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10 YEARS OF KCE TRIALS: PUBLIC FUNDING OF INDEPENDENT PRAGMATIC CLINICAL RESEARCH IN BELGIUM. EXTERNAL EVALUATION 2016-2025

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
BeNeFIT	Belgium-Netherlands Funding of International Trials
CI	Chief investigator
CRMS	Clinical Research Management System
CRO	Contract Research Organisation
CSR	Clinical Study Report
CTC	Clinical Trial Centre
CTIS	Clinical Trial Information System
CTR	Clinical Trial Regulation
FPS	Federal Public Service
FRP	Full Research Proposal
FWO	Fonds Wetenschappelijk Onderzoek
GCP	Good Clinical Practice
HTA	Health Technology Assessment
ICH	International Council for Harmonisation
NCC	National Coordinating Centre
NIHR	National Institute for Health and care Research
PG	Prioritisation Group
PM	Project Manager
RIZIV–INAMI (NIHDI)	Rijksinstituut voor Ziekte- en Invaliditeitsverzekering – Institut National d'Assurance Maladie-Invalidité (National Institute for Health and Disability Insurance)
RO	Research Outline
ROI	Return On Investment
SOP	Standard Operating Procedure
TB	Trials Board
WHO	World Health Organization
ZonMw	Dutch Organisation for knowledge and innovation in health, healthcare and well-being

KCE REPORT

1 BACKGROUND

Many questions in healthcare are of high societal importance but are not sufficiently studied in clinical research, despite the large benefits those studies could bring to patients and to the healthcare system. This was the topic of a KCE report published in 2015, which concluded that public funding of such trials would be beneficial, provided that studies are carefully selected, professionally conducted, and that their results are translated into clinical practice.[2, 3] The report also concluded that these trials contribute not only to a better care for the patient but also to a more efficient use of public resources. Following the KCE report publication, the Minister of Public Health at that time decided to allocate new budgets to a national funding programme for pragmatic and practice-oriented clinical trials, and to entrust this new task to the KCE. The KCE Trials Programme was born. The current annual budget is €12 million, entirely supported by the budget of RIZIV–INAMI.

The KCE Trials programme got off to a start in 2016 and to date[a], over 20 calls for proposals have already been launched and 78 clinical trials have been selected and funded within the programme [4, 5], with participants being recruited all over Belgium, in hospitals but also in primary care practices. The selected studies are primarily large, confirmatory, non-commercial, multicentre, pragmatic randomised clinical trials, comparing existing interventions (comparative effectiveness trials), with an average budget of around €2 million. A few studies also investigate new indications for off patent drugs (drug repurposing trials). Belgian studies (coordinated by a Sponsor in Belgium) as well as Belgian participation to international studies are funded by the programme. To date, 29 trials have successfully published their results, many of them in high impact journals.

After the first ten years of existence, an evaluation of the KCE Trials Programme and its impact was due. The aim of this evaluation is to

1. assist the Minister of Public Health and RIZIV–INAMI in evaluating their investment in the KCE Trials programme.
2. help KCE to identify opportunities for future improvement.
3. inform scientists, health care providers, patients and the general public about the programme and its impact, as it is publicly funded.

In this report the process and results of this evaluation are described, as well as a first reflection of KCE on the recommendations and potential ways to address them (Table 1).

Table 1 – Structure of the report

This report presents:

- the methods used to select the evaluator (section 2),
- a summary of the evaluation report by Deloitte (section 3),
- and a critical reflexion of KCE on the report's recommendations (section 4).

The complete **evaluation report by Deloitte** including its methodology, findings, discussion, and conclusions, is provided in appendix.

[a] Status on 07/09/2026, which explains the small difference with the Deloitte evaluation report.

2 EXTERNAL EVALUATION METHODOLOGY

2.1 Independent evaluation

2.1.1 External evaluator: Deloitte

To allow for an independent evaluation, it was decided to fully outsource this project to an external contractor. Therefore a public tender was launched in May 2025.[6] The list of outsourced tasks encompassed the full execution of the project, more specifically the identification of the evaluation framework, the design and conduct of the evaluation and the writing of the evaluation report. After finalisation of the tender procedure, the project was attributed to Deloitte in July 2025.

2.1.2 Supervisory committee

KCE Trials' Prioritisation Group (PG) was asked to function as supervisory committee in the context of this project This is an existing group of external stakeholder representatives (partly delegated by the KCE Board and partly comprised of representatives from the University hospitals), that oversees the selection process, portfolio of studies and activities coordinated by the KCE Trials team. Professor A. Dupont, member of the PG, served as chair of the supervisory committee for the evaluation. A full list of members of the committee and their affiliations, is available in the colophon of this report. The KCE trials policy on "confidentiality and potential conflict of interest of reviewers involved in the assessment of proposals" applies to all members of the PG.[1] The final findings and recommendations presented in the external evaluation are those of Deloitte and do not necessarily reflect the views of the members of the supervisory committee.

2.2 Timelines

A kick-off meeting with the external contractor team, the chairperson of the supervisory committee and the internal project group took place in September 2025 after which the project started. The work was broken down into various deliverables, each of which was submitted to the supervisory committee for review and comment after completion by Deloitte.

1. Evaluation framework & analysis plan (November 2025)
2. Process evaluation chapter (March 2026)
3. Impact evaluation chapter (April 2026)
4. Draft final report (June 2026)

Throughout the project biweekly status updates were planned with the Deloitte project team and the internal KCE project group during which the progress of the project was discussed as well as the various data and information requests. In parallel, discussion meetings between the Deloitte project team and the chairperson of the supervisory committee were regularly planned to discuss preliminary findings.

The methodology applied by Deloitte is fully described in the evaluation report which was finalised in August 2026 and is presented in appendix.

3 SUMMARY EXTERNAL REPORT

Executive Summary

The KCE Trials Programme is a public funding initiative established in 2016 by the Belgian Health Care Knowledge Centre (KCE). It supports pragmatic, non-commercial clinical trials addressing research questions of significant public health and societal importance in Belgium, particularly those lacking commercial viability. Supported research areas include examples like comparative effectiveness studies, drug repurposing and medical device evaluation. Additionally, the Programme promotes answering questions important for underserved populations (e.g., women, children, and elderly populations).

From 2016 to 2025, KCE Trials funded 75 trials across 20 calls, including four BeNeFIT calls as part of the partnership with the Dutch Organisation for Health Research and Development (ZonMw). During this time, 327 research proposals were evaluated and 75 trials were funded, of which 25 have been closed. Collectively, the funded research involved more than 32,000 participants across 129 sites and generated 91 peer-reviewed publications. The Programme achieved a 76% successful study completion rate, a 96% publication rate, a five-year average impact factor of 31.3 and 3 guideline uptakes. These achievements and outputs are summarized in the table below.

KCE Trials at a glance from 2016 until 2025	
20 calls	Conducted between 2016 – 2025, including 4 BeNeFIT calls
327 research proposals	Evaluated across the 20 calls
75 trials	Funded by KCE Trials
25 trials	Closed to date
> 32,000 participants	Included across 129 sites
91 publications	Peer-reviewed publications generated
76%	Successful study completion rate
96%	Publication rate
31.3	Five-year average impact factor
3	Guideline uptakes

KCE Trials is highly relevant to societal and health-system needs because it funds pragmatic, practice-oriented trials addressing evidence gaps that are unlikely to be resolved through

commercial research funding. Its relevance is supported by investigator-justified evidence gaps that are confirmed by a panel of healthcare professionals, pragmatic trial design, broad coverage of therapeutic areas, inclusion of pharmaceutical, medical device, surgical and procedural interventions, systematic consideration of economic impact, and involvement of patients and clinicians in assessing clinical relevance. The portfolio also addresses emerging and under-addressed priorities such as endometriosis, COVID-19, antimicrobial resistance and the needs of elderly populations demonstrating responsiveness to neglected chronic conditions, acute public health crises, and long-term population-level threats. Amongst investigators, 92% rate the trial selection process as fair and transparent and 57% agree that objectives align with health priorities.

Research topics are mostly driven by investigators. This limits the extent to which the Programme can demonstrate that it funds the highest-priority societal or policy needs. In addition, links with policymakers and regional health authorities could be further developed, and regional participation is uneven, with Wallonia being slightly under-represented among recruited patients. KCE Trials is highly relevant by design and stakeholder perception, and its strategic relevance could be strengthened through more systematic priority-setting, closer engagement with federal and regional decision-makers, and continued monitoring of regional representativeness.

Overall, **KCE Trials is effective in generating high-quality, practice-oriented evidence and strengthening Belgian capacity** for non-commercial pragmatic trials. Amongst investigators, 84% expect trial results to improve patient outcomes and 90% report that the Programme has strengthened their team's clinical research capability.

Its publication record, high-impact outputs, integration of economic evaluation, investigator support and examples of guideline-relevant findings all support a positive effectiveness assessment. The strongest evidence presents itself in intermediate outcomes: guideline uptake, publications, capacity building (even though not an explicit objective of the Programme), and perceived usefulness of the Programme and its findings. Evidence is less strong for final outcomes: formal policy uptake, reimbursement decisions, systematic practice change, patient-level impact across the portfolio and realised healthcare savings. This is partly explained because the Programme has been in place for just ten years, while full policy and practice impact often take longer than trial completion and publication. Also, not all trial results warrant a change in formal reimbursement decisions or criteria. The main effectiveness priority is to continue output tracking and strengthen impact tracking by monitoring whether trial results reach intended audiences, enter guidelines or influence policy decisions, change clinical practice, improve outcomes and generate measurable value for the Belgian healthcare system.

KCE Trials has **built an efficient support infrastructure for non-commercial pragmatic trials**, including budgeting tools, protocol support, templates, training and close communication with investigators. KCE Trials works with a €12.3 million budget annually of which approximately 80% goes to funding clinical trials. The average duration from research application to trial selection is 306 days, and the average period from trial selection to contract is 221 days. A large majority (92%) of surveyed investigators agree that KCE Trials provides a clear and relevant framework for pragmatic trials in Belgium, and 68% of investigators indicate KCE Trials support enabled timely and qualitative study execution.

These mechanisms **improve the feasibility of complex pragmatic trials and support their successful and on-budget completion**. Procedural efficiency, on the other hand, remains an attention point with 31% of investigators reporting that administrative and reporting procedures are disproportionate to the complexity of their trial. While only partially under control of the KCE Trials Programme, selection, contracting, start-up and publication timelines tend to be long. While KCE Trials provides many tools and templates to support the efficient selection and conduct of the trials in its portfolio, the main efficiency priority is not to reduce quality assurance, but to investigate where administrative, contractual and start-up processes can be made more proportionate and risk based.

KCE Trials demonstrates strong coherence with Belgian and international policy priorities. At federal level, the Programme is closely aligned with KCE's advisory mandate, NIHDI's appropriate care agenda, and ministerial priorities around quality, accessibility and efficiency. Its focus on pragmatic, non-commercial comparative effectiveness trials directly support policy needs for evidence on interventions that are already used, insufficiently compared, or not commercially attractive to study. The integration of economic impact into trial design further strengthens coherence with public payer objectives and the responsible use of health-system resources at both federal and federated levels. The Programme is also coherent with international developments, for example the World Health Organization's (WHO) call to strengthen clinical trials and generate high-quality evidence on health interventions, the European Commission's harmonised clinical-trial framework, and ZonMw's practice-oriented effectiveness research model. The BeNeFIT collaboration with ZonMw is a particularly strong example of operational coherence, as it enables Belgian and Dutch institutions to jointly conduct non-commercial pragmatic trials on questions relevant to patients, providers and policymakers in both countries. Coherence is stronger at the level of policy principles than at the level of systematic decision linkage. The main limitation is the absence of a structured mechanism through which federal and federated health authorities routinely translate policy priorities into research questions that can be addressed via trials.

Overall, **KCE Trials is a relevant, effective, efficient and coherent programme with a clear role in generating real-world evidence in Belgium.** Most remaining areas for improvement reflect its **growing maturity** rather than fundamental weaknesses.

This report presents a comprehensive evaluation of the KCE Trials Programme against four criteria: **relevance, effectiveness, efficiency and coherence**.

Criteria	Key message
Relevance	KCE Trials is highly relevant to societal and health-system needs, addressing evidence gaps through pragmatic, practice-oriented research, unlikely to be resolved through commercial funding.
Effectiveness	KCE Trials is effective in generating high-quality evidence and strengthening Belgian capacity for non-commercial trials, with peer-reviewed publications, guidelines and capacity-building outputs.
Efficiency	KCE Trials has built an efficient support infrastructure that supports the feasibility and conduct of complex non-commercial pragmatic trials.
Coherence	KCE Trials demonstrated strong coherence with Belgian and International policy priorities and supports evidence generation that is relevant to healthcare decision-making.

KEY RECOMMENDATIONS

RELEVANCE

- **Recommendation 1: Formalise payer and policymaker involvement in priority-setting**
  - Establish formal governance (e.g., yearly priority-setting meeting) with federal and federated health authorities to anchor selection to pressing decision-making needs.
  - Facilitate early dialogue between NIHDI, FPS Public Health, and investigators to define policy-relevant research questions.
- **Recommendation 2: Create awareness on regional capacity-building in Wallonia**
  - Conduct targeted outreach with Walloon clinical trial centres and publish results in national medical journals.
  - Engage policy makers on the need for targeted support to address infrastructure differences.

EFFECTIVENESS

- **Recommendation 3: Integrate dissemination and implementation planning into trial process**
  - Develop practical guidance and templates for investigators on dissemination planning, target audiences, engagement with payers, and data-sharing protocols.
  - Offer as a resource without adding mandatory.
- **Recommendation 4: Establish systematic post-trial impact tracking**
  - Introduce a structured tracking tool to monitor uptake in clinical guidelines, reimbursement decisions, and policy documents.
  - Conduct routine follow-up at two and five years after publication.

- **Recommendation 5: Leverage KCE's HTA capabilities more systematically**
  - Formally link Trials, HTA and policy advisory functions.
  - Use HTA needs to inform trial priorities and have HTA teams lead dissemination to policy makers and NIHDI reimbursement decisions.

EFFICIENCY

- **Recommendation 6: Analyse and reduce the application-to-contract timeline**
  - Conduct detailed analysis of administrative timelines through process mapping and interviews.
  - Identify bottlenecks and assess feasibility of efficiency improvements while maintaining methodological rigour.
- **Recommendation 7: Implement differentiated reporting requirements based on trial complexity and risk profile**
  - Introduce a risk-based model tailoring oversight, reporting and monitoring to each trial's risk profile.
  - Lower-risk trials follow streamlined pathways; higher-risk trials receive closer oversight.
- **Recommendation 8: Index KCE Trials budget to preserve existing capacity and funding predictability**
  - Index the clinical-trial funding portion annually against a transparent benchmark reflecting cost drivers (personnel, site, data-management, monitoring) to preserve real value.

COHERENCE

- **Recommendation 9: Establish regular dialogue with domestic Belgian funders**
  - Implement a shared annual portfolio review with other funders (FWO-TBM, Kom Op Tegen Kanker) to reduce duplication, identify synergies, and align with new policy initiatives
- **Recommendation 10: Expand international partnerships, particularly for areas with challenging recruitment**
  - Strengthen joint calls with other public funders for rare diseases and surgical trials.
  - Develop formal data-sharing agreements to enhance scientific power and Belgium's global influence.

4 REFLECTION ON THE EXTERNAL EVALUATION REPORT AND ITS 10 KEY RECOMMENDATIONS

The external evaluation report concludes that "KCE Trials is a relevant, effective, efficient and coherent programme with a clear role in generating real-world evidence in Belgium. Most remaining areas for improvement reflect its growing maturity rather than fundamental weaknesses." The strengths of the programme as well as areas for development are described in detail. Ten key recommendations are formulated to build on the Programme's scientific foundations (see external report in appendix). In this section we offer some initial reflections on these recommendations and potential ways to address them.

4.1 Formalise payer and policymaker involvement in priority-setting

As a first recommendation, the evaluation report underscores the importance of involving payers and policymakers in setting priorities. Although this involvement is structurally embedded in KCE Trials' selection processes, the evaluation report shows that it is not yet sufficiently visible or well-known within the organizations involved and that KCE Trials is not making full use of it.

Decisions regarding the organisation of calls for proposals and the selection of studies, as well as study results, are routinely placed on the agenda of the KCE Board of directors, which includes both payers and policymakers. On a more operational level, representatives of the KCE Board member organisations serve on the PG (Table 2) that prioritises submitted research proposals and oversees the selection process, the portfolio of studies and the activities coordinated by the KCE Trials team.

Table 2 – Composition of the PG

- Representative(s) of RIZIV–INAMI
- Representative of the Ministry of Social Affairs and Public Health
- Representative of Sciensano
- Representative(s) of the Federal Public Service (FPS) Health, Food Chain Safety and Environment
- Representatives of the different health insurance funds
- Representative of the of the physicians' syndicate
- A delegate of each university

A full list of members and their association at the time of this report is added in the colophon.

Once the preliminary results of the process evaluation conducted by Deloitte became clear, the KCE Trials team sought to further encourage this engagement. Some initiatives have been launched, and further efforts will be needed to fully address this issue.

An initial exercise was conducted with the FPS Health, Food Chain Safety and Environment. Their priorities were compared with the scope of KCE Trials in order to look for synergies. This has led to the launch of two new themed calls in 2026: one on palliative care and one on care for addictions,[7] two areas of high priority for the FPS and underrepresented in clinical research. Those two themed calls are scheduled to be repeated in 2027 and 2028 to give research teams in these fields the opportunity to think about new ideas and build their research network.

In addition, the presence of payers and policymakers in the PG was further reinforced by adding additional representatives. Through the representatives in the PG, active contact is also made with

the appropriate experts within the RIZIV–INAMI when this is relevant for reimbursement information and/or decisions.

Finally, further consideration will be given to how the Standard Operating Procedures (SOPs) should be adjusted to make active priority-setting an annual focus area within the PG or a separate meeting.

4.2 Create awareness on regional capacity-building in Wallonia

The evaluation report highlights the imbalance in the geographical distribution of participating sites and patients as an area for future attention. This is important in order to maximise the national representativeness of the evidence generated. A representative national distribution of recruiting sites is one of the programme's selection criteria and for most calls at least one centre from each region is required for a proposal to be in scope, unless there is a good justification not to do so. However this does not automatically translate into equal site selection and recruitment during the trials. Lower Clinical Trials Centre (CTC) maturity and fewer established trial infrastructure compared to Flanders, were revealed as main barriers in the stakeholder interviews performed by Deloitte. Another additional reason might be that some Walloon patients go to Brussels for more specialised care as only one out of seven Belgian university hospitals is located in the Walloon region.[8]

This imbalance is also reflected in the distribution of sponsors and National Coordinating Centres (NCCs) of trials in the KCE Trials portfolio. Language and regional organisation of healthcare may facilitate the collaboration between sponsors and participating sites within the same region, which could also contribute to the imbalance in the distribution of participating sites and recruited patients. One mitigating action undertaken by KCE Trials was to assign part of the budget to a coordinator in the other part of the country. This has been integrated in the budget tool since the 2020 investigator-led call but proves insufficient as a remedy.

There is a noticeable trend towards more French-speaking sponsors and NCCs. While initially almost only Dutch-speaking hospitals took up sponsorship for large multicentre trials within the KCE Trials programme, this started to change . In the period 2022–2026, 25% of KCE-funded trials had a French-speaking sponsor or NCC (Table 1). Nevertheless, regional differences remain. It is important to note that this imbalance is not limited to trials funded by the KCE. A simple search query in the European Clinical Trial Information System (CTIS)[b] yields 145 academic studies - falling under the Clinical Trial Regulation (CTR) 536/2014 - with a Belgian sponsor, of which only 18% are French-speaking (Table 2).

Table 3 – Studies funded by KCE Trials Programme, by call year (2016-2021 and 2022-2026) and language of Sponsor (French-speaking or Dutch speaking)

Call Year KCE Trials programme	2016-2021	2022-2026
*Number of trials funded (n=80)**	52	28
French-speaking sponsor or NCC	**6 (12%)**	**7 (25%)**
Dutch-speaking sponsor or NCC	46 (88%)	21 (75%)

NCC=National Coordinating Centre

[b] 18/08/2026; Locations (Country)=Belgium; Sponsor Type = “Health Care”, “Educational institution” OR “Hospital/Clinic/Other health care facility); 208 results filtered on Sponsor, 145 BE sponsors.

Table 4 – Non-commercial studies with a Belgian Sponsor authorized in Belgium (2022-2026), by language of Sponsor (French-speaking or Dutch speaking)

CTIS decisions (excluding transition trials)		2022-2026
*Number of academic trials with a BE sponsor**		145
French-speaking sponsor		**26 (18%)**
Dutch-speaking sponsor		119 (82%)

**situation on 18/08/2026; CTIS = Clinical Trial Information System*

The Belgium-Netherlands Funding of International Trials (BeNeFIT) initiative may also favour Dutch-speaking Belgian (sponsor) sites, even though the same criteria for a representative geographical distribution in Belgium apply. Only two out of the 20 projects selected in the four BeNeFIT calls have a French-speaking NCC in Belgium. Although no funding decisions have been taken yet, a different distribution can be seen among the trials in the ERA4Health call selection process, which allows for collaboration with other European partners, e.g. France. This may also be reflected in the distribution of the participating sites and recruited patients.

Despite the actions already undertaken, this second recommendation still requires ongoing monitoring and consideration.

4.3 Integrate dissemination and implementation planning into trial process

As a third recommendation, the KCE Trials team is advised to develop more practical guidance for investigators on dissemination and implementation planning. Given the growing portfolio of trials, a more structured approach to supporting research teams in this area would be useful.

Some tailored follow-up is already provided by the KCE Trials study leads. Each funded trial is assigned a study lead from the KCE Trials team who supports the research team and monitors progress from the selection stage right through to the completion of the project. At the end of the study, dissemination and implementation activities are discussed by the KCE Trials study lead with the research team. Guidance for these discussions is included in the internal end-of-study checklist for the KCE Trials study leads.[9]

In addition, a new end report template has been recently developed for completion by research teams upon completion of their study.[10] The report is mandatory for studies funded through calls from 2026 onwards and, in the meantime, it is also requested on a voluntary basis from all study teams completing their Clinical Study Report (CSR) from 2026 onwards. This new report collects basic information for economic evaluation in a more structured way and encourages research teams to consider dissemination and implementation activities.

Further work will be undertaken to identify what additional guidance and support research teams would benefit from at different stages of the trial process, while avoiding the introduction of additional mandatory requirements at the application stage. To this end, KCE Trials will examine what activities other similar funders support and whether additional funding would be needed for this. This work will also take into account the nature of the KCE Trials portfolio, with studies that generally evaluate existing treatment strategies rather than focusing on innovation.

4.4 Establish systematic post-trial impact tracking

The fourth recommendation concerns the introduction of a structured post-trial tracking tool to monitor the uptake of findings in clinical guidelines, reimbursement decisions, clinical practice and policy documents. Routine follow-up two and five years after publication is suggested. The KCE project team fully endorses this finding and sees value in establishing a structured approach to tracking impact. At the same time, implementation should take into account the additional reporting requirements that

may arise once the project has ended and funding has ceased. In addition, research shows that the full impact of research can take considerably longer to emerge, sometimes taking a decade or more to realise.[11]

An alternative approach could be to carry out impact tracking across the entire portfolio at fixed intervals. This will be included in the scope of the next evaluation, which will be scheduled in 5 years, and, for example, repeated every five years thereafter. In the meantime, the new end report containing basic information for economic evaluation and implementation (see 3.3) will provide more structured information on relevant outcomes for economic evaluation of completed trials.

4.5 Leverage KCE's HTA capabilities more systematically

The fact that the KCE Trials programme is organised by the KCE – which is also an Health Technology Assessment (HTA) body – does indeed place the programme in a unique position to create synergies in this area. The HTA perspective is included from the selection process onwards and selected research teams can be supported in the set-up of their trials to allow for an economic evaluation and also in their economic evaluation itself. KCE can also carry out an HTA itself where this adds value. There has been strong collaboration between the various branches of the KCE since the programme was established. This collaboration was also formalised in 2026 in an internal SOP regarding economic evaluation of KCE Trials' funded studies.[12]

A second part of the text accompanying the recommendation suggests that KCE reports may also give rise to new priorities for KCE Trials. For example, following the KCE report on endometriosis care, a call for proposals on this topic was launched.[7] This pathway for new topics will be further explored. The importance of existing relationships with policymakers and payers is also emphasised in this regard (see also the first recommendation 3.1)

4.6 Analyse and reduce the application-to-contract timeline

As a sixth key recommendation, KCE is encouraged to conduct a detailed analysis of administrative timelines and reduce the time between application and contract signing. For research teams, it is important to receive a timely decision on whether their project will be funded. The relevance and impact of research findings also often depend on their timely availability, providing an additional rationale for keeping each step of the process as short as possible.

At the same time, a balance needs to be struck between streamlining the process and introducing additional upfront procedures that may help prevent delays at later stages. One example is the feasibility assessment that KCE Trials regularly requires, with the support of an external contract research organisation (CRO). An advance payment is provided to the applicant to cover this additional work. While the feasibility assessment extends the application-to-contract timeline, it may save time during subsequent stages of the study by allowing improvements to be made to the protocol and recruitment plan at an early stage. The added value of this feasibility assessment is currently being analysed by the KCE Trials team, with the results to be published separately.

In addition, we disaggregated the timelines by type of call (see Table 5). The time to final approval is slightly shorter for BeNeFIT calls than for investigator-led KCE calls (427 versus 453 days). However, the average time to contract signing is longer for BeNeFIT calls (612 versus 556 days). The COV (COVID-19) calls are clear outliers, with substantially shorter timelines due to the exceptional circumstances under which they were selected, approved and conducted. For example, at that time a rolling call for proposals was organised, whereby the selection committees were convened ad hoc for each proposal, rather than working with a fixed deadline for submission and a competitive ranking. Studies approved in 2016, at the start of the programme, are another outlier, as they were approved under different procedures.

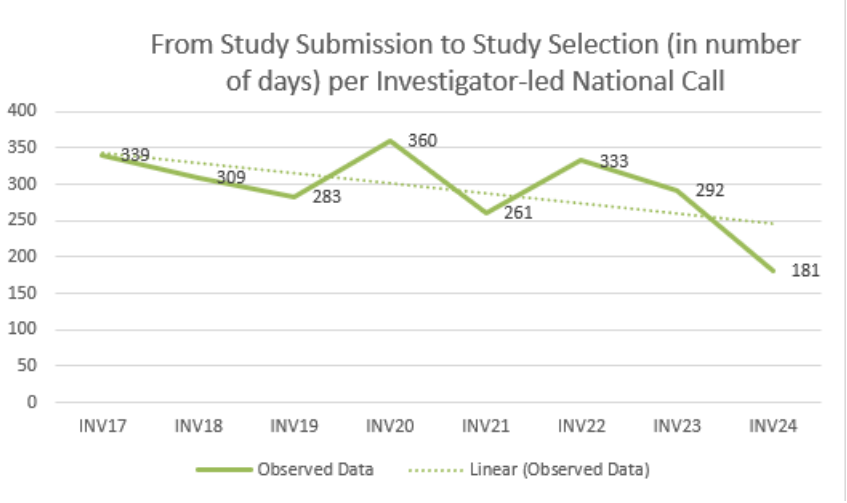
Table 5 – Timelines by type of call

Call Type	# Calls	# funded applications*	Application to final approval (average # days)	Application to contract (average # days)
BeNeFIT	4 (2018, 2021, 2023, 2025)	20	427	612
COVID-19	3	9	70	123
Commissioned	1 (2016)	4	266	370
Investigator-led	8 annual calls (2017-2024) and 1 themed (2024)	45	453	556
TOTAL	**17**	**78**	**295**	**508**

**excluding two Dutch studies selected by ZonMw of which Belgian participation was funded in 2016*

When only analyzing the annual KCE national calls following the general procedures (INV17 to INV24; 44 studies), there appears to be a slight downward trend in the timelines, although continued monitoring is warranted (see Figure 1).

Figure 1 – Analysis of the mean time from Study Submission to Study Selection (in number of days) – all studies funded in investigator-led calls 2017 to 2024 (N=44 studies)



The KCE Trials selection process is iterative. Prioritised applications are initially assessed by the Trials Board (TB) as research outlines (ROs) and may subsequently be invited to submit a Full Research Proposal (FRP), including a study protocol. At each stage, multiple review rounds may take place. The rationale is to ensure that the probability of success increases in line with the effort required from applicants, while allowing the methodological quality of proposals to be improved as much as possible. This should ensure that selected projects are able to answer the research questions in a scientifically robust manner. To avoid unnecessarily lengthy selection processes, the maximum number of RO review rounds by the TB was reduced to two from the 2024 investigator-led call onwards. For the 2026 comparative effectiveness call the maximum FRP review rounds was also set at two. This measure may contribute to further shortening selection timelines in the future.

More generally, finding the right balance between lean processes that minimize the administrative burden for applicants, on the one hand, and the due diligence required of a funder managing large public resources, on the other, remains a continuous challenge. This balance will also require attention when implementing several of the other key recommendations (e.g. 3.3 and 3.4).

4.7 Implement differentiated reporting requirements based on trial complexity and risk profile

The seventh recommendation concerns the exploration of the introduction of a risk-based model that tailors programme oversight, reporting, monitoring and support to each trial's risk profile, within all applicable legal and Good Clinical Practice (GCP) requirements.

The latest revision of the International Council for Harmonisation (ICH) GCP Guideline (E6(R3)) encourages a risk-based and proportionate approach to the conduct of a clinical trial. KCE Trials should integrate risk-based approaches into its own processes, and stimulate sponsors conducting KCE-funded studies to do the same.

Reporting requirements currently imposed by KCE Trials consist of the organisation of regular status update meetings, the reporting of recruitment progress via an online webform and adherence to KCE Trials' general research transparency policy.[13] No other detailed financial reporting in specific templates is required, since the KCE Trials programme adopts an activity-based budget and a milestone-based payment approach.[14]

REGULAR STATUS UPDATE MEETINGS

The Sponsor is responsible to set-up and lead monthly update meetings until the end of the study, providing information on recruitment, study progress, budget and any issues. The KCE Trials study lead can facilitate the set-up of these meetings. During this meeting at least the Project Manager (PM) should be present. The Chief Investigator (CI) should participate to the meeting on a regular basis. Minutes are drafted by the PM and provided to KCE. In case of a long-term follow-up, the frequency of meetings can be lightened.[15] A reduced frequency is also possible for studies with a low recruitment rate.

A PUBLIC WEB DYNAMIC DASHBOARD ON RECRUITMENT PROGRESS FOR ALL STUDIES AND ALL SITES

KCE expects study teams to use the KCE web-based system to update the recruitment progress every two-weeks. This information feeds into the KCE Trials dashboard[5] that aims to keep KCE, the participating sites, patients, the general public, the research community, healthcare payers and policy makers informed on the funded KCE trials, their status, progress and results.

In a first stage KCE Trials attempted to implement a cloud-based clinical research management system (CRMS) across all funded sponsors and participating sites. This system was funded by KCE Trials and had the advantage that the sponsor could also use it to monitor recruitment at the participating sites, both for KCE funded and other non-commercial studies. Nevertheless, this was seen as a significant administrative burden by many hospitals, which often had (to a greater or lesser extent) already implemented other CRMSs. That is why, in 2022, KCE Trials switched to a different platform for post-award reporting, featuring a simplified procedure within the same system used for grant submission.

