Perspective

Ethical challenges in conducting clinical research in lung cancer

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Abstract: The article examines ethical challenges that arise with clinical lung cancer research focusing on design, recruitment, conduct and dissemination. Design: problems related to equipoise can arise in lung cancer studies. Equipoise is an ethics precondition for RCTs and exists where there is insufficient evidence to decide which of two or more treatments is best. Difficulties arise in deciding what level of uncertainty constitutes equipoise and who should be in equipoise, for example, patients might not be even where clinicians are. Patient and public involvement (PPI) can reduce but not remove the problems. Recruitment: (I) lung cancer studies can be complex, making it difficult to obtain good quality consent. Some techniques can help, such as continuous consent. But researchers should not expect consent to be the sole protection for participants' welfare. This protection is primarily done elsewhere in the research process, for example, in ethics review; (II) the problem of desperate volunteers: some patients only consent to a trial because it gives them a 50/50 option of the treatment they want and can be disappointed or upset if randomised to the other arm. This is not necessarily unfair, given clinical equipoise. However, it should be avoided where possible, for example, by using alternative trial designs; (III) the so-called problem of therapeutic misconception: this is the idea that patients are mistaken if they enter trials believing this to be in their clinical best interest. We argue the problem is misconceived and relates only to certain health systems. Conduct: lung cancer trials face standard ethical challenges with regard to trial conduct. PPI could be used in decisions about criteria for stopping rules. Dissemination: as in other trial areas, it is important that all results, including negative ones, are reported. We argue also that the role of PPI with regard to dissemination is currently under-developed.

Keywords: Research ethics; lung neoplasms; therapeutic equipoise; therapeutic misconception; vulnerable populations

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Introduction

The aim of this article is to examine the types of ethical issue that arise with clinical research in lung cancer and to suggest possible resolutions. Lung cancer research does not raise any unique challenges. Those discussed here have arisen in other types of research. However, as the brief history below shows, ethical problems have hindered research in this area because it has features, such as high mortality, that raises such challenges particularly sharply, for example, randomisation and equipoise remain problematic. It is on these acute ethical issues that this article will primarily focus.

A brief history of lung cancer research

Lung cancer is one of a group of conditions said to carry a stigma related to the idea that sufferers have in general contributed to it (by smoking) (1). This has been said to lie behind its status as under-researched (2). However, Timmerman's historical research shows this phenomenon to be fairly recent (3). In the 1950–1960s no such stigma was attached to the condition. The UK Medical Research Council (MRC) viewed it as a particularly promising area of

research as it was a relatively well-understood condition. It was thus the subject of much research activity. At the same time, the randomised controlled trial (RCT) had come to be seen as the gold standard design for evaluation in evidence based health care and, as such, was the chosen vehicle for MRC research. Two problems followed for lung cancer research, one ethical and one empirical. The ethical one was that in order to run an RCT there needs to be at least two credible treatment options to compare. Often clinicians did not feel this to be the case, to use the term we shall soon introduce more fully, they lacked equipoise. In particular, clinicians felt there was insufficient evidence to run trials comparing novel chemotherapy with the standard surgical treatments (3). Randomised trials could thus be run only in the investigation of fringe cases or in comparing treatments with marginal variation rather than in the investigation of the major questions of lung cancer treatment. The empirical problem was that the results of such trials were disappointing. And at the same time, the link between smoking and lung cancer became established both empirically and in the minds of clinicians and the public. It seemed that the most effective treatment for lung cancer was via the prevention of smoking. Lung cancer developed a reputation of being difficult to study as well as associated with what was becoming a stigmatised activity, smoking, in turn, what has been termed a culture of nihilism developed (4,5).

Arguably, the situation has gradually changed. In the first place, public health policy on smoking may have hit bedrock, a large minority of people are resistant despite bans on smoking in public places, high rates of tax and garish public information. The rates are changing unevenly also, with women and lower economic groups faring worse (6). Lung cancer remains the leading cause of cancer deaths worldwide and its early detection and treatment must now be considered a public health priority (2). There are also new developments in treatments which require an evidence base (7) and, as this paper will show, developments in research design that help researchers to tackle some of the ethical problems with which the earlier MRC trials struggled. The paper now turns to the specific ethical challenges in lung cancer research. This is done in research process order, beginning with trial design and ending with dissemination.

