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Review

Why don't cancer patients enter clinical trials? A review

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ABSTRACT

Despite widespread agreement about the value of clinical trials, the proportion of patients who are enrolled in such trials is often considered to be too low. A comprehensive literature search was carried out for the period 1980 to the present, in order to review current data on barriers and facilitators to the development of multicentre clinical trials. Of 364 articles initially identified, 35 articles and 1 book were selected in order to assess the reasons that doctors and/or patients participate in clinical trials. This review emphasises the fact that doctors play a key role in the development and non-development of clinical trials. More studies, in particular studies outside the United States of America (USA), are needed in order better to understand doctors' attitudes towards clinical trials. Such studies should combine multivariate analyses and comparative approaches in order to associate doctors' behaviours with their individual characteristics, with the organisational context of their working environment and with the healthcare system.

1. Introduction

Two main objectives are pursued through increased participation in multicentre clinical trials: first, improvement in patient management by more rapid evaluation of treatment efficacy and toxicity, and, secondly, improvement in medical practice, doctors' participation in clinical trials being considered an efficient way to change routine practice.[1] Key factors in the timely completion of a clinical investigation are patient accrual and the dedication of investigators. Both are closely linked.

However, even if the value of multicentre clinical trials is now barely questioned, the proportion of patients actually enrolled in such trials is often considered too low.[2,3]

Thus, it seems relevant to identify factors that impede recruitment in clinical research.

The aims of this article are to review current data on barriers and facilitators to the development of multicentre clinical trials, taking cancer as a case study, and to assess the reliability of these data and identify areas for further investigation.

2. Materials and methods

A comprehensive review of the literature was carried out to identify barriers and facilitators to the development of multicentre clinical trials.

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All articles, limited to oncology, appearing in MEDLINE from January 1980 to December 2004 were searched. Candidate titles with the MeSH descriptor *clinical trials* and one of the following terms: "*attitude of health personnel*" or "*attitude*" or "*perception*" were used. A total of 364 articles was found.

Articles that focused on the reasons why patients and doctors had participated or not participated in past clinical trials, were participating in current trials, or would be likely to participate in clinical trials, were included.

American studies focusing on the barriers to recruiting ethnic minority cancer patients into clinical trials and studies on the attitudes or behaviours of nurses towards clinical trials were excluded. Articles whose main objective was to present the results of a given clinical trial, but did not develop a substantial methodology to determine the reasons why doctors participated or not in this trial were also excluded. Reviews and editorials were excluded since we were looking for evidence, i.e. results from qualitative or quantitative observational or experimental studies.

One investigator (PC) abstracted the following information from each article: type, setting and sample, accrual rate of the trial(s) under study (when available), description of factors affecting enrolment. First, evidence of, and reasons for, patients' reluctance to participate on the one hand, and evidence of, and reasons for, doctors' reluctance to accrue patients on the other hand were identified and gathered. Reasons for reluctance related to personal factors only were then distinguished from those related to other factors.

3. Results

3.1. Search yield

A total of 35 original papers were read and analysed. One book, based on a longitudinal study concerning the National Cancer Institute (NCI) policy aiming at inciting community hospital doctors to participate in clinical research, was also included.[1]

Only 7 studies had not been conducted in North America: 3 in Australia,[4–6] 1 in Sweden[7] and 3 in the United Kingdom (UK).[8–10] Fourteen of the 35 selected articles had been published by the *Journal of Clinical Oncology*.

One may distinguish four types of studies:

- 12 studies[7,8,11–20] used a prospective methodology: a definite population was identified *ex ante* and data on their attitudes and behaviours towards clinical trials were gathered from then on. These studies tried to correlate the number and rate of accrual to clinical trials with the characteristics of doctors and/or patients;
- 9 studies were retrospective:[1,9,21–27] they tried to identify *ex post* the reasons of accrual once the trials had been completed. These studies provide no information on refusal to participate;
- 11 studies were attitude surveys regarding clinical research in general. Only one category of actors was interviewed: either doctors,[2,10,28–30] patients,[5,31] clinical research associates (CRAs)[32,33] or the general population.[34] Only 1 study attempted to measure the attitudes and opinions of patients, doctors and CRAs;[35]
- the fourth type comprises only 4 studies.[4,6,36,37] They consisted in asking doctors,[37] doctors and patients[4] and patients[6,36] whether they would agree to participate in a hypothetical randomised clinical trial.

