How may clinical research improve healthcare outcomes?

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Healthcare outcomes such as overall survival or quality of life are the end results of a complex interaction between the patient, treatment and the healthcare system. Research may identify superior interventions but their dissemination and changing the behaviour of healthcare providers is challenging. Demonstrating and measuring the benefits of clinical research on healthcare outcomes is an important issue but there is remarkably little empiric work to date in this area. In this chapter we explore benefits that may arise in healthcare from contributing to clinical research, and consider the mechanisms which may be relevant. Improvements in infrastructure, the processes of care and workforces are important. Complex adaptive systems theory provides a framework for considering the many feedback loops that relate research, health outcomes and the behaviour of healthcare providers. Given the costs of research, additional studies to examine the impact of research on healthcare outcomes and to explore the mechanisms are justified and highly desirable.

introduction

Demonstrating and measuring the benefits of clinical research – and therefore the value to any health system of supporting a research infrastructure – is extremely challenging. Healthcare professionals, policy makers and the public at large seem to recognise intuitively that clinical trials and studies are worthwhile, and are broadly supportive, as reflected in regular and sustained financial support from governments (for instance US NIH budget of $31.2 billion and UK healthcare research budget of £1.7 billion) and by public support for health research charities (e.g. Cancer Research-UK about £400K).

Nonetheless, demonstrating the impact of the clinical research enterprise as a whole upon subsequent healthcare outcomes is difficult and there is surprisingly little clear evidence. In this paper, we discuss the potential mechanisms through which research participation may improve healthcare outcomes, summarize such evidence as is available, and propose a framework that may be helpful for stimulating and focusing research on the association between research activity and outcomes in healthcare.

It is becoming increasingly important to demonstrate that research participation and research systems bring benefits to patients and to society as a whole in addition to those of the research itself in leading to advances in health care. Engaging and maintaining the necessary support for clinical research at all levels – ethical, logistic and financial – requires that we demonstrate that healthcare systems or institutions that participate in clinical research have better outcomes – and that these are not limited solely to research participants, i.e., that there may be a potential institutional or system effect that comes with research participation. Clinical research is a resource intensive and costly undertaking; it could be especially difficult to sustain support for research infrastructure in periods of economic contraction without some demonstrable estimate of the associated societal benefit. Conversely, it also would be difficult to make the case for increasing support in the future without some persuasive characterisation of the benefit. This is especially true for health systems in poorer countries or regions: if engagement in clinical research does provide system and societal benefits but it remains difficult to recognise, their systems are unlikely to undertake the necessary investment.

Governance and health authorities will need evidence that resources required for research (beyond those required for care itself) are necessary and beneficial. Moreover, public understanding of benefits may be critical, for instance, to the development of efficient access to identifiable patient data for research, a major issue in many countries.

Demonstrating the beneficial effects of clinical research is certainly not a simple matter of measuring health care outcomes in a given catchment, comparing these to current or preceding research expenditure, and tracking trends over time. Healthcare outcomes such as overall survival or quality life are the end results of a complex interaction between the patient, treatment and the healthcare system. Health outcomes are also influenced by socioeconomic factors, demographic trends, the nature of the healthcare and public health infrastructures, economic cycles, and numerous other variables. Even the improvement in outcomes that arise when research identifies a superior intervention and its use is disseminated is not straightforward to measure due to differences between trial participants and those treated in routine care and the variable willingness of healthcare providers to adopt change.

However, what we are seeking in this paper is distinct from the latter: it is to tease out any benefits that arise from
contributing to clinical research, not just learning about positive results after the fact. Table 1 lists several types of mechanisms or intermediate benefits by which this may occur, suggests what sorts of research might be able to show such a benefit, and cites what evidence is currently available. The remainder of this chapter discusses these mechanisms and potential evaluation approaches in more detail and complements a recent systematic review of the effects on patients of participation in clinical trials by healthcare providers and institutions [1].

**potential mechanisms through which outcomes may be improved in research-active settings**

**improvements in infrastructure**

Infrastructure refers to attributes of the setting in which care is delivered such as accommodation, equipment and personnel. The conduct of clinical research often requires physical infrastructure such as space and specialized equipment and services to perform research-related activities. While the infrastructure is usually used for research-related activities, there is potential that once the research is complete the infrastructure remains. Any improvements in infrastructure in relation to research may be especially relevant in resource-poor settings where many basic aspects of infrastructure may be limited to begin with.

