How can clinical research improve European health outcomes in cancer?

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Abstract

Introduction

Improvements in diagnosis and treatment of cancer have improved patient survival to above 50% in many developed countries, and the best results now approach 60% long term survival (1). However, there remains tremendous variation globally and across Europe and it has been estimated that our failure to implement best practice results in 50,000 – 100,000 avoidable deaths every year in Europe (2). We have estimated that using best practice could improve overall survival in Europe to 60% and that maintaining the momentum in existing cancer research programmes could further improve that towards 70% by 2035 (1). Research and Innovation will have to be central to that effort. Clinical cancer research is conducted primarily to provide evidence to set optimal therapeutic strategies and improvements in healthcare delivery, leading to better outcomes and improved quality of life for patients. Research-informed interventions can be effective across the cancer control continuum (3 – 6). Randomised Controlled Trials (RCT), however, may be conducted in highly selected patient populations and have limited generalisability. This paper focusses on how modern health informatics can help us evaluate the ways in which RCT and other well-designed clinical/translational research studies can maximise health benefits for patients.

We explore the implications of this for healthcare and research policy. Our objective is to evaluate the evidence, especially that derived from the very large datasets which can be studied using modern informatics, and to show in a model how the several different ways in which clinical research can improve patient outcomes.

The ways by which research improves health outcomes are known to be complex. Research participation itself may improve the performance of hospitals (4, 5) and the uptake of new evidence-based practice may be faster in research-active hospitals (6). We have chosen to focus particularly on recent large studies from the Southwest Oncology Group (SWOG) on the impact of positive RCTs on cancer patient survival in the USA (3), the National Institute for Health Research (NIHR) Cancer Research Network in England (NCRN) on the impact of research participation on hospital patient survival in England (4, 5) and the European Organisation for Research and Treatment of Cancer (EORTC) on the uptake of new research evidence (6). Each study is based on the analysis and linkage of large healthcare and research datasets (in two cases over 200,000 patients), covering whole countries using modern health informatic approaches and data linkage. We present a review of the effect of clinical research participation on hospital outcomes and synthesise the findings into a model of the impact of research outcomes.

It has been claimed that patients who participate in clinical trials have better outcomes than patients in the same institutions who are not in trials. Some early studies appeared to support this view but trial participants are a selected group. Systematic reviews do not support this assertion (7). A different and more pertinent

question is to ask whether a clinical team or hospital which is research-active delivers better outcomes for all the patients treated by that hospital or multidisciplinary team, when compared to the outcomes for a research-inactive hospital or team. Research participation might stimulate teams to consider new evidence, introduce new improved cancer treatments and equipment, and improve the quality assurance of treatments and investigations. If such improvements are stimulated by research activity, they should improve decision making and have an impact on all patients treated with the disease, or even a wider group of patients with other conditions. The association between research activity and healthcare performance has recently been evaluated in systematic reviews which support the positive influence of research activity on the processes of care delivery (8, 9).

Only a few seminal studies have investigated whether a hospital's research activity is associated with improved survival for all of their patients with the disease studied in their clinical trials (10 – 14). Karjalainen et al (10) studied Finnish counties which were active in clinical trials in multiple myeloma and showed substantial improvements in survival in those which became research-active compared to those counties that did not. Collette et al (11) showed that hospitals which recruited more than five patients into an EORTC trial on the treatment of testicular cancer had better survival of trial patients than those with less recruitment. Majumdar et al (12) showed better outcomes for patients with coronary artery disease treated at hospitals that participate in clinical trials for patients with coronary artery disease. Rochon and du Bois (13, 14) evaluated the impact of clinical research in epithelial ovarian cancer upon patients' outcome in German hospitals during a hospital audit, showing positive benefits in the research-active hospitals and inferred a causal link (13 – 15). Ozdemir et al (16) studied trial recruitment and hospital mortality data. All of these studies highlight positive associations between research participation and patient survival but studies to date are too small in size and number to be conclusive. However, modern information technology now allows us to examine the impact of research in greater detail and much larger numbers.

