Research Article

Publicly funded practice-oriented clinical trials: of importance for healthcare payers

Aim: Many questions of relevance to patients/society are not answered by industry-sponsored clinical trials. We consider whether there are benefits to governments in funding practice-oriented clinical trials. **Methodology:** A literature search including publications on institutions' websites was performed and supplemented with information gathered from (inter)national stakeholders. **Results:** Areas were identified where public funding of clinical trials is of importance for society, such as head-to-head comparisons or medical areas where companies have no motivation to invest. The available literature suggests publicly funded research programs could provide a positive return on investment. The main hurdles (e.g., sufficient funding and absence of equipoise) and success factors (e.g., selection of research questions and research infrastructure) for the successful conduct of publicly funded trials were identified. **Conclusion:** Governments should see public funding of pragmatic practice-oriented clinical trials as a good opportunity to improve the selection and quality of treatments and stimulate efficient use of limited resources.

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Keywords: comparative effectiveness research • healthcare economics and organizations • pragmatic clinical trials • randomized controlled trials

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Background

Health policy makers strive to optimize healthcare and maximize citizen's health while developing a highly accessible, cost-effective and durable healthcare system. In the context of limited resources, difficult choices have to be made with regard to the reimbursement of interventions and the organization of care. Not taking into account the acceptability (cost–effectiveness/utility) and affordability (budget impact) of decisions will eventually have an impact on the system's accessibility and/or quality, for example, by asking more copayments from patients or taking away resources from other places in the healthcare sector that may provide better value for money (opportunity cost).

Investing in research can assist the decision-making processes, by providing a rigorous evidence base for informed decision-making. In general, Health Technology Assessment reports try to support policy makers by summarizing the evidence base covering several aspects of healthcare such as medical effectiveness, economics, ethics and health system logistics. However, many questions of relevance to society (see further) will never be answered with the clinical trials conducted by the manufacturers (typically for-profit organizations). Therefore, there is a case for public funding of practice-oriented comparative clinical trials. These trials aim to optimize clinical practice in terms of clinical effectiveness and cost–effectiveness and to have a relatively immediate impact on clinical practice or healthcare decisions. Funding such trials could be an efficient investment of public resources.

In this article, we consider the arguments for publicly funded practice-oriented trials, their possible return on investment and hurdles and success factors to set up such a system. This is based on work by the Belgian Health Care Knowledge Centre (KCE), [1] an independent federal institute providing advice to our Belgian policy makers, to determine whether our healthcare system should begin to finance practice-oriented clinical trials, and what would be required to realize this.

Methodology

In August 2014, a search was performed in PubMed (OVID) to identify reports with examples of research impact based on publicly funded trials and on (non-commercial) clinical trial hurdles and success factors. The applied search terms were related to financing, government and trials. All details are available in appendix of the full report [1]. References were also identified in the gray literature (Google search using the terms 'non-commercial trial' or 'public funding' and 'trial') and using contacts in the field (e.g., European Clinical Research Infrastructure Network [ECRIN] members). Several interesting reports provided by experts were not identified in our PubMed search. We checked how these relevant articles were indexed and, unfortunately, no systematic use of similar index terms could be identified. This experience is similar to what other researchers have been confronted with: "The complexity and heterogeneity of the topic made the conceptualization of this overview much less straightforward than typical review on medical interventions" [2]. These researchers noticed that a large part of the literature in this field is made up of heterogeneous publications and critical appraisal reports published by the main funding agencies. In their research, only 30% of the included publications were found by searching the traditional biomedical databases (i.e., MEDLINE) and many relevant studies were retrieved in the 'gray literature' (i.e., funding agency's reports) [2].

