RCSIsmj ETHICS CHALLENGE WINNER 2011/2012

Randomised controlled trials and tribulations

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Introduction
The 2011/2012 RCSIsmj Ethics Challenge presents the case of two cousins with stage IV B-RAF positive malignant melanoma. Both cousins were enrolled in a phase III randomised controlled trial (RCT) comparing the current standard of care, dacarbazine, with the new B-RAF-inhibiting drug, PLX4032 (also known as vemurafenib, now marketed as Zelboraf™). Early data was promising for the new drug, with a dramatically decreased tumour progression demonstrated in the phase II trial. However, there were concerns that patients treated with PLX4032 may not experience increased survival, due to accelerated rate of tumour growth post treatment. One cousin was allocated to the treatment arm, experienced a dramatic improvement in his condition and remains alive today. The other cousin was randomised to the control arm and, despite the misgivings of his oncologist, was treated with dacarbazine. Sadly, his condition deteriorated and he passed away nine months later. This article will discuss the relevant ethical issues evident in this case and provide guidelines for addressing difficult cases such as these.

This complex case highlights a debate concerning RCTs that has been occurring in the medical ethics community for the past 30 years. Both sides of the debate will be addressed.

Relevant principles of medical ethics

- Respect for autonomy: to respect a patient’s opinions and choices and refrain from opposing their actions, so long as they are not causing harm to another.
- Beneficence: to maximise potential benefits and minimise potential harms.
- Non-maleficence: to do no harm to a patient.
- Justice: the distribution of medical resources within a society.

The current use of RCTs in medical research

The movement of medicine from foundations in opinion and anecdotes towards evidence-based medicine has resulted in the dominance of RCTs. RCTs are key players in the advancement of new therapies, providing highly reliable data that further knowledge about the effectiveness of a treatment. Drug development follows a logical sequence: determining toxicity and dosing in phase I; efficacy in specific disease processes in phase II; and, determination of the “true benefit” in phase III. While many RCTs are blinded or double-blinded, this trial was not, due to the pharmaceutical company desiring increased participant uptake and approval for the widest possible range of indications. Currently, the Consolidated Standards of Reporting Trials (CONSORT) guidelines are used by researchers worldwide to design and report their RCTs. Although the guidelines provide clear advice on randomisation methods, they fail to address certain ethical issues encountered in trials such as this. These issues will be discussed overleaf.
Ethical issues highlighted in this case

- Rights-based versus utilitarian ethics models;
- enrolment of terminally ill patients in clinical trials;
- interim data analysis and early termination of a clinical trial;
- off-trial access to experimental agents; and,
- the arguments for and against equipoise in RCTs.

Rights-based versus utilitarian ethics models

RCTs have been deemed necessary because without them, one could not be certain that a new drug is superior to the current standard of care. However, there are important ethical considerations beyond this. A physician's primary responsibility is to his individual patient, and not to the hypothetical patients that may benefit from the information gleaned from the trial.10 From the standpoint of a scientist, the goal of the RCT is not to deliver therapy, but rather to address a scientific question, so that the drug may be delivered to everyone that it may benefit. This reflects the classic conflict between rights-based and utilitarian theories of ethics. Rights-based ethics state that humans are worthy of dignity by virtue of their capacity for rational thought. Therefore, people should be treated not as a means to an end, but rather as ends in themselves. In contrast, proponents of the utilitarian theory assert that what provides the greatest good for the greatest number of people is optimal.7 It would be nearly impossible to ask physicians to adopt a role of utilitarianism, as they have the obligation to provide the best care available for their patients under the principle of beneficence.6,14 In the case of the two cousins, the oncologist abided by the rights-based theory by entering his patients in the clinical trial. He believed that the PLX4032 drug was the best therapy, and because it was not available outside of the trial, his only option was to enrol the cousins in the trial for a 50:50 chance of receiving the drug. Even if they were randomised to the control arm, they would still be receiving the best standard of care available.

Should terminally ill patients be enrolled in clinical trials?

