



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

# Closing the evidence gaps

## Considerations for publicly-funded trials

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*COMET Amsterdam, 15 November 2018*



# KCE, Belgian Health Care Knowledge Centre

[www.kce.fgov.be](http://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

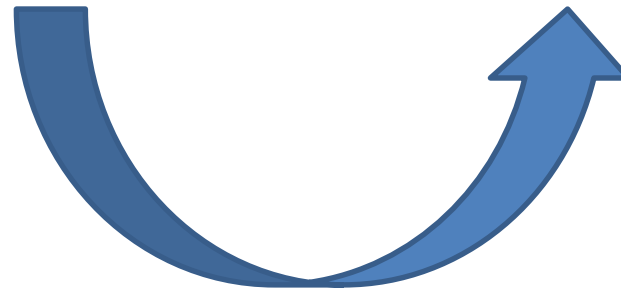
# What is innovation in healthcare?

**Technical innovator**

**New pathway**

**Technical breakthrough**

***Clinical Development***



**The evidence gap**

**HTA**

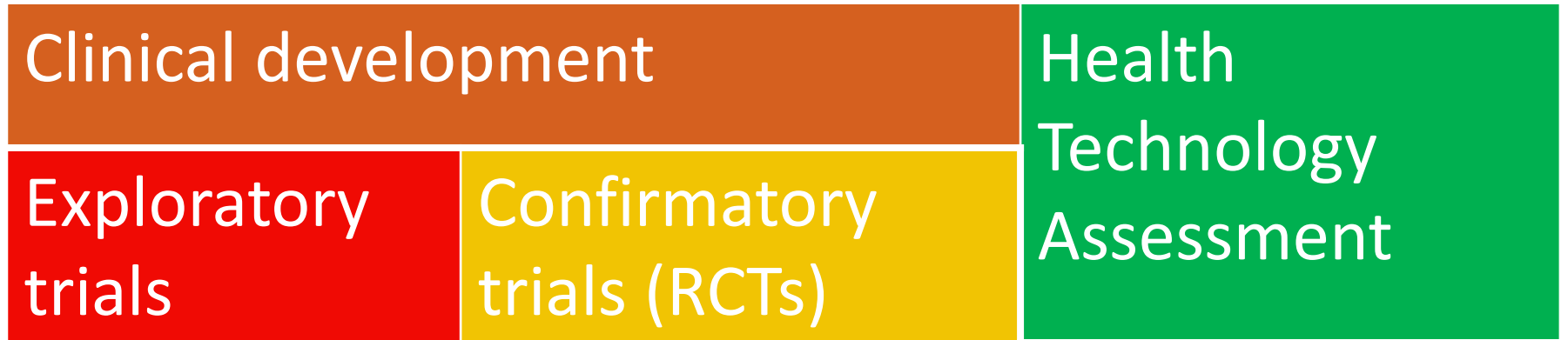
**Patient benefit**

**Routine practice**

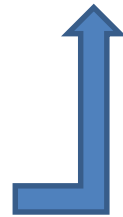
**MIND THE GAP**



# Clinical development and HTA



**HTA early  
dialogue,  
parallel  
scientific  
advice**

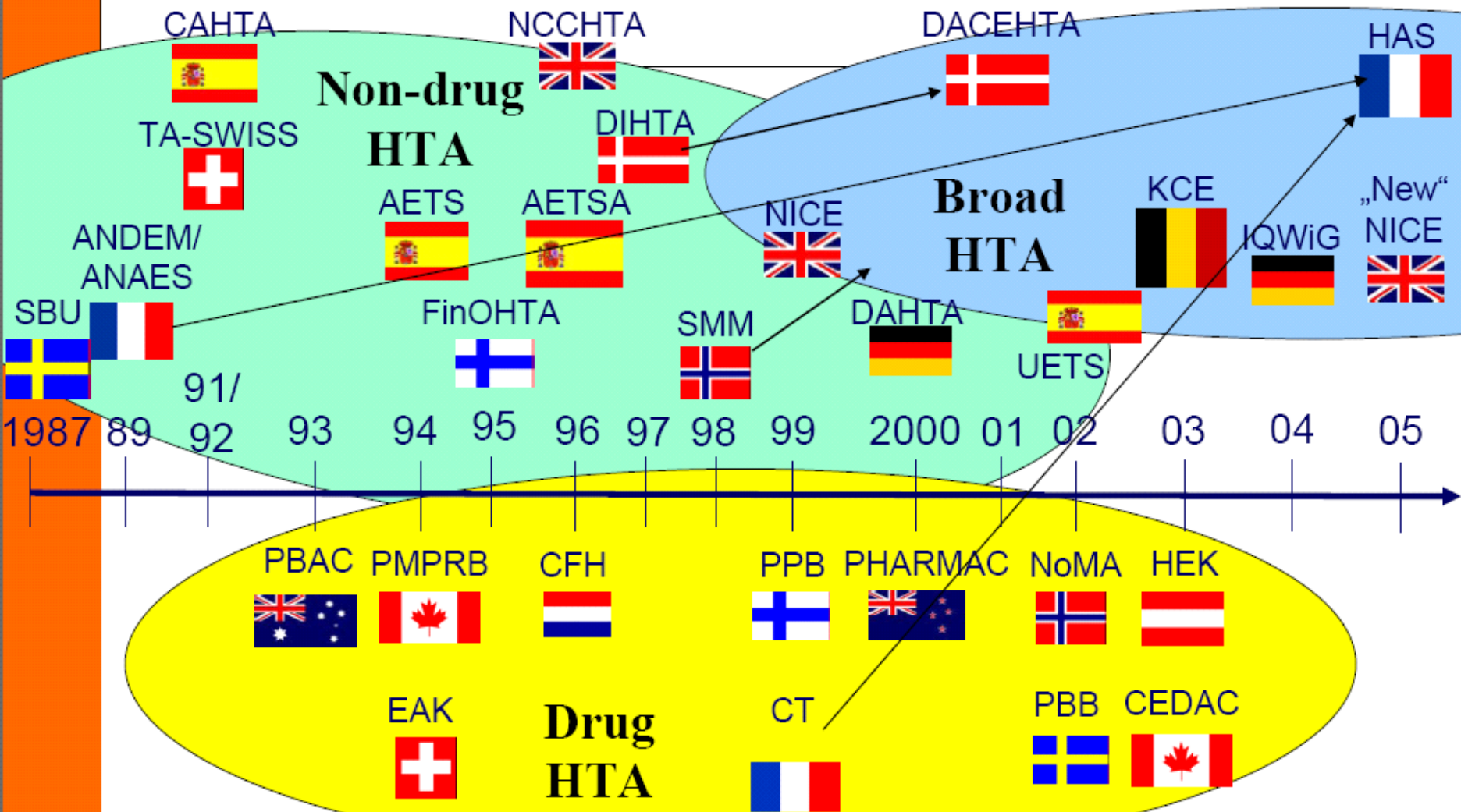


- internal validity
- safety
- efficacy

- external validity
- comparative effectiveness
- cost-effectiveness
- budget impact

