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EDITORIAL

Competing for patients: an ethical framework for recruiting patients with brain tumors into clinical trials

George M. Ibrahim · Caroline Chung · Mark Bernstein

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Abstract With more rapid advances in potential treatments for brain tumours, the number of clinical trials for brain tumour patients is rising. In the context of the challenges of recruitment and enrollment of patients with brain tumors, the dichotomy between the paucity of subjects and abundance of clinical trials creates a unique ethical dilemma, whereby a single patient may be eligible for several studies. Here, we identify and present three approaches for recruiting and enrolling patients who may be eligible for several trials. The ethical implications of the full disclosure, paternalistic, and random approaches are discussed. The full disclosure approach presents information to patients regarding all ongoing concurrent trials, allowing them to make an informed decision, while the paternalistic approach allows the healthcare providers to select the trial for which they believe the patient is most suitable. These introduce the biases into circumstances where equipoise is necessary and risk selection bias in study design. The random approach randomly allocates patients to each trial, which may erode patient autonomy and decrease trial enrollment. Brain tumor patients comprise a vulnerable population and it remains incumbent on healthcare providers to maintain the highest ethical standards when approaching them for clinical research. Changes in clinical trial design are required to mitigate the conflicts created by competition for patients.

G. M. Ibrahim (✉) · M. Bernstein
Division of Neurosurgery, Toronto Western Hospital, University of Toronto, Toronto, ON, Canada
e-mail: george.m.ibrahim@gmail.com

C. Chung
Department of Radiation Oncology, Princess Margaret Hospital, University of Toronto, Toronto, ON, Canada

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Illustrative case

A previously healthy 50 year old female, recently diagnosed with non-small cell lung carcinoma presents to a multi-disciplinary neuro-oncology clinic for evaluation of a single 1.5 cm metastasis in the right temporal lobe, discovered on screening magnetic resonance imaging (MRI). Standard treatment options would include surgical resection with adjuvant whole brain radiation therapy (WBRT), WBRT with radiosurgery boost or WBRT alone. She is also eligilible for two clinical trials offered at the hospital at which she is receiving treatment. One investigates the efficacy of a small molecular tyrosine kinase inhibitor in combination with radiosurgery and one investigates the inclusion of WBRT with radiosurgery treatment. The multi-disciplinary team meets to inform the patient of the institutional standard-of-care treatments and the two clinical trials available. They are faced with the challenge of effectively, fairly and ethically presenting the treatment options available.

Introduction

It is incumbent upon the medical profession to strive to improve patient care with investigation of new drugs and treatment techniques in clinical trials, as this is the mainstay of legitimizing these new treatments. Patient recruitment and enrollment are among the most challenging aspects in conducting clinical trials [1]. The process can be broken down into discrete steps including: (1) identification of eligible

patients; (2) explanation of the study; (3) informed consent; (4) recruitment of an adequate sample; (5) retention of subjects; and (6) minimizing the risk-to-benefit ratio [1]. The maintenance of the high ethical standards is essential throughout the recruitment process as outlined by the Nuremburg codes and subsequent Declaration of Helsinki, which are now enshrined in the missions of numerous institutional review boards (IRBs) [2].

Seventy-five to 85% of trials are delayed due to low subject accrual and 30% of trial sites fail to recruit even a single participant [3–5]. It is estimated that each day of delay in the development of an investigational drug represents $1.1 million in lost revenue [6]. Furthermore, the human costs of delays in availability of new drugs and techniques due to slow trial completion are incalculable. Healthcare professional have a responsibility in clinical care and research to be stewards of available resources. Factors that contribute to inefficient resource utilization must therefore be subject to scrutiny to establish better approaches to clinical trial design and patient accrual.

According to the National Cancer Institute database, currently there are 323 clinical trials actively recruiting new adult patients with high grade glioma alone [7]. The annual, global, age-standardized incidence of brain tumors is 2.6–3.7 per 100,000 suggesting that the number of eligible patients for these numerous clinical trials is small [8]. To add to the challenge of accrual, Lasagna's law, the so-called 'funnel effect', suggests that a minority of patients meeting inclusion criteria would be willing to participate in clinical trials [9]. It is not surprising therefore that the dichotomy between the large number of clinical trials and the paucity of subjects results in competition for patients.

We identify three possible approaches for positioning information to patients for consideration of enrollment in clinical trials. A sample patient conversation for each approach is as follows:

(i) Full disclosure approach: "We actively participate in several clinical trials. I will explain the potential risks and benefits of each intervention within each trial and you may choose the trial in which to enroll, should you choose to enroll at all."
(ii) Paternalistic approach: "We actively participate in several clinical trials. I think you would be best suited for Trial X, should you choose to enroll."
(iii) Random approach: "We actively participate in several clinical trials. You have been randomly assigned to Trial X, should you choose to enroll."