Trial design

As in the 1950–1960s, randomisation remains the preferred method for isolating genuine from spurious effects when testing clinical treatments (8) with the RCT entrenched as the gold standard design (9). This requires there to be viable comparators, it would be both unethical and rather odd to test a treatment of known benefit against one of unknown benefit. A more difficult ethical question arises, however, when there is disagreement of the viability of comparators. This question is usually put in terms of equipoise. Approximately, equipoise is the condition of there being insufficient evidence to prefer one treatment over another, paradigmatically novel over standard treatment. Equipoise can be thought of as either a subjective or an intersubjective phenomenon. As subjective, it is the belief of an individual, for example, that a clinician is in equipoise over whether to use the novel or standard treatment. The problem with this as a basis for setting up and running RCTs is that clinicians will often have preferences one way or another, perhaps based on their own anecdotes and experience. If this were to be used as a requirement for RCTs then it is likely that few could ever be run. The preferred notion of equipoise is thus generally the intersubjective one, first suggested by Freedman and which he termed "clinical equipoise" (10), this exists where the clinical community is undecided over which of two or more treatments to prefer. This notion did not exist in the 1950–1960s, a fact that could lie behind a problem of clinicians being reluctant to randomise "their" patients to "others'" treatments at that time.

Clinical equipoise does not resolve all ethical issues concerning randomisation. At least four might arise in lung cancer studies.

- The first concerns the point at which clinical equipoise can be said to exist. It is unlikely that clinicians will be split 50/50 in their preference for one treatment over another. But would 40/60 still constitute equipoise, or 20/80? And should weight be given to clinicians with more experience?
- The second problem concerns the issue of who is supposed to be in equipoise i.e., whose equipoise has priority? In particular, is it reasonable to offer randomisation to a patient who is not in equipoise but rather has a strong preference for one treatment arm over another? We return to this point in the discussion of informed consent (in the next section) when we consider the problem of desperate volunteers.
- The third (and related to the second) problem concerns the clinician who is a long way from equipoise, perhaps in relation to a particular patient. One feature of many lung cancer studies is that the treatments can vary enormously. Thus an individual patient or clinician might view as important not

simply the likelihood of certain outcomes of a treatment, such as relief of symptoms, but also what is involved in the treatment itself. Offered a choice between radical surgery, chemotherapy and radiotherapy, different individuals might have quite different preferences based on previous experiences, fears and beliefs. Although the clinical community and perhaps the patients themselves might be in equipoise about efficacy they may nonetheless not be in equipoise about which arm of the study they would prefer. For this reason an individual may prefer, and an individual clinician prefer to offer, non-randomised treatment, outside the trial if necessary.

- Finally, the range of clinicians involved in a patient's care [i.e., the lung cancer multi-disciplinary team (MDT)] will be wider than the immediate study team. What should be said of their equipoise (or its lack) in relation to particular patients? For example, if they are asked their opinion by the patient, or they have a small role in the study itself, such as alerting the team to potential recruits?

Some help can be offered with regard to these four problems. Regarding the first is the growth of systematic evidence reviews. These give the researcher access to all relevant evidence such that clinical equipoise comes close to being a matter of fact rather than opinion. Where a systematic review concludes there is insufficient evidence to recommend one treatment over another it seems reasonable to state there is community equipoise. The second problem will be tackled more fully in the discussion of desperate volunteers below. However, both the second and third problem can be at least partially tackled at the research design stage through the fairly recent trend towards patient and public involvement (PPI) in research (11). PPI can help pick up early any potential problem in the equipoise of patients and thus in their recruitment on a randomised basis. Where this is the case new and alternative research designs offer another aid for the researcher. For example, where patient equipoise is a problem alternatives might be considered, such as patient preference designs, pragmatic designs, cohort multiple RCTs design and outcome adaptive allocation trials (12-15) (although there are ethical concerns too about unequal allocation and adaptive preference designs as well as a general requirement for a larger sample size (16,17). Finally, as with PPI, a similar involvement of a wider range of clinicians in research development should also help alleviate the fourth problem.

