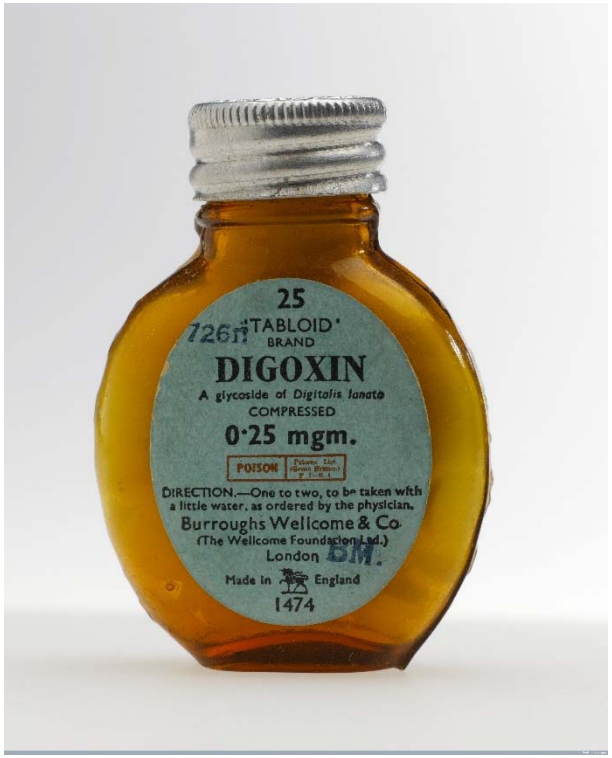
Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

SUMMARY

PUBLICLY FUNDED PRACTICE-ORIENTED CLINICAL TRIALS



KCE REPORT 246Cs
HEALTH SERVICES RESEARCH

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SUMMARY

PUBLICLY FUNDED PRACTICE-ORIENTED CLINICAL TRIALS

MATTIAS NEYT, THIERRY CHRISTIAENS, JACQUES DEMOTES, FRANK HULSTAERT

FOREWORD

Clinical trials are not only important to test new medicinal products before they can be marketed. Comparative effectiveness trials are necessary to inform the patient and the physician on the most appropriate treatment option.

For the health insurance, such information can be used to adapt reimbursement. Products with a higher price are not always better. It is clear that a company marketing such a high priced product may not want to compare this product with an old and lower priced alternative.

Besides this example of comparing the effectiveness of existing medicines or medical device interventions in a broad patient population, there are many other questions that can only be answered with publicly funded clinical trials. Treatments based on a surgical technique or psychotherapy are of little interest for the medical industry. Therefore, it is up to the government to finance the necessary clinical trials. The same reasoning applies in part for trials in pediatrics or for rare diseases. Also large trials on population screening or on diagnostic tests can only be performed with the financial support of the government.

Organising a system of publicly funded trials not only concerns the identification of the most relevant questions and the trial conduct. As important is making sure that the results of the trial are implemented in the routine care.

A number of countries have developed such a trial programme and have demonstrated it is a good investment of public money. For certain trials, e.g. involving rare disorders, international collaboration is a must in order to recruit the necessary number of trial participants. For other trials, international collaboration could increase the trial impact and lower the costs. Therefore, KCE worked together not only with local experts and the competent authorities, but also with international experts and representatives of organisations experienced in the conduct of publicly funded trials. We wish to thank them all for their input and their cooperation.

Christian LÉONARD
Deputy general director

Raf MERTENS
General director

SYNTHESIS

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KEY MESSAGES

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, that will never be answered by trials funded by the pharmaceutical and medical device industry.

Publicly-funded practice-oriented clinical trial programmes have shown to have a direct positive impact on patient care and use of healthcare resources.

Funding of clinical trials is a wise investment of public money if done in the context of well-organised programmes where authorities collaborate with experts in the field.

Key success factors are:

- a good selection process of the research questions to be answered with a clinical trial

- the presence of the necessary competences and research infrastructure to conduct clinical trials in a professional manner

- the presence of procedures to implement the findings in the trial

Clinical trials take time, healthcare decision makers may need to take transient measures while the trial is ongoing.

1. INTRODUCTION AND PROJECT SCOPE

In this report we try to answer the question whether it would be a good idea for the Belgian health care system to finance practice-oriented clinical trials and what would be required to realise this.

Evidence-based medicine and health technology assessment (HTA) are primarily based on the results of clinical trials and are important for healthcare payers to allocate the available resources in an efficient way.