Therefore, in October 2014, we searched the websites of international public institutions involved in funding of trials, based on a published list [3]. The websites of the following institutions were visited: Clinical and Translational Science Award program (USA) [4]; James Lind Alliance (UK) [5]; National Institute for Health Research (NIHR, UK) [6]; NIH (USA) [7]; Patient-Centered Outcomes Research Institute (USA) [8]; The Health Maintenance Organisation Research Network (USA) [9]; The National Health Service (UK) [10]; and The Netherlands Organisation for Health Research and Development (ZonMw) [11]. Citations of identified reports were screened to find other relevant references. We complemented this with suggestions from our external experts. These experts included a wide range of stakeholders: investigators from seven different Belgian hospitals, representatives of the National Institute for Health and Disability Insurance and the three largest Sickness Funds, the Flemish government agency for Innovation by Science and Technology (Innovatie door Wetenschap en Techniek [IWT]), the European Organisation for Research and Treatment of Cancer, the Scientific Institute of Public Health (Wetenschappelijk Instituut Volksgezondheid [WIV]), the Federal Agency for Medicines and Health Products and a consumer organization (Test Aankoop). Contacts were also made with foreign funding agencies, for example, ZonMw in The Netherlands, the Italian Medicines Agency (Agenzia Italiana del Farmaco [AIFA]), the Medical Research Council and NIHR in the UK (see colophon in the full report for further details [1]). Information was gathered during the two meetings at KCE and informal email contacts afterward.

Results

Reasons for public funding of clinical trials

Comparative effectiveness trials with medicinal products

For society it is important to know what the real clinical therapeutic benefit is in comparison with best available alternatives. However, regulatory authorities require the demonstration of safety and efficacy, but not therapeutic benefit, before a medicinal product is granted marketing authorization. Trials are often performed in a highly selected population and placebo is often used as a comparator, although designs including an active comparator are encouraged. Ideally, the new intervention should be compared with the best available active comparator, which could be a non-drug intervention. Important statements in this regard are provided in a draft reflection paper of the European Medicines Agency (EMA): [12] "Where feasible, three-arm trials including experimental medicine, placebo and active control represent a scientific gold standard and there are multiple reasons to support their use in drug development … there are few circumstances where an indirect comparison might be considered sufficiently reliable." Once marketing authorization and reimbursement are obtained, the company may not be willing to generate data that might hamper the marketing of their product. For example, there may be a commercial risk (promotion, price discussion) associated with the conduct of a direct head-to-head trial in case the company's product proves to be inferior (or not superior) to the existing alternative treatment (which may be less expensive). Industry might also be less interested in research to improve existing procedures and

prescriptions, for example, finding the optimal drug combination or duration of treatment [13]. Furthermore, in addition to the selected patient population in Phase IIb/III clinical trials, it might be important to have a more pragmatic approach and to include a broad real-life population in comparative effectiveness trials.

Comparative effectiveness trials with medicinal products in children, women, older people & in people with rare diseases

Trials in children, women, older people or testing treatments for rare diseases have long been neglected. Despite incentives created to stimulate the development of medicinal products for children and in rare disorders, there remains a need for more clinical research in these areas. "The market-driven pharmaceutical industry does not pursue research and development for a number of diseases because of the small number of patients involved … and the insufficient profitability of the treatments (e.g., pediatric therapies…)" [13].

Comparative effectiveness trials with medical devices, diagnostics, on screening & in medical areas not 'owned' by companies

Non-commercial clinical trials may be necessary for medical devices since only safety and performance, and not efficacy, are assessed in the premarket phase in Europe [14,15]. In comparison with drug interventions, evidence generation is also less developed for diagnostics, which are very relevant as companion diagnostic for targeted therapy or as screening tools at the population level. In the field of companion diagnostics, there is a need for robust data on the test accuracy in the real life setting, as compared with centralized testing often used in confirmatory randomized controlled trials (RCTs) and used for the evaluation of the (cost–)effectiveness of the test–drug combination during the reimbursement procedure. Maintaining a high test specificity in routine care is crucial for the cost–effectiveness of the targeted treatment, much more than the cost of the test or even the cost of the drug [16].

In screening, the funding of a large-scale clinical trial may be the best strategy both from a healthcare perspective (the fastest route to obtain hard evidence) and from an economic perspective. For example, thanks to the existence of a large-scale clinical trial on prostate cancer screening (PROTECT), [17,18] policy makers were able to avoid the implementation of a non-evidence-based prostate cancer screening program in the UK for the past 20 years.

