

Ethical issues in the development of new agents

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Summary

In the early drug development process for cancer therapy, several ethical dilemmas result from the use of cancer patients with advanced disease as the subjects of research in clinical trials studying agents of unknown toxicity and/or efficacy. Although several accepted ethical principles guide the behavior of involved physicians and investigators, many of these principles are allowed to be violated in order to achieve the overall goal of clinical research in improving medical care for future patients. Informed consent has been a process viewed by many as a mechanism which protects potentially vulnerable patients from harm in the clinical trial process. However, the ability of the traditionally regulated process of obtaining informed consent for clinical research may be inadequate to ensure appropriate understanding of the purposes and the goals of early clinical trial research by potentially vulnerable advanced cancer patients. This creates further dilemmas with regard to physician-investigator and patient-subject communications. In the setting of phase I trials, where the specific goal of the research is to obtain toxicity information regarding a new potential anticancer agent, many heightened ethical conflicts are present. The fact that patients do not participate in these studies as a result of altruism, and that their main goals of participation are intensely therapeutic, create issues that may be in direct conflict with the research purpose of phase I trials. As well, the presence of therapeutic intentions on the part of involved physician-investigators creates challenging issues when one realizes the very low likelihood of benefit for individual patients participating in these studies. Within the phase II setting, the statistical constraints placed on new drug trials and, again, the low likelihood of benefit for participating-subjects, also creates challenging dilemmas. These statistical requirements may be in direct conflict with involved clinicians' attitudes and beliefs regarding potential efficacy of an agent in this setting. As well, these issues become problematic when thinking about the desired structure and outcome for informed consent in phase II anticancer trials. The ability to conduct clinical research on advanced cancer patients using agents of unknown efficacy and toxicity is a daunting privilege granted to physicians and accompanying institutions. The weight of this privilege should not be underestimated, and involved physician-investigators should be aware of the significant ethical challenges involved in appropriately and successfully conducting this form of research.

Introduction

The main objective of clinical research in oncology is to improve medical care for future cancer patients. From both a societal and ethical perspective, this is viewed as a laudable and important goal. As such, no meaningful criticisms can truly be offered up against the need and desire to better care for those with cancer. However, when one examines the methods by which this goal is pursued, problematic issues can be

found. As will be discussed, it is the process in which medicine uses current patients as research subjects as a means of achieving this goal where true ethical dilemmas are created.

Ethical principles guide individuals toward correct paths of behavior whether they are operating within the context of medicine or in their daily lives [1,2]. As well, whether in the context of clinical practice or clinical research, several specific principles guide the management of patients by physicians. The first

such principle worthy of mention in this context is, "One ought not to use others as means to an end". In the process of clinical research this general ethical principle is, in many ways, allowed to be violated. However, to allow violation of this principle, it is expected that no patient can participate as a research subject unless there is a significant potential for benefit beyond improving care for future patients, i.e., there must be (in addition) the potential for benefit to the participating patient-subject. No doubt, in considering what is an acceptable degree of potential benefit, this safeguard is in place for a great proportion of clinical research. However, ethical dilemmas which challenge this safeguard are created in the early drug development process involving cancer patients, where the potential for such benefit may be exceedingly small. Here, benefit is implied as it is traditionally measured in oncology, i.e., as a specific anticancer response or improvement in a patient-subject's symptoms.

A second related ethical principle which must guide behavior in this context is, "One should not allow harm to come to others". Certainly, oversimplification or generalization of this principle would lead to the prohibition of specific patterns of behavior in the clinical (non-research) setting of cancer care, where the harm from toxicities is deemed acceptable because of the known benefits to be achieved. Thus, as with the first principle mentioned, the specific issue of harm cannot truly be weighed without consideration of the relative benefit that may be achieved for cancer patients. However, when cancer patients participate as research subjects in early clinical trials of anticancer agents, there is a greater relative potential for harm to come to patients as a result of the specific methodologies and research objectives employed in these trials. In addition to the recognition that benefit is not likely, there is even an expectation that harm will come. In fact, it may even be a goal of the study to produce harm. The safeguard which is in place that allows the violation of this ethical principle is that the potential for harm to participating subjects must be warranted either as a result of the potential benefits to be achieved or (more commonly) that, given the circumstances of many advanced cancer patients participating in such trials, there are perceived to be no other available meaningful anticancer alternatives.