1.1. Scope of this report

In this report the focus is on one subgroup of the non-commercial trials: those practice-oriented confirmatory trials, that aim to have an immediate impact on clinical practice or healthcare decision making, In contrast to pre-market commercial trials, such practice-oriented trials are pragmatic: they enrol a broad patient population representative of the clinical routine practice. Non-commercial trials are also referred to as publicly funded trials, investigator-driven trials or academic trials. However, the separation line between commercial and non-commercial intent may not always be clear. Often, academic trials are co-financed by industry in return for rights on ownership which may delay the publication of the study results.

Table 1 presents the characteristics of commercial versus non-commercial clinical trials..

1.2. Research questions

This report tries to answer the following research questions (referring to specific chapters in the full report).

- What is the impact of publicly funded non-commercial practice-oriented clinical trials (chapter 2) and why do we need such trials (chapter 3).
- What are the hurdles and quality requirements to perform such trials (chapters 4 and 5)
- Which steps could or should be taken to succesfully conduct such trial programmes, learning from the experience abroad (chapters 6 and 7).

Table 1. Differences and similarities in objectives of commercial versus non-commercial clinical trials

	Commercial clinical trials	Practice-oriented non-commercial clinical trials	Other clinical trials
In/out of scope	Out of scope	In scope	Out of scope
Primary objective	For profit. Create or expand the market.	Health benefits. Optimize clinical practice in terms of clinical effectiveness and cost-effectiveness.	Create new scientific knowledge that requires confirmation before being implemented in practice.
Owner of the data	The commercial sponsor.	The non-commercial sponsor	As defined in the contract.
Topic selection	Research question and study design selected by company management.	Research question and study design selection delegated by government to an independent body of working clinicians, patients, representatives of the health care payers and health care providers, statisticians, health economists, …Topics can be proposed top-down and bottom-up.	Research question and study design selection mainly by academia.
Study funding	Company.	Publicly funded, link with healthcare budget, sometimes universities or charities.	Scientific research funds or charities, sometimes co-funded by industry in return for intellectual property rights.
Trials with industry-owned products	To obtain marketing authorisation or label extension for medicinal products or medical devices (rarely for reimbursement purposes only)	Treatment optimisation (e.g. paediatrics), comparative clinical effectiveness trials (pragmatic) and cost-effectiveness studies with medicinal products or medical devices.	Academic proof of concept studies and exploratory translational research with medicinal products and medical devices.
Trials with interventions not owned by industry	None	Confirmatory trials (pragmatic), treatment optimisation, comparative effectiveness and cost-effectiveness for surgical techniques, psychotherapy, screening, or interventions of a different type.	Academic proof of concept studies and exploratory translational research in areas not covered by industry.
International trials	Mainly phase 2b/3 trials, sometimes in collaboration with publicly funded organisations (e.g. in oncology)	When appropriate, using e.g. ECRIN (European Clinical Research Infrastructures Network).	Rarely.
Risk-level	Moderate to high (rarely low)	Low to moderate	Moderate to high

1.3. Different types of clinical trials

Clinical trials may be grouped by the fact they need a clinical trial application (CTA) or not. Databases kept by the competent authorities only track trials with a CTA. In Belgium, only clinical trials with medicinal products currently need a CTA and approval by the local competent authorities. Pre-market trials with devices need to be notified. In this report however, we use a broad definition, not restricted to clinical trials with a CTA, but also including trials evaluating the safety and efficacy of other types of interventions, e.g. using medical devices, lifestyle interventions, surgical techniques, psychotherapy, radiotherapy, or diagnostic interventions including population screening,…

Clinical trials can either be exploratory of confirmatory. Exploratory hypothesis-generating clinical trials are needed to understand the disease pathophysiology and to find a first "proof of concept" (translational research: moving the intervention from the laboratory setting to the clinical trial setting). These smaller, often single centre trials are to be distinguished from large multicentre clinical trials designed to confirm a pre-specified hypothesis.

A second aspect concerns the trial design, and in particular the way the intervention is allocated to the patients in the trial: this can be done "at random" or not. The type of trial design needed will depend on the research question. The randomized controlled clinical trial (RCT) is the main study design used to control for bias and the impact of "random" (unexplainable) variability. Therefore, RCTs remain the most reliable means of identifying the drugs, devices, and treatment strategies that will improve human health.

