Ethics of Randomized Clinical Trials and the 'ALARA' Approach

Matjaz Zwitter

From the Institute of Oncology, Ljubljana, Slovenia

Correspondence to: Dr Matjaz Zwitter, Institute of Oncology, Zaloska 2, 1105 Ljubljana, Slovenia. Fax: + 386 61 1314 180. E-mail: mzwitter@onko-i.si

Acta Oncologica Vol. 38, No. 1, pp. 99–105, 1999

A balanced discussion on the ethics of randomized clinical trials should not be based on a single ethical aspect such as respect for the patient's autonomy. Rather, the analysis should consider the four ethical principles—respect for autonomy, non-maleficence, beneficence, and justice—as applicable to all groups of persons concerned. We present the ethical benefits and costs of the present practice of randomized clinical trials for four groups: patients involved in clinical trials, patients not involved in trials, participating physicians and society. The ALARA (As Low As Reasonably Achievable) approach is then introduced and practical measures to achieve a positive balance between ethical benefits and costs of randomized trials are proposed.

Received 15 June 1998
Accepted 28 September 1998

Randomized clinical trials are one of the most valuable and also the most disputed methods of clinical research. One hundred years ago, the Danish physician Dr Johannes Fibinger tested a serum against diphtheria and presented the earliest reports on a prospective, controlled, clinical trial [(1, 2); references courtesy of Dr C. Gluud]. In his novel 'Arrowsmith' (3), first published in 1925, Sinclair Lewis presents an excellent story of the dilemmas of medical research: passion for unambiguous results is often in conflict with personal ambition favouring premature publication; the quest for scientifically convincing observations (which demand that only half of the population would be offered preventive vaccination of unproven efficacy) comes into conflict with the ethical reasoning of a physician responsible for the lives of people on a Caribbean island during an epidemic of plague.

More than 70 years later, these dilemmas remain unresolved. The progress of medical technology has not been accompanied by a consensus regarding the rules of experimentation on human beings. Those discussing the ethics of randomized clinical trials usually stand on either of the two extreme positions. On one side are those for whom the question is whether it is ethical not to promote randomized trials (4). Their argument holds that experience gained from randomized trials is saving the lives of many new patients; that physicians' intuition is often an unreliable guide to the best treatment; that more treatment is not always better; and that randomized trials protect future patients from treatments which are ineffective or overtly toxic (5). These authors feel that there is no inherent incompatibility between the trials and the promotion of patients' rights and welfare and they consider randomized clinical trials as a powerful way to eliminate bias and prejudice (6). The physician's individual preferences should be disregarded in favour of collective, or community equipoise (7) and it would be a severe handicap to medical progress if physicians were to participate in a randomized clinical trial only when they have no preference for either treatment (8).

On the other side are those who base their ethical view on the unique relationship between physician and individual patient. Th possibility of interfering with a sincere relationship is the main reason for physicians' reluctance to propose participation in a randomized trial to their patients (9, 10). Even in cases where patients have given informed consent, relevant information about the trial is often framed in such a way as to induce a patient's participation by appeal to their non-rational preferences (11). The uncertainty principle as the ethical basis for randomization is rarely applicable since the decision about the preferred treatment does not depend on a single parameter, such as a survival curve. Patients and physicians do have their preferences; choosing the most appropriate treatment for a particular patient depends on careful evaluation of values linked to quality of life. The treatment of human disease is clearly different from experimentation

 ISSN 0284-186X

on mice; other methods of improving clinical knowledge such as careful accumulation of experience from non-randomized Phase II clinical trials should be given proper attention (12).

These two opposing views leave little room for compromise. My intention is not to join this 'pro' and 'anti' discussion. Instead, I present an analysis of the current practice in randomized clinical trials, seek to identify the greatest ethical costs of the present practice, and propose practical solutions in order to reduce these costs.