# Health technology assessment

## HTA Institutions



# The split in governance and the evidence gap

*One government?*

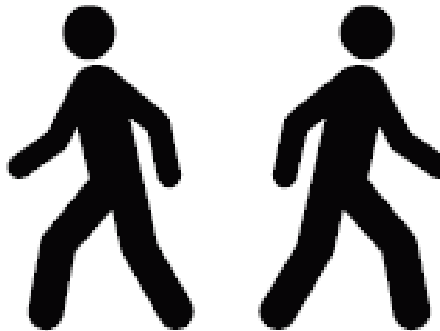
## Regulator

**EMA/national regulator**

- Drug efficacy/safety

**Notified bodies/national  
regulator**

- 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

G. Tafuri et al.

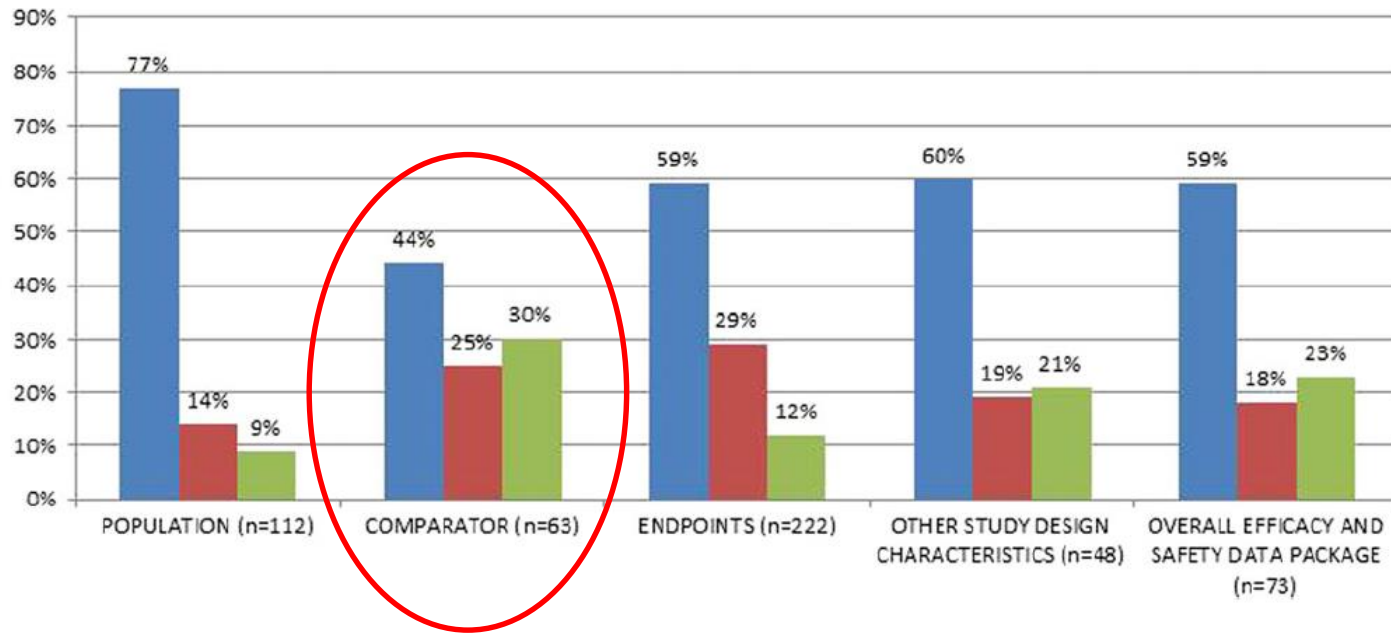


Figure 3

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

[Br J Clin Pharmacol](#). 2016 Oct;82(4):965-73



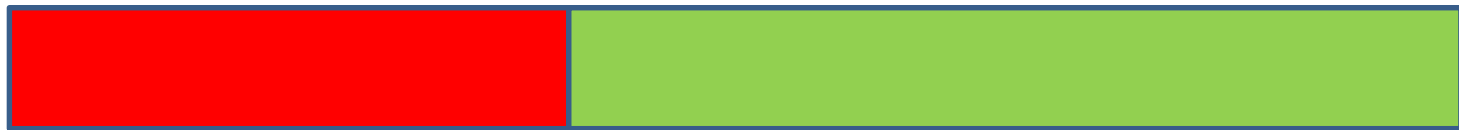
# How to fill the evidence gap?