A third ethical principle which guides behavior in this context is, "One ought never to deceive others". Within clinical research, several safeguards are in place which are designed to prevent the deception of patients who become the subjects of research.

The informed consent process itself, and other federal and institutional regulations, provide mechanisms in which oversight of both specific research protocols and the described methods of information provision are present to prevent any intentional deception of patients in order that they may willingly become the subjects of research. More importantly, the conscientious communication efforts of participating physician-investigators are also relied upon to prevent deception. However, in the setting of early trials of investigational agents, where research subjects are most often those with far-advanced disease, many have wondered about the potential vulnerability of these subjects and their ability to be easily led. Indeed, the very fact that the agents under study in early drug trials have shown promise in preclinical models creates a variety of stated or unstated inducements that may play upon some advanced cancer patients potentially overwhelming desire for therapeutic benefit and lead to a process akin to deception, albeit unintentional.

In a final principle worthy of mention, medical ethics itself teaches us that, "The interests of an individual physician's patient should never be placed beneath the interests of others". One can easily argue that placing a cancer patient on a clinical trial involving a new investigational agent does not at all compromise their interest in receiving state of the art care. However, one must keep in mind that the overall goal of clinical research (improving care for future patients) remains intact whenever a patient enters a clinical trial. Thus, at the very least, other interests beyond the individual care of a patient are present when that patient becomes a research subject and enters a clinical trial. As will be discussed, these potentially competing interests can lead to dilemmas. This may be especially true when some trial methodologies are present in order to obtain needed information which will guide the further conduct of a trial, but will not necessarily impact on the care of current subjects in the trial.

To a great extent, the informed consent process for clinical research has come to be relied upon as one mechanism through which these ethical principles are allowed to be violated. With an ethically sufficient consent process, patients may knowingly allow themselves to be used and even harmed in therapeutic research, provided the above mentioned safeguards are in place. As will be discussed below, several elements must be disclosed in this process. In order for the outcome to be an ethically desirable one, these elements must not only be disclosed to subjects but should

also be *understood*. However, difficulties arise when faced with the obstacles of promoting understanding of these elements, as opposed to the easier task of simple disclosure. Within the setting of clinical trials involving investigational agents of unproven efficacy, this is particularly true when one realizes the potential for vulnerability on the part of advanced cancer patients who are the predominant target of such trials. Because of the severity of their disease and overall poor prognosis, the resultant potential vulnerability of advanced cancer patients may inhibit them from benefiting from the traditional informed consent process, and reaching a measurable understanding of the required elements involved in informed consent. Further insight into these issues and dilemmas can be gained by specifically examining the early phases of cancer clinical research and the attendant informed consent process.

Informed consent: concept and ethics

The concept of informed consent, which acknowledges the rights of patients to voluntarily participate in health care, applies both to clinical practice and clinical research [3,4]. Informed consent in clinical research is related to, but recognized as being more stringent than, informed consent outside the context of clinical trials. This heightened consent standard exists for at least two reasons [5]. First, from an ethical perspective, a patient considering clinical trial participation is always viewed as potentially vulnerable [6]. As a result of this potential vulnerability, he or she may have great difficulty in appreciating the differences between the therapeutic and research aspects of a given alternative of care or treatment. Without this distinction, patients cannot make uncoerced and autonomous health care decisions. Thus, the informed consent process, and the ethics of clinical research, require that such a clear distinction be made [7,8]. Second, the physician-investigator is seen as having an intrinsic conflict of interest in his or her role both as a physician for an individual patient and as a scientific investigator attempting to develop improved methods of medical care and treatment [5,6,9]. Within the sole context of a therapeutic relationship, the physician places his or her patient's interests above all else [10]. However, within the context of clinical research, an investigator has additional interests which may not be relative to his or her patients' interests [11–15]. From an ethical perspective, many concerns exist about the

ability of clinical investigators to provide the requisite information to patients regarding participation in research in such a way that allows patients to recognize the distinction between research and therapy [8,16,17].

