The impact of the process of clinical research on health service outcomes

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Chapter 1 introduces the key questions and context for the work described in the supplement, on the impact of the process of clinical research on healthcare outcomes. The distinction between the influence of research activity on the outcomes for individual patients involved in clinical trials and other well-designed studies when compared to similar individuals cared for within similar healthcare institutions are considered. The evidence is reviewed and broadly the conclusion is that there is little evidence to support the hypothesis that individuals included in randomized trials do better than individuals with the same clinical characteristics in such trials within the same institution. However, the more important question of the influence of research activity on the outcomes of healthcare institutions is identified and clarified. There are less research data which address this question and it is harder to study. However, the existing data are encouraging and suggest that the hypothesis that research-intensive healthcare institutions provide improved outcomes is worthy of further study. There is a pressing need for additional high-quality, methodologically robust studies of this question.

Introduction

Randomized controlled trials (RCT) and other well-designed studies are essential to the progress of evidence-based medicine and RCT provide the highest levels of evidence that allows improvements in health care to be made with confidence. In addition to providing such evidence, the process of conducting clinical research also has a direct impact on the conduct of care of individuals who consent to join trials and studies, and a less direct effect on the healthcare institutions and services that provide their care in the trials and in general. Most focus so far has been on therapeutic clinical research conducted in resource-rich healthcare systems. The literature on the relationship between the process of clinical research and healthcare outcomes is sometimes confusing. A common question in the literature is ‘Do patients treated within trials do better than similar patients treated outside trials in the same institution or health care service?’ Such comparisons are inherently biased by the selection criteria. Attempts to produce comparable non-randomized control groups and to correct imbalances by multivariate analysis are largely unconvincing. There is little robust evidence that there is a direct benefit from participation for individual patients which can be demonstrated in this way.

The question which may be of greater importance to healthcare professionals and policy makers is ‘Do healthcare institutions or service providers which are active in research tend to deliver better care and outcomes than those that are not active in clinical research?’ To answer this question studies have to carefully define ‘research active’ and ensure that all patients with the disorder being studied in the compared institutions are included. Multivariate analysis is essential to determine whether there is an independent effect of research activity. Such studies are uncommon because of their logistic difficulty and the limited opportunities. Two studies of patient survival published since 2000 have met our methodological requirements [1, 2] and both are discussed here and also in Chapter 3 [3]. We are encouraged by the available evidence that institutional research participation may improve the quality of healthcare by introducing state-of-the-art activities, adherence to guidelines and providing a focus for workforce excellence. However, the data are limited, relate mainly to studies of treatments (not screening or prevention) and may not be generalizable to resource-poor healthcare systems. More good studies of this question are urgently needed.

The relationship between research activity and the delivery of excellence in cancer care is complex and challenging to study. Work on outcomes in European Cancer Centres had been conducted through the Eurocan Plus project and coordinated by the International Agency for Research on Cancer in Lyon (www.eurocanplus.eu). There is still no systematic recognition of ‘Cancer Centres of Excellence’ (CCE) in any of the subjects of research or clinical care. The oncology community provide evidence that CCE which tend to have high scientific activity have better results in terms of patient outcome and satisfaction. However, evidence is still inconclusive in many areas. At first examination this may seem a relatively simple problem in which CCE identify the outcome of their patients, as recorded in cancer registries or in other databases and these are compared with outcomes in other centres. Statistics on institution size, specialization, technical equipment and patient
outcomes can be collected and may focus on the care for patients who require the attention of skilled complex and extensive teams. These outcome data may then be compared to research activities in terms of translational research for drugs, imaging, techniques and biomarkers, phase I and II trials including the early evaluation of new technologies or phase III trials and testing for new imaging techniques and biomarkers. Unfortunately lack of data, barriers to linkage between databases, lack of agreement on outcome measures and lack of appropriate monitoring of non-outcome data makes it difficult for CCEs to convince Health Ministries and Social Security Offices that cancer patients should be managed in such institutions and in particular be managed in institutions which are research active. These issues are scientific and clinical but they are also financial and political with resource allocation depending substantially upon the conclusions of these analyses and the policies derived from them.

the key questions

The key questions may be summarized as:

Question 1: Do patients in clinical trials do better than patients outside trials given the same treatment in the same healthcare services?