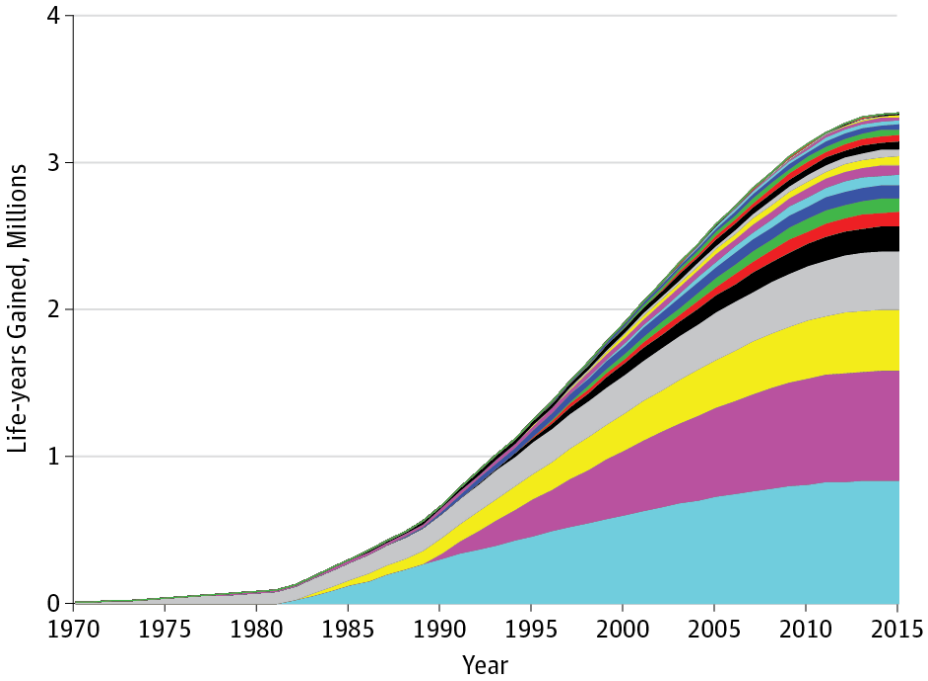
The impact of positive clinical trials on long term patient outcomes: SWOG studies (3)

SWOG was established in 1956 as a cooperative clinical research group in the USA providing leadership and infrastructure for a portfolio of clinical trials. During its 60th anniversary, SWOG indicated that it comprised approximately 12,000 members from cancer clinics and centres at more than 650 institutions, with more than 200,000 patients enrolled to SWOG clinical trials.

Treatment trials during SWOG's 60-year history for which the new, experimental therapy provided a statistically significant improvement in overall survival ($p<0.05$) were evaluated (3). It was assumed that the new, proven treatments from these trials established new standards for cancer care in the treatment community. They estimated population life-years gained from 23 positive treatment trials through 2015 by mapping the effect of the new treatments onto the US cancer population (Figure 1).

Figure 1

Cumulative life-years gained through 2015 by SWOG studies



The cumulative life years gained through the implementation of positive RCTs is plotted for each trial through to 2015. The colour coded areas represent cumulative life-years for each of the 23 studies evaluated. For each colour the cumulative life years saved are plotted 1970 – 2015. The impact of each individual study is added with a new coloured segment so that the total cumulative, additive impact of all 23 studies combined is shown with the contribution of each study shown by a separate colour. Four studies are shown to contribute two thirds of the life years saved. This was done using an area under the Kaplan-Meier survival curve approach that combined trial-specific hazard function and hazard ratio results, along with Surveillance, Epidemiology, and End Results programme and life table data. All calculations were age adjusted. The US dollar return on investment was estimated as the ratio of the total investment by the National Cancer Institute (NCI) in the treatment trial programme, divided by the estimate of life-years gained. (3) Reproduced with permission.

In total, 12,361 patients were enrolled to the 23 positive trials from 1965 to 2012. The study estimated that 3.34 million (95% confidence limit, 2.39-4.15 million) life-years were gained from these 23 trials through 2015 by the implementation of the results across the whole population. Estimates were greater than 2 million life-years gained under most model simulations. The US dollar return on investment was $125 per life-year gained. Figure 1 shows the impact of each positive trial. Although it is possible that in some cases the uptake of the new evidence may have been slower and less complete than had been modelled, these data still represent an impressive return on investment in lives saved for the dollars spent.