TRANSPARENCY REQUIREMENTS

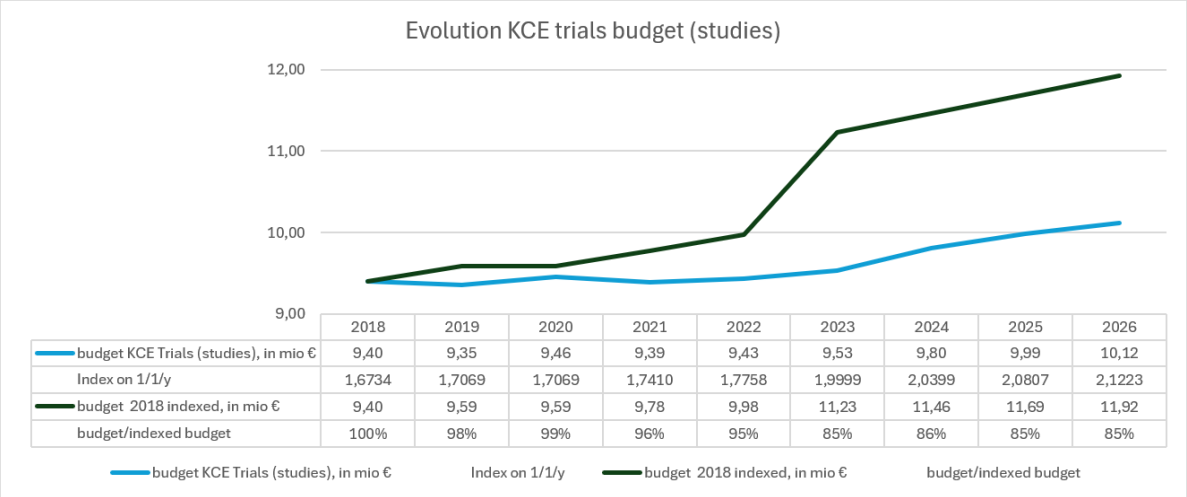
As transparency in clinical research plays a critical role in advancing scientific knowledge, improving patient care, and facilitating evidence-based decision making, KCE Trials attaches great importance to research transparency through its clinical research transparency policy. This policy aims to align with the highest standards in the field of medical research funding as the World Health Organization (WHO) Best Practices in Clinical Trials Transparency and the National Institute for Health and care Research (NIHR) Policy on Clinical Trial Registration and Disclosure of Results. [16, 17]. KCE considers this best practice rather than administrative burden, as prospective registration and timely disclosure of results of KCE-funded trials increase the likelihood that KCE-funded research will have meaningful impact.

In conclusion, when imposing reporting requirements, it is important to carefully consider the added value each time. This is an ongoing focus area for the programme that will continue to be a point of attention in the future. KCE Trials will explore how differentiated reporting requirements can be further implemented and formalised. This will also need to be taken into account if reporting requirements should increase in the light of the implementation of recommendations 3.3 and 3.4.

4.8 Index KCE Trials budget to preserve existing capacity and funding predictability

Although the KCE Trials programme budget has increased slightly over the years (see evaluation report), the budget available to fund studies has not fully kept pace with inflation. This reduces the "purchasing power" of the available funding budget and the number of clinical studies that can be funded, since the majority of the budget is used to pay research personnel. Figure 2 shows the evolution of the KCE Trials budget from 2018 (the first year with a full budget) onwards in comparison with an indexed budget as proposed in the evaluation report.

Figure 2 – Evolution of the KCE Trials budget compared with the indexed[c] budget



	2018	2019	2020	2021	2022	2023	2024	2025	2026
budget KCE Trials (studies), in mio €	9,40	9,35	9,46	9,39	9,43	9,53	9,80	9,99	10,12
Index on 1/1/y	1,6734	1,7069	1,7069	1,7410	1,7758	1,9999	2,0399	2,0807	2,1223
budget 2018 indexed, in mio €	9,40	9,59	9,59	9,78	9,98	11,23	11,46	11,69	11,92
budget/indexed budget	100%	98%	99%	96%	95%	85%	86%	85%	85%

The amounts in the budget tool were indexed from 2021 onwards to secure sufficient funding for the research teams. To illustrate the index in the reference year for the call 2020 was 1,7410 whereas this was 2,1647 for the 2026 call, which represents a 24% budget increase for the same trial. This effect was only partially mitigated by reducing the margin from 10 to 5% which is meant to account for higher seniority, future increases in inflation, unforeseen delays and extra costs or capacity needs during the study.[14] This reduction of margin was deemed reasonable in light of the growing budget building experience at KCE Trials as well as the research teams.

Another factor contributing to budgetary uncertainty for the KCE Trials programme is the fact that it operates with an annual budget coming from RIZIV-INAMI, with unused funds to be returned at the end of the financial year. This is contradictory with the reality of clinical trials, where a budget is allocated upfront for a project spanning several years. Furthermore, given the milestone-based payments, there is always a degree of uncertainty as to when payments will be due. Delays are inherent in clinical research.[11] This makes budget planning and forecasting a very difficult and time-consuming balancing act, as optimal use of the budget must be combined with mitigating the risk of going over budget.

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[c] 04/09/2026; 2018 budget multiplied by adjustment factors as applied on wages in the public sector; https://bosa.belgium.be/nl/themas/werken-bij-de-overheid/verloning-en-voordelen/loonwedde/indexatie

To ensure optimal budget management, it would be much preferable that the allocated budget can be carried forward across multiple years, allowing KCE to manage the funding over the full duration of the funded studies. If a fully flexible multi-annual mechanism is not feasible, an alternative solution would be to provide multi-year budget envelopes (e.g. five-year cycles), enabling the programme to commit funding for studies whose duration typically ranges between three and five years.

4.9 Establish regular dialogue with domestic Belgian funders

There is no visible formal coordination with other domestic Belgian funders, which could in theory create risks for duplication and missed collaboration. In practice, however, we consider these risks to be limited. Various measures are in place to help avoid duplication and research waste.

First, the KCE Trials Program has a specific scope that complements the existing funding landscape and overlaps with it only to a very limited extent. Second, KCE Trials does systematically verify with the Fonds wetenschappelijk onderzoek (FWO) whether they have similar projects in the selection process, as we assess the potential overlap to be highest with this funder. Third, applicants must provide information on existing literature as well as upcoming and ongoing studies to demonstrate the project's added value. An additional literature search and database check by the KCE Trials team is part of the selection process. Fourth, applicants are actively asked about submissions to other funders so that, if applicable, a dialogue between the funders can be initiated and double funding is avoided. Finally, ethics committees will also assess and monitor the scientific relevance and added value of the funded trials.

Furthermore, Deloitte also mentions the future Post-Reimbursement Fund, which does overlap significantly with the current scope of KCE Trials. Several projects funded by KCE Trials could fit entirely within this framework. This could significantly increase the risk of overlap, duplication and missed opportunities for collaboration. How these two initiatives will be managed, coordinated and aligned in the future still needs to be worked out in more detail.

4.10 Expand international partnerships, particularly for areas with challenging recruitment

The tenth and last recommendation of the evaluation report encourages KCE Trials to expand international partnerships and joint calls with other public funders.

In some cases, international collaboration is the only way to generate the necessary evidence, for example when sufficient recruitment is not possible in Belgium alone within a reasonable timeframe. From an economic point of view, the return on investment may also be higher as research questions can be solved with a more limited investment when other public funders participate in the costs. On the other hand, an additional level of complexity is added to international trials which can make them more challenging from an organisational point of view. Furthermore, the funder may have less influence over the selection process, quality and execution of the trial, as compromises must be reached between the focus areas and timelines of several funders.

KCE Trials enables international collaboration in two ways. Firstly, international trials are not excluded from KCE Trials' national calls. Applicants can apply for Belgian participation in an international trial as long as it falls within the scope of the specific call. The call text specifies the conditions for this, and separate templates are provided for this case (support letter, budget calculation tool, etc.). KCE Trials also organises joint calls with other funders, which gives applicants the advantage of being able to secure funding in several countries with one submission. In this context four joint calls have been organised in collaboration with ZonMw (the BeNeFIT initiative). Currently KCE Trials participates in the ERA4Health partnership that brings together 37 partners from 24 countries.

Joint calls require significant resources in comparison with the assigned budgets as they have slightly different processes and alignment with the other funders is necessary. To also be able to continue in the national calls, choices must be made within the current budget (see also 3.8). This led to the

decision in 2026 to (temporarily) terminate the BeNeFIT initiative in favour of the ERA4Health partnership which allows for broader collaborations within Europe (see also 3.2).

5 CONCLUSION

For ten years, KCE Trials has been committed to its role as a public funder of non-commercial pragmatic trials, with the aim of contributing to better patient care and a more efficient use of public resources. After a decade of activity, the time had come for the programme to undergo a thorough external evaluation.

While ten years is a relatively short period in which to assess the full impact of clinical research, the evaluation has demonstrated very positive results. Among the programme's key strengths are a fair and transparent selection process, funding levels that enable studies to be conducted to high professional standards, particular attention to transparency and the dissemination of results, and strong collaboration with healthcare payer and other relevant stakeholders.

Decision makers and payers would naturally have liked the evaluation to quantify the programme's return on investment (ROI). At this stage, however, this was not yet possible. Such analyses have been conducted for other, more mature funding organisations, but they generally require a longer period of follow-up to capture the impact of funded clinical research. Assessing ROI could potentially therefore be an important objective of the next evaluation round, potentially in around five years.

The report provides many valuable recommendations, enabling KCE Trials to further strengthen and improve the programme. An initial reflection on these recommendations is presented in this short KCE report. Some recommendations have already been taken on board or translated into specific objectives for the near future; other recommendations may serve as a guide for future policy decisions regarding the programme.

Beyond the positive evaluation of KCE Trials itself, these results also emphasize the importance of sustained public investment in independent, non-commercial clinical research. Many questions that are highly relevant to patients, healthcare professionals and healthcare systems have limited commercial incentives and would therefore remain unanswered without public funding. This is particularly true for comparative effectiveness research, which directly compares existing treatments, interventions or care strategies to determine what works best for patients in everyday practice. By supporting research driven by patient and societal needs rather than commercial interests, public funders can generate robust and independent evidence to improve clinical practice, inform healthcare decisions and ensure a more effective use of limited public resources. Continuing to invest in this type of research is therefore not only an investment in better evidence, but ultimately in better and more sustainable healthcare.

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APPENDIX

APPENDIX 1. EXTERNAL EVALUATION REPORT

Deloitte.

10 Year Evaluation KCE Trials Programme

Final report

16 September 2026

Colophon

Title	10 Year Evaluation KCE Trials Programme
Prepared by	Deloitte Belgium
Commissioned by	KCE
Version	Final report
Date	16 September 2026

Disclaimer This report is based on data provided by KCE Trials, complemented by desk research, an online survey and interviews with relevant stakeholders. Data points were reviewed and cross-checked for consistency where possible. However, no formal validation or audit of the underlying raw data was performed. The findings, interpretations and conclusions presented in this report reflect the analysis conducted by the evaluation team and do not necessarily coincide with the views of individual survey respondents, interviewees or organisations consulted during the evaluation.

List of abbreviations

Abbreviation	Definition
AMR	Antimicrobial Resistance
AVIQ	Agence pour une Vie de Qualité (Walloon agency for quality of life)
BCFI	Belgian Centre for Pharmacotherapeutic Information
Be-SNAP	Belgian Sepsis National Action Plan
BeNeFIT	Belgium-Netherlands Funding of International Trials
BMJ	The British Medical Journal
COCOM	Commission communautaire commune (Brussels)
CRIGH	Clinical Research Initiative for Global Health
CTC	Clinical Trial Centre
ECRIN	European Clinical Research Infrastructure Network
EBP	Evidence-Based Practice
EMA	European Medicines Agency
EU	European Union
EULAR	European Alliance of Associations for Rheumatology
EViR	Ensuring Value in Research
FAMHP	Federal Agency for Medicines and Health Products (Belgium)
FNRS	Fonds de la Recherche Scientifique (Research Foundation – Brussels and Wallonia)
FPI	First Patient In
FRP	Full Research Proposal
FWO	Fonds Wetenschappelijk Onderzoek (Research Foundation – Flanders)
GCP	Good Clinical Practice
GP	General Practitioner
GZD	Gezondheidszorgdoelstellingen (Healthcare Objectives)
HTA	Health Technology Assessment
ICU	Intensive Care Unit
JAMA	The Journal of the American Medical Association
KCE	Belgian Health Care Knowledge Centre
LoS	Length of Stay
Lymph-ICF	Lymphoedema-specific International Classification of Functioning, Disability and Health
MRC	Medical Research Council
NEJM	New England Journal of Medicine
NIH	National Institutes of Health
NIHDI	National Institute for Health and Disability Insurance
NIHR	National Institute for Health Research
OECD	Organisation for Economic Co-operation and Development
OR	Odds Ratio
PG	Prioritisation Group
PIs	Principal Investigators
QALY	Quality-Adjusted Life Year
QoL	Quality of Life

Abbreviation	Definition
RCT	Randomised Controlled Trial
RO	Research Outline
ROI	Return on Investment
SOFA	Sequential Organ Failure Assessment
SOP	Standard Operating Procedure
TB	Trials Board
TBM	Toegepast Biomedisch Onderzoek met een primair Maatschappelijk finaliteit
WHO	World Health Organization
ZonMw	The Dutch Organisation for Health Research and Development (Zorgonderzoek Nederland Medische Wetenschappen)

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1. Executive Summary

The KCE Trials Programme is a public funding initiative established in 2016 by the Belgian Health Care Knowledge Centre (KCE). It supports pragmatic, non-commercial clinical trials addressing research questions of significant public health and societal importance in Belgium, particularly those lacking commercial viability. Supported research areas include examples like comparative effectiveness studies, drug repurposing and medical device evaluation. Additionally, the Programme promotes answering questions important for underserved populations (e.g., women, children, and elderly populations).

From 2016 to 2025, KCE Trials funded 75 trials across 20 calls, including four BeNeFIT calls as part of the partnership with the Dutch Organisation for Health Research and Development (ZonMw). During this time, 327 research proposals were evaluated and 75 trials were funded, of which 25 have been closed. Collectively, the funded research involved more than 32,000 participants across 129 sites and generated 91 peer-reviewed publications. The Programme achieved a 76% successful study completion rate, a 96% publication rate, a five-year average impact factor of 31.3 and 3 guideline uptakes. These achievements and outputs are summarized in the table below.

KCE Trials at a glance from 2016 until 2025	
20 calls	Conducted between 2016 – 2025, including 4 BeNeFIT calls
327 research proposals	Evaluated across the 20 calls
75 trials	Funded by KCE Trials
25 trials	Closed to date
> 32,000 participants	Included across 129 sites
91 publications	Peer-reviewed publications generated
76%	Successful study completion rate
96%	Publication rate
31.3	Five-year average impact factor
3	Guideline uptakes

KCE Trials is highly relevant to societal and health-system needs because it funds pragmatic, practice-oriented trials addressing evidence gaps that are unlikely to be resolved through commercial research funding. Its relevance is supported by investigator-justified evidence gaps that are confirmed by a panel of healthcare professionals, pragmatic trial design, broad coverage of therapeutic areas, inclusion of pharmaceutical, medical device, surgical and procedural interventions, systematic consideration of economic impact, and involvement of patients and clinicians in assessing clinical relevance. The portfolio also addresses emerging and under-

addressed priorities such as endometriosis, COVID-19, antimicrobial resistance and the needs of elderly populations demonstrating responsiveness to neglected chronic conditions, acute public health crises, and long-term population-level threats. Amongst investigators, 92% rate the trial selection process as fair and transparent and 57% agree that objectives align with health priorities.

Research topics are mostly driven by investigators. This limits the extent to which the Programme can demonstrate that it funds the highest-priority societal or policy needs. In addition, links with policymakers and regional health authorities could be further developed, and regional participation is uneven, with Wallonia being slightly under-represented among recruited patients. KCE Trials is highly relevant by design and stakeholder perception, and its strategic relevance could be strengthened through more systematic priority-setting, closer engagement with federal and regional decision-makers, and continued monitoring of regional representativeness.

Overall, **KCE Trials is effective in generating high-quality, practice-oriented evidence and strengthening Belgian capacity** for non-commercial pragmatic trials. Amongst investigators, 84% expect trial results to improve patient outcomes and 90% report that the Programme has strengthened their team's clinical research capability.

Its publication record, high-impact outputs, integration of economic evaluation, investigator support and examples of guideline-relevant findings all support a positive effectiveness assessment. The strongest evidence presents itself in intermediate outcomes: guideline uptake, publications, capacity building (even though not an explicit objective of the Programme), and perceived usefulness of the Programme and its findings. Evidence is less strong for final outcomes: formal policy uptake, reimbursement decisions, systematic practice change, patient-level impact across the portfolio and realised healthcare savings. This is partly explained because the Programme has been in place for just ten years, while full policy and practice impact often take longer than trial completion and publication. Also, not all trial results warrant a change in formal reimbursement decisions or criteria. The main effectiveness priority is to continue output tracking and strengthen impact tracking by monitoring whether trial results reach intended audiences, enter guidelines or influence policy decisions, change clinical practice, improve outcomes and generate measurable value for the Belgian healthcare system.

KCE Trials has **built an efficient support infrastructure for non-commercial pragmatic trials**, including budgeting tools, protocol support, templates, training and close communication with investigators. KCE Trials works with a €12.3 million budget annually of which approximately 80% goes to funding clinical trials. The average duration from research application to trial selection is 306 days, and the average period from trial selection to contract is 221 days. A large majority (92%) of surveyed investigators agree that KCE Trials provides a clear and relevant framework for pragmatic trials in Belgium, and 68% of investigators indicate KCE Trials support enabled timely and qualitative study execution.

These mechanisms **improve the feasibility of complex pragmatic trials and support their successful and on-budget completion**. Procedural efficiency, on the other hand, remains an attention point with 31% of investigators reporting that administrative and reporting procedures are disproportionate to the complexity of their trial. While only partially under control of the KCE Trials Programme, selection, contracting, start-up and publication timelines tend to be long. While KCE Trials provides many tools and templates to support the efficient selection and conduct of the trials in its portfolio, the main efficiency priority is not to reduce quality assurance, but to investigate where administrative, contractual and start-up processes can be made more proportionate and risk based.

KCE Trials demonstrates strong coherence with Belgian and international policy priorities. At federal level, the Programme is closely aligned with KCE's advisory mandate, NIHDI's appropriate care agenda, and ministerial priorities around quality, accessibility and efficiency. Its focus on pragmatic, non-commercial comparative effectiveness trials directly support policy needs for evidence on interventions that are already used, insufficiently compared, or not commercially attractive to study. The integration of economic impact into trial design further strengthens coherence with public payer objectives and the responsible use of health-system resources at both federal and federated levels. The Programme is also coherent with international developments, for example the World Health Organization's (WHO) call to strengthen clinical trials and generate high-quality evidence on health interventions, the European Commission's harmonised clinical-trial framework, and ZonMw's practice-oriented effectiveness research model. The BeNeFIT collaboration with ZonMw is a particularly strong example of operational coherence, as it enables Belgian and Dutch institutions to jointly conduct non-commercial pragmatic trials on questions relevant to patients, providers and policymakers in both countries. Coherence is stronger at the level of policy principles than at the level of systematic decision linkage. The main limitation is the absence of a structured mechanism through which federal and federated health authorities routinely translate policy priorities into research questions that can be addressed via trials.

Overall, **KCE Trials is a relevant, effective, efficient and coherent programme with a clear role in generating real-world evidence in Belgium.** Most remaining areas for improvement reflect its **growing maturity** rather than fundamental weaknesses.

This report presents a comprehensive evaluation of the KCE Trials Programme against four criteria: **relevance, effectiveness, efficiency and coherence**.

Criteria	Key message
Relevance	KCE Trials is highly relevant to societal and health-system needs, addressing evidence gaps through pragmatic, practice-oriented research, unlikely to be resolved through commercial funding.
Effectiveness	KCE Trials is effective in generating high-quality evidence and strengthening Belgian capacity for non-commercial trials, with peer-reviewed publications, guidelines and capacity-building outputs.
Efficiency	KCE Trials has built an efficient support infrastructure that supports the feasibility and conduct of complex non-commercial pragmatic trials.
Coherence	KCE Trials demonstrated strong coherence with Belgian and International policy priorities and supports evidence generation that is relevant to healthcare decision-making.

KEY RECOMMENDATIONS

RELEVANCE

- **Recommendation 1: Formalise payer and policymaker involvement in priority-setting**
  - Establish formal governance (e.g., yearly priority-setting meeting) with federal and federated health authorities to anchor selection to pressing decision-making needs.
  - Facilitate early dialogue between NIHDI, FPS Public Health, and investigators to define policy-relevant research questions.
- **Recommendation 2: Create awareness on regional capacity-building in Wallonia**
  - Conduct targeted outreach with Walloon clinical trial centres and publish results in national medical journals.
  - Engage policy makers on the need for targeted support to address infrastructure differences.

EFFECTIVENESS

- **Recommendation 3: Integrate dissemination and implementation planning into trial process**
  - Develop practical guidance and templates for investigators on dissemination planning, target audiences, engagement with payers, and data-sharing protocols.
  - Offer as a resource without adding mandatory.
- **Recommendation 4: Establish systematic post-trial impact tracking**
  - Introduce a structured tracking tool to monitor uptake in clinical guidelines, reimbursement decisions, and policy documents.
  - Conduct routine follow-up at two and five years after publication.
- **Recommendation 5: Leverage KCE's HTA capabilities more systematically**
  - Formally link Trials, HTA and policy advisory functions.
  - Use HTA needs to inform trial priorities and have HTA teams lead dissemination to policy makers and NIHDI reimbursement decisions.

EFFICIENCY

- **Recommendation 6: Analyse and reduce the application-to-contract timeline**
  - Conduct detailed analysis of administrative timelines through process mapping and interviews.
  - Identify bottlenecks and assess feasibility of efficiency improvements while maintaining methodological rigour.
- **Recommendation 7: Implement differentiated reporting requirements based on trial complexity and risk profile**
  - Introduce a risk-based model tailoring oversight, reporting and monitoring to each trial's risk profile.
  - Lower-risk trials follow streamlined pathways; higher-risk trials receive closer oversight.
- **Recommendation 8: Index KCE Trials budget to preserve existing capacity and funding predictability**

- Index the clinical-trial funding portion annually against a transparent benchmark reflecting cost drivers (personnel, site, data-management, monitoring) to preserve real value.

COHERENCE

- **Recommendation 9: Establish regular dialogue with domestic Belgian funders**
  - Implement a shared annual portfolio review with other funders (FWO-TBM, Kom Op Tegen Kanker) to reduce duplication, identify synergies, and align with new policy initiatives
- **Recommendation 10: Expand international partnerships, particularly for areas with challenging recruitment**
  - Strengthen joint calls with other public funders for rare diseases and surgical trials.
  - Develop formal data-sharing agreements to enhance scientific power and Belgium's global influence.

2. Programme overview

This chapter **introduces the KCE Trials Programme** as the object of the evaluation. It first describes when and why the Programme was established, and how it fits within the Belgian health research policy landscape. It then outlines the Programme's objectives, governance, funding model, selection procedures, types of trials supported, and mechanisms for scientific, methodological, and operational support. This descriptive overview provides the basis for the subsequent evaluation chapters, which assess the Programme's relevance, effectiveness, efficiency and coherence.

2.1 Rationale for the foundation of KCE Trials

KCE Trials is a programme established in 2015, extending KCE's mandate from evidence synthesis and policy advice to evidence generation at the request of the federal Minister of Health at that time [1, 2]. **The Programme fills a critical gap in Belgium's research landscape** by providing systematic funding for non-commercial pragmatic clinical trials. Commercial pharmaceutical and medical device companies predominantly fund trials aligned with their product-development and business priorities, while academic funding often focuses on fundamental and early-stage research. Consequently, important evidence gaps remain in areas of societal and health system relevance but limited commercial attractiveness. These include drug repurposing, comparative effectiveness of existing treatments, surgical technique evaluation, interventions for rare diseases, research on underrepresented populations, lifestyle interventions, psychotherapy, and pragmatic evaluation of diagnostics and care models. [3, 4, 5, 6, 7].

The Programme was designed to address this gap by funding non-commercial, pragmatic, practice-oriented trials in real-life settings, generating high-quality, policy-relevant evidence capable of informing clinical guidelines, reimbursement decisions, and healthcare system efficiency [3, 4, 8]. **The emphasis on real-world populations and care settings is deliberate**. Trials conducted under highly controlled conditions primarily establish whether an intervention can work under ideal circumstances, but their findings may not translate to routine practice. KCE Trials therefore aims to generate real-world effectiveness evidence that is directly applicable to the Belgian healthcare system.

2.2 Programme structure and governance

The **KCE Trials team** oversees the Programme's day-to-day operations, including coordination of calls, support to research teams, monitoring of funded trials, and follow-up of project progress.

KCE Trials is governed by four independent, programme-specific bodies with distinct roles. Final oversight remains with the KCE Board [9, 10].

1. The KCE Trials **Prioritisation Group (PG)** is composed of independent experts in clinical trials delegated by the organisations presented in the KCE Board (e.g. NIHDI, FPS Health, health insurers) and Belgian universities [11, 10]. They assess whether submissions are in scope of the call for proposals, prioritize the competing ones based on clinical relevance and value for money, oversee the selection process and provide advice on funding decisions.
2. The **KCE Trials Panel** is a multidisciplinary group of healthcare professionals and patient representatives that assesses clinical relevance and the need for new evidence for each proposed research question. It ensures research questions reflect the needs of routine

clinical practice across the Belgian healthcare system. Its composition depends on required expertise for application review and strives for a balanced representation of Dutch and French speaking members. Clinicians and other healthcare professionals can express interest in becoming a Panel member. The Panel has an advisory role only [12].

3. The **Trials Board** includes senior clinicians and methodologists, such as statisticians or health economists, as well as representatives of patients and public. It reviews the methodological and scientific robustness of research outlines and proposals, the presence of the required experience in the research team, the potential economic and societal value, and level of patient involvement. The KCE Trial Board recommends research proposals to fund to the Prioritisation Group [13].
4. The **KCE Board** approves the list of full research proposals recommended for funding by the Prioritisation Group. The KCE Board is composed to reflect Belgium's health-policy and healthcare landscape, bringing together representatives from government, health authorities, health insurers, healthcare providers, social partners, and patient representatives to ensure oversight from multiple perspective [14, 12] s.

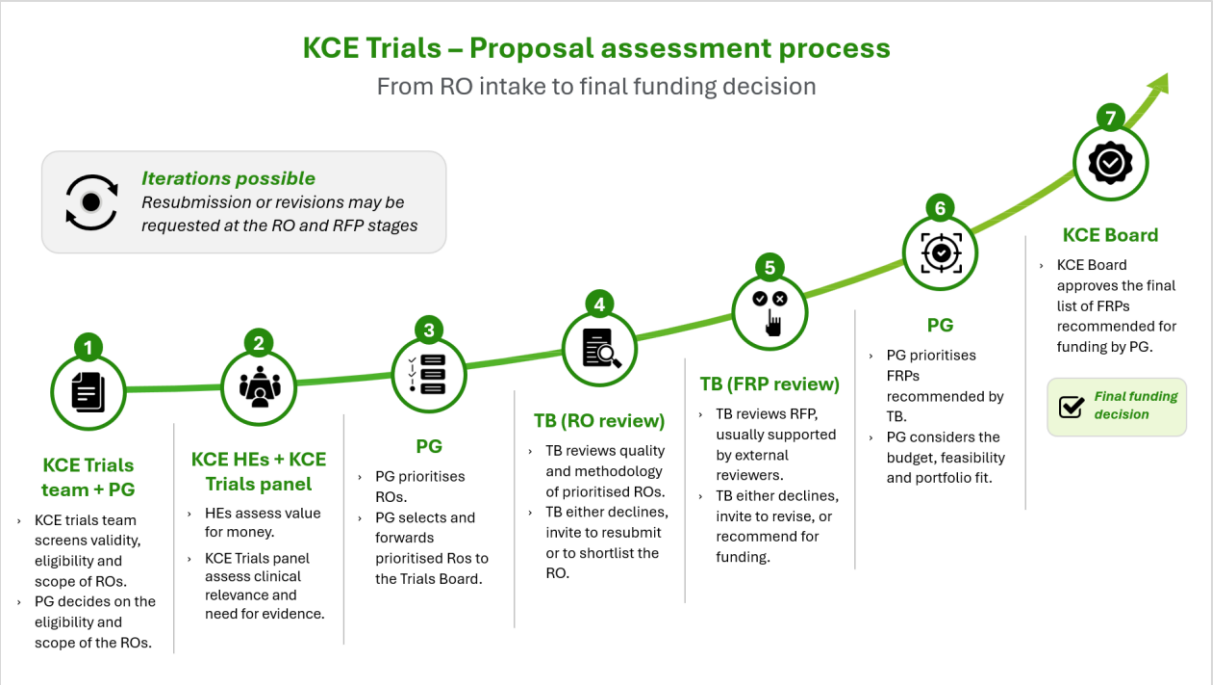


Figure 1. *KCE Trials proposal assessment process from initial research outline to final funding decision. PG: Prioritisation Group; RO: research outline; HE: health economist; TB: Trials Board; FRP: full research proposal.*

2.3 Funding model

KCE is a type B parastatal body with high independence from its funding authorities. KCE's annual organisational budget is funded by the National Institute for Health and Disability Insurance (NIHDI) and the Ministry of Health and Social Security. KCE Trials is funded with additional budget coming exclusively from NIHDI [15, 16, 17].

2.4 Activities and processes

The KCE Trials Programme operates as a **funder** of pragmatic trials, not as a sponsor. Therefore, KCE Trials does not directly conduct clinical trials, employ trial staff, or hold primary responsibility for trial execution. Instead, it provides financial resources, methodological and administrative

guidance, and governance oversight that enable independent research teams to conduct high-quality pragmatic trials, preserving investigator independence while ensuring rigorous quality standards and alignment with public health priorities.

Through its **core activities**, **KCE Trials identifies research priorities, selects and funds trials, and supports investigators** throughout the trial lifecycle.

2.4.1 Identifying research interest and priorities through calls

Calls for proposals (calls) are organised regularly and advertised by KCE Trials at least via the website [18, 19] and newsletter, and may be complemented through presentations at hospitals, publications on LinkedIn via the Programme's online presence and dissemination of information via clinical trial centres [12]. KCE Trials uses four types of calls, each serving a different function in the funding strategy.

1. **Investigator-led calls** are the standard open calls, where research teams submit research proposals on topics the investigators identify as relevant to Belgian healthcare.
2. **Themed calls** are more targeted. They remain open to investigator research proposals, but within a predefined disease or research area that was selected, because it has been considered a healthcare priority. Examples include the themed call on endometriosis (2024) [20] and more recently the ones on palliative care and care for addiction (2026) [21, 22].
3. Calls linked to **international collaboration** are joint calls with public funders from other countries and for which KCE Trials funds the costs of Belgian participation. These include BeNeFIT calls with ZonMw, designed to support Belgian Dutch non-commercial comparative effectiveness trials, and ERA4Health calls, a European partnership to increase European transnational collaborative research funding [6].
4. **Commissioned calls** are more specific and aimed at addressing an evidence need defined by policymakers, payers, healthcare professionals, patients or the public. They can be organised through a call for topic suggestions open to everyone, such as the 2016 commissioned call [23] or based on ad-hoc questions, such as the commissioned call on the comparative effectiveness of multiple myeloma treatment [24].

2.4.2 Trial selection process

For investigator-led calls, **researchers submit research outlines via the KCE Trials grant management system** (SmartSimple). The KCE Trials team screens all submissions for validity and alignment with call-specific published eligibility criteria. Applicants can correct and resubmit their application in the event of administrative errors or omissions, provided they are made within the deadline. The Prioritisation Group has final decision over the scope of outlines. Applicants are informed through the grant management system [12, 19, 9, 25].

Valid outlines undergo dual assessment. At least two health economists from KCE or KCE Trials score each proposal based on expected patient benefits and cost savings, while generally two to three rapporteurs of the Trials Panel evaluate clinical relevance and evidence need. They present their findings during a Trials Panel meeting where a patient representative provides additional perspective. All Trial Panel members then score each proposal anonymously and research outlines are ranked based on mean score [9, 12, 13, 19]. Feasibility assessments of proposed

sites and investigators are also conducted to identify operational risks before a proposal advances.

The final list of prioritized research outlines is selected by the Prioritisation Group. If capacity allows, the KCE Trials Team performs a search for existing evidence and ongoing trials to inform the Panel and Prioritisation Group in their decision-making. The Prioritisation Group consolidates scores and prioritises outlines based on clinical relevance and value for money, with budget availability determining how many proceed to the Trial Board. The Prioritisation Group can deviate from the ranking provided by the panels and health economists, and change the prioritisation by consensus [19, 12, 13, 9].