Question 2: Do research active healthcare systems deliver better outcomes than research inactive healthcare systems for their patients?

These are different questions requiring different methodologies and probably the answers are different. The literature identifies a variety of ways in which patients in clinical trials or studies may benefit:

- Treatment effect – the test treatment being evaluated in a trial is found to be better. Patients who receive it will therefore be shown to have benefited and if the trial is disseminated to change practice for appropriate patients, others will subsequently benefit;
- Participation effect – all patients in trials and other well-designed studies do better regardless of what treatment they receive. This implies improvements in control/test arms as well for those receiving the test treatment under study;
- Protocol delivery of care – clinical trials are conducted with rigorous protocols and if these improve the delivery of care, then there would be a participation effect;
- General improvement in care. This may arise if research activity has a global impact on care provision perhaps by recruitment/retention of key staff or the availability of unproved technologies.
- Changes in behaviour as a result of healthcare professionals’ awareness of evaluations. Trials closely monitored; healthcare workers might respond with enhanced performance in all their work;
- Placebo effect especially for subjective outcome measures.

The available methodologies for studying these questions are RCT of trial participation; natural experiments where it is possible to monitor impacts from changes in research activity in healthcare systems; studies of eligible patients who decline randomization but whose outcomes are monitored and were compared to those in trials; patient preference (comprehensive cohort) studies prospectively designed to compare randomized groups to eligible but non-randomized groups; retrospective cohort comparisons with case-mix adjustments and comparisons of whole service outcomes for research active/intensive institutions or healthcare services to comparable research inactive institutions or services. These are considered further in Chapter 10 [4].

There have been a series of important reviews of this area [5–8]. The first review was done by Braunholtz et al. [5] and addressed more specifically Question 1. This review concluded that overall, clinical trials seem to have a positive rather than a negative effect on the outcome of patients, Peppercorn et al. [6] conducted a comparison of outcomes in cancer patients treated within and outside clinical trials and established a very valuable conceptual framework and structured review. This important review thoroughly and critically evaluates the older literature in this field, with 26 comparisons, 24 published articles, 21 retrospective cohort designs. Fourteen studies provided some evidence that patients enrolled in trials have improved outcomes. They often did not distinguish between the two questions discussed above and were only able to identify eight studies which restricted a comparison group to eligible patients. Their observations suggested that positive findings were more likely to be found in older studies conducted before 1986 and that the methodologies in many studies were inconsistent and incomplete, and multivariate analysis was inconsistently applied.

Vist et al. [7] conducted a systematic review of patients who participated in randomized controlled trials compared to similar patients receiving similar interventions who did not participate in such trials reporting five RCT (412 patients randomized in these direct comparisons), 80 cohort studies, 130 comparisons and 86 640 RCT patients in all of the trials and 57 205 other patients. They concluded that there was heterogeneity between studies, 11 ‘favoured’ RCT participation; 10 the reverse and there was no support for better outcomes in RCT in general. This review did not distinguish between the two key questions but did conclude that there was no convincing evidence in support of benefits for individual patients who are included in clinical trials. This systematic review is the most robust study to date which supports the conclusion that individual patients treated in trials do not have better health outcomes than individuals outside trials but in the same healthcare systems. Hence, according to this systematic review, the answer to Question 1 is probably no.