Finally, other fields have less or no medical industry support such as surgical techniques, diagnostic/imaging techniques, diagnostic strategies, radiation therapy, psychotherapy, physical therapy, lifestyle interventions or prevention, traditionally areas not 'owned' by private companies. Here too, the decision makers need high-quality data from comparative effectiveness trials to decide on the approval and financing of specific techniques and interventions. For example, as illustrated in a network of available comparisons, there is a need for more direct comparisons between exercise versus drug interventions in coronary heart disease, stroke, heart failure and prediabetes [19].

Is it worth the money?

The main purpose of publicly funded health research is to improve the health of the general population in the form of better quality of life and increased longevity [20]. However, the direct and indirect cost of running a research program and the time to implementation of results should not be underestimated. A government should try to invest its limited resources wisely. The opportunity cost of investing in clinical research might have as an outcome not to reimburse another intervention. Therefore, it is important to evaluate the efficiency of such a government funded program.

Optimistic (biased?) literature

There are several studies examining the costs of a single RCT and the consequences for society. One of the most spectacular examples is the study analyzing the economic return from the Women's Health Initiative estrogen plus progestin clinical trial [21]. At a cost of approximately US$260 million (in 2012 US$, US$1 = €0.900 = GB£0.652; 23 September 2015), this Women's Health Initiative estrogen plus progestin trial was one of the most expensive studies ever funded by the US' NIH [22]. After publication of RCT evidence of increased cardiovascular disease, venous thromboembolism and breast cancer risk among postmenopausal combined hormone therapy users, combined hormone therapy use decreased in the USA by approximately 50% and continued to decline at 5–10% annually as the US FDA and other groups endorsed the study conclusions [23–29]. According to the authors, the corresponding net economic return of the trial was US$37.1 billion (US$140 per dollar invested in the trial) at a willingness-to-pay level of US$100,000 per quality-adjusted life-year (QALY) [21].

Of course, a research program does not only include success stories. Costs of non-completed trials for which the analyses could not be performed as planned should also be taken into account and lessons should be learned from such failures. Seven studies were found, trying to calculate the return on investment of research programs. Evaluations of publicly funded clinical

research and clinical trial programs were identified for selected NIH trial programs in the USA and clinical research programs funded by the National Health Service in the UK. Health economic evaluation reports of clinical trial programs in Australia, Sweden and The Netherlands were also identified.

In the UK 'Medical Research: What's it worth?' study, [30] the research programs of the 11 principal funders in cancer research, accounting for over 95% of research spending, were analyzed. Between 1970 and 2009, total expenditure on cancer-related research was GB£15 billion (2011/12 prices). Over the period 1991–2010, the interventions included in the study produced 5.9 million QALYs and health benefits equivalent to GB£124 billion (at a GB£25,000 per QALY value and including the costs of delivery). Smoking reduction accounted for around 65% of the net monetary benefit. The annual rate of return was estimated to be 10%. Spillover effects were described as the indirect impact of public and charitable research on the wider economy, such as leveraging private sector R&D activity. When these effects were included, the rate of return even increased to 40% [30].

A study on the effect of a US NIH program of clinical trials on public health and costs [31] looked at all Phase III randomized trials funded by the US National Institute of Neurological Disorders and Stroke between 1977 and 2000, including 28 trials with a total cost of US$335 million. The effects of a trial on total costs and savings or quality of life could only be assessed if such information was available. This was the case for eight trials, resulting in an estimated additional 470,000 QALYs at a total cost of US$3.6 billion (including costs of all trials and additional healthcare and other expenditures). At a per-head gross domestic product value of US$40,310 per QALY, this resulted in a net benefit to society by 10-years of US$15.2 billion.