Full disclosure approach

The full disclosure approach would require practical disclosure of all clinical trials for which a patient is eligible to participate. The perceived risks and possible benefits of each studied intervention should be explained thoroughly allowing the individual patient to make an informed decision. Three conditions, which must be met when obtaining informed consent are: (1) full patient capacity, (2) lack of undue influence, and (3) full disclosure of all information [10]. One can reasonably make the argument that true informed consent cannot be obtained without adequate disclosure of alternative options, including the current standard treatment and concurrent clinical trials available in the centre. This is particularly important, as there may not be equipoise between trials. That is, some trials may be associated with less perceived risk than others. Some authors have gone further to advocate for a contractual agreement that is legally binding between research sponsors and the participants [11].

The full disclosure approach however introduces the patients' biases into study enrollment as patients' perceptions may constrain or undermine autonomy in decision-making. Patients' perception and assessment of risk is complex and value-laden [12]. The lay public may apply social and cultural rationality in their assessment of risk and therefore actual risk may not influence risk perception [13]. By virtue of the unproven nature of the intervention, the risk and benefits of clinical trials are inherently uncertain; therefore, patient choice based on perceived risk may be misguided. This phenomenon also plays a role in a patient's decision to participate in a single study in addition to choosing amongst studies. Patients frequently underestimate the risks and overestimate the benefit of participation in clinical research [14, 15]. For instance, in one study, the majority of cancer patients surveyed failed to recognize that the main objective of clinical trials is to benefit future patients. As patients intuitively choose interventions with higher perceived benefit and lower perceived risk, offering patients more choices of therapies may reinforce patient expectations of higher clinical benefit with less toxicity.

Furthermore, patients do not retain much of the information communicated through informed consent in a manner correlating with the underlying disease severity [16]. Brain tumor patients are a particularly vulnerable population, in which clinicians need to be aware of challenges of informed consent due to their underlying disease-related impairment [17]. One study found that subjects frequently consent to treatment with only modest appreciation of the risks involved, with 23.9% of subjects reporting no risks despite being explicitly informed otherwise [18]. Specifically, patients with brain tumors may have altered cognition and may lack the capacity to understand a rigorous informed consent process that covers several concurrent trials [17]. In other vulnerable populations, patients with a thought disorder, willingness to participate in trials was correlated with higher education and

lower cognitive impairment [19]. Brain tumor patients may therefore demand greater attention and may require more education to improve their ability to make capable decisions about any research participation. While is true when recruiting patients even for a single trial, clinicians need to be cognizant of the unique challenges of providing a greater volume of information and the complexity of decision-making when multiple potential trials are presented, each with their own perceived risks.

Some authors have argued that full-disclosure is not possible [20]. This may be due to the presence of unforeseen risks as well as the tendencies of investigators to overplay the benefits of experimental treatments, where accurate outcomes are uncertain. Others have suggested that the legalistic culture of expanding obligations of IRBs to oversee clinical research results in overregulation and underproduction, which compromises the central goals of clinical research [21].

Paternalistic approach

With a paternalistic approach to patient recruitment, the healthcare providers choose the clinical trial for which they feel the patient is best suited. This approach is least complex, and is based on fiduciary trust in the doctor-patient relationship. The paternalistic approach also allows clinicians to acknowledge historically marginalized groups and make efforts to include them accordingly. There is an increasing wealth of literature showing that patients from visible minorities are underrepresented in clinical trials [22–24]. This has been hypothesized to result from racially-influenced distrust, reduced access to healthcare research, or the failure of clinicians to advertise in a culturally competent manner [25, 26]. One large study of 70,000 patients suggests that minorities are willing to enroll in trials, but may lack opportunity to participate. In the Glioma Outcomes Project for instance, Caucasian race and younger age were significantly associated with clinical trial participation [27].

The difficulty with the paternalistic approach is that the roles of healthcare provider and clinical investigator may carry different and competing obligations [18, 28, 29]. Subjects manifest a therapeutic misconception when they fail to realize that by participating in clinical trials they sacrifice some degree of personal care, which is the primary allegiance that healthcare workers have towards them [30]. An approach whereby physicians appoint patients to individual clinical trials may further obscure the distinction between the consequences of participation in a trial and receiving ordinary treatment and increase therapeutic misconception. Less optimism about one's current health state and hopefulness about future health state are associated with a higher likelihood of therapeutic misconception [30]. Therefore brain tumor patients are again particularly vulnerable as they often have concerns about their health and many have difficulty coping with the diagnosis [31].

The paternalistic approach augments the biases of the investigator into a situation where equipoise should be present. For example, investigators may perceive enrollment as a right rather than a choice for sought-after but unproven treatments for which access is limited [32, 33]. Patients often form strong bonds with healthcare providers and may enroll in a clinical trial to please their medical team [34]. This approach can therefore erode patient autonomy. A selection bias may also be introduced, which may diminish the generalizability of the study results. The introduction of physician bias in the decision-making may lead to delayed obligations (or perceived obligations) pertaining to access to effective therapies after trial completion as well as disclosure of delayed adverse effects [32].

A modification of this approach may include the presentation of all available trials with associated benefits and risks, with a subsequent recommendation of a particular trial that may be more appropriate for the patient. Depending upon the extent of encouragement to participate in a particular trial, this may continue to introduce many of the biases discussed for the paternalistic approach. This however emphasizes that in clinical practice, there is often overlap between these approaches.