3.2. Is patients' attitude an obstacle to the development of clinical research?

All studies were designed to test the hypothesis of patients as a barrier to the development of clinical trials. The results are very diverse, but, in any case, none concluded that patients are the most crucial obstacle to clinical research.

Of course, an important proportion of patients refused or would refuse to participate in clinical trials. Some studies reported a refusal rate greater than 50%.[4,6,19,26,36] Quite unsurprisingly, fear of placebo-controlled, double-blind, randomised trials, or concern for side-effects and quality of life, were identified as reasons to refuse to enter a clinical trial.[4,6,12,26]

Nonetheless, other studies observed that patients' refusal rates were lower than 50%. In particular, in 3 studies concerning enrolment into real clinical trials, refusal rates were 28%,[8] 49%[16] and 40%.[23] Interestingly, and paradoxically, the only study focusing on a randomised controlled trial[8] reported the lowest refusal rate.

Other studies showed that patients are not always reluctant to enter clinical trials.[5,6,26,31,33–35] In particular, 4 studies reported that patients have quite high expectations regarding phase I clinical trials.[14,18,22,27] Three of them[14,18,22] reported that patients tend to have even higher expectations than doctors.

However, great caution is advised when trying to associate patients' attitudes towards clinical research with their actual agreement to be enrolled in specific protocols. The rate of patients acknowledging the value of enrolling patients in clinical trials to improve medical knowledge may be lower when they considered their own participation.[31] In a study,[5] women with breast cancer were significantly more likely to decline participation in clinical trials than women presenting for screening mammography or diagnostic assessment.

3.3. Contextual barriers to accrual

Two main contextual factors have been identified as constraints to the development of clinical research.

First, and quite obviously, the overall rate is much too low, not because patients do not agree to enter protocols but because there are only few protocols that meet their needs. This has been appraised by some authors as an organisational barrier to the further development of clinical research. Indeed, some categories of patients will be *de facto* excluded because they do not meet eligibility criteria.[13,16,19,29]

The second factor has been documented only in the American literature. Insurance coverage appeared as a significant predictor of enrolment.[1,16,25] Patients with private insurance, such as Health Maintenance Organisations, are significantly less likely to enrol than patients with government insurance such as Medicare and Medicaid.[16,25] Along the same vein,

patients with fee-for-service coverage are more than twice as likely to be enrolled compared with patients with other types of coverage, including managed care.[23]

3.4. *Are doctors the main barrier to clinical trials?*

Most studies insisted on the crucial role played by doctors in the success or failure of clinical trials. Four main points were underlined.

3.4.1. *Patient–doctor relationship is crucial for recruitment into clinical trials*

First, the quality of information transmitted by doctors has been sometimes reported to have a great influence on the willingness of the patients to participate in trials: the better the quality of information the more likely the agreement of the patient.[5,32,33,35] A single study[36] proposed a completely opposite analysis: irrelevant information by doctors explains patients' agreement to enter clinical trials, since it generates unrealistic expectations. In this study 52% of the patients who had received the information orally consented to the principle of participating in a trial versus only 35% of the patients who had been given written information.

Secondly, patients' choice depends on their trust in their doctor.[5] Solomon and colleagues[4] provided evidence that many surgeons are pessimistic about their ability to convince patients to participate in clinical trials. Authors then hypothesised that this attitude might represent a self-fulfilling prophecy: less confident doctors might be less prone to convince patients.

However, these studies neither explored the kinds of information that are important for patients nor documented the reasons why patients trust their doctors.