ETHICAL ANALYSIS OF THE PRACTICE OF RANDOMIZED CLINICAL TRIALS

In ethical analysis, all individual and collective subjects who are affected by a problem are registered. For each subject, an assessment is made of the balance between ethical benefits resulting from respect of the principles of autonomy, non-maleficence, beneficence and justice, and between the ethical costs as a result of violation of these principles (13–15). The same action may bring both ethical benefits and costs to the same individual: including a patient in a prospective clinical trial without his/her informed consent may offer a better chance of successful treatment (ethical benefit) but violate the patient's autonomy (ethical cost). Usually some subjects benefit from a certain practice while others suffer ethical costs. For example, benefits to patients included in prospective clinical trials adversely affect those not participating in trials but competing for the same resources.

The greatest obstacle to the ethical analysis of the practice of clinical research is our ignorance of the perception of trials from the patients' side. Once they have obtained informed consent, researchers have little interest in exploring what their patients actually remember. Apart from anecdotal personal experience (16), patients' understanding of a proposal to join a trial, their reasoning, and their recalling of what they had agreed to remain unknown.

An indirect and, admittedly, biased reflection of the patients' side of randomized clinical trials is interviews with physicians in charge of clinical research. While physicians may sincerely report on what they usually tell their patients, listening is not the same as understanding: physicians probably overestimate patients' understanding of a clinical trial. The representativeness of respondents to an interview is also an important question: respondents may be more attentive to ethical issues when compared to the physicians who do not return a questionnaire. With these biases in mind, I nevertheless believe that interviews with physicians contribute towards an understanding of what patients in clinical research are told and how their autonomy is respected.

The question of respect of the other ethical principles—*non-maleficence*, *beneficence*, *and justice*—has been approached in a different way. Most information concerning respect of these principles can be derived from published reports, taking into account eligibility criteria for entering a trial, statistical aspects of a trial and the compliance of the published report with the proposed standards for the reporting of randomized controlled trials (17).

This analysis has its basis in published reports on ethics of randomized clinical trials and in four pieces of my own research. The first one is a survey of the practice of informed consent in twelve randomized trials published in the *European Journal of Cancer* (EJC) (18). The second survey was conducted on 92 published randomized trials for lung cancer. Analysis of the published reports and a questionnaire mailed to the first authors enabled us to assess the ethical benefits and costs linked to these trials (19). The third survey was performed among members of the Breast Cancer Group of the European Organization for Treatment and Research on Cancer (EORTC) (manuscript in preparation). Finally, we studied the question of publication bias among papers on cancer treatment published in 1997 (submitted for publication).

Four groups of persons affected by the practice of randomized clinical trials are be included in this analysis: patients participating in trials, patients not included in trials, physicians involved in trials and society at large, including future patients. When the four ethical principles are applied to these four groups, we get a matrix table with 16 fields (see Table 1). This allows us to assess the ethical benefits and costs of the current practice of randomized clinical trials for nine fields.

Table 1

Ethical analysis of the practice of randomized clinical trials. Our discussion is limited to the nine fields marked with an asterix (*)

Subjects	Ethical principle			
	Autonomy	Non-maleficence	Beneficence	Justice
Patients in trials	*	*	*	
Patients not participating in trials		*		*
Participating physicians	*		*	
Society and future patients	*		*	

Respect for the autonomy of patients in trials

The key question is the patients' understanding of the diagnosis, standard treatment options, and prognosis. In many parts of the world, patients with cancer are still not informed about the true nature of their disease. However, even in Western society, which nowadays so explicitly favours individual freedom, self-determination and responsibility, many patients with newly diagnosed cancer or with advanced disease are in severe emotional distress, a condition that by itself diminishes their autonomy (20). Relying upon a doctor's expertise is an anchor to which all patients' decisions and hopes are bound. In such a situation, proposal for a random choice of treatment is distressing and has a negative influence upon the physician–patient relationship. Many physicians intuitively feel that what patients really need is basic information about the nature of the condition, told with proper empathy and clear advice regarding the preferred treatment.

The practice of informed consent is often far from recommendations and rules, as specified in the Helsinki and other similar declarations and documents. Patients are not always given a clear explanation about random choice of treatment or are informed about the trial in which they are invited to participate only after randomization (18). The written information often falls into one of two extremes: it may be too general, lacking essential information which a reasonable person would expect in order to make an informed choice; or it contains too detailed and extensive medical information, in which case informed consent becomes a legalistic device to shift unpleasant physician responsibilities onto the patient (21). All too often, a patient is tempted to sign the form without a proper understanding of it and only rarely would a patient keep a copy of the consent form, signed by the responsible investigator.