Although the oncologist's best option was to enrol his patients in this clinical trial, some would argue that terminally ill patients should not be enrolled in RCTs at all. This is for several reasons: patients who are desperate for an experimental treatment cannot be in equipoise (a state of indifference between treatment arms, as discussed comprehensively below); physicians are not able to offer individualised care in trials; and, these patients often do not fully understand the concept of informed consent.15 Another concern with enrolling patients in RCTs is that ‘randomisation’ is poorly understood by trial participants.16,17 One study found that 74% of participants believed that the physician would ensure that they were receiving the best possible treatment in the trial.8,18 Others would uphold the oncologist's decision as ethically sound. Patients enrolled in RCTs receive arguably better-than-standard care (despite a lack of individualisation), as they are subject to close and extensive monitoring.2 Additionally, informed consent is not only feasible, but is a prerequisite for inclusion in a clinical trial. The concept of autonomy allows for competent individuals, regardless of disease status, to choose their own course of action. Because informed consent includes offering patients reasonable alternative therapies, which may include drugs still in trial, it can be asserted that enrolment in RCTs that allow access to these drugs is morally permissible.19

Interim data analysis and early termination of clinical trials

As RCTs are increasingly under scrutiny from investigators and the public alike, pressure to provide findings earlier has made interim data analysis routine.20 In most instances, data monitoring during a clinical trial is performed confidentially, prohibiting public access. Since potential participants would not be exposed to discouraging preliminary findings, RCT enrolment would continue unhindered, resulting in swift trial completion. Critics argue that withholding findings from those enrolled in clinical trials violates respect for their autonomy and invalidates true informed consent. However, if participants are made aware – prior to enrolment – that no interim data will be provided, they can decide whether or not this is acceptable. This is an exercise in self-determination, and thus respect for autonomy is upheld.21,22 In the case of the PLX4032 trial, data were made public following phase II, with mixed responses. Interest in enrolment was increased by promising efficacy data indicating marked tumour regression with this new drug. On the other hand, the results were so positive that many called for early trial cessation.3 Early termination of a trial is not a decision to be taken lightly, as it may prevent researchers from reaching statistically sound conclusions.23 It is best practice to carefully outline defined endpoints prior to commencement of the trial. If these endpoints are reached, this would prompt termination. Before cessation, the data and results must be sufficient to convince the overwhelming majority of physicians and scientists of the validity of the conclusion.20,24

Off-trial access to experimental agents for terminally ill patients

Development of new cancer therapies often stretches on for years. Terminally ill patients rarely have the opportunity to benefit from experimental drugs unless enrolled in a clinical trial. However, this requires that the patient is treated in a facility participating in the trial, is eligible to enrol and is allocated to the treatment arm.14 As a result, many terminally ill patients call for access to experimental drugs outside of trials. Off-trial access to new therapies could be detrimental to the scientific process. Most participants enter clinical trials hoping for allocation to the treatment arm; this motivation may be lost if the drugs were readily available outside the RCT. Additionally, if patients could access new therapies directly, pharmaceutical companies would have little incentive to fund scientific research before marketing the latest ‘wonder drug’.9 This poses serious harm to future patients who rely on the clinical trial process to ensure the safety and efficacy of new therapies. The middle ground to this debate allows patients to exercise their autonomy while ensuring that research continues uncompromised. In
the 1990s, the US Food and Drug Administration (FDA) initiated compassionate use programmes for experimental drugs. These programmes allow access to drugs in phase III trials, but are procedurally difficult to secure and critics complain that their scope is too limited. If such programmes were expanded, with patients enrolled in a registry, data collection could continue. Such programmes have actually been shown to accelerate drug development.14 Were there a programme in place for PLX4032, the cousin allocated to the control arm could have opted out of the trial and availed of the new treatment while still contributing to its development.

