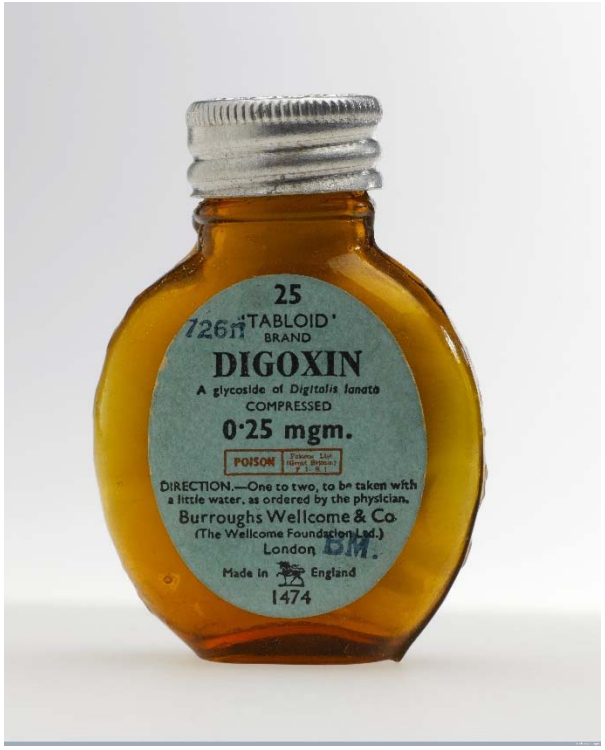
KCE REPORT 246

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

PUBLICLY FUNDED PRACTICE-ORIENTED CLINICAL TRIALS



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HEALTH SERVICES RESEARCH

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AAHRPP	Association for the Accreditation of Human Research Protection Programs
Ab	Antibody
ACRP	Association of Clinical Research Professionals
AE	Adverse Event
AIFA	L'Agenzia Italiana del Farmaco , Italian Medicines Agency
ANRS	Agence Nationale de Recherche sur le Sida et les hépatites virale
AMG	West Germany Drug Law (Germany's equivalent to Food, Drug and Cosmetic Act)
BCFI - CBIP	Belgian Centre for Pharmacotherapeutic information
BeAPP	Belgian Association of Pharmaceutical Physicians
BGA	Bundesgesundheitsamt (Germany's equivalent to FDA)
BID	Twice a Day
BMI	Body Mass Index
BP	Blood Pressure
CAGR	Compound Annual Growth Rate
CBER	Center for Biologics Evaluation and Research (FDA)
CDC	Center for Disease Control
CDER	Center for Drug Evaluation and Research (FDA)
CDISC	Clinical Data Interchange Standard Consortium
CDRH	Center for Devices and Radiological Health (FDA)
CE	Conformité Européenne
CFR	Code of Federal Regulations (FDA)
CIOMS	Council for International Organizations of Medical Sciences (post approval international (ADR)
COPD	Chronic Obstructive Pulmonary Disease
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms (FDA)
CRF	Case Report Form
CRO	Clinical Research Organization
CTA	Clinical Trials Application

CTTI	Clinical Trials Transformation Initiative
DIA	Drug Information Association
DSM	Diagnostic and Statistical Manual
EBM	Evidence-based medicine
ECG	Electrocardiogram
ECRIN	European Clinical Research Infrastructures Network
ECU	European Currency Unit
EDCTP	European & Developing Countries Clinical Trials Partnership
EEC	European Economic Community
EFGCP	European Forum for Good Clinical Practice
EFPIA	European Federation of Pharmaceutical Industries Associations
EMA	European Medicines Agency
EORTC	European Organization for Research and Treatment of Cancer
EOS	End of Study
ERA-Net	European Research Area Network
ERIC	European Research Infrastructure Consortium
EVAR	Endovascular Aneurysm Repair
FAGG-AFMPS	Belgian Federal Agency for Medicines and Health Products
FDA	Food and Drug Administration
G-BA	The Federal Joint Committee (Der Gemeinsame Bundesausschuss)
GCP	Good Clinical Practices
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HBOT	Hyperbaric Oxygen Therapy
HTA	Health Technology Assessment
IB	Investigator's Brochure
ICER	Incremental Cost-Effectiveness Ratio
ICH	International Conference on Harmonisation
IDCT	Investigator-Driven Clinical Trials

IDE	Investigational Device Exemption
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
ISO	International Organization for Standardization
IVD	In Vitro Diagnostic
IVD	In Vitro Diagnostic (test that works on a body fluid sample)
IWT	Innovatie door Wetenschap en Techniek (agency)
KKS	Koordinierungszentrum für Klinische Studien, Coordination Centre for Clinical Research
MAA	Marketing Authorisation Application
MTX	Methotrexate
MRC	Medical Research Council
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
NDA	New Drug Application
NEJM	New England Journal of Medicine
NETS	NIHR, Evaluation, Trials and Studies
NETSCC	NIHR Evaluation, Trials and Studies Coordinating Centre
NHLBI	National Heart, Lung, and Blood Institute
NHMRC	National Health and Medical Research Council
NIAID	National Institute of Allergy and Infections Disease
NIH	National Institutes of Health
NIHR	National Institute for Health Research, UK
NMR	Nuclear Magnetic Resonance
NINDS	National Institute of Neurological Disorders and Stroke
NPV	Net Present Value
NSAID	Nonsteroidal Anti-Inflammatory Drug

OECD	Organisation for Economic Co-operation and Development
PI	Principal Investigator
PMA	Pre-Market Approval
QA	Quality Assurance
QOL	Quality of Life
QALY	Quality-Adjusted Life Year
RA	Rheumatoid Arthritis
R & D	Research and Development
RCT	Randomized Clinical Trial
RoR	Research on Research
RUZB-CHAB	Raad van Universitaire ziekenhuizen - Conférence des Hôpitaux Académiques
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
TBM	Toegepast Biomedisch Onderzoek
UKCCR	United Kingdom Coordinating Committee on Cancer Research
UKCRC	United Kingdom Clinical Research Collaboration
VA	United States Department of Veterans Affairs
VLK	Vlaamse Liga tegen kanker
WBC	White Blood Count
WHO	World Health Organization

SCIENTIFIC REPORT

1 INTRODUCTION

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.

1.1 Background

1.1.1 The importance of RCTs for evidence-based medicine and health technology assessment.

Policy makers strive to have a high accessible, high quality and durable health care system. In the context of limited resources, difficult choices have to be made e.g. between the different interventions that can be reimbursed, how to organise the health care system, whether to invest money in further research, etc. Not taking into account the acceptability and affordability of decisions will eventually have its impact on the system's accessibility and/or quality, e.g. by asking more co-payments from patients or taking away resources from other places in the health care sector (opportunity cost) that may provide more value for money. The focus on evidence-based medicine and health technology assessment (HTA) is growing to support policy makers in making these difficult choices and make efficient use of available resources.

An important aspect of HTA is the evaluation of the existing clinical evidence, and this evidence is mainly generated using clinical trials. Clinical trials can be conducted to better understand the disease pathophysiology, to show "proof of concept" (translational research)[a], to bring a new product to the market or explore new indications for existing products, to compare effectiveness among different clinical management options in real-life populations (comparative effectiveness), to identify risk factors or to prevent disease.[1] Vice versa, the participation in clinical trials is likely to create a culture of evidence based clinical practice, with all the benefits that follow on from that.

[a] We refer to Appendix 1 for a short description of this terminology.

There is no universal database where all clinical trials can be identified. Databases kept by the competent authorities only track trials with a Clinical Trial Application (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 only need to be notified. In this report, 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,…Statistics based on trial registries where trials with all types of interventions can be registered (e.g. clinicaltrials.gov) will thus be different from those based on a CTA database.

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). 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. Both the perspective of the patient (effectiveness) and of society (cost-effectiveness) should be considered in the design of the trial. In this context is could of relevance to mention the results of a large survey by KCE. The results point to disease severity in terms of quality of life under current treatment, and opportunities for improving quality of life through health care interventions as the most important criteria for resource allocation decisions in health care by the Belgian general population. Compared to the decision makers, the general public attaches relatively less importance to changes in life expectancy (KCE report 234, 2014).

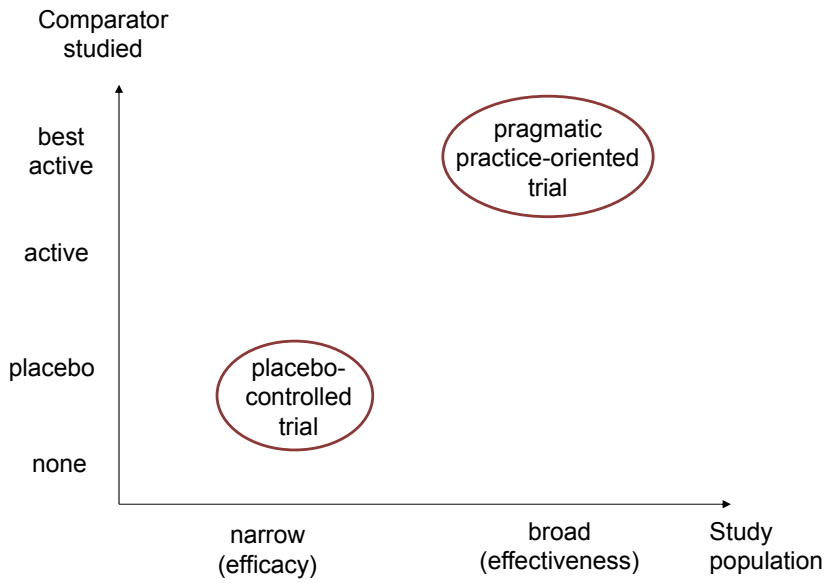
The randomized controlled clinical trial (RCT) is the main study design used to control for bias and the impact of "random" (unexplainable) variability. "*Randomized clinical trials (RCTs) remain the most reliable means of identifying the drugs, devices, and treatment strategies that will improve human health.*"[2] The importance of a well-designed RCT was illustrated for the evaluation of the devices to perform renal denervation to treat hypertension. Those devices were marketed in Europe based on observational data, reimbursed in 13 EU countries and believed to help patients. The US Food and Drug Administration required a single-blind RCT for renal denervation whereby a sham procedure was used as a control. The RCT showed an absence of efficacy of renal denervation.[3]

A third classification method of clinical trials, of importance in this report, is by the type of sponsor, the organisation designing the trials and 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. The classification of trials by the source of funding is illustrated in Table 1.

Unfortunately, there is often a lack of appropriate RCTs to answer important research questions posed within the context of a health technology assessment or the production of good clinical practice guidelines. 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 (Figure 1).

Even if efficacy is demonstrated in a phase 3 registration RCT, this does not automatically result in real-world effectiveness if the studied population was highly selected and not representative of the real-world routine care population. The real-world population may e.g. have more comorbidity, concomitant medication or have a less frequent visit schedule. Therefore, pragmatic practice-oriented clinical trials including the real-life target population can be essential for policy decision makers.

Figure 1 – Clinical trials by comparator and representativeness of the study population.



Clinical trials, and RCTs in particular, are quite expensive to perform and require not only a study protocol, patients and investigators but also the procedures and logistics with regard to the study medication or medical devices, the randomization procedure, the recording of the data, the study monitoring, the data analysis and the study reporting. Whether clinical trials should be considered a public good and therefore be funded and overseen by government rather than industry remains a matter of debate.[4] The current reality is that the medical industry is paying for the clinical trials needed to market its products (pharmaceuticals or medical devices). Therefore, policy makers may look at the industry to perform these trials. Especially in cases where the industry profits from the benefits of performing such trials, e.g. by obtaining market approval and to support their reimbursement request, one may expect they will also take the responsibility to perform these studies.

However, in some cases, open questions still remain. **There are important research questions of interest for patients and society for which the industry has no interest to perform the necessary trials**. "*The failure of private research to exploit opportunities to reduce mortality is likely to be greatest where the pharmaceutical house or medical equipment maker is unable to capture the bulk of the return – or as economists would say, where the "social" benefits far exceed the private benefits*",[5] or where there are no benefits at all for the private stakeholder to perform the research.

As mentioned by Christensen in the Lancet:[6] "*By contrast with publicly sponsored research, industry-sponsored research often focuses on profitable areas and future profits instead of areas where important health improvements could result.*[4] *The industry's reluctance to do relevant head-to-head trials*[7, 8] *contributes to the fact that the drug of interest is often found to be superior.*[9, 10] *These issues make independent clinical research highly necessary.*" In fact, in such cases, **public funding of clinical trials may be the only way to answer such important research question**: "*it won't be done unless [government] covers the costs*".[5]

The conduct of non-commercial clinical trials, and certainly comparative effectiveness trials, could be considered as **an important research and development component of a public healthcare system**, providing key information to identify the real innovations. There seems to be a contrast between the high potential impact non-commercial clinical trials can have on the decision making by health care payers and their low level of involvement in the design and financing of such trials in many countries.

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 this report	In scope or report if publicly funded	Out of scope of this report
Primary objective	For profit. Expand the market.	Health benefits. Optimize clinical practice in terms of effectiveness and cost-effectiveness.	Create new scientific knowledge that requires confirmation before being implemented in clinical practice.
Owner of the data	The commercial sponsor.	The non-commercial sponsor	As defined in the contract.
Topic selection	Selection by company management.	Selection delegated by government to an independent body of clinicians; experts representing patients, the health care providers and the health care payers; health economists, statisticians and other scientists. Topics can be proposed top-down and bottom-up.	Selection mainly by academia.
Study funding	Company.	Publicly funded 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	Trials to obtain marketing authorisation for medicinal product or medical device, can be for label extension.	Treatment optimisation (e.g. paediatrics), comparative 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 studies for surgical techniques, psychotherapy, screening, or comparing interventions of a different type.	Academic proof of concept studies and exploratory translational research in areas not covered by industry..
International trials	Phase 2b/3, using affiliates and contract research organisations; sometimes in collaboration with publicly funded organisations (e.g. in oncology)	When appropriate, using e.g. ECRIN.	Rarely.
Risk-level	Moderate to high	Low to moderate	Moderate to high

1.1.2 Publicly funded clinical trials

The initiative to conduct a non-commercial clinical trial often comes from medical faculties. Different countries have different sources of funding of non-commercial clinical trials. In the UK, the financing is often provided by publicly funded organisations such as the National Institute for Health Research (NIHR). Also charities such as the Wellcome Trust are important in this regard. The departments financing non-commercial clinical trials vary: in Germany, the funding mainly comes from 'the research department' money whereas in France the funding is provided through 'the healthcare department' money.

The CardioScape survey of the European cardiovascular research landscape, including clinical trials, identified 2476 projects and €876 million of funding by 187 bodies in 2010-2012. Government/public funding accounted for 53% of the total funding (EU funding for 37%, followed by the Deutsche Forschungsgemeinschaft). Charity/private agencies provided 47% (British Heart Foundation funded 14% of the total, followed by the Wellcome Trust). Over 70% of the projects have a grant below €100 000 per year. Fifteen randomized trials funded for over one million euro were identified in the online database. (http://www.cardioscape.eu/CVD-Research-Inventories/CVD-Research-Database)

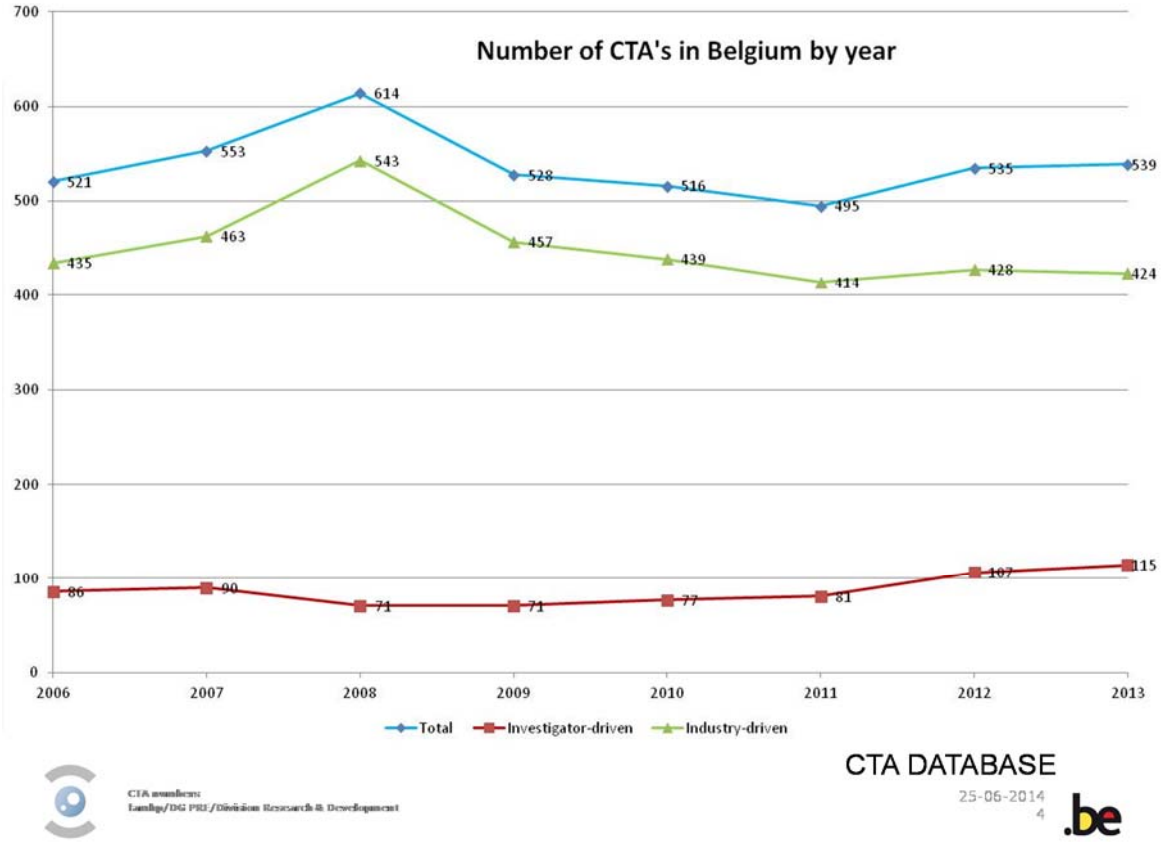
The registration of a clinical trial in a publicly accessible trial registry (e.g. clinicaltrials.gov) is a condition to publish the trial in high-ranked peer reviewed journals, independent of the type of intervention. Analysis of trials registered into the clinicaltrials.gov registry after June 2011 shows that 5886 trials with only government sponsorship are interventional versus 30 036 industry-only sponsored trials.[11] Industry-sponsored interventional trials were most likely to report a drug intervention (81%), followed by biologics (9%) and interventions using a device (8%). **Government-only interventional trials were significantly more likely to test behavioural interventions and procedures than industry-only trials**. Government-only funded trials were more likely to study mental health (19% vs. 7% for industry), and viral infections including HIV (15% vs 7% for industry).

According to data of the Clinical Trials Application (CTA) database from the Belgian Federal Agency for Medicines and Health Products (FAGG-AFMPS), the majority of clinical trials in Belgium with a CTA are industry-driven (Figure 2). A slight increase in industry-sponsored clinical trials is seen until 2008, followed by a slight decline.

The proportion of clinical trials reported as non-commercial depends on the database used. Among the CTAs received by the competent authorities, the number of non-commercial trials tends to be fairly small as the focus is on medicinal products. Higher proportions for non-commercial trials are found for example in the WHO trial registry (http://www.who.int/ictrp/en/). Also the German Registry for Clinical Trials (www.drks.de) lists 2357 out of a total of 3145 entries as non-commercial clinical trials. Many non-commercial trials are needed and are conducted in areas not owned by industry. The broad range of non-commercial trials funded by the healthcare system in the UK (NIHR) illustrates this point (Figure 3).

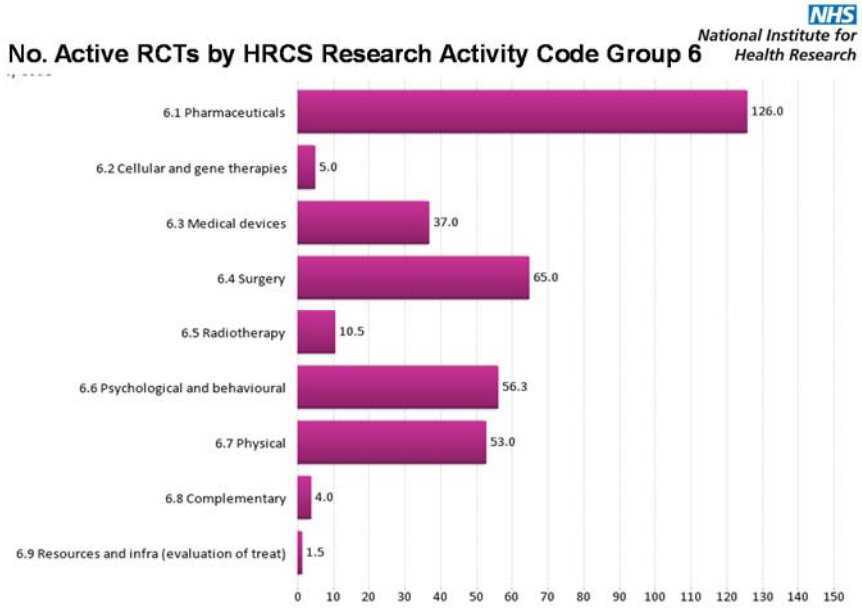
Many of the investigator-driven clinical trials (IDCT) can be categorised as non-commercial. For such trials the investigator is also the study sponsor. Sometimes the discrimination of non-commercial from commercial clinical trials is not straightforward, as illustrated by discussions about access to a reduced fee for review of non-commercial trials by Ethics Committee's or Competent Authorities, as is the case in Germany.[12] Sometimes the trial is in part financed by industry and in part with public money (Public Private Partnerships). For example, in Germany, over half of the non-commercial trials are co-financed by industry.[12] An important criterion in this regard is the purpose of the trial: has the sponsor a commercial objective or not. This is typically detailed in the contract section on ownership and public disclosure, whereby the sponsor/company wants to control the publication of the trial results in one way or another. A document prepared by the Leuven University Hospital provides some clarification with regard to the definition of a non-commercial clinical trial in the Belgian context.[13] This document specifies that **ownership of the data is regarded as the main criterion to distinguish "Investigator-Initiated" from "Industry-Initiated" clinical trials**.

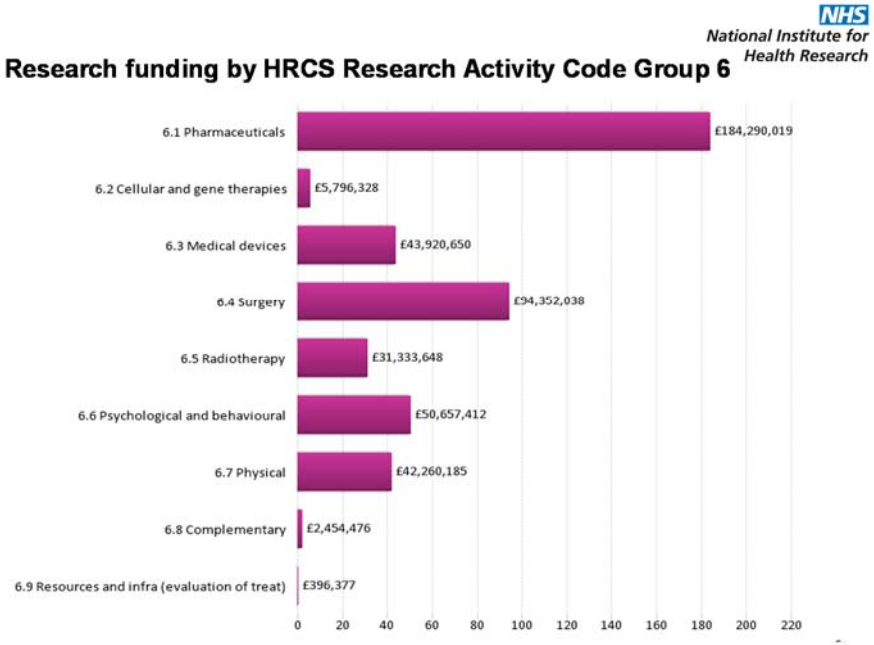
Figure 2 – Investigator versus industry-driven clinical trials with medicinal products in Belgium



Source: FAGG-AFMPS

Figure 3 – NIHR-funded number of active trials and budget by domain in the UK (2014)

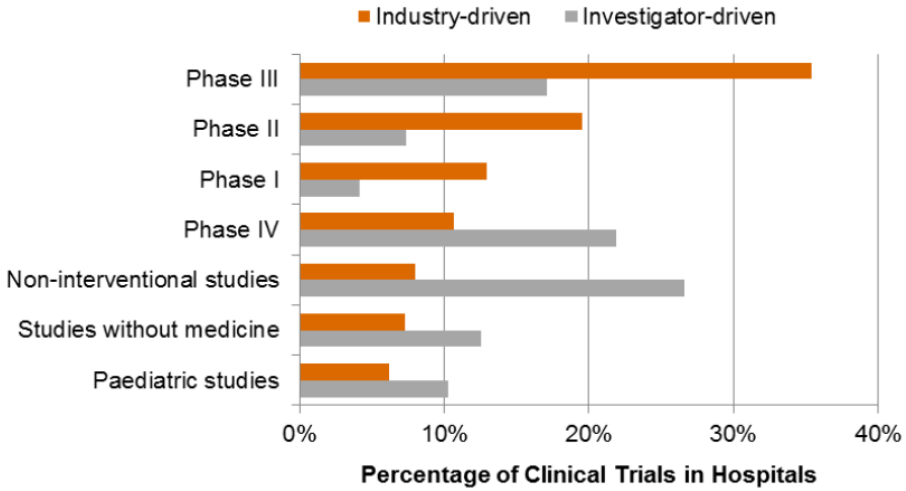




Left: the x-axis shows the number of active trials, a trial concerning two types of interventions was attributed for half in each category.
Right: the x-axis shows the funding by research activity in million pounds.

Based on an online survey, conducted by the PwC company in 2012 amongst 53 stakeholders involved in clinical studies, industry-driven trials in Belgian hospitals were mostly Phase III, II and I, while investigator-driven (non-commercial) trials were mainly non-interventional studies and Phase IV (Figure 4). Belgian hospitals responding to their survey reported to have recruited 8 times more patients for exploratory industry-driven trials conducted in their hospitals than for exploratory investigator-driven trials. For confirmatory trials, the difference is even higher: 20 times more patients were recruited in industry-sponsored trials compared with investigator-driven trials.[14]

Figure 4 – Clinical trials with CTA in Belgium



Source: 2012 PwC report[14]

1.2 Scope

The scope of this report is on non-commercial clinical trials that are likely to have an immediate impact on medical practice and policy decision making (Table 1). Therefore the focus is on the **confirmatory and pragmatic type of trials** in particular, that are **not performed by industry** because they have no interest in performing these trials. The **focus is primarily on RCTs** and this reflects "*the wide consensus that they provide one of the best methods of filtering out beneficial interventions from those that have no important effects or are positively harmful, and identifying those treatments that are likely to be most cost-effective.*"[15]

Table 1 provides an overview of differences and similarities between the in scope practice-oriented non-commercial clinical trials and commercial or other clinical trials. Other designs of confirmatory trials should also be considered as long as the trial is likely to provide a clear answer for decision makers. Patient registries are not the first focus of this report as these non-interventional studies are often not able to answer efficacy questions. In scope are also prospective registry based randomized clinical trials, a concept reported by a Swedish team.[16] Topics such as coverage with evidence development and adaptive licensing[17] are not the focus of this report.

Within the scope of these confirmatory non-commercial clinical trials, we include national and international trials, trials with medicinal products, medical devices and other interventions, trials with products used within the approved label as well as off-label use supported by a sufficient level of evidence. Out of scope are investments in basic research, early stage proof-of-concept and translational research studies and epidemiologic research.

1.3 Research questions

This report tries to answer the following research questions:

- 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 requirement to perform such trials (chapters 4 and 5)
- Which steps could or should be taken to succesfully realise such trials, learning from the experience abroad (chapters 6 and 7).

1.4 Methodology

In August 2014, a search was performed in PubMed (Appendix 2). Reports with examples of research impact based on publicly funded trials and on the international and local situation with respect to (non-commercial) clinical trials were identified in the grey literature (Google search using the terms "non-commercial trial" or "public funding" and "trial") and using contacts in the field (e.g. ECRIN members). The results of this search strategy were compared with the identified literature received by external experts and found in the grey literature and through searching references of relevant articles. The initial search seemed to be not very sensitive and not very specific. In October 2014, PubMed was used to find out how relevant articles were indexed. 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.*"[18] These researchers experienced several difficulties in planning their search strategy, all caused by the heterogeneity of definition and the lack of a standard terminology to describe "research impact".[18] We had similar problems to identify relevant literature on "public funding". Furthermore, as mentioned above, the definition of a non-commercial clinical trial is not straightforward.

Other researchers studying this area also noticed that a large part of the literature in this field would be 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 through the traditional biomedical databases (i.e. Medline) and many relevant studies were retrieved in the "grey literature" (i.e. funding agency's reports).[18] Therefore, we decided to search the websites of institutions being involved in public funding of trials. This list is based on information mentioned in a recent published BMJ article[19] and complemented with suggestions from our external experts (see colophon). Eventually, the following websites were visited:

- Clinical and Translational Science Award program (US): https://www.ctsacentral.org
- James Lind Alliance (UK): www.lindalliance.org
- National Institute for Health Research (NIHR, UK): www.nets.nihr.ac.uk
- National Institutes of Health (NIH, US): www.nih.gov
- Patient-Centered Outcomes Research Institute (US): http://www.pcori.org/
- The health maintenance organisation research Network (US): http://www.hmoresearchnetwork.org
- The National Health Service (NHS, UK): www.nhs.uk
- ZonMW (The Netherlands Organisation for Health Research and Development): www.zonmw.nl

The citations of identified reports were screened to find other relevant references.

Finally, we had several meetings with experts from different stakeholders (see colophon). At the first meeting, we decided to list some examples where public funding of clinical trials would have an added value. In addition to the examples identified in the literature, this gives the research team extra inspiration on opportunities, hurdles and other important elements based on the knowledge and experience of the involved stakeholders. An excel file was distributed to these external experts asking for a.o. the research question, a short description or some background information, reasons why industry is not going to perform the trial, and possible hurdles.

Key Points

- **There are important research questions of interest to society that will never be answered by industry-sponsored trials as industry has no commercial interest to perform these trials.**
- **Publicly funded, randomized, practice-oriented clinical trials are needed to answer the research questions not answered by commercial trials.**
- **The participation in clinical trials is likely to create a culture of evidence based clinical practice, with all the benefits that follow on from that.**
- **The focus of this report is on practice-oriented clinical trials that have a direct impact on patient care or health care decision making.**
- **The number of publications investigating this field is rather limited.**

2 EXAMPLES OF RESEARCH IMPACT

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.[20] Few studies have systematically analysed the impact of a publicly funded clinical research program on medical care, public health, and health care costs. Different types of impact can be identified. These costs and benefits can be distinguished in different categories, whether they are direct or indirect (Table 2).

