

EDITORIAL

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“...demonstrating a trial effect would mean that the vast majority of cancer patients who receive treatment considered as ‘best standard of care’, are, in fact, not receiving the best care available.”

Does enrollment in a trial carry a survival advantage for patients?

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A widespread belief among physicians is that patients benefit from participating in clinical trials even if they are randomized to the control arm. The belief that patients treated within clinical trials have a better outcome is sometimes attributed to a ‘trial effect’ [1], or alternatively, an ‘inclusion benefit’ [2].

A benefit from participating in clinical trials has been reported in a diverse range of clinical settings, from sick newborns [3] and newly treated HIV carriers [4], to patients given thrombolysis for acute myocardial infarction [5] or healthy individuals receiving an oral cholera vaccine [6]. A trial effect, if present, may be of particular significance in the area of oncology. At best, only 4% of adult cancer patients are treated within clinical trials in the USA [7]. Obviously, demonstrating a trial effect would mean that the vast majority of cancer patients who receive treatment considered as ‘best standard of care’, are, in fact, not receiving the best care available.

The presence of a trial effect has been addressed in several systematic reviews across a wide range of diseases. A recent Cochrane review of 80 non-randomized cohort studies came to the conclusion that participation in randomized clinical trials (RCTs) is associated with similar outcomes to receiving the same treatment outside RCTs [8]. Similarly, Peppercorn *et al.* have compared the outcome of cancer patients treated within and outside clinical trials in 24 carefully selected publications, and concluded that there are no sufficient data to support the existence of a trial effect [1]. Conversely, in a systematic review of the literature, Braunholtz *et al.* concluded that while the evidence is not conclusive, clinical trials probably have a positive effect on cancer patients’ outcomes and have suggested that the treatment benefit may be a result of strict protocol care or better clinicians [9]. Likewise, Stiller found that enrollment in clinical trials was associated with improved survival, particularly for less common malignancies [10].

Several limitations preclude us from drawing any unequivocal conclusions from these reviews. First, the analyzed data included old trials, some dating back to the 1970s and 1980s. Clinical trials in that era were significantly different from current practice. Most of these old studies, recalled Temple, who started working for the FDA in 1972, were “*inadequate beyond belief... You would be horrified [at the clinical trial data] submitted to the agency. There was often no protocol at all*” [11]. Another significant limitation in several studies is that the criteria used for selecting the non-trial patients were inappropriate. For example, comparing the outcomes of patients in the control arm with patients who were non-eligible for participating in the trial would obviously lead to a significant bias. Arguably, the non-participants would have inferior baseline characteristics, skewing towards a misleading favorable outcome among study participants. Studies that compared trial participants to historical controls may also be strongly biased by selection.

Keywords: clinical trials • glioblastoma • oncology • survival analysis • trial effect

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In an effort to address the presence of a trial effect in glioblastoma patients who participate in clinical trials, and to minimize as far as possible the selection bias, we have recently compared patients who participated in clinical trials with similar patients who were found to be potentially eligible to enroll in a clinical trial, but did not participate. These patients had received the 'best standard of care'. In an attempt to compare outcomes between two homogeneous groups, we carefully selected for only patients with primary glioblastoma with similar baseline characteristics of age, Karnofsky performance status and time of diagnosis (before or after 2005, when a new treatment standard was introduced in neurooncology [12]). Since patients who participate in clinical trials typically had at least one tumor resection surgery, we excluded patients who were diagnosed by biopsy only (as major tumor resection is considered to be a predictor of favorable outcome [13]). Even after rigorous efforts to match patients participating in clinical trials and non-participants, it was evident that participation in clinical trials carried a favorable impact, with participants enjoying a survival advantage even if randomized to the control arm [14]. Another approach for eliminating the selection bias is by taking advantage of incidental randomization. West and colleagues have investigated the outcomes of women with preeclampsia treated in the Yorkshire region of England. In this area, all women with preeclampsia are managed according to a strict unified protocol. The area is divided into 16 functional units, and between 1998 and 2001, six of the 16 units participated in a clinical trial, and women with preeclampsia were randomized to receive an infusion of magnesium sulphate or normal saline as placebo. In this study, the authors found no significant difference in outcomes between women treated within clinical trials and patients treated outside clinical trials [15]. Both the glioblastoma and the preeclampsia studies took substantial means to control for selection bias. Intriguingly, a trial effect was demonstrated in the glioblastoma study, and not in the preeclampsia study, suggesting that the presence of a trial effect is, perhaps, context specific.

Several aspects of a clinical trial setting are substantially different from the routine clinical practice and may contribute to a trial effect. First is the psychologically mediated benefit that patients gain from participating in a trial. This effect, often regarded as a 'placebo effect', may be less powerful than previously appreciated. In a provocative meta-analysis of RCTs that in addition to the treatment arm included both placebo and 'no-treatment' arms, there was no evidence that patients in the placebo arm did better than patients in the 'no-treatment' arm [16]. Second is the effect of patients and clinicians being under observation in clinical trials. In a classic series of studies on a group of workers at Western Electric's Hawthorne

plant (IL, USA), researchers noticed that when workers were under observation, any change in working conditions, regardless of the specific intervention employed, resulted in increased productivity.

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For example, the same improvement of productivity was observed following increasing or reducing the lighting in the production areas, as long as it was done under an experimental setting [17]. In the context of clinical trials, the 'Hawthorne effect' is the improvement of outcome in response to treatment only by the care giver and patients mere awareness of being under observation. A more intensive follow up of patients in clinical trials may result in a stronger 'Hawthorne effect'. A recent study suggests that this indeed may be the case. In a RCT of a new drug for mild to moderate dementia, patients who were randomized to the placebo arm and were followed more frequently had shown a better outcome than those who were only minimally followed [17].

Finally, a better adherence to a defined treatment regimen and better care for participants in clinical trials, often described as 'protocol effect' and 'care effect', respectively, may also contribute to the benefit from participating in a trial. In fact, this may be the most important component of the 'trial effect'. Patients enrolled in clinical trials are closely monitored by extra nursing care and frequent follow-up visits allowing early recognition of changes in the patients' health, which is followed by immediate appropriate responses by the caregiver. Adherence to clinical guidelines improve clinical practice [18] and may result in improved outcomes for patients enrolled in clinical trials regardless of the arm. In fact, the absence of a clear 'trial effect' in the preeclampsia study was attributed to the protocol-driven care of patients who were not recruited to the study.

Participating in a clinical trial is an altruistic act that patients are taking to improve care for future patients. A Mayo Clinic and North America Central Cancer Treatment Group study recently assessed patient satisfaction with their clinical trial experience. When asked, most patients said that trial participation was worth it (74% of the patients), would do it again (85% of the patients), and would recommend others to participate (85% of the patients). Satisfaction, at least, was not related to treatment outcome [19]. An interesting observation is that the mortality rate in hospitals with a high clinical trial enrollment rate was lower compared with hospitals where enrollment rate was low [20]. Regardless of participation in a trial, patients treated at hospitals with a high enrollment rate are likely to receive a better quality

of care by more competent and motivated staff. Participating in a clinical trial generally ensures adherence to strict follow-up and treatment protocols. This by itself may lead to improved patient outcomes. However, there are cases where a trial effect is weak or even absent. For those patients who get high quality, protocol-driven care outside a clinical trial, we cannot reliably ensure that participating in a clinical trial would lead to an improved outcome.

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