A definition of informed consent for clinical research that encompasses all relevant aspects of the process remains somewhat elusive, with varying definitions having been described [3–6]. Informed consent is currently and most commonly viewed as a means of protection of a potentially vulnerable research subject from harm. It occurs through a process of communication and information provision between a patient-subject and a clinician-investigator regarding an investigational or experimental treatment. Within this process, several elements must be disclosed. These include the disclosure of the specific type of research to be performed, the risks and benefits of the treatment or research, the unproven nature of the research, the alternatives other than participation in the clinical trial, and finally, disclosure of the subject's freedom to withdraw from, or not to participate in, the research without any detrimental effect on the patient's continued access to adequate health care. Separate from the issue of disclosure within this process is the issue of actual understanding on the part of the patient with regard to these disclosed elements. Whether the definition of informed consent should also imply an actual understanding of these elements, or how much of an understanding it should include, remain matters of controversy [3,17,18]. However, from an ethical standpoint it is accepted that the process of informed consent requires at least some attempt on the part of the clinician-investigator to help a patient understand those aspects of the consent process which have been disclosed to them so that they may autonomously and voluntarily decide to participate [19,20]. Other elements which have been described as an important part of the informed consent process include maintaining the confidentiality of a research subject's participation and, controversially, possible disclosure of potential conflicts of interest on the part of the clinician-investigator.

Most ethical regulations governing clinical research have focused on the informed consent process as a means of protecting potentially vulnerable research subjects from physical and psychological harm [5,6,21]. These regulations have relied heavily on written informed consent documents to achieve full disclosure of the important elements of consent, including the risks of research participation, the nature of the research, and alternatives to research particip-

ation. However, from their inception to the present day, many critics have recognized the imperfect nature of the methods used to regulate the informed consent process [17,22–26]. More recent empirical research on the consent process itself, a great proportion of which as been conducted in the cancer setting, has increasingly demonstrated that although regulations are being followed, informed consent documents have become increasingly unreadable, lengthy, and uninformative [27–30]. Indeed, they may actually be interfering with what might otherwise be an ethically appropriate informed consent process for patients, including not only those with cancer but any patient considering therapeutic clinical trial participation.

In considering the available empiric data, one is certainly left to wonder about the utility and value of the current consent process for therapeutic clinical trials. Particular concerns develop when one recognizes that great emphasis continues to be placed on consent forms and their content. Such concerns become even more challenging in areas where consent forms detail investigational therapies with relatively extreme toxicities or relatively low benefits, and where the therapeutic goals of the alternatives to clinical trial participation may be quite different from the inherent or perceived goals of investigational therapy. The informed consent process for clinical trials of new anticancer agents in phase I and II trials is a setting in which these issues take on great significance, especially if we are to continue to recognize the value of patient-subject autonomy and the moral importance of the consent process as a mechanism of protection for potentially vulnerable patients attempting to make difficult decisions regarding their medical care. Separate from the content of the consent forms themselves, concerns also exist about the overall impact (or lack thereof) of the forms on different aspects of the consent process, including its outcome on the decision-making process of patients *prior* to the eventual decision to actually participate in a therapeutic clinical trial. Several dilemmas have arisen as a result of uncertainty regarding what the actual structure and outcome of the informed consent process should be for patients considering participation in these trials.

The dilemmas of phase I trials

It is in the specific setting of phase I cancer trials involving new agents where the general concerns about informed consent in therapeutic clinical trials are es-

pecially troubling and challenging [6,27,31,32]. This is because phase I trials typically involve patients with advanced, eventually life-ending disease in a research endeavor where the chance of meaningful objective therapeutic benefit has traditionally been described as being quite low, less than 5% [33–36]. As a result of the dose escalation methods in these trials, a more specific dilemma is the relative ratio of toxicity and benefit for patients who participate. Further complicating this is the need to adequately inform patients about these particular issues and then allow them to willingly and freely consent to participate in such studies. The complexities of the consent process for advanced cancer patients in phase I trials relate both to what degree such patients should be viewed as vulnerable, and to what extent a participating physician's own expectations and interests play a role in guiding patients to decide to participate. This unique form of therapeutic clinical research creates an intense environment of medical decision-making where arguably, many patients may not benefit from the traditional informed consent process.

If patients were to participate in phase I trials solely for altruistic reasons, i.e., to help forward cancer research and potentially help future cancer patients, phase I trials would probably carry less ethical conflict. As well, this would imply that the traditional informed consent process might more readily achieve the desired ideal outcome of understanding of all elements of consent, including an understanding of the nature of phase I research and the alternatives to trial participation, as these less vulnerable patients would not necessarily be seeking benefit for themselves. However, the objective information available regarding the informed consent process for patients participating as research subjects in phase I trials tells us that altruism is not the primary motivating factor for patients participating in such clinical research. In addition, as reviewed below, the empiric studies examining the phase I consent process further highlight the true ethical dilemmas associated with this early stage of clinical research.