On the side of the **direct costs** there are the financial resources made available to perform the research. Both investment costs to start the research and operating expenses to run the study should be included. While the direct costs are probably relatively easy to measure, other indirect cost items may pose more difficulties. For example, there might be **indirect costs** for setting up the research. New methods that necessitate reorganisation can temporarily lower productivity.[20] Unreported work and input on the part of doctors and clinical staff should also be included.[20] Clinical trial work in part overlaps with other working activities of performing and documenting clinical routine care. As mentioned in the study of Roback, it is difficult to find any data regarding such costs, but one study of input in clinical trials in the USA[21] indicates that these costs are significant, and that the research work is only partly compensated.[20] The addition of new technologies might also entail increased on-the-job stress, might heighten the risk of improper treatment, and may lead to higher maintenance and administrative costs.[22] Furthermore, there are also overhead costs for these research activities to select, follow-up, report, etc.. In case studies of research impact, these costs are usually not included, while costs of running a research program should not be underestimated. 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 research results.[23]

These direct and indirect costs are to be compared with the benefits achieved by performing research. **Direct benefits** include improved health which should be reflected in patient-relevant outcomes, the most important ones being improved survival and/or quality of life (see Table 2).[20] Research can eventually also lead to less or more expensive diagnosis, treatments, have an impact on the costs for treating side-effects (e.g. avoided hospitalizations), etc. **Indirect benefits** might include non-medical social effects such as increased productivity, greater competitiveness and economic growth.[20] Roback mentions two different types of production gains: first, the avoidance of production losses as the result of a healthier population[24, 25] and second, an increased production in the form of higher employment in various sectors of the economy, including healthcare and research.[26, 27] There is also the general knowledge gain, however, quantifications for this (e.g. bibliometrics) might not relate well to the ultimate goal of performing medical research, that is, improving health outcomes.[28] Of course, gaining knowledge on general principles of evidence-based medicine (EBM) and indirectly stimulating its application will also have a positive impact on improving health outcomes. Finally, capacity building,[18] reflected in e.g. an increased number of researchers involved in trials, an improved research infrastructure and coordination of activities, etc. is also part of the indirect benefits.

Table 2 – Direct and indirect costs and benefits of (publicly funded) research

Direct costs	Direct benefits (or loss)
Research funding (both investment costs to start the research and costs to perform the study)	Improved health: lower mortality (life-years gained) and/or higher quality of life (quality-adjusted life-years gained Lower (or higher) costs for diagnosis, treatment, less (or more) side-effects, etc. More efficient health care
Indirect costs	**Indirect benefits**
Production losses	Impact on productivity and gross domestic product
Voluntary efforts	Expanded knowledge base
Overhead costs for running the research program	Capacity building
Implementation costs	Increased awareness of evidence-based medicine (EBM)
Others	Others

Source: Based on Roback et al., 2011.[20]

In general, a distinction can be made between **two types of analyses studying the benefits of publicly funded research**: 1) studies which examine the impact of a single RCT in which researchers try to link the financed project and consequences for society; and 2) evaluations of funds spent in a specific research program and their impact. In what follows, we provide an overview of research impact of both individual cases (2.1) and research programs. Note that some research programs, e.g. in Australia and the UK, are much broader than practice-oriented clinical trials and include more basic research. First, we just provide the information and results as stated by the authors. Afterwards, we provide some reflections on these research results (2.3).

Not discussed in this overview are potential economic benefits from setting up a clinical research infrastructure, i.e. a network of well-trained clinical trial centres. It is clear that such a professional network will also attract and may also support commercial clinical trials, as speed of recruitment and quality aspects are key elements in any clinical trial.

2.1 Individual cases

Economic return from the Women's Health Initiative estrogen plus progestin clinical trial: a modeling study[29]

"*The findings of the Women's Health Initiative (WHI) estrogen plus progestin (E+P) trial led to a substantial reduction in use of combined hormone therapy (cHT) among postmenopausal women in the United States. At a cost of approximately $260 million (in 2012 U.S. dollars, 1$=0,914EUR, 28 April 2015), the WHI E+P trial was one of the most expensive studies ever funded by the NIH.*

In 2002, approximately 5.5 million U.S. women used cHT, largely based on clinical trial evidence of vasomotor symptom and osteoporosis benefit and observational evidence that suggested reduced cardiovascular disease risk.[30-33] In July 2002, publication of the E+P trial results provided randomized, controlled trial evidence of increased cardiovascular disease, venous thromboembolism, and breast cancer risk among cHT users.[34] After publication of these results, cHT use in the United States decreased by approximately 50% and continued to decline at 5% to 10% annually as the U.S. Food and Drug Administration and other groups endorsed the study conclusions.[30, 31, 35-39] Although other studies influenced this shift in use, the timing and magnitude of the shift suggests that most is attributable to the WHI E+P trial.[30, 31, 36, 37, 40] It was assumed that 75% of the decline in cHT use (and thus value) was attributable to the WHI E+P trial in the base case.

The researchers compared disease incidence, survival, health-related quality of life, and direct medical expenditure outcomes between a "WHI" scenario with observed cHT use and a "no-WHI" scenario. The WHI scenario resulted in 4.3 million fewer cHT users, 126 000 fewer breast cancer cases, 76 000 fewer cardiovascular disease cases, 263 000 more fractures, 145 000 more quality-adjusted life-years, and expenditure savings of $35.2 billion. The corresponding net economic return of the trial was $37.1 billion ($140 per dollar invested in the trial) at a willingness-to-pay level of $100 000 per quality-adjusted life-year. Of the $37.1 billion in net economic return attributable to the WHI E+P trial, $26.4 billion was attributable to medical expenditure savings. These savings were driven by 25 million fewer person-years of cHT use, as well as cost savings from avoided diseases. The remaining $10.7 billion represents the value of additional quality-adjusted life expectancy resulting from lower incidence of breast cancer, cardiovascular disease, and venous thromboembolism.

The authors concluded that the WHI E+P trial made high-value use of public funds with a substantial return on investment. These results can contribute to discussions about the role of public funding for large, prospective trials with high potential for public health effects."[29]

Funding First: Exceptional Returns, The Economic Value of America's Investment in Medical Research[5]

This US study mentions the following: "*Equally impressive, but still measured using conventional practices, are the cost savings of diagnostic and treatment procedures for particular diseases. We know, for example, that the development of lithium for the treatment of manic depressive illness results in health cost savings of more than $9 billion annually; that preventing hip fractures in postmenopausal women at risk for osteoporosis saves $333 million annually; and that a 17-year program which invested only $56 million in research on testicular cancer has led to a 91% cure rate and an annual savings of $166 million.*"

Is technological change in medicine worth it?[41]

"*Medical technology is valuable if the benefits of medical advances exceed the costs. We analyze technological change in five conditions to determine if this is so. In four of the conditions – heart attacks, low-birthweight infants, depression, and cataracts – the estimated benefit of technological change is much greater than the cost. In the fifth condition, breast cancer, costs and benefits are about of equal magnitude. We conclude that medical spending as a whole is worth the increased cost of care. This has many implications for public policy.*"

The return on investment in health care: from 1980 to 2000[42]

"*We calculated that each additional dollar spent on overall health-care services produced health gains valued at $1.55 to $1.94 under our base case assumptions. The return on health gains associated with treatment for heart attack, stroke, type 2 diabetes, and breast cancer were $1.10, $1.49, $1.55, and $4.80, respectively, for every additional dollar spent by Medicare. The ROI for specific treatment innovations ranged from both savings in treatment costs and gains in health to gains in health valued at $1.12 to $38.00 for every additional dollar spent.*

Conclusion: The value of improved health in the US population in 2000 compared with 1980 significantly outweighs the additional health-care expenditures in 2000 compared with 1980."

2.2 Research programs

Medical Research: What's it worth? (UK)[43, 44]

"*In this cancer-focused study, the UK's leading funders of cancer research were identified by examining the National Cancer Research Institute's Cancer Research Database. The eleven principal funders used in the analysis account for over 95% of cancer research spend and include government, research councils and medical research charities.[44]*

Estimates of the numbers of individuals affected, and patient costs and effects, were obtained from published studies for the following areas: smoking prevention/cessation; cervical, breast and bowel cancer screening; and treatment of breast, bowel and prostate cancer which together account for over 70% of the additional life years gained from improvements in 5 year survival rates for cancer patients over the study period.[44] For the selected interventions, the researchers assembled the lifetime monetised quality-adjusted life years (QALYs) gained, and the net lifetime costs to the NHS of delivering those QALYs. For the monetary value of QALYs, the authors used the mid-point of the normal criteria for acceptance of interventions by the National Institute for Health and Care Excellence (£20-30,000 per person per year, 1£=1.186EUR, 28 April 2015).[44]

Expressed in 2011/12 prices, total expenditure on cancer-related research from 1970 to 2009 was £15 billion. Over the period 1991-2010, the interventions included in the study produced 5.9 million QALYs. Using a value of £25 000 per QALY and allowing for the costs of delivery, this resulted in health benefits equivalent to £124 billion. Of the interventions considered between 1991 and 2010, smoking reduction accounted for around 65% of the net monetary benefit to the UK, followed by cervical screening (24%) and breast cancer treatments (10%). The study estimates that the rate of return from public and charitable funding in this area between 1970 and 2009 is 10%. This greatly exceeds the UK Government's minimum threshold return of 3.5%[45] for its own investments.[44]

If this is brought together with the current best estimates of 'spillover' gains[46] – the indirect impact of public and charitable research on the wider economy, such as leveraging private sector R&D activity – the total economic return is estimated to be in the region of 40%. Each pound invested in cancer-related research by the taxpayer and charities returns around 40 pence to the UK every year. This is consistent with the findings of the 2008 What's it worth? study,[46] which estimated that the annual rate of return for cardiovascular disease research and mental health research was 39% and 37% respectively.[44]

The study provides evidence to support this continued investment in science by demonstrating how funding for cancer research delivers health gains for patients and benefits to the UK economy."[44]

Effect of a US National Institutes of Health programme of clinical trials on public health and costs[47]

"*In this study, all phase III randomised trials funded by the US National Institute of Neurological Disorders and Stroke (NINDS) between 1977 and 2000, were included.*

28 trials with a total cost of $335 million were included. The effects of a trial could be assessed if information on use and the intervention's effect on total costs and savings or quality of life were available. Such information was available for eight trials. Six trials (21%) resulted in measurable improvements in health, and four (14%) resulted in cost savings to society. At 10 years, the programme of trials resulted in an estimated additional 470 000 QALYs at a total cost of $3.6 billion (including costs of all trials and additional health-care and other expenditures). Valuing a QALY at per-head gross domestic product ($40 310),[48] the projected net benefit to society at 10-years was $15.2 billion. 95% CIs did not include a net loss at 10 years.

Although the trials have led to increased expenditures on health, the resultant health benefits have a much greater value than these costs."

Cost savings through research and innovation in healthcare (The Netherlands)[49]

"*In 2000, the Dutch organisation for health research and development ZonMW started with a so called "efficiency research" program. The program enabled a lot of medical research and innovations in healthcare. The return of this program was calculated by comparing the costs of this program (2001 - 2015) with the expected cost savings in health care arising from the subsidized studies within the program. In a conservative scenario, the program shows a very high (minimum) return of 327%. The authors conclude that this program pays for itself more than 3 times.*"[49]

Exceptional Returns: the value of investing in health R&D in Australia (2003)[50]

"*Investment in health R&D surpasses every other source of rising living standards in our time. Our 8-year (11.5%) gain in life expectancy as well as improved wellness over 1960-99 were worth $5.4 trillion to Australians – a figure more than 8 times larger than the entire national output last year. The gains associated with the prevention and treatment of cardiovascular disease alone totalled $1.7 trillion.*

While it is not always entirely possible to pin down cause and effect, the likely returns from health R&D are so extraordinarily high that the payoff from any strategic portfolio of investments is enormous. This paper estimates that half the historical gains in healthspan are attributable to global health R&D – as opposed to public health awareness, promotion and prevention programs and other factors. 2.5% – Australia's share of global R&D activity – is assumed attributable directly to Australian R&D. These assumptions lead to the conclusions that, historically, annual rates of return to Australian health R&D were up to $5 for every $1 spent on R&D.

This report has shown that every dollar invested in this challenge in Australia has historically been recouped as highly valued healthspan, even in the worst case scenario, and in most cases, many times over. The findings of this paper should change the way that Australian policy makers view health spending, in particular investments in health R&D. The conclusion for the future must be that Australian health R&D represents an exceptional investment, with exceptional returns."

Exceptional Returns: the value of investing in health R&D in Australia II (2008)[51]

"*The ROI is around 117%, which means that a dollar invested in Australian health R&D is estimated to return an average net health benefit valued at $1.17. To put it another way, the B/C ratio is 2.17, which means that a dollar invested in Australian health R&D returns $2.17 in health benefits on average.*

The benefit/cost (B/C) ratio of 2.17 (90%CI 1.16 to 3.34, min 0.57, max 6.01) compares with 2.4 (min 1.0, max 5.0) in the 2003 analysis. The slight decline largely reflects the increased expenditures on health R&D in the interim together with lower expected future gains as the disability burden of the chronic diseases of ageing are projected to increase in coming decades, despite the contribution of R&D."

Extrapolated returns on investment in NHMRC medical research (Australia)[52]

In this study, the link between investment in National Health and Medical Research Council (NHMRC) funded medical research and financial and health returns on that investment was studied. Several major assumptions were made. One of these assumptions was that "*the time lag between the mid-point of the R&D expenditure and the mid-point of the wellbeing gains, on average, was estimated as 40 years.*" This is of course much too long for phase III RCTs which are the scope of this report.

The authors calculated that "*the undiscounted value of the health expenditure saving was estimated as $25.9 billion for the period 2011-12 to 2062-63, which in net present value (NPV) terms (with a 7% discount rate) was estimated as $1.0 billion, since the benefits only accrue in the model from 2052-53. This means that for every dollar spent on additional NHRMC R&D, seven cents would be returned in health expenditure savings in the future. The benefit-cost ratio would naturally be much higher (and above unity) if other financial savings and the wellbeing gains were included.*"

Evaluation of Health Research: Measuring Costs and Socioeconomic Effects (Sweden)[20]

"*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. Information in support of decisions about future allocation of research resources is preferably produced by a combination of general analyses and strategically selected case studies."*[20]

"The paper concludes that positive effect of clinical research benefits excess costs. However, because of vast methodological problems none of the presented research evaluation approaches are sufficient to obtain confident results. The tentative model applied to Swedish health research indicates that the positive effects are predominant, but that the return is in a lower range than the studied literature would imply."[20]

2.3 Some remarks

In general, the above examples are very positive about the return on public investments in R&D and indicate that benefits broadly exceed the research costs.[20] In almost all economic evaluations, assumptions have to be made. Usually, this is as much as possible based on evidence from different sources providing information on treatment effect for both survival and quality of life, adverse events, costs, etc. and uncertainty around estimates is taken into account. However, for the above studies **there is often a lack of reliable resources for several of the most important variables**. All of the above studies have several important weaknesses which makes that results should be interpreted with caution.

2.3.1 Methodological issues

There is no consensus about which of the effects mentioned in Table 2 should be included and how they can/should be valued. Whereas costs of R&D are relatively easy to identify and value, **both identification and valuation of benefits is very difficult** and associated with very large uncertainty. This is a problem that all of the above evaluations have in common. As mentioned in an overview of reviews, "*a shared and comprehensive conceptual framework does not seem to be available yet and its single components (epidemiologic, economic, and social) are often valued differently in different models*".[18]

2.3.2 Bias

The above mentioned studies are very optimistic. However, a review in this field has shown that researchers generally are more interested in the benefits and may ignore some negative effects:[20] "*It is easy to find examples of research based innovations that have yielded manifold returns. Many have tried to demonstrate the importance of research by calculating the value generated through the use of such innovations, while failing to take the research and development costs into account. Furthermore,* ***a pro-innovation bias is readily evident in the studied literature****. The authors have accepted in advance that research and innovation are profitable, and have then either simply described the positive effects, or described the costs and effects for a number of successful medical technologies in relation to older alternatives.*" Furthermore, "*The problem with case studies is that it is difficult to make calculations for a large enough number of different disease conditions to enable us to draw conclusions about the entire healthcare system, and overlapping effects often occur, with the result that the effect is overestimated.*" Economic assessments of technologies with positive conclusions are also more likely to be published,[15] and these individual examples may not be representative for other R&D investments. For example, in the RAND study,[44] there was a clear dominance of smoking cessation in the estimate of the return for both cancer and cardiovascular disease research. The authors mention that it would be beneficial to assess the magnitude of the return in an area where smoking is not a dominant determinant on incidence of disease.[44]

2.3.3 Real-world impact versus projections

The Dutch study mentions that the estimated cost savings are 'potential' cost savings. Two scenarios are applied including 40% or 80% of these potential savings. These **projections may be very different from the real-world impact** and over- or underestimate 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 e.g. by looking at practice guidelines, change in behaviour, reimbursement decisions, etc.

The method in the RAND study to measure the benefits in the area of cardiovascular disease consisted of the following three steps: 1) a review of the published economic evaluations to obtain figures for the QALYs gained per patient from specific patient group/intervention combinations for cardiovascular disease; 2) multiplication of these figures by estimates of the numbers of users of each intervention, adjusted for compliance rates, to give an estimate of the total QALYs gained from each intervention, and 3) multiplication of these estimates with £25 000 per QALY, i.e. the mid-point of NICE's threshold range of £20 000–£30 000 per QALY.[46] Again, both under- and overestimations of outcomes is possible. For several interventions involved in R&D there was for example no robust clinical and cost-effectiveness data.[44] On the other hand, there is also a publication bias for economic evaluations since stakeholders with a major conflict of interest will very probably not be very willing to do an effort to publish evaluations with a negative outcome. It is also not clear in how far the published incremental cost-effectiveness ratios (ICERs) are context specific and if they were critically assessed before they were generalised to other countries or patient groups. **The valuation of the QALYs is also very different**

between studies. While the UK is the only country with an explicit ICER threshold of £20 000–£30 000,[53] other studies often use very different values: e.g. a willingness-to-pay level of $100 000[29] versus $40 310[47] per QALY in two US studies. The Dutch study is conservative and underestimates the benefits by not including a valuation for the health benefits.[49]

2.3.4 Problem of attribution and spillover effect

One of the most determining variables in the above studies is how much of the benefits were attributed to R&D. The US study of Johnston and colleagues[47] for example looks at the costs and public health benefits of all 28 phase III clinical trials supported by the US National Institutes of Health's NINDS between 1977 and 2000. **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.*"[47] In their study, the authors calculated that the benefits from the clinical trials alone ($50 billion) were large enough to cover all the expenses of both basic and clinical research in the research program ($29.5 billion).[47]

Next to the costs and benefits of both basic and clinical research, it is **not clear what the impact is of other variables**: "*The major macroeconomic studies of cardiovascular research assumed that a substantial proportion of gains in lowered morbidity and mortality resulted from new treatments for the immediate aftermath of acute events, such as stroke. They attributed much of the credit to research, but this might not properly take account of other variables, including the effects of improved prosperity, lifestyle, and diet in delaying the onset of disease. Those benefits cannot necessarily be considered as successes for medical research.*"[15] One of the Australian evaluations is a nice example showing the multiplicative effect (and uncertainty/arbitrariness) of these assumptions:[52] 1) 50% of gains were attributed to R&D rather than other causes (such as improvements in environmental factors (e.g. sanitation) or public policies (e.g. health promotion); 2) 3.14% of R&D gains were attributed to Australian R&D rather than overseas R&D; and 3) 25.04% were attributable to NHMRC R&D rather than other Australian R&D.

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 e.g. involving more physicians in research which might have a positive influence on the evidence-based medicine attitude and result in more appropriate use of interventions, results of a public funded trial might be the basis to set up a similar trial in other indications, have a positive impact on the quality of future (non-)private trials, etc. The RAND publication defines it as follows:[46] "*The total social rate of return to an investment comprises the return to the organisation making the investment, the return to other organisations in the same sector (e.g. medical) and the return to all other parts of the economy. The last two are referred to in economic literature as 'spillovers', but that is not to imply that they are accidental. On the contrary, 'spillovers' are often an explicit objective of investment in research.*" The authors also mention that the literature is clear that the spillovers exist, but less clear about the relative importance of different transmission mechanisms. Nevertheless, the largest part of the benefits in the RAND study comes from the spillover effect: health benefits were equivalent to around 10 pence plus a further 30 pence which was the best estimate of the 'spillover' effect from research to the wider economy.[44] While this might be an overestimation, other studies do not take this effect into account, which might result in an underestimation of the benefits of publicly funded research.

2.3.5 Conclusion on return on investment

The benefits of research activities are difficult to measure. We agree with the conclusions of a previous review that "*care must be taken in interpreting economic evaluation studies on health research. **Be it positive or negative, these results may be the effect of various methodology flaws that over-represent or under-represent the true effects of research**, and should be taken into account while interpreting their results.*"[23]

Several studies show that the benefits of publicly funded research might largely exceed the costs. "*Large public investments directed toward trials that address questions with high clinical relevance and public health influence may yield considerable returns.*"[29] Amongst others, a good selection of research topics, the willingness of policy makers to take measures based on provided evidence, appropriate research infrastructure,

etc. will determine the success of such investments. We come back to these and other elements in our discussion.

Key Points

- **Compared with assessments of individual trials, evaluations of the impact of a complete clinical trials program provide a more realistic view of costs and benefits.**
- **Costs of trials are more easy to calculate than the benefits where there are e.g. problems of attribution or difficulties to measure spillover effects.**
- **The number of publications investigating this field is rather limited.**
- **The return on investment depends a.o. on how well the research topics were selected, the research infrastructure, and the willingness to implement the results of the trial.**

3 WHY DO WE NEED NON-COMMERCIAL CLINICAL TRIALS

Non-commercial clinical trials can be conducted to answer questions of relevance for the routine clinical practice, not answered by the company-sponsored trials. This independent approach forms a critical element of medical research and includes the assessment and evaluation of the safety, efficacy and effectiveness and health-economic aspects of both established and novel interventions within the real conditions of the health systems. Several reasons can be distinguished for the conduct of non-commercial clinical trials.[12]

This does not mean that industry cannot be consulted before the start of publicly funded trials. A **non-binding consultation of industry can be of use** for specific trials in order to make use of their expertise in specific research fields. This should be performed in a way that does not jeopardise the independence of the research group conducting the trial.

The focus of this report is on pragmatic clinical trials with a direct impact on clinical practice. In contrast to commercial trials and even some academic trials that focus more on the gain of scientific knowledge, the practice-oriented trials are more likely to be patient-driven. Involvement of patients and working clinicians in the study proposal and selection process is key.

In this part, we provide several reasons why it is important to have such publicly funded trials.

In Appendix 3 we provide several examples of (possible topics for) publicly funded research which provide inspiration and input for this and the next chapter of this report, i.e. reasons for publicly funded clinical trials and hurdles to set up and perform such trials.

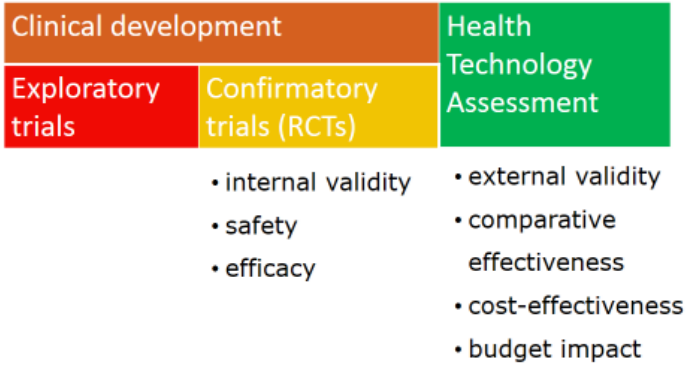
3.1 Comparative effectiveness trials with medicinal products

First, non-commercial trials are essential for the research of comparative effectiveness of different pharmacological treatment options and to identify the real innovations.[54] The current paradigm of drug development includes clinical trials set up in the context of obtaining product marketing authorisation. In Europe many medicines are now evaluated by the European Medicines Agency (EMA) and the trials needed to demonstrate safety and efficacy are sponsored by the company developing the product

(see Figure 5). **In commercial trials, the patient population is often highly selected and the comparator is still often limited to placebo**, despite a trend towards more trials with an active comparator. Important statements in this regard are provided in a draft reflection paper of EMA:[55] "*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.*"

Health technology assessment (HTA) agencies, health care payers, policy makers and care providers have a main interest in comparative effectiveness research. For health care payers, this information is preferably combined with economic evaluations and budget impact evaluations (see Figure 5). As comparative effectiveness research is not a requirement for marketing authorisation and reimbursement, companies are not willing to invest in such comparative trials. 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 such a trial in case the own product proves to be inferior (or not superior) to the existing alternative treatment (which may be less expensive). Companies may even try to influence potential investigators or block the conduct of such a trial using e.g. competitive recruitment at trial sites. Similarly, the evidence generated in a program of coverage with evidence generation may be in conflict with the marketing strategy of the company. **Companies** will be satisfied with receiving the coverage, but **might not be interested in generating further evidence since this might also result in withdrawal of reimbursement or price negotiations** in case this evidence is not favourable. Also related to this issue is the level of compliance of companies with postmarketing commitments. Between 1992 and November, 2008, the FDA approved 90 applications for drugs based on surrogate endpoints through its accelerated approval process. Only two-thirds of the postmarketing studies ordered had been closed. For molecules approved using the traditional approval process only half of the requested 175 postmarketing studies had been closed.[56]

Figure 5 – Clinical development and HTA for drugs



In case a commercially sponsored head-to-head trial is conducted it is more likely the product of the trial sponsor is shown to be superior over the competitor drug.[57] In addition, one needs to carefully exclude bias based on the selection of the comparator dose, the study population or endpoints. This was illustrated for head-to-head comparison studies of second generation antipsychotics: "*Why olanzapine beats risperidone, risperidone beats quetiapine, and quetiapine beats olanzapine: an exploratory analysis of head-to-head comparison studies of second-generation antipsychotics.*"[58] It was concluded that because most of the sources of bias identified in this review were subtle rather than compelling, the clinical usefulness of future trials may benefit from minor modifications to help avoid bias.

Of course, it is also possible that the company-sponsored trial was started before the currently most appropriate comparator became the golden standard. Also in these cases, non-commercial trials might be essential to identify the real added value of interventions.

In addition to the selected patient population in phase 2b/3 clinical trials, it is important to have a more pragmatic approach and to include a broad real-life population in comparative effectiveness trials.

Repurposing trials with old off-patent medicinal products

Therapeutic progress can also be achieved with **good old and often relatively very cheap off-patent drugs** in which the pharmaceutical industry no longer wants to invest. Repurposing is common practice in current pharmaceutical research and development, but is often limited to drugs where patent life remains, new "use" patents are or data exclusivity are possible to support the necessary financial returns. The economic return of repurposing approved drugs, particularly generics, can be insufficient.

In these cases, trials may be of high relevance for policy makers and non-commercial trials are often the only possibility. Repurposing approved drugs for a new indication using publicly funded trials is fraught with significant commercial, regulatory, and reimbursement challenges that go beyond the scope of this report.

From the examples provided in Appendix 3, we learn that there are several categories of head-to-head trials that might need public funding to be performed:

- Two drugs, both used in accordance with their label, e.g. salmeterol versus tiotropium for the treatment of COPD (chronic obstructive pulmonary disease), denosumab versus a specific bisphosphonate in osteoporosis.
- Two drugs, one used within the label and one off-label, e.g. ranibizumab versus off-label use of bevacizumab (Lucentis versus Avastin) in age-related macular degeneration; gabapentine or pregabaline versus off-label use of amitriptyline in neuropathic pain.
- A single drug, comparing the labelled treatment duration with a much shorter treatment duration in combination with an inversed treatment order, e.g. E2198, FINHER and SOLD trials of trastuzumab in early breast cancer.
- Rheumatoid arthritis (RA) partial responders to methotrexate (MTX), randomised to MTX plus etanercept or MTX plus sulfasalazine plus hydroxychloroquine.
- Natural vitamin D treatment in the treatment of secondary hyperparathyroidism in patients with severe renal failure.
- Direct comparisons between a registered drug and non-drug alternatives, e.g. antidiabetic drug versus lifestyle intervention in type 2 diabetes.
- Other examples provided by BCFI (Appendix 3.2).

3.2 Trials with medicinal products in children and in rare diseases

Second, trials in children or treatments for rare disease have long been neglected. We lack well-designed trials for drugs evaluated in these indications. "*The market-driven pharmaceutical industry does not pursue research and development for a number of diseases because of the **small number of patients involved** (as is the case with orphan diseases such as cystic fibrosis) and the **insufficient profitability of the treatments** (e.g. paediatric therapies, treatments for pathologies in developing countries), or because the objective is simply **to improve existing procedures and prescriptions** (finding the optimal drug combination or timing, for instance).*"[59] Specific regulations and incentives have now been created to stimulate such clinical developments by the pharmaceutical industry.

Examples in this category showing the need of government support to run such trials are the following:

- EORTC trials (Appendix 3.3):
  - CREATE: Cross-tumoral Phase 2 clinical trial exploring crizotinib in patients with advanced tumors induced by causal alterations of ALK and/or MET.
  - Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma.

Also the SAFE-PEDRUG trial initiative to improve clinical research in children can be mentioned here (Appendix 3.6.3).

In addition, also women of childbearing age and elderly may be underrepresented in clinical trial programmes conducted for obtaining marketing authorisation.

3.3 Non-commercial trials to counterbalance possible publication bias

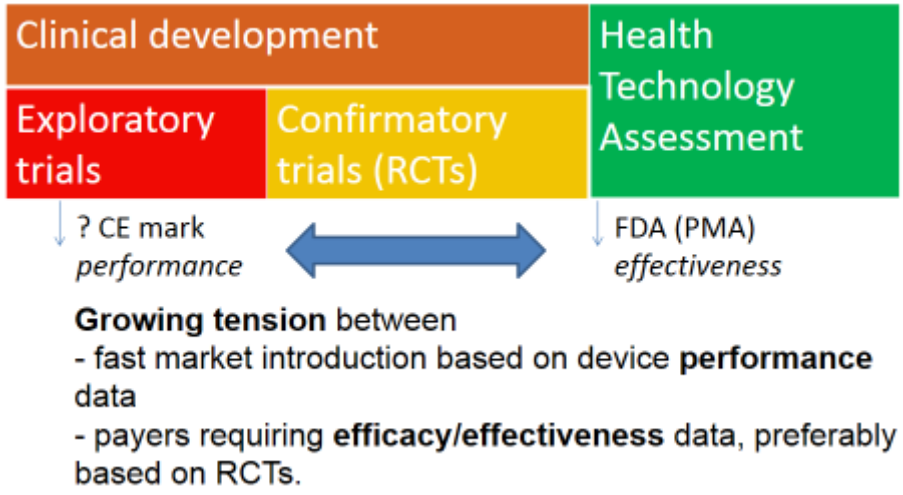
Over the years there has been an increasing pressure from the public at large to make publicly available the results of all trials (http://www.alltrials.net/). Also WHO supports this statement (http://www.who.int/ictrp/results/reporting/en). Awaiting full transparency in terms of trial registration and publication,[60] non-commercial trials are still seen as a way to counterbalance any publication bias of commercial clinical trials.[61] EMA has developed a policy on the proactive publication of clinical-trial data,[62] which came into effect in 2015 (www.ema.europa.eu). However, practice will have to show in how far this new policy provides a good solution to the problem of publication bias. In addition, as detailed under 3.1, the patient selection criteria, the choice of the comparator and its dose may be more subtle forms of bias, that ideally should be identified and remediated during the regulatory and ethics committee review.