Random approach

The equiprobable and independent assignment of patients to various clinical trials may remove both the subject and investigator's biases in recruitment and enrollment in a manner analogous to the reduction of bias from confounding variables through randomization within clinical trials. This approach has the distinct advantage of minimizing investigator, subject and selection biases.

Randomization of patients into clinical trials however precludes patient choice and therefore may result in resistance to participation in clinical trials [35]. The perception of treatment as a threat to freedom of choice has been correlated with poor compliance in some vulnerable populations [36]. Participant-centered clinical research, which addresses the patients' goals, interests, and abilities has been advocated by some authors [35]. Not only is it proposed that this decreases attrition from clinical trials, but may also align the research strategy with the patient's goals of care. For instance, some patients may choose to avoid the perceived toxicity of radiation therapy and prefer trials investigating novel cytotoxic chemotherapy. Others may present to a clinician with a particular trial in which they are interested.

One strategy is to provide patients with the opportunity to be randomized into a clinical trial if they refuse to

participate in a particular trial that was deemed to be appropriate for them. Although equipoise may exist between trials, this may yet violate the fundamental principle of 'primum non nocere' as the clinicians may be aware that the remaining trials may not be ideal for the specific patient. Other strategies include randomization of treatment by site, rather than by individual [37]. One may also randomize clinical trials by site, such that each site recruits patients for a single trial. Aside from the obvious biases introduced by geographic assignment, this approach may disadvantage smaller centers that may not be able to support expensive recruitment strategies. Patients may also be at a disadvantage, as they may lack access to potentially beneficial experimental therapy.

Discussion

Due to the paucity of subjects relative to the large number of clinical trials concurrently recruiting brain tumor patients, often a single patient may meet eligibility criteria for several trials. This creates a conflict, which is augmented by pressures to expeditiously recruit subjects into clinical trials for academic, financial, or even altruistic reasons. Brain tumor patients are a vulnerable population due to their potential, and often subtle, cognitive and functional disabilities as well as the emotional burden of the diagnosis. It is therefore incumbent on healthcare providers to ethically present information to patients for recruitment and enrollment in clinical trials. Here, we discussed the ethical principles associated with three identified approaches to patient recruitment: the full disclosure, paternalistic and random approaches.

Regardless of the approach used to position information to patients, clinicians should consider the value of coordinating all aspects of a particular patient's care. For instance, it may be suboptimal to place a patient with brain metastasis in a study examining stereotactic radiosurgery when this may prohibit them from participating in a trial of systemic therapy for which they may be better suited. The value of considering a patient's overall condition and care may decrease the number of patients who are truly eligible for multiple trials.

Greater resources need to be allocated to recruitment of patients into clinical trials to decrease the biases discussed with the various approaches. For instance, clinical coordinators, who are not directly involved in the patient's care may be best suited to present study options as this may decrease therapeutic misconception. The recruitment of minorities may be facilitated by provision of transportation, and interpretation services for non-English speakers. While smaller centers may not have these resources, larger centers are often faced with time pressures that discourage their utilization. Both scenarios hinder accrual of patients from minority groups.

Systematic changes to the design of clinical trials and the ways in which they enroll patients are also required to attenuate the conflict created by competition for patients. Highly selective inclusion criteria should be developed to limited the population of subjects to those who are scientifically meaningful and necessary, thereby reducing the number of patients eligible for multiple trials [1]. This would need to be balanced with the generalizability of the study findings to all patients who may benefit from the particular treatment. Large cooperative groups (such as the Children's Oncology Group, Eastern Cooperative Oncology Group, etc.) may also increase patient recruitment and decrease the number of subjects a single site would be required to enroll. More funding should be allocated to patient recruitment and enrollment in clinical trials. Specifically, involvement of a full team of healthcare professionals including nurses and allied health increases recruitment and retention [38]. The use of evidence-based recruitment strategies should be encouraged. These include the dissemination of printed educational materials, use of local opinion leaders, use of reminders, provision of feedback and, adapting protocols according to perceived needs [39]. Finally, triangular test design, allowances for early study termination and other strategies to minimize sample size may decrease competition for patients [40, 41].

Conclusion

We describe three approaches for presenting the available clinical trials to patients with brain tumors who may be eligible for multiple concurrent clinical trials, along with the strengths and limitations of each approach. The full disclosure and paternalistic approaches may introduce the bias of the patient and healthcare provider, respectively into a situation where equipoise should exist. The random approach may erode patient autonomy and deviate from participant-centered clinical trial design. Integral to the recruitment and enrollment of patients with brain tumor in clinical trials is the appreciation that this population is vulnerable due to burden of disease and possible cognitive impairment. Although each of the approaches for patient accrual discussed have their inherent challenges and biases, the recognition of these issues and pursuit of improving the processes of patient recruitment to clinical trials is a key factor in upholding the ethical principles of patient-centered care, societal justice and financial responsibility.

Conflict of interest None.

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