In The Netherlands the 'efficiency research' program set up by the Dutch organization for health research and development ZonMw, was evaluated [32]. The return on investment of this program was calculated by comparing the costs of this program (2001–2015) with the expected cost savings in healthcare arising from the subsidized studies within the program. In a conservative scenario, assuming that 40% of the potential cost savings are actually achieved, the program shows a very high return of 327%. The authors conclude that this program pays for itself more than three times [32].

Several Australian studies [33–35] also report positive results, like a benefit/cost ratio of 2.17, [34] which means that a dollar invested in Australian health R&D returns $2.17 in health benefits on average. We do not discuss these studies further since the results hinge on some major assumptions (e.g., a time lag between the mid-point of the R&D expenditure and the mid-point of the wellbeing gains of on average 40 years, [35] or attributing half the historical gains in health span to global health R&D and allocating 2.5% to Australian R&D since this is Australia's share of global R&D activity [33]).

Finally, a Swedish study concludes that the positive effect of clinical research benefits exceeds costs, but acknowledges that an "accurate determination of the economic value of research would require significantly better basic data and better knowledge of relationships between research, implementation of new knowledge and health effects" [20].

Limitations of these studies

While all identified studies are positive about public funding of trials, the results should be interpreted with caution. It is possible that there is a pro-innovation bias [20] in which authors have accepted in advance that research and innovation are profitable and have selected examples or made assumptions to support their view. Furthermore, all of the above studies have several important weaknesses. Both identification and valuation of benefits is very difficult and associated with very large uncertainty.

Even if the benefits can be identified, quantified and valued, it is difficult to know how much should be attributed to R&D efforts from the research program. For example, the US study [31] only included costs of Phase III clinical trials. Costs for basic research were not included. Nevertheless, as mentioned by the authors, "all the interventions from these clinical trials required understanding brought about through basic science research. Thus, the overall investment in basic and clinical research was important to achieving these health gains" [31]. On the other hand, they calculated that the benefits from the clinical trials alone (US$50 billion) were large enough to cover all the expenses of both basic and clinical research in the research program (US$29.5 billion) [31]. It is also not clear what the influence is of other elements, like an improved prosperity, lifestyle and diet, on delaying the onset of disease [36].

Another difficult to quantify important variable is the spillover effect. This externality may take different forms. For example, publicly funded research may improve the infrastructure and knowledge to perform trials and might have a positive influence on, for example, involving more physicians in clinical research and making them familiar with the foundations of evidence-based medicine. In addition this expertise might also attract industry-sponsored trials. In the UK study, [30] the largest part of the benefits comes from the spillover effect. While this might be

an overestimation, other studies do not take this effect into account, [31,32] which results in a conservative estimation of the benefits of publicly funded research.

It may also be difficult to know whether the study conclusions were implemented in routine care and whether the results achieved are similar to those identified in the trial**.** The Dutch study [32] calculated the 'potential' cost savings, applying two scenarios in which 40 or 80% of the potential savings are achieved. The US study [31] also based its calculations on published economic evaluations, which were only available for part of the interventions in the research program. These projections from potential cost savings or published economic evaluations may be very different from the real-world impact and may over- or under-estimate the impact of publicly funded research. It would be desirable to check if the outcomes of this research had an impact on real-world practice, for example, by looking at practice guidelines, change in behavior, reimbursement decisions among others.

Finally, to avoid any misunderstanding, studies mentioning R&D investments result in cost savings do not always mean that, in the end, less money will be spent. Several studies provide a monetary value to the QALYs gained [21,30–31]. In the US study, [31] applying a US$40,310 value per QALY, the health benefits have a much greater value than the increased expenditures on health. For this aspect, the Dutch study [32] is more conservative by not including a valuation for the health benefits.

Hurdles for publicly funded research

Based on our meetings with experts and investigator interviews in Germany, [37] the most important hurdle to run a successful publicly funded trial is obtaining sufficient funding to be able to conduct a large practice-oriented trial. According to experts, the budget for a large confirmatory randomized trial is often in the range of €1–€5 million, on top of the cost of the trial site network infrastructure, with competent personnel that work according to standard operating procedures. It may be more efficient to select a limited number of sufficiently financed trials than to underfund a lot of smaller trials that are unable to produce robust data. Insufficient financing may lead to studies that are underpowered or are not conducted in a professional way. Lack of funding may lead to insufficient resources to perform the trial fully in accordance with all applicable regulations. This may have an impact on the fee for the investigator, the level of study monitoring and safety reporting, the quality of the data capture, data management, and data analysis and reporting.