A third classification method of clinical trials, of importance in this report, is by the type of sponsor, the organisation designing the trials and most often providing the funding. For pharmaceutical products, the current reality is that the majority of the clinical trials are run and paid by a pharmaceutical company as part of the product development cycle. These trials can be pre-marketing (exploratory trials in phase 1, 2a and more confirmatory trials in phase 2b and 3 or post-marketing phase 4). However, important research questions, of interest for patients and society, remain unanswered if one would solely rely on this paradigm. Industry may not have any interest to perform these trials. For example, public health decision makers and clinicians alike not only want to know whether the new treatment is superior to placebo, but they also need to assess whether the new treatment is superior to the existing alternative, certainly if the new intervention has a higher price tag. In addition, they want to have this comparative effectiveness evaluated in a broad population of patients as seen in routine practice. This is different from the highly selected population typically studied in commercial trials designed to obtain marketing authorisation, in agreement with the directives for clinical trials.

In this case the only option to generate the comparative effectiveness data is to perform a pragmatic practice-oriented head-to-head randomized controlled trial. As the medicines agencies may not require the pharmaceutical companies to perform this type of trial, non-commercial sources of funding have to be found.

Publicly-funded trials are not only of use for medicinal products or medical devices but are even more needed in areas that are not 'owned' by the medical industry, such as psychotherapy, population screening, surgical techniques, … In these areas publicly-funded trials may be the only solution to answer important healthcare questions. Such non-commercial trials are typically funded with tax payer money, university hospitals or by charities. Also healthcare payer organisations may have a funding role.

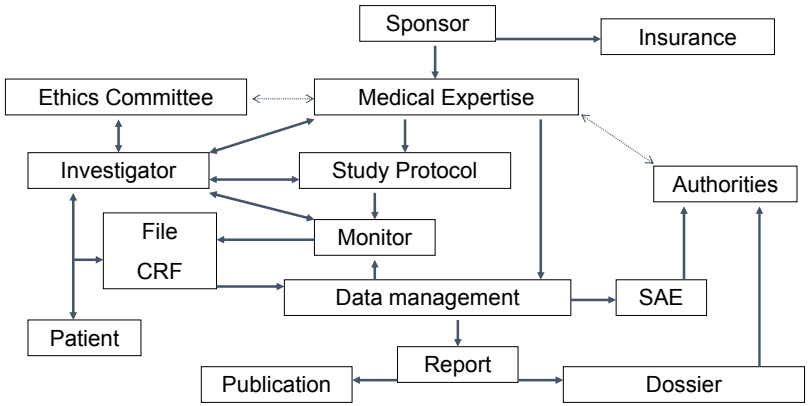
1.4. Clinical trials need expertise, are expensive, and take time

Clinical trials are a heavily regulated activity. Clinical trials, and confirmatory RCTs in particular, require standard operating procedures, specialized personnel and remain quite expensive to perform. Steps in a clinical trial are simplified in Figure 1 and include the following items.

- Study protocol and contract
- Trial insurance
- Ethics Committee(s) review
- In case of medicinal products,
  - Clinical trial application, to be reviewed by the Competent Authority
  - Double-blind study medication as applicable
- Logistics for storing and shipping trial material (including medication)
- Registration of the trial
- Central randomization procedure
- Inviting and enrolling patients after informed consent

- Study visit scheme with studied interventions and follow-up procedures
- Logistics for central facility (e.g. for tests)
- Study data recording on case report forms (CRF)
- Study monitoring procedures, audit
- Timely reporting of serious adverse events (SAEs)
- Data analysis and reporting, archiving
- Overhead/administrative costs;
- Etc.

Figure 1 – Complexity of a clinical trial



CRF= case report form; SAE= serious adverse event

Compared with pre-market clinical trials the risk level and the intensity (and cost) of study monitoring is lower for comparative effectiveness trials with marketed medicines used in their approved indication.

Once a study protocol and contract is finalized and the logistics are in place, the timeline of a clinical trial is dictated by the time for ethical/regulatory review, patient recruitment, the minimum follow-up in the trial, the data collection, analysis and reporting. Because the trial can take a number of years before results are available, health care decision makers may need to put in place transient measures before a final decision is made and trial results are adopted in routine practice.

2. NEED FOR PUBLICLY FUNDED TRIALS

Whether clinical trials should be considered a public good and therefore be sponsored and overseen by government rather than industry remains a matter of debate. For pharmaceutical products, the current reality is that the majority of the clinical trials are run and paid by a pharmaceutical company as part of the product development cycle. The primary aim of the medical industry is to make a profit. This may be reflected in a study design that is more likely to produce a favourable outcome for their product, e.g. in the selection of the dose or of the active comparator. Publication bias is another consequence of this current reality, but regulators have started to make public the study results of trials with medicinal products. In contrast, for medical devices, there is still a complete lack of transparency of the commercial clinical trials run to obtain a CE mark.

We believe that spending public money in "more objective" clinical trials purely to avoid the sources of bias previously mentioned would not be reasonable. Instead, adjusting and enforcing regulations that provide a more independent review of the design and ensure the transparency of the results would offer a more efficient route.

