Clinical trials and studies are essential to the progress of evidence-based medicine. Randomized clinical trials provide the highest levels of evidence, and this evidence allows healthcare providers to make appropriate improvements. In addition to providing such evidence, the process of conducting clinical research also has a direct, protocol-related, impact on the conduct of care of those individuals who consent to join clinical trials. Furthermore, this process may have a less direct but valuable effect on those healthcare institutions and services providing their care in trials as well as in daily practice through the impact of research activities upon staff, facilities and the culture of the institutions. Keeping the research agenda as a high priority for healthcare institutions enables maintaining intellectual curiosity, positive questioning of practices and search for optimal services to patients.

The conduct and outcomes of clinical research must translate into improved clinical care to justify the major investments it requires. Investigators interested in Translational Research recognize the important gap between laboratory and clinical research, which is sometimes termed the ‘first translational gap’. However, less attention has been paid to the gap between clinical research and the implementation of results to improve outcomes for patients across diverse healthcare systems and different populations – the ‘second translational research gap’. The usual approach to bridge the second translational gap is to disseminate positive trial results and explore their relevance to clinical research conducted in resource-rich healthcare systems. However, the process of conducting clinical research within a healthcare system may be another way of bringing benefits to patients through research activity. Surprisingly, the benefits of research-active or research-intensive healthcare systems are poorly understood.

The literature on the relationship between the process of clinical research and healthcare outcomes is sometimes confusing, and the main focus so far has been on therapeutic clinical research conducted in resource-rich healthcare systems.

The literature is marked by a lack of clarity on the key questions. A common question is whether patients treated within trials do better than similar patients treated in the same institution or healthcare service but outside trials. This effect is commonly referred to as a ‘participation effect’. Such comparisons are inherently biased by the selection criteria. Even attempts to produce comparable non-randomized control groups and to correct imbalances by multivariate analysis are largely unconvincing. Any benefits resulting from this participation effect is only likely to influence the outcomes of the minority of patients who actually participate in the trials.

A question of importance for many patients, healthcare professionals, and policy makers is ‘Do healthcare institutions, networks of service providers or regional or national health services, who are actively involved in clinical research tend to deliver better care and outcomes than those who are not?’ The answer to this question is considered crucial by health professionals and researchers in order to determine whether conducting research (especially clinical and translational research) benefits patients and healthcare systems within which it is undertaken [1, 2]. To answer this question, studies have to carefully define ‘research active’ and ensure that all relevant patients in the compared institutions are included. Multivariate analysis is essential to determine whether the effect of research activity is independent and to address the level of causality between intervention and outcome. Such studies are uncommon, especially when an impact on health outcomes is examined, because of their limited opportunities, the logistic difficulty of access to high quality and detailed data on service outcomes, the process of care and research activities in those services, and the methodological complexity of this field. As Allen [1] elegantly observes ‘We must avoid the temptation to measure what we can count rather than measure what counts.’ However, if it can be shown that in retrospect research activity is causally linked to improved outcomes, then prospectively this would provide added justification for the creation and funding of research activities and infrastructure, and then the benefits should be felt by all patients cared for in the research-active institutions and healthcare systems.

In September 2009 a workshop was held at the International Agency for Research on Cancer in Lyon, France. This workshop focused on the available evidence and the role of future research for a better understanding of the relationship between clinical research and healthcare outcomes. Particular interest was paid to the benefits of establishing research-intensive healthcare systems in the developed and developing world. The participants of the workshop drew the following conclusions:

1. The participants have subsequently conducted further work and literature analysis.
• Clarity about the question asked was vital for the progress in this field. Up to now, the literature has lacked clarity. The workshop participants concluded that the question about the benefits of developing research activity within a healthcare system was of considerable importance. Benefits from a research-intensive healthcare system should affect all patients cared for within that system, not only those actually included in research protocols. This question is particularly worthy of extensive further study, and the methodological challenges were outlined in the workshop. For understanding how increasing research activity may lead to improved healthcare outcomes, workshop participants suggested the theoretical framework of the Donabedian quality of care triad of structure–process–outcome [3].

• Substantial literature is available evaluating benefits for individual patients included in clinical research protocols compared to similar patients cared for in the same institutions. This ‘participation effect’ has been quite extensively studied. Several reviews have been published [4–6]. Overall, the workshop participants felt that this field was marked by methodological difficulties and a lack of convincing evidence that individual patients benefited from participation in clinical trials unless they were fortunate enough to benefit from being included in an experimental arm of a trial that proved to be significantly better than standard care.

• The literature is less extensive on the impact of research activity on the quality of healthcare outcomes within research-active institutions and healthcare systems in general. Only a few papers [7–9] evaluating the impact of a research intensive healthcare system on health outcomes have met rigorous methodological standards. A recent overview has examined the impact of research activity on the outcomes and process of healthcare [10]. These reports provided some evidence for benefits from the process of clinical research and improvement in survival. The workshop participants were encouraged that institutional research participation may improve the quality of healthcare probably by introducing state-of-the-art activities and technology, motivating clinicians, increasing adherence to guidelines and providing a focus for workforce excellence. On the other hand, the data are still too few and mainly relate to studies of treatments (not screening or prevention) and are hence limited. Further, no generalisation may be made with regard to resource-poor healthcare systems. In addition, bias resulting from selection, treatment and participation effects may affect the results reported from the literature.

• Some preliminary evidence was provided (Sullivan, unpublished) that a research active system per se (i.e. clinicians engaged in ANY sort of research) seems to improve clinical performance.

• Research activity, whether in screening or therapy, significantly changes the process of care. Studies on screening for cervical cancer in the developing world were discussed where the evidence for the introduction of new healthcare activity through the opening of trials is clearly demonstrable. Not only have these shown the feasibility and effectiveness of screening in several low income countries but also through the introduction of new technologies, staff training and the development of clinical care teams, there is reason to expect that there are changes in the process of care which would be expected to result in improvements in healthcare outcomes that would go beyond the trial.

• The workshop summarized some of the efforts made across the world, particularly in the UK and the rest of Europe, to develop a comprehensive infrastructure within healthcare systems to support and promote clinical research. The effectiveness of these approaches in developing more intense healthcare systems was presented in the workshop. However, approaches vary between countries and depend critically on the nature of the healthcare system and the nature of the clinical academic research systems. In some countries, infrastructure has been focused on healthcare, as in the National Health Service in the UK, and in others around Clinical Trials Units and academic institutions.

• There is a pressing need for more research in this area, and workshop participants identified at least three priority research types:

- Large, rigorous quantitative studies in which major health outcomes such as survival in research active healthcare systems are compared to similar healthcare systems which are research-inactive or less active. Such studies are not only methodologically demanding, but also potentially expensive and logistically difficult. The workshop participants felt that opportunities should be sought to link evaluations of research benefits with large regional or national service quality evaluations to make such studies feasible and affordable. Measures of research activity will be mainly numbers of studies and people recruited but may also include bibliometric studies.

- Descriptive studies evaluating the impact on whole healthcare systems of clinical research initiatives are valuable and may be particularly important for obtaining information about the benefits of research in the developing world as comparative whole healthcare outcome data sets will be rare in these countries. Studies evaluating the impact of research activity on processes of healthcare are also important, especially when they contain valid controls.

- If a causal link between research intensive healthcare systems and improved outcomes is demonstrated, it becomes important to understand the mechanisms involved in order to allow us to maximize the benefits and to take account of these in designing clinical research.

references


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