It is the opinion of the authors that **public funding of trials is a very expensive way to counterbalance possible publication bias**. To solve this bias it might be more efficient to focus the efforts on two other aspects: 1) the **timely registration of all trials**, i.e. before the trial starts; and 2) the **timely publication of trial results** or reasons why the trial was prematurely terminated. Demanding full information before taking a reimbursement decision might be an option. The BMJ article "drug studies: a tale of hide and seek"[63] from the German HTA institute IQWiG (Institute for Quality and Efficiency in Health Care) illustrates this: "*IQWiG requests manufacturers of drugs under assessment to sign a voluntary agreement requiring submission of a list of all sponsored published and unpublished trials. … Pfizer, although providing a list of published trials and European submission documents, did not submit a complete list of unpublished trials as requested by IQWiG. … IQWiG therefore issued the preliminary conclusion that because of the high risk of publication bias, no meaningful assessment of reboxetine was possible and thus no benefit of the drug could be proved.*[64-66] *… Pfizer then decided to provide most of the missing data. The subsequent assessment showed that, overall, reboxetine had no benefit.*[67] *… An additional analysis of published versus both published and unpublished evidence shows that published evidence overestimates the benefit of reboxetine, while underestimating harm.*"[63] In other words, there are more efficient approaches available than setting up government-funded trials to solve the problem of publication bias. None of the above-mentioned examples fall within this category.

3.4 Trials with medical devices

Fourth, non-commercial clinical trials may be necessary for medical devices. Compared with medicinal products, the uncertainty about efficacy and safety of medical devices is greater when they are introduced on the European market, as for devices only the performance (a non-defined term) is assessed in the pre-market phase (Figure 6).[68] Also specific methodological issues of device trials need further study and standardization.[69]

Figure 6 – Clinical development and HTA for innovative high-risk medical devices



CE: Conformité Européenne; FDA: The US Food and Drug Administration; PMA: Premarket approval; RCTs: randomized controlled trials.

In the case of medical devices, the solution may not be expected from government-funded trials since it is not desirable that government takes over all the financial risks of performing research for new high-risk devices that enter the market if industry does not provide any evidence on their efficacy.

This observation helps to explain why in some domains of healthcare only few prospectively designed trials or RCTs are conducted. For example, an analysis of published orthopaedic studies was reported in 2003.[70] Only 21% of published studies were prospective, 3.5% were randomized, and 10.5% stated an experimental hypothesis.[70] The same analysis found that commercial funding was significantly associated with a positive outcome; 78.9% of commercially funded studies concluded with a positive outcome, compared with 63.3% of the non-commercial studies.[70]

However, **there may be situations whereby a comparative effectiveness trial of two medical devices or a medical device intervention versus a surgical or pharmaceutical intervention is needed**. The EVAR trial, comparing endovascular aneurysm repair versus open repair in patients with abdominal aortic aneurysm is an example of such a public funded trial (Appendix 3.6.2).

3.5 Trials on diagnostics and screening

Fifth, the field of diagnostics, including in vitro diagnostics (IVD), is very broad. In comparison with therapeutic interventions, evidence generation is less developed. Diagnostics are also important in screening programs, for example large RCTs define the role of HPV tests for cervical cancer screening (KCE report 238[71]) or PSA (KCE report 31[72]) for prostate cancer screening. From a public health perspective, 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), one was able to avoid having a prostate cancer screening programme in the UK for the past 20 years.

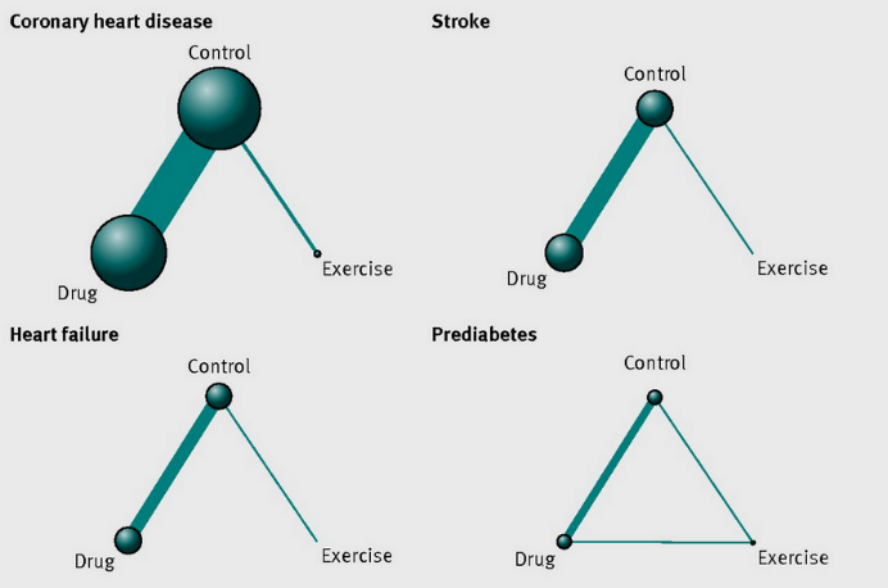
One field of growing importance is the role of the companion diagnostic to realise the promise of targeted therapy. In a separate KCE report we studied the impact of changes in test accuracy (i.e. diagnostic sensitivity and specificity) on the economic value of test-intervention combinations.[73] There is a **risk that tests used in clinical routine might be less accurate as compared with the centralized tests of the confirmatory RCTs used for the evaluation of the cost-effectiveness of the drug during the reimbursement procedure**. Many EU countries including Belgium still lack an integrated reimbursement review of the drug and the companion diagnostic. 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.

The example in Appendix 3.6.3 of improving the participation in cervical cancer screening falls within this category.

3.6 Trials in medical areas not owned by private companies

Sixth, non-commercial clinical trials are essential to advance the field of surgical interventions, diagnostic/imaging techniques, radiation therapy, psychotherapy, lifestyle interventions or prevention, **areas traditionally not 'owned' by private companies**. This includes head to head comparative effectiveness trials between two completely different types of interventions. As illustrated in a network of available comparisons in Figure 7, there is a need for more direct comparisons between exercise versus drug interventions in coronary heart disease, stroke, heart failure, and prediabetes.[74]

Figure 7 – Network of available comparisons between exercise and all drug interventions in coronary heart disease, stroke, heart failure, and prediabetes.



Source: Naci et al., BMJ, 2013[74]
Size of node is proportional to number of trial participants, and thickness of line connecting nodes is proportional to number of participants randomised in trials directly comparing the two treatments.

Several examples in Appendix 3 fall within this category:

- The treatment of diabetic foot ulcers with hyperbaric oxygen (HBOT) versus standard therapy.
- Reduction in type 2 diabetes with lifestyle interventions.
- Comparison of bypass versus angioplasty in severe ischaemia of the leg.

Key Points

- **Publicly funded clinical trials are needed to answer research questions that will never be answered by the medical industry:**
  - **Pragmatic comparative effectiveness trials: head to head trials including a broad patient population**
  - **Repurposing trials for old off-patent drugs**
  - **Trials in pediatrics and orphan diseases**
  - **Trials with medical devices**
  - **Trials on diagnostics and screening**
  - **Trials in areas not owned by industry (surgical techniques, psychotherapy, screening, ...)**

4 HURDLES TO PERFORM PUBLICLY FUNDED RCTs

All of the previously mentioned examples have in common that industry has no financial interest in performing these trials or that investing in this kind of research could even have a negative impact on their own profits. **Not providing sufficient public funding is the most important hurdle to successfully run such trials**. Next to this, there are also several other points of attention.

For investigators, participation to clinical trials is often an opportunity to learn more about new treatment options at an early stage. Patients participating to a trial may have an early access during and after the clinical trial to new treatments that are not yet available to the general population. These patients contribute to the advancement of medicine and healthcare in general. Trial participants may also benefit from a closer follow-up from clinical trial staff, especially the treating doctor.

Sufficient and timely accrual of patients is primordial for the success of a trial. For RCTs, equipoise is a must: **there should be a genuine uncertainty in the expert medical community over whether a treatment will be beneficial**. Surgeons and other health care providers are sometimes very quickly convinced their technique is superior, without justification. In such a situation performing RCTs is clearly impossible. An open mind for performing RCTs and a culture of evidence based practice tend to be linked. Also the **financial incentives/disincentives** of participation in the trial need to be reasonable and balanced for all parties involved. **Testing the feasibility** of the trial with investigators active in the field is therefore an essential step before a protocol, contract and timeline are finalised. The **eligibility criteria need to be realistic** and the **study-specific burden of extra investigations must be reasonable both for patients and investigators**. A systematic literature search and a check of similar research projects are essential. Ideally, there should be a database of planned and ongoing trials that can be consulted. Opening more trial sites while the trial is running can sometimes rescue the study. It is also crucial to take into account that not every patient will agree to participate in the trial and this may even be more relevant if the patients are for example young children.

4.1 Advantages and disadvantages of trial participation

The EORTC sponsored LAMANOMA study comparing conservative local treatment versus mastectomy after induction chemotherapy in locally advanced breast cancer was closed due to insufficient accrual. The total number of patients enrolled over a period of 21 months was only 23, which was completely insufficient to reach the 1210 required patients to be randomised over a period of 5 years.[75] Among the most common answers from a questionnaire to reveal the reasons for this failure where the following: several institutions decided to stand by their own current therapeutic strategy, there was a lack of consensus on participation in a local team, and there was a large proportion of patient refusals.[75]

In an editorial comment reflecting on the reasons why the LAMANOMA study failed the following is mentioned reflecting on patient involvement: "*Many patients may not wish to participate in a clinical experiment.* ***Communication with cancer patients about randomised clinical trials is difficult*** *and poorly trained professionals may deter patients from entering trials.[76] In an assessment performed by Jenkins the main reasons for patient clinical trial participation were: that 'others will benefit' (23.1%); and 'trust in the doctor' (21.1%). The main reason for refusing trial entry was 'worry about randomisation' (19.6%).* ***Trials providing active treatment in every arm had a significantly higher acceptance rate*** *as compared with those with a no treatment option.[77"78]*

The same editorial also reflects on physician involvement: "*The hospitals frequently lack an appreciation for clinical research. … A survey, conducted in Britain among oncologists, identified constraints imposed by the healthcare system as significant impediments for trial participation (lack of time and support, and conflicts between the role of clinician and scientist).[79"78]* Furthermore, "*physicians sometimes have well founded or biased treatment preferences that may reduce the likelihood of offering their patients the chance of participation in a trial.[80-83"78]* At a symposium of the Flemish Academy of Medicine different participants mentioned that colleagues are often interested to participate in a clinical trial, however, their **clinical tasks often come at the first place 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. In a guide to research partnerships for pragmatic clinical trials, Johnson and colleagues formulate it as follows: "*Getting the attention of busy managers is challenging, especially before funding is assured. Researchers approaching healthcare organization managers to propose research embedded in clinical practice should highlight advantages such as the potential for gains in patient outcomes, staff efficiency, or health information technology (IT) improvements, along with congruence with other organization-wide priorities. After getting leadership buy-in, interviewees recommended networking to find people throughout the organization with the knowledge, interest, and authority to contribute to the study, as well as the time to maintain regular contact with researchers. … **Pragmatic trials require that researchers and healthcare system clinicians, senior management, and staff develop the attitudes, skills, resources, and shared vision for close collaboration**.*"[19]

4.2 Competition between trials for inclusion of patients

In the previously mentioned LAMANOMA study, one of the institutions that initially declared to participate mentioned that there was another study in the same population preventing them from including patients for this trial.[75] **Different trials running at the same time within similar indications might compete for the same patients**. This might slow down the progress of trials as was mentioned by some Belgian investigators participating to the non-commercial SOLD trial (trastuzumab short duration in early breast cancer, https://clinicaltrials.gov/ct2/show/NCT00593697).

One should also take into account possible differences in study fees paid to the investigators and the hospital, e.g. of commercial versus non-commercial trials. Hospitals may prefer the better financial arrangements and support of industry-sponsored trials.

4.3 Lack of research infrastructure

Despite the fact that a high number of clinical trials are performed in Belgium, there is a **lack of a well-established and networked research infrastructure** to stimulate an efficient performance of government-funded trials, both at micro, meso and macro levels.

At the hospital micro level, physicians complain about time to participate in trials and also the lack of supporting personnel to e.g. gather data. Nurses who could be involved in this task are already under time pressure. Grants for publicly funded clinical research often only include the financing of the researcher and not for the necessary research infrastructure while hospitals frequently have inadequate infrastructures to support participation in trials: "*American oncologists, interviewed by Somkin,[84] complained about internal health plan resources and identified a critical need for infrastructures to support trials, especially additional support staff and research nurses.*"[78] The same remark was heard at the symposium of the Flemish Academy of Medicine. The indirect costs for research infrastructure could be integrated when funding trials.[85]

At the meso level, there is no well-established national network of experienced centres to perform research in different disease areas. This investment may be a sunk cost in the short term providing advantages for future trials. For example, the SAFE-PEDRUG program in paediatrics can lead to the creation of an interuniversity platform on paediatric drug research including centres of excellence, available to all stakeholders for advice.

At the macro level, a formal participation in international research networks is lacking. For example, Belgium is not (yet) involved in ECRIN (European Clinical Research Infrastructures Network), a European network to conduct non-commercial trials. A link between national centres of excellence and a pan-European infrastructure could facilitate collaboration in international trials and lower the costs to perform trials (see part 7.4).

4.4 Free-rider behaviour or international collaboration

A page on Wikipedia provides a clear definition of the free-rider problem: "*In economics, the free rider problem occurs when those who benefit from resources, goods, or services do not pay for them, which results in either an under-provision of those goods or services, or in an overuse or degradation of a common property resource.[86] … The free rider problem may occur when property rights are not clearly defined and imposed.[87]*"(http://en.wikipedia.org/wiki/Free_rider_problem) In the case of government-funded trials, the danger of free-rider behaviour is real. In other countries like the UK and US, governments already fund such trials and results are published in international journals. Other **governments might clearly benefit from these results without doing many effort themselves** to set up or participate in these trials.

It is inevitable that a relatively small country like Belgium would have to be a free rider on research conducted elsewhere, as indeed all countries are to some extent. However, Belgium can undoubtedly contribute to research partly by participating in international multicentre studies and occasionally as the leader of large trials when it could reasonably expect that other countries would support the Belgian effort. Belgium could be a key co-player in many such trials. This is of course one of the aims of ECRIN and is a way for small countries to punch above their weight in clinical research.

International collaboration might be difficult due to differences in standard treatment or organization of care between countries, the previously mentioned lack of participation in a pan-European research infrastructure, etc. Under the condition that there is appropriate funding to set up a large clinical trials, these might be reasons to set up a national trial if sufficient patients in Belgium are eligible for the study. For example, a comparative trial between salmeterol, tiotropium and other drugs for the treatment of COPD could be conducted in Belgium alone because of the large target population (up to 700 000 in Belgium (www.uza.be/behandeling/copd)). Sometimes a local trial will be needed to tackle a research question arising from a local situation. However, in other cases, **international collaboration might be required for several reasons**: the need to include sufficient patients (e.g. for rare diseases), to provide more reliable results due to a larger sample population, to finish the trial earlier and provide the necessary information to the different stakeholders due to a faster accrual, to benefit from joining a trial set up by experienced researchers and taking advantage of their knowledge (e.g. the SOLD trial), etc. The international impact of a large trial conducted in multiple countries may also be higher. The pros and cons of both the national and international approach have to be weighed case by case. Hopefully, the idea of setting up (inter)national trials and creating potential benefits for both the Belgian and foreign health care systems outweighs the free-rider idea.

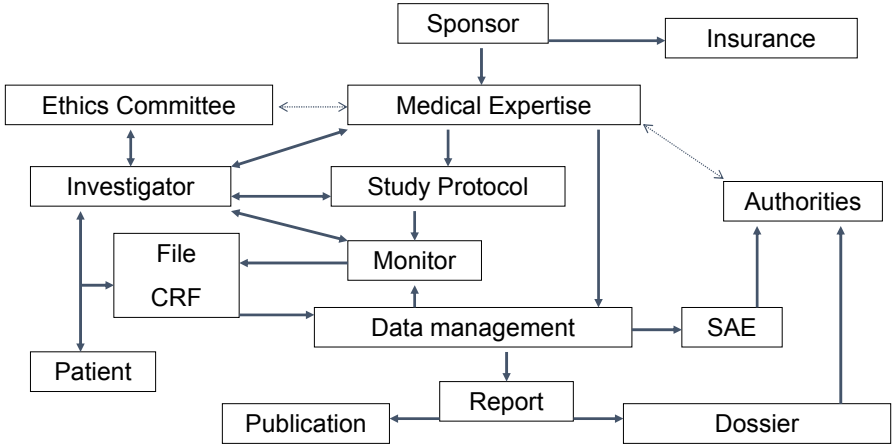
In economic evaluations, effectiveness results are based on the totality of the data collected in the trial. Context-specific cost data can be obtained in each country.

4.5 The design, initiation and conduct of trials takes time, realistic planning needed

Clinical trials, and confirmatory RCTs in particular, require standard operating procedures, specialized personnel and remain quite expensive to perform. They require not only a trial insurance, a study protocol that passes the Ethics Committee(s) and, if applicable, Competent Authority review, patients and investigators, but also a randomisation procedure, study medication (blinded or not), trial data recording on case report forms (CRF), monitoring, analysis and reporting.

The complexity of conducting a clinical trial is illustrated in Figure 8.

Figure 8 – Complexity of a clinical trial



CRF= case report form; SAE= serious adverse event

Compared with pre-market 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 or in off-label indications supported by a sufficient level of evidence ('low-intervention trials').

After the identification of the research question, it may take very long before a trial is set up, conducted and provides answers to these specific research

questions. For example, the recommendation to run a head-to-head trial between a short and long treatment schedule with trastuzumab was already formulated in 2006 by independent researchers in Belgium[88] and the UK.[89] The SOLD trial started inclusion of patients in 2008 (https://clinicaltrials.gov/ct2/show/NCT00593697). It took some more years before Belgian centres were involved in this trial and accrual of sufficient patients took longer than expected. Involvement of Belgian centres in this trial could have been improved if there would have been sufficient financing to support this trial.

The editorial of Dellapasqua also mentions several causes linked to the **time it takes to set up a trial** which **may take much longer than expected**. "*Regulatory Authorities, Ethical Committees, Institutional Review Boards can be unnecessarily bureaucratic leading to further delays in trial initiation. … The research funding entities with their frequently long review processes and complex decision pathways may hold trial start.*"[78] Furthermore, "*the trial itself may be unrealistically planned or have restrictive eligibility criteria. This could then cause a major hindrance in patient accrual, increase trial complexity and costs, and limit the generalisation of results.*[79, 84, 90]"[78] Previously mentioned hurdles are linked to this problem and a.o. an improved research infrastructure with collaboration with experienced research centres might improve both the timing and realistic planning of government-funded trials to answer important research questions.

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. It should be clear that research gaps and questions identified during HTA will most often not be answered within the next year or so. The health care decision makers may therefore need to install transient measures before a final decision is made and trial results are adopted in routine practice.

The design of clinical trials is an active field of research, and new study designs may lower costs and shorten the overall timeline. For example, an innovative 'adaptive trial design' uses patient outcomes to immediately inform treatment assignments for subsequent trial participants. This design is used in the I-SPY 2 trial, a clinical trial for women with newly diagnosed, locally advanced breast cancer to test whether adding investigational drugs to standard chemotherapy is better than standard chemotherapy alone prior to having surgery. The new design allows to test new treatments in half the time, at a fraction of the cost and with significantly fewer participants.(http://ispy2.org/).

There is in Belgium already a lot of **expertise available** at pharma companies, contract research organisations (CROs) and at universities and larger hospitals. If the **collaboration and standardisation between centres can be improved**, it should be possible to conduct also publicly funded trials without unnecessary delay and in a highly professional way.

4.6 Access to and price of the comparator

The focus of this report is on publicly funded research that is necessary to answer important research questions that industry will not try to answer because of 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 this trial. The provision of placebo drugs, appropriate dosage forms and formulations for off-label use or the access to expensive drugs can pose problems.

Out of scope are the publicly funded translational studies which face another set of hurdles, including the challenge to identify a facility that can produce a small batch of clinical grade product under GMP (Good Manufacturing Practices).

4.6.1 Placebo

A correspondence in the Lancet nicely describes this issue: "*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**.*"[6] They describe an anonymous example in which a drug company was approached by researchers with the aim of obtaining placebo medication (in a specialised injection pen for patients with diabetes) for an independently financed trial. After more than 6 months, the company finally agreed to supply placebo devices provided that a.o. the protocol was changed according to their suggestions. In another example, the researchers mention that a drug company charged an extraordinary amount of money for providing a simple placebo tablet, effectively preventing the planned clinical trial from going ahead. They also mention that in another example the drug company plainly refused to deliver the placebo.[6] Having the placebo manufactured elsewhere

can be extremely costly and cumbersome[7] – or even impossible. The authors of this correspondence question "*whether it is acceptable that drug companies with an established placebo-manufacturing process (for their own marketing authorisation trials) can choose whether they wish to sell placebo to independent researchers?*"[6] Of course, if the company supplies the placebo, they legally have some responsibility for the trial. However, commercial considerations are probably more important in the decision making.

4.6.2 Off-label drugs

The optimal **availability of off-label drugs** may also be a hurdle. For example, in the Avastin-Lucentis case, the strength and volume of the formulation which is available for intravenous use in oncology is 100mg in a 4ml vial or 400mg in a 16ml vial.[91] This formulation was not designed for intravitreal use and the volume is clearly a large multiple of the volume and dose needed to treat age dependent macular degeneration. Furthermore, sterility and stability data of the prepared syringes have to be generated.

Asking for collaboration of the original manufacturer is unlikely as the same company also developed Lucentis, which is priced much higher.

4.6.3 Expensive drugs

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 trials cost considerations should also become part of all clinical evaluations in oncology.[92] 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.[92] On the other hand, performing a publicly funded trial comparing the expensive drug with a cheaper treatment alternative may already provide the financial resources to perform the trial and may be less expensive than just reimbursing the expensive industry-marketed alternative (see part 7.3.2).

4.6.4 Governance issues

In case the results of a publicly-funded trial create a new market for the medicine or device that was studied, the question arrises on the "governance" of the consequences of such a trial, with regard to the use of the data for registration/marketing purposes and the possible impact on the pricing of the drug or device.

Key Points

- **Several potential hurdles are to be considered when a publicly funded practice-oriented trial is initiated, a.o.:**
  - **For RCTs, equipoise is a must: there should be a genuine uncertainty in the expert medical community over which one of the treatments compared is more effective.**
  - **Set up a good communication strategy to all involved stakeholders: researchers, patients, hospital management, etc..**
  - **Provide sufficient financial incentives to get clinical investigators involved in the study.**
  - **Provide sufficient time to clinicians, nurses, etc. to perform the trial.**
  - **Having the support of an efficient research infrastructure at micro, meso and macro level e.g. to be able to set up the trial in due time and/or to start international collaboration.**
  - **The willingness of government to provide public funding for a selection of trials.**
  - **The accessibility to relevant (industry-owned) comparators.**

5 THE FRAMEWORK OF CLINICAL TRIALS

Clinical trials, especially trials with medicinal products, are heavily regulated, not only to protect patients participating in a trial but also to make sure the trials results are valid. These regulations apply both to commercial and non-commercial trials.

5.1 Quality assurance

5.1.1 GCP guidelines and SOPs

The quality assurance of clinical trials with pharmaceuticals is guided by the **Good Clinical Practice as defined by the International Conference on Harmonisation** (ICH-GCP, http://ichgcp.net/). It also describes the most essential responsibilities of the investigator, sponsor and sponsor-investigator. Important aspects of a clinical trial include the patient informed consent, the documentation and labelling of the trial medication, the trial insurance taken by the sponsor, the study monitoring, and the adverse event reporting. A guide to clinical trials can be found on the internet: http://www.pfizer.com/files/research/research_clinical_trials/ethics_committee_guide.pdf. Over the last few decades pharmaceutical companies have invested in the training of investigator teams in Good Clinical Practice (GCP) regulation for the conduct of clinical trials. Industry has also developed s**tandard operating procedures** (SOPs). These are detailed work procedures for all personnel involved in clinical trials, for each step of the process, from trial design to final report. SOPs are essential to manage industry-driven clinical trials as well as publicly funded trials, as the level of complexity of both is high.

The study monitoring and audit functions are essential to ensure the **validity** of the data and to help to identify **research fraud**, an underreported problem that has led to the withdrawal of reports of clinical trials (both commercial and non-commercial) published in high-ranked journals. Often however, the scientific community must depend on whistleblowers to report fraud. Increased reporting by potential whistleblowers will not occur until they are acknowledged for their contributions and convinced that they will receive truly adequate protection from retaliation. A "Retraction Watch" initiative was launched in August 2010, and keeps a comprehensive and publicly accessible database of retractions. For a long list of articles on the subject we refer the reader to the website http://guides.library.umass.edu/scientificpublication. FDA also keeps a publicly accessible "blacklist" of investigators. http://www.fda.gov/ICECI/EnforcementActions/FDADebarmentList/ucm2005408.htm

Incremental patient costs for patients enrolled in a non-commercial clinical trial have been reported to be relatively small[93] or non-significant.[94] Patients enrolled in industry-sponsored clinical trials cost substantially less than average because the (expensive) medication is supplied for free.[93] **Study monitoring remains an important cost item in the conduct of a clinical trial. Procedures can be risk-adapted**, e.g. depending on the status of the trial medication (with marketing approval and used within the label versus off-label or not yet approved for marketing). For many low risk non-commercial clinical trials a less intensive and less costly study monitoring may be sufficient, when compared with the pre-marketing trials run by the pharmaceutical industry. Regulatory initiatives were started to accommodate these considerations.

"*The ICH GCP guidance is not specific about which methods should be used but suggests that 'the extent and nature of monitoring should be based on considerations such as the objective, purpose, design, complexity, blinding, size and endpoints of the trial'.*[95] *The guidance highlights a general need for on-site monitoring during different phases of the trial, but recognizes that 'in exceptional circumstances the sponsor may determine that central monitoring in conjunction with procedures such as investigators' training and meetings, and extensive written guidance can assure appropriate conduct of the trial in accordance with GCP'.*[95] *However, this has been criticized in the literature, with concerns raised that inefficient methods of monitoring are being used unnecessarily in some trials due to misinterpretation of the guidance*[96] *and a misconception that on-site monitoring is a legal requirement. This has in part led to recent initiatives on risk-adapted approaches to monitoring from the Clinical Trials Transformation Initiative (CTTI),*[97] *Department of Health,*[98] *Food and Drug Administration (FDA),*[99] *and the European Medicines Agency (EMA).*[100] *These are substantial developments, both for commercial and non-commercial clinical trials, and will* ***provide the potential to reduce costs and increase efficiency***."[101]

This approach was implemented at some of the 45 of the United Kingdom Clinical Research Collaboration (UKCRC) clinical trials units.[101] In addition, statistical methods have been developed to support risk-based trial monitoring.[102]

There is now also the possibility of accreditation of clinical trial centres, hospitals or organisations. Such accreditation can be obtained from the AAHRPP (the association for the accreditation of human research protection programs). (www.aahrpp.org)

5.1.2 Quality of non-commercial trials

In order to assure that international non-commercial RCTs are the best source of high level evidence, care is to be taken that all quality standards are assured in these trials. Industry-sponsored studies had more complete information in the trial registry clinicaltrials.gov when compared to non-commercial clinical trials.[11]

Some non-commercial trials included in Cochrane reviews were reported to be of lower quality compared with commercial trials.[103] Trials funded by pharmaceutical companies were larger (median sample size 126 vs. 45, P<0.001) and more likely to have avoided ascertainment bias 11/14 vs. 15/41 (P=0.05). Starting from a search in Medline and Cochrane Central Register of Controlled Trials databases for RA drug therapy RCTs, it was concluded that industry funding was not associated with a higher likelihood of positive outcomes of published RCTs of drug therapy for RA. Industry-funded RCTs were more frequently associated with double-blinding, an adequate description of participant flow, and performance of an intent-to-treat analysis. Industry-funded RCTs however showed a trend toward a higher likelihood of non-publication (P=0.093).[104]

5.2 Regulatory requirements

In Belgium and in other EU countries, all clinical trials are regulated in terms of review by an ethics committee. Clinical trials with medicinal products also need to submit a clinical trial application (CTA) to the competent authorities that includes the protocol, the investigator's brochure and the IMPD (investigational medicinal product dossier). (http://www.fagg-afmps.be/en/human_use/medicines/herbal_medicinal_products/research_development/clinical_trials/).

For trials with medical devices, the following clinical investigations must be notified to the competent authorities (http://www.fagg-afmps.be/en/human_use/health_products/medical_devices_accessories/clinical_evaluation/studies_to_notify/):

- Clinical studies conducted with medical devices that do not bear the CE marking

- Clinical studies conducted with medical devices that bear the CE marking but are used for another indication than the one for which it has been accepted (note that the concept of indication is not well-developed for medical devices in Europe[105]).

Clinical trials in Belgium are regulated by the law of May 7, 2004 ('experimenten op de menselijke persoon'). Investigator-initiated trials with medicinal products are also to be conducted according to the GCP-principles following the implementation of the EU Clinical Trial Directive 2001/20/EC for medicinal products.[106]

As detailed in the following section, the EU Directive 2001/20/EC did not achieve its aims and is being replaced by a new Regulation for clinical trials with medicinal products.[107] In separate reports, the European Science Foundation[108] and the Organisation for Economic Co-operation and Development (OECD) Global Science Forum[59] recommended a harmonisation of the procedures, a risk-based approach for the management and monitoring of clinical trials, and a better training and structure to perform clinical trials (see also 6.1)

The **new European Regulation on Clinical Trials** was published in the Official Journal of the European Union on 27th May 2014.[107] The **new rules facilitate cross-border collaboration for larger clinical trials**. Applications will be processed via a single clinical trial approval system to ensure a single outcome per country, thus avoiding multiple applications for trials in different member states, and reducing fees and time for application approval. 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. The coordination of the review by the Ethics Committee(s) is left to the member states, but strict review timelines will have to be respected. 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. The new Regulation will come into effect in mid-2016 at the earliest.

5.3 Impact of the regulatory requirements

The European Clinical Trials Directive (2001/20/EC)[106] tried to harmonise clinical research environment for medicinal products in Europe. However, **Directive 2001/20/EC was implemented as different variants in different EU countries, adding to the burden to conduct clinical research**, especially for international non-commercial trials.[109] The administrative burden and regulatory requirements imposed as a consequence of differences in interpretation and implementation at national level of the Clinical Trials Directive, as well as increasing fees resulted in a small decline (rather than the expected increase) in clinical trial numbers, both commercial and non-commercial, in many EU countries over the last decade.[14, 59, 106, 108, 110, 111]

The evolution in number of clinical trial applications (trials with medicinal products) is illustrated for selected European countries for the period 2001-2009 in Figure 9 and for 2007-2013 for the EU in Figure 10.

In 2007, more than 5000 clinical trials were applied for in the EU while by 2011 the number had dropped to 3800.(http://europa.eu/rapid/press-release_IP-12-795_en.htm). According to the European Medicines Agency,[112] "*In the European Economic Area, approximately 4000 clinical trials are authorised each year. This equals approximately 8000 clinical-trial applications, with each trial involving two Member States on average. Approximately 61% of clinical trials are sponsored by the pharmaceutical industry and 39% by non-commercial sponsors, mainly academia.*"

A large survey published in 2013 concluded that "*Investigator-dependent factors and ease of approval dominate trial site selection, while costs appear less important. Fostering competitiveness of European clinical research may not require additional government spending/incentives. Rather, harmonisation of approval processes, greater visibility of centres of excellence and reduction of 'hidden' indirect costs, may bring significantly more clinical trials to Europe.*"[111]

Whereas large pharmaceutical companies or contract research organisations with affiliates in the various countries may be able to overcome the extra administrative burden imposed by the Clinical Trial Directive, this is more of a challenge for small and medium size enterprises and for non-commercial clinical trials, certainly if these are international and are not a routine practice for the organisation, e.g. a scientific society.