We were particularly concerned by our observation that the level of information offered to a patient was inversely related to the importance, for the patient, of the question addressed by the trial. Patients in trials comparing measures of supportive care, such as antiemetics, with no impact for the outcome of the disease were well informed while those in trials comparing the efficiency of specific anti-cancer treatments often remained uninformed (18). This observation can be explained not only in the traditional attitude to protect the patient from the truth about unfavourable prospects but also in the probability that well-informed patients would not accept randomization.

The fact that very few patients refuse to complete the treatment is a further indication of their incomplete understanding of the trial. Even in trials comparing a treatment of substantial toxicity with a no-treatment (control) arm, only about 5% of patients did not complete the treatment (19). It seems that many patients do not realize that randomization was used in assigning them to a treatment of no proven benefit.

Benefits offered to patients participating in clinical trials (to be discussed later) also influence patients' autonomy. As an example, if patients in trials are offered priority in admission to treatment, then the practical patient's dilemma is to join a trial and get immediate treatment or to choose standard treatment and find his/her name on a waiting list. Similarly, a patient without health insurance may find participation in a prospective trial to be the only option for free treatment. In many countries without socialized medicine (here including some countries at the forefront of democracy), speaking of patients' autonomy is often similar to talking about homeless person's freedom to choose between hunger, food in a community shelter, or a five-star restaurant.

Surveys of the practice of informed consent show that formal rules for consent are more strictly observed in the USA and North-Western Europe than in Eastern Europe, the Mediterranean countries, and other parts of the world (18, 19). In comparison with others, physicians from Northern and Western Europe spend significantly more time explaining a prospective clinical trial to their patients (manuscript in preparation). This reflects a greater respect for patients' autonomy in some parts of the world. There is also no doubt that in recent years physicians have shown greater sensitivity to this question. However, the implementation of true patient autonomy is a complex issue that extends beyond formalistic rules for a written and signed consent form and strongly depends upon cultural and economic backgrounds. We will return to this question in the second part of the paper when discussing recommendations for the ethical conduct of randomized trials.

Beneficence to patients in trials

It has been shown that patients included in a carefully planned clinical trial do better than those on routine treatment (22). Our studies support these findings and reveal several advantages to patients in clinical trials when compared with those not included in research. These include precise standards for diagnostic and therapeutic procedures, quality control, drugs not available outside a trial, more attention from the physician, and easier appointments and access to hospitalization (19).

Non-maleficence to patients in trials

Trials with a prolonged patient recruitment period are ethically problematic. Our ethical analysis of published randomized trials for lung cancer confirmed that slow recruitment is not rare. Although lung cancer is a common disease with a relatively short median time to event of around 9 months, 20% of trials in our survey were recruiting new patients for more than 5 years and one through 11 years (19).

The uncertainty principle as an important ethical requirement for randomization is seriously compromised if a trial is still open for new patients while preliminary results already point to an advantage of one of the treatment arms (23). Continuing with randomization (in order to complete the trial and bring it to a statistically 'significant' conclusion) means that half of patients are given treatment which is felt to be inferior. In such a situation, efforts to gain reliable knowledge about the efficiency of treatments come into conflict with the physician's therapeutic obligation to treat patients in the way that will be most beneficial to them (24); a proposal for randomization would violate the ethical principle of non-maleficence. Experience from AIDS therapy clearly shows that a patient should be randomized only when there is substantial uncertainty about the choice of recommended treatment and points to a need for a more flexible approach (25).

In seriously ill patients with a grim prognosis, fully informed consent can be needlessly cruel (26). Therefore, adherence to rigid rules for informed consent can occasionally lead to violation of the principle of non-maleficence.

Non-maleficence and justice to patients not in trials

We have already mentioned the advantages to patients in clinical trials in comparison with those not included in research. These advantages may imply ethical costs to patients on routine treatment. Patients who are ineligible or who did not consent to enter a trial often compete for the same resources Benefits to patients in clinical trials could lead to discrimination against other patients, in which case the ethical principles of non-maleficence and justice towards these patients are not being respected.