Participation in clinical research may also allow early access to novel technologies such as new surgical techniques or medications, which may be applied to non-research participants earlier than in institutions which did not participate in the research. This would seem likely to be the case but we could identify only one study directly bearing on this possibility, in the field of cardiology, and this failed to show that participation in a specific clinical trial resulted in faster uptake of the intervention in the participating institutions [2]. On the other hand, acquisition of new skills or technology as required for some clinical trials may lead to their systematic application and outcome improvements throughout an institution or health system. There is evidence that the training and quality assurance associated with a large study in the Netherlands of a new colorectal cancer surgical technique led to rapid improvement in national outcome statistics [3].

The other component of infrastructure is that of human capital. Physicians, nurses and other allied health professionals that practice in research-active environments may be systematically different than their peers in non-research-active settings and may deliver better care. This may be as a result of personal characteristics, multi-disciplinary collaboration, additional training and education, or through specialization. In oncology, there are some data to support a volume outcome relationship for certain surgical procedures with respect to both institutions [4] and providers [5], but the literature has not been consistent [6]. For ovarian cancer specifically, evidence suggests that outcomes may be better when patients are managed by gynaecologic oncologists, but once again this is not a consistent finding across all studies [7]. However, there are no data to show that high volume or very specialized institutions or providers are more likely to be research active.

**processes of care**

The processes of care received by a patient can have a significant impact on outcomes and it is possible that such processes differ systematically between research active and non-research active settings or practitioners. Research active institutions or providers may be more likely to follow clinical guidelines or may be faster to uptake new evidence into practice. A study in patients with acute coronary syndromes showed that compliance with clinical guidelines was better and mortality was lower among patients treated in institutions that participated in clinical trials in acute coronary syndromes despite the fact that very few patients actually participated in trials in any given institution [8]. In ovarian cancer, a study from Germany showed that patients treated in institutions that participated in clinical trials had more complete surgical staging and debulking and had better survival than patients treated in institutions not participating in clinical trials [9]. In contrast, another study which evaluated the impact of participation in a pharmaceutically sponsored clinical trial in asthma showed that trial participation did not influence guideline adherence but did increase use of drugs made by the sponsor [10]. However, surveys of institutions [11] or providers [12] that participated in a particular clinical trial have reported that the quality of care improved as a result of taking part in the trial.

**Other potential benefits of research activity**

The value of negative clinical trials is easily overlooked, but some are especially important in terms of the costs, resource use, and side effects that are commonly associated with newer, more technological, or more complex interventions. While it may be challenging to estimate the impact of not adopting interventions that are found to be ineffective (or no more effective than prior standards), the research that provides this evidence could be argued to provide indirect benefit to all relevant patients, both within and outside of the participating sites.

Additionally, the implementation of clinical research programmes within an institution, region or nation is assumed to be helpful in retaining outstanding and gifted clinicians and scientists, who might otherwise be attracted elsewhere. An active research environment should also serve to promote collaborative research with the commercial pharmaceutical, biotechnology and medical device sectors, which generates wealth within the relevant community. However, these relationships may be quite challenging to demonstrate, and we are not aware of any robust relevant data.

**potential evaluation approaches**

Understanding the links between clinical research and its impacts is a nascent and thus rich field for novel evaluation approaches. Broadly, at the heart of understanding the relationship between research and its impact, whether through infrastructure, processes of care or other areas such as knowledge generation, lies complex adaptive systems theory [13]. This does not ‘see’ research and outcomes as limited or static but as a long history of feed-back loops, both positive and
negative. Such a framework is capable of integrating the myriad of socio-political and socio-cultural forces at work with sensitivity for both temporal and emergent phenomena. The underlying assumption of this approach is that medical research is shaped through interactions within a social system; and that flexibility offers a direct measure of complexity [14]. Thus, we do not need to make assumptions about mental representations occurring within an individuals’ mind (the individual researcher), since cognition is understood as a process that occurs not just within but also between individuals [15]. The main advantage is that socio-cognitive complexity of research is more easily observed and measured, and is always situated in context. Thus if such models for studying complex systems as cancer research and patient outcomes are available what has held back their application? The short answer is that there are blocks both in policy and epistemological terms. In the case of the former the use of evidence-based policy remains a relative nascent approach in cancer. Opinion-based policy making is the dominant culture and that holds as self-evident a positive relationship between research activity and better outcomes. There has been, until relatively recently little challenge to this normative construct. In much the same way as collaboration has been held to be self evidently good for research productivity, the positive link between research and better patient outcomes has also been accepted. In the case of the former, however, empirical research has demonstrated collaboration to be a very mixed blessing [16].

Cancer research provides a rich arena for studying infrastructural changes associated with surgery-imaging-pathology; radiotherapy; medicines and organisational aspects such as multi-disciplinary care. Early work on cancer medicines for example has found evidence of early adoption of novel targeted therapies by research active systems once certain variables such as state-sponsored access control measures, e.g. Health Technology Assessment programme (HTA), are taken into account [17]. Organisational theory that links research activity with infrastructure provides another rich area for novel projects. For example, the US model of cancer centres provides a good model to study how research activity measure, for example using bibliometrics, does (or does not) correlate with early organisational innovation for patient care [18].