A scientific society does not have 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 can help international scientific societies. This was illustrated for a trial in the field of transplantation.[113] The authors state: "*If a large trial has sufficient financial support certain tasks can be outsourced and delegated to contract research organizations, coordinating centers for clinical trials or partners in the medical industry*."

Scientific societies may want to build an own trial network, e.g. the European Cystic Fibrosis Society has formed a Clinical Trial Network (ECFS-CTN). The aim of the ECFS-CTN is to increase the quality and quantity of CF clinical research by realizing efficient and high quality clinical trials. The network provides access to large and experienced CF centres throughout Europe. 30 sites in 11 countries, caring for a total of 14.000 CF patients are part of the ECFS-CTN. All centres have ample experience in clinical research. The question remains whether this solution is as efficient as making use of generic clinical trial units to overcome e.g. the administrative burden of a trial.

Pharmaceutical clinical research is a global undertaking and more and more pharmaceutical clinical trials are conducted in countries outside Europe. Important reasons are cost and speed of recruitment. Furthermore, affiliates of the pharmaceutical companies in Europe not only have to compete for clinical trials among each other[114] but also with external contract research organisations. Large pharmaceutical companies perform only part of the clinical trials through the network of their local affiliates, for a variety of reasons (for example, limited company staff available versus high transient capacity needs or specific requirements for expertise not available internally). In several European countries, national initiatives were started, often in collaboration with the local pharmaceutical industry, to stimulate and facilitate the local conduct of clinical trials, which is also an important economic activity.[14, 114, 115] These initiatives included e.g. in the UK and Germany, the set-up a network of clinical trials units to support the conduct of both commercial and non-commercial trials in a professional way. Despite our focus is on non-commercial clinical trials, it is important to also consider

the pharmaceutical clinical trial setting to better understand the situation and the actions taken in the various countries.

Tools to improve the efficiency and quality of clinical trials

Another important item concerns data management. Clinical research in Europe lacks a common terminology and standards for data management, hampering the conduct of international trials.[116, 117]

The Clinical Trial Transformation Initiative (CTTI) is a public-private partnership, mainly based in the US (www.ctti-clinicaltrials.org) and actively trying to make clinical trials more efficient and quality-driven by

1. engaging all stakeholders in the clinical trials enterprise
2. using evidence to issue official recommendations that will improve the quality & efficiency of trials
3. creating tools to facilitate the adoption of CTTI's official recommendations.

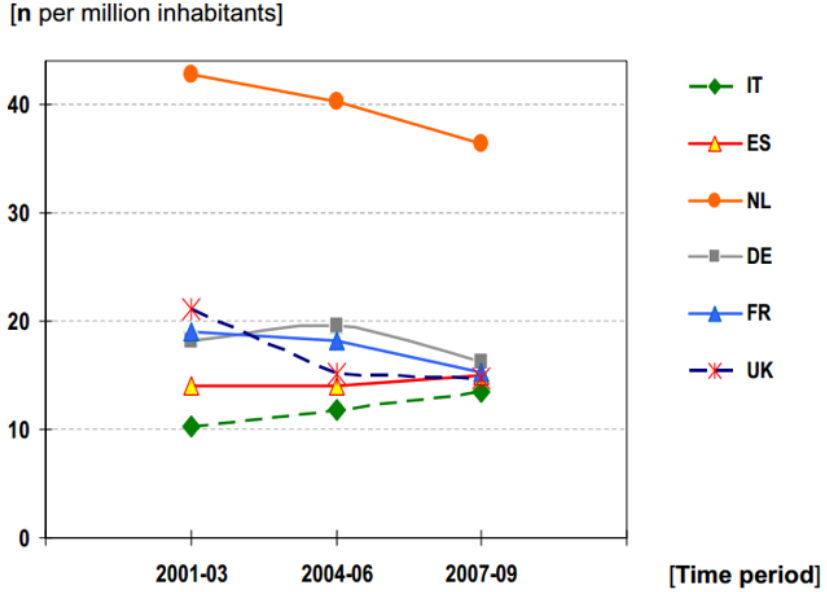
Tools that can make clinical trials more efficient while maintaining a high quality include tools to extract data from a structured electronic medical records. A uniform electronic patient record, based on international standard terminology, could reduce the workload of trial data extraction. This could significantly improve the quality and speed of performing clinical trials and potentially lower the overall costs.

Efficiency gains may also come from the use of “apps” in clinical trials, an area that is currently being explored.

Interoperability

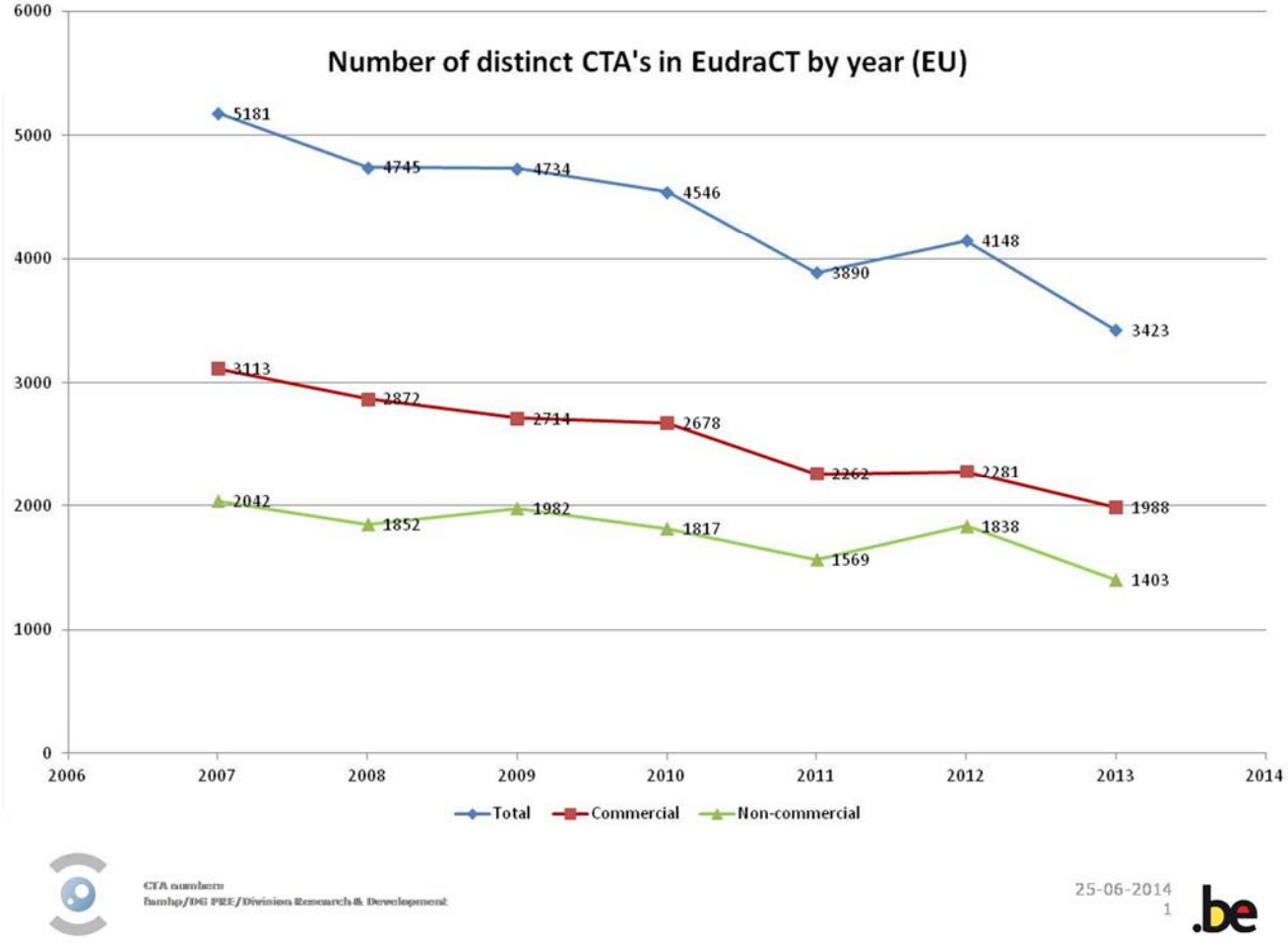
Furthermore, trial data exchange can be facilitated using standards like CDISC (Clinical Data Interchange Standard Consortium). CDISC is a global, open, multidisciplinary, non-profit organization that has established standards to support the acquisition, exchange, submission and archive of clinical research data and metadata. The CDISC mission is to develop and support global, platform-independent data standards that enable information system interoperability to improve medical research and related areas of healthcare. CDISC standards are vendor-neutral, platform-independent and freely available via the CDISC website, www.cdisc.org.

Figure 9 – Number of clinical trials with CTA over time per million inhabitants in selected European countries[160]



Note: UK data do not include phase 1 trials, CTA=Clinical Trial Application

Figure 10 – Number of clinical trial applications for trials with medicinal products, by year (EU)



Key Points

- **Publicly funded clinical trials should follow Good Clinical Practice guidelines and standard operating procedures in order to assure their quality.**
- **Risk-adapted regulatory review and study monitoring should be applied to reduce costs and increase efficiency.**
- **Publicly funded trials should be the example in terms of timely and transparent trial registration, publication of results, etc..**
- **Instead of being a facilitator, the Clinical Trial Directive has hampered the conduct of international clinical trials with medicinal products in Europe.**
- **The new European regulation on clinical trials will introduce the concept of low-intervention clinical trial, will increase transparency and foster the conduct of international clinical trials with medicinal products.**
- **A publicly-funded network of clinical trials units can help overcome the administrative complexity and provide the infrastructure for education and training.**

6 NON-COMMERCIAL CLINICAL TRIALS IN EUROPE

In this chapter the landscape of non-commercial clinical trials in Europe and in selected European countries is illustrated. The heterogeneity in funding sources, amount of available funding and the level of organisation are documented. Where available, the process of study selection is also given. First, we present reports from international organisations on the subject (6.1), second we discuss international organizations (6.2), third for selected countries national reports and structures for non-commercial trials are given (6.3).

6.1 Existing reports

In addition to some reports describing the situation in a specific country, our grey literature search yielded some important reports on the topic.[59, 108]

The European Science Foundation studied the role of investigator-driven clinical trials (IDCT) and provided policy recommendations.[108] "*Such studies deal with potential diagnostic and therapeutic innovations that do not attract or could even be against commercial interest. Typical examples are proof of concept studies, studies on orphan diseases, comparison of diagnostic or therapeutic interventions, surgical therapies or novel indications for registered drugs. IDCT thus have a much broader scope and potential impact than industry-driven clinical trials.*"[108] The **top five recommendations to strengthen IDCT in Europe as ranked by a consensus conference are as follows**:

1. To improve the education, training and career structure and opportunities for scientists involved in patient-oriented clinical research.
2. To increase levels of funding for IDCT.
3. To adopt a 'risk-based' approach to the regulation of IDCT.
4. To streamline procedures for obtaining authorisation for IDCT.
5. To ensure that IDCT are carried out with an appropriate number of patients to produce statistically reliable results so that the trials are 'correctly powered'.

The Organisation for Economic Co-operation and Development (OECD) Global Science Forum also produced a report "*Facilitating International*

Cooperation in Non-Commercial Clinical Trials"[59] The report states "*Non-commercial clinical research therefore contributes to the evaluation of various treatment strategies and options as a basis for developing rational therapeutic guidelines and governmental policies.*"[59] The recommendations in this report address three **main challenges**:[59]

1. The excessive administrative complexity of clinical-trial processes;
2. The desirability of introducing a risk-based approach to the management of clinical trials;
3. The need to improve the education and training support as well as the infrastructure framework in clinical research, and the involvement of patients.

The concept of 'low-intervention trial' has been introduced in the new clinical trial regulation for medicinal products,[107] referring to the recommendation of the OECD Council on the Governance of Clinical Trials of 10 December 2012, see also section 7.4.1. Efforts are ongoing, currently coordinated by the European Clinical Research Infrastructures Network (ECRIN) and the US National Institute of Health (NIH), to implement all OECD recommendations in order to facilitate the conduct of international publicly funded clinical trials.

6.2 International clinical research organizations

6.2.1 European Clinical Research Infrastructures Network (ECRIN)

The Community legal framework for a European Research Infrastructure Consortium (ERIC) entered into force on 28 August 2009. This specific legal form is designed to facilitate the joint establishment and operation of research infrastructures of European interest.

For clinical research in Europe the following infrastructures are to be mentioned: the Biobanking and BioMolecular resources Research Infrastructure (BBMRI-ERIC) the European Infrastructure for Translational Medicine (EATRIS-ERIC) and the European Clinical Research Infrastructures Network (ECRIN-ERIC) (Figure 11).

For this report however, BBMRI and EATRIS are out of scope as their focus is on the lab and translational research, facilitating the transfer from the lab to the clinical research setting, and the development of innovative products by industry.

Efforts to create a European network to conduct non-commercial trials have resulted in the European Clinical Research Infrastructures Network (ECRIN, www.ecrin.org).[118, 119] ECRIN offers integrated support to multinational clinical research projects through information, consultancy, and a set of flexible services, for any category of clinical research, in any medical field as illustrated in Figure 11. This support is provided by the infrastructure connecting national ECRIN partners (networks of Clinical Research Centers or Clinical Trials Units).

ECRIN stimulates the **standardisation across participating centres of procedures and data management software solutions**, including the implementation of data exchange, standards like CDISC (Clinical Data Interchange Standard Consortium).

ECRIN became a European Research Infrastructure Consortium in 2013 (ECRIN-ERIC), receiving funding from the member countries. Founding members are Germany, Spain, France, Italy and Portugal. The members of ECRIN are shown in Figure 12. A detailed list of members is given in the Appendix 4.

ECRIN infrastructure can also be used for commercial clinical trials or for public private partnerships. However, to maintain its independence, such funding should not pass 10% of all funding of ECRIN. Belgium is currently not a member of the ECRIN network, but efforts have started to move in this direction. ECRIN received €2 million from the 7th framework programme and €1.5 million per year from the participating member states.

Figure 11 – Pan-European research infrastructure

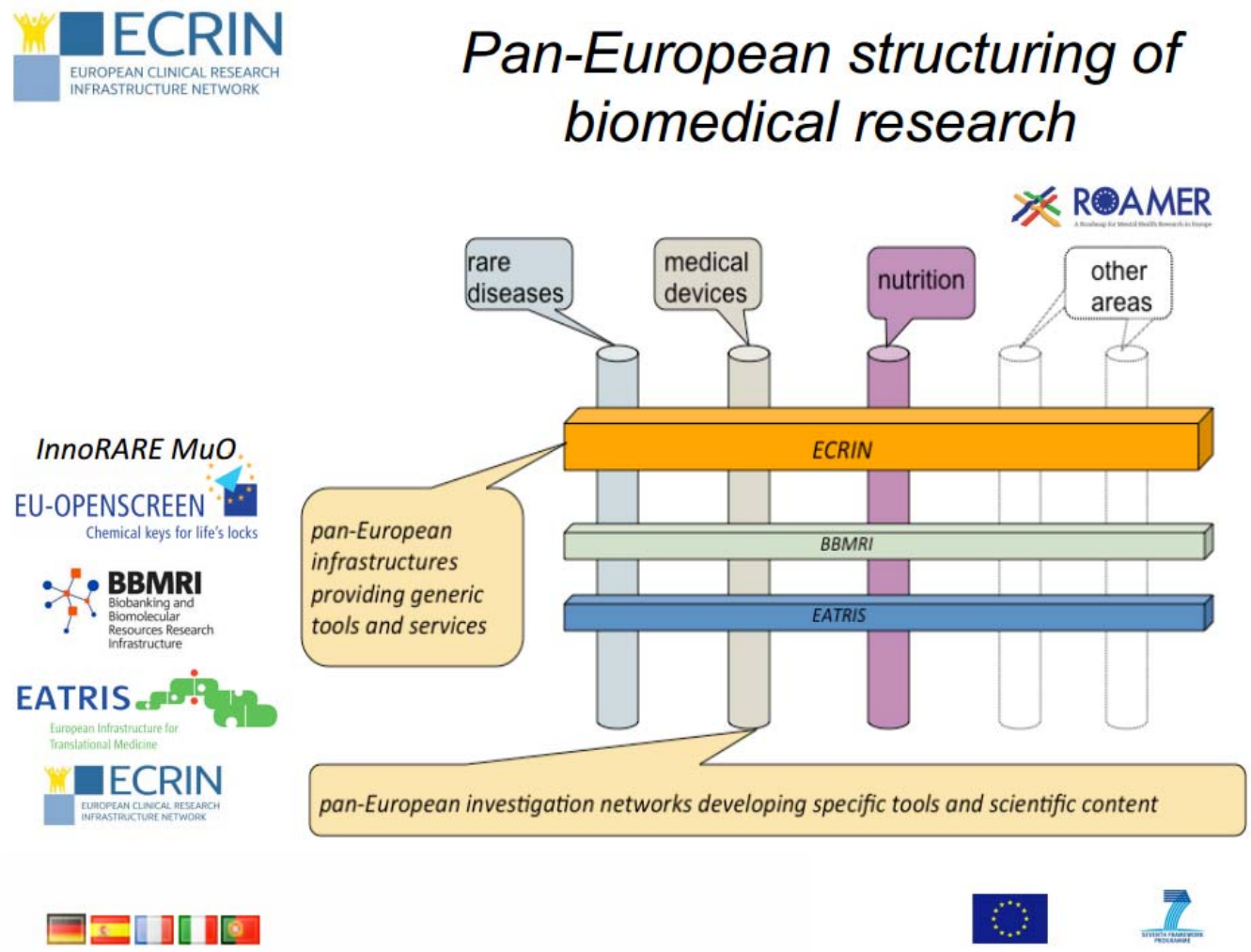
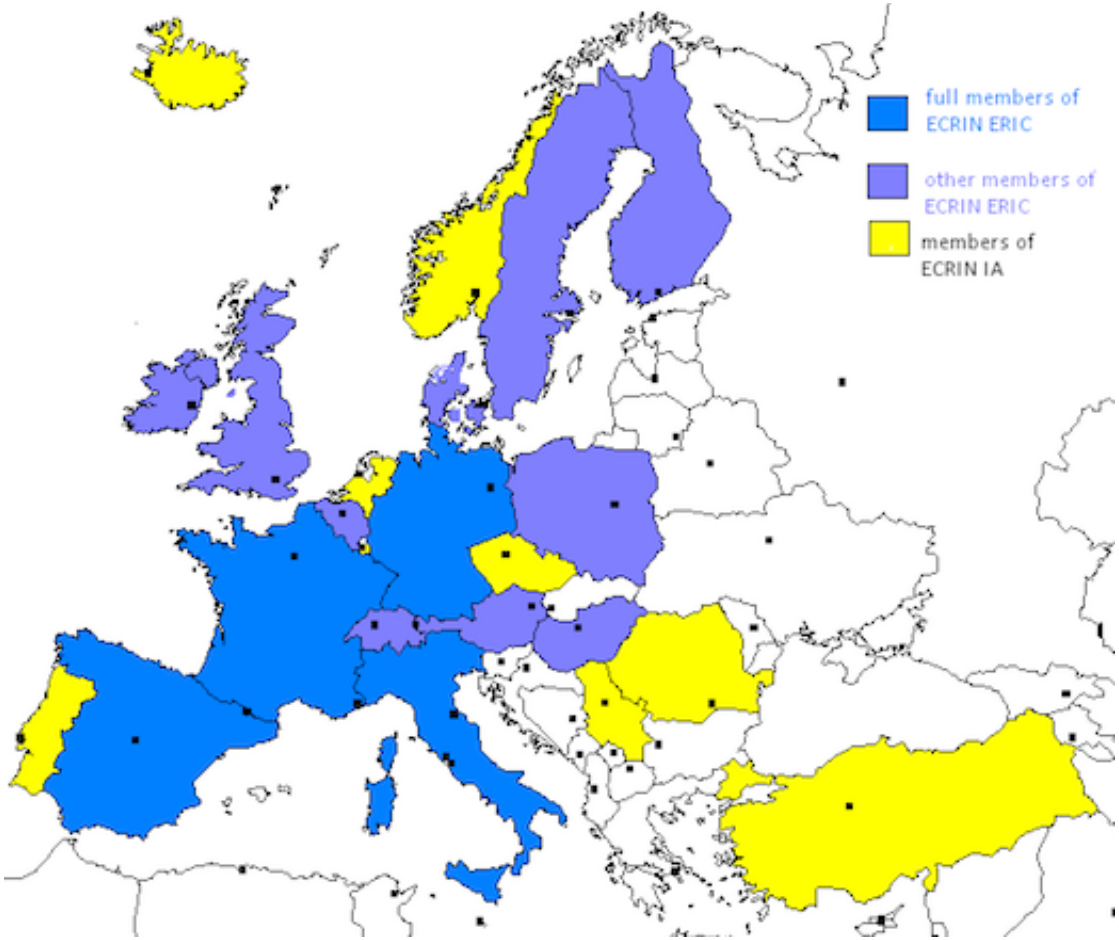


Figure 12 – ECRIN members



Source: www.ecrin.org; Note that Belgium is not yet member of this network. The member indicated in Belgium is the European Organisation for Research and Treatment of Cancer. In yellow: ECRIN IA= ECRIN integrated activity (2012-2015), the fourth step of the ECRIN programme, funded by the FP7 Infrastructure programme

6.2.2 European Organisation for Research and Treatment of Cancer (EORTC)

Created in 1968, the EORTC is an **independent research organization dedicated to investigator driven clinical trials and translational research in the field of oncology**. It consists of both a network and a coordinating scientific and operational infrastructure based in Brussels.(www.eortc.org)

The EORTC is funded through several sources including the EORTC Charitable Trust providing a core grant which is mainly supported by numerous national cancer leagues. Since 1972, the US National Cancer Institute (NCI) has provided core support to EORTC Headquarters, and with this support a close scientific collaboration has been maintained to promote transatlantic research projects. EORTC staff has increased to 175.

Clinical studies evaluating new drugs for potential registration or testing innovative therapeutic agents, including some educational projects, are conducted in cooperation with pharmaceutical industry partners.

EORTC is a partner of ECRIN.

6.2.3 Trials funded by the EU

At EU level, in 2011, 26 studies (investigator-driven, comparative effectiveness trials, including RCTs) were financed by the 7th framework for a total budget of €152 million. This amounts to an average budget of €6 million per trial.

The Innovative Medicines Initiative (IMI) is a public-private partnership (PPP) in the 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 finances clinical trials, specifically to develop new antibiotics (€90 million).

Many trial applications were submitted to receive funding through the EU funded Horizon2020 project but the success rate was only 4%.

Important budgets of €683 million were provided by the EU in addition to the same amount contributed by the participating countries, plus about €500 million by third parties (including industry) to the European & Developing Countries Clinical Trials Partnership (EDCTP). EDCTP aims to accelerate the development of new or improved drugs, vaccines, microbicides and diagnostics against HIV/AIDS, tuberculosis and malaria as well as other poverty-related and neglected infectious diseases in sub-Saharan Africa, with a focus on phase II and III clinical trials.

ERA-Net (European Research Area Network), e.g. E-RARE (on rare diseases), is based on a “virtual common pot” with no cash crossing national borders. ERA-nets were created by the European Commission to accelerate coordination and cooperation in research activities. In the ERA-Net scheme, the EU Commission supports the coordination and the common evaluation procedure, whereas national funding agencies fund the projects. In the ERA-Net+ the EU Commission also contributes to the funding of projects, thus improving the national budget / project balance. In the ERA-Net-Cofund scheme, the EU Commission contributes to additional coordination activities. ERA-Nets were developed as an instrument supporting research in a given thematic area (rare diseases, neurosciences, cancer, etc), and given the amount of budget available (in the range of 10 to 20M€/year) most of them prefer to focus on basic and translational research, excluding clinical trials. There is a growing support for a generic ERA-Net, supporting multinational clinical trials in any medical field.

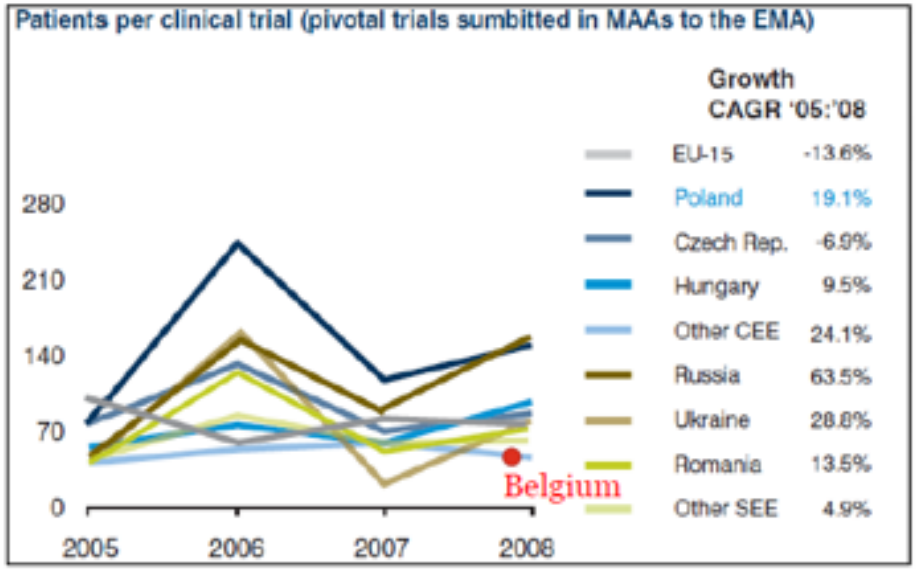
6.3 National organizations

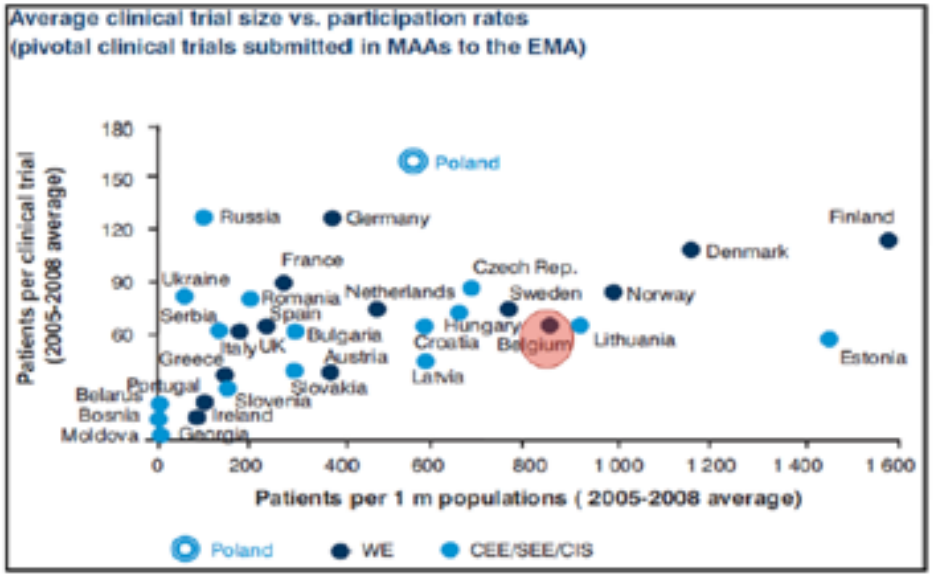
6.3.1 Belgium

Belgium is one of the countries with the highest participation rate for clinical trials with medicinal products in Europe (Figure 13). As in most EU countries, most of the clinical trials with a clinical trial application in Belgium are sponsored by the pharmaceutical industry and only 21% are non-commercial trials. The largest part (74%) of these non-commercial trials are mononational, as is the case in most EU countries (Table 3 – Number of clinical trial applications and (mononational) academic trials in EU countries (FAGG data 2013).).

In Belgium, “The initiative” (www.theinitiative.be) was started by the pharmaceutical industry and related organisations to reinforce the position of Belgium in the international landscape of clinical trials. Although non-commercial research is also mentioned, the main focus is on commercial trials with medicinal products.[14, 120]

Figure 13 – Clinical trials with CTA, situation of Belgium within Europe.[14, 120]



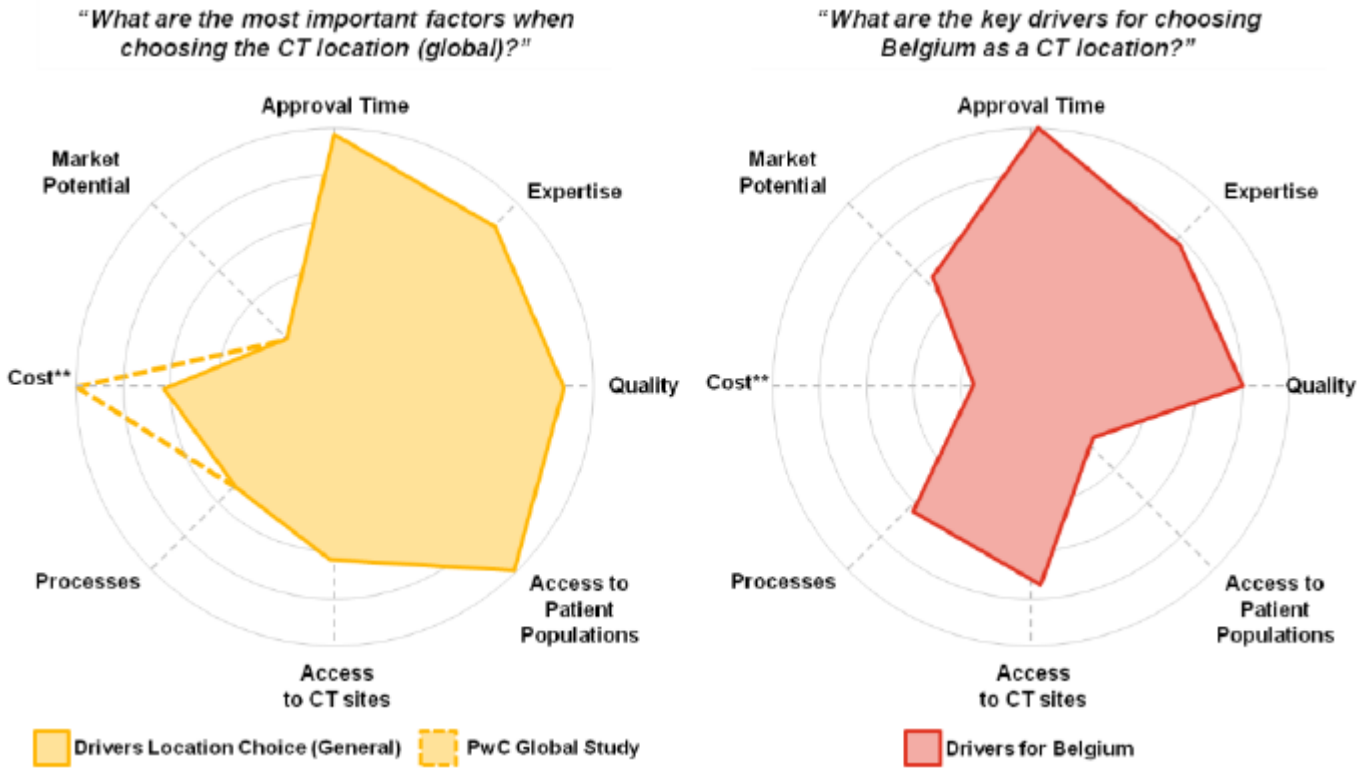


When comparing the **number of patients participating in clinical trials, Belgium ranks lower** (with an average of 54 patients), due to its relatively limited patient population.