Respect for autonomy and beneficence for physicians participating in trials

An important obstacle to recruiting more patients into randomized trials is the personal preferences of well-informed and experienced physicians. These preferences cannot be replaced by the concept of collective equipoise. A physician cannot ignore a patient's question for personal advice. Still, physicians often hide their preferences: only a minority of urologists or pulmonologists would themselves, as patients, accept randomization for a trial that they were offering to their own patients (27, 28).

According to our survey among first authors of published randomized clinical trials, many institutions strive to include as many patients as possible in trials. A constant pressure upon physicians to increase patient recruitment was reported in 18.2% of the answers; an additional 11.4% indicated that the physician's personal opinion should be disregarded with all eligible patients having to enter the trial.

Physicians participating in clinical trials benefit from co-authorship of prospective publications and from participation at conferences, with the resulting professional and academic promotion.

An increasing percentage of clinical research is sponsored by companies primarily looking for profit. Physicians participating in some commercially motivated trials are offered substantial financial compensation. While certainly beneficial to physicians, such compensation is a threat to the physician's autonomy and to their primary devotion to a patient's best interests.

Respect for autonomy and beneficence for society

By analogy to an individual whose autonomy and beneficence depend upon objective information and availability of the optimal choice, the principles of autonomy and beneficence can also be applied to society as a collective subject (29).

Sooner or later, we will all be patients. We seek to base our future decisions on reliable knowledge; we seek rational allocation of available resources for healthcare; and we want to spend these resources in accordance with our own priorities, rather than those of profit-making companies. We also have hopes that the treatment of tomorrow will be more efficient than that of today. Randomized clinical trials—including those reporting 'negative' results—are of importance to society and contribute towards these goals.

In the case of publication bias, objective information—and hence respecting the ethical principles of autonomy and beneficence towards society—is seriously compromised. Publication bias is defined as the practice of favouring publication of reports on a significant advantage of one of the treatments in comparison to negative or non-significant reports (30, 31). Publication bias has been demonstrated by tracing the fate of clinical trials approved by a protocol review board, ethics committee or a similar body (32), by looking for full publication of results initially presented as abstracts (33, 34) and by plotting effects estimates against sample size, also called funnel plots (35). Owing to unreported negative or inconclusive trials, publication bias leads to a distorted impression of the value of a certain treatment and to its premature or unjustified acceptance as the standard or superior approach.

The above evidence has shown that publication bias really exists. To amend the situation it is important to know on whom to lay blame: investigators for their non-reporting of negative trials, or editors of journals who may be looking for breakthrough reports in order to attract readers and raise their journal's impact factor. With this question in mind, we analysed 124 published reports. Plotting trial size against a journal's impact factor revealed the following: (i) non-specialist journals with a very high impact factor favour publication of large and/or positive trials; (ii) journals with an impact factor between 1.0 and 10.0 publish over 80% of trials and do not appear to favour publication of positive reports; (iii) journals with an impact factor under 1.0 publish a high proportion of small

to medium-sized positive trials. Those that probably remain unpublished are small, negative and often low-quality trials. It therefore seems that most editors are not influenced by the positive or negative results of a trial. Rather, publication bias is predominantly attributable to the lack of interest among clinical investigators in publishing inconclusive or negative experience.

While support for clinical research from public resources is diminishing, medical conferences and journals depend on selling their space to companies. Clinical research and practice are under increasing commercial pressure. Such a practice may give rise to misleading conclusions and should be interpreted as aviolation of the ethical principles of autonomy and beneficence in relation to society.

'ALARA' AND THE ETHICAL COSTS OF RANDOMIZED CLINICAL TRIALS

The 'ALARA' ('As Low As Reasonably Achievable') approach has been originally discussed in connection with radiation protection. ALARA is a response to the two extreme positions—radical opposition to all use of radiation, or views favouring its uncritical expansion. ALARA demands restriction of the use of radiation in situations where the environmental and health burdens from alternative technologies would exceed those of radiation and demands every reasonable measure to keep the radiation dose as low as possible. For example, mammographic screening for breast cancer is justified under the conditions that (i) screening is limited to the population at substantial risk of developing breast cancer; (ii) modern equipment is used in order to expose the women and the medical personnel to the lowest possible dose of ionizing radiation; (iii) all stages from screening to treatment are under continuous monitoring of quality control so that small cancers are detected and successfully treated; and (iv) no alternative to mammography for screening for occult breast cancer has been developed. Under these conditions, to argue against mammography would mean to accept the alternative—high mortality from advanced breast cancer. Still, future development of a cost-effective ultrasound examination of comparable specificity and sensitivity and of a lower health risk may soon render mammography unacceptable.