- **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  $\leftrightarrow$  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



# Impact of KCE Report no 246

June 2015

**“In addition to patient benefit, publicly funded trials can provide a positive return on investment”**

2016 €5m

2017 €5m

2018 €10m per year

ROI

PUBLICLY FUNDED PRACTICE-ORIENTED CLINICAL TRIALS



**2016 challenge: first patient in trial**

**End 2016 first patient in VINCA trial**



2015

www.kce.fgov.be

.be

# 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

active

placebo

none

pragmatic practice-  
oriented trial

placebo-  
controlled trial

Endpoints

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

Please involve HTA agencies in  
the development of outcome sets

narrow  
(efficacy)

broad  
(effectiveness)

Study  
population



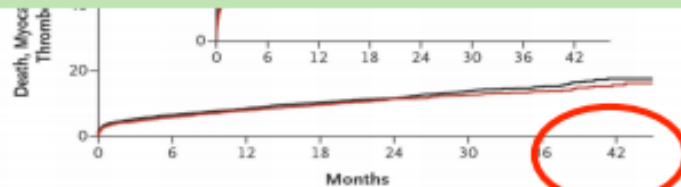
# Registry-based RCT, towards EHR-based RCTs

## R-RCT vs. RCT STEMI Thrombectomy Story

### TASTE (R-RCT)



**500,000 €**



No. at Risk

PCI+TA	3623	3404	3328	2821	2180	1505	864	184
PCI only	3621	3386	3315	2796	2200	1494	862	190

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

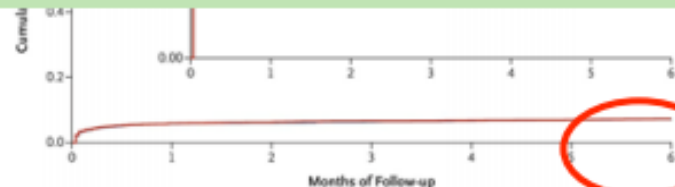
Lagerqvist B et al. N Engl J Med 2014;371:1111-1120

### TOTAL (traditionell RCT)

A Primary Outcome



**15,000,000 €**



No. at Risk

Thrombectomy	5053	4734	4696	4678	4662	4647	4628
PCI alone	5050	4727	4688	4666	4653	4642	4618

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

Jolly SS et al. N Engl J Med 2015;373:1389-1398



# KCE Trials programme

Pragmatic &  
practice-  
oriented

Comparative  
effectiveness

Commissioned  
&  
investigator-led

Patients &  
policy makers

National &  
international

Clinical trials  
units (CTU)