There are many situations where public funding is required to answer important questions in health care.

2.1. Comparative effectiveness trials with medicinal products

Patients and clinicians want to know the best intervention among the treatment options available. A head to head comparative trial can answer this question but none of the companies concerned may want to take the initiative. In pre-market trials the use of an active comparator may not be required by the competent authorities. Once marketing authorisation and reimbursement are obtained the company may even try to avoid the generation of data that might hamper the marketing of the product. There is a commercial risk (promotion, price discussion) associated with the conduct of a head to head trial in case the own product proves to be inferior (or not superior) to the existing alternative (which may be less expensive). In such a situation it is up to the public health decision maker to make sure the comparative effectiveness data are generated, in collaboration with

clinicians. Previous KCE reports have highlighted the need for such comparative effectiveness trials, e.g. comparing standard duration of trastuzumab administration in early breast cancer with a shorter course; or comparing the effectiveness of salmeterol versus tiotropium in chronic obstructive pulmonary disease.

2.2. Trials in children and in rare diseases

Paediatrics and orphan diseases sometimes remain commercially less appealing to the industry despite specific regulations and advantages that were created. These areas therefore continue to rely heavily on publicly funded trials for the generation of clinical evidence.

2.3. Trials with medical devices

When compared to pharmaceuticals, the pre-market clinical development of medical devices is less regulated in Europe. All too often no high quality efficacy data are available when innovative high-risk devices are placed on the market with a CE mark, ranging from implants to radiotherapy devices. More and more healthcare payers want to see high quality trial results before reimbursing innovations. The ongoing debate on the new EU device regulation concerns, among others, the requirement to conduct pre-market efficacy trials for high-risk devices and their level of transparency.

2.4. Trials on diagnostics

The comments made for medical devices are also valid for diagnostic devices, including in vitro diagnostics. In comparison with therapeutic interventions, evidence generation is less developed for diagnostic interventions. Diagnostic interventions may however be very relevant as companion diagnostic for targeted therapy or as screening tools at population level. Population screening tools may require specific trials, designed in collaboration with public health decision makers.

2.5. Trials in medical areas not owned by private companies

Other fields have less or no medical industry support such as surgical techniques, lifestyle interventions or psychotherapy but also here the decision makers need high quality data on effectiveness to decide on the approval and financing of specific techniques and indications. Also interventions of different types deserve to be compared in a direct way, e.g. exercise versus medication to control diabetes.

3. THE FRAMEWORK OF CLINICAL TRIALS

3.1. The European clinical trials Directive did not help

Obtaining national and local approvals needed to start an international clinical trial with medicinal products in Europe became more burdensome after the clinical trials Directive was introduced some 15 years ago. The additional requirements associated with a lack of real harmonisation are considered one of the reasons for the decrease in clinical trial activity seen in Europe, both for commercial and non-commercial trials. Many European countries therefore have taken national actions to keep this research and economic activity. For example, the length of the procedures to start a clinical trial was reduced. Large hospitals have created contact points for companies that want to perform a clinical trial. The importance of (commercial) clinical trials for the hospital sector is illustrated by the fact that the three university hospitals of Brussels have decided to collaborate to attract and conduct pharmaceutical clinical trials.

The new clinical trial Regulation for medicinal products entered into force on 16 June 2014 and will apply no earlier than 28 May 2016. The aim is to reduce the time and complexity to obtain approval of a clinical trial application for all participating sites in a country. The new regulatory requirements will be adapted according to the level of risk to which patients are exposed during a trial. The Regulation thereby introduces the concept of ‘low-intervention clinical trial’, for instance for studies comparing already authorised medicines used in an approved indication. Another major objective of the Regulation is to increase transparency. All results, positive and negative, will have to be published in a publicly-accessible database.

3.2. National and international trial programmes

We looked at publicly funded clinical trial programmes using a grey literature search, completed with personal contacts. We documented the funding and supporting structures of public funded clinical trials at international level (ECRIN, EORTC[a]) and at national level (UK, Germany, France, Italy, the Netherlands, Nordic countries and Spain). In only few countries there is a direct involvement of the healthcare payers in the funding, the selection and implementation of results of the publicly funded clinical trials.

Obtaining funding for a large non-commercial clinical trial is a challenge in most countries; and international collaboration is even more difficult. Europe may have an important role to play. The European budget spent on practice-oriented non-commercial trials remains low (a few hundred million euros, only in 2011) when compared to the expenditure of the Innovative Medicines Initiative (a few billion euros).