However, when these figures are expressed **in per capita terms, Belgium emerges as one of the countries with the highest participation rate** in Europe.

EMA= European Medicines Agency; MAA= marketing authorisation application; CAGR '05-'08= compound annual growth rate in the period 2005-2008

Figure 14 – Drivers for a pharmaceutical company to choose Belgium as clinical trial location, compared with global drivers for location choice.[14, 120]



Source: PwC survey 2012[14]

Table 3 – Number of clinical trial applications and (mononational) academic trials in EU countries (FAGG data 2013).

NCA	Total number of CTA's	Total number of academic trials	% academic of total	Mononational academic trials	% mononational of total academic trials
Austria - BASG	549	168	30,6%	130	77,4%
Belgium - FPS Health-DGM	1029	219	21,3%	161	73,5%
Bulgarian Drug Agency	393	2	0,5%	1	50,0%
Czech Republic - SUKL	707	34	4,8%	19	55,9%
Denmark - DHMA	562	251	44,7%	208	82,9%
Estonia - SAM	126	2	1,6%	2	100,0%
Finland - Fimea	260	71	27,3%	58	81,7%
France - ANSM	608	197	32,4%	158	80,2%
Germany - BfArM	1424	240	16,9%	183	76,3%
Germany - PEI	456	62	13,6%	46	74,2%
Germany - TOTAL	1880	302	16,1%	229	75,8%
Greece - EOF	219	18	8,2%	13	72,2%
Hungary - National Institute of Pharmacy	650	32	4,9%	20	62,5%
Iceland - IMCA	15	7	46,7%	6	85,7%
Ireland - HPRA	166	45	27,1%	26	57,8%
Italy - Italian Medicines Agency	1369	395	28,9%	325	82,3%
Lithuania - SMCA	143	4	2,8%	1	25,0%
Luxembourg - Ministry of Health	8	2	25,0%	0	0,0%
Netherlands - Competent Authority	1158	445	38,4%	392	88,1%
Norway - NOMA	203	63	31,0%	46	73,0%
Poland - Office for Medicinal Products	796	9	1,1%	4	44,4%
Portugal - INFARMED	216	26	12,0%	9	34,6%
Romania - National Agency for Medicines and Medical Devices	179	4	2,2%	3	75,0%
Slovakia - SIDC (Slovak)	299	5	1,7%	2	40,0%
Slovenia - JAZMP	55	7	12,7%	4	57,1%
Spain - AEMPS	1425	296	20,8%	234	79,1%
Sweden - MPA	528	150	28,4%	125	83,3%
UK – MHRA	1724	381	22,1%	330	86,6%

Despite Belgium has a high participation rate in clinical trials with medicinal products per capita, as illustrated above, **pharmaceutical companies identified two critical factors against Belgium: costs and access to patients** (Figure 14). In comparison with other countries, even university hospitals in Belgium are rather small and **specialised care is not centralised**. Therefore, for disorders that are not common even the larger hospitals may not meet the minimum requirement for trial participation in terms of minimum number of eligible patients per trial site. As a reaction, ClinicoBru was created as a pilot project by the three academic hospitals of Brussels, Erasme, Saint-Luc and UZ Brussel, to improve their competitiveness in the field of clinical research (personal communication, Florence Bosco). **A move towards centralisation of specialized care might also stimulate the conduct of clinical trials in Belgium for rare diseases**.

In contrast to the situation abroad (e.g. KKS network in Germany, UKCRC in the UK), no well-integrated infrastructure in terms of data management, monitoring or statistical services is currently available in Belgium to conduct non-commercial clinical trials. First steps to standardize contracts and logistics have started at an interuniversity level (Raad van Universitaire ziekenhuizen /Conférence des Hôpitaux Académiques RUZB/CHAB).

Funding of non-commercial clinical trials in Belgium

Public funding of practice-oriented clinical trials in Belgium is limited and is not well-integrated in the health care system. A non-exhaustive overview of the fragmented funding sources is given.

Part of the funding of university hospitals is aimed to support research at large. The amount is not well documented and is not earmarked.[121]

At federal level some translational research studies were covered by the federal cancer plan.

Also charities such as “Stichting tegen Kanker – Fondation contre le Cancer” (www.cancer.be), “Vlaamse Liga tegen kanker (VLK)” (www.tegenkanker.be), “Koning Boudewijnstichting - Fondation Roi Baudouin” and “Televie” (http://www.rtl.be/televie) have facilitated non-commercial clinical research in oncology, providing project support.

The Scientific Research Funds in Belgium are managed by the regions. For example, in Flandres, the FWO budget in 2013 was €224 million, ca. 80% originating from the Flemish Government. 30% is dedicated for medical sciences, mainly fundamental research. FWO will cover salary costs of investigators but do not cover the heavy costs to run a clinical trial. (http://www.fwo.be/nl/actueel/nieuws/presentatie-infosessie-onderzoeksprojecten-2014/)

Regional agencies for Innovation (Biowin in Wallonia and IWT in Flandres) fund collaborative projects with the healthcare industry. In addition, IWT spends a budget of €6 to €7 million each year for non-commercial clinical trials under the programme “Toegepast Biomedisch Onderzoek (TBM)”.[122] This programme focuses on a niche in biomedical research: advanced application-driven research with a pronounced societal applicability, but only a limited potential for the industry. Possible causes for the limited industrial interest may be difficult patentability, small patient populations or patient-specific treatments which do not allow standardised products. 19% of candidate projects are accepted and receive funding. The project selection looks at societal applicability (in addition to scientific aspects). There is a meeting between selection committee and candidate which is perceived as a positive element in the process.

The mean project duration is 41 months, funding on average €0.7 million (€1 million is the maximum). On average there are 5 partners per project (however often from the same university, sometimes university plus non-university hospitals). The number of international collaborations is low. In the full project funding, maximum 50% can be allocated for a centre abroad (20% directly and another 30% using subcontracting). **Patient inclusion rate is reported as the main problem**. In 70% of the funded trials, the expected impact (utilisation) of the trial was either realised or expected to be realised within 18 months.[122] This TBM initiative will move to the regional Scientific Research Fund FWO.

The “Centrum Medische Innovatie” (CMI) (including the Flemish Biobank) was given the task in 2013 by Minister Lieten to prepare a roadmap to join 3 European Research Infrastructure Networks, more specifically BBMRI-ERIC (EU Biobank), EATRIS-ERIC (www.eatris.eu) and ECRIN-ERIC (www.ecrin.eu). Meanwhile Belgium has become a founding member of BBMRI-ERIC and the Belgian (node) includes the Walloon biobank and the Belgische Virtual tumor bank. The decision to join EATRIS and ECRIN are still to be taken (personal communication Sofie Bekaert).

6.3.2 The Netherlands

The amount spent on healthcare research in the Netherlands is about €750 million per year, corresponding to 0.8% of the healthcare budget. Public funded clinical trials with a direct impact on healthcare are managed for over 15 years by ZonMw. This organisation currently has an overall budget of €130 million and funds health research. It also stimulates use of the knowledge developed to help improve health and healthcare in the Netherlands. The ZonMW programmes on healthcare efficiency research (€10 million per year) and rational pharmacotherapy (€13 million per year) mainly consist of public funded clinical trials. **In addition to the quality of care improvement, these ZonMW programmes aim to minimise healthcare expenditures**. Therefore, **studies proposed** for funding in the open call system **have to indicate their potential impact on the efficient use of the healthcare budget**. Additional studies funded concern issues observed by the healthcare decision makers and these are the subject of targeted calls (about one third of the budget is spent this way). After the trial is completed, **specific implementation projects** may be required and **are funded to increase the impact of the clinical research in the routine clinical practice**.

Other sources of funding for non-commercial clinical trials in the Netherlands are diverse and include charities. The Koninklijke Nederlandse Akademie van Wetenschappen has **recommended** to the minister of health **to build a more professional network of research infrastructure in order to facilitate the conduct of non-commercial clinical trials**, referring to the implementation of such infrastructure in Canada, Germany, Sweden and Australië.[123] This initiative should stimulate comparative effectiveness research.

A 2012 masterplan[115] for clinical research was prepared for The Netherlands by the Dutch Clinical Trial Foundation (DCTF), a network organisation that includes the medical industry. This plan is to be seen as a reaction to the decline in clinical trial activity that is also seen in The Netherlands.

Many informal networks exist between the 8 Dutch Academic Medical University hospitals and all 28 Top Clinical Training Hospitals. This platform tries to coordinate and improve all aspects of Clinical Research in The Netherlands. (http://www.ecrin.org/index.php?id=410). A training certificate in clinical research can be obtained at the university medical centres (3-4 days course). (http://www.nfu.nl/onderzoek/basiscursus/)

6.3.3 France

A publication was identified focussing on the institutional clinical research infrastructures and their environment in France. This report was based on a meeting of ECRIN.[124] More recently, a report on public funding of clinical trials, including policy recommendations, was prepared in 2012 by Aviesan (Alliance pour les sciences de la vie et de la santé, the French National Alliance for Life Sciences and Health) created in 2009 and grouping the main stakeholders of life and health sciences in France.[1] The budget of industry-funded clinical trials in France is over €3 billion.[1] In addition, many "academic" trials are financed in part or completely by industry.

Public funding of infrastructure for clinical trials

Infrastructure is funded for €126 million by the MERRI (les Missions d'Enseignement, de Recherche, de Référence et d'Innovation) budget, which resorts under the healthcare department, and for €9 million by INSERM (research). A public private partnership structure CeNGEPS spends €10 million, mainly to facilitate industry-sponsored trials. Part of the €250 million fund of "Investissements d'avenir" for selected university hospitals is spent on clinical research. F-CRIN, the ECRIN infrastructure in France, receives €18 million of funding over 8 years. Universities contribute mainly through the funding and training of researchers.

Public funding of clinical trial projects

The charity fund 'Ligue contre le Cancer' spends €6 million per year and 'AFM/Généthon' €25 million per year.

INSERM in France is dedicated to biomedical research and has a total budget of nearly €1 billion (2012). The main public funding source of clinical trial projects in France however comes from the healthcare budget. A joint PHRC (Programme Hospitalier de Recherche Clinique) / ANR (Agence nationale de recherche) call for translational research was launched since around 2010. The "Programme Hospitalier de Recherche Clinique": €90 million per year (incl €16 million for cancer research). This includes some RCTs. It covers all hospital based clinical research except for €20 million spent by the "Agence nationale de recherche sur le sida et les hépatites

virale (ANRS)" for trials of HIV and hepatitis viruses. PHRC is currently segmented into various calls (cancer vs. non-cancer, regional vs. national, etc), and this resulted in criticisms leading to reform the system. Recently, it was agreed the health research public funding strategy should be coordinated at the national level (by Aviesan, an alliance of life science and health research organizations), and that all the applications should be dealt with by ANR acting as a one stop shop. If this is implemented, this means that the funding strategy for clinical research should no longer be decided by the Ministry of Health alone, and that the applications will be managed by ANR.

The Agence nationale de sécurité du médicament et des produits de santé (ANSM) has a budget of €6 million per year to fund non-interventional pharmacovigilance studies.

The research department funds proof of concept trials (€25 million per year) through the "L'Agence Nationale de la Recherche (ANR)". "Investissements d'avenir" large cohort studies programme receives €68 million over 10 years.

Mixed Healthcare-Research budgets also exist: INSERM plus direction générale de l'offre de soins: translational research projects: €3 million per year and Institut National du Cancer plus direction générale de l'offre de soins, translational research: €18 million per year.

The **recommendations in the Aviesan report include**.[1]

- Improve financing of translational research and of cohort studies
- Reduce segmentation based on region, theme or institution
- Assure coherence within a single theme
- Standardise project evaluation
- Find a better mix of intramural versus extramural projects
- Further develop the tools in order to participate in large international trials
- Allow the financing of (fewer) but larger projects (allow funding per trial of €1-2 million as by AIFA in Italy or by BMBF/DFG in Germany, or even €6 million as is the average per trial funded by the 7th EU framework)
- Further strengthen the use of clinical research as a tool for policy decisions (HAS should be stimulated to propose clinical trials using a call for tender that would be of use for reimbursement decisions or to formulate recommendations)
- Improve transparency and simplification across institutions to avoid duplication and to fill the gaps
- Improve the presence of the clinical research in France at European level

6.3.4 Germany

For Germany, a report on non-commercial clinical trials was identified based on a Google search: "Stand und Bedingungen klinischer Forschung in Deutschland und in Vergleich zu anderen Ländern unter besonderer Berücksichtigung nichtkommerzieller Studien" by Büro für Technikfolgen-Abschätzung beim Deutschen Bundestag (TAB, Arbeitsbericht Nr 135, Jan 2010).[12]

The TAB report[12] included a literature search in Pubmed/Medline in March 2009 with search terms "investigator" and "initiated"; "non-commercial" and "trial"; "non-industry" and "sponsored". The authors state that the yield was poor.

Based on the databases of CTAs kept by the German competent authorities (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM and the Paul Ehrlich Institute, PEI) the non-commercial clinical trials constitute about 17% of the 1338 studies reviewed in 2008, which is similar to the 20.5% of the trials reviewed in Europe 2004-2009.[12] According to a report by the European Forum for Good Clinical Practice (EFGCP) the proportion of non-commercial clinical trials that were international varied from 18% in 2004 to 20% in 2007.[125]

A 2009 survey in 16 medical faculties in Germany showed that:[12]

- over half of the non-commercial clinical trials were single centre trials
- the distribution of phase 1 through phase 4 trials is similar for commercial and non-commercial trials
- under 20% of the non-commercial clinical trials are multinational trials
- 21% of the non-commercial trials are in hemato-oncology

The **main problems cited for the conduct of non-commercial clinical trials is the financing**. Also **patient recruitment and problems with health insurers** were frequently cited.

Organisation and Financing

In 1999 the Bundesministerium für Bildung und Forschung (BMBF) started with a €30 million total budget a **network of coordinating centres for clinical trials** (KKS network). Today, the KKS network now includes 18 centres, mostly central units of a medical faculty or university hospitals. They offer a whole spectrum of services comprising consulting, study design, study and site management, monitoring, data management, quality management, pharmacovigilance, statistical evaluation, reporting, publication, archiving. These services are offered to the pharmaceutical industry and manufacturers of medical devices, as well as to researchers for investigator-driven clinical trials. In trials financed as a public-private partnership the KKS is **running the trial at a cost that is lower compared with rates of Contract Research Organisations or pharmaceutical company standards**.[12]

Six centres received extra funding (€4 million) to stimulate study site management activities to facilitate patient recruitment in trials.

The KKS network overall has about 560 employees. All KKS centres are audited from time to time by external experts or organisations and are conducting independent internal audits of their study processes. In addition, the network provides a platform for different expert groups and task forces sharing best-practice through internal and external transfer of information and joint training courses.(http://www.kks-netzwerk.de) It is recognised that this initiative has largely improved the quality of clinical trials. The KKS network is the German scientific partner in ECRIN.

It remains difficult to conduct non-commercial clinical trials with innovative technologies without industry support. Over half of the academic clinical trials in Germany are co-financed by industry (indicating a situation of insufficient public funding).[12] Another important source of financing are the dedicated programmes by the Bundesministerium für Bildung und Forschung (BMBF) and the Deutsche Forschungsgemeinschaft (DFG). The BMBF budget of approx. €15 million per annual call is aimed to finance multicentre clinical trials that pass a first-stage selection via a prioritisation board comprised of scientists, clinicians, health care providers and patient representatives. The DFG allocates a similar budget of €15 million annually to its confirmatory clinical trials programme. Main selection criteria are scientific quality and clinical impact as determined by a board of scientists. About €1.5 million were spent on average per trial (personal communication Frank Wissing, DFG).

Other sources of financing are the Länder (Regions) for trials by medical faculties as well as the charities (mainly Deutsche Krebshilfe with a research budget of €37.7 million that includes a.o. clinical trials) for trials supported by KKS. The funding by EU was very small in the 2009 survey and is still small today (personal communication Insa Bruns, KKS).

The BMBF also spends about €82 million (2007) for basic medical research at the German centres for health research (Interdisziplinären Zentren für Klinische Forschung, IZKF), but this research does not include the confirmatory type of clinical trials that are the focus of this report. Integrated treatment and research centres for specific (mainly chronic) disorders receive a yearly BMBF budget of €5 million, in part used for clinical trials.

Recently, four new DZG (Deutschen Zentren der Gesundheitsforschung) were created for translational research in Infectious Diseases, Cardiovascular, Lung Diseases and Cancer. They complement the centres for translational research in Neurodegeneration and Diabetes, created in 2009. The interdisciplinary centres link the research performed at multiple universities and university hospitals in Germany, aiming to bring the research faster to the clinic, in collaboration with the medical industry. (http://www.bmbf.de/de/gesundheitszentren.php) The overall annual funding of the DZG amounts to over €750 million. Some of this amount can be spent for clinical trials. Four of those universities / university hospitals already received funding for a KKS.

The survey also mentions that the healthcare payers have a high interest in non-commercial clinical trials and that they should finance such trials.[12] In 2009, the G-BA (The Federal Joint Committee (Der Gemeinsame Bundesausschuss)) started to provide financing of pharmaceuticals used off-label in the context of a clinical trial. The focus is on pediatric oncology.[12] The legal base is § 35c SGB V i.V.m. §§ 31-39 of the “Arzneimittel-Richtlinie”. (https://www.g-ba.de/institution/presse/pressemitteilungen/290/) In addition, the new ”Erprobungsregelung” (https://www.g-ba.de/institution/themenschwerpunkte/erprobungsregelung/) allows the G-BA to initiate and fund a clinical trial in order to evaluate the potential of a new diagnostic or therapeutic intervention. The legal base is § 137e SGB V and §§ 135 und 137c SGB V.(http://www.gesetze-im-internet.de/sgb_5/__137e.html)

According to the current legislative outline, from 2016 onwards, also class 3 medical devices (with a potential yet unproven impact on healthcare) will be part of an evaluation "Erprobungsstudie" according to §137 SGBV to be covered by health insurance. Originally, it was the aim to also include class IIb products but this proposal was not kept.

As part of the same legislative package, an "innovation fond" is to be established with €75 million per year from 2016 onwards for "health systems research". It will be part of the GB-A, and the actual remit as to what will be covered by "health system research" is still under debate. This could include e.g. pragmatic trials and comparative effectiveness studies. The funding would in part be supported by the healthcare payers, in part by the public at large.

The TAB report mentions **participation of ambulatory care and non-university hospitals in clinical trials is to be improved as is international cooperation**, especially for rare disease trials. Finally, there is a **need for more integration with patient registries and a standardized trial software integrated with the patient management database**, if possible at EU level.[12]

Knowledge transfer for investigators and study nurses can be achieved using a system of "rotating surgeons and flying nurses".[126]

An important limitation of non-commercial clinical trials is a low level of recognition (level of publications, career) of this type of research in comparison with basic research. The image may however be favourable compared with industry-driven clinical trials. The fact that e.g. the DFG, which was traditionally a basic research funding agency, has been funding clinical trials and has established this as a regular program within its portfolio has already given a considerable boost to the scientific recognition for scientist performing clinical trials.

In addition, there are now 4 junior research academies for clinical trials, providing aspiring clinical researchers with training, mentoring, and seed funding for their study ideas. During workshops up to 20 junior scientists can take part, bring with them their own study idea and receive methodological training (e.g. conceptually, biometry, regulatory, specific clinical methodology) and mentoring in small groups to develop the project further. The discussions with their peers in the groups are usually very fruitful and help establishing networks. As a result of the workshop, the trainees submit their first proposal to the DFG for seed funding (usually 1 year, 65.000 Euro). The aim of this could be to write a systematic review, to do a small pilot study or to have protected time to prepare larger proposals, study protocols or to prepare regulatory work. This should then prepare the ground for full proposals for DFG-individual grants, the clinical trials programme or with other funders. The general funding scheme is summarized under http://www.dfg.de/en/research_funding/programmes/individual/workshops_early_career_investigators/in_brief/index.html

The situation could further be improved by the inclusion of number of study patients as a quality indicator for the hospital. An increase in the interest in clinical trials in daily practice has indeed resulted through the certification of hospitals for special treatment that specifies that at least 5% of all patients are included in clinical trials.[127] A working solution was found for the sponsor of investigator-initiated clinical trials.[128]

A competitive payment and contractual status of the investigators in trials is needed. **Stimulating education in clinical trials and making a career in clinical trials possible were high priority policy recommendations in the report by the European Medical Research Councils**.[108] Experience and knowledge of clinical trials could be made a prerequisite to become a clinical department head.

6.3.5 UK

The UK Government invests approximately £1.6 billion yearly on medical research. The British public donated an estimated £1.7 billion to medical research charities in 2012/13.[44] The **National Institute for Health Research (NIHR), created in April 2006, is now the research arm of the NHS in England**. Before the NIHR was created, applied (patient-based) research in the NHS was conducted and funded through a range of ad-hoc funding programmes and schemes managed by the Department of Health to address questions raised by front-line professionals and policy makers.

The sources of funding and the spending for the different clinical research activities in the UK were reported by the UK Clinical Research Collaboration (UKCRC) with the UK Health Research Analysis for 2004/5[129] and 2009/10 (Table 4).[130] The detailed analysis of public and charitably funded research in this report do not include research funded by smaller UK charities, funding from organisations based outside the UK, quality-related funding to universities, and NHS support for clinical academics.

The UK health research funding is much broader than clinical trials, which constitute only a relatively small fraction of research funding. More precisely, most clinical trials are in activity group 6, 'Treatment Evaluation', see also Figure 3 – NIHR-funded number of active trials and budget by domain in the UK. Overall, 'Treatment evaluation' accounts for 8.1% of the 2009/10 health research expenditure in the UK and most of the practice-oriented clinical trials are now funded by The National Institute for Health Research (NIHR). NIHR was created in April 2006 and is the research arm of the NHS in England.

Table 4 – Volume of UK health research funding for 2004/5[129] and 2009/10.[130]

Group	Organisation	Number of Awards 2004/05	2004/05 Amount (£m)	Number of Awards 2009/10	2009/10 Amount (£m)
Charities	Arthritis Research UK	286	17.3	304	26.2
	British Heart Foundation	1038	46.3	912	59.8
	Cancer Research UK	1001	175.3	1476	230.7
	Wellcome	2303	219.0	2310	341.6
Health Depts [16]	England	1040	96.9	1570	200.9
	Northern Ireland	180	8.5	126	9.5
	Scotland	311	13.6	273	22.3
	Wales	43	1.8	163	16.1
Research Councils	BBSRC	249	15.1	279	28.1
	EPSRC	407	26.3	572	89.0
	ESRC	116	9.7	250	26.2
	MRC	2927	335.3	3236	585.6
A) Total HRCS coded research funding [17]		**9901**	**965.0**	**11475**	**1636.1**

BBSRC: Biotechnology and Biological Sciences Research Council; EPSRC: Engineering and Physical Sciences Research Council; ESRC: Economic and Social Research Council; MRC: Medical Research Council

The National Institute for Health Research (NIHR)

The National Institute for Health Research has transformed research by creating an integrated health research system supporting projects with direct research funding, with a robust and comprehensive research infrastructure in the National Health Service, and ensuring high quality training for new potential researchers. Despite their important budget for health research, the number of practice-oriented trials in the UK funded by MRC and the Wellcome Trust in the UK is now low – their role is preclinical research, or in developing countries. In oncology, many trials are still funded by the CRUK. Overall however, **most practice-oriented confirmatory type of clinical trials are managed by NIHR**.

In November 2014, NIHR was funding over 800 trials involving over 600 000 patients for a total cost of nearly £1 billion (most trials run over multiple years). The NIHR's approach to increasing value in research has been highlighted in a recent series of articles.[131] This means **selecting only the most important questions informed by the needs of patients and the public and by systematic review of existing research to avoid duplication, efficient conduct and delivery of projects, and finally their publication in a form usable to clinicians and the public**. This publication of the results of research, whether successful or not, is extremely important to NIHR; **the HTA programme for instance has a publication rate of 98% of all projects.**[132] Those unpublished usually fail in development before recruiting patients. Some examples of important NIHR research and their impacts are shown in Appendix 3.4.

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.

The Clinical Research Networks (a series of linked networks each covering a geographical area) in the UK are based in the NHS, and provide support services. These services include research nurses to support research by recruitment etc, also pharmacy, radiology services where needed over and above usual NHS care to support research etc. NIHR spends ~£250 million a year for this extensive network system. Industry can apply to use the people in these networks but is expected to pay for them – the advantage to industry is a research-wise workforce already in place so speed and quality should be improved. This makes the UK a more attractive place to run trials for industry, an economically important argument.

In addition, there is an **infrastructure of academic units, which has developed standard operating procedures (SOPs) to design and deliver clinical trials in different areas. They are experts in trial design and trial delivery without necessarily being dedicated to a particular clinical area.** They generally do not get involved with industry trials but are focused on academic or clinically led studies (columns 2&3 in table 1) funded by charities or by public money (industry usually has all the necessary skills in house).

Above and beyond the expenditures for the networks and academic units, £150 million per year is spent directly on NIHR funded clinical trials (personal communication Tom Walley, NIHR). This amount does not include the routine care of the patient, the support from the networks, or treatment costs which may be carried on after the research, which are technically called "excess treatment costs" and are paid by the health service rather than by the researchers

This may make publicly-funded clinical trials conducted in the UK look a lot less expensive compared with trials in other jurisdictions. For example, both the IVAN study in the UK and the CATT study in the US looked at Avastin versus Lucentis in age related macular degeneration (both were publicly funded by NIHR and NIH, respectively). The nominal cost of the IVAN study was about £3 million whereas the US study (for twice the number of patients) had a cost in the order of £25million (not US dollars). It relates a lot to the fact that in the US everything has to be paid for out of the clinical trial budget, whereas in the UK there are often hidden subsidies as described above. Based on a detailed costing study comparing IVAN and CATT, the cost per trial patient in the UK was about 40% less than in the US, but not the 90% that the publicly available figure may make one think at first glance.(personal communication Tom Walley, NIHR)

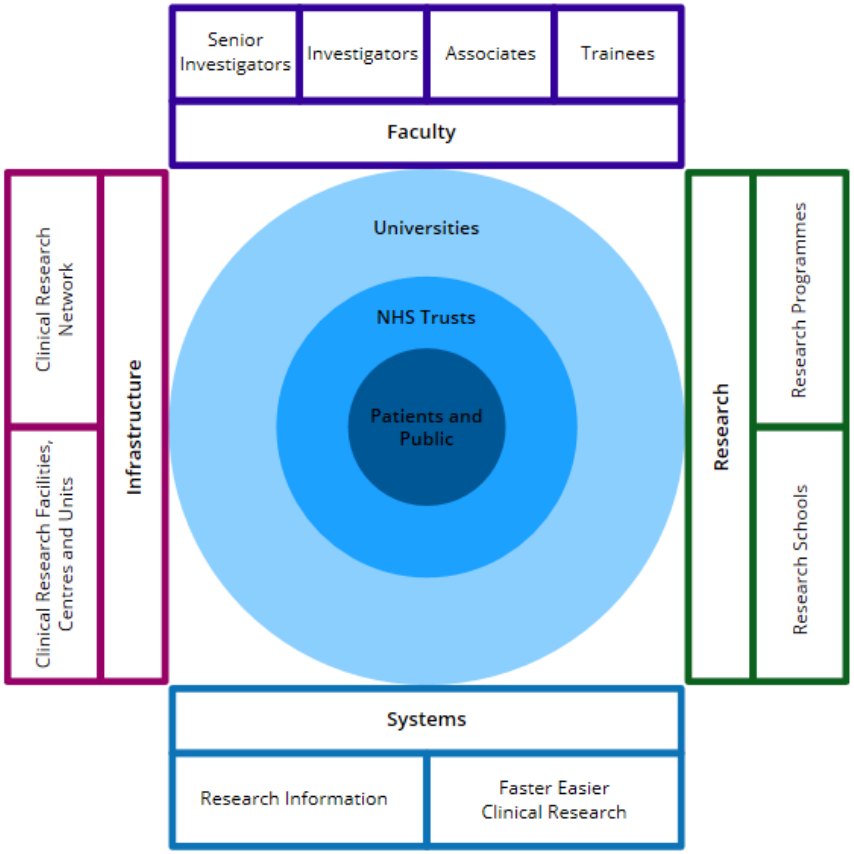
This local complexity in funding structure and hidden costs is another hurdle if one wants to fund international trials and transfer budgets across national borders for this purpose. **Coordinated international clinical trials with each country funding its own in a coordinated way** are therefore much easier to implement.

The NIHR manages its health research activities through four main work strands (Figure 15):

- Infrastructure: providing the facilities and people for a thriving research environment
- Faculty: supporting the individuals carrying out and participating in research
- Research: commissioning and funding research
- Systems: creating unified, streamlined and simple systems for managing research and its outputs.

The NIHR Clinical Research Network (CRN) provides free support to help the life sciences industry deliver high quality research in the NHS. The Coordinating Centre delivers and manages NIHR Clinical Research Network (NIHR CRN) in England and facilitates a range of activities across the UK, working closely with the Health Departments in Northern Ireland, Scotland and Wales. The **importance of a clinical research network in the trial design and patient recruitment** has been well documented not only for the UK,[133] but also in the US.[134] A UKCRC Registration Process has been established for Clinical Trials Units responsible for coordinating multi-centre clinical studies. This is intended to help improve the quality and quantity of available expertise to carry out UK clinical trials. UKCRC Registered Clinical Trials Units (call in 2007): 26 are fully registered, 14 have a provisional registration.(http://www.ukcrc.org) Most of these units receive funding from NIHR.

Figure 15 – The four main work strands in the NIHR



Source: www.nihr.ac.uk

Medical Research Council (MRC)

The Medical Research Council (MRC) is a publicly funded organisation.

Currently most of the MRC's support for clinical trials are funded through the following schemes:

- the Biomedical Catalyst: Developmental Pathway Funding Scheme (DPFS) (http://www.mrc.ac.uk/funding/browse/developmental-pathway-funding-scheme/)
- the Global Health trials schemes (http://www.mrc.ac.uk/funding/science-areas/global-health/).
- the NIHR administered Efficacy and Mechanism Evaluation scheme (EME) (http://www.nets.nihr.ac.uk/programmes/eme)

As applications for MRC funding are submitted in 'response mode', applicants will submit an application identifying the research area and research questions for the trial, and are also responsible for putting together a team for carrying out the trial. The MRC does not commission studies or identify teams to conduct specific trials. Decisions about MRC funding is made through two stages of independent peer review (http://www.mrc.ac.uk/funding/peer-review).