Prioritised outlines proceed to a second review and voting stage conducted by the full Trial Board, with at least three members (ideally including one clinical expert, one statistician, and a patient representative) acting as lead reviewers. **Proposals are assessed on quality and methodology** on a 1-6 scale. Proposals scoring five or above are shortlisted for full research proposals. Those scoring three to five may resubmit once. Proposals with a score below three are declined with written feedback. Shortlisted teams may receive €12,500 in advance to support full research proposal development. A maximum of five Board review rounds is organised per call, and unfunded projects may resubmit once in future calls. KCE reserves the right to postpone, suspend, or withdraw calls at any stage [12].

The Prioritisation Group will review full research proposals recommended for funding by the Trial Board and cross-check implementation of changes requested by the Trial Board. The Prioritisation Group provides final list of trials recommended for funding to the KCE Board, who holds final approval [19, 12, 13, 9].

For commissioned calls, where the topic definition phase differs, the remainder of the process mirrors the investigator-led workstream. Both pathways converge at the Research Outline stage and proceed through the same multi-stage evaluation process [12, 19, 13].

2.4.3 The monitoring process

Once trials are selected, KCE Trials provides comprehensive support throughout the trial lifecycle, including, but not limited to, the below activities [26]:

- Provision of methodological tools and templates for protocol development, budget planning and feasibility assessment.
- Support with navigating ethics approvals, site activation and recruitment planning.
- Organization of regular update meetings, depending on the (phase or intensity of the) study.

2.5 Other processes and activities

Beyond its core activities of trial selection and support, the **KCE Trials Programme engages in complementary activities that strengthen the Belgian research ecosystem** and **extend the Programme's impact**. A non-exhaustive list of such strengthening activities includes:

- Capacity and capability assessment process for Clinical Trial Centres, including follow-up visits at Belgian hospitals
- Training programmes
- Independent audits as part of continuous quality improvement cycles
- Patient and public involvement promotion

- Representation of Belgium in international research networks, including negotiations on non-commercial research agreements, intellectual property, and data sharing arrangements

KCE Trials **maintains and strengthens infrastructure**. This includes, but is not limited to, the methodological tools and templates and support for the conduct of clinical trials in the form of audits, feedback and follow-up [27, 26]:

Training courses are also regularly organised for study teams that are involved in KCE Trials funded studies. The training of the KCE Trials Programme is established every year based on training needs identified by the study teams themselves or by KCE Trials (for instance clinical operations or Good Clinical Practice (GCP) domains such as risk management, budget management, Clinical Study Report writing, safety reporting in pragmatic trials, and computer system validation) [26]. During the entire lifecycle of the study, the Programme remains in an **actively supporting role**.

In 2016, KCE Trials started performing **capacity and capability assessments at the clinical trial centres (CTCs) of Belgian hospitals** who had the ambition to be the sponsor of a KCE Trial. In total, 13 of these visits were conducted, with 12 hospitals being visited in 2016 and one candidate sponsor in 2022. The outcomes of this evaluation were used by the CTCs to strengthen their competencies by centralising the already available expertise in the hospital or by expanding the services to be offered to investigators. A follow-up of the first capacity assessment was done in the CTCs that are actively managing KCE trials [28].

Study audits are performed by an independent quality assurance consultant on a selected number of studies as part of a continuous quality improvement cycle [26].

Beyond trial conduct, KCE Trials has established a **systematic approach to economic analysis** of trial results. All trials are designed to collect economic-relevant data (e.g., quality of life (QoL), healthcare resource use, productivity impacts, and patient-reported outcomes) to enable potential future economic analysis. Whether a formal economic evaluation is conducted depends on several factors:

- If a trial demonstrates **no clinical benefit** on its primary endpoint, a formal economic evaluation is typically not needed.
- If an intervention is **clearly cost-effective** (e.g., inexpensive with demonstrated clinical benefit) **or clearly not cost-effective**, a formal analysis may not add any further value.
- **Pilot trials and feasibility studies** by design are not powered to support definitive clinical effectiveness (and thus cost-effectiveness) conclusions.
- In some cases, **the clinical or epidemiological context may change** between trial conduct and completion, affecting the relevance of economic analysis[1].

This **approach ensures that formal analysis is pursued only when it meaningfully informs implementation decisions** and is detailed in the KCE Trials' SOP on the Economic evaluation after KCE-funded trials [29]. This report assesses the economic dimension in the analysis

[1]For example, several COVID-19 trials conducted during the pandemic found that by the time results were available, the target population or clinical context had shifted, affecting the relevance of certain economic analyses.

presented in section 4.2.2 (*Longer-term impact*), specifically the subsections *Synthesis of trial outcomes* and impact and 4.2.2.3 *Economic data collection vs. economic evaluation*.

The Programme's **knowledge dissemination model** relies primarily on principal investigators (PIs) leading communication of their findings, with KCE Trials providing support through a multilingual website, LinkedIn presence, symposia, and stakeholder engagement events [30, 31, 32, 27]. Brief updates on completed studies are presented during Prioritisation Group and KCE Board meetings attended by, amongst others, NIHDI representatives. KCE Trials maintains a publicly accessible dynamic dashboard with a complete portfolio overview, including trial status, recruitment progress, disease areas, geographic distribution, publication records, and impact metrics.

The Programme also **maintains relationships with clinical trial centres, regulatory bodies, and international collaborators**, including peer funders and research organisations. These relationships illustrate formal joint-funding funding initiatives (such as BeNeFIT with the Netherlands and ERA4Health) as well as informal collaboration (such as with ECRIN) [19, 27].

KCE Trials also **contributes to the broader evidence base** through its **unique dual role** as both a health technology assessment body and a research funder [33, 34]. Through these activities, KCE brings together diverse Belgian and international stakeholders (such as PIs, payers, regulators, and patient representatives) to advance pragmatic clinical research in Belgium and Europe [33, 35].

3. Evaluation framework and methodology

3.1 Evaluation Criteria and Intervention Logic

The **evaluation framework** is built on two complementary methodological pillars: the **Intervention Logic and the Evaluation Matrix**. Together they establish a causal link between the KCE Trials Programme's activities and its intended results, and systematically structure data collection and analyses across four evaluation criteria: relevance, effectiveness, efficiency, and coherence. The approach aligns with established evaluation frameworks used by comparable international research funders, including ZonMw [36], the NIHR [37], and the Medical Research Council (MRC) [38]. It also draws on broader public-policy standards, such as the European Commission Better Regulation Guidelines [39, 40] and the OECD Organisation for Economic Co-operation and Development's (OECD) evaluation criteria framework [41].

3.2 The intervention logic

The Intervention Logic serves as the **foundational analytical tool for the evaluation**. It maps the KCE Trials Programme's expected causal pathways, making the assumed links between each stage of the Programme cycle and the assumptions and contextual factors that could affect realisation explicit. It is used as the primary reference both for the process evaluation (assessing whether the Programme is being implemented as intended) and for the impact evaluation (assessing whether the assumed causal links are valid and materialising in practice).

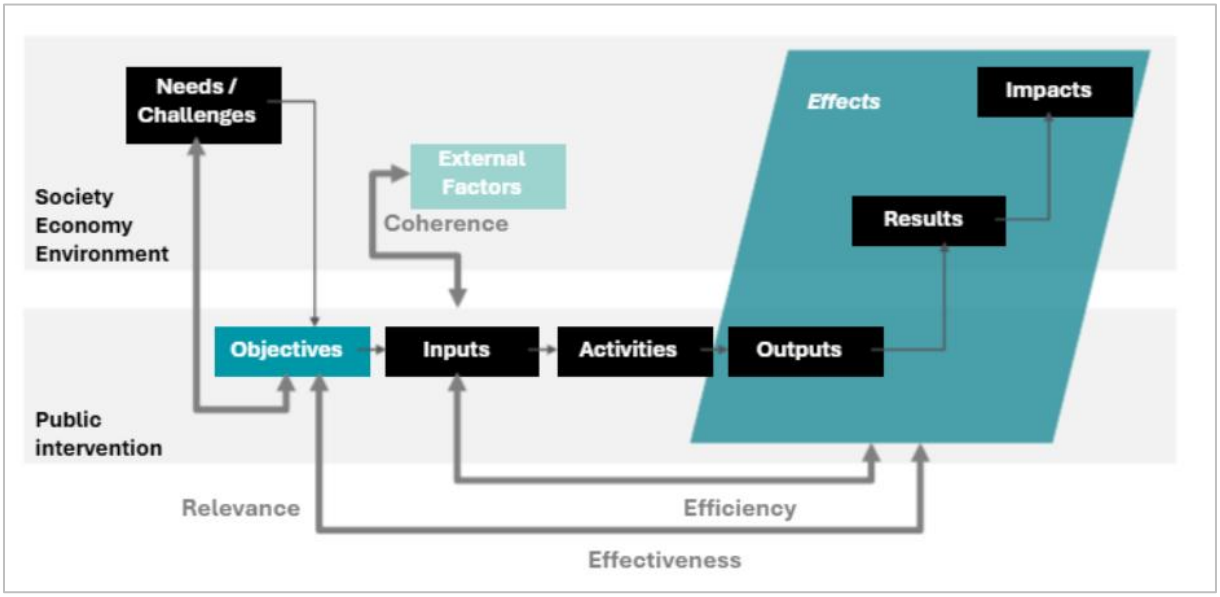


Figure 2. *The intervention logic maps out the causal links between the resources invested, the activities undertaken, and the expected results, from short-term outputs to long-term impacts.*

The Intervention Logic is structured around **six sequential components**:

1. The intervention logic starts from the societal and health-system **needs** the Programme intends to address and identifies the underlying challenges that justify public intervention and shape the Programme's **objectives**.
2. **Inputs** comprise the financial, human, organisational and technical resources allocated to launch and sustain the Programme, and enable its planned activities, outputs and expected results.

3. **Activities** encompass the actions and core processes undertaken to transform resources into outputs.
4. **Outputs** are the immediate, direct deliverables produced by the Programme's activities that KCE Trial's Programme can influence directly, such as organisation of calls and trial selection.
5. **Results and impact** capture what happens, because of the Programme's outputs and where the Programme's influence is only indirect, but consequential, such as knowledge gain and capacity building, improved research infrastructure, and changes in clinician behaviour. Results focus on the practical application and utilization of research results and focus on how these materialize in society, the economy or environment in the medium term. While the KCE Trials Programme facilitates these processes through targeted interventions, the ultimate responsibility for implementation lies with healthcare professionals and field partners.
6. **Long-term Impact** is the most challenging to measure, as it is the furthest from direct KCE Trials' control, such as improved health of the general population through increased QoL or longevity or economic benefits from more appropriate care. Impact connects to the objectives of the intervention: the broad, systemic implementation of results across the healthcare field and the resultant long-term effects of the KCE Trials Programme. While the KCE Trials Programme contributes significantly to these impacts, its activities do not necessarily result directly into measurable or attributable long-term impact, nor is the organization the sole party responsible for achieving systemic change.
7. **External factors** describe contextual conditions outside the Programme's direct control that could influence output, results, and effects. For example, regulatory changes, healthcare system evolution, the COVID-19 pandemic, and political and policy changes.

3.3 Evaluation criteria

Four evaluation criteria are applied through the lens of the KCE Trials **Programme's Intervention Logic**:

- **Relevance** asks how well KCE Trials addresses healthcare needs that are socially important and insufficiently covered by other research funders.
- **Effectiveness** asks to what extent the Programme achieves its intended scientific, clinical, and societal outcomes, and through which mechanisms.
- **Efficiency** asks how efficiently the Programme uses available resources to deliver high-quality research at acceptable cost.
- **Coherence** asks how well KCE Trials is aligned with and complementary to other national and international research initiatives and health system priorities.

3.4 Evaluation matrix and research questions

The Evaluation Matrix, outlined in Table 1, is the **operational backbone of the methodology**. It translates the four evaluation criteria and their primary research questions into measurable indicators that are each linked to defined data sources and methods. This hierarchical structure provides a transparent link between the Intervention Logic, the evaluation criteria, and the evidence base, facilitating systematic analysis and robust interpretation of findings. Each criterion is operationalised through a primary research question and a set of secondary research questions, as detailed in the Evaluation Matrix.

Criterion	Primary research question	Secondary research questions	Key indicators
Relevance	How well does the KCE Trials Programme address healthcare needs that are socially important and insufficiently covered by other research actors?	• How transparently and appropriately are research priorities identified, and do selected trials reflect unmet needs? • How does KCE Trials balance scientific opportunity with societal value? • To what extent are diverse stakeholders engaged in identifying and shaping research priorities? • How does the portfolio evolve in response to emerging health challenges and policy priorities over time?	• Funded topics linked to evidence gaps or health priorities • Diversity of intervention types and disease areas • Diversity of trial settings • Stakeholder diversity and perceived inclusiveness • Portfolio responsiveness to emerging priorities
Effective-ness	To what extent does KCE Trials achieve its intended scientific, clinical, and societal outcomes, and through which mechanisms?	• What are the main pathways through which trials contribute to knowledge generation, clinical practice, and policymaking? • To what extent do results inform clinical guidelines, reimbursement decisions, or policy priorities? • What is the perceived relevance and usability of trial outputs among clinicians, patients, and decision-makers? • What are the observable effects on healthcare quality, patient outcomes, and cost-effectiveness?	• Number of calls • Number of trials funded • Number of publications and publication rate • Percentage of completed trials resulting in publications • Number of trials informing policy/guideline changes • Journal impact factors and citation counts • Number of NIHDI policy decisions informed by trials • Evidence of changed clinical behaviour • Perceived international influence
Efficiency	How efficiently is the Programme using available resources to deliver the intended outcomes?	• What factors enable or hinder project selection, management, and completion? • How effectively are existing infrastructures and collaborations leveraged? • What is the cost-efficiency across trial types and settings? • How does the KCE Trials Programme compare to international benchmarks on timeliness, cost, and resource utilisation? • How transparent and predictable are funding and reporting mechanisms?	• Average duration across timeline phases, focusing on application-to-selection, selection-to-contract and contract-to-FPI • Contract-to-FPI timelines versus EU targets • Investigator satisfaction with processes and perceived administrative burden
Coherence	How coherent and complementary is the KCE Trials Programme with other national and international research initiatives and health system priorities?	• How well does the Programme align with Belgian and EU funding mechanisms (FWO, FNRS, ZonMw, post-reimbursement fund)? • How do collaborations with universities, hospitals, and networks add value? • What synergies and overlaps exist with private, academic, or public research funders? • How does KCE's role contribute to Belgium's positioning in European and global evidence-based healthcare research?	• Overlap and complementarity with other funders • Logical consistency between the Programme's objectives and funding mechanisms • Qualitative evidence of alignment with federal and federated strategies and reforms

Table 1. *Overview of evaluation matrix' primary research question, secondary research questions, and key indicators per criteria.*

3.5 Evaluation design and data sources

3.5.1 Evaluation design

The **assessment employs a mixed-methods design** integrating qualitative and quantitative analyses across all four evaluation criteria. Quantitative analyses use administrative, bibliometric, and survey data to generate descriptive statistics and assess performance against benchmarks. Qualitative analyses draw on stakeholder interviews, document reviews, and case studies to interpret causal mechanisms, contextual factors, and institutional dynamics. Integration occurs through triangulation for each evaluation question, enabling convergence of evidence across data types. Validation is ensured through sessions with key stakeholders to test emerging findings, reconcile contradictions, and produce final recommendations.

3.5.2 Data sources and analyses

Qualitative and quantitative analyses were performed based on provided databases:

- **KCE trial portfolio database**

  The portfolio analysis took place based on the snapshot of trials in January of 2026, resulting in 83 research proposals and trials in scope. Trial data includes trial characteristics, disease areas, intervention types, settings, recruitment targets and actuals, time to reach project milestones (e.g., contracting, first patient in), status and milestone dates. These trials were at different stages of completion and were classified based on their last-known trial status:

  - **In selection process**: trials submitted in the call of September 2025, for which no decision (go vs. no go) had been made in January. Eight trials are part of this group;
  - **Selected**: trials that have been selected but have not started yet. Eight trials were identified in this group, which showed a variety of stages from contract negotiations over contract signed to first activities. Selected trials are primarily assessed based on their relevance and coherence, and PIs have been surveyed on their experiences throughout the selection process;
  - **Ongoing, recruitment ongoing**: trials that are currently running and are actively recruiting. 28 trials still had active recruitment in January 2026, and have been assessed based on relevance, efficiency of the processes, and coherence, both through a survey and in-depth stakeholder interviews;
  - **Ongoing, recruitment closed**: trials that are currently still running and are no longer recruiting patients. 14 trials have been assessed based on their relevance, the efficiency of the process, effectiveness of preliminary outcomes, recruitment and coherence;
  - **Stopped**: trials that have been selected for funding but were stopped either before first-patient-in or during recruitment. In total, six trials have been stopped before completion, due to recruitment issues. Stopped trials are included in the analysis regarding relevance of the topic, therapeutic area covered, trial setting, as well as efficiency of the process. Experiences and lessons learned of stopped trials have been gathered through the survey and in-depth stakeholder interviews;

- **Completed:** trials for which a clinical study report is available. These 19 trials provide the broadest coverage of insights across all the evaluation criteria, as most of these have resulted in publications, some of which have, in turn, informed clinical guidelines and practice.

Descriptive statistics were used to analyse the data. However, to further assess impact across the 19 completed trials, the evaluation adopted a narrative synthesis approach, grouping trials into four categories that each share a common type of value proposition:

- Demonstrated in-trial economic return
- The value of negative and null results
- Positive clinical results with potential for practice-change
- Mixed and inconclusive results.

The trial designs, as their reported outcomes, were extremely heterogenous. Therefore, for the purpose of this evaluation, attempting to impose a common quantitative metric[2], across such heterogeneous populations and endpoints would not have created reliable insight. The categorical synthesis allowed for the evaluation to be transparent about what each trial demonstrates, and to distinguish between documented impact, expected impact, and self-reported impact, without obscuring the underlying evidence with inappropriate aggregation.

- **KCE trials site database**
  Covers all trials and the associated trial sites engaged for patient recruitment, including trial setting and number of recruited patients. Additional analyses covered the regional distribution of these trial sites, as well as more details on the type of hospitals, for example. Descriptive statistics were used to analyse the data.

- **KCE budget file**
  Covers the allocated and consumed budget per trial. Descriptive statistics were used to analyse the data.

- **KCE call database**
  Covers all calls issued between 2015 and 2025 by call type, and topic area and strategic focus. Descriptive statistics were used to analyse the data. Calls closed before October 2025 were considered for the analysis.

- **Publication records**
  Bibliometric and citation analysis of publications from all 75 funded trials, as well as completed trials, including journal impact factors, citation patterns, and policy document citations.

- **Desk research**:
  - Analysis of Belgian health policy priorities
  - Benchmarking selected metrics against comparable international funders (ZonMw, NIHR)

[2]Such as, for example, a pooled effect size or a QALY-based comparison.

- Systematic review of published trial protocols and results
- Selected literature and policy review to contextualise evaluation findings

- **Economic assessment**
  All 19 completed trials across the portfolio were evaluated to identify:

  - Which trials conducted formal economic evaluations (e.g., cost-effectiveness analysis, cost-consequences analysis, budget impact analysis) and what economic measures were the focus (e.g., cost savings, productivity impacts, resource utilization)
  - Whether health-economic data (QoL, healthcare resource use, productivity) were systematically collected during the trial
  - Gaps between planned and reported economic data collection
  - For trials without formal economic evaluations, whether this absence reflected a deliberate methodological choice (e.g., negative clinical results, pilot design, contextual factors) or a genuine data gap

This analysis revealed the breadth and depth of health economic evidence generated by the Programme, identified where economic data were collected consistently across trials, and distinguishes between strategic decisions not to conduct formal evaluation and actual gaps in economic assessment coverage.

In-trial cost savings: As part of the economic (impact) assessment, a subset of trials was selected specifically for the estimation of in-trial cost savings. These trials are all cancer trials focused on dose optimizations, and have not completed recruitment (PULSE, OPT-PEMBRO, and OSI-SAVE). The evaluation estimates the in-trial cost saving by comparing projected pharmaceutical acquisition costs under standard of care versus the intervention arm, multiplied by the number of (projected) Belgian trial participants. This is then compared with the trial investment cost. Cost estimates are restricted to pharmaceutical acquisition costs and exclude administration costs and downstream healthcare cost impacts.

Key assumptions applied to all three trials:

- **Drug costs** are based on NIHDI list prices. Because list prices are subject to confidential discounts, the evaluation reports these savings across a range of hypothetical discount scenarios (10–90%).
- **Participant numbers**: in multinational trials, calculated as proportional allocation of Belgian participants from global enrolment targets, based on publicly available data [30].
- **Cost scope**: restricted to pharmaceutical acquisition costs. Downstream healthcare cost impacts (e.g., hospitalisation, length of stay, and healthcare utilisation) are not considered.
- **Time horizon**: savings are calculated over the treatment period specified in each trial protocol only, not over the full follow-up period or beyond.
- **Outcome independence**: the in-trial cost saving accrues the moment a patient is randomised to the lower-cost arm and is therefore calculated independently of the trial's outcome.

- **Online investigators survey**
  An online survey was distributed to **PIs and National Coordinators of all KCE-funded clinical trials and declined applicants from the most recent KCE investigator call** to gather systematic feedback on Programme processes, efficiency, perceived impact, and added value. It was conducted between December 2025 and January 2026. Out of 84 eligible respondents, comprising unique PIs of KCE-funded trials plus applicants from the latest investigator call who could be contacted, 47 returned usable questionnaires (56% response rate). The investigator survey used tailored routing so that respondents received status-specific questions depending on whether their proposal had been rejected, their trial was ongoing, or their trial had been completed. The full questionnaire can be consulted in the appendix.

- **Semi-structured stakeholder interviews**
  17 semi-structured interviews of 45-60 minutes with in total 18 interviewees were conducted virtually between November 2025 and May 2026, with tailored interview guides based on their most relevant perspective and experience.
    - KCE leadership including the Director General and senior Programme staff (n=6)
    - Payers (n=3)
    - External funders and international partners including ZonMw, NIHR, and ECRIN (n=2; 1 double interview)
    - PIs for case studies (n=6)

- **Case studies**
  Five in-depth case studies were conducted to complement the quantitative portfolio analysis and to contextualise the mechanisms through which KCE-funded research translates into real-world impact. They combine document review, trial monitoring data, and principal investigator interviews.

  Trial selection followed a sampling strategy designed to maximise diversity across the following dimensions: trial status at time of evaluation (completed, ongoing, stopped), intervention and therapeutic area, trial population and setting, funding modality (KCE only vs. co-funded) and outcomes (high impact, low impact, negative results, feasibility challenges). Case studies are presented for illustrative purposes only.

  1. **ARON Trial (completed, high impact)**: demonstrates strong scientific output and policy relevance in a priority area (antimicrobial resistance)
  2. **C-EASIE Trial (completed, negative results):** illustrates the value of rigorous evidence generation even when primary outcomes are not met
  3. **Pressure Ulcer Trial (completed, included in national and international guidelines):** shows translation of evidence into clinical practice and guideline development
  4. **SurLym Trial (ongoing, surgical study):** represents the potential for internationally relevant research in a challenging setting
  5. **FOOT DROP Trial (stopped):** provides lessons learned about challenging recruitment, and the value of feasibility research

Each case study examines the trial's clinical context and evidence gap, study design and key findings, scientific impact and dissemination, relevance to healthcare needs, implementation and policy potential, and economic considerations.

3.5.3 Evaluation timeline and planning

The evaluation spanned a 13-month period, from September 2025 to October 2026, and is structured around **three main phases**: inception, data collection and analysis, and triangulation and validation. This phased approach, consistently supported by thorough stakeholder consultation, ensured that the evaluation progressed from framework development to evidence gathering, synthesis, reporting, and final presentation in a structured and sequential manner.

During the **inception phase**, from September to November 2025, the evaluation questions, methodology, intervention logic, and evaluation matrix were refined. Exploratory interviews with KCE leadership, programme management stakeholders, and other key actors supported this process by helping to validate the scope, clarify expectations, and identify priority areas for analysis. This phase resulted in the evaluation framework and analysis plan, completed by 20 November 2025.

The **data collection and analysis phase**, running from November 2025 to April 2026, focused on gathering and analysing evidence across the evaluation criteria of relevance, efficiency, effectiveness, and coherence. This includes document review, portfolio analysis, the investigator survey, and stakeholder interviews. The work was organised around **two key analytical milestones**: **process evaluation** findings, completed by 19 March 2026, and **impact evaluation** findings, completed by 15 April 2026.

The final phase, **triangulation and validation**, ran from April to October 2026. In this phase, evidence from different sources was brought together to test emerging findings, resolve inconsistencies, and strengthen the robustness of conclusions and recommendations. Stakeholder consultation plays a supporting role in this phase, allowing key findings to be sense-checked against operational experience, policy priorities, and stakeholder perspectives. The main reporting milestones are the draft final report, completed by 11 June 2026, the final report, completed by 31 August 2026, and the presentation to the KCE Board, scheduled for 13 October 2026.

Overall, the planning of the evaluation combined a clear sequence of deliverables with iterative engagement of relevant stakeholders. **Stakeholder consultation** is therefore not a separate workstream, but an embedded input into the evaluation process, supporting the refinement of the framework, the interpretation of findings, and the validation of final recommendations.

4. Evaluation findings

4.1 Relevance

How well does KCE Trials address healthcare needs that are socially important and insufficiently covered by other research actors?
• 92% of investigators rate the **selection process as fair and transparent** • 57% of investigators agree that **objectives align with health priorities** • Justification of evidence gaps by investigator is systematically embedded in research outlines through the selection process>60% of **trials can be linked to Belgium's highest-burden disease categories** despite no formal link between documented healthcare evidence gaps and KCE Trials portfolio • 10% of calls for proposals were **commissioned calls** • **Topics for themed calls are relevant** but there is no formal SOP to select these topics

Table 2. *Relevance indicator highlights*

KCE Trials was established with **the mandate to fill the evidence gap in areas where the healthcare system has genuine needs**, but private, for-profit organisations, nor some academic institutions are unlikely to invest, by funding rigorous, large-scale trials that generate evidence for clinical decision-making and policy [5, 42]. These needs include:

- **Head-to-head comparisons of existing treatments and techniques**, including non-drug interventions such as surgical procedures, to inform clinical decision-making
- **Validation of intervention effectiveness in real-world populations** and settings through pragmatic research designs
- **Growing demand from Health Technology Assessment (HTA) processes** for robust evidence to support policy decisions and optimise limited healthcare resources
- **Critical gap in cost-effectiveness evidence for existing interventions** and technologies that constrains sustainable healthcare funding and resource allocation

Objectives specify what the Programme seeks to achieve [4, 5, 42, 43]:

- **Fund trials prioritising comparative effectiveness and drug repurposing** (for off-patent drugs), including research in medical devices and diagnostics where it falls within these categories
- **Address areas typically neglected**, but of high **societal relevance**
- **Increase pragmatism and representativeness of clinical research**, ensuring findings are generalisable to broader populations and real-world practice
- **Stimulate pragmatic trial conduct** and contribute to increased research capacity and capabilities
- **Facilitate knowledge translation** into policy and clinical guidelines
- **Enhance data quality and sharing**, ensuring open access to resulting databases for public interest research
- **Enable independent cost-effectiveness analyses** that support reimbursement and healthcare resource allocation decisions

This evaluation assesses KCE Trials' relevance through four interconnected research questions:

(1) How transparently are research priorities identified, and to what extent do selected trials reflect unmet needs in the Belgian healthcare system?

(2) How does KCE balance scientific opportunity with societal value?

(3) To what extent are diverse stakeholders engaged in priority-setting? and

(4) How does the portfolio evolve in response to emerging health challenges?

4.1.1 Research priority setting: balancing scientific opportunity and societal value

Investigators' perception of the trial selection process is very positive. 92% rate the process as fair and transparent, and 57% agree that Programme objectives align with national health priorities [44].

Funded trials **address identifiable evidence gaps by design**. Trial applicants are required to justify the clinical relevance and need for evidence in their Research Outlines. The KCE Trials Panel assesses this justification during the selection process, requiring investigators to explain why the trial is needed, what uncertainty it intends to resolve, and how the results could inform practice. Evidence gap justification is a responsibility of the investigators, facilitated through a template that is part of the application document.

KCE Trials primarily follows a **bottom-up model**, with most research topics proposed and developed by investigators. Justification of unmet need is systematically embedded in the selection processes yet gives no guarantee that the topics with the highest unmet need are being selected. The number of themed and commissioned calls remains limited. Formalizing the process on how topics are selected could strengthen stakeholder confidence in the strategic alignment of future calls.

The **systematic integration of economic impact into trial design** (see also section 4.2.2.3 *Economic data collection vs. economic evaluation*) reinforces the Programme's health-system relevance. It ensures that trials are not only designed around clinical outcomes, but also around questions of optimal resource use, which are central to public decision-making. This distinguishes KCE from many peer funders that address economic questions separately and only secondary to, or after clinical aspects.

A **centralized record linking the portfolio to documented healthcare evidence gaps**, health policy questions or uncertainties identified during HTAs, is **not available**. This means that relevance is embedded at the level of individual research submissions but does not guarantee that the highest unmet needs are prioritised. The number of commissioned calls remains limited compared to investigator-led calls. One interviewee stressed that the process is too much driven by a bottom-up approach and too little linked to policy research questions [27]. This suggests that KCE Trials has less calls directly steered by predefined policy or payer decision needs. The Prioritisation Group conducts final portfolio-level prioritisation assessing portfolio fit and budget constraints, mitigating the risk of biased research funding.

Topics chosen for themed calls are relevant to documented Belgian and international health priorities and include under-addressed conditions such as endometriosis. However, the process

for identifying and selecting these topics is not clearly described in a dedicated SOP, which limits transparency on how priorities are set and how alternative themes are compared.

Despite not having a formal link between documented health priorities and the KCE Trials Programme, the **portfolio is concentrated around Belgium's highest-burden disease categories**. 45 of the 75 funded trials (60%) address topics like infection, cancer, musculoskeletal, mental health or cardiovascular conditions. These are the top five burden categories identified by Sciensano's national burden-of-disease publication [45].

4.1.2 Breadth of research portfolio

KCE Trials addresses a **wide range of therapeutic areas and interventions**, including topics that are clearly underrepresented in clinical research.

KCE Trials includes **pharmaceutical, biological, surgical, device and procedural interventions**. This diversity is appropriate because clinical uncertainty is not restricted to specific therapeutic areas or medicines. Evidence is also needed for procedures, surgical techniques, biological interventions and care practices where comparative effectiveness, safety, cost-effectiveness or implementation value may be uncertain.

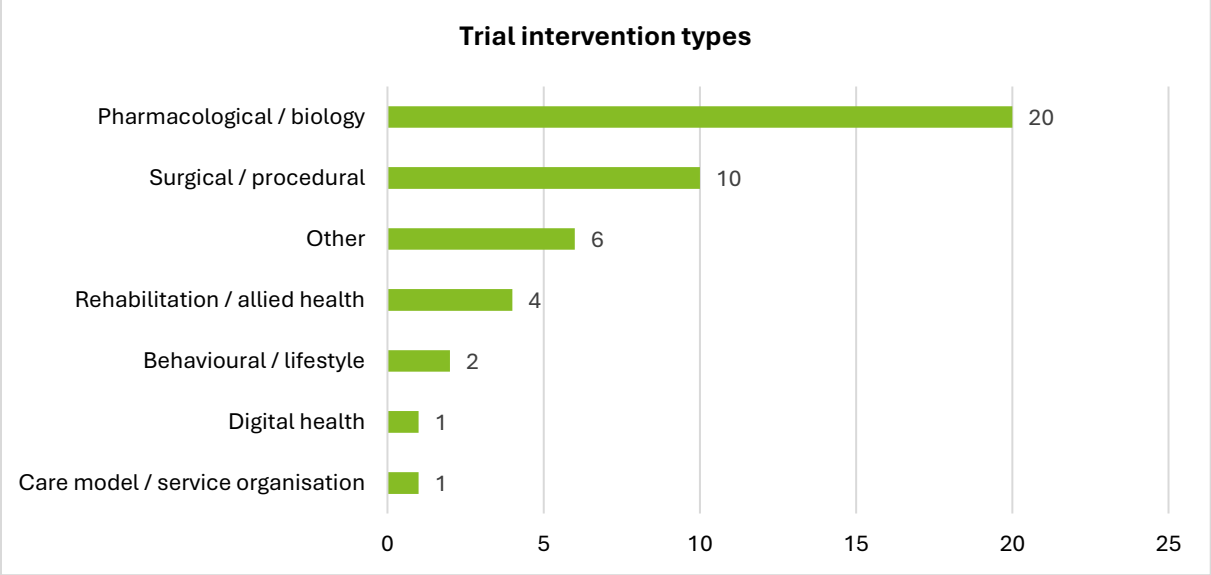


Figure 3. *Intervention types of KCE funded trials, based on results from the investigator survey.*

KCE Trials **spans 20 disease areas** (Figure 5), including studies in less-researched areas, such as mental health and speech-disorders. Mental health research has repeatedly been found to be underfunded relative to disease burden [46], while the evidence base for stuttering interventions remains limited, with Cochrane reporting very low-quality evidence for some child interventions and systematic reviews calling for further replication and clinical trials [47, 48]. KCE Trial's infectious disease portfolio strengthens the relevance of the Programme as it responds to persistent unmet needs in infectious prevention, sepsis care, antimicrobial stewardship and pandemic preparedness. Infectious diseases remain a major source of avoidable mortality, while the evidence base for optimal use of interventions, including duration, dosing, and administration strategy, is often incomplete [49, 50].