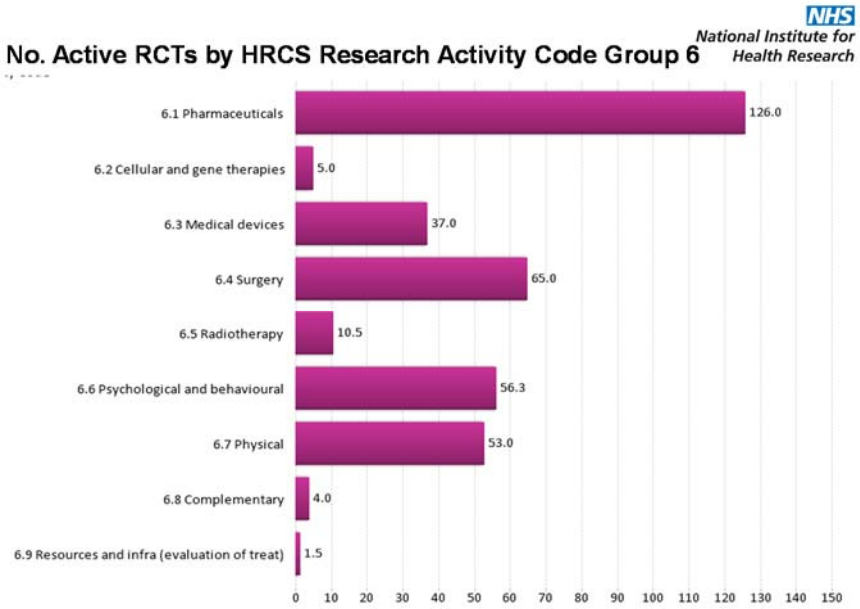
The most developed and integrated system of clinical trials in Europe can be found in the UK. It is embedded in the national healthcare system and since 2006 coordinated by the National Institute for Health Research (NIHR). The trials supported cover a broad range of interventions, including areas not owned by industry, as illustrated in Figure 2.

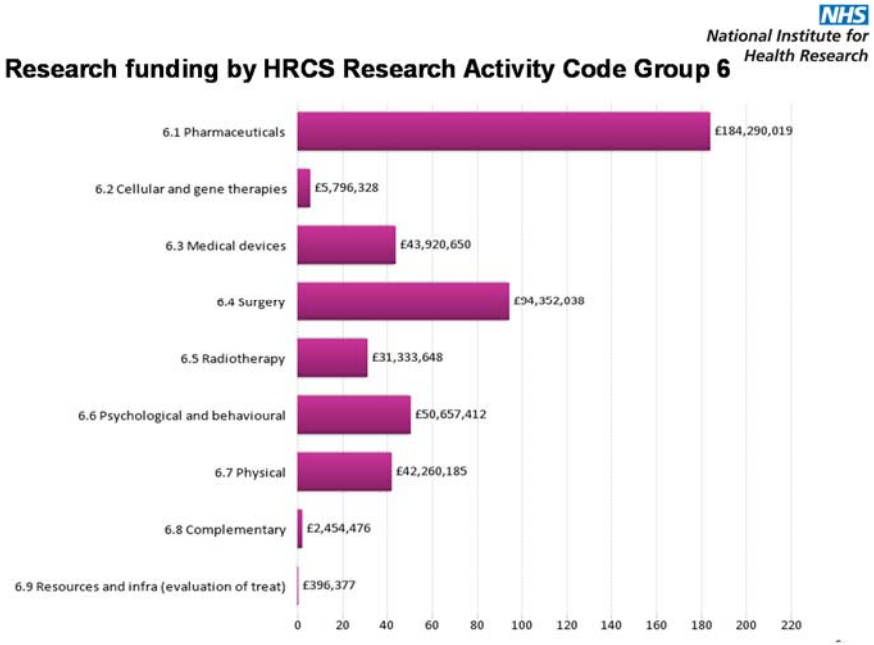
Another example worth mentioning is the programme of trials funded by ZonMW in the Netherlands, focussing on efficiency in healthcare. The trial proposal has to outline the health-economic impact of the trial. Furthermore, an implementation project often follows the trial to make sure the trial results are implemented in daily practice.

The programme run by the Italian Medicines Agency focusses purely on medicinal products. This programme is funded using a 5% tax on the expenditure for promotional activities of the pharmaceutical industry.

[a] European Organisation for Research and Treatment of Cancer

Figure 2 – NIHR-funded number of active trials and budget by domain in the UK (2014)





3.3. A wise investment of public money

The main purpose of health research at large, covering basic and clinical traditional medical research, is to improve the health of the general population in the form of better quality of life and increased longevity.