6.3.6 The Nordic Countries

The past 10 years have seen a decrease in the number of clinical trials in the Nordic countries. Five countries have created The Nordic Trial Alliance (NTA), a three-year pilot project running from 2013 to 2015, funded by the Nordic Council of Ministers and NordForsk. (http://nta.nordforsk.org/) for a total amount of €2.4 million. The aim is to make it easier to carry out clinical research in the Nordic countries. The funded project should have partners from a minimum of three Nordic countries (Denmark, Finland, Iceland, Norway, Sweden or the autonomous areas of Faroe Islands, Greenland and Åland Islands). The Project Leader should be an established senior researcher based in one of the Nordic countries. The formal applicant must be an institution or other research-performing legal entity based in one of these countries. NordForsk will enter into a contract with this institution, which will be responsible for the administration of the project. This is also the legal entity to which NordForsk will disburse the grant. The funded project must have binding institutional commitment from at least three Nordic countries. Letters of intent are required from all partners in the proposal stage. The proposed total time frame for a project should not exceed two years. The total available funding for this call is NOK6 million for one to two projects. Each project may apply for up to NOK4 million. (1 NOK=0.119213 EUR, 28 April 2015)

Examples of projects of interest are those including new drugs, new indications for existing drugs, development of new medical devices, studies utilising tissue banks, or registry studies, and in particular those evaluating the introduction of new treatments. Evaluation of new treatments and new methods including new or revised surgical procedures is also of relevance. Of note, Denmark is financing international clinical trials if the principal investigator site is located in Denmark.

6.3.7 Italy

In Italy, an increase in clinical trial activity was seen as a consequence of specific measures and funding[135, 136] made available through the Medicines Agency AIFA to stimulate non-commercial clinical trials.[110] The list of tasks of the Italian Medicines Agency (AIFA) includes pricing, HTA, and the promotion of independent research on drugs.[135, 136] AIFA set up the program on independent clinical research in 2005. Calls for proposals are aimed at investigators working in public (e.g. NHS, universities, etc.) or non-profit organisations (e.g. scientific foundations, patient associations, etc.).

For the funding an ad hoc fund was set up, requiring pharmaceutical companies to contribute 5% of their yearly expenditure devoted to promotional initiatives (e.g. seminars, workshops, etc.) aimed at physicians. This ad hoc fund consists of about €40 million each year and it guarantees not only the AIFA research program funding, but other AIFA-related activities as well (independent drug information, reimbursement of orphan drugs, and "life saving" drugs, not yet marketed).[135, 136]

An independent scientific committee (Research and Development Committee, R&D) has been founded, in order to coordinate the different aspects of the public scientific research. Moreover, the R&D committee plays a fundamental role in proposing research areas where to address the public funded research, in conducting the first phase of the selection process, and in supervising the implementation of the projects. A team of 8 full time equivalents is managing this effort.(personal communication Carlo Tomino, AIFA) The priorities are set by the AIFA board. The focus is on pharmaceuticals. Funded trials belong to the area of orphan drugs, head to head comparisons of drugs and therapeutic strategies, appropriateness of drug use and pharmacoepidemiology studies. The trials can be part of a large international trial. All funded trials are exempted from the Ethics Committee fee.

The sponsor and investigators of such non-commercial clinical trials should not have a conflict of interest (e.g., no patent ownership). The research concerns drugs reimbursed within the National Health System. The evaluation procedure mirrors the accredited standards of internationally recognised scientific institutions. The **evaluation of projects is based on the following criteria**:

- Relevance of the expected results for the clinical practice within the NHS;
- Scientific validity, in order to select projects with the highest scientific merit;
- Potential impact on the regulatory activity of AIFA, with specific attention to guide the decision about drug reimbursement and use limitations within the NHS;
- Lack of commercial interest for the objectives of the study, in order to use available resources on important but neglected areas of interest.

The project to be funded are selected via a **two-step review process**. In the **first step**, researchers are required to submit a "letter of intent" (i.e. a synthesis of the study protocol). This protocol synthesis is evaluated by the R&D Committee at AIFA, and scored for scientific and study quality; relevance towards the NHS; scientific qualification and experience of the proponents and of the participating unit; and budget adequacy. Investigators passing to the **second phase** of the evaluation are required to present a fully detailed study protocol.[136]

The second step, the evaluation of the study protocols involves more than 20 experts (half from Italian institutions and half international). At least two written comments are obtained for each study protocol before the study session meeting. Study protocols are ranked on the basis of the final score and, starting with the highest score (the average of each expert's vote) the available funds (€35 million in 2005, €31 million in 2006, €13 million in 2007 and more than €11 million in 2008) were distributed accordingly. A total of 1772 proposals for trials were introduced 2005-2009 and over 200 received funding for a total of about €100 million (Table 5).[136]

Table 5 – Funded protocols by the AIFA programme (2005-2009)

Area	Funded protocols (N)				
	2005	2006	2007	2008	2009
✓Rare diseases and orphan drugs	20	24	20	- (*)	- (*)
✓Head to head comparisons	13	16	9	12	10
✓Pharmacovigilance and appropriateness	21	11	17	26	8
Total	54	51	46	38	18

(*) The rare diseases topic has not been included in the 2008 and 2009 Calls

Source: AIFA presentation[136]

These trials included over 4200 clinical sites and 42 000 patient suffering from a number of different diseases. About 40% of these trials were completed in 2013. Over 250 high impact peer-reviewed publications were generated based on these trials.[136]

The intensity of the programme was decreased after 2009 but was activated again more recently.

In addition, clinical trials are also funded directly by the ministry of health. The total amount spent on clinical research is about €40 million per year.

6.3.8 Spain

Over 80% of the RCTs with a CTA in Spain are sponsored by the pharmaceutical industry. Individual investigators, cooperative groups, and scientific societies are the sponsor of the remaining RCTs. Public funding of biomedical research (mainly basic research, very few RCTs) is mainly through the department of health and some through the regions.[137] A system of calls and peer review is used. In 2004, the Spanish Clinical Research Network was created to stimulate the conduct of RCTs.[137]

A **system similar to the 5% withholding of marketing expenses for pharmaceuticals in Italy is followed**.[12]

Spain supports the **synchronised call approach for the public funding of clinical trials**. The aim of this pilot activity is **to promote co-operation between national/regional funding bodies and contribute to increasing the quality of research in Europe**.

http://ec.europa.eu/research/participants/portal/desktop/en/opportunities/h2020/topics/2474-inso-8-2014.html

For each Synchronised Call, research funding bodies will determine a scientific field in which they publish a call on a synchronised basis in several European countries. There will be a common deadline for proposal submission as well as common evaluation criteria and a common scoring method. There will be a common working language for proposals. A common evaluation panel will be composed of internationally recognised experts.

After the joint international peer-review the participating funding bodies will receive the evaluation summary reports only for their national research proposals. The abstracts and metadata of proposals which are above the threshold will be made available across the participating research funding bodies, e.g. to facilitate benchmarking. The actual selection of proposals for funding would ultimately be made by each national funding body: individual funding bodies would not be bound by the evaluation result, but would be encouraged to fund only those proposals which are above the threshold. The project proposals may, but are not required to, have a transnational dimension.

This means proposals for study in Spain need to compete with other study proposals from other EU countries. Finally the best ranked local study proposals receive local financing (about €10 million per year) but the procedure allows to evaluate the quality of the proposals and to eliminate duplication of research. An ERA-Net cofund could however be an alternative instrument to promote co-operation between national/regional funding bodies and contribute to increase the quality of clinical research in Europe. In addition, this route could provide EU co-funding under the Horizon 2020 framework (Report on the Workshop on "Funding multinational independent trials" organized by Instituto de Salud Carlos III (ISCIII) and European Clinical Research Infrastructure Network (ECRIN), January 2015, Madrid, Spain).

Key Points

- **Some of the main challenges/recommendations to strengthen non-commercial clinical trials mentioned in previous reports are the following:**
  - **Levels of funding**
  - **Research infrastructure**
  - **Education, training and career structure/opportunities**
  - **Competitive payment and contractual status for investigators**
  - **Apply a risk-based approach (~reduce costs)**
  - **Patient recruitment (~Produce statistically reliable results)**
  - **Reduce administrative/regulatory complexity**
  - **Standardisation: electronic patient records, procedures, data management software, etc.**
  - **Centralization of specialized care (~especially for rare disorders)**
  - **Solve problems of reimbursed care in trial setting.**
  - **Provide a publication vehicle to present the results of the trials.**
- **Some of the interesting features of a public funding system identified in other countries are the following:**
  - **Study proposals have to indicate their potential impact on the efficient use of the healthcare budget**
  - **Budget is foreseen for specific implementation projects which try to increase the impact of the clinical research in routine clinical practice.**
  - **The existence of synchronised calls for public funding of clinical trials (possibly ERA-net cofund in the future)**
- **Selection criteria mentioned:**
  - **Relevance, needs of the patients and public**
  - **Scientific validity**
  - **Potential impact**
  - **Lack of commercial interest**

7 DISCUSSION

In this report we argue that government has a primordial task in performing key clinical trials that industry does not perform. Based on the rationale presented above the focus of the discussion is not so much on whether this activity should be developed but rather on the modalities to have the right trials identified and selected for funding by the government and to make sure the selected studies are performed in an efficient way. This should support a more efficient health care system providing more and better health care for everyone within our limited resources.

7.1 Identification and selection of publicly funded trials

The scope of this report is on non-commercial clinical trials, and confirmatory practice-oriented, pragmatic type of trials in particular, that are **not performed by industry because they have no interest in or no possible benefit from performing these trials**. Furthermore, the **trials should have an immediate impact on the clinical practice**. **Both the perspective of the patient (effectiveness) and of society (cost-effectiveness) should be considered.** These criteria are important for the identification and selection of publicly funded trials.

As mentioned by the authors of the "Funding First: Exceptional Returns" report[5] "*the inability to set research priorities with complete confidence should not be allowed to distract from the principal findings*" that public funding of clinical research, if well selected, offers value for money. There is no perfect 'one size fits all' identification and selection process. However, the identification and selection process of other institutes might provide inspiration for the setup of such a process in Belgium. We provide the example of the National Institute for Health Research (NIHR) and add some further reflections.

7.1.1 NIHR

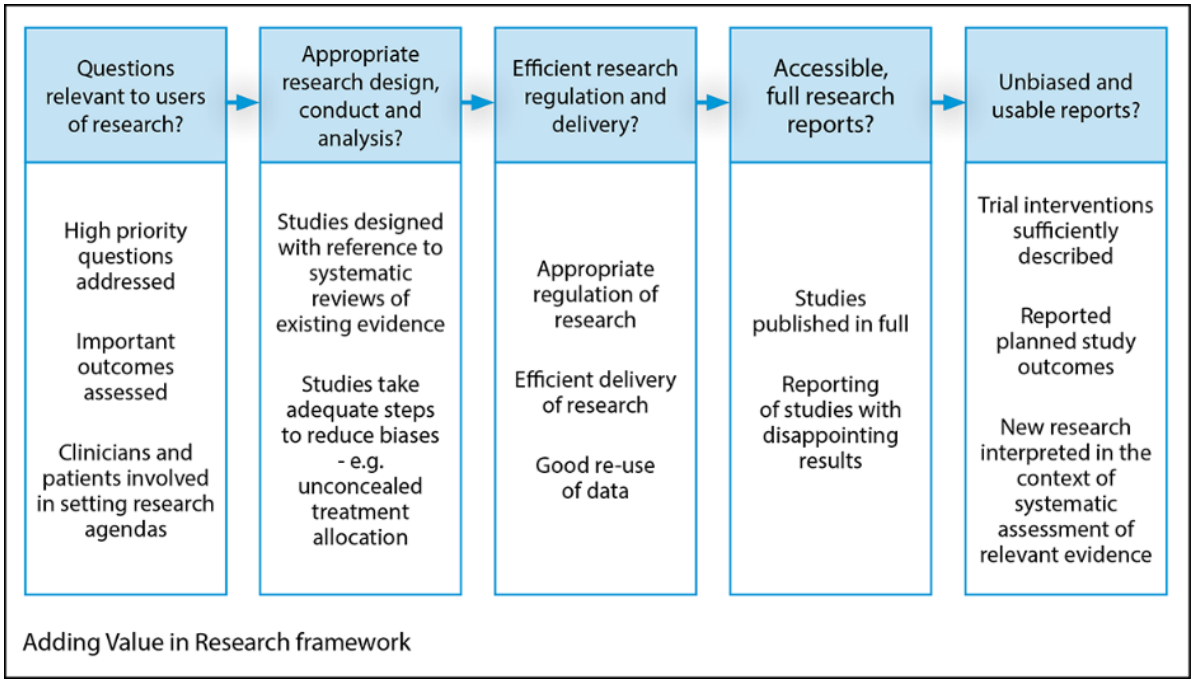
"*The NIHR, Evaluation, Trials and Studies (NETS) programmes fund valuable independent research for health and social care decision-makers. These programmes are a key part of a portfolio of work managed by the NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC), based at the University of Southampton.*" They "*manage the identifying, prioritising, funding, delivery, publication, and dissemination of high-quality research and lead other NIHR initiatives to meet the needs of the public, patients and the NHS.*"(http://www.nets.nihr.ac.uk/about)

Adding value in research

"*The NIHR is committed to Adding Value in Research to maximise the potential impact of research that it funds for patients and the public. … Adding Value in Research ensures that NIHR funded research:* (Figure 16)

- *answers **questions** relevant to clinicians, patients and the public;*
- *uses appropriate **design and methods**;*
- *is **delivered** efficiently;*
- *results in accessible full **publication**; and*
- *produces unbiased and usable **reports**.*" (http://www.nets.nihr.ac.uk/about/adding-value-in-research)

Figure 16 – Adding Value in Research Framework



Source: http://www.nets.nihr.ac.uk/about/adding-value-in-research

Needs-led: "*Ensuring that research reflects the **key information needs** of decision-makers."*(http://www.nets.nihr.ac.uk/about/needs-led-science-added)

- ***Identifying needs**: "We work with a wide range of stakeholders, such as NICE and the National Screening Committee (NSC), to identify gaps in knowledge. Systematic reviews also reveal areas where good evidence is lacking. This 'topic identification' process generates many possible ideas for research."*

  NIHR mentions a number of ways to identify important research questions:(http://www.nets.nihr.ac.uk/identifying-research)

  - "*Engaging with key stakeholders within the NHS, public health community and the NIHR*" (e.g. the NIHR Horizon Scanning Centre (NHSC))
  - "*Working with the James Lind Alliance (JLA) Priority Setting Partnerships (PSPs) which bring patients, carers and clinicians together*."
  - "*External engagement with people and organisations that are most likely to know where research is needed. This includes policy makers and organisations representing health professionals … or patients and carers*."

- "*Extracting research recommendations from high quality research and guidelines.*" (e.g. the Cochrane Library and NICE)
- "*Inviting anyone to suggest a research question at any time by visiting our website.*"

- **Prioritising topics and proposals**: "*Possible topics for research are reviewed by advisory groups of external experts and public members to assess the need for the proposed research.*"(http://www.nets.nihr.ac.uk/about/needs-led-science-added)

Science-added: "*Ensuring that research generates **high-quality** evidence.*"(http://www.nets.nihr.ac.uk/about/needs-led-science-added)

- ***Reviewing proposals**: Proposals are reviewed by a range of experts.*
- ***Scrutinising proposals**: The panels and boards consider the scientific quality of applications and value for money. Deliverability is a critical factor so proposals are carefully assessed to ensure that the research teams' plans are achievable.*
- ***Monitoring projects**: We maintain regular contact with projects that are funded, so we can offer support if they run into difficulties, for example with recruitment. This ensures they deliver meaningful and timely results. Thanks to active monitoring, nearly all our projects complete successfully.*
- ***Publishing results**: We promote active dissemination of results in the scientific literature. We also publish comprehensive reports of projects in the NIHR Journals library.*

7.1.2 Other reflections on setting up a clinical trials programme

The NIHR system shows a combination of a top down and bottom-up approach were all stakeholders can submit their ideas (this is actually similar to the way study topics are collected at KCE for its annual work programme). The selection of topics out of these suggestions is of great importance and is a first essential element in the success of a public funded program.[15] Since the government funds the studies, they should have the final word in the selection process. However, researchers should also be included in this process.

- In the first place, unnecessary efforts should be avoided by excluding topics were the answer on the research question is already available with high certainty from published evidence. Both from a scientific and efficiency point of view, a **systematic review and critical assessment of available evidence** should be performed before large sums of public money are invested in clinical trials. "*Wise investments in systematic reviews by NHS R&D will have saved the Medical Research Council and other funders considerable sums by preventing wasteful use of resources on unnecessary further research.*"[85]
- A pooled database of **planned and ongoing trials** could facilitate international collaboration, as is being tried for HTA projects in Europe.
- Furthermore, the selection of topics should also include a **critical appraisal of the suggested study design**. If the trial is badly designed, the study will produce unreliable results,[15] resulting in waste of the invested resources. This critical assessment should be performed before the funding is provided and, as mentioned by NIHR, it should be further monitored to increase the completion success of funded projects.

The availability of evidence is also linked to the **possible health impact**, which should be another element in the selection process. While drug firms have an incentive to direct their efforts where it is most profitable,[138] government should focus on health benefits. "*An important factor in any such selection process would be the overall public health impact of the candidate drug. This factor would be measured by the relative burden of the underlying disease, by the availability of existing clinical options to treat the disease, by the need to stimulate greater competition within a given therapeutic class, and by the need to treat certain neglected diseases, including both rare or orphan diseases, by means that might otherwise not be developed absent government assistance.*"[139]

Costs and possible future cost savings should also be taken into account. Some might prefer to focus on the possible health impact and available evidence. Nevertheless, the resources for public funding are limited and should be invested efficiently trying to optimise the return on investment. We come back to the costs of research proposals (part 7.4.1) and the possible economic benefit of public funded research which can be linked to sustainable future financing opportunities (part 7.2).

7.1.3 When can we start with public funding of trials

A transparent identification and selection process should be set up to determine which trials should receive public funding taking into account a.o. the above mentioned elements. This will take some time. This does not mean that public funding of clinical trials should be postponed until the involved stakeholders agree on this process. For the bottom-up questions (from e.g. specialists and patients) it is necessary to have such a process to avoid arbitrariness. However, for the most urgent top-down questions identified by government (e.g. after a systematic literature review was performed), the setup of the necessary trials can already be initiated. The absence of a final identification and selection process should thus not be a reason to put public funding of RCTs on hold.

7.2 Evaluation of publicly funded RCTs

7.2.1 Government-funded trials and the Declaration of Helsinki: a prime example

The declaration of Helsinki (2013 version, http://www.wma.net/en/30publications/10policies/b3/) is very clear on the registration, publication and other ethical principles for medical research involving human subjects. For example:

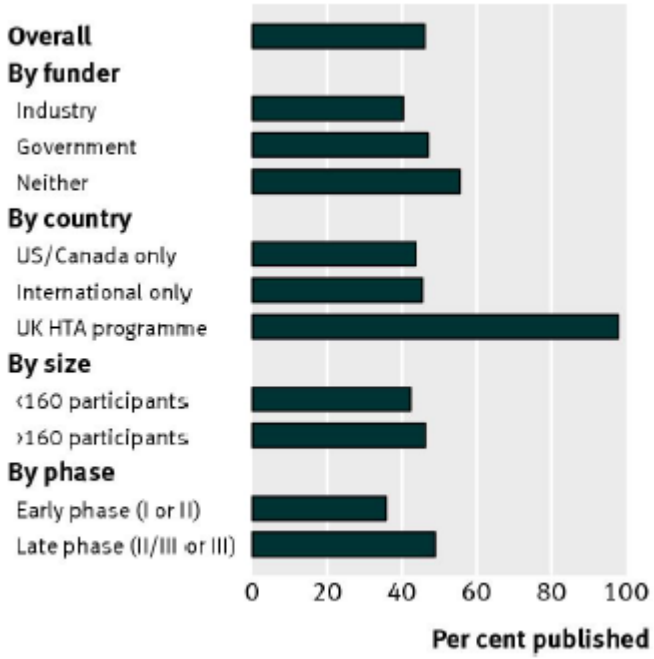
- "*Every research study involving human subjects must be **registered** in a publicly accessible database **before recruitment of the first subject**.*
- *The **design** and performance of each research study involving human subjects must be **clearly described and justified in a research protocol**.*
- *Researchers have a duty to **make publicly available the results** of their research on human subjects and are accountable for the completeness and accuracy of their reports. …. Negative and inconclusive as well as positive results must be published or otherwise made publicly available.*"

These principles are often violated, and not just by industry. A BMJ editorial[132] entitled "All trials must be registered and the results published – Academics and non-commercial funders are just as guilty as industry" mentions the following: "*Biased under-reporting of research has been documented for well over two decades and the evidence for it is now overwhelming.*[140-143] *Under-reporting is research misconduct and has serious consequences.*[144, 145] *It leads to overestimates of the benefits of treatments and underestimates of their harmful effects.*[61] *Because of this it puts patients at risk and wastes healthcare resources.*"

The editorial published the Figure 17 presenting the proportion of clinical trials registered by 1999 and published by 2007, of which the results are not very positive. However, it also shows that there are exceptions: "*98% of the studies funded by the NIHR Health Technology Assessment Programme have led to the publication of full reports (Ruairidh Milne, personal communication). The programme has achieved this by holding back a proportion of the research grant (5%, red.) 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.*

This shows what can and should be done." Clear rules with responsibilities for different stakeholders and consequences should be set up to achieve this.

Figure 17 – Proportion of clinical trials registered by 1999 and published by 2007



Source: published in Chalmers et al.,[132] referring to Ross et al.[146]

7.2.2 A good investment?

In the first place, the **scientific impact** of publicly funded trials should be evaluated. Did the trial results provide the requested information and did this have an impact on clinical practice? For example, the Cancer Drugs Fund in the UK has been criticized: "*One of the most lamentable features of the Cancer Drugs Fund has been the lack of quality data collection to steer future decision making. There has been no request for data on quality of life or patient reported outcome measures.*"[147] As a result, the authors question "*where else might this money have been better spent?*"

Next to this, the **financial impact** should also be evaluated. "*Financial returns may not be the key driver in research decisions, but the demands on public funding are substantial and it is therefore important to evaluate investment in research.*"[44] "*Because resources used for publicly and charitably funded medical research, including cancer research, could potentially be put to other purposes for the benefit of society, there is an obligation to demonstrate that such investments represent good value.*"[43]

"*How to assess the impact of research is of growing interest to funders, policy makers and researchers mainly to understand the value of investments and to increase* ***accountability****.*"[18] As part of this transparent evaluation, policy makers and researchers should in advance set up a list of indicators and use these indicators in their impact assessment. Both scientific and financial elements should be included in this set.

7.2.3 Research on research: improving processes

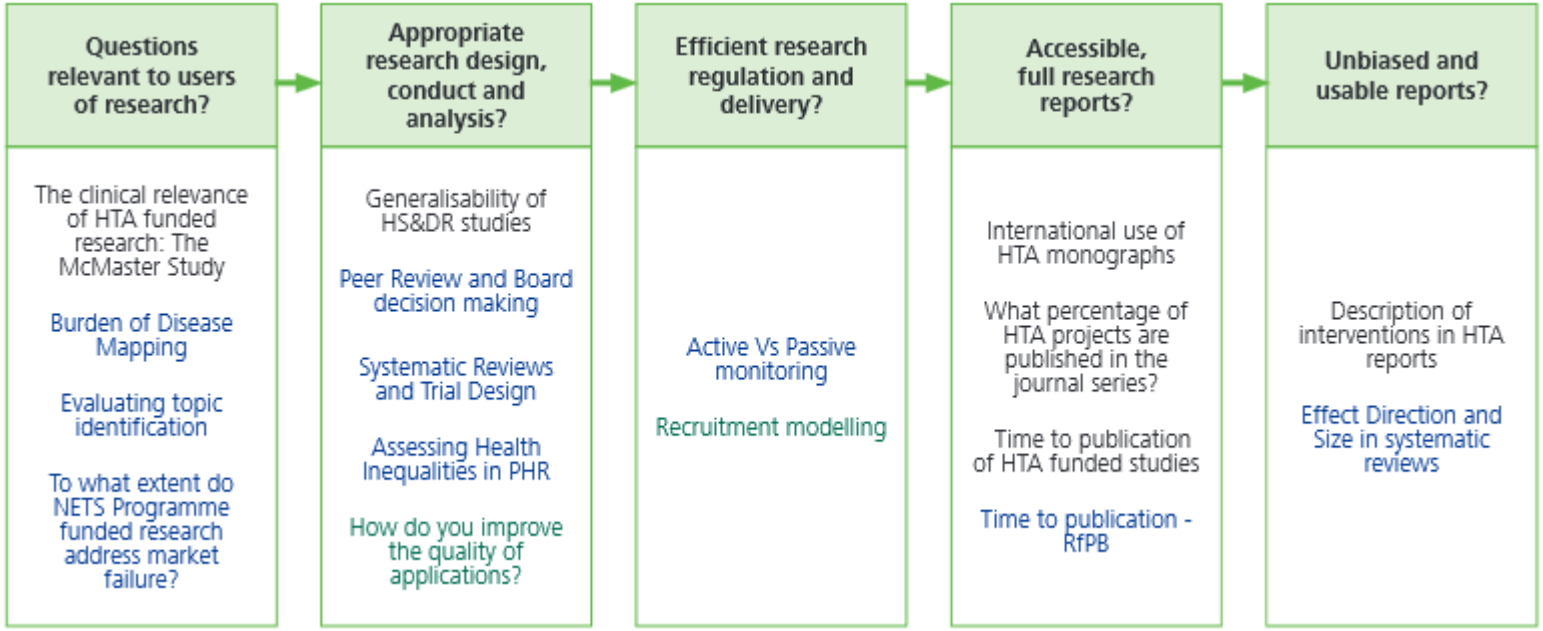
NIHR performs '**Research on Research**' (RoR): "*We carry out our own research, to generate evidence about research management processes. This can help us improve our processes, and also provides valuable information for other research funders.*"(http://www.nets.nihr.ac.uk/about/needs-led-science-added)

"*The core purpose of the programme is:*

- *To provide scientific evidence in order to improve research management and research processes,*
- *To build the skills, capacity and interest within NETSCC to improve the delivery of our research management function and,*
- *To enhance the reputation of NETSCC as a 'needs-led, science-added' centre.*"(http://www.southampton.ac.uk/netscc/research/index.page)

Figure 18 provides a diagram with completed, active and prioritised studies supporting this improvement of processes, which could be very useful to support the setup of such processes in Belgium.

Figure 18 – Research on Research (RoR) projects contributing to the Adding Value in Research agenda



Completed studies, Active Studies, Prioritised topics
Source: http://www.southampton.ac.uk/assets/imported/transforms/peripheral-block/UsefulDownloads_Download/A833D0D39B844BB782C563FAE0F97388/RoR.pdf

7.3 Financing of trials with public money

In chapter 2, several examples were provided of individual trials and research programs studying the economic return of publicly funded research. Taking into account the shortcomings of these studies, the findings suggest "*that large public research investments can yield considerable clinical and economic value when targeted to address research questions with great clinical relevance and public health effect.*"[29] The Dutch organisation for health research and development ZonMW mention that "*it is a logical response of wanting to curb the growth in health care expenditures by implementing budget cuts and targets. However, there are smarter alternatives ... through targeted investments in research and innovation.*"[49]

Of course, the next question might be: How will government finance these trials? Where will we get the money from? How much should we invest? Several opportunities have been mentioned by experts to finance these government-funded studies from taking a fixed percentage of the NIHDI budget to taxing part of the industries turnover or marketing expenses. Whatever the source of funding, it should be regarded as part of the limited resources which we would like to use in an efficient way.

7.3.1 Public money used to fund public-private partnerships

The aims of publicly funded practice-oriented clinical trials are different from public-private partnerships. It was out of scope and it is difficult to judge their relative importance for society and public health, but in terms of EU tax-payer money spent it looks like PPPs are considered more important. For example, the Innovative Medicines Initiative (IMI) is a public-private partnership (PPP) in the 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).

Some projects focus on specific health issues such as neurological conditions (Alzheimer's disease, schizophrenia, depression, chronic pain, and autism), diabetes, lung disease, oncology, inflammation & infection, tuberculosis, and obesity. Others focus on broader challenges in drug development like drug and vaccine safety, knowledge management, the sustainability of chemical drug production, the use of stem cells for drug discovery, drug behaviour in the body, the creation of a European platform to discover novel medicines, and antimicrobial resistance. In addition to research projects, IMI supports education and training projects. These efforts also contribute to the standards of clinical trials in general.

The budget for the first phase (2008-2013) was €2 billion, half of which came from the EU's Seventh Framework Programme for research (FP7), and half of which came from in kind contributions by EFPIA companies.

For the ongoing IMI 2programme, it has a €3.3 billion budget for the period 2014-2024, of which half is coming from the Horizon 2020 EU framework programme and half is contributed by the life science industries or organisations that decide to contribute to IMI 2.

7.3.2 The start of a self-sustaining system?

ZonMW recommended to "*finance the investment agenda 2014-2020 with an initial budget provided by the government and subsequently share the potential cost savings that result from this investment agenda with the research institutes, the parties engaged in research and the parties implementing the research results and innovations.*"[49]

In the short term, priority might be given to research projects that might result in large savings or those that even would not cost so much in the short term.

Reference pricing with evidence development might be considered. In fact, the US Centers for Medicare and Medicaid Services (CMS) will reimburse the cost of medical devices studied under an investigational device exemption (IDE) if they meet certain criteria up to the cost of a currently marketed, similar product.[105] This concept could also be applied to some pharmaceutical trials e.g. interventions within the same indication which both have been compared to placebo and showed an added value but where no direct comparisons are available. In e.g. the case of Herceptin (see the SOLD trial in part Appendix 3.1), the cost difference between the short (9 weeks) and long treatment schedule (52 weeks) is more than €30.000. Instead of immediately reimbursing the one year treatment schedule, setting up a scientifically justified direct head-to-head comparison would have resulted in cost savings that could be used to finance this head to head trial.

Therapeutic progress can also be achieved with **good old and very cheap drugs**. It is very likely that older, often less expensive products are no longer promoted or do no longer fit in a company portfolio because they are unlikely to generate profit. Short-term costs for performing the trial can already be partially born by the price differences. Large cost savings may be possible

in the longer term. For example, the health care payer costs for Etanercept 50mg 1x/w and Sulfasalazine+hydroxychloroquine is about €1109/month (www.bcfi.be) versus <€25/month, respectively. An independent publicly funded trial[148] already showed that efficacy of both treatments was very similar for specific outcomes. This could result in large long-term savings if these findings find their way to the clinical practice (see Appendix 3.5).

Resulting economic benefits in the long term should be taken into account when considering the sustainability of a programme of publicly funded trials.

A special situation can occur in case an important new indication for an existing drug or device is developed with a publicly funded trial, leading to a potentially important financial benefit for the company. This type of trial, **generating new knowledge**, is not the primary focus of this report. Organisation like EORTC are however confronted with such questions from time to time. Such trials are preferably conducted either by the industry or as a public-private partnership, with potential returns also for the public partner.

7.3.3 The necessary budget and expertise to set up a good trial

How much is reasonable to invest in a selected trial? A good cost calculation and justification is necessary. This might seem very logical. However, the (hidden) costs of all necessary cost items need to be considered. An interesting slide show on the subject is available from http://medicine.umich.edu/medschool/sites/medicine.umich.edu.medschool/files/Res_Grants_Budgeting%20a%20Clinical%20Trial%202012%20Web%20Version.pdf.

It is better to spend a little bit more to launch a very interesting trial than to spend too small budgets which might be insufficient to set up a good trial and provide reliable and useful results. The latter would perhaps **please more investigators but is essentially a waste of money**. It is necessary to have a correct funding and not to compromise (too much) on the quality of your research and the ability to provide a correct answer to your original research question.