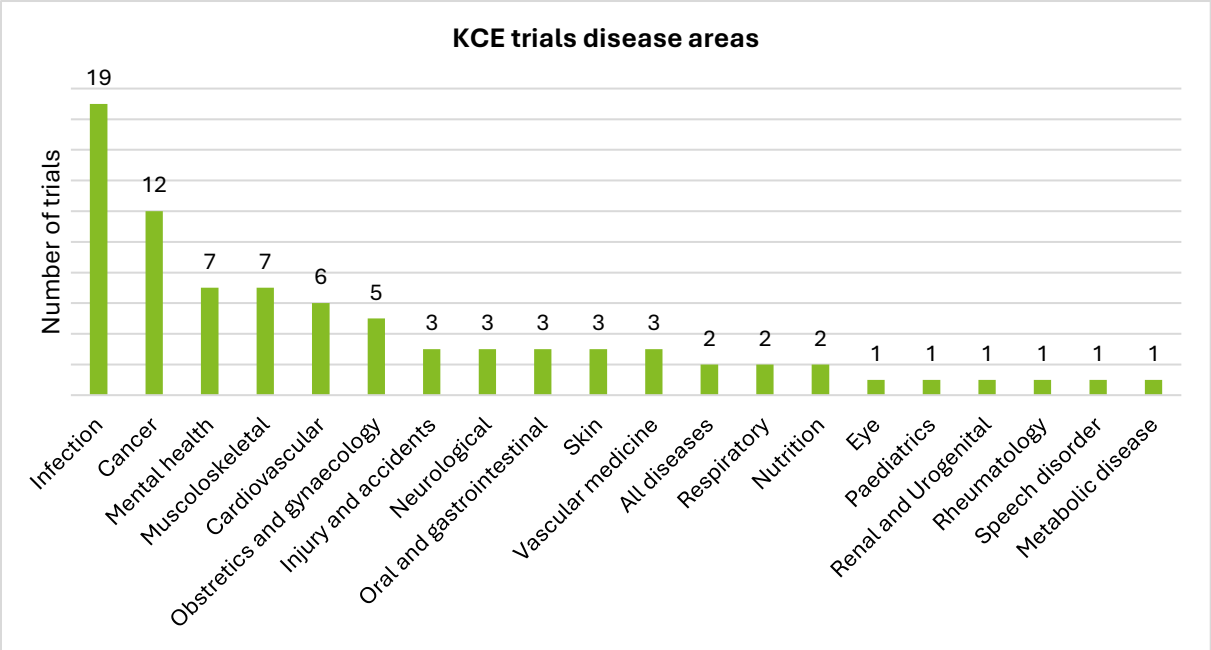


Figure 4. *Distribution of KCE Trials (n=83) by disease area, based on KCE's internal database. Note that the 83 in-scope trials include 8 trials in selection process (incl. 2 on mental health, 1 on infection, 1 on cardiovascular, 1 on vascular medicine, 1 on cancer, 1 on musculoskeletal and 1 on metabolic disease)*

4.1.3 Patient recruitment across care settings

KCE Trials has **recruited more than 28,500 patients across 33 trials** since the start of the Programme. Trial setting is diverse as patients are recruited across primary care settings (i.e. GP practices, speech therapists and physiotherapists, 67% of trial participants), hospital settings (31% of trial participants), and other settings such as nursing homes and mental health centres (2% of trial participants).

On average, the number of **recruited participants in primary care studies equals 2,386**, which is significantly higher than the average number of patients recruited in hospital (i.e. 386) and other (i.e. 296) study settings. This is likely linked to two cluster randomised trials (ELMO and ARON).

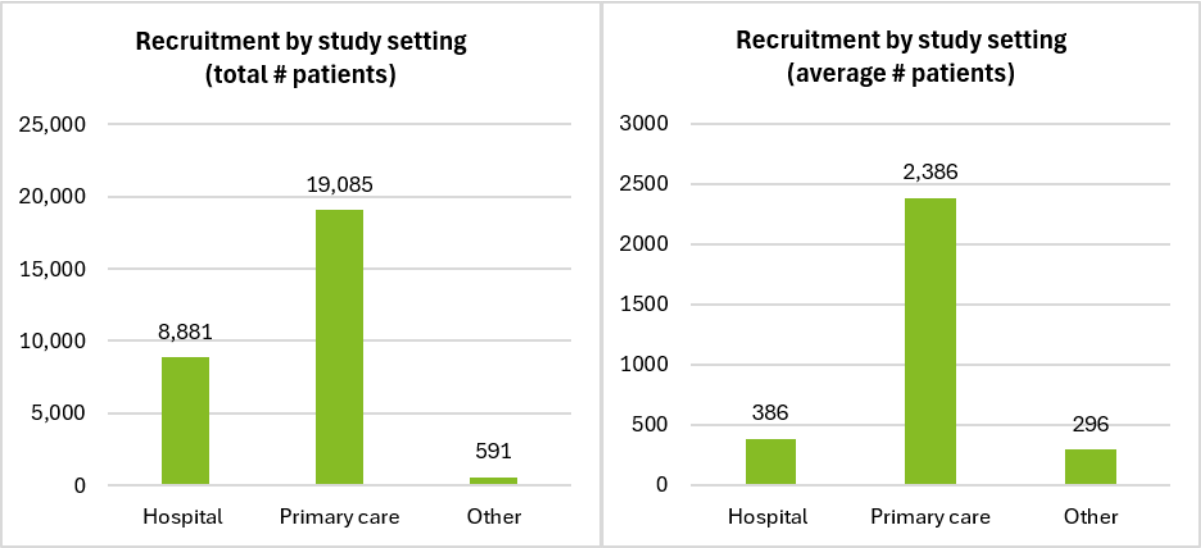


Figure 5. *Distribution of recruited patients by study setting, both in total and on average per study setting.*

Trials conducted in **primary care settings** recruit participants primarily through GPs (98% of patients).

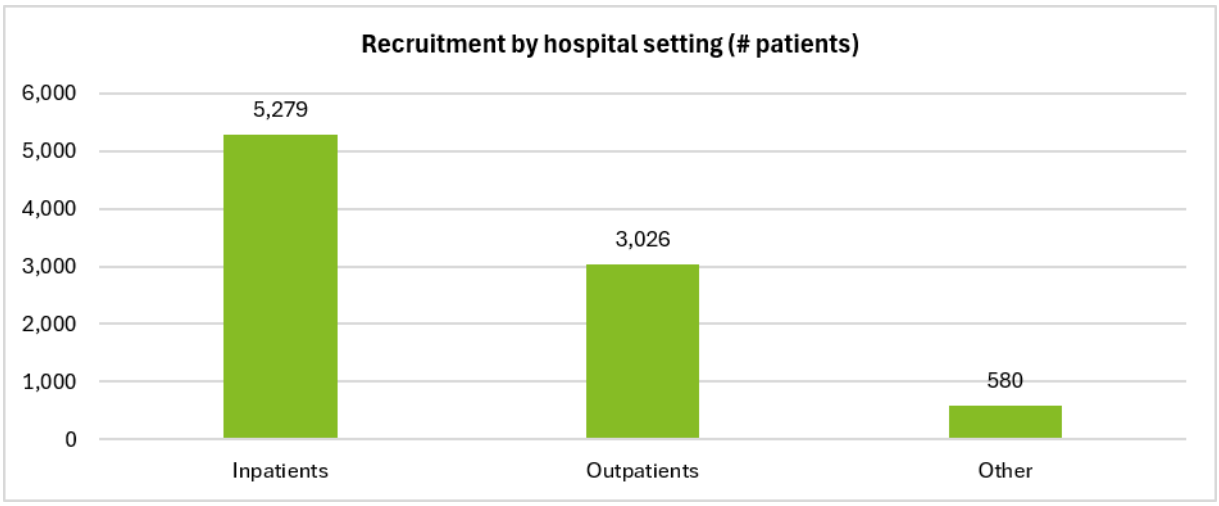
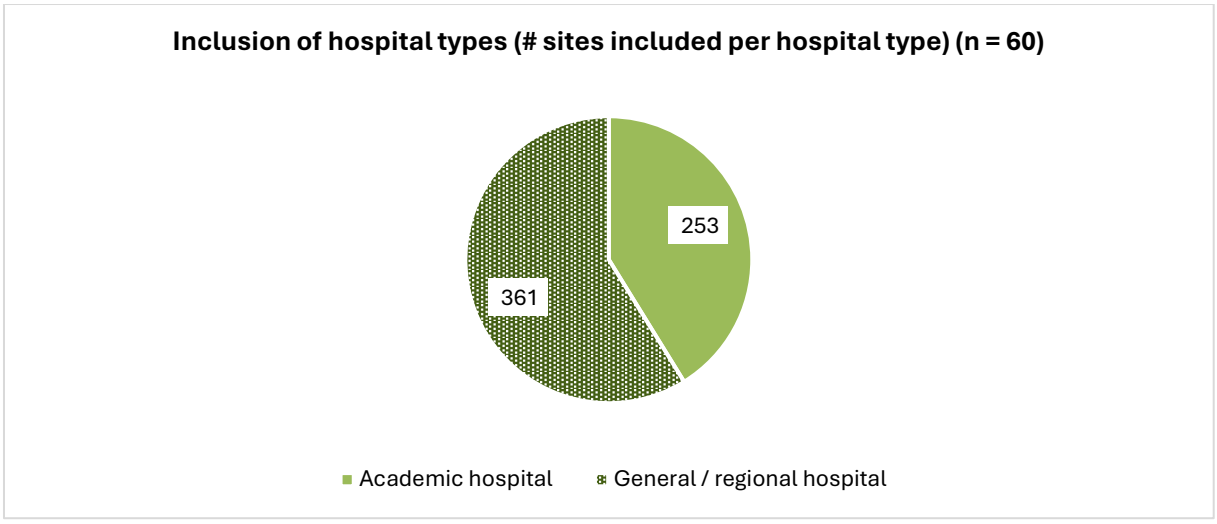


Figure 6. *Distribution of recruited patients by hospital setting.*



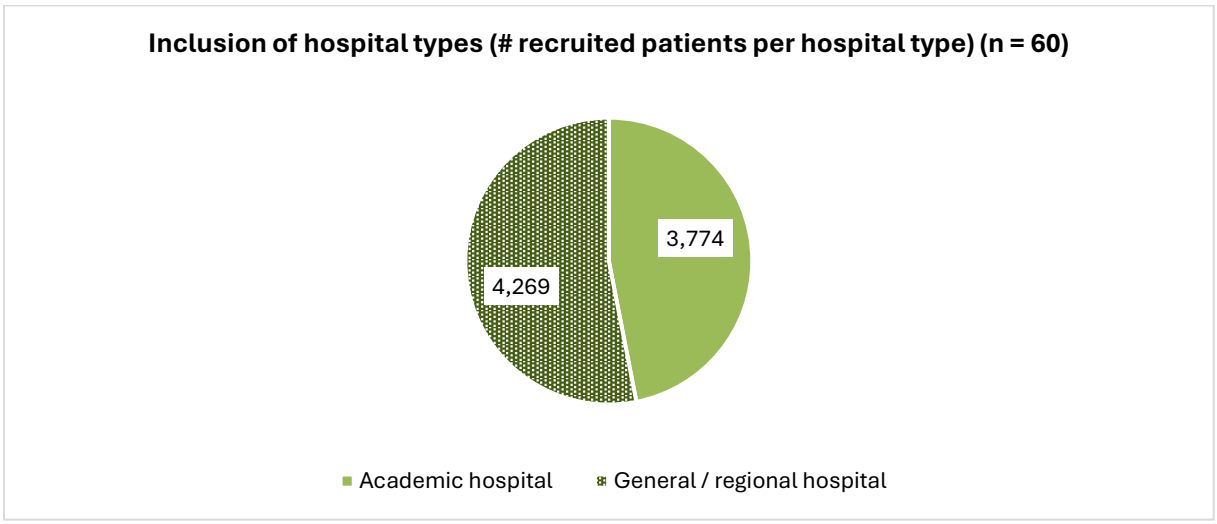


Figure 7. *Inclusion of Hospital Types: General and regional hospitals represent 59% of hospitals sites across trials and recruit 53% of patients in a hospital setting, while academic hospitals account for 41% of trials and 47% of patients.*

For trials taking place in hospital settings, **59% of all patients are recruited via inpatient care versus 34% in an outpatient setting**. The 7% in "other" are linked to the IMCOVAS study sponsored by the University of Antwerp and that took place in the Institute of Tropical Medicine.

Within hospital-based trials, the **Programme engages different hospital types**: general and regional hospital sites represent 59% of all hospital sites, recruiting 53% of recruited patients, while academic hospitals make up for the other 41% of hospital sites and recruit 47% of patients. (**Figure 7**) [51].

The relevance of KCE Trials also depends on whether trial populations reflect the patients and care settings to which results are expected to apply, including the breadth of eligibility criteria and the regional distribution of trial participants. The investigator survey pointed out that 84% of funded trials include **broad eligibility criteria with** minimal exclusions, 63% recruit from **geographically diverse urban and rural sites**, and 50% explicitly include **underrepresented or vulnerable groups** (see also Programme Highlight 1) [44].

The pragmatic design of the trials further strengthens the KCE Trials Programme's relevance. **All 75 funded trials are pragmatic in design**, intended to generate evidence under conditions as close as possible to routine clinical practice. This is important for a policy-oriented KCE Trials Programme as the objective is not only to test whether an intervention can work under ideal conditions, but also whether it is feasible and valuable in real-world settings.

Overall, **KCE Trials generates evidence across a broad set of trial settings**. The distribution of trials across care settings demonstrates the Programme's commitment to generating real-world evidence throughout the Belgian healthcare system. Hospital-based studies appropriately address interventions such as drug repurposing and dose optimisation that require specialist expertise, while primary care trials target evidence gaps related to common chronic conditions, multimorbidity and integrated care. By studying patients where treatment decisions and continuity of care routinely occur, these trials broaden the programme's relevance and include **populations often underrepresented in traditional explanatory research**. The portfolio also **reflects the structure of the Belgian hospital landscape**. General and regional hospitals provide most acute and routine specialist care, whereas academic hospitals concentrate specialised expertise and research infrastructure.

1. Programme Highlight – Pragmatic trials for aging populations

The KCE Trials Programme's **commitment to funding research on underrepresented populations** is exemplified by its **investment in trials addressing the healthcare needs of older adults**. To date, KCE has funded six trials exclusively dedicated to elderly populations, addressing clinical questions that are typically neglected by commercial funders due to limited market incentives. These trials span diverse healthcare settings and clinical areas [51]:

- **BEST CORNEA** (hospital inpatient): Comparing surgical approaches for corneal endothelial disease in older patients
- **SHAPERS** (hospital inpatient): Efficacy and safety of short-course radiotherapy in older patients with locally advanced rectal cancer
- **ADVOR** (hospital inpatient): Acetazolamide in decompensated heart failure with volume overload in elderly patients
- **Pressure Ulcer Prevention** (hospital inpatient): Adding multilayer dressings for pressure ulcer prevention in hospitalized older adults
- **OPTIMED** (nursing home): A complex intervention for multidisciplinary medication review in nursing homes
- **RECOVER@HOME** pilot (primary care with physiotherapy): Feasibility of home-based rehabilitation for older people

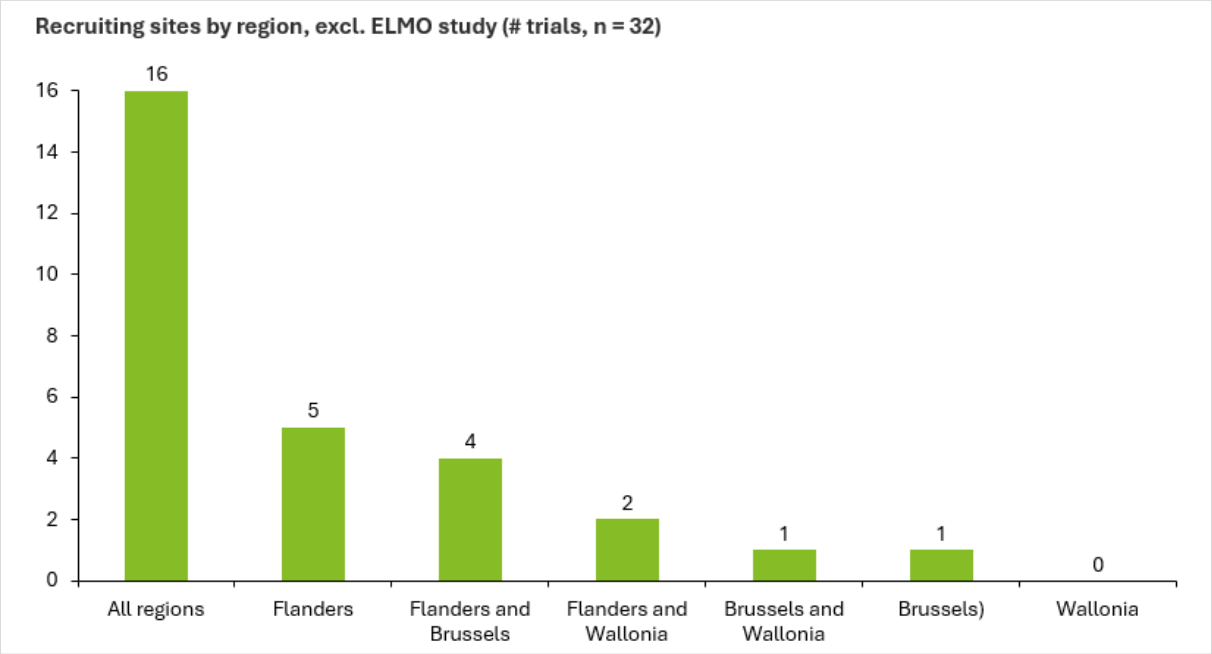
This portfolio showcases **KCE's responsiveness to genuine healthcare needs in Belgium's aging population**. Older adults are often underrepresented in clinical trials due to comorbidities, polypharmacy, and perceived recruitment challenges [52, 53, 54], yet they represent a substantial proportion of healthcare users and benefit disproportionately from evidence-based interventions [55]. By funding trials **across diverse settings** (in this specific example from acute hospital care to nursing homes to community-based rehabilitation), KCE generates **evidence that is directly applicable to the real-world contexts** where older adults receive care. This approach reflects international best practice in pragmatic trials, where evidence generation is tailored to the populations and settings most likely to benefit from the research.

4.1.4 Geographical distribution of participating patients and sites

Trial participation is **more concentrated in Flanders than in Wallonia and Brussels**. Among the completed trials and ongoing trials that have finished recruitment (n=32)[3], 70% of recruited patients at portfolio level come from Flanders, 15% from Wallonia, and 15% from Brussels (Figure 9) [51], suggesting overrepresentation in Flanders (70% vs. 58%) and Brussels (15% vs 11%), and underrepresentation in Wallonia (15% vs. 31%) compared to Belgium's population distribution [56].

[3]The ELMO study, which recruited 9,683 patients exclusively in Flanders because of technical feasibility, has been excluded from this analysis to avoid bias.

Analysis of trial site distribution shows that **19 of 32 trials recruit across all regions**, five recruit exclusively from Flanders, four from Brussels and Flanders, two from Wallonia and Flanders, one exclusively from Brussels, and another one from Brussels and Wallonia. No trials recruit exclusively from Wallonia [51]. These results **point toward an underrepresentation from Wallonia**, yet **KCE Trials includes recruitment (planning) across all geographical regions explicitly in its trial selection criteria**. Whether these plans materialize during the **trial cannot be guaranteed**. This pattern may reflect underlying structural differences as stakeholder interviews [19, 27] revealed that **Wallonia has lower CTC maturity and fewer established trial infrastructure** compared to Flanders. Access barriers, including travel costs, mobility challenges, and awareness of trial opportunities, may disproportionately affect recruitment in regions with less developed research infrastructure. While this **imbalance likely reflects infrastructure and capacity constraints** rather than selection bias, it **limits the national representativeness of evidence generated by KCE Trials**.



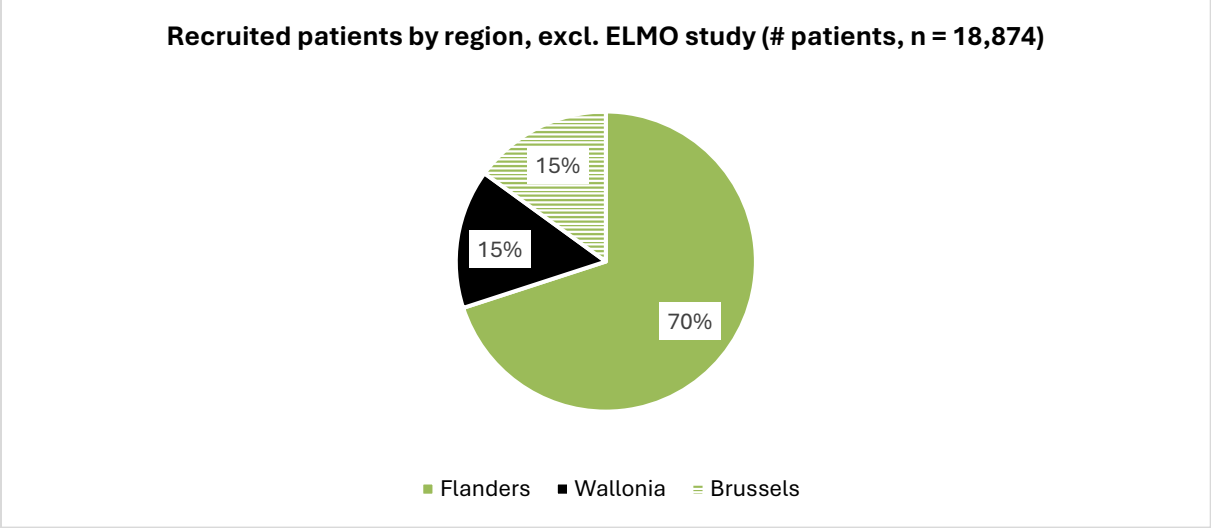


Figure 8. *Regional distribution of KCE-Funded trials by sites (above) and by recruited patients (below) for all trials with completed recruitment status excluding ELMO (n=32).*

Regional imbalance does not invalidate the relevance of the KCE Trials Programme, but it **suggests a need for continued monitoring and targeted engagement** to ensure proportionate participation, beyond previous and ongoing efforts from KCE Trials (e.g., inclusion criteria in the selection process, support on inclusion of Walloon trial sites, or support on translation of informed consent forms). Strengthening engagement with regional health authorities and supporting capacity building in Wallonia could help enhance geographic equity in future trial recruitment.

4.1.5 KCE Trials response to emerging health challenges

The portfolio also **demonstrates relevance through its coverage of emerging health challenges**, such as **COVID-19** (see Programme Highlight 2: COVID-19 Responsiveness), endometriosis (see Programme highlight 3: **Women's health** – Responding to an Emerging Priority), and **antimicrobial resistance**. These examples illustrate different dimensions of societal need: acute system-wide shock that exposed weaknesses in preparedness for public health emergencies, under-recognized and under-prioritised in biomedical research funding, and the combination of high scientific and trial complexity with weak commercial incentives. Funding trials in these areas strengthens the relevance of the portfolio, provided that these topics were selected because of clearly identified evidence gaps and not merely because they were trending at time of submission.

2. Programme Highlight – COVID-19 Responsiveness

When the COVID-19 pandemic struck in early 2020, the **KCE Trials Programme responded fast and adequately** (see also Programme Highlight 11 on the acceleration mechanisms used). **Nine COVID-related trials were funded** (IMCOVAS, PuRe COVID, COV-COG, DisCoVeRy, COV-AID, DAWN antivirals, DAWN Plasma, UNLOCK and CONFIDENT), evaluating treatments for COVID-19 and long-COVID.. **Seven of these were successfully completed**, one was stopped before end of recruitment (DAWN antivirals), and one (UNLOCK) had not yet been published at the time of this evaluation's data cutoff. It has since been published[51, 57].

★ 3. Programme Highlight – Women's Health: Responding to an Emerging Priority [58, 59, 60, 61, 62, 63, 64, 65]

Women's health has long been a research blind spot. Women were historically excluded from clinical trials by regulation, and even when included, women remain underrepresented and research into conditions that predominately or uniquely affect women remains limited. This left an evidence gap that Sciensano's 2023–2024 Women's Health Report identifies as still open in Belgium, naming reproductive health, endometriosis and PCOS prevalence specifically as data gaps. **Three trials in the KCE Trials portfolio address it directly**:

- **ENDO-REAL** investigates letrozole co-treatment during ovarian stimulation as a way to improve IVF outcomes for women with endometriosis or adenomyosis. These are conditions that significantly reduce fertility but remain understudied in assisted reproduction.
- **HYFOIL** examines whether oil-based tubal flushing following a standard Hyfosy scan can boost live-birth rates in infertile women. This builds on emerging evidence that the procedure may have unexpected benefits.
- **AGNOHSTIC** evaluates an anti-adhesion gel applied after operative hysteroscopy to prevent scar formation and improve live-birth chances in women with intrauterine pathology.

Two further trials extend this value through pregnancy, targeting perinatal outcomes:

- **PRIORI** assesses a symbiotic intervention against placebo in women at high risk of preterm birth. The trial explores whether targeted microbial support can improve pregnancy outcomes.
- **LIFETWIN** combines coaching on nutrition, activity, and stress reduction to reduce preterm birth in twin pregnancies, which is a high-risk population where lifestyle interventions remain underexplored.

These five trials show how **KCE can fill important evidence gaps** by funding research in an area that has historically received too little attention.

4.1.6 Clinician and patient engagement in identifying and shaping the research portfolio

Stakeholder engagement is **embedded at multiple levels of the selection process**. The Trials Panel mandates the involvement of patient representatives and clinicians in assessing clinical relevance. Patient representatives and the public are invited to be members of KCE Trials panels. Clinicians and healthcare professionals can express their interest in becoming panel members at any time during the year. KCE maintains a 'long list' of potential panel members and composes the final panel annually based on the proposals received and the expertise required to evaluate them. Panel members are remunerated for their work and time.

Similarly, the Trials Board also includes patient and public representatives, **ensuring that patient perspectives inform decisions at every stage of the selection process** (See also section 2.2 *Programme structure and governance*). Patients therefore have a direct voice in the selection

process, in trial design, execution and dissemination. In the FOOT DROP Trial, patient engagement led to a shift of the primary endpoint from a functional strength measure to a walking endurance test that patients identified as more meaningful. An investigator stated that this was a direct result of patients being explicitly involved in the protocol design [27]. Another PI reported during the interview that KCE insisted on patient involvement, which in the end led to meaningful exchanges between researchers and patients [27]. In funded studies such as BIG BIRD (support to stop benzodiazepine use [66],) or BLENDED (treatment of depression with online tools [67]), patients were involved in study design, and the development of questionnaires and electronic tools to be tested [68]. They helped to improve the structure of the tools, language use and communication with future participants in the study [66, 67].

1. Case Study – SurLym: Patient Co-Design Embedded in Protocol Development

Lymphoedema, a chronic condition causing pain, functional limitations, frustration, and depression, affects cancer survivors and others. Reconstructive lymphatic surgery offers a potential alternative to conservative decongestive therapy, but a 2019 Cochrane review found only one relevant Randomised Controlled Trial (RCT) (36 patients, single technique), insufficient to guide clinical decision-making.

In designing SurLym, an ongoing multicentre RCT across three academic centres targeting 180 patients, **seven patients with lymphoedema participated in questionnaires during protocol development**. All but one confirmed the Lymph-ICF as the right primary outcome, all found technical examinations including indocyanine green lymphofluoro-scopy acceptable, and all confirmed feasibility of attending eight study visits over 36 months. Three of the seven expressed reluctance about undergoing surgery, underscoring precisely why patients need robust evidence. Two patient representatives serve as ongoing steering committee members. This **genuine patient co-design demonstrates the Programme's stakeholder engagement model at its best and reinforces the relevance of the research question to the people it will ultimately serve** [32, 27].

Overall, the Programme can be judged as **highly relevant to societal and health-system needs**. Its relevance is supported by pragmatic trial design, investigator-justified evidence gaps, coverage of emerging and under-addressed health challenges, broad disease and intervention scope, embedded economic assessment, and stakeholder involvement in assessing clinical relevance. KCE Trials occupies a distinctive funding niche by supporting trials that are difficult to fund elsewhere, but important for Belgian clinical practice. The KCE Trials Programme is relevant by design and is perceived as such by interviewed and surveyed stakeholders, but its strategic relevance could be strengthened through systematic evidence gap assessment beyond investigator justification and a more balanced portfolio between investigator-led and themed calls.

4.2 Effectiveness

To what extent do KCE Trials achieve their intended scientific, clinical and societal outcomes, and through which mechanisms?
• **20 calls with 327 research proposals** being evaluated • **75 funded trials**, of which 25 are closed • **76% successful completion rate** • **91 peer reviewed publications** from 67 trials • **96% publication rate** • Average 5-year impact factor of 26.3 and median of 6.8 (for all trials); 50.3 as average and 25.3 as median impact factor for the main publications for published trials only • **3 guideline uptakes** • Strong **commitment** to calculate **quality of life and economic data** • 89% of investigators expect inclusion in clinical guidelines • 84% of investigators expect results to improve patient outcomes • 74% of investigators expect results to improve cost-effectiveness • 90% of investigators report that the Programme has **strengthened their team's clinical research capability**

Table 3. *Effectiveness indicator highlights*

Effectiveness assesses whether KCE Trials **has achieved, or is plausibly on track to achieve, its intended objectives:** generating high-quality pragmatic evidence where data is lacking, improving clinical decision-making, informing practice and policy, and ultimately contributing to better patient outcomes and more efficient use of public resources. To structure this assessment, the evaluation used four research questions linked to measurable indicators and diverse data sources, presented in Table 3.

To assess the effectiveness of the KCE Trials Programme, this **evaluation traces impact along the pathway the Programme is designed to generate:** a completed trial leads to a peer-reviewed publication, which may inform clinical guidelines or formal policy, which may in turn change clinical practice, which in turn may ultimately generate measurable savings or improved patient outcomes at system level. The strength and traceability of the evidence differ sharply at each stage of this pathway (Figure 10). The Programme's own processes and the documentation available to this evaluation capture the earliest stages, trial completion and publication, with high confidence.

Confidence decreases at each subsequent stage. Guideline and policy uptake is documented for a small number of trials, but systematic tracking across the portfolio remains difficult. While KCE monitors guideline adoptions and updates its records, some adoptions may be missed, as they may take years to manifest [27, 19, 69], and KCE has to rely on regular interactions with PIs. This means **the Programme's actual impact on guidelines may be larger than documented**. Interviews revealed that that was the case for at least one trial [19, 27]. Practice change is reported almost exclusively through investigator self-report. System-level savings or health system-level

impact estimations would require dedicated health economic analyses on top of the Programme's activities.