Public health decision makers may want to know whether an investment in a clinical trial is a wise way to spend public money.

A search was performed to find evaluations of medical and health-economic impact of clinical trials and clinical trial programmes, funded with public means.

For individual trials it may be easy to pick a non-commercial trial that changed clinical practice and brought huge health-economic benefits. Two famous examples of publicly funded clinical trials that yielded a high return on investment are given below. Both were funded by the National Institute of Health (NIH) in the US.

The Women's Health Initiative trial demonstrated the negative health impact of combined hormone therapy among postmenopausal women. This clinical trial led to a substantial reduction in the use of combined hormone therapy in this group and a very important reduction in the number of breast cancer and cardiovascular events.

The ALLHAT clinical trial compared different antihypertensive drug classes and concluded that thiazide-type diuretics were superior in preventing cardiovascular events while being less expensive.

More relevant however are evaluations of all trials funded under a single programme.

Such analyses should not only consider direct trial-related costs but also indirect cost items associated with starting and running a trial, e.g. costs of a transient decrease in productivity.

Among the benefits, there is a general knowledge gain and capacity building of researchers involved in trials, an improved research infrastructure and logistics. Finally, for the evaluation of the economic impact of healthcare research at large, not only the cost of conducting research should be considered, but also the cost of implementing the research results.

Few studies have analysed the impact of a publicly funded clinical research programme on patient survival and/or quality of life and on health care costs. Evaluations of publicly funded clinical research and clinical trial programmes were identified for selected National Institute of Health (NIH) trial programs in the US and clinical research programmes funded by the National Health Service in the UK. Health economic evaluation reports of clinical trial programmes in Australia, Sweden and the Netherlands were also identified. We also accessed the impact report of the TBM (Toegepast Biomedisch Onderzoek) programme of the Flemish Institute for Science and Technology (IWT).

All reports indicate methodological shortcomings which may result in an under- or overestimation of the reported return on investment. Despite these shortcomings, all authors conclude that clinical research and clinical trials are a good investment of public money and/or that the impact on clinical practice is significant. The economic benefit can even be estimated to be very high when gains in life years or quality-adjusted life years are valued at £25 000 in the UK or at $40 000 to $100 000 in the US.

Key success factors are not only a professional conduct of the trial, but also the quality of the trial topic selection and design and the post-trial implementation of the results. This way savings for the healthcare system may be realised, which can be reinvested in the programme.

What is the role of Europe?

The European legislation is important for clinical trials with industry-owned products (medicinal products and medical devices). For all other types of interventions, clinical trial regulations remain a national competence, be it guided by ethical principles as detailed in the Declaration of Helsinki (e.g. concerning informed consent, trial registration and publication...).

The new EU Regulation on clinical trials with medicinal products should correct the unnecessary hurdle for non-commercial trials that was imposed by the EU clinical trial Directive, as previously discussed.

For medical devices, it is still not clear to what extent the future EU Regulation will stimulate the conduct of pre-market commercial clinical trials, and improve the transparency as is ongoing for pharmaceutical trials.

The same research questions likely to be answered with a publicly funded trial often arise around the same time in different countries. One approach is to wait for another country to solve the problem and spend the money. This free-rider behaviour however cannot be recommended.

Much to be preferred is some form of collaboration between countries facing the same issues. A pooled database of planned trials could facilitate international collaboration, as is being tried for HTA projects in Europe. However, this requires not only that investigators arrive at a common study protocol, but also that the infrastructure and procedures are in place in the countries concerned. To meet this demand, ECRIN (European Clinical Research Infrastructure Network) has been created. It is an ERIC (European Research Infrastructure Consortium). This consortium receives nearly €2 million of funding per year from the EU. ECRIN has a growing number of member countries, but Belgium is not yet a member.

An important bottleneck for the conduct of international clinical trials in Europe remains the funding. Most national funding bodies are reluctant to fund trial sites that are not within their territory. Several options are currently being explored to facilitate European collaborations (ranging from the European Research Area Network Cofund scheme to the synchronised call system).

Public money spent by the EU on non-commercial clinical trials is relatively low in comparison with the budget spent on public private partnerships. In 2011, 26 trials were financed by the 7th framework for a total budget of €152 million (€6 million per trial on average), but this effort is not repeated each year. The Innovative Medicines Initiative (IMI) is a public-private partnership (PPP) in life sciences, launched in 2008 and funded for 50% by the European Commission, corresponding to an overall contribution of public money of €2.65 billion (2008-2024). For the first time in 2012, the Innovative Medicines Initiative financed clinical trials. The focus of these trials is more on translational research, in this case, the development of new antibiotics (€90 million).