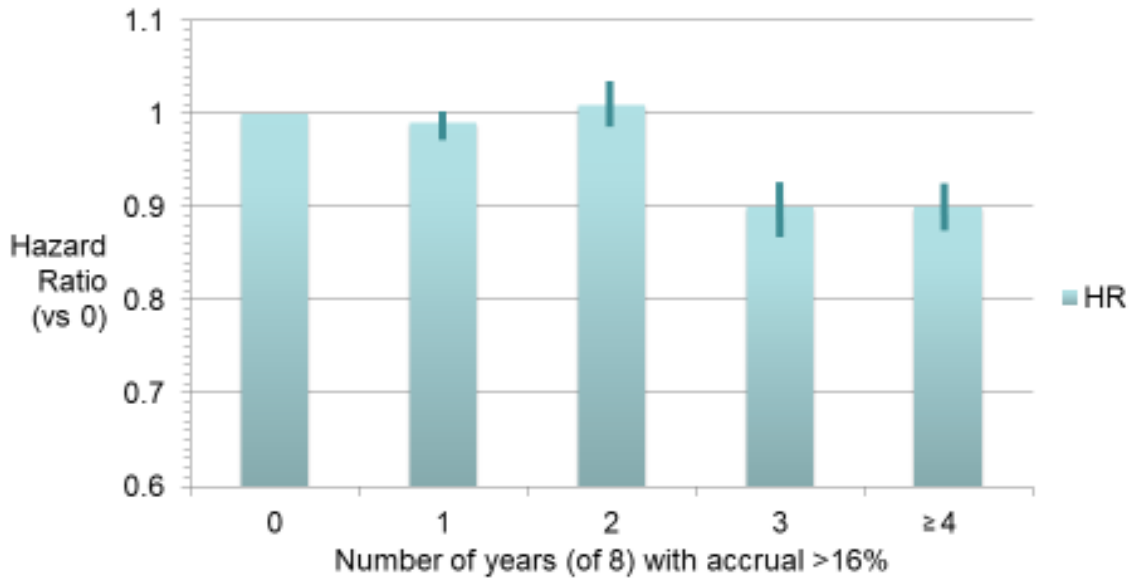
The impact of research participation on patient outcomes: NCRN studies

In 2001, the National Institute for Health Research Cancer Research Network (NCRN) was established to provide the English NHS with the clinical infrastructure required to improve the recruitment, speed, quality and integration of clinical cancer research in all parts of the NHS. An important goal of the NCRN was to involve all types of hospital in clinical cancer research. Studies within the NCRN portfolio were offered for

participation across the Networks through the clinical trials units and network managers. Recruitment centres were not selected by chief investigators alone. This approach converted much of the NHS to engage in research-intensive activity. It increased the number of clinical studies in the national portfolio, the number of patients recruited was increased four-fold and there were significant increases in the number of staff involved in research (4, 17). Over the same period, the National Cancer Data Repository (now the National Cancer Registration and Analysis Service) (18) collated and combined existing datasets (such as cancer registrations and hospital admissions) to create comprehensive individual-patient records of cancer diagnoses, demographics, treatments and mortality (18). Linking cancer registry data, hospital episode data and clinical trials datasets became possible under rigorous conditions of confidentiality. The NCRN studies of colorectal cancer (CRC) (5) showed, in a multivariable casemix adjusted analysis of over 200,000 patients, that there was a strong association between research participation and patient survival, with a temporal change which may infer a causal relationship. Hospitals became research-active in CRC intervention studies before they then showed evidence of improved survival for CRC patients. This supported the conclusions of the earlier studies (5, Figure 2).

Figure 2

Multivariable analysis of intervention trials research activity and five-year overall survival