This section aims to present the evidence available at each stage of the pathway, distinguishing throughout between documented impact (i.e. verifiable through publications, citations, or formal guideline text), and expected or self-reported impact. The latter is based on investigator perception and captured through survey data and interviews conducted with investigators and internal KCE stakeholders.

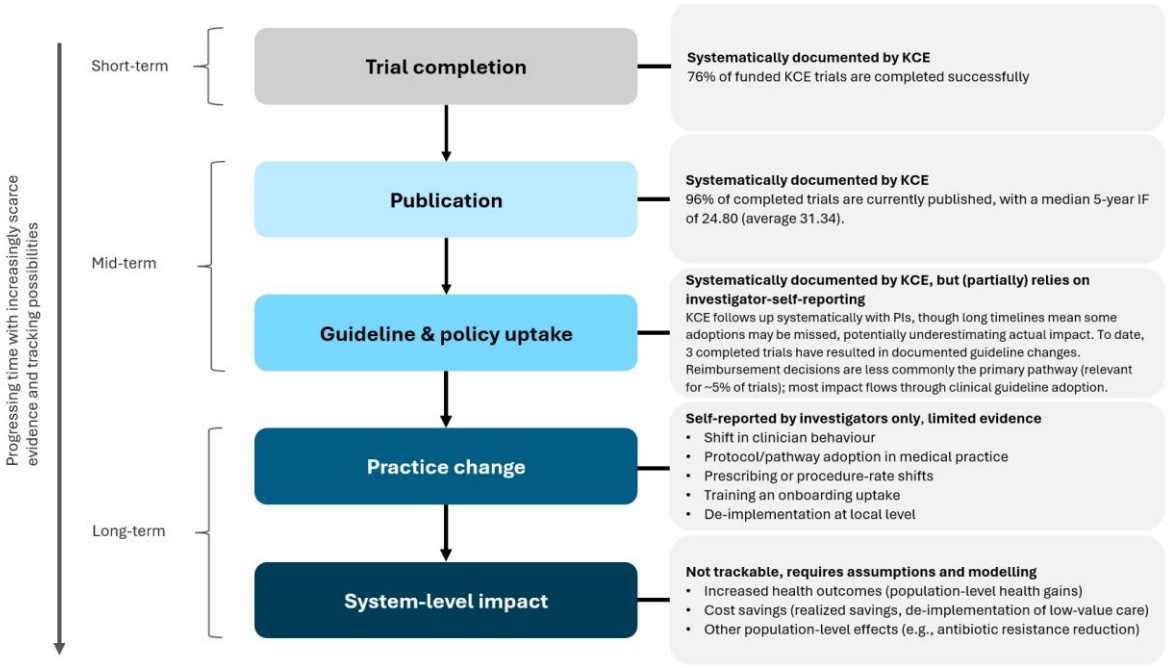


Figure 9. *KCE Trials impact pathway and evidence documentation status. The pathway shows five stages from trial completion to system-level impact. Evidence strength and documentation vary by stage: trial completion and publication are systematically documented by KCE; guideline and policy uptake is also documented, though confidence starts to drop here, as timelines get longer (1.7–3.0 years are typically lost between trial publication and guideline updates) [69]; practice change relies exclusively on investigator self-report with limited possibilities of verification, and it is frequently reported to take 17 years for clinical research to change practice [70, 71], which makes tracking impossible for a young programme such as KCE Trials; and system-level impact remains the most difficult to track and quantify. The colour gradient (light to dark blue) reflects increasing difficulty in measuring and documenting impact at each stage.*

4.2.1 Trial performance from selection to completion and publication

KCE Trials has initiated **20 calls for research proposals between 2016 and 2025**. Investigator-led calls accounted for the largest share (65%, or 13 out of 20), including four joint BeNeFIT calls with the Netherlands. Four calls were themed on specific topics (three on COVID-19 and one on endometriosis), including the ERA4Health call [4]. Two calls, or 10%, were commissioned (the call from 2016 on several predefined topics, and the 2021 multiple myeloma calls) [51]. The number of calls for proposals per year is also shown in Figure 11 below.

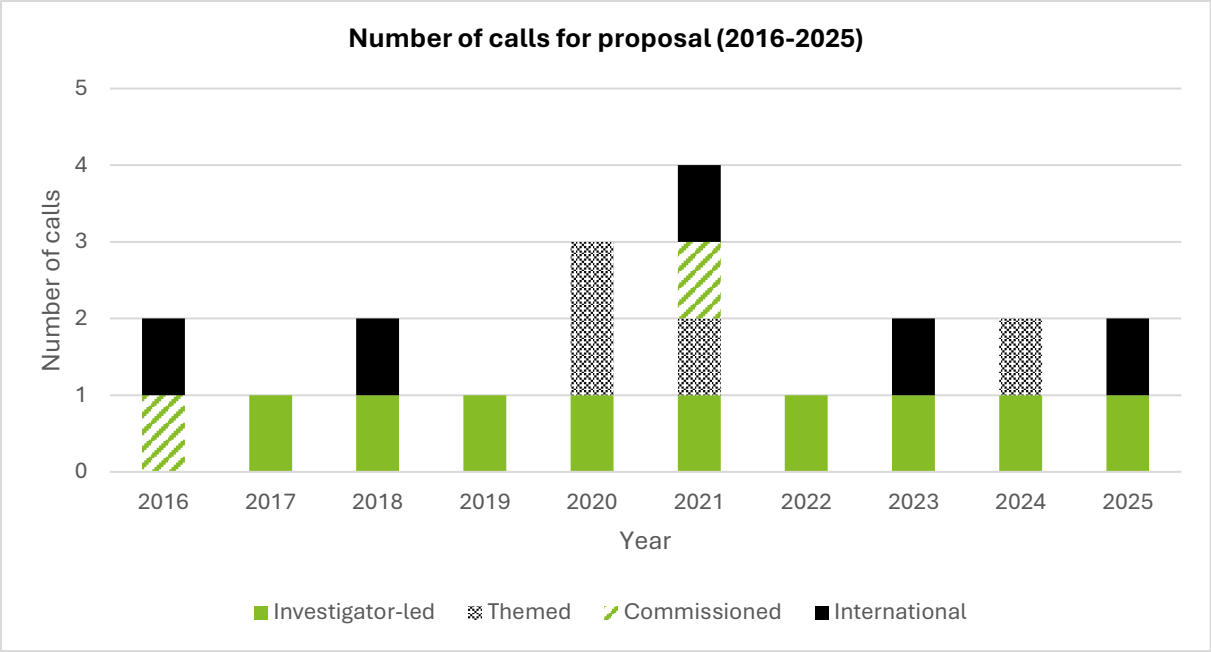


Figure 10. *Number of calls for proposals over time (2016-2025), broken down by type. Note that Investigator-led in the above figure means purely local investigator-led calls, as there is an overlap in call types, as the international BeNeFit calls are also investigator-led, and ERA4Health is themed.*

Between 2016 and 2025, **327 proposals have been submitted across all calls**, of which **75 have been selected**, 239 were declined, and 13 are still in the selection process at the time of observation. This results in an overall selection rate of nearly 24% (75 out of 314 proposals that have resulted in a decision) [51]. The 2021 Commissioned call on Multiple Myeloma could not allocate funding to an adequate research proposal and is the only call without approved research proposal. Two calls were still reviewing submissions and had not selected trials at time of analysis.

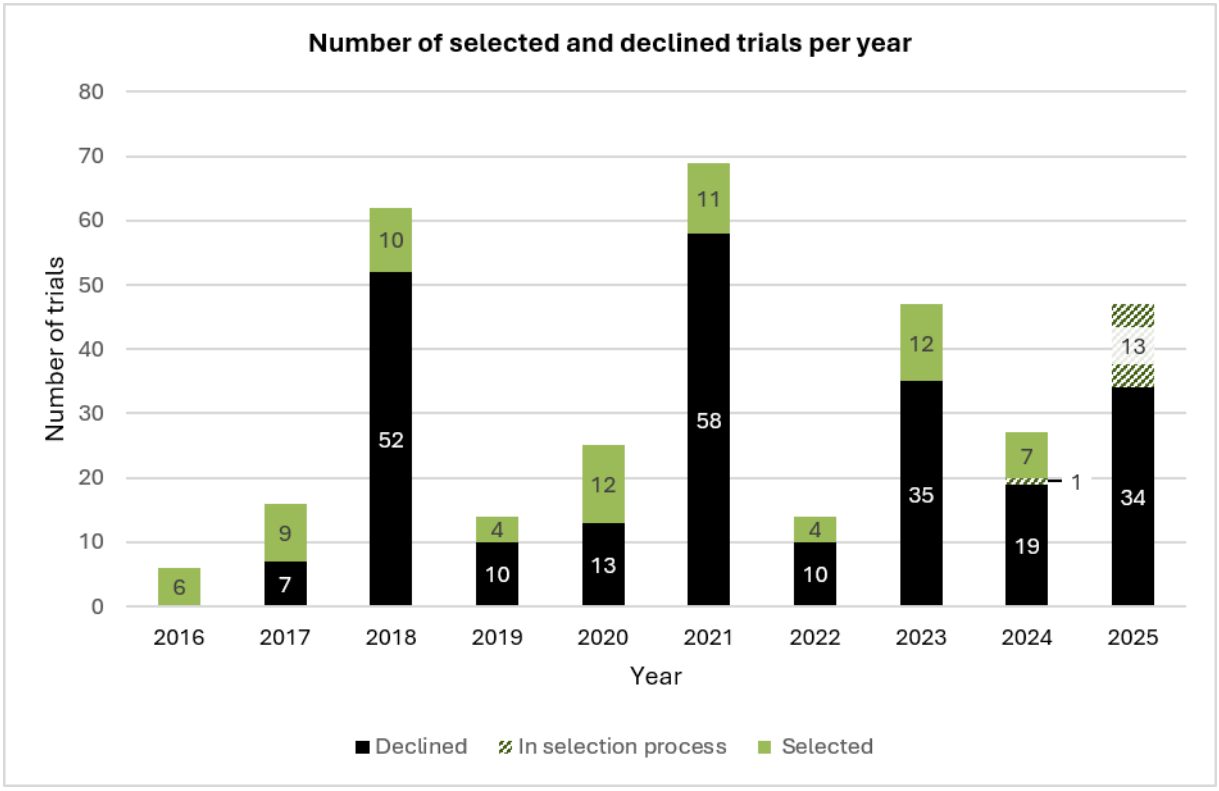


Figure 11. *Number of submitted proposals, with a breakdown of selected, declined and in selection process per year.*

The KCE Trials Programme **funded 75 trials between 2016 and 2025**. Out of the 25 trials that have been closed, **19 have been completed** and **six have been stopped** (Figure 13), representing a 76% successful completion rate across all closed trials [51].

The Programme has produced **91 peer-reviewed publications from 67 trials**. This means there are more publications than trials, reflecting that individual trials often generate multiple outputs. It has achieved a **publication rate of 96%**, and several funded trials have been published in high-impact journals, showing effectiveness in producing scientific outputs [51]. For example, the ADVOR trial (see Programme Highlight 4) and the COVID-19 convalescent plasma trial were both published in the New England Journal of Medicine [72, 73, 74]. The DOMINO trial on diet versus medication in primary-care patients with irritable bowel syndrome was published in Gut, illustrating that KCE Trials can also generate practice-relevant evidence outside hospital-based specialist care [51]. Impact factor is a measure of how frequently articles in a journal are cited by other researchers. This is a proxy for influence and reach within the scientific community. KCE funded trials have an **average five-year impact factor of 30.6 and median of 6.8 across all publications for all trials**, and **50.3 as average** and **25.3 as median** impact factor for the **main publications for published trials only** [51], meaning they are published in journals that rank among the most influential globally. The median impact factor across biomedical journals is approximately 1-2.7. Journals with impact factors above 10 are generally considered high-impact, and those above 20 are among the most prestigious in their fields [75].

KCE's **commitment to publishing negative results** (exemplified by C-EASIE's publication in Critical Care despite null primary outcomes [32]) showcases effectiveness in generating evidence regardless of outcome direction. In addition to publishing negative studies, KCE Trials ensures that failed studies also get published to avoid research waste (e.g., the Aspergillus study DUET).

KCE Trials' emphasis on pragmatic trial design in real-world settings generates evidence with **immediate clinical relevance**, making findings attractive to high-impact journals seeking translatable research. Its strong publication record in high-impact journals supports the conclusion that KCE Trials is effective in producing credible clinical evidence with international visibility. It reflects the Programme's scientific rigor and provides a solid foundation for downstream translation into clinical practice and policy.

4. Programme Highlight – The ADVOR Trial: International Citation Impact

Heart failure affects approximately 150,000 Belgians and represents a substantial burden on healthcare resources. The **ADVOR trial's** cost-effectiveness findings provide direct **evidence for efficient resource allocation in a high-prevalence condition**. The trial, evaluating acetazolamide in decompensated heart failure, was **published in the NEJM (five-year impact factor 86.6)** and has accumulated **199 citations**, some of highest in the KCE Trials portfolio. This citation count also indicates that ADVOR ranks highly among pragmatic clinical trials in its therapeutic area [51].

Figure 12. *Classification of all assessed trials according to last-known trial status[4].*

[4]BeNeFIT trials are only entered in SmartSimple the moment they are selected as the procedure runs through ZonMw's software. This causes the difference between figure 12 and 13 of 5 trials that were still in the selection process end 2025 but were not taken into consideration for the analysis.

The KCE Trials programme is **highly effective in trial completion** and availability of results in comparison with both industry and non-industry sponsored RCTs abroad. The Programme has a higher success rate of funded trials compared to similar programmes [37], but differences need to be interpreted with caution as success are influenced by both the quality of the research proposals and budget availability. A recent systematic review assessing 347 RCTs receiving ethics approval in 2016 in the UK, Switzerland, Germany and Canada, found that 31.1% of trials were discontinued, mostly due to poor recruitment. Non-industry sponsored trials performed worse than industry-sponsored trials (33.7% vs. 28.7% discontinuation rate). Results at any source were available in 79.5% of trials (66.3% non-industry sponsored vs. 91.7% industry-sponsored). Peer-reviewed publication was available in 71.8% of trials (65.7% non-industry sponsored vs. 77.3% industry-sponsored) [76].

4.2.2 Longer-term impact

4.2.2.1 Synthesis of trial outcomes and impact

Completed trials generate four distinct types of long-term value: direct economic evidence, prevention of ineffective practices, positive clinical results and hypothesis-generating (mixed) findings. Table 4 presents all 19 completed trials organized by these impact patterns, showing what each trial demonstrated and how far along the impact pathway the evidence has reached.

Three trials (GonoScreen, Pressure Ulcer Prevention, and BLING III) have already reached **guideline uptake**. This is materially stronger evidence than anything else in the completed portfolio. The BLING III rial offers a particularly instructive example of how guideline adoption can occur, even when trial results are negative, as detailed in the Programme Highlight 5.

5. Programme Highlight – The BLING III Trial: statistical significance is not always needed to have impact on guidelines [77, 78, 79, 80]

The BLING III trial narrowly missed statistical significance on its primary endpoint, and **still became one of the most impactful trials in the KCE portfolio**. The trial tested continuous versus intermittent infusion of beta-lactam antibiotics for treating critically ill patients with sepsis in ICU settings. While the trial's results showed no superiority of continuous infusion over intermittent dosing, albeit narrowly, there was a clear signal: both groups achieved similar 90-day mortality rates (~25%), suggesting the intervention was at least as effective as standard practice.

However, BLING III realised its full potential n**ot through its main publication, but through a meta-analysis** conducted by another research team [77]. BLING III contributed the largest patient sample to a pooled analysis that combined data from multiple trials testing beta-lactam administration strategies in sepsis. When analysed together with other trials, the meta-analysis reached statistical significance, confirming what BLING III had suggested: continuous infusion is an effective alternative administration strategy. This meta-analytic evidence directly informed global sepsis clinical guidelines, demonstrating that a single trial's non-significant result can still drive meaningful practice change when synthesized with complementary evidence.

BLING III illustrates an important principle: **statistical significance at the individual trial level is not always necessary for clinical impact**. The trial's pragmatic design, large sample[5] (7,031 patients across 104 ICUs), and clear signal contributed essential evidence to the broader research landscape, ultimately influencing how healthcare systems approach antibiotic administration in sepsis management.

[5]BLING III was a large international multi-country trial. KCE Trials funded the Belgian contribution to this study, not its full international scope

Trial	Year	Category	Type of impact	Pathway reached
ELMO: The effect of evidence-based decision support for ordering laboratory tests in family practice: a cluster randomised trial	2020	Economic return & positive clinical	• **Clinical:** Smart computer system helped doctors order the right lab tests. Appropriate testing improved from 38% to 58%. Doctors ordered seven fewer tests per patient without missing any diagnoses. • **Economic:** Cost savings of €7.37 per lab test panel. Fewer unnecessary follow-up tests and referrals.	Publication ✓
Pressure Ulcer: A medical device trial to evaluate the use of a silicone adhesive multilayer foam dressing as prevention for pressure ulcer development in hospitalised patients	2021	Economic return & positive clinical	• **Clinical:** Special foam dressings help prevent serious pressure ulcers in hospitalized patients. When added to standard care, they reduced ulcers by about one-third, especially on the lower back. • **Economic:** Silicone foam dressings cost €1,726 per sacral ulcer prevented (NNT=50), but avoid €1,631 in treatment costs, achieving cost-neutrality with potential for savings under less conservative assumptions.	**Guideline adopted** ★
GonoScreen: Efficacy of screening STIs in MSM	2024	Economic return & positive clinical	• **Clinical:** In a trial testing whether stopping routine screening was non-inferior to continued 3-monthly screening, non-inferiority was not shown[6]. Infections were significantly higher without screening, driven by chlamydia. Screening was, however, associated with significantly higher antibiotic use without a corresponding gonorrhoea benefit, pointing to refinement of antibiotic-treatment practice rather than abandoning screening. **Economic:** Screening however led to significantly higher antibiotic use (21-45% increase without clear benefit), which drives antibiotic resistance and makes infections harder to treat in the future. The study proved *less frequent screening might be equally effective* while reducing this public health risk[7].	**Guideline adopted** ★

[6]GonoScreen was a non-inferiority trial: the hypothesis tested was whether non-screening was non-inferior to screening. Failure to demonstrate non-inferiority indicates screening superiority for chlamydia prevention.

[7]The “Economic return” classification reflects the trial's significant economic implications (higher antibiotic consumption and antimicrobial resistance risk). The trial's findings support refining antibiotic-treatment protocols within a screening framework rather than abandoning screening.

Trial	Year	Category	Type of impact	Pathway reached
BLING III: A phase III randomised controlled trial of continuous beta-lactam infusion compared with intermittent beta-lactam dosing in critically ill patients	2024	Negative/ null value[8]	• **Clinical:** Continuous infusion of antibiotics in critically ill sepsis patients did not reduce death rates on the primary endpoint compared to standard intermittent infusion. However, a subsequent meta-analysis combining BLING III data with other trials reached statistical significance, confirming the intervention's effectiveness and directly informing guideline adoption. • **Economic:** An economic analysis is currently underway by the international study team. While the meta-analysis confirmed clinical effectiveness, the resource implications (equipment costs and nursing time requirements) require further economic evaluation to determine whether continuous infusion also offers economic advantages over the current standard intermittent approach.	**Guideline adopted** ★
IMCOVAS: Assessment of the immunogenicity and safety of marketed vaccines for COVID-19 after regular schedule and adapted vaccine schedules and routes: Comirnaty® (Pfizer), Covid-19 vaccine Moderna® (Moderna) and Vaxzevria® (AstraZeneca)	2024	Positive clinical[9]	• **Clinical:** Adapted COVID-19 vaccine schedules (lower doses, longer intervals between doses, mixing different vaccine brands) provided non-inferior immune protection compared to standard schedules, without compromising vaccine effectiveness. • **Economic:** Economic data on work absenteeism and productivity were collected and reported. Heterologous vaccine schedules produced higher absenteeism (up to 38.89%) compared to low-dose or intradermal schedules (3.77-4.35%). This highlights a trade-off between immunogenicity and short-term productivity burden. No formal cost-effectiveness analysis was conducted.	Publication ✓

[8]BLING III only narrowly missed statistical significance on its primary endpoint. However, the trial subsequently contributed to a meta-analysis that reached statistical significance and directly informed guideline adoption (see Programme Highlight 5: BLING III for details). Therefore, this trial can also be seen having positive clinical results and downstream impact.

[9]IMCOVAS demonstrated non-inferior immune response across adapted vaccine schedules. However, a trade-off should be clarified: some vaccine were associated with higher work absenteeism rates (up to 38.89%) in the 5 days following the second vaccination, attributed to vaccine side effects.

Trial	Year	Category	Type of impact	Pathway reached
PuRe COVID (pilot): Pulmonary rehabilitation for Long COVID	2025	Positive clinical[10]	• **Clinical:** A 12-week exercise programme in primary care improved patients' ability to walk and reduced fatigue. Patients who received the programme walked about 40 metres further and reported significantly less tiredness compared to those who didn't receive it. • **Economic:** No economic analysis was published, as this was a pilot trial.	Publication ✓
COV-COG: Immediate and long term cognitive and QoL improvement after cognitive versus emotion management psychoeducation programs: a randomised trial in covid patients with neuropsychological difficulties	2025	Negative/ null value	• **Clinical:** Brief psychoeducational training (six hours total) did not improve cognitive outcomes compared to emotional management training. Both groups showed similar improvements in attention, memory, and fatigue at eight months. • **Economic:** Work productivity data were collected. Given the modest clinical improvements (many patients remained below clinical thresholds despite gains), no separate economic analysis was pursued.	Publication ✓
DisCoVeRy: Multi-centre, adaptive, randomized trial of the safety and efficacy of treatments of COVID-19 in hospitalized adults	2022	Negative/ null value	• **Clinical:** Remdesivir did not improve patient recovery or reduce deaths in hospitalized COVID-19 patients requiring oxygen support. Patients treated more than seven days after symptom onset showed no benefit. • **Economic:** No economic analysis was conducted due to negative results. The trial's design also focused exclusively on clinical outcomes and viral kinetics.	Publication ✓
COV-AID: A prospective, randomized interventional study to assess the safety and efficacy of interleukin-6 and interleukin-1 pathway blockade in COVID-19 patients with acute hypoxic	2021	Negative/ null value	• **Clinical:** Anti-inflammatory drugs (anakinra, tocilizumab, siltuximab) did not help COVID-19 patients recover faster from severe respiratory illness. Patients improved at the same speed whether they received the drugs or standard care.	Publication ✓

[10]PuRe COVID was a pilot study, so results are not powered to fully confirm findings at a definitive, portfolio-representative level. The positive clinical category and the improvements in walking distance and fatigue should be read as promising early signals supporting the feasibility and clinical rationale for a larger, adequately powered trial.

Trial	Year	Category	Type of impact	Pathway reached
respiratory failure and systemic cytokine release syndrome			• **Economic:** No economic analysis was conducted due to negative results. The trial's design also focused exclusively on clinical efficacy and safety outcomes.	
DAWN Plasma: Donated antibodies working against nCoV	2022	Negative/ null value	• **Clinical:** High-dose convalescent plasma with high neutralizing antibodies did not reduce mortality or the need for mechanical ventilation in hospitalized COVID-19 patients. The proportion of patients alive and free of mechanical ventilation on day 15 was similar in both groups (83.7% plasma vs. 84.1% control). • **Economic:** No economic analysis was conducted, due to negative results.	Publication ✓
CONFIDENT: A multicentre randomized trial to assess the efficacy of convalescent plasma therapy in patients with Invasive COVID-19 and acute respiratory failure treated with mechanical ventilation	2023	Positive clinical	• **Clinical:** Convalescent plasma reduced death rates in severely ill COVID-19 patients on breathing machines (35% mortality versus 45% with standard care). • **Economic:** No economic analysis was conducted despite positive clinical results. By the time the trial was published in Belgium, the patient population (severely ill COVID patients requiring mechanical ventilation) was no longer clinically relevant due to changed pandemic circumstances.	Publication ✓
C-EASIE: Early administration of Vitamin C in patients with sepsis or septic shock in emergency departments: a multicentre, double blinded, randomized controlled trial	2025	Negative/ null value	• **Clinical:** Early vitamin C treatment did not significantly reduce organ dysfunction in sepsis patients. The SOFA score was 8.7% lower in the vitamin C group but not statistically significant. • **Economic:** No economic analysis was conducted due to negative results. However, vitamin C is inexpensive, so if efficacy had been demonstrated, the intervention would likely have been very economically attractive.	Publication ✓
PRECISE: The impact of high vs standard enteral protein provision on functional recovery following Intensive Care admission: a triple blind randomized controlled trial in mechanically ventilated, critically ill patients	2024	Negative/ null value or positive	• **Clinical:** High protein nutrition did not improve QoL in critically ill patients. The EQ-5D-5L score was lower (worse) in the high protein group compared to standard protein. Mortality was similar between groups. • **Economic:** Economic analysis is currently underway, with data linkage to hospital billing records. Results are pending.	Publication ✓

Trial	Year	Category	Type of impact	Pathway reached
		clinical[11], depending on point of view		
BigBird: The effectiveness of a blended care program for the discontinuation of benzodiazepines use for sleeping problems in primary care: a clustered randomized trial	2023	Negative/ null value	• **Clinical:** Blended care (online learning tool + GP consultations) was not superior to usual care for discontinuing long-term benzodiazepine use for insomnia (GP consultations alone). Both groups achieved similar discontinuation rates (~19% at 12 months). The intervention did not improve QoL, self-reported discontinuation, or prescribed doses compared to usual care. • **Economic:** No economic analysis was performed due to negative results. However, if clinical effectiveness had been demonstrated, the intervention would likely have been very cost-effective due to the e-tool's scalability and minimal marginal cost per user.	Publication ✓
ADVOR: A multi-center, randomized, double-blind, phase IV clinical trial on the diuretic effects of Acetazolamide (Diamox ®) in patients with Decompensated heart failure and Volume OveRload	2022	Positive clinical	• **Clinical:** A new heart failure medication helped patients recover faster and spend less time in hospital (about one day shorter stay). • **Economic:** The trial measured hospital stay length (which was shorter with the new treatment) with the goal of assessing healthcare cost reduction. However, no formal cost-effectiveness analysis was published. Given the medication's low cost and clear clinical benefit, a formal analysis was not necessary to support implementation.	Publication ✓
DOMINO: Diet Or Medication in Irritable bowel syndrome	2022	Positive clinical	• **Clinical:** Primary care patients with IBS were given either a smartphone app with dietary guidance (reducing certain hard-to-digest foods) or standard medication. The diet app worked better: 71% of patients improved with the app compared to 61% with medication. benefits lasted at least six months.	Publication ✓

[11]The results for PRECISE can be interpreted differently depending on perspective. PRECISE was a comparative effectiveness trial where both arms represent standard of care. The primary statistical hypothesis was not met (negative outcome), but one arm (standard protein) was clinically superior to the other (high protein). Investigators may view this as a positive result demonstrating the superiority of standard protein, while a strict statistical interpretation classifies it as negative.

Trial	Year	Category	Type of impact	Pathway reached
			• **Economic:** Economic outcomes were measured and reported. The diet app was clearly more cost-effective than standard medication, making a separate formal cost-effectiveness analysis unnecessary. This trial exemplifies cases where economic gains are so straightforward that they support implementation without additional analysis.	
BeNeDuctus: Multi-center, randomized non-inferiority trial of early treatment versus expectative management of patent ductus arteriosus in preterm infants	2022	Positive clinical	• **Clinical:** Very premature babies with a heart condition were either given medicine to close it or simply monitored without treatment. Babies monitored without medicine had better outcomes: fewer developed serious lung disease and overall health was better. • **Economic:** Economic analysis was assessed but not conducted for the Belgian arm of this international trial, as Belgium's participation did not provide sufficient data for a separate Belgian economic analysis.	Publication ✓
VINCA: Comparison of the impact of two routes of vincristine administration on vincristine-induced neuropathy in children treated for cancer	2020	Mixed/in-conclusive	• **Clinical:** In most children, the way vincristine is given (quick injection vs. slow infusion over one hour) does not change nerve damage. However, children taking antifungal medicine at the same time had less severe nerve damage when given the slow infusion. This finding needs confirmation in larger studies. • **Economic:** Economic analysis was not formally reported, because primary clinical analysis showed no significant differences between the two administration routes. The intervention may offer cost savings if the one-hour infusion approach reduces severe side effects in children needing antifungal treatment, but this requires further investigation.	Publication ✓
OptiMEDs (pilot)[12]: OptiMEDs intervention for multidisciplinary medication review in nursing homes to evaluate the appropriateness of prescribing – a pilot study	2021	Mixed/in-conclusive	• **Clinical:** A structured medication review tool (OptiMEDs) helped doctors, nurses, and pharmacists reduce unnecessary medicines in nursing home residents. One in three residents had fewer medicines, and one in four had fewer potentially harmful medicines. The intervention was safe (very few side effects from stopping medicines).	Publication ✓

[12]OptiMEDs was a pilot study, so results are not powered to fully confirm findings at a definitive, portfolio-representative level.

Trial	Year	Category	Type of impact	Pathway reached
			• **Economic:** Economic data were collected (medication costs, hospital visits, QoL) and reported. However, as a pilot study, OptiMEDs was not designed to support a formal economic assessment of the intervention. Confirmation in a larger study would be needed before drawing conclusions about cost-effectiveness.	

Table 4. *Completed KCE trials by impact category: clinical result (positive, negative/null or mixed/inconclusive) and economic return, and the impact-pathway each has verifiably reached. 3 of 19 completed trials (GonoScreen, Pressure Ulcer Prevention, BLING III) have verified guideline or policy adoption. However, several other trials are expected to impact guidelines as well [19, 27, 44].*

Category 1, demonstrated in-trial economic return: ELMO, Pressure Ulcer Prevention[13]

These are the two completed trials with a calculated, reported economic result, and they represent two different economic mechanisms.

ELMO tested a clinical decision support system (CDSS) embedding evidence-based order sets into laboratory test requesting across 272 GPs in 72 primary care practices, covering 10,270 laboratory panels from 9,683 patients. The CDSS reduced mean cost per panel from €50.27 to €42.90, a saving of €7.37 per panel ($p<0.0001$), by cutting the number of tests ordered per panel from 31.17 to 24.02, without any corresponding increase in diagnostic error (2.40% CDSS vs 3.04% control, non-significant). This is a rare example in the portfolio of a trial demonstrating that reducing low-value care is both clinically safe and directly cost-saving. The exploratory data go further as CDSS use was also associated with a 2.4 percentage-point reduction in downstream referrals and a 6.0 percentage-point reduction in treatment changes, suggesting the savings identified may understate the intervention's full economic footprint.

The **Pressure Ulcer** trial reached a different kind of economic conclusion: cost-neutrality with upside potential. Silicone foam dressings reduced pressure ulcer incidence from 6.3% to 4.0% overall and cut sacral ulcers specifically by 41% (NNT=50). The subsequent cost-consequences analysis, published separately as KCE Report 368C [81], found an investment of €1,726 per sacral ulcer avoided against €1,631 in avoided treatment costs under conservative assumptions. This is a near break-even result that would tip into net savings under less conservative assumptions (e.g., accounting for dressing discounts or post-discharge costs). Pressure Ulcer Prevention is also one of the Programme's three trials with verified guideline adoption (see below), making it the strongest trial impact story in the completed portfolio: trial selection, completion, publication, a separately published health-economic report, and international guideline influence.

Both results describe savings realised within the trial population and its immediate care pathway, not extrapolated system-level savings across the Belgian population living with these conditions. This is a distinction the Programme should continue to state explicitly, consistent with reviewer feedback already logged against the portfolio-level in-trial cost savings in Section 4.3.4 *Illustrative estimated in-trial cost savings*.

Category 2, the value of negative and null results: C-EASIE, PRECISE, BigBird, BLING III, DisCoVeRy, COV-AID, COV-COG, DAWN Plasma

Negative trial findings create public value by showing what healthcare systems should not do. Robust evidence that an intervention is ineffective or harmful can prevent its introduction or support its discontinuation, thereby avoiding low-value expenditure, freeing-up resources for more effective care, and protecting patients from preventable harm. Negative or null results should not be interpreted as a shortfall of the Programme’s performance.