In summary, the ethical issues of trial design in lung cancer research revolve around the notion of equipoise. Equipoise is can be problematic for lung cancer trials because the interventions being tested may involve substantial and onerous degrees of intervention for the participant, for example radical surgery or radiotherapy. However, developments such as systematic review, PPI and research design can help the researcher to tackle some of the problems at the research design stage.

Recruitment

It is all-but universally accepted that participants in health care research must give informed consent, although there are exceptions, particularly where those without capacity to consent are involved (18). A standard model of informed consent includes three elements such that it is said to occur where a person with capacity freely consents to a study having been adequately informed (and having understood that information) (19). These three elements to informed consent are capacity, information and understanding, and voluntariness. In the main, capacity does not greatly impinge in lung cancer research as in general it involves adults with capacity. In older patients, dementia may be an issue but we shall leave that aside here and focus on the other two elements, where there are issues of importance in lung cancer research.

Information and understanding

The first issue straddles capacity and understanding: it is whether many or perhaps most patients are unable to understand complex trials adequately. Mackillop *et al*. compared the decisions of a panel of lay people and of doctors when asked to consider hypothetical participation to six clinical studies of treatments for non-small cell lung cancer (20). The study found, first, that lay persons were more likely to consent than doctors and, in particular, that they did not discern a difference in acceptability between two clinical trials which were markedly different from the point of view of the doctors. The researchers suggest that "lay people appear ill-equipped to judge for themselves the risks and benefits of participation in a clinical trial" (P392). The study found also that lay people were more affected by framing effects than the panel of doctors (that is, the decisions of lay people were more affected by the way in which information was presented). Again, this leads to doubts about lay people's ability to make truly informed decisions. This type of finding is echoed in a large

number of empirical studies of informed consent (21,22). Alternatives based on giving participants only partial information have been suggested [based on a Zelen design in which participants are asked to consent after they have been randomised and then given information primarily about the arm to which they are randomized (23,24)]. However, these have generally been thought unacceptable, and empirical studies of participants suggest that they would rather give imperfect consent than none at all (25). Doing without any consent has only been credibly defended with regard to data-based research and research in emergency situations (26,27).

A second issue, related to the first, concerns understanding. This is the so-called therapeutic misconception first identified in psychiatric research (28) but which has been and is still discussed in relation to clinical trials generally (29). The misconception occurs where those who consent to a clinical trial believe they are being treated primarily as patients rather than research participants. The misconception is significant, or becomes significant, where it is tied up with a misunderstanding of important elements of the study, such as risk and benefit (30). Where participants say of randomisation, for example, that the computer "selected a treatment" for them, this may mask a misunderstanding that the choice was somehow made in his or her best interest, as would be the case if a clinician had made the choice for the person as a patient.

Voluntariness

The concept of acting voluntarily is imprecise. Someone seems both voluntarily and involuntarily to hand over my wallet to the mugger with a knife. In UK law, the boundary is set by the equally imprecise notion of undue influence. In the case just described, the mugger is an undue influence on the victim's action (31). In relation to clinical trials there are a number of factors that might be deemed undue influences, these include: inducements, particularly payments, a feeling of obligation to (or a fear of inferior treatment by) your clinicians who are also researchers, deference to clinicians deemed by participants to be socially superior, and desperation (21,32).

The last has particular force in lung cancer trials and requires further explanation. People often make choices they would rather not: the mugging case is one example but another is a cancer patient who chooses to have surgery; in both cases it seems the best option of a bad lot. If the crime victim fails to hand over the wallet then physical harm may ensue. If the cancer patient fails to consent to the surgery then harm may ensue. But only in the first case does the person presenting the choice have control over that harm, he will directly cause the harm: that is the undue influence. A similar undue influence occurs where someone has control over good consequences, as when someone is offered a large amount of money to consent to a potentially harmful procedure.

The problem with randomised trials is that some manipulation of choices and outcomes can appear to be involved. A decision to offer a treatment only through a randomised trial creates a situation where patients can only opt for a randomised chance of having that treatment. At this point the problem of equipoise can transform into one of coercion. Consider a patient diagnosed with a lung cancer who is thus seriously ill with a poor prognosis. He is told of a promising new treatment. The evidence base for this treatment is not strong enough to recommend it as a new standard and, therefore, a RCT has been set up. From the patient's viewpoint, however, the existence of a treatment which is promising in a situation which is otherwise grim might be enough to recommend it: this person is desperate. By restricting his choice to a 50% chance of receiving the treatment he wants by opting for participation in a RCT have the researchers not exploited his vulnerability, put undue pressure on him to consent? A recent study of patients consenting to lung cancer surgery showed they had a high tolerance for perioperative mortality risk and that they tended to find it hard to imagine the risk eventuating (33). This supports the argument that equipoise of patients and clinicians could differ markedly. It also shows the difficulty of presenting information about risk in such a way that people can fully understand and weigh it up.