The eligibility criteria need to be realistic and broad enough to ensure a real-life population and the study-specific burden of extra investigations must be reasonable both for patients and investigators.

For RCTs, equipoise is essential: there should be a genuine uncertainty in the expert medical community over whether a treatment will be beneficial. Surgeons and other healthcare providers are sometimes very quickly convinced that a new technique is superior, without justification. In such a situation where healthcare providers are not willing to randomize patients, performing RCTs is clearly impossible. An open mind for performing RCTs and a culture of evidence based practice tend to be linked. For example, the European Organisation for Research and Treatment of Cancer sponsored LAMANOMA study comparing conservative local treatment versus mastectomy after induction chemotherapy in locally advanced breast cancer was closed due to insufficient recruitment. Reasons cited to explain this failure were the decision of several institutions to stand by their own current therapeutic strategy and the large proportion of patients who refused to participate [38]. Communication with cancer patients about RCTs is difficult and poorly trained professionals may deter patients from entering trials [39]. Trials providing active treatment in every arm had a significantly higher acceptance rate as compared with those with a no treatment option [40].

There might also be competition for the same patients between different trials running at the same time in the same institute. This might slow down the inclusion rate of trials as was mentioned by some Belgian investigators participating to the non-commercial SOLD trial (trastuzumab short duration in early breast cancer [41]). As mentioned before, the budgets of non-commercial trials are often very limited. This results in study fees paid to investigators and hospitals that are usually higher for commercial versus non-commercial trials, favoring participation in commercial trials.

A well-established and integrated network of research infrastructure is necessary to stimulate the efficient performance of government-funded trials, both at micro, meso and macro levels.

At the hospital micro level, physicians and nurses may have limited time available to participate in running and supporting clinical trials. For example, there might be a lack of support personnel to gather data. Nurses who could be involved in this task are already under time pressure. In a study among American oncologists, [42] a critical need for infrastructure to support trials, especially additional support staff and research nurses, was identified.

Physician involvement may be hampered by a lack of appreciation for clinical research in the hospital [43]. Lack of time and conflicts between the role of clinician and scientist might impede trial participation [44]. At a

symposium of the Flemish Academy of Medicine different participants mentioned that colleagues are often interested to participate in clinical trials, however, their clinical tasks often take priority and participation is often also not interesting from a financial point of view. Next to convincing physicians and patients, the involvement of managers is also important. "Pragmatic trials require that researchers and healthcare system clinicians, senior management, and staff develop the attitudes, skills, resources, and shared vision for close collaboration" [3].

At the meso level, there is not always a well-established national network of experienced centers to perform research in specific disease areas. This investment may be a sunk cost, in other words, costs that cannot be recovered afterward, but might provide advantages for future trials. For example, in Belgium, the SAFE-PEDRUG program in pediatrics should lead to the creation of an interuniversity platform on pediatric drug research including centers of excellence, available to all stakeholders for advice.

At the macro level, a formal participation in international research networks is of considerable added value for the conduct of multinational trials. ECRIN [45] is a research infrastructure supporting multinational clinical trials in Europe. ECRIN is based on the connection of national networks of clinical trial units. Each national partner has the capacity to design, manage and analyze trials inside its country, but faces major obstacles (due to differences in regulations, ethics, funding, hospital system, infrastructure, language, among others) in the conduct of multinational trials. By coordinating (without duplicating) the activities of these national partners, ECRIN is able to provide operational support to multinational trials in Europe, providing access to patients and to medical expertise, avoiding duplication and sharing the cost of independent trials.