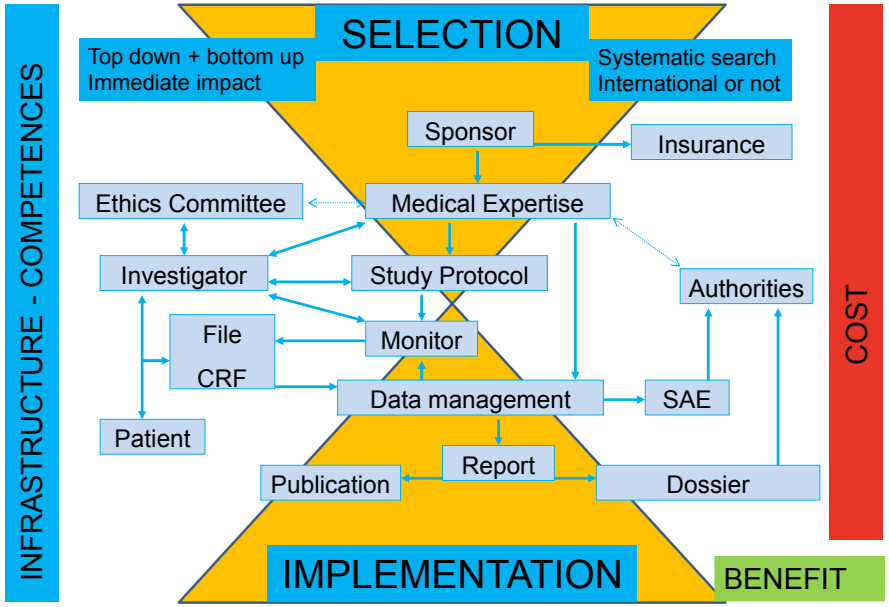
3.4. Success factors for publicly-funded clinical trials

A first critical step is the **selection of the research questions** that should be answered (Figure 3). The trial design and selection should be delegated by government to an independent body of working clinicians, patients, experts representing the health care payers and the care providers, statisticians, health economists... Both top-down and bottom-up procedures should be available. Both research questions on clinical effectiveness and cost-effectiveness should be considered. It should be checked whether the research questions can be answered using the analysis of administrative databases. In addition, a systematic review should be conducted before a trial is selected, including an investigation of possible reasons for previous trial failure. Patient recruitment problems are frequent but can often be predicted and avoided e.g. making sure the eligibility criteria and study procedures are realistic. Procedures and people should also be available to do the trial follow-up once funding is granted. As an example, the trial programme of the Italian Medicines Agency is managed by 8 staff members.

A second key element is a **budget** that allows a professional conduct of a large practice-oriented trial. The budget per trial is often in the range of €1 million to €10 million, on top of the costs of the trial site network infrastructure, with competent personnel that makes use of standard operating procedures.

Competences and an infrastructure are needed 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. For example, scientific societies may want to initiate a clinical trial but do not have an in-house infrastructure and specialists in the logistic, regulatory, legal and ethical challenges of a RCT. Therefore, sufficient funding and access to a research infrastructure for trials are needed to help scientific societies. For an international trial, it is preferable that the same procedures are followed in all participating countries and study sites.

Figure 3 – Success factors for publicly-funded clinical trials



In the UK, routine care of the study patients does not have to be paid as this is covered by the NHS. NIHR spends £250 million a year for an extensive network system. This infrastructure supports not only NIHR trials but also charity trials and industry trials. This makes the UK a more attractive place to run trials for industry and greatly facilitates the conduct of clinical trials funded by charities. In addition, £150 million is spent directly on NIHR funded clinical trials. In order to make sure trials are published, NIHR pays 5% of the budget upon publication of the results.

Also Germany has a well-developed network of clinical trial sites (KKS), integrated in the European network ECRIN (see box above).

A third factor to make a publicly funded trial programme a success from a health care perspective is the **implementation of the trial results**. The ZonMW programmes spend over €20 million per year on practice-oriented clinical trials. In addition, there are specific projects to implement the trial results in routine practice. These implementation projects cost up to €50 000 each and run over a few years.

3.5. What can we do in Belgium?

With regard to pharmaceutical trials, Belgium is participating in a large number of trials, mainly sponsored by pharmaceutical companies. Sometimes however, even large hospitals may not be able to participate in trials for rare indications because of the strong fragmentation of specialized care in Belgium.

No public funding sources are available in Belgium for large trials. The IWT TBM comes close, but funding is mainly for translational projects and the maximum amount of funding is €1 million per trial. Each large hospital in Belgium has some expertise or contact point for clinical trials but there is no real network of experienced clinical trial centres to tackle large multicentre trials, nor is Belgium part of the ECRIN network infrastructure. Three university hospitals in Brussels have started to collaborate, mainly to attract commercial trials.