Eight of 19 completed trials (42% of the completed portfolio) found no clinical advantageon their primary endpoint. One of these negative-result trials, BLING III, went on to influence clinical

[13]Pressure Ulcer's economic evaluation was not an in-trial objective. It was a post-hoc cost-consequences analysis published separately (KCE Report 368C), conducted after the trial using its results as the most relevant available evidence. It is grouped here with ELMO because both are the portfolio's only completed trials with a calculated, reported economic result, though the mechanism by which each result was produced differs.

guidelines, demonstrating that negative evidence can be just as impactful as positive findings. A different situation and illustration that statistical significance is not always determinative was realized through the BLING III trial. **BLING III** tested continuous beta-lactam infusion compared with intermittent dosing in critically ill sepsis patients. Although the trial narrowly missed statistical significance on its primary endpoint, a subsequent meta-analysis by other researchers combining BLING III data with other trials confirmed the intervention's effectiveness and influenced guideline adoption (see Programme Highlight 5: BLING III for full details).

The other six trials with negative results also merit recognition on their own terms. Two distinct forms of value are present within them: waste prevention and harm avoidance.

Waste prevention means the tested intervention did not outperform standard care, and the value lies in preventing the future adoption of a practice that would have added cost or clinical burden without gain, or discontinuing practices already in use that provide no benefit. **C-EASIE** tested whether application of early and high doses of vitamin C in sepsis patients in the emergency department could prevent progression to shock. The trial was set up following observational studies suggesting a potential benefit of vitamin C. The primary SOFA-score endpoint showed no clinical gain, closing off a line of practice that some clinicians had already begun adopting based on weaker evidence (see also case study 2 below which highlights the value the C-EASIE trial provided despite null clinical results). BigBird tested blended care, an online learning tool combined with GP consultations, against usual GP care for benzodiazepine discontinuation. The trial was done across 916 patients and 99 GPs (18% vs. 20% discontinuation, p=0.72) and found no superiority over usual care. **COV-COG** compared a brief cognitive psychoeducation programme against an emotional-management programme in long-COVID patients with cognitive complaints, and found no difference between the two arms in attention, memory, or fatigue at eight months. The trial's own publication frames this as both groups improving, but the absence of any between-arm difference means the cognitive-specific content added no measurable advantagebeyond generic emotional support. Still a useful negative finding, since it challenges the intuitive assumption that structured cognitive training must outperform simpler alternatives

Each of these negative results contributed to more appropriate care. KCE's trials contributed to the evidence base that was needed to inform clinical decision-making during the COVID-pandemic uncertainty. **DisCoVeRy** found no clinical gain from remdesivir (which received conditional marketing authorization by the EMA in 2020 [82]) at day 15 or 29 (OR=0.98, p=0.85) or on mortality (8% vs 9%, p=0.77) in 832 hospitalised COVID-19 patients. **COV-AID** found no clinical advantage from anti-inflammatory drugs (anakinra, tocilizumab, siltuximab for IL-1 or IL-6 blockade) in COVID-19 cytokine release syndrome across both arms of its study design (n=342). **DAWN Plasma** found no clinical gain from convalescent plasma on its primary endpoint in 483 patients (83.7% vs. 84.1% alive and ventilator-free at day 15, p=0.977).

2. Case Study – The C-EASIE Trial: The value of negative evidence

Previous observational studies suggesting benefits of vitamin C in sepsis, based on plausible biological mechanisms including endogenous catecholamine synthesis and anti-inflammatory signalling, led some clinicians to adopt it despite limited evidence. **C-EASIE** was designed to test whether early administration (within six hours of emergency department arrival) could prevent progression from sepsis to septic shock, addressing an untested timing gap left by prior trials that administered vitamin C 12–48 hours after ICU admission.

Conducted across eight Belgian hospitals from June 2021 to August 2023, the trial enrolled 300 patients in a double-blind RCT. The primary outcome (average post-baseline SOFA score on days two to five) did not reach significance (p=0.30, ratio 0.91, 95% CI 0.77–1.08). None of the secondary outcomes differed significantly. Further analysis confirmed that vitamin C added costs without improving outcomes or QALYs. **This negative clinical evidence paired with negative financial impact on healthcare costs provides definitive guidance**: healthcare systems do not need to invest in this intervention for unselected sepsis patients. An exploratory subgroup finding in patients with baseline SOFA ≥6 (ratio 0.76, p=0.042) provides a hypothesis for future targeted research. Published in Critical Care (IF 10.4) in April 2025 [83, 32, 27], with 10 citations at moment of evaluation.

Harm avoidance relates to evidence that an intervention already in use is actively worse than standard care. **PRECISE** found that high-dose enteral protein (2.0 g/kg/day) in 935 mechanically ventilated critically ill patients resulted in worse health-related QoL than standard dosing (EQ-5D-5L: −0.05, p=0.031), with no compensating functional benefit. This is evidence of harm from a plausible, previously adopted nutritional strategy, meaning the trial protects patients from a practice that was already spreading, rather than merely avoiding a wasted future investment. **BeNeDuctus** carries a similar signal: expectant management was non-inferior to early ibuprofen for patent ductus arteriosus in extremely preterm infants on the composite primary outcome (46.3% vs. 63.5%, p<0.001), and moderate-to-severe bronchopulmonary dysplasia was substantially lower with expectant management (33.3% vs. 50.9%). This is consistent with early ibuprofen exposure causing harm via inhibited angiogenesis, in a previously standard early-treatment approach. Results change practice by removing something already happening, with an immediate patient-safety benefit.

The trials in this category (with the exception of BLING III, which influenced guideline adoption) have successfully reached the publication level of the impact pathway (Figure 10), despite having negative/null results.. **Publication itself represents a significant achievement in preventing publication bias** and ensuring negative evidence enters the scientific records. Whether these results have measurably de-implemented existing practices in Belgium is difficult to establish, as de-implementation is inherently challenging to track across healthcare systems. However, these trials have undoubtedly contributed to strengthening the evidence base and informing clinical decision-making by providing robust evidence of ineffectiveness or harm.

Category 3, positive clinical results with practice-change potential: ADVOR, DOMINO, CONFIDENT, PuRe COVID, BeNeDuctus, IMCOVAS and GonoScreen

Seven trials produced a positive result on their primary clinical endpoint with a clearly stated effect size.

ADVOR (n=519) found that acetazolamide added to loop diuretics achieved successful decongestion in 42.2% of patients versus 30.5% on placebo (an 11.7 percentage-point difference, $p<0.001$) in acute decompensated heart failure. The trial also showed a secondary reduction in hospital length of stay (8.8 vs. 9.9 days).

DOMINO (n=459) found a FODMAP-lowering diet delivered via a smartphone app achieved a significantly higher responder rate than standard medication for irritable bowel syndrome (71% vs. 61% at eight weeks, $p=0.03$), with the diet arm also showing higher treatment adherence (94% vs. 73%). This is a rare example of a positive primary-care, self-management result in a chronic, high-prevalent condition. A 2018 literature review screened 7,533 abstracts but identified only two papers providing evidence on the effectiveness of self-management education for primary healthcare professionals in terms of measured outcomes in patients [84].

CONFIDENT (n=475) found convalescent plasma reduced 28-day mortality in COVID-19 ARDS from 45.0% to 35.4% ($p=0.03$). It has a directly calculated gain of 0.096 QALYs per patient, or 45.6 QALYs across the trial population.

BeNeDuctus, next to its potential to avoid harm, also belongs in this category. The trial was designed as a non-inferiority study comparing expectant management (monitoring without immediate treatment, “wait and see”) to early ibuprofen treatment for patent ductus arteriosus in extremely preterm infants. Not only did expectant management prove non-inferior, it showed a 17.2 percentage-point reduction in the composite mortality/complication outcome, suggesting potential harm from early ibuprofen exposure.

PuRe COVID, a pilot study, demonstrated improvements in long-COVID rehabilitation, though it was affected by early termination and modest effect sizes that the trial teams themselves flag as warranting further, larger-scale research.

IMCOVAS is included here as “positive, but with limitations”: several adapted COVID-19 vaccine schedules achieved non-inferior immunogenicity to standard dosing, but the accompanying productivity analysis found certain schedules associated with substantially higher work absenteeism (up to 38.89% vs. 3.77–4.35% for low-dose or intradermal schedules). This is a reminder that a positive immunological result does not automatically imply a positive net societal outcome once economic burden is factored in, and the reason IMCOVAS is also one of three trials in the portfolio with a reported economic analysis (Category 1).

GonoScreen was a non-inferiority trial designed to test whether stopping routine 3-monthly screening for gonorrhoea and chlamydia was non-inferior to continued screening in men on HIV prevention medication (PrEP users). The trial found that non-screening was not non-inferior, meaning screening was superior. Infections were significantly higher in the non-screening arm (IRR 1,318, 95% CI 1,068–1,627), driven primarily by chlamydia. This is a positive finding supporting continued screening for chlamydia prevention. However, this benefit also came with a trade-off: screening was associated with significantly higher antibiotic consumption (21-45% increase) without a corresponding benefit for gonorrhoea specifically. This raises public health concerns about antimicrobial resistance. The trial's nuanced findings (screening prevents

chlamydia but at the cost of increased antibiotic use) pointed to an opportunity to refine antibiotic-treatment protocols within a screening framework rather than to abandon screening itself. These findings directly informed updates to current PrEP screening guidance.

Taken together, these seven trials constitute **documented clinical gain, and all address high-prevalence or high-burden conditions directly relevant to Belgian** healthcare resource allocation. However, downstream impact on clinical guidelines and practice typically takes time to materialize. Research shows that guideline inclusion of trial evidence occurs on average within several years of publication [69], but full clinical adoption can take considerably longer (up to 14-17 years from initial publication to widespread practice change) [70, 71]. As the portfolio matures and more trials enter this post-publication window, the Programme's long-term impact on clinical guidelines and practice is expected to become increasingly evident.

Category 4, mixed and inconclusive results, informing future research: VINCA, OPTIMED

Two trials provide a more limited, hypothesis-generating evidence base rather than an immediate clinical or economic claim, and both illustrate a legitimate and under-recognised form of Programme value: producing the methodological groundwork, drug-interaction signal, or feasibility evidence that makes a future, adequately powered trial possible, without themselves resolving the underlying clinical question.

VINCA (n=90) found no overall difference in vincristine-induced peripheral neuropathy between one-hour infusion and push-injection administration in paediatric oncology patients but identified a significant benefit of the one-hour infusion specifically in the subgroup of patients on concurrent azole antifungal therapy (CTCAE score reduction of 1.58 points, p=0.04), a targeted drug-interaction signal worth dedicated follow-up rather than a portfolio-wide claim.

OptiMEDs, a pilot cluster trial of multidisciplinary medication review in three Belgian nursing homes (n=148), was terminated early due to the COVID-19 pandemic before reaching its planned four-month follow-up. Medication use fell in 35.8% of residents and potentially inappropriate medication use in 25.9%, short of the pre-specified 30% target, but the trial did demonstrate feasibility and acceptability of the intervention with minimal discontinuation (n=2).

4.2.2.2 Collection of patient-relevant data

The KCE Trials Programme is also **committed to measuring patient-relevant data**. Quality-of-life data capture symptoms, functioning, and well-being, and directly inform clinical decision-making in ways that clinical endpoints alone cannot [85]. QoL was measured in 13 of the 19 trials, using several different instruments across populations. For example, DOMINO (comparing dietary intervention vs. medication for irritable bowel syndrome) collected EQ-5D-5L data across several follow-up timepoints, capturing the patient experience of two competing treatment strategies. Similarly, PRECISE (high vs. standard protein in ICU patients) measured QoL as a primary outcome at multiple timepoints, directly informing clinical decision-making in critical care.

This quality-of-life and utility data allowed for economic analyses after trial completion, where this was relevant[14]. In the six trials that did not measure or report on QoL, the decision was made

[14]A QALY (quality-adjusted life year) integrates a utility score over time into a single summary figure, and is distinct from the utility or quality-of-life score itself. Several trials, including PRECISE (whose primary

deliberately. This systematic approach and dedication to measuring what matters to patients is explored in the Programme Highlight 6 below.

outcome is the EQ-5D-5L health utility score) collected the underlying utility data a QALY could be built from.

★ 6. Programme Highlight – Measuring what matters: QoL across the KCE Trials portfolio

While QoL data are reported in only about 30–50% of published clinical trials globally [86], the **KCE Trials Programme outperforms this by having measured QoL in 13 of 19 completed trials** (68%). This higher-than-average inclusion of QoL measurements reflects KCE's deliberate prioritization of patient voices and efforts to capturing what patients experience and feel across its portfolio.

Of the six completed **trials that did not measure QoL**, five had **deliberate methodological reasons** for this decision, while one (OptiMEDs) was affected by **external circumstances**:

Trials focused on objective clinical outcomes (not patient-reported measures):

ELMO: The ELMO trial tested a clinical decision support system to improve laboratory test ordering in primary care. QoL measurement was deliberately left out because the intervention operates at the process level, nudging GPs toward appropriate testing, not at the level of patient outcomes.

BeNeDuctus: At 36 weeks postmenstrual age, extremely preterm infants remain acutely hospitalized, making QoL measurement via proxy reporting neither validated nor meaningful. Long-term neurodevelopmental assessment at 24 months corrected age was the planned approach for functional outcomes instead.

Discovery and COV-AID: Both trials focused on acutely hospitalized COVID-19 patients in critical care, a population and context where QoL measurement is neither validated nor clinically meaningful.

Trials where QoL measurement would be confounded by intervention beliefs

GonoScreen: Not measuring QoL was a deliberate, methodological decision, as QoL measurement would be confounded by participants' beliefs about screening efficacy.

Trials affected by time-sensitive or pragmatic constraints:

IMCOVAS: While initially designed to include quality-of-life measurement, the decision was made to remove this outcome from the final protocol due to the rapid pace of the COVID-19 vaccination campaign. By the time IMCOVAS results would be available, the target population of naive unvaccinated patients would have largely disappeared in Belgium, rendering QoL measurement irrelevant for informing vaccination strategy decisions. The trial instead focused on immunogenicity and safety as primary outcomes, with some economic data collection (absenteeism/productivity questions).

External circumstances:

OptiMEDs: OptiMEDs was a pilot study prematurely terminated due to the COVID-19 pandemic (March 2020). While the protocol planned to collect quality-of-life data as part of testing the feasibility of measurement procedures for a future full trial, data collection was cut short before QoL assessments could be completed. The trial demonstrated feasibility of the medication review intervention itself, but the planned economic evaluation was not conducted.

4.2.2.3 Economic data collection vs. economic evaluation

KCE ensures that all funded trials are designed to collect economic-relevant data by including health economists in the review process from the outset. This ensures economic analyses are enabled, if needed[15]. Of the 19 completed trials of the portfolio, an economic evaluation was planned at protocol stage in 13 (68%). Of the 13 trials with a planned evaluation in the protocol, two (15% of the relevant completed portfolio) have reported more extensive economic analyses and data to date: ELMO and Pressure Ulcer (see Programme Highlight 7: Three Trials with Reported Economic Findings). Others, such as IMCOVAS or DOMINO, have also recorded and reported economic-relevant findings: productivity data for IMCOVAS (see also Programme Highlight 7), and cost/resource-use outcomes for DOMINO. However, neither example constitutes a full, published economic evaluation weighing costs against benefits.

The remaining 11 trials have economic-relevant data collected, but no separate evaluation conducted. Trials are designed to collect economic-relevant data, enabling economic analysis if justified. The perceived gap between planned and reported economic evaluations is a deliberate choice of KCE and the PIs to collect the data systematically and conduct analysis only when it matters for further decision-making. Where formal economic evaluation was warranted, the results demonstrate the range and quality of economic evidence the Programme can generate, from direct cost savings over productivity impacts to cost-neutrality assessments (see also sections 3 (methodology) and 2.4 *Activities and processes*). Table 5 provides an overview of the strategic reasons why formal economic analyses were not conducted for certain trials.

As of February 2026, KCE Trials has implemented a Standard Operating Procedure [29] that **establishes systematic processes for economic evaluation planning**. The SOP requires that trials are designed with future economic analysis in mind, that relevant cost and quality-of-life data are collected during the trial, and that decisions about the type and level of economic evaluation (light vs. full) are made prospectively based on clinical results, rather than retrospectively as has occurred in the past.

[15]E.g. pilot studies are typically not powered to support definitive conclusions on clinical effectiveness, economic analyses or QoL measures, and by design they do not set out to do so. Their primary value lies in feasibility testing and generating hypotheses for future, adequately powered trials.

★ 7. Programme Highlight – Three Trials with Reported Economic Findings [51]

ELMO Trial: Direct cost savings from reduced test volume

The ELMO trial measured cost impact directly: the Clinical Decision Support System reduced average cost per laboratory panel by €7.37 (from €50.27 to €42.90) by ordering 7.15 fewer tests per panel. This cost benefit is valid because diagnostic error did not increase.

Pressure Ulcer Trial: Cost-consequences analysis reaching break-even

The Pressure Ulcer trial conducted a cost-consequences analysis. Silicone foam dressings on the sacrum cost €1,726 per ulcer prevented (NNT=50) but avoid €1,631 in treatment costs, achieving break-even. This applies only to sacral prevention as heel and trochanter dressings lack clinical benefit and pose safety risks. The break-even conclusion relies on conservative assumptions about hospital length-of-stay impact. Relaxing these assumptions (dressing discounts, post-discharge costs, greater length of stay (LoS) increases) would yield cost savings.

IMCOVAS Trial: Productivity impact via work absenteeism[16]

IMCOVAS assessed productivity burden through work absenteeism in the five days following vaccination. Heterologous schedules (Pfizer-Moderna 38.89%, Pfizer-AstraZeneca 35.29%) and standard mRNA-1273 (30.19%) produced the highest absenteeism, while Pfizer low-dose (3.77%) and intradermal (4.35%) schedules minimized work loss. Moderna low-dose showed intermediate absenteeism (18.37%). No monetary valuation was assigned to the absenteeism. The finding highlights a trade-off: schedules with superior immunogenicity often carried higher short-term productivity loss.

[16]IMCOVAS reported economically relevant outcomes (productivity), but not a full economic evaluation weighing costs against benefits, unlike the ELMO and Pressure Ulcer trials above. It should be read as an example of how KCE captures and reports economically useful data even when standalone evaluation is not conducted, because it was not warranted or impossible due to external factors (see also Table 5).

Reason	Explanation	Trials
Negative/null results	When a trial shows no clinical benefit, there is no intervention to evaluate economically. The trial's value lies in preventing adoption of an ineffective practice.	C-EASIE, DisCoVeRy, BigBird, COV-COG, VINCA[17]
Obvious cost-effectiveness	Either the clinical benefit is clear, and cost is not a barrier to implementation, or the evidence of no benefit (or harm) is clear enough that continued use is obviously not warranted. In both cases, formal economic analysis would add limited decision-making value.	ADVOR, GonoScreen, DOMINO
Pilot study design	Pilot studies and feasibility trials are not powered to support definitive clinical effectiveness (and thus cost-effectiveness) conclusions. Their value is in hypothesis generation and feasibility testing for future research.	OptiMEDs, PuRe COVID
Contextual factors / external circumstances	Clinical or epidemiological context might change between trial conduct and completion, affecting the relevance of economic analysis. This occurred in several COVID-19 trials where, for example, the target population or clinical landscape shifted by the time results were available.	IMCOVAS, CONFIDENT, DAWN-Plasma[18], COV-AID[19], BeNeDuctus[20]
Economic analysis ongoing	Economic analyses are planned and in progress, with publication expected separately.	PRECISE, BLING III

Table 5. *Strategic decisions on full economic evaluation in the KCE Trials portfolio. This table explains why formal economic evaluations were not always published. Rather than conducting analyses for every trial, KCE prioritizes analyses that have the potential to inform implementation decisions. The table also notes which analyses are currently ongoing and are not yet published for that reason.*

4.2.2.4 Effectiveness beyond trial completion: future publication, guideline adoption, and practice change

Investigator expectations also support the perceived effectiveness of KCE Trials. Surveyed investigators expect KCE Trials results to improve patient outcomes (84%), increase the generalisability of evidence (77%), improve cost-effectiveness (74%), and strengthen clinical decision-making (65%) [44]. These perceptions are important, because investigators are close to

[17]The VINCA trial had mixed/inconclusive results, rather than strictly negative/null. It is grouped here with the null-result trials because the practical outcome regarding an economic analysis was the same.

[18]DAWN Plasma been linked to the shifting context of the pandemic. The trial had negative primary results, which independently could also place it in the "negative/null results" category.

[19]COV-AID has also been linked to the shifting COVID-19 context. The trial had negative primary results, which independently could also place it in the "negative/null results" category.

[20]BeNeDuctus' Belgian arm, as part of a larger international trial, did not have sufficient patient numbers to support a standalone Belgian economic analysis; this was also not planned for that reason.

the clinical uncertainties being studied and can judge whether results are likely to influence practice. However, as these are expectations rather than measured effects, they are best interpreted as evidence of plausible effectiveness and perceived usefulness and not as proof of actual impact.

Investigators recognize that KCE Trials contributes to **strengthening research capacity** and that the programme has c**lear added value compared to other funders**. Measuring the full impact of capacity building efforts is inherently difficult. It would entail isolating the causal effect of KCE's investments from other factors influencing trial performance (trial complexity, investigator experience, funding adequacy) and would require substantial additional data collection and analysis. Establishing systematic metrics (such as, e.g., tracking changes in CTC capabilities over time, monitoring protocol adherence rates, or measuring investigator satisfaction) might provide evidence for optimizing future capacity development investments, but would in turn also impose additional administrative burden on CTCs and study teams, while both already stretched by complex trial management. Nevertheless, the evidence presented above suggests that meaningful capacity building is occurring, even if its full scope remains difficult to quantify [27, 19].

Translation into clinical guidelines is a strong downstream effect. Three completed KCE-funded trials have achieved documented incorporation into clinical guidelines (as detailed in section 4.2.2.1 *Synthesis of trial outcomes and impact*), demonstrating that the Programme can and does move evidence from publication to formal guidance. The Pressure Ulcer trial exemplifies this pathway in action. It demonstrates how a pragmatic trial can move from rigorous evidence generation through publication, HTA synthesis, international guideline influence, and emerging practice change (see Case study 3, the Pressure Ulcer trial). However, this pipeline of expected impact extends well beyond these documented cases, as illustrated in Programme highlight 8.

3. Case Study – The Pressure Ulcer Trial: The KCE Impact Pathway Operating as Intended

Conducted across eight Belgian hospitals (three academic, five general) in 2018, the **Pressure Ulcer trial** enrolled 1,633 at-risk adult patients and compared silicone adhesive multilayer foam dressings against standard care. Primary finding: a statistically significant 36% risk reduction in overall pressure ulcer incidence (4.0% vs. 6.3%; RR 0.64, 95% CI 0.41–0.99; p=0.04; NNT 43) and a 41% reduction in sacral pressure ulcers specifically. While no benefit was demonstrated for heel ulcers, the trial yielded an important safety signal: two patient falls were linked to slippery heel dressings, which informed implementation protocols and demonstrated the value of pragmatic trial design in capturing real-world safety concerns [87].

Published in the British Journal of Dermatology (IF 9.7) in 2021, the trial **generated 16 citations** and i**nformed a comprehensive KCE HTA report in 2023** providing cost-neutrality evidence with potential for savings. In November 2020, the European Pressure Ulcer Advisory Panel and National Pressure Injury Advisory Panel established an international task force on prophylactic dressing performance standards, directly informed by this trial's evidence. Industry has taken up key findings. Belgian reimbursement impact however is pending. This trial exemplifies the full KCE impact pathway (a rigorous trial, HTA synthesis, clinical guidance, international standard-setting, emerging practice change and reimbursement discussion), working as the Programme was designed to deliver [32, 27].

8. Programme Highlight – Guideline adoption pipeline across the portfolio

As mentioned previously, three KCE-funded trials have already achieved documented **incorporation into clinical guidelines (GonoScreen, Pressure Ulcer, BLING III)**. However, beyond these three documented adoptions, the pipeline of expected impact is substantial. Investigators whose trials have completed recruitment report **that 89% expect inclusion in clinical guidelines and 73% expect uptake in policy briefs** [44]. Trials including ARON, PRECISE, ADVOR, BENEFICIAL, DAWN and CONFIDENT have all been cited by investigators as having strong expected policy translation [44]. **ARON**, published in The Lancet in September 2025, **is already in discussions with the NIHDI antimicrobial stewardship implementation group**, with formal guideline incorporation anticipated by 2027 to 2028 [32]. **CareRA** 2020 is expected to contribute to EULAR recommendations for rheumatoid arthritis management. As the portfolio matures and more trials enter the two-to-three-year post-publication guideline adoption window, the pace of documented policy translation is expected to accelerate substantially [51, 44].

KCE's **effectiveness in translating evidence into formal policy and reimbursement decisions is less obvious**. Among investigators with completed studies, 33% expect formal policy or reimbursement change, a lower proportion than those expecting guideline inclusion (89%) or practice changes (100%) [44]. This lower expectation reflects the nature of KCE's

portfolio: pragmatic trials often test interventions, dosing strategies, or de-implementation approaches that **may not require new reimbursement decisions** or test existing drugs in new contexts where reimbursement is already established. The responsibility for translating evidence into reimbursement policy is also shared. The KCE Trials PG includes NIHDI representatives, positioning them to champion evidence uptake within their organization. While **KCE can facilitate connections** and **ensure evidence reaches decision-makers**, the ultimate responsibility for integrating trial findings into reimbursement decisions rests with NIHDI. At the same time, practice change is occurring through other pathways as well, often driven by investigators and trial participants themselves, and supported by KCE.

In practice, reimbursement change is one specific mechanism of policy uptake rather than a separate tier of impact. **Guideline inclusion is the dominant pathway** for most of the portfolio, and a new reimbursement decision is only a relevant outcome for a minority of trials, given how many test, dosing, de-implementation or comparative-effectiveness questions where reimbursement is already settled.

9. Programme Highlight – Practice-change through investigator-led dissemination

Practice change is occurring through multiple pathways. One investigator described how, in the centres that participated in their trial, the technique being studied is now actually being used consistently [27]. This type of practice change, generated through the trial process itself and amplified by investigator engagement, is precisely the outcome the Programme aims to achieve.

Investigator survey data support this: 73% expect their results to be adopted in practice, 89% expect guideline inclusion, and 78% expect increased awareness among patients or professionals [44]. Individual investigators conduct their own dissemination strategies, such as presenting at conferences, engaging with professional networks, creating websites, often at their own initiative [27, 32]. K**CE Trials supports these efforts through multiple channels**: consistent publication and updates on the KCE website, LinkedIn presence, symposia, stakeholder engagement events, social media assistance and communications support for PIs, and facilitation of connections to governmental bodies such as NIHDI through the PG, if so required by the PI [19]. While dissemination remains primarily an investigator responsibility and is not a coordinated portfolio-level function, this model reflects KCE's core focus on trial funding and execution. Dissemination and uptake is not considered a key activity or direct objective of the KCE Trials Programme but may provide opportunities for future improvement. At the same time, these dissemination efforts, driven largely by investigator initiative and supported by KCE infrastructure, demonstrate that evidence translation is effectively occurring at multiple levels simultaneously. Some of this impact may go somewhat underreported, but the breadth of dissemination channels and investigator engagement suggests meaningful practice change is underway [19, 27, 44].

While practice change is demonstrably occurring, translating this into measurable healthcare savings at system level presents a different challenge. **Quantifying healthcare savings at system level remains inherently difficult**. Realised savings require trial evidence, implementation, behaviour change, reimbursement alignment, and sustained monitoring across the healthcare

system. And attributing system-level savings to individual trials is methodologically challenging. This limitation reflects a broader challenge in evidence translation.

However, trials demonstrating clinical benefit in cost-conscious contexts, such as e.g. ADVOR (shorter hospital stays), DOMINO (primary-care delivery), and de-implementation trials preventing unnecessary interventions, can reasonably assumed to be generating healthcare savings, even if these are not formally quantified. **KCE's structural commitment to study design that enables potential future economic analyses** ensures that economic data are captured and can be analysed where this is needed (as further detailed in section 4.2.2.3 *Economic data collection vs. economic analysis*) [19, 27, 12, 9].

4.2.3 Ancillary benefits

KCE Trials generated **several unanticipated beneficial outcomes beyond its intended objectives**.

One example is the **research capacity systematically built alongside its funding role**. 90% of surveyed investigators report the Programme has strengthened their team's clinical research capacity, and 91% report it added clear value compared to other national or international funders they have worked with [44]. These findings reflect the Programme's broader impact on individual professional development and career advancement in clinical research, strengthening the overall Belgian health research ecosystem (see also Programme highlight 10).

K**CE strengthens Belgium's clinical trial infrastructure through formal capacity and capability assessments for Clinical Trial Centres** (CTCs). These institutional evaluations determine which sites have operational capacity to run large, complex, multicentre randomised controlled trials, assessing site readiness, staff competencies, data management infrastructure, regulatory compliance capabilities, and experience with clinical trial conduct. Unlike individual trial monitoring, these assessments focus on underlying infrastructure that enables reliable, high-quality trial execution at scale [28].

10. Programme Highlight – Capacity Building Beyond Individual Trials

The KCE Trials Programme's **impact on Belgium's clinical research infrastructure extends well beyond the trials it directly funds**. Through the organization of trainings, data management coaching, budget planning tools, protocol development support, and monthly investigator monitoring, the Programme builds institutional capability across participating sponsor sites. 78% of investigators believe it strengthens national research capacity and collaboration networks. These are effects that persist long after individual trials are completed [44].

The human stories illustrate this impact but are difficult to quantify. One junior researcher noted that she "learned enormously from the experience with KCE, who supported with extra training and extra support, which was very important for the success of the trial". In another example, a study nurse transitioned to a dedicated clinical research role following her trial experience. Another PI reported that funds were allocated to support early-career researchers at a University Hospital, including two research assistants who received mentorship and training in clinical research methodology [27, 32]. All three stories showcase the professional development opportunities that trial participation can provide. Investigators develop skills in pragmatic trial design, regulatory navigation, and health economic analysis that they apply in subsequent research. Junior researchers gain structured trial experience that shapes entire research careers [88]. This exemplifies the broader impact of KCE Trials beyond its primary objectives. While illustrative examples, they suggest that the Programme's impact extends beyond its intended objectives and strengthens the overall Belgian health research ecosystem.

Beyond Belgium, methodological innovations developed for the Programme prove valuable to the wider European research community. ZonMw, the partner organization in the Belgian Dutch BeNeFIT collaboration, has praised the internally developed KCE budget tool and indicated to have learned a lot from it regarding budgeting. This illustrates that methodological innovations developed for the Programme also prove to be valuable to the wider European research community. These spillover effects represent a return on public investment that complements the direct value of individual trial outputs [44, 27].

Two rounds of CTC assessments have been completed to date (13 visits total), with findings from the first round available through the KCE Trials Programme website [28]. Initial assessments conducted between 2016 and 2019 at 12 Belgian hospitals (all seven academic hospitals and five non-university hospitals) identified significant gaps in sponsor expertise, oversight, and standardization. Subsequent follow-ups at these same sites reveal that hospital management have responded by investing in CTC development, expanding centralized monitoring, data management, and oversight activities, demonstrating that KCE's assessment process has prompted institutional investment in research infrastructure [88].

KCE integrates capability assessments into its application process for all candidate sponsors, ensuring institutional readiness before committing trial funding. These assessments evaluate site capacity, staff competencies, data management infrastructure, and regulatory

compliance capabilities. Over time, KCE has observed tangible evolution in CTC capacity and capability. This is a result of both the Programme's direct investments in training, coaching, site support, and the broader maturation of Belgium's clinical research infrastructure driven by sustained trial participation. The Programme's internal tracking documents this evolution. Beyond individual trial completion, KCE's training and support has created a cross-institutional platform for knowledge sharing and expertise development in large-scale, non-commercial, multicentre trials, strengthening the overall Belgian research ecosystem.