International collaboration might be advantageous for several reasons: the ability to include sufficient patients (e.g., for rare diseases), provide more reliable results due to a larger sample population, to finish the trial earlier and provide the necessary information sooner to the different stakeholders after a faster recruitment, to benefit from joining a trial set up by experienced researchers and take advantage of their knowledge, among others. The international impact of a large trial conducted in multiple countries may also be higher. However, costs eligible for public financing of trials differ between countries and hamper the installment of a standard financing system. In addition, the danger of free-rider behavior remains real, as some governments (e.g., USA, UK) already fund such trials and publish the results in international journals. Other governments might benefit from these results without contributing to efforts themselves to set up or participate in these trials. This might result in an underinvestment in publicly funded trials in some countries. Sufficient public funding and international collaboration should be encouraged instead of free-rider behavior.

The focus of this article is on publicly funded research that is necessary to answer important research questions that industry will not answer because of, for example, a conflict of interest with their company profits. In such cases, it is possible that the non-cooperation of industry will provide an extra hurdle to perform these trials. The provision of placebo drugs, appropriate dosage forms and formulations for off-label use or the access to expensive drugs can pose problems. "Independent researchers might end up compromising – or even abandoning – their research design because of the unwillingness of some pharmaceutical companies to deliver placebo drugs or devices" [46]. An anonymous example describes a case in which a drug company was approached by researchers with the aim of obtaining placebo medication for an independently financed trial. After more than 6 months, the company finally agreed to supply matching placebo provided that among others the protocol was changed according to their suggestions. In another example, the drug company charged an extraordinary amount of money for providing a simple placebo tablet, effectively preventing the planned clinical trial from going ahead or plainly refused to deliver the placebo [46].

The high price of the comparator itself might be a major financial hurdle to perform a large scale RCT. It has been argued that in comparative effectiveness research using head-to-head comparisons, cost considerations should also become part of all clinical evaluations in oncology [47]. While it has repeatedly been argued that the high price of cancer drugs is unsustainable, the authors point to the fact that because of the high drug price, it becomes very expensive, even impossible, to conduct a non-commercial clinical trial evaluating comparative effectiveness versus cheaper alternatives [47]. On the other hand, in such cases, it is the responsibility of the industry to show the added value of the expensive drugs versus cheaper alternatives and show that this intervention provides value for money [48].

Success factors

A first critical step is the selection of the research questions that should be answered. In our opinion, the trial design and selection should be delegated by government to an independent body of working clinicians, patients, experts representing healthcare payers and care providers, statisticians, health economists, among others. Procedures for submitting topics should include

both top-down (e.g., commissioned by government bodies) and bottom-up (investigator-led) approaches. Both research questions on clinical effectiveness and cost–effectiveness should be considered. In The Netherlands, the ZonMw programs on healthcare efficiency research (€10 million per year) and rational pharmacotherapy (€13 million per year) mainly consist of publicly funded clinical trials. In addition to the improvement in quality of care, these programs aim to support efficient use of healthcare resources. Therefore, studies proposed for funding in the open call system have to indicate their potential impact on the efficient use of the healthcare budget. A systematic review should also be conducted before a trial is selected both to check whether the research question cannot be answered by currently available evidence or if relevant trials are already running. It should also be excluded that existing registry data could provide the answer to the research question. Ideally, there should be a database of planned and ongoing trials that can be consulted. As mentioned before, selected trials should receive sufficient funding.

Another element contributing to success of publicly funded trial is the availability of competences and an infrastructure at different levels: at the level of the trial site, at the level of a national trial site network and at the European or international level. Scientific societies may want to initiate a clinical trial but do not always have an in-house infrastructure and specialists in the logistic, regulatory, legal and ethical challenges of an RCT. Therefore, sufficient funding and access to a research infrastructure for trials are needed to help scientific societies. Such a research infrastructure would not only benefit publicly funded trials, but would also be beneficial for industry-sponsored trials. For international trials, it is preferable that the same procedures are followed in all participating countries and study sites.