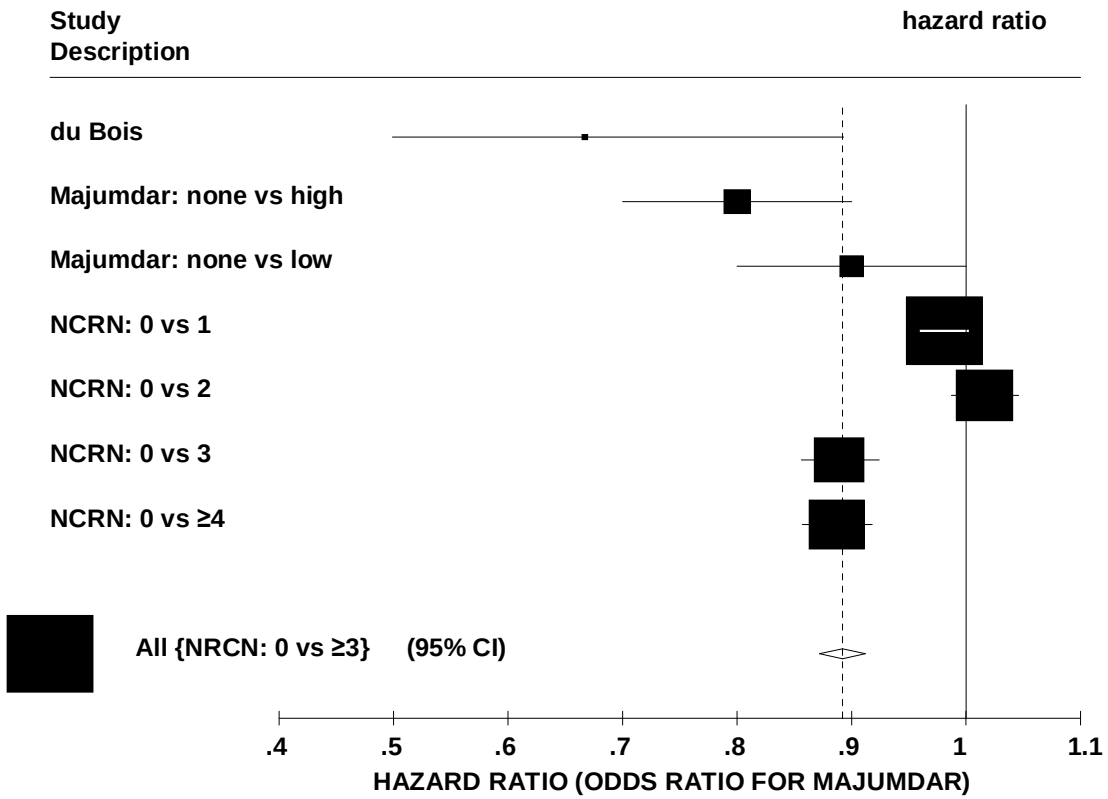
The studies described in reference 5 involved over 200,000 patients and evaluated the association between the percentage participation in NCRN colorectal portfolio interventional clinical trials in England in each year and five year survival in the National Cancer Data Repository for each hospital for each year. A strong association was shown which followed a pattern over time which inferred a causal relationship. The statistical significance increased with the percentage participation and peaked at 16%. Sustained participation was linked with improved survival. In the figure, the hazard ratio of survival at five years is shown for the number of years (out of a maximum of 8) with sustained recruitment (over 16%) into CRC studies, with the 95% Confidence Limits.

We have conducted a literature meta-analysis of studies which report the impact of research participation on the survival of patients within research intensive hospitals, compared to those that were less research-active (Figure 3). The collective data analysed in this manner give an effect size (hazard ratio) for high clinical

research participation of 0.89 (95% CI 0.87-0.91). The meta-analysis suggests a consistent impact and although we must infer causality with caution, both the mediation analysis in ovarian cancer (15) and the temporal association in colorectal cancer (5) do provide some support for a causal inference.

Figure 3

Meta-analysis of studies assessing the impact of research activity on patient outcomes



We have shown the data from du Bois et al (13), Majumdar et al (12) and the NCRN data (5). The Majumdar data compared hospitals with no research activity to those with high activity and found a very positive association between outcome and high research activity which was less, but still positive, for lower levels of activity. The data in the NCRN study (5) used the high participation definitions described in Figure 2 (>16% participation in interventional clincal studies comparing 0 years above this 16% level with 1, 2, 3 and ≥4 years above this level respectively). Highly significant positive associations were found for 3 or 4 years sustained above that level (Figure 2, reference 5). Hazard ratios are shown for the du Bois and NCRN studies; odds ratio for the Majumdar study. The box sizes reflect the sample size for each group, via the variance of the hazard ratio/odds ratio estimates.