Empiric research on the phase I cancer trial consent process

Rodenhuis was the first to attempt to evaluate the quality of informed consent among patients with advanced cancer who were offered participation in a phase I trial [37]. In this study, the informed consent process consisted of three separate conversations taking

place between patient, family and investigators (including both physicians and nurses). Following the three consent sessions, patients were surveyed regarding their attitudes and motivations for participation. The majority of patients who gave their consent were motivated either by hope for improvement of their condition, pressure exerted by relatives and friends, or simply because they felt they had “no choice”. Some patients did mention the desire to contribute to the progress of medicine. The investigators concluded that encouragement by relatives or friends appears to be a powerful force in motivating some patients to participate in phase I trials. In similar series of advanced cancer patients from Europe, the United States, and Japan, others have found corroborating results with regard to patient motivations for participation in such trials [38–42].

In one of the most in-depth examinations, investigators at the University of Chicago conducted a survey study of twenty-seven cancer patients who had given informed consent to participate in phase I trials at their institution [42]. Concurrently, the oncologists identified by the surveyed patients as responsible for their care and consent were also surveyed. Eighty-five percent of patients decided to participate in a phase I trial for reasons of possible therapeutic benefit, 11% because of the advice or trust of physicians, and 4% because of family pressure. Ninety-three percent said they understood all (33%) or most (60%) of the information provided to them about the trial in which they had decided to participate. Only 33% were able to state the purpose of the trial in which they were participating, with patients able to state the purpose of phase I trials as dose escalation or dose finding studies being more educated ($p = 0.01$). The surveyed oncologists had wide ranging beliefs regarding expectations of possible benefits and toxicities for their patients participating in a phase I trial. However, the median expectation of benefit on the part of surveyed oncologists was 20%, higher than would be expected from the published phase I trial experience. The authors concluded that patients who participate in phase I trials are almost exclusively motivated by the hope of therapeutic benefit. Altruistic feelings, while perhaps present, appear to have a very limited role in motivating patients to participate in these trials. Subsequent studies conducted by these investigators in a much larger series of subjects have found similar findings. In fact, in larger series of subjects, quantifiable survey data show that patients may even be less aware of the research purposes of phase I trials, and are

unable to recall whether alternatives to clinical trial participation, including palliative care or other non-experimental therapies, were either discussed with, or disclosed to, them [43]. This is despite the fact that all surveyed patients had signed consent forms detailing the research purpose of phase I trials, and the alternatives to trial participation.

A troubling finding from these studies is the potential discrepancies among what has been disclosed to patients, what they think they understand, and what they may actually understand. For example, the University of Chicago study found that 90% of patients stated they understood all or most of the information provided to them about the phase I trial in which they had agreed to participate [42]. However, the data suggests that many patients’ measured understanding of the research purpose of a phase I trial and alternatives to trial participation is quite poor. These discrepancies likely result from several problems, including inadequate informed consent. It may also lie in the methodologic obstacles present in attempting to determine what a patient actually understands in relation to the information they have been given regarding highly sensitive and difficult issues. These obstacles potentially include the ability of such patients who are so highly motivated by the hope of therapeutic benefit, and have come to genuinely believe that they have no other options except investigational therapies, to openly and honestly respond to an interviewer’s questions. Even if subjects had the benefit of disclosure regarding the nature of phase I research, the small possibility of benefit, and alternatives to trial participation, admitting to these elements could potentially have significant detrimental effects on their ability to remain hopeful in the face of an eventually life-ending illness. The process of denial may be a powerful protective mechanism for these highly selected cancer subjects and requires further study.

The available data regarding motivations for trial participation and stated knowledge of the research purpose of phase I trials also suggest that these patients appear to lack a significant degree of understanding with regard to possible therapeutic outcomes from trial participation. A large proportion of surveyed subjects clearly have had therapeutic goals and/or expectations that simply were not achievable [39–43]. Whether these data reflect a true lack of understanding on the part of such terminally ill subjects and how this influences their overzealous expectations is not clear. With regard to unattainable expectations, in a recent prospective study of 37 subjects participating in phase I

cancer trials, Yoder found that patients' expectations not only for tumor response, but also for increased communication with their physician were not met [40]. Their expectations were also not met with regard to improvement of symptoms such as fatigue, nausea and vomiting, and weight loss. They noted that one strong theme that emerged from the data was hope and optimism.