This CTC assessment programme represents a significant and **under-recognised contribution to Belgium's clinical research infrastructure**. Further formalisation and public reporting could strengthen the Programme's visibility as a system-level investor in research capacity, particularly relevant for making the case for continued investment in regions like Wallonia where CTC maturity is lower [14, 22].

4.2.4 Influence on European Research Infrastructure

Beyond its direct impact on Belgian trials and capacity building, **KCE's pragmatic trial model has influenced European research infrastructure**. ECRIN, which facilitates multinational clinical research across Europe, has explicitly identified KCE's approach as exemplary, noting that "no other HTA body in Europe has this approach" of aligning calls with public health priorities defined by key opinion leaders. This external recognition centres on KCE's rigorous evaluation methodology. The evaluation (see section 4.1 *Relevance*) nonetheless identifies room to further strengthen the systematic, documented link between call topics and policy-defined evidence gaps.

ERA4Health, in which ECRIN participates as a partner organisation, **has adopted an evaluation approach similar to KCE's**, and the ERA4Health initiative itself was reportedly inspired in part by KCE's methodology. This external adoption shows that KCE's model addresses genuine gaps in how European research infrastructure supports pragmatic, policy-relevant trials, and is an important unanticipated benefit of the Programme's methodological rigor [27].

4.3 Efficiency

Efficiency assesses whether the KCE Trials Programme converts inputs, such as funding, staff time, investigator effort, administrative processes and research infrastructure, into useful trial outputs in a timely and proportionate way. Some of the arguments often associated with efficiency also relate to other evaluation criteria. For example, the pragmatic design of trials and their expected implementation mainly concern relevance and effectiveness, while alignment with BeNeFIT or European trial networks also concerns coherence. They become efficiency arguments for example when they reduce duplication, accelerate recruitment, share infrastructure, or improve the ratio between resources invested and evidence generated.

How efficiently are KCE Trials using available resources (funding, infrastructure, expertise, partnerships) to deliver high-quality research?
• KCE Trials works with a **€12.3 million budget annually with more than 80% going to funding clinical trials** • **Clinical trial funding is not indexed** (personnel costs are fully indexed) The average duration **from research application to trial selection** is **306 days** • The average period from **trial selection to contract** is **221 days** • **KCE Trials focuses on efficient ways of working** through tools, templates, and trainings • 92% of investigators agree that **KCE Trials provides a clear and relevant framework for pragmatic trials** in Belgium • 68% of investigators indicate KCE Trials support enabled timely and qualitative study execution • 31% of investigators report that administrative and reporting procedures are disproportionate to the complexity of their trial • **BeNeFIT and other international collaborations** support producing stronger evidence with shared resources

Table 6. *Efficiency indicator highlights*

4.3.1 Budget and spending

Between 2016 and 2025, the total annual budget for the KCE Trials Programme increased from €5 million to €12.3 million. The most important driver of the increase over time is the augmentation of the budget for clinical trials from €5 million in 2017 to €9.4 million in 2018. These budgets are small compared to peer funders like NIHR that spent more than £600 million in 2025/26 on research programmes alone [89].

Across the evaluation period, the Programme had a **cumulative budget of €102.2 million**. Of the total programme budget of €12.3 million in 2025, €10 million (81.5%) was allocated directly to clinical trials. Personnel costs represented €2.1 million (17%), while operational expenses accounted for €0.2 million (1.5%) (Figure 14, see below). The staffing capacity dedicated to KCE Trials increased from 4.3 FTEs in 2016 to 6.9 FTEs in 2025 (+72%). Personnel budget changed from €1.5M in 2018 to €2.2M in 2025. Taken together across the 2016 and 2025 period, for every euro spent on programme management and operations, €5.8 was allocated to clinical trials.

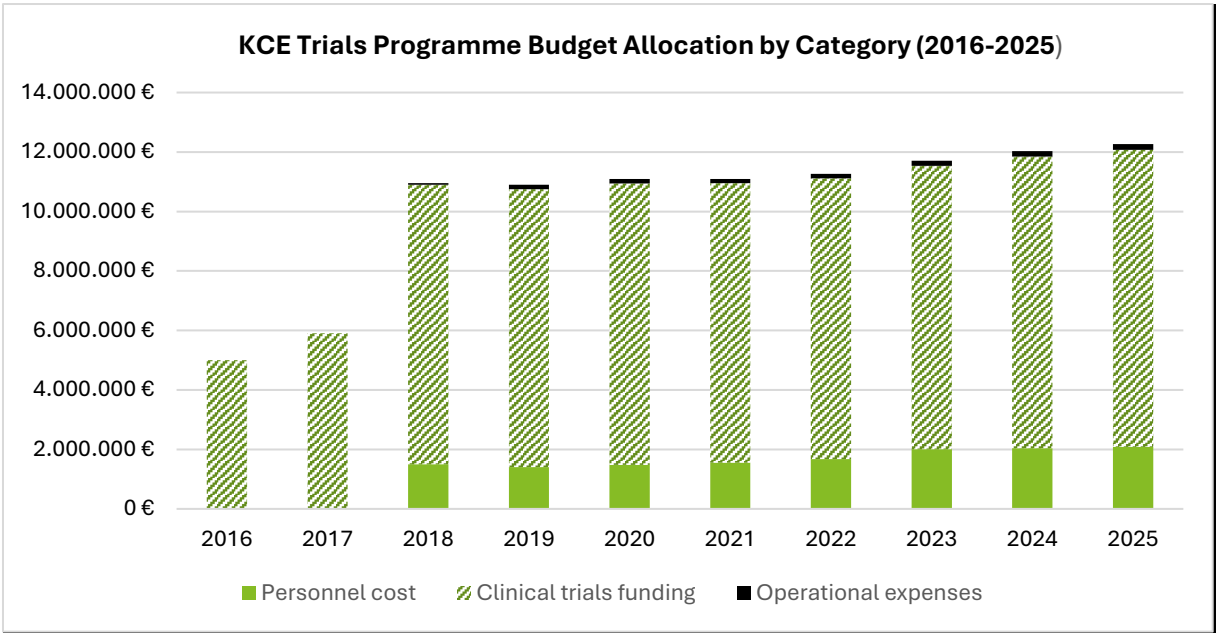


Figure 13. *KCE Trials budget by clinical trials, personnel, and operating expenditure (2016-2025).*

KCE Trials is presented with the s**tructural challenge of working with an annual budget**. Because clinical trials are multiannual, funding is committed when the contract is signed while not yet formally secured for subsequent years. Another structural challenge is that the clinical-trial funding portion of the budget is not indexed, while personnel costs are. An unchanged trial-funding budget gradually loses purchasing power and can support fewer or smaller trials.

Throughout the duration of the Programme, a **total budget of approximately €119 million was allocated across 75 trials, of which around €60 million was spent so far**. Actual spending for the 25 closed trials that the Programme has funded (including the six trials that were stopped) amounts to approximately €28 million. By design, none of the trials have exceeded the contracting budget, due to their milestone-based payment structure. Trials that were stopped, consumed only part of the budget. In four out of six trials, this was less than 25% of the contractual budget, demonstrating timely decision to discontinue the trial and thereby avoiding unnecessary spending of public funds [90, 51].

4. Case Study – The FOOT DROP Trial: An example of resource stewardship

Peroneal neuropathy causing foot drop affects an estimated 40 per 100,000 inhabitants and is characterised by variation in practice between surgical decompression and conservative management. An international survey of 181 specialists confirmed this variation. No RCT had ever compared the two approaches directly.

The **FOOT DROP trial's feasibility pilot** (April 2021 – October 2022) successfully randomised 15 patients across three centres, exceeding the pre-specified criterion of 14, and identified two assessments requiring modification before scale-up. When it became clear that the full-scale trial could not achieve required recruitment rates due to physician bias and patient reluctance to accept randomisation, KCE and the investigator team agreed to **discontinue in mutual agreement rather than continue investing in a trial unlikely to achieve its objectives**. The trial protocol was published in Trials [91] and pilot results in Pilot and Feasibility Studies [92], preserving methodological groundwork for future research. Researchers from a larger-volume hospital are already exploring a repeat trial. The episode illustrates KCE's efficient resource stewardship: the staged design contained the investment, the timely stop prevented further waste, and the published lessons advance the field regardless [32, 27].

4.3.2 Timelines and procedural efficiency

The **KCE Trials process** is a **sequential pathway from study proposal submission to evidence dissemination**. After investigators submit a dossier, the proposal undergoes scientific, methodological, and relevance assessment after which the Prioritisation Group issues a recommendation on whether the study should be funded [19, 12]. For selected trials, this is followed by the contracting phase, during which the sponsor, participating institutions, and KCE Trials agree on the final protocol, budget, responsibilities, timelines, and contractual arrangements. Once the contract is signed, the trial enters the start-up phase, leading to first patients being recruited [19].

The **main efficiency parameter is the time required to move from application to study completion and publication**. KCE Trials has its strongest direct influence on timelines up to contract signature. Subsequent phases are increasingly shaped by external factors, such as sponsor readiness, site activation, recruitment feasibility, and publication processes.

Portfolio data, displayed in Figure 15 below, show that the average period from application to trial selection is 306 days (range 25 days during the Covid-19 calls to 623 days), while the average period from selection to contract is 221 days (range 41 to 556 days) [51].

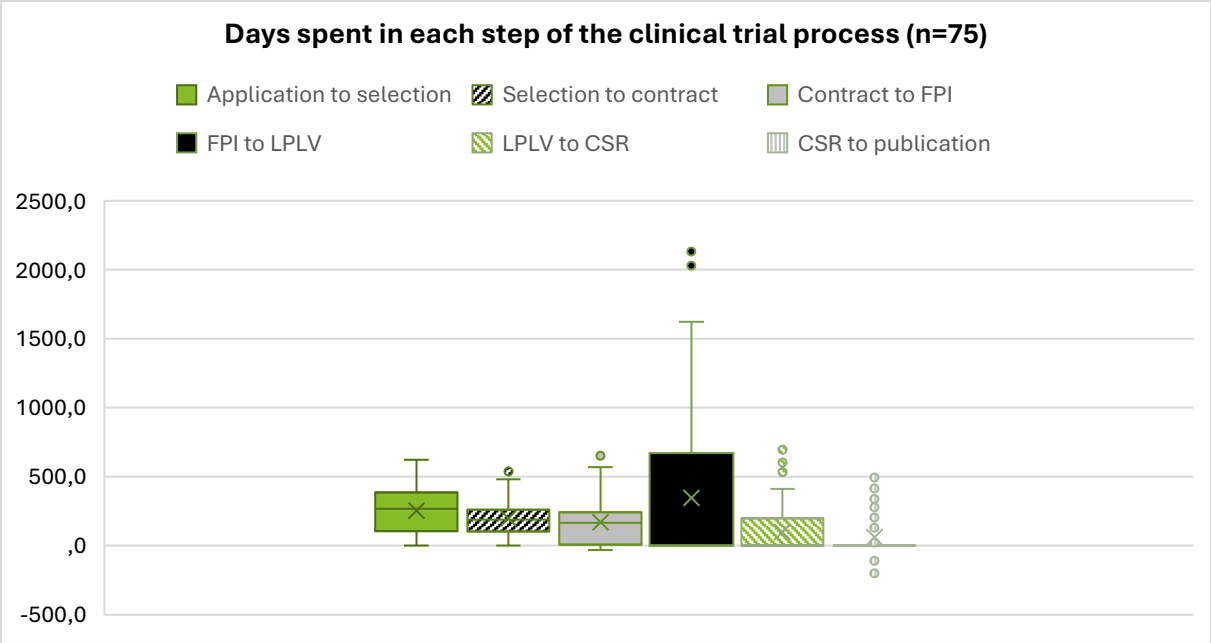


Figure 14. *Days spent in each step of the clinical trial process across all trials (n=75): 1. Initial dossier submission to Trial Board recommendation for funding; 2. Trial selection to contract signature; 3. Contract signature to First Patient In; 4. First Patient Last Visit; 5. Last patient Last Visit to Clinical Study Report; 6. Clinical Study Report (actual) to publication [51].*

For the **completed trials that have reached publication, the mean time from application to publication is 4.7 years** [51]. Although KCE Trials does not directly control the completion or publication timelines of the trials it funds, it actively monitors progress and supports trial teams in achieving timely completion and dissemination. Application-to-publication time therefore serves as a proxy for how quickly the programme can generate impact. The longer the interval between topic identification and publication, the greater the risk that clinical practice, evidence, or policy needs evolve before results are available.

KCE Trials' leadership acknowledged that t**rial start-up is a very intensive process** involving multiple actors (investigators, sponsors, KCE Trials) and budget-setting challenges. However, the interviews did not provide information on which specific factors (e.g., regulatory complexity, ethics approvals, site activation delays, data-protection procedures, sponsor capacity constraints, or greater complexity of trial designs) are the primary drivers of the timelines. Further discussions with KCE suggest contract negotiations with trial sites might be most time-consuming, but this remains a point for further validation.

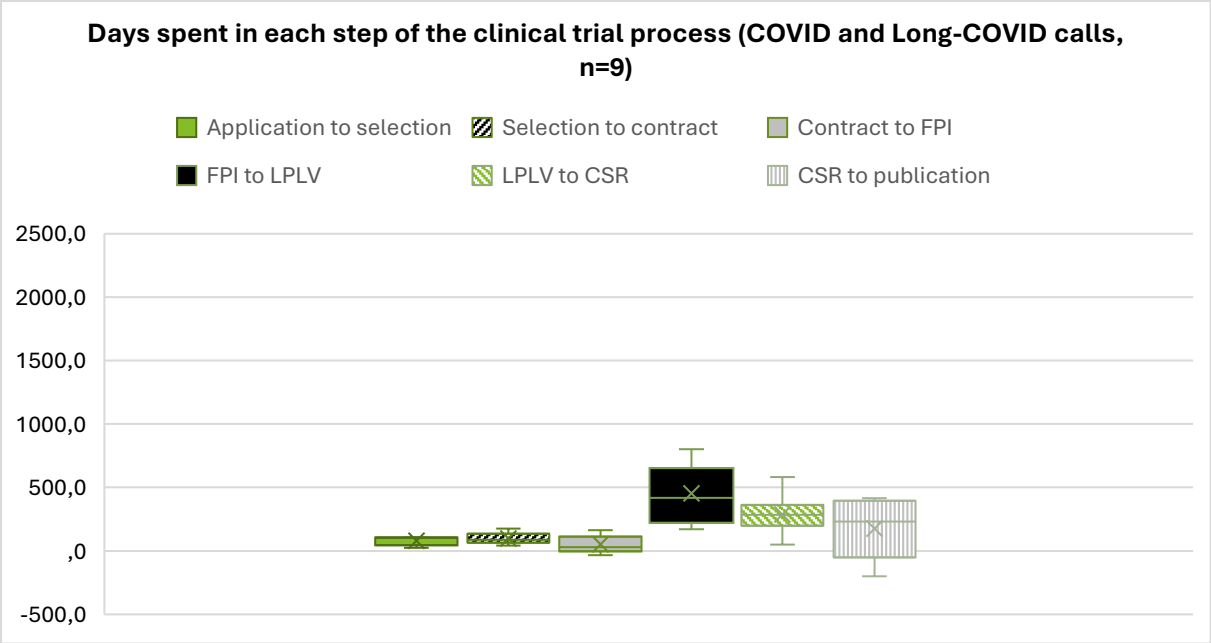


Figure 15. *Days spent in each step of the clinical trial process across only COVID and long-COVID trials (n=9).*

The **COVID-19 response**, illustrated in Figure 16, where the application-to-contract timeline for trials selected in COVID calls and long-COVID calls compressed to 193 days, demonstrates that acceleration is achievable under specific conditions. However, the COVID-19 experience should not be interpreted as proof that all standard calls can or should follow emergency timelines. Shorter timelines were partly achieved through postponement of other trials. Rather, it provides hypotheses for identifying which steps can be accelerated without compromising scientific quality, legal compliance or patient safety.

★ 11. Programme Highlight – COVID-19 Responsiveness: Accelerated Timelines

Building on the COVID-19 portfolio described in Programme Highlight 2, KCE Trials also demonstrated speed in its response: **During the pandemic, KCE Trials introduced fast-track and rolling calls for COVID-19 studies**, allowing urgent clinical uncertainties to be assessed more rapidly than under standard procedures. KCE's COVID-19 call documentation explicitly referred to a fast-track, rolling process for non-commercial randomised interventional trials, and later included a fast-track call on long COVID treatment. Four KCE-funded pharmacological studies in hospitalised COVID-19 patients recruited 1,359 participants across 62 Belgian centres. Five additional trials addressed long-COVID rehabilitation and vaccine immunogenicity in primary care and outpatient settings, recruiting a further 895 participants across 17 sites. In total, KCE-funded COVID-19 research mobilised 2,254 participants across 79 Belgian centres, demonstrating the Programme's capacity to rapidly scale research infrastructure under emergency conditions. [51].

4.3.1 Tools, templates, and support as efficiency mechanisms

KCE Trials has developed a **comprehensive suite of tools and support mechanisms that strengthen efficiency** by reducing duplication, improving standardisation and lowering transaction costs of non-commercial trial development.

The KCE budget tool is a distinctive and important asset. It allows investigators to develop realistic cost estimations based on trial characteristics including site numbers, monitoring intensity, and intervention complexity. KCE Trials describes correct budgeting as essential for allowing non-commercial sponsors to allocate necessary resources. The published budget tool describes its role in estimating realistic trial costs and combining budgeting with risk-reducing measures such as multistep-selection, feasibility checks, progress monitoring, and milestone-based payments [19]. Realistic budgeting contributes to efficient trial completion by reducing the risk of underfunded trials, delayed delivery, unplanned amendments, or failure to complete recruitment. The tool has been consistently praised by investigators as useful for making realistic estimations, though some noted that refinement is needed for primary care settings with large numbers of sites, an area for further development [44, 27].

The Programme offers **regular training courses covering relevant topics** such as data management, safety reporting and trial operations. Investigators also **receive intensive protocol development support and access** to internationally recognized methodological tools and templates. Two protocol templates have been specifically designed for non-commercial studies: one for clinical trials involving drugs or medical devices, and another for clinical trials involving other interventions. Templates for research agreements (between KCE and the Sponsor(s) or Belgian Coordinating Centre) and site agreements have been adapted to KCE Trials' requirements, particularly its non-commercial aim and specific data sharing and intellectual property policies [26]. The availability of standardised templates reduces drafting time, improves methodological consistency, limits legal renegotiation, and lowers the risk of incomplete submissions. These **support mechanisms are highly valued by researchers**, with 78% of investigators indicating satisfaction with the support provided by KCE. This is also supported by investigators that confirmed in interviews that KCE provided good support on protocol and study design, ensuring methodological rigour [44, 27].

The adoption of KCE-developed approaches beyond the Programme also suggests efficiency spillovers. KCE's investment in trial infrastructure generates value beyond its own portfolio. This is visible in BeNeFIT-related documentation, where the **KCE budget tool has been said to have influenced ways of working for international peer funders** [33, 93]. KCE also shared its experience on this tool with the broader scientific community through a publication [93]. Such tools therefore improve efficiency within individual trials and across the broader public clinical-research ecosystem.

12. Programme Highlight – Best-in-class selection process

The **selection process has earned international respect.** An interviewed stakeholder indicated that ERA4Health has adopted a similar two-stage approach in its selection process, which has been established as best-in-class and modelled after NIHR and ZonMw's processes. Next to this, KCE's approach to thorough review has informed elements of the newly set up ERA4Health call's extended-outline stage (see also section 4.2.4 *Influence on European Research Infrastructure*).

Additionally, the external partner stated that **no other HTA body in Europe has this approach to aligning calls with the expectation of the public health system**, leveraging its position as HTA body. KCE has several criteria for proposal assessment, covering validity, alignment with Programme purpose, significance for the Belgian healthcare system, and scientific, methodological, and practical feasibility. These criteria are broadly consistent with principles the WHO later articulated [94, 95].

4.3.2 Administrative tasks and proportionality

Overall, respondents viewed the Programme's administrative framework and support positively, confirming that efforts put in the administrative requirements and follow-up are broadly experienced as relevant. Among all investigators, **92% agree that KCE Trials provides a clear and relevant framework for pragmatic trials in Belgium**, and **68% indicate KCE Trials support helped enable timely and qualitative study execution**. Nevertheless, 31% of investigators report that administrative and reporting procedures are disproportionate to the complexity of their trial [44]. Qualitative evidence reinforces this mixed picture. One investigator noted that the KCE selection process takes very long, while another acknowledged that the intensive follow-up helps to maintain structure and progress [32, 27].

The **monitoring model is also intensive by design**. One investigator described it as very demanding (e.g., regular update meetings and strict follow-up), while immediately acknowledging that this helps to maintain structure and guarantee trial quality. KCE Trials mitigates this burden through feasibility assessments conducted during the selection process and site audits. These early evaluations determine whether proposed sites and investigators have the capacity to deliver the trial as designed, identifying and addressing operational risks before implementation. By **screening feasibility upfront**, KCE **increases administrative effort** for the sponsor **at the selection stage**, but this investment **increases the likelihood of successful recruitment** during trial execution.

The same **rigour** that produces high trial completion rates is also the **source of the administrative burden** [44]. Similarly, **reporting transparency requirements** can increase administrative burden, but they are **necessary to avoid research waste** [96]. Publicly funded trials should be registered, reported and published regardless of whether results are positive, negative or inconclusive, and KCE's approach to monitoring and reporting supports this commitment.

Administrative burden consumes chief investigator resources that could otherwise be used for trial delivery, recruitment, data quality or implementation. At the same time, **administrative**

requirements are not inherently inefficient. For publicly funded pragmatic trials, requirements around protocol quality, contracting, transparency, budget justification, monitoring and reporting are necessary to protect public investment and ensure credible results. **Milestone-based payments** are relevant mechanisms for protecting the public value of trial funding while managing burden [33].

K**CE Trials could review whether its requirements are proportionate to trial risk and complexity**. An investigational medicinal product trial and care pathway study should not necessarily face the same operational burden. Standardisation can improve efficiency, but if templates or requirements are too detailed, rigid, or insufficiently adapted to low-risk studies, they may contribute to the administrative burden. If investigators perceive requirements as disproportionate, this may indicate a need for more risk-adapted procedures, clearer guidance, or differentiated templates by intervention type.

4.3.3 International collaboration

There is a **trend toward more international collaboration in trials**. International collaboration offers an important efficiency and coherence opportunity for publicly funded pragmatic trials. Many pragmatic trials face recruitment challenges, especially when studying less common conditions, subgroup-specific questions, long-term outcomes, or complex interventions such as surgery (See Case Study 5: The SurLym and FOOT DROP Trials). When the same clinical uncertainty exists across countries and collaboration increases scale without duplicating infrastructure, multinational collaboration can accelerate recruitment, increase statistical power, share methodological and operational expertise, avoid duplication of similar trials, and improve the generalisability of findings across health systems [97]. For non-commercial comparative-effectiveness trials, many questions concern interventions already used in routine care, where individual countries may have insufficient patient numbers, limited funding, or parallel research agendas. It simultaneously aligns KCE Trials with European public trial-funding initiatives, and it can produce stronger evidence with shared resources.

The **BeNeFIT calls in 2018, 2021 and 2023 have been attributed KCE Trials contributions of €3.5 million, €3.4 million and €4.1 million respectively** (reflecting KCE's share only, not ZonMw's contribution – note that the budget for the 2025 BeNeFIT call is excluded from this analysis, as the call was launched in late 2025 and lies beyond the report's observation period), and have resulted in 15 funded trials to date, representing approximately a fifth of all funded trials and 10.5% of the total KCE Trials funding budget [98].

13. Programme Highlight – The BeNeFIT Collaboration

Four BeNeFIT calls organised jointly with ZonMw have produced approximately a fifth of all KCE-selected trials, making the **Belgium and Netherlands partnership the largest source of international trials in the portfolio**. The collaboration has demonstrated improvements in methodology and support for funded trials. ZonMw has adopted learnings from KCE's budget tool, and cites shared learning on feasibility studies, intensive monitoring, and protocol support as direct gain of the partnership.

Beyond its long-standing collaboration in BeNeFIT and participation in various international trials, KCE Trials also maintains **active partnerships and exchanges with NIHR and ECRIN**. One external partner stated that the KCE Trials Programme is a perfect model and that this is how many other funders should be organised. **International partners specifically cite learning from KCE's approaches to feasibility studies, budget tool development, and intensive monitoring**, evidence that methodological innovations are diffusing beyond the KCE Trials portfolio [35, 33].

Yet international collaboration cannot overcome all recruitment issues. FOOT DROP was discontinued partly because the planned Belgian Dutch multi-centre design still could not achieve the required recruitment rates [35, 90].

5. Case Study – The SurLym and FOOT DROP Trials: the challenge of surgical trials

Both **SurLym and FOOT DROP illustrate the recruitment challenge for trials involving surgical patients**. SurLym has enrolled only 86 of its target 180 patients as of April 2026, more than a year beyond its planned completion date, despite operating across three Belgian university hospitals. FOOT DROP was discontinued because a Belgian Dutch multi-centre design spanning two countries still could not achieve required recruitment rates.

These experiences are in no way specific to KCE funded trials but rather reflect a broader issue: for areas with small patient populations or other recruitment barriers, joint calls with international public funders could enhance both statistical power and the robustness of evidence generated. However, it is important to consider the limitations that exist for single-country trials and assess whether these will be alleviated in multi-country trials. For surgical trials specifically, international collaboration likely amplifies these single-country challenges. Here, collaboration may even increase complexity due to default preferences or differences in hospital organisations in these types of trials.

4.3.4 Illustrative estimated in-trial cost-savings

Assessing the value generated by public investment in KCE Trials is both important and genuinely difficult: research impact accrues with significant time lags, attribution is shared across multiple actors, and the most consequential outcomes (such as population health

improvements, systemic practice change, or antimicrobial resistance reduction) are diffuse and play out over decades. A comprehensive valuation of the Programme's investment is therefore beyond the scope of this evaluation.

What follows is a narrower, **illustrative exercise**. Among the trials funded under the Programme, dose-optimization trials in oncology have a distinctive property[21]. Because these trials compare a standard drug regimen against a reduced or discontinued one, they **generate pharmaceutical cost savings by design**. This happens the moment a patient is randomised to the reduced-cost arm, regardless of whether the trial ultimately proves non-inferior or not. Three such trials, **OPT-PEMBRO, PULSE,** and **OSI-SAVE**, are used here to illustrate that mechanism. These trials were chosen because they make the mechanism easy to see. However, they are not representative of the wider KCE portfolio. The figures below are projections and estimations, not realised results, since the trials have not yet completed recruitment. They represent the savings that would accrue if enrolment proceeded as planned, calculated at publicly available NIHDI list prices [99]. Participant numbers and dosing schedules are taken from KCE's published trial data [100, 101, 102].

4.3.4.1 OPT-PEMBRO: Optimizing Adjuvant Pembrolizumab in Triple-Negative Breast Cancer

The logic is most straightforward in **OPT-PEMBRO**, a trial that tests whether pembrolizumab can be stopped once early-stage triple-negative breast cancer patients achieve a complete pathological response to neoadjuvant treatment. Of the 200 Belgian participants, split evenly between the two arms, the 100 in the control arm will continue pembrolizumab for a further six months at €50,634 per patient. The 100 in the intervention arm are simply observed, at zero drug cost. That difference, applied across the control arm, comes to approximately €5 million in projected drug cost savings over the six-month treatment period. This stands against a trial investment of €1.48 million, for a net saving of €3.58 million at NIHDI list prices [51, 99].

4.3.4.2 PULSE: Maintenance Pembrolizumab Dosing Optimization in Lung Cancer

PULSE works the same way but through frequency rather than discontinuation: patients with non-squamous lung cancer already stable on maintenance pembrolizumab are randomised to continue on the standard three-weekly schedule (35 cycles over six months, €196,910 per patient) or to move to a six-weekly schedule (17 cycles, €95,642 per patient). Belgian enrolment is expected to reach 200 participants, again split evenly across the two arms. Applied to the 100 patients in the control arm, the price difference translates into €10.13 million in projected savings over the same six-month window, against a €1.43 million trial investment — a net saving of €8.70 million (source: at NIHDI list prices; [51, 99].

4.3.4.3 OSI-SAVE: Osimertinib Dosing Interval Optimization in Lung Cancer

OSI-SAVE follows the identical logic in a third cancer type: patients with EGFR-mutated non-small cell lung cancer stable on daily osimertinib (€6,000 per month) are randomised to continue daily dosing or to move to every-other-day dosing (€3,000 per month). Of the 100 Belgian participants, the 50 in the control arm anchor the comparison; over the trial's twelve-month treatment period, halving their dosing frequency would represent €1.80 million in projected savings against a €0.76 million trial investment, for a net saving of €1.04 million [51, 99].

[21]The trial investment figures below reflect KCE Trials' own contribution only. All three are international studies with total budgets substantially larger than KCE's share

Taken together, the three trials point to €13.32 million in projected net pharmaceutical cost savings against €3.67 million invested, set out in full in Table 7. This represents a 3.6-fold in-trial return on investment (aggregate net savings divided by aggregate trial investment).

Table 7 shows the illustrative in-trial cost savings for three KCE-funded dose-optimization trials. Savings are calculated for the trial treatment period only and based on NIHDI list prices. "Belgian participants" reflects the arm whose drug cost changes, and total Belgian enrolment across both arms is roughly double this figure for OPT-PEMBRO and OSI-SAVE (confirmed against public KCE trial data) [30]. This analysis uses the publicly available list prices published on the NIHDI website and KCE website. Because many innovative oncology medicines are subject to confidential discounts of unknown magnitude, we model a range of assumptions. These include also deliberately unlikely scenarios to stress-test the findings and illustrate the outer bounds of potential cost savings. Table 8 models all three trials across a full range of possible discount levels, with corresponding estimated net savings. Net savings in both tables are calculated as total drug cost savings minus trial investment.

Trial	Control arm cost per patient	Intervention arm cost per patient	Cost difference	Planned Belgian Participants (affected arm)	Total drug cost savings	Trial investment	Net savings
OPT-PEMBRO	€50,634	€0	€50,634	100	€5.06M	€1.48M	€3.58M
PULSE	€196,910	€95,642	€101,268	100	€ 10.13M	€1.43M	€8.70M
OSI-SAVE	€72,000	€36,000	€36,000	50	€1.80M	€0.76M	€1.04M
TOTAL				**250**	**€16.99M**	**€3.67M**	**€13.32M**

Table 7. *Estimated in-trial savings for selected trials at NIHDI list prices.*

Discount on list price	OPT-PEMBRO net savings	PULSE net savings	OSI-SAVE net savings
0% (list price)	€3.58M	€8.70M	€1.04M
10%	€3.08M	€7.68M	€0.86M
20%	€2.57M	€6.67M	€0.68M
30%	€2.06M	€5.66M	€0.50M
40%	€1.56M	€4.65M	€0.32M
50%	€1.05M	€3.63M	€0.14M
60%	€0.55M	€2.62M	-€0.04M
70%	€0.04M	€1.61M	-€0.22M
80%	-€0.47M	€0.60M	-€0.40M
90%	-€0.97M	-€0.42M	-€0.58M
Breakeven discount	**~71%**	**~86%**	**~58%**

Table 8. *Projected net savings and breakeven point under alternative discount assumptions. Discounts are applied uniformly to list price. Trial investment cost is unaffected by the discount level.*

Conclusion depends on pricing assumptions this evaluation cannot verify. The value of these three trials, in any case, is not confined to their own participants or to the length of their treatment periods. Should they go on to demonstrate non-inferiority or superiority of the optimised regimen (the one question the in-trial savings above do not depend on, but that everything beyond the trial does), the same logic would extend to thousands of future patients in Belgium and beyond, at a scale of savings substantially larger than shown here, and, by the same token, substantially more sensitive to the same pricing uncertainty.

4.4 Coherence

The evaluation specifically how KCE Trials aligns with national health priorities set by health policy actors and how it complements funding from other actors by addressing evidence gaps they do not prioritise.