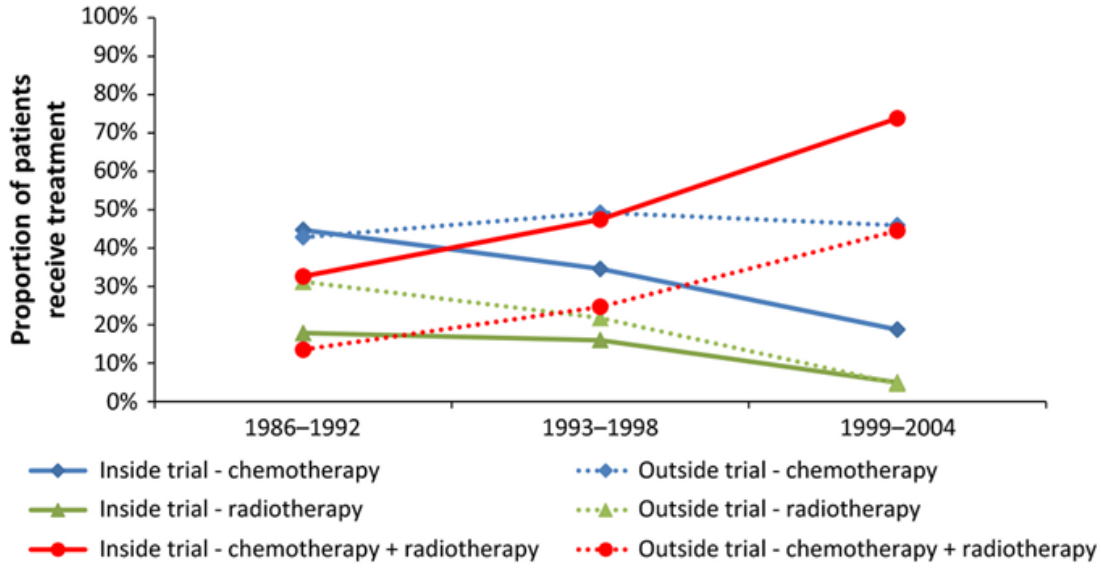
The impact of participation in trials on the uptake of innovation in hospitals: EORTC studies

The EORTC is Europe's leading clinical cancer research organisation (www.eortc.org) conducting a broad portfolio of RCTs including trials leading to registration of innovative compounds such as such as imatinib, pazopanib, temozolomide as well as the new immunotherapy agent-pembrolizumab (19 – 24). Between 1964 and 2004, the Lymphoma Group of the European Organisation for Research and Treatment of Cancer (EORTC) has conducted a series of phase III randomized clinical trials (RCTs), aiming to improve the efficacy of treatment in Hodgkin's disease (HD), while minimising long-term treatment-related toxicities. These trials have successfully improved the 10-year relative survival of patients, diagnosed with early stage HD between

1964 and 2004, from 72% to 93% and with advanced staged HD from 63% to 78% (25). However, compared to the high survival rate observed in the most recent clinical trials, the survival of the general patient population in The Netherlands shown in Registry data seems to be lower.

The EORTC attempted to identify the reason for the apparently better survival in HD in the trials population and its relationship to the uptake of new treatment practice in Dutch hospitals shown in the Registry data (6). The apparent better survival for patients treated within the trials was due to their better prognostic casemix (6). Older patients with more co-morbidity are commonly excluded from trials (26, 27). Figure 4 shows that there was, however, an important impact of participation in the trials. Combined chemotherapy and radiotherapy for early-moderate stage HD was found to be superior to either alone (6, 28). The use of the combined treatment was greater in the hospitals that participated in the trials. In Figure 4, the proportion of patients receiving combined therapy is higher in the trials active hospitals than outside at all timepoints. The authors emphasise that HD is a rare cancer and the proportion of all patients entering trials in their participating hospitals, is high. So caution is required before extending these findings to other cancers.

Figure 4



Uptake of different treatments in patients with Hodgkin lymphoma treated inside and outside of clinical trials. A study based on the EORTC-Netherlands Cancer Registry linked data with 20 years of follow-up. (6) Reproduced with permission.

Clinical trials and patient satisfaction with care

It is apparent from systematic reviews (8, 9) and our overview that the literature on the impact of clinical research on health outcomes is mainly evaluating healthcare processes and patient survival. Although methods for patient reported measures of QoL have existed for 40 years (29, 30) and been widely used in RCTs for 25 years (31), it is still difficult to show their benefits for cancer patients. Patient advocates have argued strongly for a greater emphasis on QoL outcomes (32) and it was a key component of a recent analysis of critical gaps in colorectal cancer research (33). The National Cancer Patient Experience Survey

(NCPES) of 60,000 patients in the UK, showed clear association between research participation and higher levels of patient satisfaction with care (http://www.ncri.org.uk/wp-content/uploads/2015/09/Keeping-the-Customer-Satisfied-1.pdf) (34). Regulators are adding pressure for increased use of patient reported outcomes in research (35, 36).