3.4.2. *Doctors' selection among eligible patients*

A variable proportion of eligible patients is not proposed for entry into trials by doctors. Some prospective studies have been able to estimate the level of such selection, which is, of course, divergent among hospitals (and no doubt dependent on the nature of protocols, although this hypothesis has not been investigated). Simon and colleagues[19] established that doctors at a large cancer centre had proposed 33% of the patients only for entry to existing clinical trials. Siminoff and colleagues[15] reported that doctors working in different hospitals located in the same area had proposed 38% of the patients for enrolment in one of the existing clinical trials, whereas 52% of the patients who were proposed entry into a trial finally accepted. In Lara and colleagues' study,[16] this level was much higher, with 62% of the patients being offered a trial.

Some patients' characteristics are highly significant in predicting trial offering, without any consideration of eligibility criteria. Age is one of these factors, older patients being less likely to be offered a trial.[9,13,15,19,26,30] Yet, of those offered a trial, there is no significant difference in participation between younger and older patients[26] and expectations regarding phase I clinical trials are not correlated with age.[27] The same kind of results have been put forward about ethnic minority patients:[19] they are less likely to be offered a trial, although there is no evidence at all that they are more prone to refuse enrolment than other patients.

Some studies have shown that the higher the stage of the disease[13,26,30] or the poorer the prognosis,[15,30] the less likely the doctor will try to enrol patients into clinical trials.

3.4.3. *Reasons for doctors' reluctance towards clinical trials*

Doctors are not necessarily prone to participating in clinical trials. Existing studies have suggested that attitudes towards clinical trials must be correlated with doctors' conception of their mission.

Some articles tried to associate participation in clinical trials with doctors' perceptions of clinical research in general. From the 1980s to the beginning of the 1990s some studies had shown that doctors considered that randomised clinical trials altered the relationship with their patients and threatened their personal autonomy.[11,21,28] Such assertions have not been renewed since, but it is unclear if this is due to an evolution of doctors' values or judgements towards clinical trials or simply to the design of the studies.

Some other studies tried to correlate doctors' participation in clinical research and medical specialties. Medical oncologists are more prone to participate in clinical trials than are surgeons.[4,9,10,15,25] Paediatric oncologists have even greater expectations, as they consider these trials the best way to apply up-to-date treatments.[2] Two other articles concluded *a contrario* that primary care practitioners refer a minority of eligible patients for enrolment into clinical trials, but did not propose explanations for such attitudes.[17,30]

Two studies tried to provide evidence of a correlation between some characteristics of the activity of doctors and their attitudes towards, and their participation in, clinical trials. Siminoff and colleagues[15] have shown that surgeons whose activity is strongly oriented towards the treatment of cancer patients, and medical oncologists working as independent practitioners or in private hospitals, are less likely to refer patients for entering clinical trials. Twelves and colleagues[9] consider that surgeons who have a high case-load are more likely to enter patients into clinical trials than are other surgeons.

Some studies have shown that doctors' decisions regarding their participation in clinical trials depend more on their evaluation of specific protocols than on their general perception of clinical research. Some have reported that doctors are unwilling to enter patients in given protocols because they personally doubt the benefits or overestimate the risks associated with them.[10,16,24,32,33] Thus, participating in such clinical trials would be considered at odds with their conception of their role as professionals whose main mission is to care for patients. Reciprocally, Del Giudice and colleagues[37] concluded that the doctors' willingness to refer patients to the placebo-controlled, double-blind, randomised trial under study was correlated with their positive dispositions towards the evaluated treatment. Hjorth and colleagues[7] showed that the doctors' participation in the specific trial they studied was significantly linked to their perception that: (i) quality of life aspects were well taken into account by the trial; and (ii) the study protocol was simple enough to manage. Paradoxically, despite these results, only one study has tried to explore the kinds of protocols that doctors judge most interesting: Taylor and colleagues[11] have reported that 89% of doctors find

it more satisfying to participate in clinical trials that aim at improving quality of life rather than overall survival.

3.4.4. Relationship between doctors as a facilitator for clinical trial development

This factor has been far less explored by existing studies. Yet some rare results suggest that it should be further investigated since relationships between doctors seem to play a crucial role in the success of clinical trials. Two studies have provided evidence of a better accrual in clinical trials when doctors who are asked to participate have frequent contacts with investigators.[1,7] Along the same vein, Siminoff and colleagues[15] have shown that doctors who have formal support from a co-operative group are more likely to refer patients to trials. Another study[25] has provided evidence that the presence of a multidisciplinary forum in the hospital is significantly associated with increased accrual to clinical trials, this factor being of even greater significance than the number of oncologists working in the hospital.