How coherent and complementary are KCE Trials with other national and international research initiatives and health system priorities?
• **KCE Trials reinforces KCE's broader mandate** by addressing evidence gaps • **Strong overall coherence with NIHDI initiatives**. More operational coherence possible through feasible themed/commissioned calls • **KCE Trials is coherent with high-level policy themes**. These themes need to be translated to research questions that can be evaluated through pragmatic trials • **KCE Trials' portfolio is coherent with international health priorities**, such as antimicrobial resistance and sepsis, and international initiatives to strengthen clinical-trial policy • 86% of investigators confirm that the **Programme complements commercially driven research** in Belgium

Table 9. *Highlights coherence indicators*

4.4.1 Coherence with Belgian federal health policy

4.4.1.1 Coherence with KCE's mandate

KCE Trials is strongly coherent with KCE's mandate as an independent producer of policy-relevant health evidence. KCE's provides scientific analyses that support decisions on health care organisation, clinical practice, reimbursement, health technology assessment and the appropriate use of public resources. The KCE Trials Programme complements this mandate by extending KCE's role from evidence synthesis and policy advice to targeted evidence generation. Where existing evidence is insufficient to answer clinically or policy-relevant questions, KCE Trials can fund pragmatic studies designed to close those gaps under real-world conditions.

4.4.1.2 Coherence with NIHDI priorities on appropriate care

KCE Trials is also **coherent with NIHDI's emphasis on appropriate care** [103]. NIHDI defines appropriate care as care delivered to the right patient, at the right time, in the right place, by the right professional, and explicitly links this approach to evidence-based practice, clinical expertise, patient preferences and responsible use of health-system resources.

This aligns closely with the KCE Trials model. Pragmatic comparative-effectiveness trials are designed to answer practical questions about what works best in routine care and whether interventions offer value for money. KCE Trials calls require studies to contribute to better patient care, show value for money, and have potential return on investment. Comparative-effectiveness studies are described as comparisons of treatment options already used in clinical practice but not yet sufficiently directly compared, including assessment of which option works best in daily practice and is most cost-effective. The coherence with NIHDI is especially visible in commissioned calls. For example, KCE Trials was commissioned by NIHDI to fund a trial on fixed-

duration daratumumab versus treatment until disease progression in newly diagnosed multiple myeloma [18], addressing a reimbursement and treatment-duration decision problem. No adequate research proposals were submitted. This is a strong example of potential operational coherence where the payer identifies a decision-relevant uncertainty with potential large budget impact on the healthcare budget, and KCE Trials provides a funding mechanism to generate the evidence. It may warrant early dialogue between KCE Trials, NIHDI, and potential PIs to jointly define the research question and assess feasibility in a Belgian context.

KCE Trials also **aligns with NIHDI's healthcare objectives** [104]. The 2025 NIHDI advisory process identified eight federal healthcare objectives, including two transversal objectives: better collection and exchange of data to inform care policy and integrated care, and improved efficiency by reducing large unexplained variations in medical practice. KCE Trials aligns particularly well with the second objective, since pragmatic clinical trials can test whether interventions used in routine practice are effective, cost-effective and appropriate, thereby helping to reduce unwarranted practice variation.

KCE Trials also contributes to the broader federal objectives on person-centred care, financial accessibility, prevention and screening, and priority sectors such as mental healthcare, if trial topics are selected in areas where evidence gaps affect these policy domains. This coherence is strengthened by the fact that the federal objectives are explicitly grounded in Belgian health-system performance challenges and the Quintuple Aim, including better population health, improved quality of care, more efficient resource use, reduced health inequalities and improved wellbeing of care providers.

At the same time, coherence is not automatic. NIHDI notes that the federal healthcare objectives still need to be translated into concrete indicators and priorities for the health insurance budget, and that the defined priorities will feed into budget discussions from 2026 onwards [105]. **KCE Trials can therefore be considered conceptually well aligned with the 2025 federal objectives, but the operational link would be stronger if these objectives were systematically used to inform themed or commissioned trial calls or used as additional criterion for funding in the trial selection process**. Without such a structured translation from federal objectives into research questions, the Programme risks remaining broadly coherent with the policy agenda, but only indirectly connected to its most urgent decision-making needs.

4.4.1.3 Coherence with federal ministerial priorities

Across recent federal policy notes, **Belgian health policy has repeatedly emphasised quality, accessibility, appropriate care, efficiency, prevention, integrated care and evidence-based practice**. For example, the 2022 federal public health policy note identified four themes in the healthcare budget: appropriate care, better accessibility, quality of care, and secondary and tertiary prevention, including care pathways and integrated care. The 2025 federal general policy note refers to support for appropriate care through practice guidelines and notes the role of the EBP network Evikey in supporting healthcare providers. Earlier federal policy documents also referred to the expansion of the EBP network after the 2018–2020 pilot phase into a 2021–2025 strategic plan.

KCE Trials is coherent with these priorities because it can generate evidence for clinical effectiveness, cost-effectiveness, quality improvement and de-implementation of low-value care. Its pragmatic design is relevant for ministerial objectives around "more health for money"

and appropriate use of resources. The Programme's systematic recording of economic data in trial design strengthens this coherence, because federal policy increasingly requires evidence not only on clinical gain but also on sustainability and affordability. By ensuring that cost and resource-use data are captured during trials, KCE Trials enables post-hoc economic analyses when policy decisions require them, without necessitating additional data collection.

At the same time, ministerial policy notes are broad political documents, while KCE Trials operates through scientific selection procedures. **Coherence therefore depends on whether broad policy priorities are translated into questions that can be addressed through clinical trials**. For example, a ministerial priority such as strengthening integrated care may not automatically lead to pragmatic trials on integrated-care pathways unless policymakers, healthcare providers and researchers jointly formulate questions that can be evaluated.

4.4.2 Coherence with policy initiatives of the federated entities

Belgium's institutional structure is important for evaluating coherence. Federal authorities are central for health insurance, reimbursement and hospital financing, while federated entities have major responsibilities in prevention, health promotion, primary-care organisation, welfare-health integration and regional implementation [106]. KCE Trials is a federal Programme, but its results are expected to inform practice across Belgium. With important health policy competencies falling largely within the responsibilities of the federated entities, coherence with federated policy is necessary for implementation and generalisability.

Across the federated levels, **KCE Trials is broadly coherent with Flemish, Walloon and Brussels health-policy priorities**. Flemish policy emphasises affordable, accessible and high-quality care, care close to home, ageing, mental health, digital or blended care, and integrated care [107]. The Walloon Plan *Prévention et Promotion de la Santé Horizon 2030* emphasises mental health, chronic diseases, infectious diseases, prevention and health-promoting environments [108]. The Brussels Integrated Social-Health Plan promotes "health in all policies", and primary-care and ambulatory-care reform [109]. KCE Trials illustrates this alignment through (pilot) studies such as RECOVER@HOME, a study originally aimed at evaluating geriatric home rehabilitation after hospital discharge [110]; IN-SPIRED, which studies home-based inspiratory muscle training after severe COPD exacerbation [111]; BLENDED, which compares blended psychotherapy with face-to-face psychotherapy for depression; and GPS-AD, which focuses on GP and pharmacist support for discontinuing long-term antidepressants [112].

Overall, **KCE Trials is compatible with federated health-policy objectives, but operational coherence would be stronger through structured engagement** with Departement Zorg, AVIQ and Vivalis/COCOM.

4.4.3 Coherence with specific (inter)national health priorities

KCE Trials is highly coherent with several specific health priorities that are simultaneously recognised at Belgian, European and international level, particularly antimicrobial resistance, sepsis, and pandemic preparedness. This cross-level coherence is important because these priorities are not isolated national concerns.

A clear example is **antimicrobial resistance**. At international level, WHO's Global Action Plan on AMR calls for countries to strengthen the evidence base through surveillance and research, reduce infection incidence, optimise antimicrobial use, and increase investment in medicines,

diagnostics, vaccines and other interventions. Belgium has adopted a One Health National Action Plan on AMR, listed by WHO, covering the period 2020–2024 [113] and a new Belgian draft AMR plan for 2026–2030 [114] sets targets across human, animal and environmental health, in line with EU objectives. At EU level, the European Commission identifies AMR as one of the top three priority health threats requiring coordinated preparedness and response [115]. KCE Trials aligns with this agenda through studies such as HIT HARD, which compares a short-course high-dose antibiotic strategy with conventional dose and duration in critically ill patients. ARON is another example, a study that aimed to strengthen the assessment of acutely ill children in primary care through an evidence-based diagnostic algorithm to support GPs in their decision when to withhold antibiotic treatment. These studies are directly coherent with antimicrobial stewardship, because they test whether antibiotic exposure can be avoided, reduced or optimised without compromising patient outcomes.

The same coherence is visible for **sepsis**. Belgium developed scientific recommendations for a Belgian Sepsis National Action Plan (Be-SNAP [116]) after professional and patient organisations called for action and the federal Minister of Health requested advice in 2023–2024. The Be-SNAP recommendations explicitly refer to the 2017 World Health Assembly resolution that declared sepsis a global health priority and urged Member States to develop and implement national strategies to improve prevention, diagnosis and management [117]. KCE Trials is coherent with this agenda through BLING III, a phase III randomised trial comparing continuous versus intermittent beta-lactam antibiotic infusion in critically ill patients with confirmed or suspected infection in ICU. The study started in 2017 and precedes the more recent policy momentum, indicating KCE Trials anticipated an important clinical evidence need. Another example is C-EASIE (see also section 4.2 *Effectiveness*). This trial tested early high-dose vitamin C in sepsis patients presenting to emergency departments. Although the trial found no clinical benefit, it provided crucial evidence that prevented the adoption of a practice that some clinicians had begun using based on weaker evidence. This aligns with sepsis management priorities by ensuring that clinical practice is grounded in rigorous evidence rather than biological plausibility alone, and by preventing unnecessary healthcare expenditure on ineffective interventions.

Pandemic preparedness provides yet another example of coherence between KCE Trials and Belgian, European and international health priorities. The COVID-19 pandemic exposed the need for rapid, coordinated and methodologically robust clinical evidence generation during health emergencies. At European level, this has translated into initiatives to strengthen pandemic preparedness and clinical trial coordination. Horizon Europe's pandemic preparedness partnership explicitly refers to the challenges COVID-19 revealed in detecting, preventing, combatting and managing infectious-disease outbreaks in a coordinated manner [118]. The European Commission has also supported coordinated COVID-19 therapeutic trial networks, including large adaptive platform trials such as EU-SolidAct [119], DisCoVeRy and REMAP-CAP [120], covering hospitalised and intensive-care patients. KCE Trials is coherent with this agenda because it was able to rapidly adapt its funding mechanism during the pandemic, including through a 2020 fast-track rolling call for COVID-19 clinical studies and a subsequent 2021 fast-track call on long COVID treatment, both focused on non-commercial randomised interventional trials intended to deliver rapid, relevant outcomes. This supports the coherence of KCE Trials with pandemic preparedness policy, because it demonstrated it can rapidly convert urgent clinical uncertainty into pragmatic, multicentre evidence generation if policy makers require this.

Overall, **KCE Trials is well aligned with specific health priorities** when these priorities require pragmatic evidence on comparative effectiveness, treatment optimisation, de-implementation, prevention of complications or cost-effective use of existing interventions. Its coherence is strongest for AMR, sepsis, and COVID-19 preparedness because these areas are recognised simultaneously in Belgian policy, EU coordination agendas and WHO priorities. The main limitation is operational as priority alignment does not automatically translate into a systematic trial pipeline. **Coherence would be strengthened** if, for example, Belgian AMR, sepsis, cancer, pandemic preparedness and chronic-disease plans were **explicitly used to identify commissioned or themed KCE Trials calls**, with **implementation routes defined from the outset**.

4.4.4 Coherence with international initiatives to strengthen clinical-trial policy

KCE Trials is highly coherent with WHO's agenda on strengthening clinical trials. In 2022, the World Health Assembly adopted resolution WHA75.8 [94] to strengthen clinical trials, improve research quality and coordination, and ensure high-quality evidence on health interventions. WHO's implementation work emphasises better clinical-trial ecosystems, stakeholder engagement, coordination and high-quality evidence generation. KCE Trials aligns with this agenda through its focus on pragmatic, practice-oriented, non-commercial trials. This is directly consistent with WHO's concern that clinical trials should produce reliable, useful evidence for health interventions and public decision-making.

KCE Trials also aligns with Horizon Europe's increasing support for pragmatic, academic, investigator-initiated clinical trials. For example, Horizon Europe calls include pragmatic clinical trials intended to optimise interventions and support implementation by health systems at local, regional, Member State and European levels [121, 122]. KCE Trials also aligns with the Clinical Research Initiative for Global Health (CRIGH), a global initiative co-led by ECRIN and the U.S. National Institutes of Health (NIH) [123, 124], which supports international collaboration in non-commercial, investigator-initiated clinical trials [125, 126], with emphasis on comparative effectiveness research and research ethics [125]. Additionally, KCE's commitment to transparency and research quality aligns with the principles of the Ensuring Value in Research (EViR) Funders' Forum, which advocates for trial registration and transparency as core standards for improving research value [127, 128].

4.4.5 Synergies and Overlaps with Other Funders

T**he KCE Trials Programme occupies a niche** as the **primary funder of broad non-commercial, investigator-led pragmatic trials in Belgium**. A large majority of investigators (86%) confirm that the Programme complements commercially driven research in Belgium [44].

The Belgian research funding landscape includes several funders whose scope may slightly overlap with specific parts of the KCE portfolio. The **FWO-TBM** (Fonds Wetenschappelijk Onderzoek – Toegepast Biomedisch Onderzoek met een primair Maatschappelijke finaliteit) funds the implementation of therapies, diagnostic techniques, and preventive methods, a scope directly aligned with KCE's pragmatic trials focus. **Kom Op Tegen Kanker** funds oncology research in Belgium. No formal coordination mechanisms exist between KCE and any of these funders, although KCE reports informal exchanges with them [19]. The portfolio call structure (mostly investigator-led) reflects the absence of structural direction from policymakers. To **increase its differentiating role in addressing public health priorities in the Belgian research**

landscape, a more balanced call structure incorporating a higher proportion of commissioned calls addressing explicit policy priorities could strengthen both coherence and relevance.

KCE Trials is highly coherent with ZonMw's policy model. ZonMw funds health research and innovation, promotes knowledge infrastructures, and supports the use of developed knowledge. Its effectiveness research Programme includes the BeNeFIT call, focused on comparative, practice-oriented clinical studies in which Dutch and Belgian institutions jointly conduct non-commercial research relevant to patients, care providers and policymakers in both countries. The BeNeFIT collaboration with 15 trials is one of the clearest examples of international coherence. KCE and ZonMw launched BeNeFIT because many healthcare questions are relevant in both countries and collaboration allows clinical trials to be carried out faster and more efficiently. KCE has organised four BeNeFIT calls to date (2018, 2021, 2024 and 2025), establishing a sustained track record of successful cross-border collaboration [51]. This coherence is strategic and operational as the collaboration involves joint calls, shared funding logic, similar evaluation criteria, and a focus on non-commercial comparative effectiveness. This international dimension extends across the portfolio as a whole: 68% of funded trials are entirely Belgian-led, 20% Netherlands-led (largely reflecting BeNeFIT), and the remaining 12% are led from France, Denmark, Sweden or Australia [51]. KCE's model also aligns with other European funders, including the UK's NIHR Health Technology Assessment (HTA) Programme and ERA4Health's EffecTrial and Trials4Health initiatives, which similarly support multi-country, investigator-initiated pragmatic trials designed to inform healthcare policy and practice across Europe [129, 130, 131, 132].

5. Conclusions

5.1 Strengths

The KCE Trials Programme has, over its first decade, **established itself as a cornerstone of Belgium's evidence ecosystem**. It established an internationally recognised programme for non-commercial, pragmatic, practice-oriented trials in real-life settings, generating high-quality, policy-relevant evidence capable of informing clinical guidelines, reimbursement decisions, and healthcare system efficiency.

The **evidence assembled** through this assessment is unambiguous on the Programme's core achievements:

- **Exceptional scientific excellence** with internationally recognized selection processes
- **Diverse portfolio** across disease areas, care settings, and vulnerable populations
- **High trial completion rates** (76%) and publication rates (96%)
- **Effective leverage** of research infrastructure
- **International recognition** as centre of excellence for pragmatic trials
- **Transparent and fair selection processes** (92% investigator satisfaction)
- **Pragmatic trial design** with broad eligibility criteria and diverse populations
- **Strong coherence with federal, federated and international policy** themes

It funds research that genuinely would not otherwise be funded. It selects that research through a **rigorous, transparent process** that investigators trust and is aligned with international best practices. It monitors and supports that research with an intensity that produces completion and publication rates that are outperforming both commercial and non-commercial research. It generates scientific outputs of international quality (in e.g. The Lancet, New England Journal of

Medicine) that are beginning to influence clinical practice and policy at a pace appropriate to the Programme's age.

The clinical results of completed trials are concrete and meaningful. A 27% relative reduction in antibiotic prescribing in children through **ARON**. A 36% risk reduction in hospital-acquired pressure ulcers through the **Pressure Ulcer** trial. Prevention of unnecessary vitamin C supplementation in sepsis through **C-EASIE**. Successful decongestion in patients with acute decompensated heart failure and volume overload through **ADVOR**, now cited 199 times in international literature. . These are meaningful results with the potential of improving clinical care when implemented in the regular healthcare system. The Programme's policy impact, though still emerging relative to the time lags inherent in guideline development and reimbursement processes, is already visible. **GonoScreen** has informed Belgian PrEP guidance. **Pressure Ulcer** is reflected in international guidelines and a 2023 KCE HTA report. **BLING III** has been incorporated into the 2026 Surviving Sepsis guidelines. With most of the portfolio having been published since 2020, **KCE Trials is just now entering the two-to-three-year window in which guideline adoption typically occurs**, and the volume of such documented translations is likely to grow substantially in the years ahead. The capacity-building effects of the Programme extend across Belgium's research landscape. Ninety percent of surveyed investigators report the KCE Trials Programme has strengthened their team's clinical research capacity. International praise for procedures and tools. These systemic contributions are difficult to quantify but consistently recognised by international stakeholders as among the most valuable aspects of what KCE does.

5.2 Areas for development

This report identifies **three development areas: evidence-to-policy translation, administrative efficiency, and regional equity**. These challenges are linked to scaling and maturity and not a lack of effectiveness of the Programme. They reflect the next priorities for the Programme as it moves beyond establishing itself as a credible and internationally recognised funder of pragmatic trials. The focus now needs to shift to ensuring that the evidence it generates reaches and systematically influences the healthcare system it was created to serve. Key areas requiring attention, which will be further detailed out in the section on Key Recommendations, include:

- **Evidence-to-policy translation** gap: Systematic mechanisms for translating trial findings into **explicit policy decisions** remain underdeveloped. The challenge is to **make that impact visible** (strengthened coordination with NIHDI, and ad-hoc economic impact studies), so that the Programme's value can be more clearly demonstrated and used to inform future priority-setting.
- Limited **systematic tracking of dissemination** and impact: Systematic measurement of dissemination reach and realized economic/health impact is absent.
- **Administrative efficiency**: Timelines and perceived administrative burden warrant a risk-based review.
- **Regional equity**: Geographic imbalance in trial recruitment limits national representativeness.
- **Domestic funder coordination**: Formal coordination mechanisms with Belgian funders not documented.

The structural advantage of being both an HTA body and a research funder **positions KCE uniquely to achieve this**, but only if the HTA and Trials functions are more deliberately integrated. The evidence-to-policy gap is addressable through targeted governance investment. The regional imbalance reflects underlying capacity and infrastructure differences in Wallonia, as well as

population differences, that require investment beyond the KCE Trials Programme itself. KCE is already engaged in efforts to strengthen clinical trial centre capacity and capability in underrepresented regions, taking on a broader infrastructure-building role that extends beyond its core funding mandate and demonstrates commitment to addressing this systemic challenge.

5.3 Strategic positioning

The KCE Trials Programme has d**emonstrated its capacity to evolve and improve** over the past decade. With focused attention to the recommendations in this report, it is well positioned to enter its second decade not only as a strong funder of clinical trials but as a model for evidence-to-policy translation in Europe, and as a systematic contributor to measurable improvements in healthcare quality, efficiency, and equity for Belgian patients.

The **Programme's role extends beyond funding individual trials** to building internationally recognised processes, best practices, methodologies, and tools that strengthen Belgium's position in the European research community. Realising its full potential requires addressing the evidence-to-policy translation gap and establishing more formalised governance structures to ensure that strong scientific output translates systematically into healthcare policy and practice.

6. Key recommendations

The following **10 recommendations** are organised by the four evaluation criteria: relevance, effectiveness, efficiency, and coherence. Each is grounded in evidence from the evaluation and designed to build on the Programme's exceptional scientific foundations toward greater systematic influence on healthcare policy and practice.

6.1 Relevance

Recommendation 1: Formalise payer and policymaker involvement in priority-setting

The current absence of a structured dialogue between KCE and other federal and federated health authorities means that the selection process, while rigorous and transparent, is not systematically anchored to the most pressing decision-making needs of those responsible for reimbursement and other health policy uncertainties.

A formal governance arrangement (e.g., a yearly priority-setting meeting) should facilitate priority-setting processes, establish clear pathways for evidence-to-policy translation, and create mechanisms for systematic feedback on policy and reimbursement decisions informed by trial results. This should be developed as a joint effort with KCE and its funders as equal partners to ensure sustained buy-in.

On a more operational level, to improve the success rate of commissioned or themed calls, KCE Trials could facilitate early dialogue between NIHDI, FPS Public Health, and potential investigators to define policy-relevant research questions that can feasibly be answered through pragmatic clinical trials.

Recommendation 2: Create awareness on regional capacity-building in Wallonia

The distribution of recruited patients reflects a range of interacting structural and trial-specific factors such as infrastructure differences and language barriers. Targeted outreach, engagement with Walloon clinical trial centres, and publishing results in national medical journals could increase awareness of the Programme and progressively address this imbalance. The KCE Trials Programme has already made efforts in this direction (e.g., bilingual recruitment support), and the recommendation is to engage policy makers on the need for targeted support for clinical research in Wallonia, enabling the region to continue its growth trajectory.

6.2 Effectiveness

Recommendation 3: Integrate dissemination and implementation planning into trial process

KCE should develop practical guidance for investigators on dissemination and implementation planning, including a template or checklist covering key considerations such as identified target audiences beyond the academic community, planned dissemination channels and timelines, engagement with payers and other relevant health authorities including NIHDI and BCFI, and data-sharing protocols. This guidance should be offered as a resource to support investigators of successfully completed trials who wish to strengthen the implementation pathway of their trials, without adding mandatory requirements to the application or contracting process. International evidence demonstrates that planning implementation from the outset, with dedicated resources and early stakeholder engagement, substantially accelerates the translation of findings into clinical practice [133]. By providing concrete tools and examples, KCE Trials can support investigators in closing the loop between trial completion, and evidence translation and

implementation, while respecting investigator autonomy and maintaining proportionate administrative requirements.

Recommendation 4: Establish systematic post-trial impact tracking

The current absence of formal documentation of policy decisions informed by KCE Trials, and reliance on investigator self-report for evidence of guideline adoption and practice change, leaves much of the Programme's actual influence invisible to funders (NIHDI) and the public. KCE Trials should introduce a structured post-trial tracking tool to monitor the uptake of fundings in clinical guidelines, reimbursement decisions, clinical practice and policy documents. Routine follow-up two and five years after publication would strengthen accountability and provide evidence to demonstrate the Programme's value to funders. Federal and federated health authorities, often represented already in the KCE governance, should inform KCE Trials when study results have been used for decision making. Potential synergies on this topic with KCE Practice should also be explored.

Recommendation 5: Leverage KCE's HTA capabilities more systematically

KCE should more formally link its Trials, HTA and policy advisory work. Upcoming HTA needs should inform trial priorities, while HTA teams should lead the dissemination of results to policy makers and channel relevant findings into NIHDI reimbursement decisions. This would shorten the path from evidence to policy without requiring new institutional relationships to be built.

More formal integration between the Trials Programme and KCE's HTA and policy advisory functions, through systematic review of upcoming HTA needs to inform future trial priority-setting, HTA-led dissemination of trial results to policymakers, and a standing pathway for findings to feed into NIHDI reimbursement discussions through KCE's existing advisory relationships, would substantially accelerate the evidence-to-policy pathway without requiring new institutional relationships to be built.

6.3 Efficiency

Recommendation 6: Analyse and reduce the application-to-contract timeline

While the rigorous processes underlying these timelines are recognised as essential to trial quality and success, the wide variation across call types warrants investigation to determine whether efficiency gains are achievable without compromising scientific rigour. . KCE should conduct a detailed analysis of administrative timelines through process mapping, timeline tracking by phase, and targeted interviews with investigators and site coordinators to identify which phases contribute most to the overall timeline and assess whether efficiency improvements are feasible while maintaining the methodological rigour that characterises KCE's selection and contracting processes.

Recommendation 7: Implement differentiated reporting requirements based on trial complexity and risk profile

KCE Trials should explore the introduction of a risk-based model that tailors programme oversight, reporting, monitoring and support to each trial's risk profile, within all applicable legal and GCP requirements. Risk drivers could include the intervention's novelty and safety profile, participant vulnerability, procedural and design complexity, recruitment and data risks, and the track record of the sponsor and investigator team. Lower-risk trials led by experienced teams could follow a

streamlined pathway, while complex or higher-risk trials and less experienced teams should receive closer oversight and additional support.

Recommendation 8: Index KCE Trials budget to preserve existing capacity and funding predictability

The clinical-trial funding portion of the KCE Trials budget should be indexed annually against a transparent benchmark that reflects its main cost drivers. Without indexation, rising personnel, site, data-management, monitoring and other costs will erode its real value, forcing the programme to fund fewer or smaller trials over time.

6.4 Coherence

Recommendation 9: Establish regular dialogue with domestic Belgian funders

No formal coordination exists with other funder such as FWO-TBM or Kom Op Tegen Kanker, creating potential for duplication and missed collaboration, particularly in oncology (15% of KCE's portfolio). A shared annual portfolio review, with each funder describing priorities and recent funding decisions, would substantially reduce duplication risk and identify synergies. This is also an opportunity to streamline funding topics with new policy initiatives such as the post-reimbursement fund. The post-reimbursement fund, a new federal treatment optimisation initiative [134, 135], is highly coherent with the objectives of KCE Trials, but it also creates a potential mandate-overlap risk, as both instruments target non-commercial, practice-oriented evidence gaps that are unlikely to be addressed by industry, particularly questions on the optimal use, duration, intensity or cost-effectiveness of existing (high-cost) interventions.

Recommendation 10: Expand international partnerships, particularly for areas with challenging recruitment

The SurLym and FOOT DROP case studies both illustrate recruitment challenges specific to surgical trial design. While surgical trials comparing two techniques generally achieve adequate recruitment, trials randomising patients to surgery versus no surgery face substantial patient acceptance barriers. **Strengthening joint calls with other public funders** for trials in rare diseases, surgical settings with inherent recruitment constraints, and other challenging areas, and developing formal data-sharing agreements to enable secondary analyses across international trial portfolios, would enhance both the scientific power of individual trials and Belgium's influence in the global trials landscape. The growing general trend toward more international collaboration in clinical trials, driven by cost pressures and the risk of reduced trial competitiveness in Europe, makes this recommendation both strategically and practically timely.

Summary

The KCE Trials Programme has **demonstrated its capacity and willingness to evolve, grow and improve**. With focused attention to the recommendations in this report, it is **well positioned to enter its second decade** not only as a **strong funder** of pragmatic clinical trials but as a **model for evidence-to-policy translation in Europe**, and as a systematic contributor to measurable improvements in healthcare quality, efficiency, and equity for Belgian patients.

7. Limitations

This evaluation of the KCE Trials Programme must be interpreted within important constraints that reflect the inherent challenges of assessing emerging research funding initiatives and specific methodological boundaries of this assessment. These limitations span programme maturity, data availability, outcome measurement, stakeholder perspectives, and analytical scope. While multiple data sources and triangulation methods have been employed to enhance robustness, transparent acknowledgment of these constraints is essential for appropriate interpretation of findings.

7.1 Programme maturity as a foundational constraint

The most significant limitation is the relative immaturity of the KCE Trials Programme itself. At just over a decade in operation, the Programme remains in an early-to-intermediate stage of development. This temporal constraint creates cascading effects across all evaluation dimensions. Long-term research impacts, including policy integration, clinical practice adoption, and patient-level outcomes, typically materialize over 10–15 years or longer. Consequently, only a fraction of funded trials has reached completion, and measurable downstream effects remain limited. The Programme's portfolio is heterogeneous in maturity, comprising completed trials with published outputs, ongoing trials still in implementation or analysis phases, early-stage trials not yet initiated, and a small number of discontinued trials. This variability constrains the ability to assess the full spectrum of intended impacts and limits the generalizability of findings to the Programme's current operational capacity. The evaluation explicitly accounts for maturity-related differences by including trials across all stages and employing lead indicators as early proxies for future impact. However, this approach necessarily yields indicative rather than definitive conclusions about long-term Programme effectiveness.

7.2 Data availability, measurement, and attribution constraints

The evaluation is constrained by incomplete systematic tracking of key outcomes. Policy impact assessment relies on investigator self-report and informal documentation. Similarly, dissemination reach and engagement metrics among target audiences are not systematically measured, limiting quantification of knowledge diffusion beyond publication counts.

The evaluation has employed contribution analysis and triangulation across multiple data sources to assess plausibility of causal links rather than establishing definitive causality. Findings are interpreted as indicative of likely impact pathways rather than proof of direct causation.

7.3 Stakeholder perspectives and external contextual factors

The investigator survey achieved a 56% response rate (n=47), introducing potential self-selection bias whereby investigators more satisfied with the Programme may be more likely to respond. Stakeholder perceptions obtained through surveys and interviews may be subject to social desirability bias, particularly among investigators dependent on KCE funding or KCE staff reluctant to provide negative feedback. The evaluation has mitigated these biases by including both funded and unfunded applicants, conducting interviews with external stakeholders independent of KCE funding, and triangulating findings across multiple data sources.

The evaluation period (2016–2025) spans significant external disruptions and policy changes that cannot be fully isolated. The COVID-19 pandemic substantially affected trial recruitment and operations; rolling COVID-19 calls accelerated contracting timelines, positively affecting average

timeline metrics but not reflecting normal Programme operations. Shifts in healthcare policy and reimbursement mechanisms may have influenced trial design and relevance independent of Programme factors. Regional differences in clinical trial infrastructure and capacity may affect recruitment patterns independent of KCE selection processes. The evaluation has documented these external factors and conducted separate analyses excluding known outliers (BeNeFIT calls, ELMO study), yet the full extent of contextual influence cannot be quantified.

7.4 Scope and generalizability boundaries

The qualitative assessment is limited by a small sample of Principal Investigator interviews, constraining generalizability to the broader investigator community, though findings have been triangulated with survey data and document review. Five in-depth case studies were purposively selected to reflect diversity in trial type and implementation status. While this selection strategy maximizes representativeness within constraints, findings are illustrative rather than generalizable to the entire portfolio.

7.5 Implications for Interpretation

When interpreting the findings of this evaluation, readers should:

- Recognise temporal constraints: The evaluation provides a snapshot of early- to mid-term impact for a relatively young Programme. Full impact may not yet be observable.
- Acknowledge attribution challenges: Observed impacts should be interpreted as contributions of the KCE Trials Programme rather than sole consequences of KCE funding.
- Consider data gaps: Conclusions about policy impact, cost-effectiveness, and dissemination reach should be interpreted in light of incomplete systematic tracking.
- Value qualitative insights: Qualitative findings from case studies and interviews provide important contextual understanding that complements quantitative metrics.
- Recognise Programme evolution: The KCE Trials Programme has evolved substantially over its decade of operation; findings may not uniformly apply to all periods.

Despite these limitations, the evaluation has employed rigorous mixed-methods approaches and triangulation to generate robust, evidence-based findings about the KCE Trials Programme’s processes and impact. The transparent documentation of limitations and assumptions enables readers to assess the credibility of findings and their applicability to specific contexts or questions. The evaluation provides a solid foundation for evidence-based decision-making regarding the Programme’s future direction while acknowledging areas where additional data collection or systematic tracking would enhance understanding of the Programme's full contribution to Belgian healthcare research and practice.

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