The ALARA concept is useful also in a discussion of the ethics of randomized clinical trials. The ethical costs of randomized clinical trials are to some extent unavoidable. However, general opposition to this method of clinical research would result in much greater ethical costs. For the established pharmaceutical companies and for emerging small businesses, the strategy is the same: vulnerable patients with cancer are an easy target for selling hopes, rather than treatments of a proven benefit. Therefore, the patients of today and tomorrow would be exposed to all kinds of treatments of unproven efficacy and rational allocation of scarce health resources would be impossible.

Three conclusions follow. First, a randomized trial should be considered only when the clinical question cannot be approached by another type of clinical research. Second, it is important to keep the ethical costs as low as reasonably achievable. Third, a trial should lead to scientifically valuable, medically relevant, and accessible new knowledge.

I now present selected proposals for an ethically acceptable practice of randomized clinical trials. As shown by the references to the ten points below, many of these proposals have been previously discussed. The reader will understand that a comprehensive review of the methodology of randomized clinical trials would be beyond the scope of this paper.

1. *A trial should be scientifically sound and should compare a promising new treatment with the optimal standard treatment, as based on current knowledge.*
2. *When a particular clinical problem is defined and a randomized clinical trial is proposed, acceptability of such a trial from the patient's perspective should be considered.* Patients' advocacy groups should be formally included in the process of evaluation and approval of the study protocol (36–38). The researchers should realize that some trials may be scientifically interesting but unsuitable for the randomized design (39, 40). Especially for trials in oncology, comparison of treatments should include an assessment of the quality of a patient's life.
3. *The statistical plan should be accompanied by a realistic assessment of the rate of recruitment of patients.* For various reasons, usually fewer than half of eligible patients with a particular disease category enter a prospective clinical trial (41, 42). Still, those preparing trial protocols often use figures of disease incidence and grossly over-estimate the rate of patient recruitment. As a consequence, most trials either never reach the planned number of patients, or have to prolong the recruitment period.
4. *When evaluating proposals for new trials, only those which can assure recruitment of patients within three years should be approved.* This figure is based on the fact that one to two years usually elapse from the first draft of the protocol to its practical implementation; that due to new knowledge, five years seems to be the upper limit for the best standard treatment to remain unchanged; that over a longer period, substantial changes in diagnostics and staging, in detecting a relapse, and in supportive care introduce a bias for interpretation of the results; that conducting a trial over many years becomes difficult because of the diminishing interests of all participants and due to their mobility; and that ethical difficulties arise when interim results become available while the trial is still open for recruitment of new patients. Three years as

the longest acceptable period of patient recruitment applies only to the planning phase of a trial. This additional rule should help to eliminate proposals for trials which are unlikely to recruit a sufficient number of patients in a reasonably short time and should not be understood as a stopping rule. Once a trial has been activated, every effort (including a moderate prolongation of recruitment of patients) is warranted to bring it to conclusion and to meaningful results.