Despite the data from these studies, we still do not yet have a good empirical understanding of what factors encourage patients to choose phase I trial participation over other alternatives of care. The information gained from this research strongly supports the argument that the current process of obtaining informed consent for phase I trials may be inadequate to appropriately insure that such advanced cancer patients have a measured understanding of both the nature of the research in which they are participating, and the alternatives to trial participation. In addition, despite recognizing the existence of their potential vulnerability, we do not know how that vulnerability specifically affects an advanced cancer patient's ability to give what is otherwise perceived to be adequate informed consent. It is possible that several poorly understood, and seldom studied, factors play a vital role in shaping the informed consent process for potentially vulnerable advanced cancer patients considering participation in phase I trials. These likely include relatively subtle and less apparent factors as may exist in other health care decision-making environments for advanced cancer patients, e.g., including patients' awareness of the certainty of their deaths [44–47], and their cultural and ethnic backgrounds [48]. In addition, advanced cancer patients' religious or spiritual beliefs, their degree of hope and emotional well-being, and their attitudes toward medical decision-making may likely influence the shape of the consent process in this setting. From an ethical perspective, these are issues which should not be ignored by clinician-investigators and are extremely likely to be appropriate for more in-depth discussion with advanced cancer patients prior to considering phase I trial participation.

Ethical issues in phase II trials

Some of the ethical issues related to phase II trials of new agents are similar to issues in phase I trials with regard to the participation of human subjects with otherwise incurable illnesses in biomedical research, and the potential vulnerability of these patients in seek-

ing therapy [27,31]. Although still troubling, issues in phase II trials can be viewed as potentially less complex for several reasons. In the phase II setting, there is less of the unknown for both oncologist-investigator and patient, as all agents studied in phase II trials have completed toxicity finding and dose determination (phase I) studies. Thus, there may be greater attitudes of certainty with regard to expected toxicities.

There may also be greater hope or expectations of benefit, in part because these agents are being administered at or near the MTD. Therefore, one unique issue in the phase II trial is the higher likelihood of toxicity developing for all patients in a trial as they are being administered agents at relatively higher doses, as compared to patients in a prior phase I study investigating the same agents. The intentions and motivations of a participating oncologist, in the role of physician-healer or physician-investigator, are central issues in both phase I and II trials. Again, however, expectations or hope of benefit for their patients may be greater in the phase II setting. This may translate into greater therapeutic intent and subsequently be communicated to patients, resulting in greater expectations or hopes on their part as well.

Although these issues may be less complex and more easily examined in the phase II setting involving new agents, they are still troubling as there is an overall low probability of benefit with regard to tumor responses in these trials [49]. In fact, this concern may actually increase even as a phase II study is accruing patient-subjects. This relates to the accepted statistical requirements of phase II trials of new agents which are present to exclude, with an accepted amount of certainty or confidence, a low level of efficacy for a new agent [50]. Traditional stopping rules for many phase II trials would allow as many as 14 consecutive non-responders to accrue to a trial before concluding that the agent lacks disease specific efficacy. Yet, physician-investigators' attitudes and beliefs may change significantly with regard to an agent under study as response data accumulates that suggests a lack of efficacy, but the trial remains open in order to reach the statistically required accrual.

How should evolving data be handled during a phase II trial that suggests a lack of efficacy, but is not sufficiently substantiated from a statistical standpoint? In a study of even a small number of patients, if an agent is given to initial patient-subjects without apparent benefits or tumor responses, but not enough patients have been involved to satisfy statistical requirements, what information should be provided to

prospective patient-subjects? For example, in a simple phase II single-agent study seeking to accrue 14 to 20 patients, if six evaluable patient-subjects have been administered the agent and are known to have not received any apparent benefits, what should the informed consent process consist of for prospective patient-subjects with regard to risks and benefits?