4. Discussion

All studies mentioned above have greatly improved our understanding of the barriers to the development of clinical research. In particular, the pivotal role of doctors in the participation of patients has been strongly asserted. Of course, other factors have been shown to impede recruitment in clinical research: (i) patients may be reluctant to enter clinical trials, especially if these trials are placebo-controlled, double-blind and randomised and/or if they do not take into account side-effects and quality of life aspects; (ii) in the USA, insurance coverage is a strong predictor of enrolment. However, most studies have insisted on the crucial role of doctors in the success or failure of clinical trials since: (i) patients' agreement or disagreement with entry into clinical trials is strongly influenced by their relationship with doctors; (ii) doctors do not offer every eligible patient to enter a trial; (iii) doctors may refuse to participate in a clinical trial when they consider it at odds with their mission; and (iv) connections between doctors may have a great impact on doctors' participation in clinical trials.

Nonetheless, some potential factors have been omitted and others should be further investigated.

Two general limitations concerning published studies can be put forward. First, they have focused more on the barriers to clinical trials than on the reasons that could incite patients and doctors to participate. Yet, there are some 'success stories' from which one could draw lessons. The National Cancer Research Network (NCRN) in the UK is one of the most spectacular examples, since it has succeeded in increasing the accrual rate from 3.75% to more than 10% in a few years.[38] Even if this case study should be further investigated, this increase has surely to do with the massive public investment, which has allowed, among other things, the recruitment of 579 research staff, such as clinical trials practitioners, data managers and research nurses. Another example is the paediatric oncology community, which accrues more than half of children to clinical trials.[25] It suggests that concentration of the resources, structured national and international networks of involved clinicians[25,39] and a more formalised and co-ordinated organisation of cancer care[25] may facilitate the development of clinical research. The extent to which this experience may be fruitful for adult oncology is unclear, but it is worth taking as a starting point, especially for clinical research in rare cancers.

The second limitation concerning published studies is that they consist more of descriptive, univariate analyses than of interpretative, multivariate analyses: they seldom evaluate interactions between the different factors and – which is partially linked – they are not able to recognise and recompose the logic of doctors' and patients' attitudes towards clinical research in general and towards specific protocols.

More precisely, three directions should be further explored.

First, more international studies are needed. Since most results have been extracted from North American studies, it is important to check whether they can be applied to other healthcare systems and cultures and to explore which factors are invariant across situations. The possible role of institutional and organisational factors in the development of clinical research could be better identified and refined. For instance, do attitudes of patients and doctors regarding clinical trials vary in countries where the tradition of clinical research is less institutionalised, e.g. more recent and less incited by public funding? More precisely, the successful experience of the NCRN in the UK seems to indicate that sufficient local, multidisciplinary resources have become a *sine qua non* condition to help doctors enrolling patients and following them up as requested by quality standards, national legislation as well as by the EU Directive for Clinical Trials.

Secondly, studies that have tried to associate doctors' attitudes towards clinical research with their individual characteristics or with the organisational context of their working place are rare. Even medical specialty, the most frequently assessed factor, could be explored in more depth and should benefit from a multivariate analysis. For instance, are medical oncologists more prone to participate in clinical trials, because of their education, because of a different concept of medicine, because it meets their professional and individual aims, or because of the (multidisciplinary and research-oriented) organisation of the hospitals they are more likely than surgeons to work in? Furthermore, beyond medical oncology, there is an apparent diversity among doctors regarding their perception of the role of clinical trials in evidence-based medicine. A general survey of all medical specialties, using the same methods, might provide new insights into this possible correlation between medical specialty and doctors' attitude towards clinical research.

Thirdly, the impact of the relationship between doctors, especially between surgeons and oncologists on the one hand and between investigators and other doctors on the other, should be explored further. The results of the rare studies that have tackled this issue suggest that this component could greatly improve our understanding of clinical trial accruals.

Conflict of interest statement

None declared.

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