The necessity of equipoise in randomised controlled trials
In the late 1980s, Benjamin Freedman developed the concept of clinical equipoise, which quickly became the standard against which all RCTs were judged.5 Clinical equipoise is defined as a state of uncertainty within the expert medical community over which treatment choice is superior.25 A clinical trial is deemed to be ethical so long as there is a lack of consensus about optimal treatment throughout the entirety of the study. Since it is unknown which treatment is preferable, both therapies can be assumed to be equivalent. Therefore, if there is a state of equipoise, it cannot be said that participants in one arm of the trial are receiving inferior treatment.26 In the case of the PLX4032 trial one might assert that clinical equipoise has been disturbed, as phase II data showed that the efficacy of the new drug was superior to the standard dacarbazine. However, this assumption may be premature, as the data only covered a narrow timeframe, and more extensive follow-up is needed to sway the entire medical community.26 So long as the medical community stands divided as to which drug will ultimately be superior, equipoise is maintained and the trial can ethically proceed.9 The oncologist in this case was convinced that PLX4032 was the superior drug, and therefore was lacking individual equipoise. Surely then he should avoid enrolling patients in a trial with a 50:50 chance of them receiving what he perceived to be substandard care. However, Freedman offers a way around this dilemma. Physicians are bound by the duty to their patients, but also by the consensus of expert opinion. Offering entry to a trial is ethically sound so long as the profession as a whole is equipoised between two treatments, regardless of the physician’s own opinions. Collective clinical equipoise takes precedence over individual equipoise, and therefore the oncologist was justified in his actions.9,26

Ethics beyond equipoise
Equipoise may be too simplistic an approach when addressing the ethics of a clinical trial. In the case of the PLX4032 trial, as demonstrated by a recent New York Times article, equipoise seemed to be lacking.3 Nearly all of the clinicians interviewed would choose to prescribe PLX4032 over dacarbazine if given the choice. Surely then this trial is unethical? However, from the standpoint of health policy, new therapies must be rigorously evaluated before they are made widely available. This requires research to continue beyond the point at which physicians and patients think they are certain about which treatment is superior, thus lacking equipoise.5 According to Miller and Joffe – in an article in February 2011’s New England Journal of Medicine – equipoise is based on a flawed perception that trial participants are in some way wronged by being denied access to a promising new treatment. They argue that this opinion is incorrect, because participants are not made worse off than they would be outside of the trial, where they would likely receive standard treatment. Their right to evidence-based medicine is not violated, because the experimental therapy has not been adequately evaluated. The cousin allocated to the control arm in this case is not disadvantaged by receiving dacarbazine, despite an apparent lack of clinical equipoise. Therefore, RCTs that violate equipoise may still be deemed ethical and necessary to provide adequate data to support health policy decisions.5

Conclusion
The necessity and value of using RCTs in the development of new cancer therapies has been upheld in the aforementioned arguments. Both rights-based and utilitarian models of ethics support the use of RCTs. The rights-based theory supported the oncologist in enrolling the cousins in a trial in which they were either receiving the current standard of care or a new therapy that would likely be found to be superior. Enrolment of terminally ill patients in clinical trials was shown to be ethically sound by virtue of respect for autonomy in allowing the patient to decide which path was most suitable for them. Keeping interim data analysis confidential was supported, so long as the participant was adequately informed ahead of enrolment and agreed that this was acceptable. Premature termination of a clinical trial is a decision that should not be taken lightly, but specific circumstances that might result in early cessation should be outlined during the design process. If these situations are encountered, it is the ethical duty of the researchers to end the trial early. Completion of RCTs should be the default choice, but certain criteria may allow validation of a new treatment on the basis of partial evidence. These criteria, as outlined by Miller, include:

■ “compelling, usually mechanism-based rationale favouring the efficacy of the new agent;
■ evidence of large effect sizes on the basis of early clinical studies;
■ well understood, typically poor outcome with limited inter-patient variability given current therapy or supportive care;
and,
■ availability of one or more concurrent or historical control groups with characteristics similar to those of the patients to be enrolled in the proposed study.”5

The concept of clinical equipoise was introduced for the ethical evaluation of an RCT, and weaknesses in the model were identified. A potential solution to the issue encountered by the cousins in this case could be expanding the compassionate use programmes established by the FDA. Allowing off-trial access to experimental drugs to terminally ill patients, while still collecting data via a
As a point of interest, in August 2011 the FDA approved PLX4032 for use in patients with metastatic melanoma. To highlight the importance of this, the American Cancer Society estimates that in excess of 70,000 new cases of melanoma and nearly 9,000 melanoma deaths occur per annum in the United States.

References