Clarke and Loudon [8] conducted a valuable systematic overview of the effect on patients of their healthcare practitioner’s or institution’s participation in clinical trials. This valuable overview searched the literature to identify studies which bore substantially on our Question 2. They found five studies which addressed the impact of research activity on the behaviour of practitioners. The end-points of all of these studies were relevant to the process of care. They identified two studies [9, 10] which they regarded as being well controlled and showed positive impacts of research participation on prescribing practice and nurse attitudes to research. Three studies [11–13] which showed positive impacts of research...
activity on adherence to guidelines, prescribing practice and length of hospital stay but there was some concern about the difficulty of controlling for changes over time which might have occurred for reasons other than research activity and about the selection of controls in one study.

Two studies addressed the impact of research activity on the survival of all patients with the diseases studied treated in hospitals which were research active compared to hospitals with less or no research activity [1, 2]. We detail these further below and in Chapter 3 [3]. Both of these studies are well controlled and positive. One study [14] compared survivals for patients with node-negative breast cancer, between hospitals in Canada. Hospitals which were radiotherapy centres and/or research active had significantly better outcomes than all others, but it was not possible to separately identify the impact of research activity.

Five studies of the impact of research activity on the process of care were identified. Two of these studies, one on adherence to guidelines for asthma [15], and one on prescribing practice for treatment following myocardial infarction in research active hospitals compared to inactive ones [16], were negative and did not show a change in those aspects of process of care as a result of research activity. Three other studies suggested positive impact of research activity of process of care but Clarke and Loudon expressed some concern about study designs. Chen et al. [17] showed the uptake of changes in practice for the management of laryngeal cancer was greater in teaching/research facilities; Clark et al. [18] showed the uptake of apheresis in institutions that were active in trials increased during the trials period. In breast cancer chemotherapy regimens in Germany [19], a questionnaire reported an improvement in professional knowledge as a result of trials participation but the response rate to this self-reported exercise was relatively low.

Clarke and Loudon [8] recognise that the available findings are inconclusive and that there is a pressing need for further research upon the impact of research activity on outcomes for practitioners and institutions.

**individual studies of relevance to cancer**

We have selected five studies that give insight into study designs and their application in this field. The first two studies relate to research that addresses the impact of involvement in a clinical trial upon the individual patients managed in similar health services (i.e. Question 1 above). The latter three address the questions of the impact of research activity on healthcare services as a whole (Question 2).

**a retrospective cohort with adjustment.** Roy et al. [20] conducted a retrospective cohort study with population-based registry comparisons consisting of the British National Lymphoma Investigation patient database (1970–1980) (2755 patients in clinical trials and studies) and the UK population-based cancer registries involved in the EURO CARE study (5064 patients outside studies or trials) (Figure 1). Their conclusions were that 10-year relative survival was identical in trial and non-trial patients. However, 10-year relative survival was better in trial patients aged 65–74 (39% relative survival versus 27%). While suggesting a participation effect in a subgroup, this study is not conclusive evidence of that effect.

**Figure 1.** 10-year relative survival by age group (adjusted within age groups) British National Lymphoma Investigation (BNLI) and population-based (EUROCARE) cases (1978–1984 period and 15–74 years age class) [20].

a rigorous comparison of RCT versus non-RCT in comparable patients in the same services: a ‘Comprehensive Cohort Study’. Schmoor et al. [21] conducted in Germany a rigorous comparison of eligible patients who entered a randomized trial started between 1983 and 1989 with those patients who did not consent to randomization but were treated within a trial-based protocol without being part of a trial (Figure 2). This comprehensive cohort study design was highly informative. Only a very small number of studies of this kind have been done and Schmoor’s evaluation represents a significant contribution to the literature. They showed no difference within the randomized trial and no difference also between trial patients and those treated on similar protocols outside the trial.