Faced with these problems it is worth asking the purpose of informed consent in relation to clinical trials. Consent has been central to research ethics at least since the period of the Nuremberg trials and the subsequent Nuremberg Code, whose opening statement is: "The voluntary consent of the human subject is absolutely essential" (34). However, whilst it is usually unacceptable to undertake clinical research without consent it does not follow that it is always acceptable provided there is consent. As well as consent procedures, Research Ethics Committees (RECs) also check inter alia the scientific validity of proposals and the balance of risks and benefits to participants. This suggests that RECs do not expect participants themselves necessarily to be able to do so. This offers some resolution of the information and understanding issues. We should

not and do not expect an ideal-type informed consent from participants. The role of informed consent is primarily to allow people to choose whether or not to take part in research based on their own beliefs and values. It does not override the responsibility of researchers and other professionals to ensure that any research offered to patients is ethically acceptable, that it does not, for example, expose them to undue risk even though they might not understand that risk (20).

In order for informed consent to play this part of allowing people to choose, the capacity, information/understanding and voluntariness criteria must still be met but to an extent that will vary between individuals. In this regard there are helpful guidelines on a minimum list of information which a person needs to be able to grasp if they are to be deemed to have capacity to consent. There are also non-standard ways in which consent can be obtained, for example, on a continuous or on a staged basis (35-37). If unable to do so, it would be better to talk in terms of assent rather than consent, or to use other measures for permission such as proxy consent. One of the items on any minimum list would certainly be an understanding that the person is taking part in a trial and that this is in some way different to standard treatment. Would this mean, therefore, that someone labouring under the therapeutic misconception has not given informed consent?

Kimmelman notes that the discussion of the misconception is located overwhelmingly in the United States (38,39). Perhaps one reason for this is the market-based nature of health provision there in which the relationship between patient and clinician is an entirely private one, like that of solicitor and client. This differs from socialised health models in which the relationship is more like a club which provides services for its members. In the private model, a clinician whose aim is to improve his service to other clients rather than overwhelmingly to provide a service to the one in front of her is operating outside the boundaries of their agreement. A clinician cannot be both a private provider to a private client and a researcher at the same time. [The situation is different with clients unable to pay and who are then only able to receive treatment via consent to a study, see the fictional treatment of this in Shriver (40)]. With informed consent, this problem is overcome, provided that consent includes an understanding on the part of the client that the clinician is no longer acting as his private physician. In the socialised (club) model, for the clinician to act as researcher still requires consent, but there is no necessary conflict between the clinician's role as the patient's physician and as a researcher.

It follows that under the socialised model, the participant who believes the physician is acting in his best interest when she treats him as part of a research protocol is not labouring under a therapeutic misconception because it is not a misconception. Snowdon *et al.* put this point well by invoking the idea of a an injurious misconception (41). It is well established that patients who take part in clinical trials generally do better than those who do not and that this is so whether in a control or treatment arm (42,43). Hence the injurious misconception exists in someone who avoids taking part in such trials on the basis of "an overstated sense of distinctions between care and research and a corresponding over-stated sense of risk and threat" (P199). Our suggestion, therefore, is that researchers and participants should not be overly exercised by the so-called therapeutic misconception.

By contrast, the problem of undue influence and desperate volunteers is of import. Before asking how it might be tackled it is worth asking first whether it is ethically wrong to recruit participants to a randomised trial who have a strong preference to one arm. In other words, does limiting access to the preferred treatment in a randomised trial only constitute an undue influence on a patient's consent to that trial? In an earlier article one of the present authors argued that it is not (32). In legal terms patients can refuse treatments and participation in research but they cannot demand it. No injustice is done in restricting a patient's choice of a treatment to within a RCT only, this is, of course, provided the decision is equitable, without, for example, some patients being offered the treatment outside the trial whilst others not. In that sense, therefore, the restriction is not an 'undue' influence on the decision.