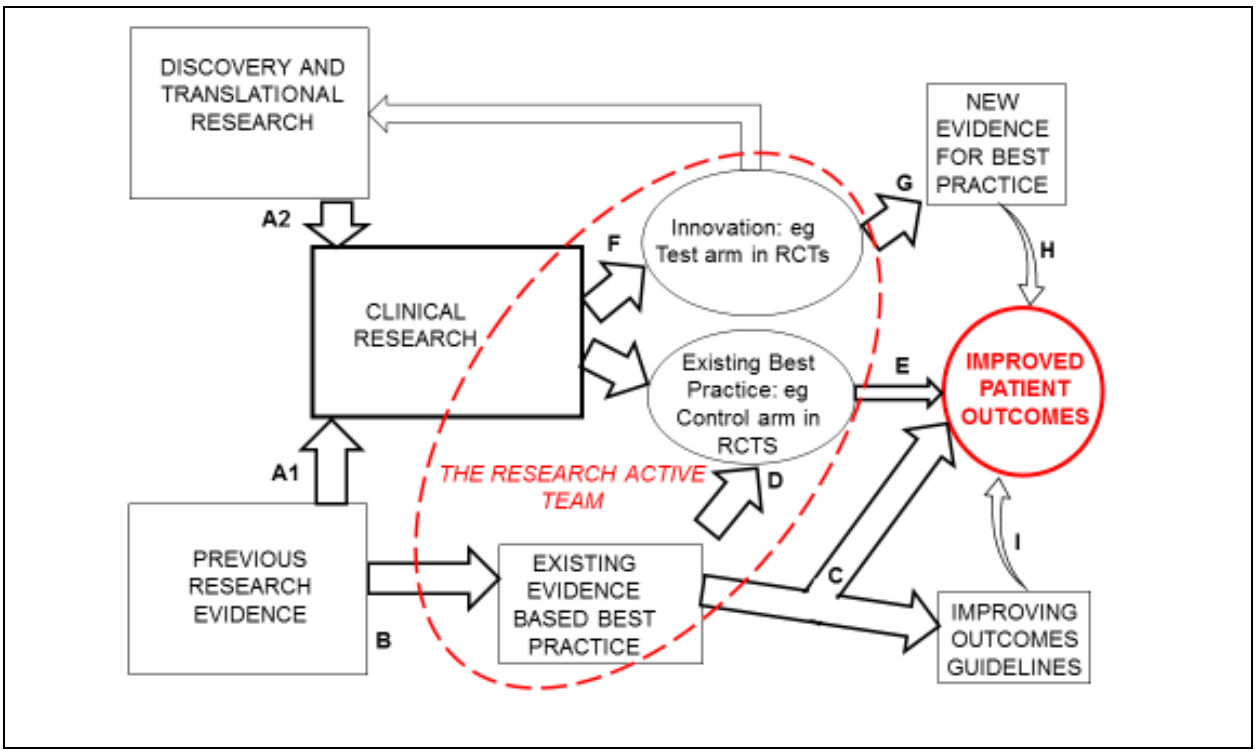
Discussion

SWOG showed how implementation of new positive research evidence developed by leadership and infrastructure through a cooperative group has proved to be a highly cost-effective initiative in cancer control (3). The NCRN report (5) of data linkage between the trials portfolio and the outcomes of 209,000 patients with CRC treated in England over almost a decade, together with our meta-analysis of published studies (Figure 3), support the view that research participation can improve the performance of hospitals and healthcare systems and improve patient survival. Indeed, the approximate effect size compares quite reasonably with a successful clinical trial of a new effective treatment. The limitations of these studies are principally in our inability to rule out residual confounding variables. Comparing results between hospitals is challenging even with modern informatics and data linkage because of the many medical and non-medical factors which can effect outcomes. However the evidence for a causal inference for the impact of research participation on outcomes is mounting. Two lines of evidence support the causal explanation: a dose-response (the greater the level of participation, the greater the improvement in survival), and the longer the duration over which a hospital had sustained high participation rates, the greater the effect.