Evaluating the link between care and research is complex. However, numerous quantitative and qualitative approaches such as cultural transmission, scientometrics, and social systems tools exist but require ‘translating’ into the study of cancer research and patient outcomes. These methodologies can provide the raw material around which models can be tested and examined against real-world observations. Boyd’s seminal work on cultural evolution suggests many frameworks, for example of understanding how cumulative knowledge in cancer research is built, thus effecting patient outcomes through both saltational leaps and gradualism [19]. Cultural transmission theory can also be used to examine how research and healthcare professionals pass on knowledge laterally and horizontally and how this can alter clinical management [20].

One of the most important recent findings and, by default, a new avenue for exploring the relationship between research and patient outcomes is the emergence and development of translational cancer research as a completely independent phenomenon from either socio-political or cultural drivers [21]. By studying the emergence of different domains of cancer research using bibliometrics one can see that frontiers in research are breached through complex processes that unfold unevenly in time and space [22]. How they then converge to change patient outcomes has been tentatively explored through relatively simple systems analysis such as the influence of publications on cancer clinical guidelines [23]. These approaches provide a method of studying knowledge generation through cancer research activity using objective methods.

Interestingly, despite the central importance of economics to policy-makers there has been little work on the economic value of cancer research. What studies there have been tend to be generic in nature. However, they provide a set of tools and health economic approaches that could be used to study the link between cancer research and economic returns [24].

Extending this further, the impact of research on the wealth of countries is also a potentially important area, although the distributed, globalised nature of research and eventual clinical utility, as well the privatisation of profits would make this a difficult study. Beyond the quantitative, there are also fascinating and fundamental questions about the ‘right’ of patients to have access to research, the role of cancer research in society and questions of global justice. In the latter case this relates to the fact that most cancer research is conducted for and by developed countries. Its results, whilst important for the citizens of these countries have little applicability to the cancer health needs and societies of the majority of the human population in low/middle income countries. Is this right? Serious studies need to be undertaken to study distributive justice in cancer research [25]. Opportunities for transdisciplinary studies with bioethics, political economics and philosophy abound in this area.

In summary, how complex systems maintain their coordinated integrity seems dependent on their capacity to co-adapt through interactive feedback loops [26]. As a complex system the relationship between cancer research activity and patient outcomes is clearly neither linear nor necessarily positive [26]. Studying research publications and other outputs of research such as patents, can be a novel and useful approach to understanding these dependencies between research activity and the eventual impact of this as long as there is an understanding of the factors that feed into this complex adaptive system [27].

Nevertheless it is important not to lose sight of the vast historical evolutions and current networks through which research ultimately delivers patient benefits. I, Pencil written in 1958 by Leonard Read describes the life of an ordinary wooden pencil [28]. It is a tale of millions of different people(s), technologies and processes required to make a pencil with no one person capable of knowing all this. In a similar way the outcome of any one patient is the result of exactly this sort of cumulative, collective knowledge from the most humble venflon to the most expensive sophisticated imaging and novel chemotherapeutic regimens not to mention the myriad of professionals required to deliver the care. Every single one of these has come into being through a process of research and
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education. It is their collective application that brings about improved outcomes.

**impact of patient characteristics**

Patient and disease characteristics have a strong impact on outcomes and it is possible that there are systematic differences in patient characteristics in relation to the institution in which they receive care. Social determinants of health such as education and income are associated with outcome in many areas of medicine including oncology. Often, patients who are poor or less educated have worse outcomes: they may present at later stage, have worse health otherwise, have less access to care or simply do not navigate the system as well. Academic institutions and research-active institutions often have better reputations for providing care and therefore more educated, wealthy patients or better 'self-managers' may be more likely to seek care there such that the patient mix between research-active and -inactive institutions may not be the same. In contrast, more complicated and sicker patients may also be more likely to be referred to research-active institutions, so the case-mix argument can work both ways. While some data are available to show that patients that participate in clinical trials are often different from those who do not participate even within the same institution [29], there is limited evidence regarding the differences in patient characteristics between research active and non-research active institutions. However, adjustment for case-mix, including both medical and social characteristics, will be essential in any studies that evaluate differences in outcomes of care between institutions in relation to research activity.

**conclusion**

Measuring the benefits associated with clinical research is an important issue but remarkably little empiric work has been done in this area. Given the costs of research, additional studies to examine the impact of research on healthcare outcomes are essential and provide an opportunity for the use of innovative evaluation methods.

**disclosures**

The authors have not declared any conflicts of interest.

**references**