However, avoiding injustice is not the whole story. The disappointment of desperate volunteers randomised to what is, from their perspective, the wrong arm is often palpable and has been recorded in some empirical research (41,44). Where possible it should be avoided and alleviated. Many of the suggestions already made could help here. PPI at trial inception should identify whether there is likely to be a widespread problem of lack of equipoise in participants. Where this is so, alternative trial designs such as patient preference types might be used. It might be possible to offer the treatments outside of the study without compromising the research, particularly where patient preferences are uncommon. Whilst there is no automatic right for a patient

to demand a novel treatment, it should be accommodated where possible.

Trial conduct

Once participants have been recruited to studies, some of the ethical issues faced in trial conduct will be fairly standard and dealt with using standard procedures, for example, those to do with privacy and confidentiality. Two issues might arise more sharply in lung cancer studies. These are related but are to do with, first, the welfare of patients and, second, the role of the Data Safety Monitoring Board (DSMB) or Data Monitoring Committee.

The welfare of patients during trials is in part a product of the onerous nature of treatment, be it chemotherapy, radiotherapy, surgery or a combination. If given as treatment, a patient and clinician can reach agreement that one treatment mode needs adjustment or abandoning, perhaps to be replaced with another. This, of course, should also be the case for patients enrolled as research participants. The difficulty is that such changes to treatment may not be compatible with continuation in the trial. Both the clinician and the patient might feel some pressure to remain within the study. This pressure could be exacerbated where recruitment to the study is difficult. There are ways to reduce the risk of reluctant continuation: (I) provision of contact information of an advocate who can be easily contacted for decision making support; (II) care staff outside the trial able to suggest withdrawal; (III) design of study such that it facilitates early withdrawal but the possibility of using data collected up to that point; and (IV) the importance of feasibility studies preceding full clinical trials; for example, the MARS2 feasibility study is focused strongly upon recruitment (45).

In Lung Cancer studies a DSMB is almost always required. This adds a safeguard to participants where, for example, a new treatment turns out to be unexpectedly harmful or beneficial. Judging this is difficult, however. Stegart *et al.* (46) show that most trials that are stopped on the basis of either early benefit or futility have not followed stopping rules. Part of the problem here relates to the philosophy of statistics: a frequentist approach might tend to the later termination of a trial than a Bayesian one. But perhaps more significant is the role of value judgement relating to the weight to be given to some benefits and harms. This problem is in some ways a variation on the equipoise one and is particularly acute in lung cancer trials precisely because of the import of the trials' potential benefits and harms. Just as patients with lung cancer may be less risk-averse than clinicians, so they might judge differently the need to stop a trial, for example, they might be more inclined to continue a trial despite a higher than expected mortality rate or to discontinue it where early signs of benefit are demonstrated. The use of PPI here may again help in making decisions about termination, as might the consideration of adopting Bayesian stopping rules (47).

Trial dissemination

Failure to report trial results is unethical and the problem is widely acknowledged, particularly with regard to non-publication of negative results (48,49). There are also measures in place to tackle them, such as through research registries. There seem to be no particular reasons to think these problems especially acute in lung cancer studies and so no more will be said here.

Throughout this discussion reference has been made to PPI and its usefulness in tackling some of the ethical issues relating to lung cancer studies. Clearly that involvement of patients and public should continue into the dissemination stage, in publications and presentations for example. Brett's review of PPI in health and social care research gives a number of examples but notes that examples of dissemination are unusual, found in only six of 200 papers (50). The six examples in a brief report from the National Cancer Research Institute similarly focus primarily on PPI as an aid to the setting up and running of studies rather than the dissemination and implementation of results (51). In the UK the work of the organisation involve has been central to developing PPI in cancer research (52).

Conclusions

As stated earlier, lung cancer trials do not give rise to unique ethical issues. However, features of such trials do tend to create some problems in acute forms. These features include the serious nature of the illness, the complexity of the trials and treatments, and the major harms associated with the treatments (such as chemotherapy and surgery). The problems these create relate to equipoise, consent and safety. Finally, developments in trial design and process such as PPI offer means for the researcher to alleviate but not to obviate these problems.

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Footnote

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