We present a model hypothesis that the research-active clinical team providing care for patients in hospitals and other healthcare institutions is the central route by which outcomes can be improved by all of the mechanisms characterised in Figure 5.

Figure 5

A model for the interrelated impacts of clinical research on healthcare outcomes



In Figure 5, a series of different mechanisms link clinical research to improved outcomes. In this model, previously available research evidence in the literature informs the generation of new clinical research questions (**A1**). Discovery and translational research will also inform the clinical research questions (**A2**). Existing research results from the literature also form the basis of existing evidence-based practice and are the basis of guidelines for best clinical practice and improving patient outcomes through this route (**B, C**). Best practice should form the basis of the control arm in a portfolio of randomised controlled trials and other studies (**D**). Being appropriately informed of such state-of-the-art practice, and through exposure to that practice within the conduct of their clinical research, should improve the process of care undertaken by the clinical team and ultimately improve patient outcomes (**E**). Discovery science and translational research informing the clinical research portfolio leads to the development of innovations which are, in this model, tested in the innovation arms of RCTs (**F**). When such trials are positive, as in examples in the SWOG portfolio, they generate a new evidence base for best practice (**G**), which in itself will lead to improvement in patient outcomes (**H**) both for those patients within the trial and for the much larger number of patients whose treatment is improved through the process of the uptake of innovation (**I, H**). This may occur more rapidly in research-active institutions as shown in the EORTC Hodgkin's Disease studies (**I**). As new evidence enters the literature, it will steadily feed into guidelines and influence practice and continue to drive the innovative research cycle.

What is less clear is which are the more important ways in which research improves outcomes? This seems likely to depend on the context and the nature and quality of the health service which is hosting the studies. For example, in a developing, economically disadvantaged healthcare system, setting up an RCT might

introduce an effective healthcare intervention for the very first time (37). For example, trials evaluating different methods of screening for cervical cancer, have been vehicles for introducing such screening into developing healthcare systems (37). Screening can be beneficial and improve health outcomes. In order to conduct trials of alternative technologies for screening in developing countries, the intervention has first to be introduced in the country. Health benefits are therefore a consequence of the trial regardless of its final results (37). Effective impacts will also depend on the pace of innovation. For example, as effective translational and clinical research matures on innovations such as cancer immunotherapy, we may expect more positive trials, with this new evidence leading to improved population outcomes. Different countries have diverse approaches and variable pace in adopting innovations. Those which welcome innovation might be expected to benefit from research results more rapidly.

Recent developments in clinical research have increasingly drawn on input from patients and patient advocates (38). Initiatives to improve patient outcomes, such as the European Cancer Patient's Bill of Rights and the European Cancer Concord (www.europeancancerconcord.eu) (1), are equal partnerships between patients and healthcare professionals which have at their core the need to effect change in a timely manner for the benefit of patients. Research and Innovation are strongly supported by patients strategically and operationally through their involvement in study design and study delivery (1, 36). Coproduction of strategic initiatives and plans and the social and political support of patients is central to the delivery of successful clinical research and its impact (39, 40).

Why does this complex examination of large datasets to evaluate the impact of clinical research matter? Why should it matter to policymakers? It might be said that since clinical research provides the basis to advance healthcare on a sound evidence base, then that is sufficient reason to conduct it. Indirect effects of participation may be a bonus – but such collateral benefits are not needed to justify our work. We propose that the collateral benefits of participation do have importance for patients, investigators, funders and policymakers. It matters where the research is done and it is important that research should become a feature of all topics and sectors of healthcare delivery. Collateral benefits seem to depend on a healthcare institution itself being involved in research. This has implications for investment in infrastructure such as research networks and research-practice partnership structures. This means that clinical research should be "everyone's business" which should improve the generalisability of clinical trials. Smaller trials ("efficient designs") may cut cost but they may also cut collateral benefits unless they are conducted across hospital networks. We believe that advances in clinical research technology and informatics (41), including for example the recent establishment of Health Data Research UK (42) may make it easier, and more affordable, to conduct clinical research across whole healthcare systems and most importantly that patients may benefit as a result. Thus, we recommend an increased focus on, and investment in, comprehensive infrastructure for clinical cancer research, representing as it does a potentially cost effective approach for improving healthcare outcomes.

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