Setting up a network infrastructure makes sense when also the funds are made available to conduct the trials. As our focus is on practice-oriented clinical trials covering the full range of healthcare, it would make sense to keep the funding and the management close to RIZIV-INAMI.

RECOMMENDATIONS[b]

To the Ministers responsible for public health, healthcare and scientific research, to all partners of the Belgian Health Research System, to the competent authorities in the regions, the medical scientific societies and the healthcare providers.

Public funding of well-selected clinical trials is recommended to answer those questions on clinical effectiveness and cost-effectiveness that are unlikely to be answered by commercial trials conducted by the pharmaceutical and medical device industry. Publicly-funded pragmatic and practice-oriented clinical trials can have a positive direct impact on patient care and the appropriate use of the healthcare resources.

- **It is recommended to provide both top-down (from health care decision makers) and bottom-up (from the field) procedures for the proposal of such clinical trials.**
- **A systematic literature search and a consultation of organisations funding trials should be conducted before a trial is funded.**
- **Both national and international clinical trials should be funded, the choice should be guided by scientific arguments, e.g. size of the required study population. Organisations such as ECRIN can coordinate international trials.**
- **It is recommended that the design and size of the trial allow the trial to have a direct impact on clinical practice and the appropriate use of the healthcare resources. Funding a large number of small trials that cannot lead to firm conclusions should therefore be avoided.**
- **As public funded clinical trials provide answers to important healthcare questions that will not be answered otherwise, and as evaluations of existing programmes (e.g. in the UK and the Netherlands) support the continued investment of public money in clinical trials, we recommend the creation and funding of a clinical trials infrastructure, a management team and a programme of practice-oriented clinical trials closely linked to the Belgian Health Research System.**
- **The management team would have the following tasks:**
  - **Rank and select the trials that can have a direct positive impact on patient care and the appropriate use of the healthcare resources, assisted by an independent body of clinicians, experts representing patients, health care providers and payers (including the CTG-CRM and CTIIMH - CRIDMI), health economists, statisticians and other scientists.**

[b] The KCE has sole responsibility for the recommendations.

- **Set the standard for a network of clinical trial centres in Belgium, in agreement with international standards and networks, in collaboration with the Federal agendcy for medicines and health products (FAMHP).**
- **Assure the quality of all funded clinical trials, in accordance with the local legislation on clinical trials. Assure that the study is monitored using a risk-based approach and that the Declaration of Helsinki is fully respected (trial registration, informed consent, publication,..).**
- **Assist the trial sites for issues on study outsourcing, logistics, insurance, intellectual property and international collaboration, e.g. using the ECRIN platform.**
- **Control the payments and progress of the selected clinical trials. Make sure significant payments are linked to trial registration and publication of the complete results.**
- **Assure that the study conclusions are communicated to the decision makers for implementation, assist in designing implementation projects if needed.**
- **Represent Belgium in international trial networks e.g. in ECRIN.**

- **It is recommended that the funding of clinical trials programme management team, the network and the funding of the trials is in part covered by the health care budget and in part by the existing taxes on sales of pharmaceuticals and medical devices. A minimum yearly budget of €10 to €15 million is suggested, of which €1 million should fund the management team.**
- **The trials could be selected in a way they optimize the care of the patients, lead to net savings or at least no extra expenditures for the obligatory health insurance.**
- **The publicly funded trial programme should be audited and evaluated at regular intervals.**

Recommendations for the European Commission, EMA, national and international stakeholders

- **It is recommended to create a database of planned and ongoing publicly-funded clinical trials that can be consulted before embarking on a new trial or to find collaborating partners.**
- **It is recommended to implement a uniform electronic patient record, based on international standard terminology, in order to reduce the workload of trial data extraction. This could significantly improve the quality and speed of performing clinical trials and potentially lower the overall costs.**
- **In order to facilitate trial data exchange, standards like CDISC (Clinical Data Interchange Standard Consortium) should be implemented.**

- **It is recommended that the European investment funds evolve to a more balanced approach between the funding of public private partnerships (e.g. the Innovative Medicines Initiative) and publicly-funded practice-oriented clinical trials.**
- **It is recommended that the European Medicines Agency requires from industry clinical trials that are pragmatic, reviewed by independent researchers and include the current optimal treatment as a direct comparator with the new proposed intervention. This could reduce the need for publicly funded comparative effectiveness trials.**

COLOPHON

Title:	Publicly Funded Practice-oriented Clinical Trials – Summary
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