Closing the evidence gaps
Considerations for publicly-funded trials

Frank Hulstaert, MD, MSc
Senior Researcher, KCE
trials@kce.fgov.be

COMET Amsterdam, 15 November 2018
KCE, Belgian Health Care Knowledge Centre

www.kce.fgov.be

- Semi-governmental institution
- Operational 2004

- 50 researchers
  - medicine, economics
  - statistics, sociology, law

- Studies (n>300)
  - Clinical practice guidelines
  - Health services research (HSR)
  - Health technology assessment (HTA)
  + KCE Trials (started in 2016)

- Policy recommendations, no decisions
What is innovation in healthcare?

Technical innovator

New pathway

Technical breakthrough

Clinical Development

The evidence gap

HTA

Patient benefit

Routine practice

MIND THE GAP
Clinical development and HTA

Clinical development

Exploratory trials

Confirmatory trials (RCTs)

Health Technology Assessment

HTA early dialogue, parallel scientific advice

- internal validity
- safety
- efficacy

- external validity
- comparative effectiveness
- cost-effectiveness
- budget impact
Health technology assessment

HTA Institutions

Non-drug HTA

- CAHTA
- TA-SWISS
- ANDEM/ANAES
- SBU
- 1987
- 89
- 91/92
- 93
- 94
- 95
- 96
- 97
- 98
- 99
- DIHTA
- AETS
- AETSA
- FinOHTA
- SMM
- DAHTA
- NICE
- UETS
- 2000
- 01
- 02
- 03
- 04
- 05

Broad HTA

- DACEHTA
- KCE
- IQWiG
- "New"
- NICE

Drug HTA

- PBAC
- PMPRB
- CFH
- PPB
- PHARMAC
- NoMA
- HEK
- EAK
- CT
- PBB
- CEDAC

- 1992
The split in governance and the evidence gap

One government?

**Regulator**
- EMA/national regulator
- Notified bodies/national regulator
  - Drug efficacy/safety
  - Device performance/safety

**HTA/payer**
- National/regional
- Added therapeutic benefit versus standard of care
- Value for money
How aligned are the perspectives of EU regulators and HTA bodies? A comparative analysis of regulatory-HTA parallel scientific advice

Figure 3
Level of agreement for each domain: Health Technology Assessment bodies (HTABs) vs. regulators (based on 31 procedures). n represents the total number of HTABs expressing an opinion for each domain. □ full agreement ▪ partial agreement □ disagreement

How to fill the evidence gap?

- Align evidentiary requirements of regulators and payers
  - Added therapeutic value

- Perform the missing comparative trial
  - Post-marketing: industry support is unlikely
  - Publicly-funded
    - But: research funding <> healthcare systems
    - Role of healthcare payers
How to manage product discontinuation under adaptive pathways?

How to inform the patient?

Old

New

Pre-market  Extended research  Post-market
In addition to patient benefit, publicly funded trials can provide a positive return on investment.

- 2016: €5m
- 2017: €5m
- 2018: €10m per year

2016 challenge: first patient in trial
End 2016 first patient in VINCA trial
Randomised trials balance for the unknown

Real-world data are not sufficient - the case of renal denervation

- EU HTA report:
  - “renal denervation using the Symplicity® system appears to decrease blood pressure, whereas the effects of other systems on blood pressure are uncertain.”

- Reimbursed in 13 countries in Europe, and in most cases regardless of the type of device.

- The same day: RCT for FDA: NO EFFICACY, all trials put on hold.
Comparative Effectiveness

Comparator

- best
- active
- placebo
- none

Comparator

- narrow (efficacy)
- broad (effectiveness)

Study population

Endpoints
- Quality of Life (EQ-5D)
- Survival

pragmatic practice-oriented trial

Please involve HTA agencies in the development of outcome sets
Registry-based RCT, towards EHR-based RCTs

R-RCT vs. RCT

STEMI Thrombectomy Story

TASTE (R-RCT) vs. TOTAL (traditional RCT)

500,000 € vs. 15,000,000 €

1st patient: June 2010
30 centers
33 months to full enrollment
7,244 patients

1st patient: August 2010
87 centers
48 months to full enrollment
10,732 patients


KCE Trials programme

- Pragmatic & practice-oriented
- Comparative effectiveness
- Commissioned & investigator-led

- Patients & policy makers
- National & international
- Clinical trials units (CTU)

- Funder
- Non-commercial sponsor
- Data sharing
Key success factors for publicly funded trials

**SELECTION CRITERIA**
- Panels
- Trials Board
- Prioritisation Group
- KCE Board
- Clinical Trial Unit

**IMPLEMENT RESULTS**
- Scope/relevance
- Value for money/ROI
- Methods

**PROFESSIONAL CONDUCT**
Guidance notes for completing KCE Trials application form

- Where established Core Outcomes exist they should be included amongst the list of outcomes unless there is good reason to do otherwise.
- Please see The COMET Initiative website at www.cometinitiative.org and www.ichom.org to identify whether Core Outcomes have been established.

**KCE TRIALS PROGRAMME**

PICO (summarized, table; for an in depth description of all parameters please use the ‘design’ field)

| Population | (Maximum 500 characters spaces included)  
| target population i.e. real patients; provide main eligibility criteria |
| Intervention | (Maximum 500 characters spaces included)  
| An intervention that is or could be used now in Belgium; also indicate the health service setting(s) in which the study will occur |
| Comparator | (Maximum 500 characters spaces included)  
| Usually next best treatment or usual care, but could be no intervention (or placebo) |
| Outcome | (Maximum 600 characters spaces included)  
| Patient centred, leading to effectiveness and cost-effectiveness. Please see The COMET Initiative website at [www.comet-initiative.org](http://www.comet-initiative.org) and [www.ichom.org](http://www.ichom.org) to identify whether Core Outcomes have been established.  
Primary outcome: define the time point and the exact measure that will be used for the primary analysis  
Secondary outcomes: list secondary outcomes |
BeNeFIT

Comparative effectiveness
Reimbursable interventions
Medicines and other interventions
Recruitment matching budget contributions

Call opens 16 Jan 2018
Outlines by 8 May 2018
Full proposals by 2 Oct 2018
Revised full proposals by 30 Apr 2019

KCE € 3M
ZonMw € 3M
Tips for applicants

- Consult a trial statistician
- Build a multi-site team in time (FR/NL)
- Collect input from patients on endpoints and feasibility
- Identify other expertise needed and work with a CTU
“Frankly sir, we’re tired of being on the cutting edge of technology.”