Public funders should consider the whole of cost items to set up a good trial, and not just the personnel costs, including a.o.:

- Fixed costs to set up the trial, e.g. designing study protocol and registration of the trial;
- Costs for inviting and selecting eligible patients, including the informed consent procedure;
- Cost for central randomisation;
- Cost for preparing the study medication (including placebo), storing and shipping.
- Costs for the studied interventions, related adverse events and patient follow-up;
- Cost for the timely reporting of adverse events;
- Logistic costs: next to the intervention, which equipment, test kits or other products or services are needed to perform the trial;
- Personnel costs: the principal investigator, a research coordinator for multi-center/international trials, researchers, data manager/analysts, research nurses, IT support, auditor, financial manager, etc.
- Overhead/administrative costs;
- Cost for audit;
- Costs related to data storage and archiving;
- Costs for statistical analysis and report writing;
- Costs for study-related meetings, presentations and publications;
- Etc.

Other decisions will have a clear impact on these costs and already have to be considered when setting up the research protocol, e.g. what is the necessary follow-up of patients in the trial.

7.4 Efficiency in conducting clinical trials and cost containment

It is important to think about strategies to reduce the costs of performing public-funded clinical trials. In first instance, we think about risk-proportionate approaches to the regulatory dossier and review by the competent authorities, the management and monitoring of clinical trials. Furthermore, a good research infrastructure should be set up and (inter)national collaboration should be considered.

As for industry also organisations running publicly funded trials need to identify their core business and may want to outsource items to cope with

transient peeks in the workload or in case the specific expertise is not available in-house.

7.4.1 Risk proportionality

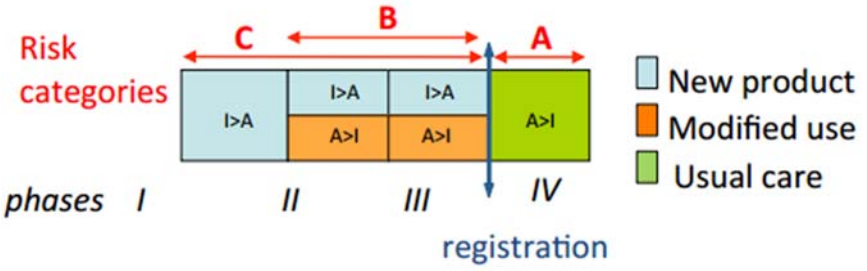
Compared with pre-authorisation trials, the comparison of two licensed alternatives for the same indication, where the safety risks are already well known, may need another review by the competent authorities and also the study monitoring approach should be adapted.

Risk-based approach in the new trial regulation

The **new EU trial regulation** for medicinal products introduces the notion of 'low-intervention' trial. "*The risk to subject safety in a clinical trial mainly stems from two sources: the investigational medicinal product and the intervention. Many clinical trials, however, pose only a minimal additional risk to subject safety compared to normal clinical practice. This is particularly the case where the investigational medicinal product is covered by a marketing authorisation, that is the quality, safety and efficacy has already been assessed in the course of the marketing authorisation procedure" or, if that product is not used in accordance with the terms of the marketing authorisation, that use is evidence- based and supported by published scientific evidence on the safety and efficacy of that product, and the intervention poses only very limited additional risk to the subject compared to normal clinical practice. Those low-intervention clinical trials are often of crucial importance for assessing standard treatments and diagnoses, thereby optimising the use of medicinal products and thus contributing to a high level of public health. Those clinical trials should be subject to less stringent rules, as regards monitoring, requirements for the contents of the master file and traceability of investigational medicinal products. In order to ensure subject safety they should however be subject to the same application procedure as any other clinical trial. The published scientific evidence supporting the safety and efficacy of an investigational medicinal product not used in accordance with the terms of the marketing authorisation could include high quality data published in scientific journal articles, as well as national, regional or institutional treatment protocols, health technology assessment reports or other appropriate evidence*."

"***The Recommendation of the Organisation for Economic Cooperation and Development (OECD) Council on the Governance of Clinical Trials*** *of 10 December 2012 introduced different risk categories for clinical trials. Those categories are compatible with the categories of clinical trials defined in this Regulation as the OECD Categories A and B(1) correspond to the definition of a low-intervention clinical trial as set out in this Regulation, and the OECD Categories B(2) and C correspond to the definition of a clinical trial as set out in this Regulation*."[107] The categories proposed by OECD are given below.

Figure 19 – The risk-based approach proposed in the OECD report.[59]



I>A= industry > academia; A>I= academia>industry; Category A = Clinical trials using already marketed medicines under the licensed indication; Category B = Clinical trials using already marketed medicinal products, exploring their use in new indications, new populations (repurposing trials); B(1) = exploratory repurposing trials; B(2) = practice-oriented trials with one of the drugs in an off-label indication but supported by sufficient evidence; Category C = Clinical trials exploring safety and efficacy of never-marketed medicinal products.

A similar approach may be used for medical devices; however, – performance is evaluated in the pre-registration phase in Europe – not efficacy, as is the case in the US. This will have an impact on the risk category of post-registration trials for high-risk devices in Europe, compared with the US.

"The sponsor shall, when applying for a low-intervention clinical trial, where the investigational medicinal product is not used in accordance with the terms of the marketing authorisation but the use of that product is evidence-based and supported by published scientific evidence on the safety and efficacy of that product, propose one of the Member States concerned where the use is evidence-based, as reporting Member State." [107]

Risk based approach in the UK

The risk-based approach in the OECD report and the new trial regulation are based on the experience with a risk-based approach in the UK. The following information is based on a paper resulting from a risk-stratification project initiated by an ad-hoc working group under the auspices of UK's Department of Health, Medicines and Healthcare Products Regulatory Agency (MHRA) and Medical Research Council (MRC) to address key issues for clinical trials in the UK.[98] The document focusses on investigational medicinal products (IMP), but a similar approach can also be applied to other interventions (e.g. devices).

Several risks are inherent to performing a clinical trial. In the first place, we think about the safety of the patients participating in the trial. Secondly, "*other risks related to the design and methods of the trial (including risks to participant safety and rights, as well as reliability of results)*"[98] are also considered since e.g. misleading results may also put future patients at risk.

Risks to participant safety

"*Within a particular clinical trial,* [risks to participant safety] *can be categorised in relation to* ***how much is known about the medicine(s) being investigated****. These potential risks should be assessed relative to the standard of care for the relevant clinical condition and the level of clinical experience with the intervention rather than the patients' underlying illness or the recognised adverse effects of the intervention.*

The potential risks should be balanced against the level of risk that a trial participant would be exposed to outside of the trial." A simple categorisation of three risk types which is **mainly based on the licensing status** of the intervention is proposed and described in Table 6. This should allow simplification where possible. For example, for lower-risk trials, the requirements for both obtaining regulatory approvals, conducting the trial, monitoring of participant safety, GCP inspections, etc. could be simplified.[98]

Another consequence of a low risk-level associated with the trial could be a reduced **trial insurance** fee. However, insurance companies are often not (yet) familiar with this situation. They are used to insure manufacturers of products and the trial insurance is often part of the overall insurance package. This **possible hurdle for non-commercial trials** may thus be overcome when the relatively few insurance companies that offer trial insurance are better informed of the new risk categories.

Table 6 – Trial categories based upon the potential risk

Trial Categories based upon the potential risk associated with the IMP	Examples of types of clinical trials
Type A*: no higher than* that of standard medical care	Trials involving medicinal products licensed in any EU Member State if: ▪ they relate to the licensed range of indications, dosage and form or, they involve off-label use (such as in paediatrics and in oncology etc) if this off-label use is established practice and supported by sufficient published evidence and/or guidelines
Type B*: somewhat higher* than that of standard medical care	Trials involving medicinal products licensed in any EU Member State if: ▪ such products are used for a new indication (different patient population/disease group) or ▪ substantial dosage modifications are made for the licensed indication or ▪ if they are used in combinations for which interactions are suspected Trials involving medicinal products not licensed in any EU Member State if ▪ the active substance is part of a medicinal product licensed in the EU (A grading of TYPE A may be justified if there is extensive clinical experience with the product and no reason to suspect a different safety profile in the trial population)*
Type C*: markedly higher* than that of standard medical care	Trials involving a medicinal product not licensed in any EU Member State (A grading other than TYPE C may be justified if there is extensive class data or pre-clinical and clinical evidence)*

CTA: Clinical Trials Authorisation; IMP: investigational medicinal product.
**If a grading other than those indicated is felt to be justified the rationale and evidence should be presented in the CTA application*
Source: copied from MRC/DH/MHRA Joint Project[98], based on Brosteanu et al.[149]

All other risks related to trial design and methods

"*a Type A trial from an IMP perspective does not mean all other risks are low. The risks associated with participant rights and reliability of results are multi-factorial, and less amenable to simple categorisation at the trial level. These risks must be assessed independently of the risks related to the IMP.*"[98] For example, "*The design of a study has a major impact on the quality of the results; the more robust the design the less dependence there is on quality control and assurance measures for reliable results.*"[98]

The following Table 7 "*provides principles for investigators and sponsors to consider when determining the focus, type and intensity of study monitoring. There are many different approaches to quality control in a clinical study, and the most appropriate modalities will depend on the number of sites and logistical issues as well as the risk.*"[98] "*For trials using unlicensed IMP (Type C), GCP inspectors would usually expect effective site visits to be part of the monitoring plan.*" For Type A trials with no particular trial design vulnerabilities, central monitoring methods predominate.[98]

Such a risk-proportionate approach does not mean that the trials can be of a low quality. Ability and reliability to give an answer to the original research question stays of utmost importance. However, it is clear that the comparison of two licensed alternatives for the same indication, where the safety risks are already well known, may need another (less costly) monitoring approach than e.g. a study with a licensed product applied in a new indication.

Table 7 – Study monitoring based upon the potential risk associated with the intervention, design, methods or conduct of the trial.

		Concerns identified in the assessment of risk associated with the design, methods or conduct of the trial (other than the intervention) which remain after mitigations are in place	
		No	**Yes**
Risk associated with the intervention /IMP	**Type A**	**Low intensity** Central monitoring of protocol adherence and data quality. No requirement for site visiting unless there are concerns identified from central monitoring that cannot be addressed by other means	**Low+** As outlined in A, plus appropriate monitoring to address the specific vulnerabilities associated with trial design, methods or conduct identified in the risk assessment.
	Type B	**Moderate intensity** Central monitoring of safety data quality and timeliness as well as protocol adherence and quality of other trial data. Triggered visits for poor data return or protocol adherence concerns as well as unusually low or high frequency of Serious Adverse Events (SAE) reports (for studies where between-site comparisons are possible).	**Moderate+** As outlined in B, plus appropriate monitoring appropriate monitoring to address the specific vulnerabilities associated with trial design, methods or conduct identified in the risk assessment.
	Type C	**Higher intensity** More intense monitoring than above to have confidence in the completeness and reliability of safety data	**Higher+** As outlined in C, plus appropriate monitoring to address the specific vulnerabilities associated with trial design, methods or conduct identified in the risk assessment.

Source: copied from MRC/DH/MHRA Joint Project[98]

7.4.2 Research infrastructure and national collaboration

The term 'research infrastructures' refers to "*facilities, resources and related services used by the scientific community to conduct top-level research in their respective fields*". (http://ec.europa.eu/research/infrastructures/index_en.cfm?pg=what) It brings together the different stakeholders needed to perform clinical research of high quality in an efficient way. Setting up a research infrastructure may be seen as a large investment for an individual trial. However, this initial investment, gathering knowledge, facilities, etc., should be seen as an investment that might benefit all future research.

A report on the clinical research footprint and strategic plan to promote clinical trials in Belgium[14] mentions this "*involves the **integration of clinical researchers in a network of specialised centres**. Such a network would offer several distinct advantages.*

- *First, a network of specialised centres would further strengthen our **attractiveness in terms of quality and expertise** by avoiding fragmentation of competencies and enabling the pooling and sharing of best practices and key knowledge.*
- *Secondly, such a network would significantly **improve access to patients**, a key barrier for Belgium. It would facilitate consultation between the different specialised centres to locate and mobilise suitable patients and specific target groups of patients within specific pathologies.*"[14]

The ClinicoBRU network, whereby the three Brussels univiversity hospitals collaborate to attract more clinical trials can be seen as a local initiative in response to this demand.

The UK experience confirms this. "*The Department of Health's support for research networks has expanded substantially the number of patients entering clinical trials. For example, the National Cancer Research Network (NCRN, established in 2001 after a successful collaboration between NHS R&D and the MRC) doubled the number of new adult cancer patients entering clinical trials after only 2 years. By 2004–05, 12% of cancer patients (24 000 individuals) in England entered NCRN trials. This number is the highest per capita rate of cancer trial participation worldwide. It has become the basis for the UK Clinical Research Network*."[85]

Involving the appropriate bodies and gathering existing knowledge is of major importance. Amongst others, we think about the Belgian Federal Agency for Medicines and Health Products (FAGG-AFMPS), the Belgian Association of Clinical Research Professionals (ACRP.be) and the Belgian Association of Pharmaceutical Physicians (BeAPP), the Flemish department of Economy, Science and Innovation (EWI) and the Directorate general for Economy, Employment and Research of the Service public de Wallonie (SPW), the Board of University Hospitals in Belgium (www.univ-hospitals.be), platforms of hospitals setting up clinical trials (e.g. ClinicoBRU).

There is also an important role for the **teaching** institutes to provide courses in clinical trial methods, or as part of the continued medical education. Any centre or network that wants to organise a clinical trial needs standard operating procedures that define in detail the role and responsibilities of all actors involved. It may be appropriate to separate the roles of the sponsor from those of the investigator where possible.

A broad range of expertise is needed involving general experts in setting up and performing RCTs, HTA and economic evaluations complemented with expertise in the studied disease domain. Centres that want to participate in clinical trials would also benefit from the involvement of hospital staff and managers. "*Clinical staff, healthcare system managers, and researchers need to work together to optimize design and implementation of the study protocol. This is especially important during design and piloting. Staff and managers know how to best use existing health IT, workflow, clinical procedures, and local champions to make study participation easier for clinical staff.*"[19]

In addition, a **uniform electronic patient record, based on international standard terminology** would reduce the workload of trial data extraction to a great extent and provide an extra stimulus for the conduct of multicenter trials.

7.4.3 International collaboration

Most non-commercial trials in Europe are still national and many even single centre. In some cases, clinical trials can perfectly be set up on a national level, e.g. when there are sufficient eligible patients. Performing the trial in a national context might even be preferred since international collaboration might slow down the process by differences in the health care system, legislation, discussions on relevant endpoints, financing discussions, etc. On the other hand, international collaboration can provide multiple advantages: accelerate the inclusion of sufficient patients, shared knowledge and experience to set up a suitable research protocol, faster delivery of results on the relevant endpoints, etc. Pros and cons of national or international trials have to be weighed. For the conduct of large randomized trials or trials in orphan diseases, international cooperation in Europe might even be essential for success.

The European Organisation for the Treatment of Cancer (EORTC) has an important role to conduct the necessary large non-commercial clinical trials in oncology. However, if national governments are convinced of the added value of public funded RCTs and they are willing to invest in such research, then they could all benefit from joining already existing research infrastructures like ECRIN and EATRIS. Next to the benefits of shared knowledge and experience, improved access to patients, better quality of trials, etc. ECRIN may also provide the trial set-up, monitoring and analysis services. In case of transient capacity needs the services of private Contract Research Organizations (CROs) may also prove very useful.

Being part of an international research infrastructure does not mean that the importance of a national infrastructure can be neglected. A clear national structure is essential to join a possible international cooperation.

Financing of international studies is still an issue for many national funding agencies. For example, NIHR is willing to consider collaboration with international agencies. However, "*Studies funded by the NIHR programmes managed by NETSCC are generally UK based. The programmes will consider funding an international study where the chief investigator and lead institution are based in the UK and the study is relevant to and a priority for the UK population, and where overseas recruitment is funded from other sources. It will be exceptional for NIHR programmes to fund recruitment overseas.*"(http://www.nets.nihr.ac.uk/about/international)

Different options are currently being explored to stimulate the conduct of more high quality international trials and to realize the recommendations formulated in the OECD report of 2012.

7.5 Speed of the total process up to the implementation of research findings

As in industry, the speed of performing a clinical trial is a key success factor. The longer it takes to perform the study, the higher the costs e.g. for personnel will be. The faster the results are provided, the sooner clinical and economic benefits can arise from it. At the end, the speed and willingness of policy makers to implement research findings is thus of major importance.

In their study on research and innovation in health care, ZonMW recommended to increase the extent and speed of implementing cost savings in practice.[49] The literature provides some examples. In their editorial, Blakemore and Davidson refer to MRC's international trial published in 1991 demonstrating that folic acid helps to prevent neural tube defects.[150] Dietary supplementation, rather than individual medication, is the only secure route to that benefit, since the effects of folic acid operate very early in pregnancy, before most mothers are certain that they have conceived.[15] It took seven years before the American and Canadian governments introduced compulsory fortification of flour with folate. "*Such delays in the public-health response to the results of research obviously erode the ratio of benefit to cost*".[15] Another example is "*the inordinate length of time that it has taken to transform knowledge of the dangers of tobacco smoking into public-health policies and changes in social attitude*",[15] going back to a preliminary report published in 1950,[151] but which has still not achieved its full impact.[20] Several authors and reports state the importance of the willingness and speed of governments to translate the research findings into clinical practice in order to realise the full promise of the research investment.[15, 47, 152]

APPENDICES

APPENDIX 1. TERMINOLOGY

Comparative effectiveness trials or head-to-head trials	Trials that allow to conclude on the relative effectiveness (and safety) of two or more interventions used in the same indication (but often having a different cost for the healthcare payer).
Confirmatory trials	Trials used to confirm a predefined hypothesis, typically phase 2b/3 in drug development.
Exploratory trials	Trials used to generate multiple hypotheses, typically phase 1/2a in drug development.
Investigator-driven trial or academic trial or non-commercial trial	Clinical trial not sponsored by the medical industry. Many investigator-driven trials are however co-financed by industry. An important criterion in this regard is the purpose of the trial: has the sponsor a commercial objective or not. This is typically detailed in the contract section on publication of the results, whereby the sponsor/company wants to control the publication of the trial results in one way or another.
Opportunity cost	Opportunity cost is a key concept in economics. It is the value of the best alternative forgone: the next best alternative given up selecting the best option. Opportunity costs are not restricted to monetary or financial costs: the real cost of output forgone, lost time, pleasure or any other benefit that provides utility should also be considered opportunity costs.
Proof of concept study	The first early confirmation of efficacy of an intervention without already having determined the right dose, treatment duration, etc. This response may be based on surrogate endpoints.
Randomized controlled trail or randomized clinical trial (RCT)	Study design considered the gold standard for clinical research, representing the best way to determine efficacy and effectiveness for many intervention and prevention programs. It has the highest internal validity because it requires the fewest assumptions to attain unbiased estimates of treatment effects. Given identical sample sizes, the RCT also typically surpasses all other designs in terms of its statistical power to detect the predicted effect.
Sponsor and sponsor-investigator	In the conduct of a clinical trial, a sponsor is an individual, institution, company or organization that takes the responsibility to initiate, manage or finance the clinical trial, but does not actually conduct the investigation. However, an investigator can also be the sponsor: a sponsor-investigator takes on the responsibility as a clinical study sponsor and also conducts or oversees the clinical trial. Thus, a sponsor-investigator must comply with the applicable regulatory requirements that pertain to both the sponsor and the investigator.
Translational research	To "translate" findings in basic research into medical practice and meaningful health outcomes; in the context of clinical trials this concept is however often restricted to a proof of concept in exploratory trials.

APPENDIX 2. SEARCH STRATEGY

The following search strategy was performed in Pubmed on 19 August 2014.

1. exp government/ (123528)
2. exp government agencies/ (12732)
3. exp international agencies/ (39854)
4. exp organizations, nonprofit/ (15914)
5. 1 or 2 or 3 or 4 (174647)
6. (financing or funding or funded or sponsorship or support or funds or money).ab,ti. (712551)
7. exp Financial Support/ (36955)
8. 6 or 7 (741465)
9. 5 and 8 (24292)
10. Financing, Government/ (18816)
11. ((public* or government*) adj3 (funding or funds or financing or money or support* or funded or sponsor*)).tw. (11827)
12. 9 or 10 or 11 (49796)
13. exp Randomized Controlled Trials as Topic/ (96518)
14. trials.ti. (48485)
15. 13 or 14 (131190)
16. 12 and 15 (647)
17. budget.ti,ab. (13497)
18. 16 and 17 (5)
19. exp Financial Support/og (2986)
20. 15 and 19 (46)
21. (funding adj3 (organization or budget)).tw. (200)
22. 15 and 21 (5)
23. 18 or 20 or 22 (56)
24. Financing, Government/sn (439)
25. 24 and 15 (5)
26. 23 or 25 (61)

APPENDIX 3. EXAMPLES OF (POSSIBLE TOPICS FOR) PUBLIC FUNDED RESEARCH

In this appendix, we provide several examples of government-sponsored trials that already have been performed or topics that could benefit from setting up such trials. No systematic search was performed to identify these examples. Most of them were provided by the experts of the external expert group (see colophon). The aim was to provide inspiration and input for the next parts of this report, i.e. reasons for government-sponsored research and hurdles to set up an perform such trials. We would like to stress that for none of these examples a systematic literature search was performed for this report to check whether the information is still up-to-date. If one would consider one of these topics for further research, a systematic literature review should be performed in the first place to see whether the research question is still relevant. Like Horton mentioned in his Lancet editorial:[85] "*others have pointed out the high and cost-effective value of systematic reviews.*[153]

We divided the examples in different categories: those with a link to research performed by the Belgian Health Care Knowledge Centre (KCE) (Appendix 3.1), those identified on the website of the Belgian Centre for Pharmacotherapeutic Information (BCFI) (Appendix 3.2), research performed by the European Organisation for Research and Treatment of Cancer (EORTC) (Appendix 3.3), by the NIHR (Appendix 3.4), some of the many examples published in the New England Journal of Medicine (NEJM) (Appendix 3.5), and other examples including a.o. NIH- and NHS-government sponsored studies (Appendix 3.6).

Appendix 3.1. KCE

Avastin versus Lucentis

- Research question

  What is the safety and (cost-)effectiveness of Avastin versus Lucentis for the treatment of wet age related macular degeneration?
- Category: off-label use of a drug in another indication.
- Background information

  "*In its anti-cancer drug, bevacizumab, drug developer Genentech has created what may be the world's first "not me" (as opposed to "me too") drug, say Robert Campbell and colleagues (doi:10.1136/bmj.e2941). Despite evidence that it works in macular degeneration, the manufacturers and marketers (Roche in the US, Novartis in the UK and elsewhere) are actively discouraging its use for this condition, even going so far as taking legal action to prevent such off-label use. Why? Because they want people to use their other drug, ranibuzimab, which is licensed for treating macular degeneration.*
  The bottom line is that ranibuzimab is about 12 times more expensive"[154]

  Two publicly funded trials have been performed (the IVAN and the CATT trial). "*The IVAN results at the end of year two show that Lucentis and Avastin have similar functional effectiveness regardless of the drug received.*"[155] "*Data from the publicly funded CATT trial in the US found similar effectiveness and safety for the two drugs in treating macular degeneration.*"[154]

  The authors of a systematic Cochrane review of "*non-industry sponsored RCTs could not determine a difference between intravitreal bevacizumab and ranibizumab for deaths, All serious systemic adverse events (SSAEs), or specific subsets of SSAEs in the first two years of treatment, with the exception of gastrointestinal disorders. The current evidence is imprecise and might vary across levels of patient risks, but overall suggests that if a difference exists, it is likely to be small. Health policies for the utilisation of ranibizumab instead of bevacizumab as a routine intervention for neovascular AMD for reasons of systemic safety are not sustained by evidence.*"[156]
- Other considerations

  As in many countries, discussions are ongoing in Belgium on this topic. The cost for the health insurance is over €800 for an injection of Lucentis (the co-payment is very low) versus a non-reimbursed cost of about €40 for per injection with Avastin, prepared from a larger vial approved for use in oncology. This situation provides a huge opportunity for more efficient use of public money. (http://sanconet.be/nieuws/200-miljoen-euro-besparingen-gemist-in-de-gezondheidszorg-lucentis-vs-avastin)

Researchers and politicians have proposed or requested Genentech/Roche several times to conduct a comparative trial. The industry's position not to do this has resulted in several publicly funded trials comparing Avastin and Lucentis. In the UK, the above mentioned IVAN trial was conceived at a cost to the public of about £10 million. An investigation by The BMJ revealed how Novartis, marketing Lucentis in Europe, and others hindered these publicly funded trials.[157, 158]

Short versus long treatment duration with Herceptin (SOLD trial)

- Research question

  What is the effectiveness (and cost-effectiveness) of a short 9 weeks (~FinHer trial) versus longer 1 year (~HERA trial) Herceptin treatment regimen for the treatment of early HER2 positive breast cancer?

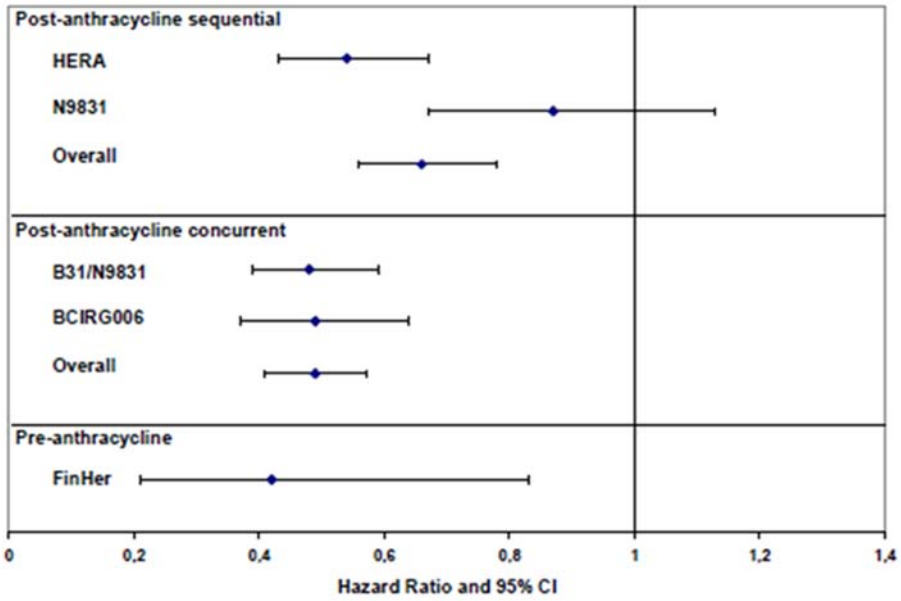
- Category: off-label use of a marketed drug in the same indication but with a different treatment schedule.

- Background information

  In 2006, KCE published a report on the use of Herceptin (trastuzumab) for the treatment of early HER2 positive breast cancer. Herceptin is registered in this indication with a treatment schedule of one year. However, at the moment the report was performed, two trials were already available indicating the potential of a short-treatment regimen. Firstly, there was the relatively small government sponsored FinHer trial[159] in which the drug was only administered for 9 weeks in a pre-anthracycline regimen. The disease-free survival of this study in comparison with the other available studies at that time showed the potential of this regimen (see Figure 20). Secondly, the E2198 phase 2 study compared 10 weeks with 12 months of trastuzumab treatment. This trial was not designed to test efficacy and not powered to determine equivalence. However, the 5-year overall survival was 88% in the 10-week treatment schedule versus 83% for the one-year treatment (p=0.29).[160] Two HTA institutes mentioned that these results supported the efficacy of short duration concurrent trastuzumab therapy when administered before anthracycline containing chemotherapy, as demonstrated in the FinHer study.[88, 89] At that moment, only indirect comparisons between the shorter and longer treatment schedule indicate the potential of the shorter treatment regimen. One of the recommendations of the KCE report was the following: "*A clinical trial comparing 9 weeks of trastuzumab pre-anthracycline with the 52-week post-chemotherapy regimen should be started without delay.*"[88]

  Also the UK researchers were confronted with the same issue. According to these researchers, one of the key issues is that "*a small study (the FinHer trial,[159] n=229), excluded from the manufacturer's submission, raises the possibility of an equally effective but shorter regimen, incurring lower cost and toxicity but with greater patient convenience.*"[89] This was unfortunately not explicitly taken into account in their economic modelling. In a comment in the Lancet, the same authors explain this and mention the following: "*New Zealand's drug-governing body, PHARMAC, is the first to suggest that the uncertainty surrounding the HERA schedule remains too great to justify the expenditure, and has commissioned a feasibility study to evaluate whether it should fund the FinHer regimen.[161] NICE could not ask us to evaluate the FinHer schedule because its remit is restricted to licensed indications and Roche sought marketing authorisation for a 1-year schedule only. We could speculate that Roche has little desire to develop a regimen that would reduce the use of trastuzumab significantly. Instead, by contrast, HERA is investigating whether more, rather than less, treatment is beneficial. In England and Wales, a schedule that might be as good and "may facilitate lower cost, greater patient convenience, and reduced risk of cardiotoxicity"[162] is not considered further.*"[163]

Figure 20 – Disease-free survival after trastuzumab by regimen type and study



Source: KCE report 34[88]

- Other considerations

  Setting up this trial and including a sufficient number of patients in due time seemed to be an issue since there is a kind of competition for the same patients to be included in other trials. Furthermore, the investigator fee may be higher in an industry-sponsored trials compared with a publicly funded trial(see part 4.2). Nevertheless, more than 8 years later, this question is still relevant. The Synergism Or Long Duration (SOLD) Study (ClinicalTrials.gov Identifier: NCT00593697) is almost finished. Heikki Joensuu, the principal investigator of both the FinHer and SOLD trial, mentions the following: "*In The Lancet, Aron Goldhirsch and colleagues[164] report long-awaited results from the HERceptin Adjuvant (HERA) trial. 5102 patients with HER2-positive early breast cancer were randomly assigned after surgery and completion of chemotherapy to observation, adjuvant trastuzumab for 1 year, or adjuvant trastuzumab for 2 years. The patients were followed up for a median of 8 years after study entry. The results confirm the clinical benefit of chemotherapy followed by trastuzumab compared with chemotherapy alone, but the comparison between the two durations of adjuvant trastuzumab is of particular interest. During the first few years of follow-up, the 2-year treatment group had slightly superior disease-free survival compared with the 1 year group (89.1% vs 86.7% at 3 years after randomisation), but this difference waned with further follow-up. At the time of the study analysis, an identical number (367) of disease-free survival events had occurred in the two trastuzumab groups (HR 0.99, 95% CI 0.85–1.14), and similar numbers of patients had died (196 in the 2-year group and 186 in the 1-year group). No difference in either disease-free or overall survival was recorded between the groups that received trastuzumab. ...*

  The optimum duration of adjuvant trastuzumab remains unknown, but we now know that it is likely to be 12 months or perhaps less. The next steps are to continue assessment of treatment durations shorter than 12 months, and inhibition of HER2 with other drugs."[165]

Hyperbaric oxygen therapy (HBOT)

- Research question

  What is the effectiveness (and cost-effectiveness) of hyperbaric oxygen therapy (HBOT) versus standard therapy in the treatment of diabetic ulcers?

- Category: devices for which there is no financial interest in performing a trial.