5. *Collaboration among several institutions and across political frontiers should be encouraged*. After considering the previous two points, it is clear that a single institution will rarely recruit a sufficient number of patients in a short time. Greater concordance of institutional and national regulations for approving a prospective clinical trial, and in particular a much quicker procedure through all steps of approval of a trial protocol should ensure that multi-institutional trials remain flexible and address the most promising new questions.
6. *Proper communication is the basis for a patient's consent to participate in clinical research*. Informed consent is a continuous process. Communication and informed consent are closely related, involving patients and physicians with their individual personalities and dependence upon a specific cultural background. Only after a sincere relationship has been established, can the most delicate question of participation in a randomized clinical trial be addressed (43). The procedure of informed consent should protect the patient, rather than the physician or sponsor of the research and should be adjusted to the clinical situation.
7. *All patients should be offered equal access to the medical services, irrespective of their participation in clinical research*.
8. *A trial within an economically and educationally disadvantageous population should consider the specific circumstances of health economics and of medical care and should be adjusted to the cultural context*. The aim of a trial should be improvement of feasible and locally affordable means of preventing and treating diseases, rather than reaching experience which is unrealistic to implement (44, 45). An agreement with the community leaders should supplement the individual patient's consent. For trials proposed by for-profit companies, ethics committees, patients' advocacy groups, and community leaders can negotiate for long-term benefits to the community in exchange for an opportunity to conduct the trial (46).
9. *For trials with a commercial background, formally appointed advocates of patients' rights or representatives of patients' organisations should monitor the consent procedure and conduct of a trial*. In such a setting, the imbalance between a lonely patient on one side, and between a powerful alliance of companies, researchers and physicians on the other is so obvious that no form of consent procedure can ensure the protection of the patient's best interests. Monitoring the conduct of a trial from representatives of patients' advocacy groups would alleviate this imbalance.
10. *Publication of the results of a trial is among the essential requirements for ethically defensible clinical research*. Editors, reviewers and in particular clinical investigators should not discriminate against publication of statistically non-significant trials. Rather than trying to demonstrate a positive result, the investigators should pay attention to scientific quality and honesty during all the stages, from the preparation of the protocol to the writing of the final report.

CONCLUSION

The purpose of this work was not to argue for ethical Puritanism but to present an analysis of the current practice of randomized clinical trials, identifying the greatest ethical costs, and recommendations for their alleviation.

ACKNOWLEDGEMENTS

This study was funded by the Ministry of Science and Technology, Republic of Slovenia, grant no. J3-0143-0302I. I also proffer my thanks to Matthew Trump for reading the English language.

REFERENCES

1. Fibiger J. Om serumbehandling af difteri. Hospitalstidende 1898; 6: 309–25.
2. Fibiger J. Om serumbehandling af difteri. II. Kruppatienter. Hospitalstidende 1898; 6: 337–50.
3. Lewis S. Arrowsmith. New York: Harcourt, 1925.
4. Segelov E, Tattersall MHN, Coates AS. Redressing the balance—the ethics of not entering an eligible patient on a randomised clinical trial. Ann Oncol 1992; 3: 103–5.
5. Passamani E. Clinical trials—are they ethical? New Engl J Med 1991; 324: 1589–92.
6. Kopelman L. Consent in randomized clinical trials: are there moral or design problems? J Med Philos 1986; 11: 317–45.
7. Gifford F. Community-equipoise and the ethics of randomised clinical trials. Bioethics 1995; 9: 127–48.
8. Royall RM. Ignorance and altruism. J Clin Ethics 1992; 3: 229–30.
9. Dudley HAF. Informed consent in surgical trials. Br Med J 1984; 289: 937–8.
10. Taylor KM, Margolese RG, Soskolne CL. Physicians' reasons for not entering eligible patients in a randomized clinical trial of surgery for breast cancer. New Engl J Med 1984; 310: 1363–7.
11. Cocking D, Oakley J. Medical experimentation, informed consent and using people. Bioethics 1994; 8: 293–311.
12. Hellman S, Hellman DS. Of mice but not men. Problems of the randomized clinical trial. New Engl J Med 1991; 324: 1585–9.
13. Zwitter M, Golouh R. Introduction to ethical analysis. Radiol Oncol 1996; 30: 305–9.
14. Beauchamp TL, Childress JF. Principles of biomedical ethics. 4th ed. New York: Oxford University Press, 1994.