Their conclusion was that there was no evidence of benefit for individuals who entered this clinical trial as individuals. In this study, case matching between trial patients and non-trial patients is achieved prospectively by the application of the eligibility criteria in both groups, a real methodological strength which provides an example of a rigorous study supporting the Vist overview analysis presented earlier in this chapter [7].

an ‘Experiment of Nature’ in Finland. In 1979 the Finnish Leukaemia Group began introducing clinical trials in the management of multiple myeloma into the hospitals of Finland and 17 of the 21 hospital districts became active in clinical trials research in myeloma. Taking advantage of these data and a high-quality registry of outcomes for patients in Finland a comparison was made between health services which were research active in multiple myeloma and health services which were not research active. This study addresses our second question – the impact of research activity on the whole outcome for a healthcare system. Karjalainen and Palva [22] concluded that there was a strong association between better survival and research activity both in that the research-active geographical hospital districts had better outcomes and their outcomes improved during the time of introduction of the clinical research activity. This ‘experiment of nature’ describes...
a relatively rare opportunity to make comparisons of whole service outcomes between those that are research active and not and to follow changes over time and provides some data to support the benefits to healthcare systems of research participation. This study, although conducted three decades ago, provides valuable information about the impact of clinical trials on the healthcare system for a specific disease in a whole country with a comprehensive, unselected, control group and the evaluation of both comparative data and change over time.

**the impact of research activity on whole healthcare systems: ovarian cancer.** Du Bois et al. [1] took advantage of a Germany-wide audit of all outcomes in epithelial ovarian cancer to collect comprehensive unselected data from all institutions providing such care. They defined being research active as any accrual into the national collaborative group trials and showed that research-active hospitals had consistently better outcomes for all of their patients than those that were not research active (highly significant on multivariate analysis). Hospital size was not a predictor of better outcomes. They also had systematically better adherence to guidelines with provision of state-of-the-art quality of care in surgery and chemotherapy. This important study is discussed further in detail in Chapter 3 [3].

**the impact of research activity on whole healthcare systems: coronary artery disease.** This study had cardiovascular outcomes but its design is of value for the cancer domain. Majumdar et al. [2] evaluated all patients treated for coronary artery syndrome in US hospitals and defined tertiles of trial participation as none (145 hospitals), low enrolment (226 hospitals) and high enrolment (123 hospitals). Among 174 006 patients with coronary artery syndrome there were improvements in research active hospitals in the process of care shown by adherence to guidelines (Figure 3a) and in outcomes shown by short term mortality (Figure 3b) which remain highly significant on multivariate analysis.

**conclusion**

For question 1 on the impact of research participation on individual patient outcomes, we have given examples from the literature and that literature is summarized by Vist et al. [7]. The overall findings of that overview and our conclusions are that the benefits for individual patients compared to similar patients in similar healthcare systems are not demonstrated by the available literature. Patients should not be told that they will definitely benefit individually by entering a trial.

Few studies addressed the impact of research activity on survival in whole clinical services and institutions as opposed to individual patient outcomes. Together, three studies, leukemia in Finland [21], ovarian cancer in Germany [1] and cardiovascular diseases in North America [2], represent the ‘state-of-the-art’ in comparisons of patient survival in research active institutions and healthcare systems. It is encouraging that...
all three show improvements associated with clinical research but further well designed studies are urgently needed.

Studies on the impact of research activity on the process of care, which have been analysed so comprehensively by Clarke and Loudon [8], show some positive findings but overall the picture is mixed. Clinical research activity may itself be improving specific aspects of process of care as well as providing the evidence base for future improvements but more studies are needed.

The impact of clinical research activity upon the outcomes for a whole healthcare service or healthcare system is of considerable importance because it is relevant to all patients in a healthcare system, not just the minority who are actually recruited into clinical trials. It has not been extensively researched and more work is needed to place policy on a sound footing. This research requires the collection of good-quality data on the whole healthcare system or institutional outcomes for the disorders under study rather than just the collection of data on patients involved in trials. Methodological challenges are discussed in Chapter 10 [4]. This question is central to clinical research and healthcare policy and requires further study.

disclosures
Professor Selby and Dr Autier have declared no conflicts of interest.

references
3. Chapter 3.