially eligible patients are offered the same trials. Fair subject selection rests on the premise that factors such as patient vulnerability (including factors such as health literacy, socioeconomic status and intellectual capacity), privilege, or investigator interests (such as direct compensation or academic or clinical interests) not dictate which patients are offered which trials. The interests of patients or society as a whole should have greater privilege over interests of institutions, industry and investigators.

2.1. Mitigating conflict of interest

Full disclosure of all competing trials to some extent may mitigate the risk of investigator conflict of interest from interfering with decisions. Without it, the risks are certainly amplified. The principle of autonomy is violated by selective presentation of a subset of available clinical trials, and this may potentially be tied to self-serving interests or pressures on investigators and institutions rather than decisions made in the best interest of the patient. This could result in studies with the highest remuneration, perceived scientific value or ability to promote individual investigator interests being preferentially presented to patients.

Political, practical, and economic factors may intentionally or inadvertently play into a physician's decision not to disclose all available investigational options to a patient and to circumvent this interference, patients should be informed of all options in an unbiased and balanced

approach.

2.2. Funding considerations

Funding through public sources which are perceived as scarce and competitive are also accompanied by a perceived prestige factor that only the most promising, innovative, and scientifically important studies are selected to receive such funding. In contrast, private funding sources may be seen as less competitive, less altruistic by virtue of ultimately being seen as a profit driven enterprise and more plentiful by comparison. Institutional and investigator reputations and livelihoods may be sustained by such research grants through public funding agencies, making these studies a preferred option to channel eligible patients [10]. When publicly funded studies are in direct competition with privately funded sources, the favored option may be the former even in cases where the risk/benefit ratio for the individual patient may favor the latter (although the benefit of the 'greater good' and contribution to science may be disputed here). The bias can also conceivably work in favor of privately funded studies due to higher remuneration and the potential to be established as strongly performing clinical research sites, increasing the chances to be selected for future industry sponsored clinical trials.

Protocols differ with respect to stringency and scope of participant inclusion and exclusion criteria. In cases where patients meet inclusion criteria for two or more studies, they may be directed to enroll in the most restrictive of the protocols resting on the justification that allowing patients to choose between them could result in an imbalance, leaving the most difficult to recruit studies ultimately under-recruited. This may result in investigators or institutions not meeting commitments established by verbal or contractual agreements and delaying progress and outcomes of these studies. Using factors such as time period of remaining recruitment to decide which studies should be offered to patients, face similar criticisms, as the importance of enrolling equitably across trials should be outweighed by the ethical priority of serving patient best interests, even when they may be in competition with the best interests of the individual studies or sponsor agencies.

Collegial and fair conduct between investigators may also be in direct conflict with ethical treatment of patients [1]. For example, channeling patients sequentially in the order in which studies were approved may be a collegial and fair distribution of eligible patients, however, this may come at the cost of failing to divulge the trial that would have been preferred by a given patient. In one published case, because of a long-standing collegial relationship between two investigators, one of these investigators chose only to recruit patients to a certain trial if they were not eligible for the other trial run by his colleague [1]. This prevented those patients who were eligible for both studies from receiving the potentially more beneficial, less risky and less burdensome of the options. While published documentation of these kinds of collegial agreements is not widely available, one can imagine that in the setting of competing trials, the opportunities are rife for *quid pro quo* arrangements to arise unspoken or even be openly established.

When resources are limited and practical or other constraints dictate an approach which includes presenting a limited subset or a single study from the available options, a driving factor in selecting which studies to present may be based on safety and efficacy profiles of investigational drugs, stage of drug development, as well as physician preference or experience. Only by systematically evaluating the evidence of available treatments can a valid comparison of treatments be made. Furthermore, failing to present all available trials to patients (on the grounds that one trial is likely to be safer or more effective than another in the eyes of the investigator), is an example of strong paternalism that diminishes patient autonomy.

2.3. Can disclosing a single trial be in patient best interest?

Physicians expressly trained to evaluate objective scientific evidence, may arguably provide more accurate probabilities of therapeutic success, and be in the best position to determine optimal treatment options. It can be argued that presenting all studies to patients, often in tight time windows, results in a high volume of information that may only serve to create confusion and undue distress for patients, resulting in decisions being made without fully comprehending the often complex nuances and attributes of different studies and treatments. Presenting trial options and requesting that patients choose may prove excessively burdensome and may ultimately result in impeding informed and timely decisions. Furthermore, in some cases, the acute or critical presentation of patients to centers in emergency situations may preclude any opportunity for discussion of trial options.

These situations do not always arise as a result of blatant and deliberate actions to serve investigator best interests but can arise innocently and from the best intentions to not overwhelm or confuse patients. The true conundrum arises as the choices made by investigators are inextricably tied to their interests, thoughts, beliefs and experiences.

Studies in clinical decision making, have theorized that there are two mechanisms for processing information in order to make diagnoses and treatment decisions, one of which is a more autonomous, intuitive or reflexive process and the other a more methodical, analytic evaluation and weighing of evidence [11,12]. While there is value in both of these processes in different circumstances, in clinical research, the complexity of study designs, risks in experimental treatments and complex patient histories which must be evaluated when determining suitability of a patient for a clinical trial warrant a more carefully weighed process. Even without an intentional omission of critical information, cognitive biases may come into play and there is a need to appreciate the role these biases may play in treatment and research decisions.

The first step to addressing this issue is to have a clear understanding of the extent and scope of competing clinical trials and to understand how such situations are currently managed within an institution. The next step would be to understand the most pertinent issues of concern from the perspective of physicians, institutions, ethics committees, patients, caregivers and patient advocacy groups. The ultimate goal would be to have some general guidelines which could be universally adopted or consulted in such instances. In some institutions, a concerted effort is made by research staff to go through all enrolling trials at their institution or other institutions in proximity to the patient, and then present all studies for which the patient qualifies by an impartial research staff member. In one institution, this starts with high level issues such as trial objectives, main risks, and intrusiveness of the trial, followed by more detailed information. Their systematic and formalized approach ensures that all patients have equal opportunity to be considered for research programs and eases burden for patients who might otherwise be approached numerous times by research personnel [13].

3. Conclusions

The problem of competing clinical trials presents a growing ethical challenge as the number of trials increase and the number of experienced clinical trial sites remains relatively stable in comparison. When clinical trials are established as an option for patients, to ensure a patient-centric and ethical approach, patients should be informed of the availability of clinical trial options that could be practically accessible to them based on geographic feasibility to participate for example. It is fully recognized that the ethical 'wins' of the full disclosure approach may have associated costs, not only limited to financial and resource related costs. However, our reliance on patients to volunteer in clinical trials comes with the superlative responsibility of serving their personal

and health interests first, before interests of investigators, institutions or industry. We therefore owe it to patients to ensure they not only understand fully, the risks and benefits of individual trials, but that they understand to the fullest extent possible, their available options.

It is ultimately, physicians, investigators, research teams and ethics committees who have a joint ethical responsibility to ensure that all viable clinical trial options are presented to patients and we may learn optimal ways to accomplish this from the experience of institutions that have successfully modeled ethical ways to ensure equitable information and access to research programs [13].

Conflicts of interest

M. Paquette is an employee of Boehringer Ingelheim Ltd.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.conctc.2019.100352>.

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