15. Gillon R. Medical ethics: four principles plus attention to scope. Br Med J 1994; 309: 184–8.
16. Thornton HM. Breast cancer trials: a patient's viewpoint. Lancet 1992; 339: 44–5.
17. Altman DG. Better reporting of randomised controlled trials: the CONSORT statement. Br Med J 1996; 313: 570–1.
18. Williams CJ, Zwitter M. Informed consent in European multicentre randomised clinical trials—are patients really informed? Eur J Cancer 1994; 30: 907–10.
19. Zwitter M, Tobias JS. A survey of the ethical considerations in randomised trials for lung cancer. Lung Cancer 1998; 19: 197–200.
20. Minogue BP, Palmer-Fernandez G, Udell L, Waller BN. Individual autonomy and the double-blind controlled experiment: the case of desperate volunteers. J Med Philosophy 1995; 20: 43–55.
21. Baum M. Do we need informed consent? Lancet 1986; 2: 911–2.
22. Stiller CA. Centralised treatment, entry to trials and survival. Br J Cancer 1994; 70: 352–62.
23. Machin D. Interim analysis and ethical issues in the conduct of trials. In: Williams CJ, ed. Introducing new treatments for cancer: practical, ethical and legal problems. Chichester: Wiley, 1992: 203–15.
24. Gifford F. The conflict between randomized clinical trials and the therapeutic obligation. J Med Philos 1986; 11: 347–66.
25. Byar DP. Design considerations for AIDS trials. New Engl J Med 1990; 323: 1343–8.
26. Tobias JS, Souhami RL. Fully informed consent can be needlessly cruel. Br Med J 1993; 307: 1199–201.
27. Moore MJ, O'Sullivan B, Tannock IF. How expert physicians would wish to be treated if they had genitourinary cancer. J Clin Oncol 1988; 6: 1736–45.
28. Mackillop WJ, Ward GK, O'Sullivan B. The use of expert surrogates to evaluate clinical trials in non-small cell lung cancer. Br J Cancer 1986; 54: 661–7.
29. Nilstun T. Paternalism and health behavior. In: Gochman DS, ed. Handbook of health behavior research IV: relevance for professionals and issues for the future. New York: Plenum, 1996: 203–13.
30. Easterbrook PJ, Berlin JA, Gopalan R, Matthews DR. Publication bias in clinical research. Lancet 1991; 337: 867–72.
31. Begg CB, Berlin JA. Publication bias and dissemination of clinical research. J Natl Cancer Inst 1989; 81: 107–15.
32. Dickersin K, Min Y-I, Meinert CL. Factors influencing publication of research results. JAMA 1992; 267: 374–8.
33. De Bellefeuille C, Morrison CA, Tannock IF. The fate of abstracts submitted to a cancer meeting: factors which influence presentation and subsequent publication. Ann Oncol 1992; 3: 187–91.
34. Scherer RW, Dickersin K, Langenberg P. Full publication of results initially presented in abstracts. JAMA 1994; 272: 158–62.
35. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. Br Med J 1997; 315: 629–34.
36. Thornton H. Clinical trials—a brave new partnership? J Med Ethics 1994; 20: 19–22.
37. Baum M. Clinical trials—a brave new partnership: a response to Mrs. Thornton. J Med Ethics 1994; 20: 23–5.
38. Baum M. New approach for recruitment into randomised clinical trials. Lancet 1993; 341: 812–3.
39. Brahams D. Randomised trials and informed consent. Lancet 1988; 2: 1033–4.
40. Brewin CR, Bradley C. Patient preferences and randomised clinical trials. Br Med J 1989; 299: 313–5.
41. Jack WJL, Chetty U, Rodger A. Recruitment to a prospective breast conservation trial: why are so few patients randomised? Br Med J 1990; 301: 83–5.
42. Hancock BW, Aitken M, Radstone C, Vaughan Hudson G. Why don't cancer patients get entered into clinical trials? Experience of the Sheffield lymphoma group's collaboration in British national lymphoma iInvestigation studies. Br Med J 1997; 314: 36–7.
43. Zwitter M. Communication with the patient in clinical research. Ann NY Acad Sci 1997; 809: 83–96.
44. Halsey NA, Sommer A, Henderson DA, Black RE. Ethics and international research. Research standards are the same throughout the world; medical care is not. Br Med J 1997; 315: 965–6.
45. Wilmshurst P. Scientific imperialism. If they won't benefit from the findings, poor people in the developing world shouldn't be used in research. Br Med J 1997; 314: 840–1.
46. Cleaton-Jones PE. Availability of antiretroviral therapy after clinical trials with HIV infected patients are ended. Br Med J 1997; 314: 887–91.