We know oncologists' attitudes, perceptions, and biases toward clinical trial chemotherapy may substantially affect clinical trial accrual [51–53]. These factors are likely to be important for phase II trial accrual. How oncologists, either as investigators or practitioners, interpret clinical trial data from ongoing trials could have a significant impact on their views toward continued accrual. How oncologists assimilate this information and communicate it to prospective cancer patient-subjects likely changes over the course of a trial. Yet, the consent forms for such trials are almost always static—potentially leading to subjects receiving conflicting information. As well, oncologists' enthusiasm or beliefs toward the potential efficacy of an agent may decline as information is acquired regarding non-responders. What is troubling about this is that, quite often, accrual will continue unabated using the same consent process until the statistical requirements for accrual have been satisfied. This may well be justified in order to establish confidence regarding lack of efficacy of a new agent in a specific disease, but the potential dilemma remains and is no less troubling. Some might argue that as non-response information accumulates, such declining enthusiasm for a new agent should be allowed to impact on accrual and should be uniformly communicated to prospective patient-subjects. However, traditionally, after the initiation of a phase II trial, subsequent patients are accrued with little formal response or toxicity information available to prospective subjects about prior evaluable patients in the trial.

Interestingly, if such information could be fully and appropriately withheld from involved clinician-investigators, some of the described dilemmas in phase II trials might resolve themselves. As well, if one could guarantee an unprecedented quick rate of accrual of all the subjects necessary to meet the statistical requirements to a phase II trial, these dilemmas could potentially be less challenging. Practically speaking, these actions are not likely to be routinely achievable.

Research on these issues in the phase II setting is needed. Areas appropriate for investigation include examining the preferences of newly participating subjects regarding whether they should, or would wish to,

receive up to date and timely information regarding all previously enrolled subjects. Research questions include: Should prospective patients be given this information? If so, how would it shape the size and accrual rates of phase II trials? From a patient perspective, how many non-responders need there be in such trials before they would view participation in an unfavorable light? As discussed, from a clinician's point of view, do the current strict statistical restraints on phase II trials create conflicts for investigators as information regarding non-responders becomes available such that it becomes unethical to put a patient on such a trial because of no expectation of reasonable benefit on the part of the clinician? These are questions which are amenable to study. Study results could potentially generate answers which would not only improve the consent process in this setting, but might even change the size and scope of the traditional process of phase II trial drug development.

Conclusions

Considering that certain well accepted ethical principles may be appropriately violated in the process of clinical research, one easily recognizes the vast privilege that society and others have bestowed upon physician-investigators and accompanying research institutions. Physician-investigators should realize the significance of this privilege, and the communication process between themselves and potential patient-subjects should be reflective of this realization. In the setting of phase I and II trials involving new anticancer agents, where the involved patients-subjects are so often those with advanced, and eventually life-ending, disease this privilege requires special recognition. The communication process in this setting should not be a process of simple disclosure. It must include a meaningfully humble and graceful attempt on the part of physician-investigator that will potentially allow patients to reach a full understanding of the important elements of informed consent. Investigators must also be prepared to deal with the psychosocial and emotional difficulties which may develop as a result of patient-subject understanding. Anyone who has discussed the option of an investigational agent with an advanced cancer patient has felt the difficult challenges of open and honest doctor-patient communication. From an ethical perspective, it is quite arguable that only those investigators who recognize these challenges and do not shy away from them are

the investigators who are worthy of the privilege to conduct these all too important phases of early clinical research.

Further research is undoubtedly needed on the difficult ethical issues associated with early cancer clinical trials. This research will need to focus on potential interventions, such as cohort-specific consent in the phase I setting, and their impact on improving physician-investigator and subject-patient communication and understanding [54,55]. Other research should continue to focus on descriptive analyses of the current communication and consent processes in order to identify deficiencies. Finally, research examining the impact of innovative pharmacologic, statistical, and trial design methodologies should continue to be conducted. These research endeavors are likely to have the greatest impact on either reducing or reshaping the magnitude of the ethical dilemmas associated with early cancer clinical trials. In the phase I setting, these would include the use of single subject cohorts, intra-subject dose escalation, rapid dose escalation (i.e., dose-doubling), and variants of the continual reassessment method [56]. In the phase II setting, this would include three stage designs (where potentially fewer initial subjects would be needed) and randomized phase II trials where multiple new agents may be concurrently, and therefore more rapidly, evaluated for efficacy [57,58].

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