- Background information

  In 2008, KCE published a report on Hyperbaric Oxygen Therapy (HBOT).[166] "*Hyperbaric Oxygen Therapy (HBOT) is the administration of oxygen at pressures greater than normal atmospheric pressure for therapeutic reasons. This therapy has been available for several decades and is used for many indications. Most of these reported indications were, however, based on little or no evidence. … When applied under optimal circumstances, hyperbaric therapy is generally safe.*"[166]

"*HBOT has become accepted standard therapy in a few life threatening conditions i.e. decompression illness and gas embolism, mainly based on historical empirical evidence. For these indications it is unlikely that evidence from RCTs will become available because such RCTs are considered unethical by many in the field.*

There is low quality evidence from small RCTs on the clinical efficacy of HBOT for three indications. In the treatment of diabetic ulcers adjuvant HBOT may help avoid major amputations in the medium term compared to standard therapy without HBOT. For acute deafness presenting early, a slightly better recovery was observed with adjuvant HBOT, although the clinical relevance of this improvement is uncertain. Finally, HBOT may improve healing in selected cases of post radiation therapy tissue damage. In all of these three indications, however, future larger and well conducted RCTs should enhance our evidence base."[166]

One of the policy recommendations of this report was that "*conditional financing for experimental treatment could be considered and/or research encouraged specifically for those indications where some evidence is already available and that are of sufficient clinical relevance. For diabetic ulcers and selected cases of radiation induced tissue injury, low quality evidence from small RCTs on the clinical efficacy of adjuvant HBOT is available. Also for acute deafness presenting early there is some evidence for a beneficial effect although the clinical relevance of this benefit is questionable.*"[166]

- Other considerations

"*Although HBOT is an old technique, evidence from well conducted RCTs is poor, due to small trials, lack of blinding and randomization problems. Possible causes for this paucity of data are the technical difficulties to conduct these trials, the small number of patients in individual centres, and the absence of a driving financial interest to perform those trials.*"[166]

Tiotropium versus salmeterol

- Research question

  What is the effectiveness (and cost-effectiveness) of tiotropium versus other long-acting bronchodilators for the treatment of chronic obstructive pulmonary disease (COPD)?

- Category: direct comparison of registered and reimbursed interventions within the same indication.

- Background information

  Reimbursement for tiotropium for the treatment of COPD was granted, in part based on claims that the budget impact for the Health Insurer would be offset by cost savings due to less hospital admissions and less use of antibiotics and oral corticosteroids, and took effect on March 1, 2014.[167]

  After three years, a revision of this decision was undertaken. The conclusions were as follows:

  "*1. Les données scientifiques confirment les connaissances initiales d'un bénéfice versus ipratropium mais non versus ß2-mimétiques à longue durée d'action (sur des critères autres que des tests fonctionnels respiratoires) dans le traitement symptomatique de la BPCO.*

  2. Le prix actuel du Spiriva est environ 33% plus élevé que celui des ß2-mimétiques à longue durée d'action dont la valeur thérapeutique est comparable dans cette indication au point de vue des résultats en termes de morbi-mortalité, sur base des résultats des études actuellement publiées (confirmé dans les guidelines anciens ou récents).

  3. L'introduction du Spiriva dans le traitement de la BPCO n'a pas permis, contrairement à ce qui était annoncé, de diminuer les coûts de traitement liés aux autres médicaments."

  (https://www.riziv.fgov.be/webprd/appl/pssp/ssp/cns2/pages/MinisterialDecisionDet.asp?qs_SpcCod=00470448&qs_EffDat=20071220&qs_DmdId=6&qs_MdId=5146)

  At that time, in contrast with these conclusions, the reimbursement remained unchanged.

In 2009, KCE published a report on this topic.[167] "*Long-acting bronchodilators are recommended in patients who remain symptomatic despite adequate treatment with short-acting bronchodilators. Nevertheless, guidelines do not recommend a specific long-acting bronchodilator. Based on a systematic review of the literature, tiotropium is not superior on clinically relevant outcomes than salmeterol. In addition, tiotropium is more expensive by which the cost-effectiveness balance for this drug is unfavourable. In conclusion, tiotropium has its intrinsic merits but is currently too expensive from a medical and payer's perspective.*"[167] In 2012, instead of reducing the reimbursement/price of tiotropium, an administrative measure was taken to reduce the use of the relatively expensive drug. The reimbursement of tiotropium was put into chapter IV instead of chapter II, which means an a priori verification of the reimbursement modalities by a medical advisor of the health insurance fund.(http://www.domusmedica.be/documentatie/nieuwskijker/4170-domus-medica-schrijft-open-brief-aan-ctg.html)

- Other considerations

In 2011, the price of tiotropium was €50.20 per month, whereas this was €28.30 for salmeterol. Because of the large population using this drug, the budget impact in 2011 for tiotropium was already more than €30 000 000. If salmeterol would have been used, or if the price of tiotropium would have been similar to that of salmeterol, these expenses would only have been €17 000 000. In the meantime, the expenditures have only increased. Based on current evidence, government could already prefer reimbursement based on the price of the cheapest alternative. If not convinced by current evidence, a government-sponsored direct head-to-head trial could be set up to check whether these drugs are equally effective. If this would be confirmed, then this could save yearly more than €13 000 000 under the condition that if something is not better, a much higher reimbursement price is difficult to accept if policy makers would like to make efficient use of the limited resources.

Appendix 3.2. BCFI

The examples retrieved from the website of the Belgian Centre for Pharmacotherapeutic Information (www.bcfi.be) can be categorized as direct head-to-head comparisons between different (registered) treatment alternatives.

Denosumab

There is a need for comparative effectiveness studies of denosumab versus other osteoporosis treatments in postmenopausal women and especially in men suffering from prostate cancer receiving hormonal ablation treatment. (http://www.bcfi.be/Folia/index.cfm?FoliaWelk=F38N09G, http://www.bcfi.be/Folia/index.cfm?FoliaWelk=F39N06B&keyword=bisfosfonaten)

Comparative effectiveness of amitryptiline versus gabapentine or pregabaline in neuropathic pain

Some practice guidelines suggest pregabaline as the first choice treatment for painful diabetic neuropathy, based on placebo-controlled trials. The cost is 20 times higher compared with the standard treatment of diabetic neuropathy with amitriptyline. There is a need for a head to head comparison between the various treatment options. (http://www.bcfi.be/Folia/index.cfm?FoliaWelk=F39N06B&keyword=Amitryptiline)

Comparative effectiveness of a combination of nicotine-replacement products versus varenicline in smoking cessation.

This comparison is currently only based on indirect comparisons and there is a need for a direct comparison, given the important difference in costs of the two options.(http://kce.fgov.be/news/pharmacological-interventions-for-smoking-cessation#.VRkPBuEnJnk; http://www.bcfi.be/Folia/index.cfm?FoliaWelk=F41N06B&keyword=nortriptyline)

Comparative effectiveness in patients with early rheumatoid arthritis (RA) of a classical disease modifying anti-rheumatic drug (DMARD) plus a corticoid versus a classical DMARD plus an anti-TNF treatment.

Methotrexate is a frequently used classical DMARD. This head to head study is needed given the high price difference between the regimens.

Comparative effectiveness of the different ant-TNF treatments in RA.

No head to head trials have been conducted so far, despite the products are on the market for more than a decade.

http://www.bcfi.be/Folia/index.cfm?FoliaWelk=F38N09B&keyword=adalimumab)

Remark: see similar research question in Appendix 3.5: Therapies for Active Rheumatoid Arthritis after Methotrexate Failure.[148]

Appendix 3.3. EORTC

The information in this part is based on research performed by the EORTC. We made a selection based on information from the abstracts of publications following from these trials. For full details we refer to the original manuscripts.

Alpha-internexin expression predicts outcome in anaplastic oligodendroglial tumors and may positively impact the efficacy of chemotherapy[168]

This is a more exploratory type of trial. The conclusions of the trials were that in a homogeneously treated group of patients with grade III anaplastic oligodendroglial tumors, alpha-internexin expression had strong favorable prognostic significance for overall survival and may have predictive value for sensitivity to chemotherapy."[168]

Early versus delayed treatment of relapsed ovarian cancer (MRC OV05/EORTC 55955): a randomised trial[169]

"Background: Serum CA125 concentration often rises several months before clinical or symptomatic relapse in women with ovarian cancer. In the MRC OV05/EORTC 55955 collaborative trial, we aimed to establish the benefits of early treatment on the basis of increased CA125 concentrations compared with delayed treatment on the basis of clinical recurrence.

Methods: Women with ovarian cancer in complete remission after first-line platinum-based chemotherapy and a normal CA125 concentration were registered for this randomised controlled trial. Clinical examination and CA125 measurement were done every 3 months. Patients and investigators were masked to CA125 results, which were monitored by coordinating centres. If CA125 concentration exceeded twice the upper limit of normal, patients were randomly assigned (1:1) by minimisation to early or delayed chemotherapy.

Interpretation: Our findings showed no evidence of a survival benefit with early treatment of relapse on the basis of a raised CA125 concentration alone, and therefore the value of routine measurement of CA125 in the follow-up of patients with ovarian cancer who attain a complete response after first-line treatment is not proven. (Funding UK Medical Research Council and the European Organisation for Research and Treatment of Cancer)"[169]

Postoperative Irradiation with or without Concomitant Chemotherapy for Locally Advanced Head and Neck Cancer[170]

"Background: We compared concomitant cisplatin and irradiation with radiotherapy alone as adjuvant treatment for stage III or IV head and neck cancer.

Methods: After undergoing surgery with curative intent, 167 patients were randomly assigned to receive radiotherapy alone (66 Gy over a period of 6½ weeks) and 167 to receive the same radiotherapy regimen combined with 100 mg of cisplatin per square meter of body-surface area on days 1, 22, and 43 of the radiotherapy regimen.

Conclusions: Postoperative concurrent administration of high-dose cisplatin with radiotherapy is more efficacious than radiotherapy alone in patients with locally advanced head and neck cancer and does not cause an undue number of late complications."[170]

CREATE: Cross-tumoral Phase 2 With Crizotinib
(https://clinicaltrials.gov/ct/show/NCT01524926)

"Purpose: The study will primarily assess the antitumor activity of crizotinib in a variety of tumors with alterations in ALK and/or MET pathways. The targeted patient population will include patients with tumors harboring specific alterations leading to ALK and/or MET activation, where tyrosine kinase inhibitors against these targets have not yet been adequately explored."

Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma[171]

"Background: Glioblastoma, the most common primary brain tumor in adults, is usually rapidly fatal. The current standard of care for newly diagnosed glioblastoma is surgical resection to the extent feasible, followed by adjuvant radiotherapy. In this trial we compared radiotherapy alone with radiotherapy plus temozolomide, given concomitantly with and after radiotherapy, in terms of efficacy and safety.

Methods: Patients with newly diagnosed, histologically confirmed glioblastoma were randomly assigned to receive radiotherapy alone (fractionated focal irradiation in daily fractions of 2 Gy given 5 days per week for 6 weeks, for a total of 60 Gy) or radiotherapy plus continuous daily temozolomide (75 mg per square meter of body-surface area per day, 7 days per week from the first to the last day of radiotherapy), followed by six cycles of adjuvant temozolomide (150 to 200 mg per square meter for 5 days during each 28-day cycle). The primary end point was overall survival. …

Conclusions: The addition of temozolomide to radiotherapy for newly diagnosed glioblastoma resulted in a clinically meaningful and statistically significant survival benefit with minimal additional toxicity."[171]

Conservative Local Treatment Versus Mastectomy After Induction Chemotherapy In Locally Advanced Breast Cancer: A Randomized Phase III Study (https://clinicaltrials.gov/ct/show/NCT00028704)

"Purpose: Randomized phase III trial to compare the effectiveness of breast-conserving therapy with mastectomy followed by radiation therapy in treating women who have locally advanced breast cancer that has been previously treated with chemotherapy.

Rationale: Breast-conserving treatments such as radiation therapy or limited surgery are less invasive than mastectomy and may improve the quality of life. It is not yet known if breast-conserving treatments are as effective as mastectomy followed by radiation therapy in treating locally advanced breast cancer."(*https://clinicaltrials.gov/ct/show/NCT00028704*)

Appendix 3.4. NIHR

Pharmaceuticals: CRASHII: transexamic acid in trauma

The CRASH II study randomised 20,000 patients bleeding after and with trauma to either tranexamic acid or placebo.[172] It demonstrated that this cheap, off-patent drug reduced mortality from trauma by 15%, with no increase in risk of vascular occlusive events. Worldwide, the potential benefit of this treatment is saving 100,000 lives per year. Its use in the NHS is now part of routine outcomes monitoring, and demonstration of the value of its early use has led to its use in many parts of the UK by paramedics in the field, as well as in the British army.[173] It has led to a range of follow on studies of tranexamic acid in other settings, including gastrointestinal bleeding, subarachnoid haemorrhage (both funded by the NIHR HTA programme), traumatic intracranial bleeding, postpartum bleeding (funded by the Wellcome Trust and NIHR).

Devices: Extracorporeal membrane oxygenation

Extracorporeal membrane oxygenation for respiratory failure was shown to save lives in neonates in the1990s[174] but its value in adults was uncertain. A pragmatic and large RCT was needed. In 1999, the HTA programme commissioned the CESAR trial which randomized 180 adults with severe but potentially reversible respiratory failure, from 68 centres, to conventional management or to transfer for consideration for extracorporeal membrane oxygenation. CESAR took 10 years to complete but its results were clear and timely when they were published in October 2009 during the H1N1 pandemic.[175] It showed an important clinical effect, with a relative risk of survival to 6 months without disability of 0.69 (95% CI 0·05—0·97), and also cost effectiveness. This demonstration of effect encouraged rapid expansion of facilities for extracorporeal membrane oxygenation for adults during the pandemic, which in turn saved many lives.[176]

Screening: ProtecT

Screening for prostate cancer and the management of patients detected by screening has been controversial for many years. An attempt to conduct a randomised trial of various treatments including watchful waiting failed to recruit in the early 1990s. In the late 1990s, two of the earliest projects of the NIHR HTA programme were systematic reviews[177, 178] which helped

formulate government policy that routine screening for cancer using prostate specific antigen was not recommended.[179]

In 1998, the NIHR Health Technology Assessment (HTA) programme supported a feasibility study to explore whether it was possible to recruit men to a three arm study comparing surgery, radiotherapy and an active monitoring protocol. This pioneered innovative ways to involve patients in communicating risks and benefits.[180] Based on its success, the PROTECT (Prostrate Testing for Cancer and Treatment) trial was funded by the NIHR HTA programme. It recruited over 100,000 men for PSA-testing, detected over 3,000 prostate cancers, and randomised 1500 patients with clinically localised disease (65% of those eligible). A further 1000 patients who chose their treatment are also followed up closely.

This study will report its ten year results in 2016. Its effect on clinical practice, even in advance of results is substantial, allowing the UK to reaffirm its policy of no routine screening.[181] It has been a platform for many other studies of trial methodology, psychosocial impact of prostate screening, suitability of patients for focal therapy and the establishment of a biorepository of human material for further study. The approach of active monitoring has recently been endorsed as national policy by English National Institute for Health and Care Excellence (NICE) in its new guidelines, CG 175 Prostate cancer: diagnosis and treatment.[182]

Appendix 3.5. Publications in NEJM

In this part we provide some examples off (mainly) publicly funded trials published in NEJM. Again, we provide information retrieved from the abstracts of these publications. For detailed results of these trials we refer to the original manuscripts.

Bariatric Surgery versus Intensive Medical Therapy for Diabetes — 3-Year Outcomes[183]

"Background: In short-term randomized trials (duration, 1 to 2 years), bariatric surgery has been associated with improvement in type 2 diabetes mellitus.

Methods: We assessed outcomes 3 years after the randomization of 150 obese patients with uncontrolled type 2 diabetes to receive either intensive medical therapy alone or intensive medical therapy plus Roux-en-Y gastric bypass or sleeve gastrectomy. …

Conclusions: Among obese patients with uncontrolled type 2 diabetes, 3 years of intensive medical therapy plus bariatric surgery resulted in glycemic control in significantly more patients than did medical therapy alone. Analyses of secondary end points, including body weight, use of glucose-lowering medications, and quality of life, also showed favorable results at 3 years in the surgical groups, as compared with the group receiving medical therapy alone. (ClinicalTrials.gov number, NCT00432809.)" "Supported by grants from Ethicon (EES IIS 19900), the Investigator-Initiated Study Program of LifeScan, the Cleveland Clinic, and the National Institutes of Health (R01 DK089547)."[183]

Therapies for Active Rheumatoid Arthritis after Methotrexate Failure[148]

"Background: Few blinded trials have compared conventional therapy consisting of a combination of disease-modifying antirheumatic drugs with biologic agents in patients with rheumatoid arthritis who have active disease despite treatment with methotrexate – a common scenario in the management of rheumatoid arthritis.

Methods: We conducted a 48-week, double-blind, noninferiority trial in which we randomly assigned 353 participants with rheumatoid arthritis who had active disease despite methotrexate therapy to a triple regimen of disease-modifying antirheumatic drugs (methotrexate, sulfasalazine, and hydroxychloroquine) or etanercept plus methotrexate. …

Conclusions: With respect to clinical benefit, triple therapy, with sulfasalazine and hydroxychloroquine added to methotrexate, was noninferior to etanercept plus methotrexate in patients with rheumatoid arthritis who had active disease despite methotrexate therapy. (Funded by the Cooperative Studies Program, Department of Veterans Affairs Office of Research and Development, and others; CSP 551 RACAT ClinicalTrials.gov number, NCT00405275.)"[148]

This independent trial shows that both treatments had a very similar efficacy in terms of clinical and radiological evolution. However, the difference for the health care payer is important: etanercept 50mg 1x/w costs 1109 euro/month (www.bcfi.be) versus Sulfasalazine+hydroxychloroquine <25€/month. The etanercept RIZIV-INAMI budget was 66 million euro in 2013 (http://www.riziv.fgov.be/SiteCollectionDocuments/infospot-2014-03-nl.pdf).

A Randomized Trial of Protocol-Based Care for Early Septic Shock[184]

"Background: In a single-center study published more than a decade ago involving patients presenting to the emergency department with severe sepsis and septic shock, mortality was markedly lower among those who were treated according to a 6-hour protocol of early goal-directed therapy, in which intravenous fluids, vasopressors, inotropes, and blood transfusions were adjusted to reach central hemodynamic targets, than among those receiving usual care. We conducted a trial to determine whether these findings were generalizable and whether all aspects of the protocol were necessary.

Methods: In 31 emergency departments in the United States, we randomly assigned patients with septic shock to one of three groups for 6 hours of resuscitation: protocol-based early goal-directed therapy; protocol-based standard therapy that did not require the placement of a central venous catheter, administration of inotropes, or blood transfusions; or usual care. The primary end point was 60-day in-hospital mortality. …

Conclusions: In a multicenter trial conducted in the tertiary care setting, protocol-based resuscitation of patients in whom septic shock was diagnosed in the emergency department did not improve outcomes. (Funded by the National Institute of General Medical Sciences; ProCESS ClinicalTrials.gov number, NCT00510835.)"[184]

Early versus Late Parenteral Nutrition in Critically Ill Adults[185]

"Background: Controversy exists about the timing of the initiation of parenteral nutrition in critically ill adults in whom caloric targets cannot be met by enteral nutrition alone.

Methods: In this randomized, multicenter trial, we compared early initiation of parenteral nutrition (European guidelines) with late initiation (American and Canadian guidelines) in adults in the intensive care unit to supplement insufficient enteral nutrition. In 2312 patients, parenteral nutrition was initiated within 48 hours after intensive care unit admission (early-initiation group), whereas in 2328 patients, parenteral nutrition was not initiated before day 8 (late-initiation group). …

Conclusions: Late initiation of parenteral nutrition was associated with faster recovery and fewer complications, as compared with early initiation. (Funded by the Methusalem program of the Flemish government and others; EPaNIC ClinicalTrials.gov number, NCT00512122.)"[185]

Intensive Insulin Therapy in Critically Ill Patients[186]

"Background: Hyperglycemia and insulin resistance are common in critically ill patients, even if they have not previously had diabetes. Whether the normalization of blood glucose levels with insulin therapy improves the prognosis for such patients is not known.

Methods: We performed a prospective, randomized, controlled study involving adults admitted to our surgical intensive care unit who were receiving mechanical ventilation. On admission, patients were randomly assigned to receive intensive insulin therapy (maintenance of blood glucose at a level between 80 and 110 mg per deciliter) or conventional treatment (infusion of insulin only if the blood glucose level exceeded 215 mg per deciliter and maintenance of glucose at a level between 180 and 200 mg per deciliter). …

Conclusions: Intensive insulin therapy to maintain blood glucose at or below 110 mg per deciliter reduces morbidity and mortality among critically ill patients in the surgical intensive care unit." "Supported by the University of Leuven, the Belgian Fund for Scientific Research, the Belgian Foundation for Research in Congenital Heart Disease, and an unrestricted grant from Novo Nordisk."[186]

Intensive Insulin Therapy in the Medical intensive care unit[187]

"Background: Intensive insulin therapy reduces morbidity and mortality in patients in surgical intensive care units, but its role in patients in medical intensive care units is unknown.

Methods: In a prospective, randomized, controlled study of adult patients admitted to our medical intensive care unit, we studied patients who were considered to need intensive care for at least three days. On admission, patients were randomly assigned to strict normalization of blood glucose levels (80 to 110 mg per deciliter [4.4 to 6.1 mmol per liter]) with the use of insulin infusion or to conventional therapy (insulin administered when the blood glucose level exceeded 215 mg per deciliter [12 mmol per liter], with the infusion tapered when the level fell below 180 mg per deciliter [10 mmol per liter]). …

Conclusions: Intensive insulin therapy significantly reduced morbidity but not mortality among all patients in the medical intensive care unit. Although the risk of subsequent death and disease was reduced in patients treated for three or more days, these patients could not be identified before therapy. Further studies are needed to confirm these preliminary data. (ClinicalTrials.gov number, NCT00115479)" "Supported by grants from the Belgian Fund for Scientific Research (G.0278.03 and G.3C05.95N), the Research Council of the University of Leuven (OT/03/56), and the Belgian Foundation for Research in Congenital Heart Diseases."[187]

Appendix 3.6. Other examples

Appendix 3.6.1. Finalized NIH-sponsored trials

Major Outcomes in High-Risk Hypertensive Patients Randomized to Angiotensin-Converting Enzyme Inhibitor or Calcium Channel Blocker vs Diuretic[188]

"Background: Antihypertensive therapy is well established to reduce hypertension-related morbidity and mortality, but the optimal first-step therapy is unknown. The Objective of this study was to determine whether treatment with a calcium channel blocker or an angiotensin-converting enzyme inhibitor lowers the incidence of coronary heart disease or other cardiovascular disease events vs treatment with a diuretic

Methods: Design: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), a randomized, double-blind, active-controlled clinical trial conducted from February 1994 through March 2002. Setting and Participants: a total of 33 357 participants aged 55 years or older with hypertension and at least 1 other coronary heart disease risk factor from 623 North American centers. Interventions: participants were randomly assigned to receive chlorthalidone, 12.5 to 25mg/d (n=15 255); amlodipine, 2.5 to 10mg/d (n=9048); or lisinopril, 10 to 40mg/d (n=9054) for planned follow-up of approximately 4 to 8 years. ...

Conclusions: Thyazide-type diuretics are superior in preventing 1 or more major forms of cardiovascular disease and are less expensive. They should be preferred for first-step antihypertensive therapy."[188] (Sponsored by the National Heart, Lung, and Blood Institute, NIH)

Reduction in the Incidence of Type 2 Diabetes with Lifestyle Intervention or Metformin[189]

"Background: Type 2 diabetes affects approximately 8 percent of adults in the United States. Some risk factors – elevated plasma glucose concentrations in the fasting state and after an oral glucose load, overweight, and a sedentary lifestyle — are potentially reversible. We hypothesized that modifying these factors with a lifestyle-intervention program or the administration of metformin would prevent or delay the development of diabetes.

Methods: We randomly assigned 3234 nondiabetic persons with elevated fasting and post-load plasma glucose concentrations to placebo, metformin (850 mg twice daily), or a lifestyle-modification program with the goals of at least a 7 percent weight loss and at least 150 minutes of physical activity per week. …

Conclusions: Lifestyle changes and treatment with metformin both reduced the incidence of diabetes in persons at high risk. The lifestyle intervention was more effective than metformin."[189]

Appendix 3.6.2. Finalized NHS-sponsored trials

An editorial in the lancet[85] refers to NHS R&D that has become an important funding source for non-commercial clinical trials. Three examples are provided: endoscopic surgery for abdominal aortic aneurysm,[190] management of leg ischaemia,[191] and feeding after stroke.[192]

Endovascular aneurysm repair versus open repair in patients with abdominal aortic aneurysm (EVAR trial 1): randomised controlled trial[190]

"Background: Although endovascular aneurysm repair (EVAR) has a lower 30-day operative mortality than open repair, the long-term results of EVAR are uncertain. We instigated EVAR trial 1 to compare these two treatments in terms of mortality, durability, health-related quality of life (HRQL), and costs for patients with large abdominal aortic aneurysm.

Methods: We did a randomised controlled trial of 1082 patients aged 60 years or older who had aneurysms of at least 5·5 cm in diameter and who had been referred to one of 34 hospitals proficient in the EVAR technique. We assigned patients who were anatomically suitable for EVAR and fit for an open repair to EVAR (n=543) or open repair (n=539). …

Interpretation: Compared with open repair, EVAR offers no advantage with respect to all-cause mortality and HRQL, is more expensive, and leads to a greater number of complications and reinterventions. However, it does result in a 3% better aneurysm-related survival. The continuing need for interventions mandates ongoing surveillance and longer follow-up of EVAR for detailed cost-effectiveness assessment."[190]

Bypass versus angioplasty in severe ischaemia of the leg (BASIL): multicentre, randomised controlled trial[191]

"Background: The treatment of rest pain, ulceration, and gangrene of the leg (severe limb ischaemia) remains controversial. We instigated the BASIL trial to compare the outcome of bypass surgery and balloon angioplasty in such patients.

Methods: We randomly assigned 452 patients, who presented to 27 UK hospitals with severe limb ischaemia due to infra-inguinal disease, to receive a surgery-first (n=228) or an angioplasty-first (n=224) strategy. The primary endpoint was amputation (of trial leg) free survival. …

Interpretation: In patients presenting with severe limb ischaemia due to infra-inguinal disease and who are suitable for surgery and angioplasty, a bypass-surgery-first and a balloon-angioplasty-first strategy are associated with broadly similar outcomes in terms of amputation-free survival, and in the short-term, surgery is more expensive than angioplasty."[191]

Routine oral nutritional supplementation for stroke patients in hospital (FOOD): a multicentre randomised controlled trial[192]

"Background: Undernutrition is common in hospital patients with stroke, can develop or worsen in hospital, and is associated with poor outcomes. We aimed to establish whether routine oral nutritional supplements improve outcome after stroke.

Methods: The FOOD trials are a family of three pragmatic, multicentre, randomised controlled trials. We measured the outcomes of stroke patients who could swallow and who were randomly allocated normal hospital diet or normal hospital diet plus oral nutritional supplements until hospital discharge. …

Interpretation: We could not confirm the anticipated 4% absolute benefit for death or poor outcome from routine oral nutritional supplements for mainly well nourished stroke patients in hospital. Our results would be compatible with a 1% or 2% absolute benefit or harm from oral supplements. These results do not support a policy of routine oral supplementation after stroke."[192]

Appendix 3.6.3. Open questions

Prescription of drugs in children

- Research question

  What is the safety and (cost-)effectiveness of drugs used for paediatric use?
- Category: off-patent and off-label drugs in children.
- Background information

  This information comes from the following research project: Integrating multidisciplinary translational bottom-up approaches towards a new paradigm for paedriatic investigations: the next step in ethical paediatric drug research [SAFE-PEDRUG].

  The rationale for this project is the identification of the gap in data knowledge on the safe and effective prescription of drugs in children. Several drugs will be studied that all have acquired a labelling for paediatric isolation, which have a large indication, so that the study-population is guaranteed, used since years in clinical practice, and lost their patent protection. The prospective clinical trials in this project have a special emphasis in desmopressin, lisinopril and fluoroquinolone.

  The goal of paediatric drug research is to deliver an improved availability of correctly labelled, safe and effective medicines for children, in age-appropriate formulations, in the age range and subtypes of patients where the drug is mandatory, with long term follow up for controlling side-effects with special emphasis on growth, development and maturation.

  The key objective of this project is to reinvent the strategy for paediatric drug research from a top down approach derived from adult data, into a multidisciplinary methodology using a bottom up approach starting from paediatric specificities and opportunities, leading to a safe labelling of an efficient drug for children in all age-groups and all indications.

  Since the drugs are off patent, future industry driven studies, even for new indications or new formulations are very unlikely. Also, the aim of

this project is to demonstrate the importance of a full research program for drugs, prescribed in children and to stress that the data from the industry driven studies as requested by FDA and EMA are insufficient to optimize treatment efficiency and reduce side-effects. This research is – especially for off-patent and off-label drugs – only possible in academic driven studies.

After years of preparation, the project started on January 1st 2014 and has an expected duration of 48 months. Most prospective clinical trials will be performed in that time period but also data from previous paediatric studies will be used in order not to repeat trials and to minimize the number of children included in clinical research.

Natural versus synthetic vitamin D

- Research question

  What is the effectiveness (and cost-effectiveness) of natural vitamin D versus synthetic analogies (such as paricalcitol) in the treatment of secondary hyperparathyroidism in patients with severe renal failure?
- Category: Off label research of natural vitamin D which is marketed for other indications.

Improving screening participation

- Research question

  Can the population coverage be increased by offering a self-sampling kit to women non-participating in cervical cancer screening?
- Category: organisation of screening
- Background information

  Since the mid 1990s to early 2000s, Flemish provinces have sent letters to the whole target population (women aged 25-64 years). According to a detailed analysis of an billing data in the database of the intermutualistic agency (containing records from all reimbursed Pap smears), the screening coverage (% women 25-64 y with Pap smear <3y ago) is at national level 61% with only small diferences between the Regions. Data do not provide evidence that sending letters to women is effective. For instance, over the period 2001-06, a coverage increase of 4% was observed in East-Flanders, where no letters were sent, whereas in Flemish-Brabant, where the call-recall of women was continued, only 2% increase was noted. A meta-analysis of the accuracy of HPV testing on self-samples vs clinician-taken samples to find cervical precancerous lesions indicated that, the former is as sensitive and specific as the latter, when a validated PCR is used. Moreover, another metanalysis concluded that sending self-sampling kits is more effective in reaching women who do no attend the regular screening programme. However, the response rates vary substantially between trials and local circumstances, indicating that introducing self-sampling requires careful piloting to examen effectiveness, cost-effectiveness and factors which influence effectivenes (personal communication M. Arbyn).

  Further evidence on the most optimal strategy can be obtained using a randomised design. For example, women without a record in the Belgian Cancer Registry with a cervical cytology over the last 3 years and who did not respond to a first invition to have a Pap smear taken are randomised in two arms: (a) receives a self-kit at home, (b) rereceive conventional reminder with a recommendation of a Pap smear. In a second example, a small trial is being prepared (WIV/Flemish consortium Cancer screening): 3x1000 non-participating women in 3 arms: a) receiving self-screening kit at home; b) receiving kit if requested by woman; c) conventional reminder.

APPENDIX 4. ECRIN MEMBERS

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- Network of Coordinating Centers for Clinical Trials (KKS Network)- Klinikum der Universitaet zu Koeln – Germany
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