Another important factor to make a publicly funded trial program a success is the implementation of the trial results. Both knowledge transfer and installing the appropriate financial incentives are needed to achieve this. For example, in The Netherlands, ZonMw finances specific implementation projects, with up to €50,000, to implement the trial results in routine practice. Of course trial results should be published transparently in the first place. Non-registration and publication is a problem of industry-sponsored trials as well as academic and non-commercial funders [49]. In the USA, less than 20% of trials subject to the FDA Amendment Act mandating reporting of results within one year adhered to this rule and government or academic sponsored studies performed the worst [50]. In the UK, exceptionally, "98% of the studies funded by the NIHR Health Technology Assessment Program have led to the publication of full reports (Ruairidh Milne, personal communication). The program has achieved this by holding back a proportion of the research grant (5%) until a report has been submitted for publication, by chasing authors on a regular basis, and by providing a publication vehicle – Health Technology Assessment – for all trials" [49,51]. Publicly funded research programs should provide the example by showing that timely trial registration and publication of all results is possible.

Conclusion & recommendations

Pragmatic practice-oriented publicly funded clinical trials can provide answers to highly relevant research questions in healthcare, both in terms of clinical effectiveness and cost–effectiveness, which are less likely to be answered by trials funded by the pharmaceutical and medical device industry. Publicly funded practice-oriented clinical trial programs can have a direct positive impact on patient care and use of healthcare resources. Despite the shortcomings of studies evaluating these programs, all authors conclude that clinical research and clinical trials are a good investment of public money or that the impact on clinical practice is significant. Therefore, funding of well-selected clinical trials should be done in the context of high-quality and well-financed programs where authorities collaborate with experts in the field to answer questions that are relevant for patients and for society.

Future perspective

We trust that governments are convinced of the need for independent clinical trials both for advancing medical science and optimizing clinical practice. We expect that strategies for funding clinical trials will evolve so that more countries will consider the efficiency of their healthcare systems as well as scientific merit. In Europe this is already the case in England and The Netherlands. These countries have recently been joined by Belgium which started a publicly funded programme of pragmatic practice-oriented clinical trials in 2016. International collaboration, from the trial concept phase, will prove necessary to design independent randomized trials targeting smaller populations. Therefore there is a growing need to facilitate such collaborative efforts at the European or even broader level, for example, coordinated by the Organisation for Economic Co-operation and Development. Finally, it should not be forgotten that it is the individual patients who will benefit most from an efficient and sustainable healthcare system.

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Executive summary

- This paper gives a clear overview of arguments why publicly funded practice-oriented trials are desirable. Many research questions are of relevance to society but will probably not be answered by clinical trials conducted by the manufacturers. Areas where public funding of clinical trials is of importance for society: comparative effectiveness trials between medicinal products, especially in underserved populations such as children, women, older people and in domains with few industry-led clinical trials such as rare diseases, trials with medical devices, diagnostics, screening tests and in medical areas without clear industry involvement, for example, psychotherapy and lifestyle interventions.
- A review of literature on the possible return on investment of public funding of trials is performed. Results are in favor of such financing. However, a limitation is the possible bias in published studies and methodological weaknesses in calculations.
- Governments should see public funding of pragmatic practice-oriented clinical trials as a good opportunity to improve health and/or stimulate efficient use of limited resources. Countries with little in the way of public financing of clinical trials should consider the benefits and returns on investment from such a program, with international sharing of knowledge and expertise helping to increase the number of successful trials.
- This paper provides an overview of both hurdles and success factors to set up a program of publicly funded practice-oriented trials. The main hurdles for the successful conduct of publicly funded trials are insufficient funding, a lack of equipoise on the part of clinicians, competition for the same patients with industry-sponsored trials, a lack of appreciation for clinical research in academia and health service, absence of infrastructure such as research nurses and trial units mastering all aspects of running clinical trials. In addition, there were obstacles hampering international collaboration, for example, free-rider behavior of smaller countries, high costs of study drugs and non-cooperation of industry. The identified success factors include a sound selection of trial topics and protocols, sufficient funding for the trial itself and the supporting research infrastructure and a well-planned implementation of the trials results in clinical practice.

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