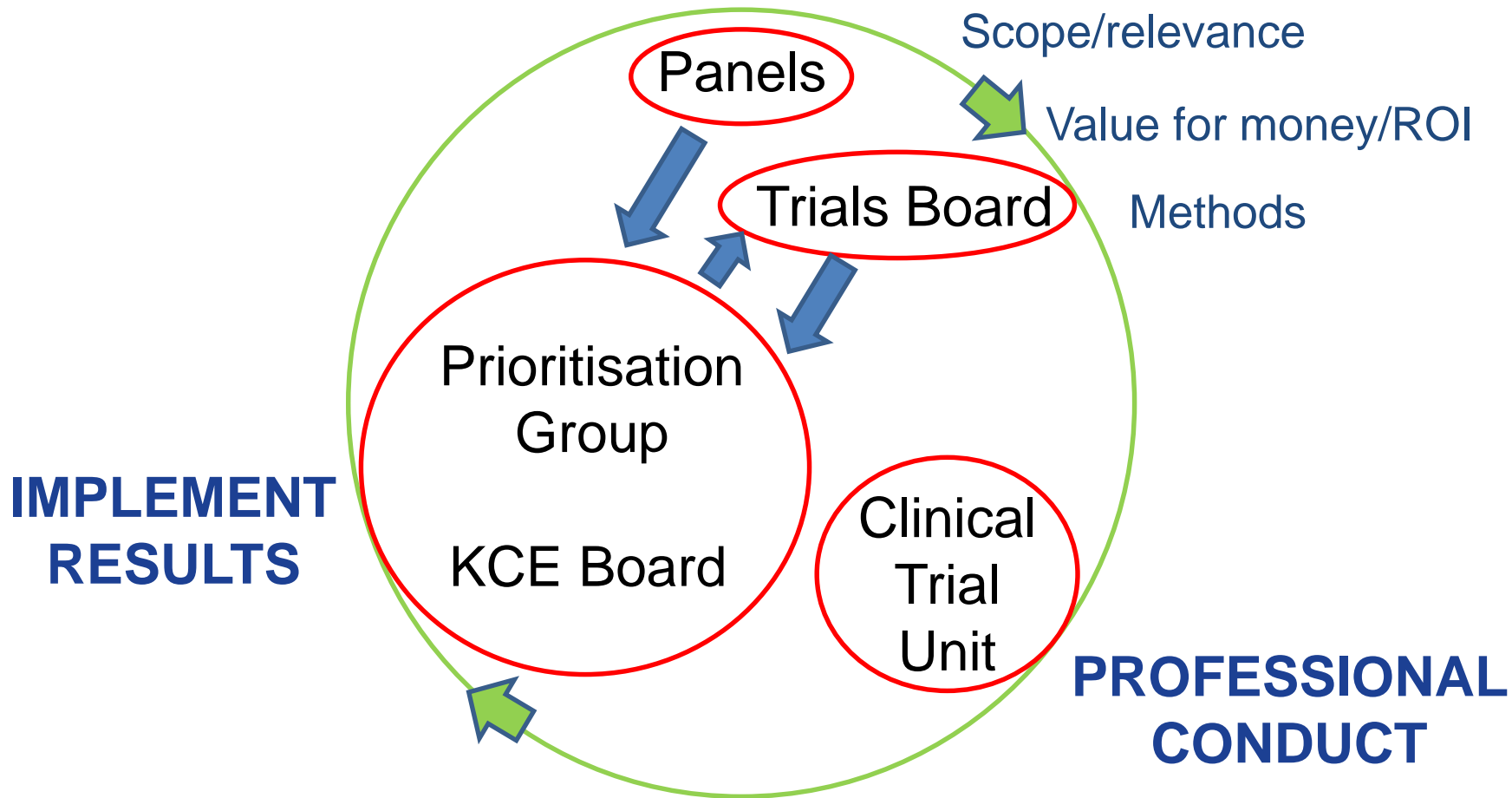
Funder

Non-  
commercial  
sponsor

Data sharing

# Key success factors for publicly funded trials

## SELECTION CRITERIA



# 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](http://www.cometinitiative.org) and [www.ichom.org](http://www.ichom.org) to identify whether Core Outcomes have been established.**

[https://kce.fgov.be/sites/default/files/atoms/files/KCE\\_Trials\\_application\\_form\\_Guidance\\_Notes\\_2018.pdf](https://kce.fgov.be/sites/default/files/atoms/files/KCE_Trials_application_form_Guidance_Notes_2018.pdf)

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

Population	<i>(Maximum 500 characters spaces included) target population i.e. real patients; provide main eligibility criteria</i>
Intervention	<i>(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</i>
Comparator	<i>(Maximum 500 characters spaces included) Usually next best treatment or usual care, but could be no intervention (or placebo)</i>
Outcome	<i>(Maximum 600 characters spaces included) Patient centred, leading to effectiveness and cost-effectiveness. Please see The COMET Initiative website at <a href="http://www.comet-initiative.org">www.comet-initiative.org</a> and <a href="http://www.ichom.org">www.ichom.org</a> to identify whether Core Outcomes have been established.  Primary outcome: <i>define the time point and the exact measure that will be used for the primary analysis</i> Secondary outcomes: <i>list secondary outcomes</i></i>





Comparative effectiveness

Reimbursable interventions

Medicines and other interventions

Recruitment matching budget contributions

KCE  
€ 3M

ZonMw  
€ 3M

Call opens  
16 Jan 2018

Outlines by  
8 May 2018

Full  
proposals by  
2 Oct 2018

Revised full  
proposals by  
30 Apr 2019

# Tips for applicants



Consult a trial statistician



Build a multi-site team in time (FR/NL)

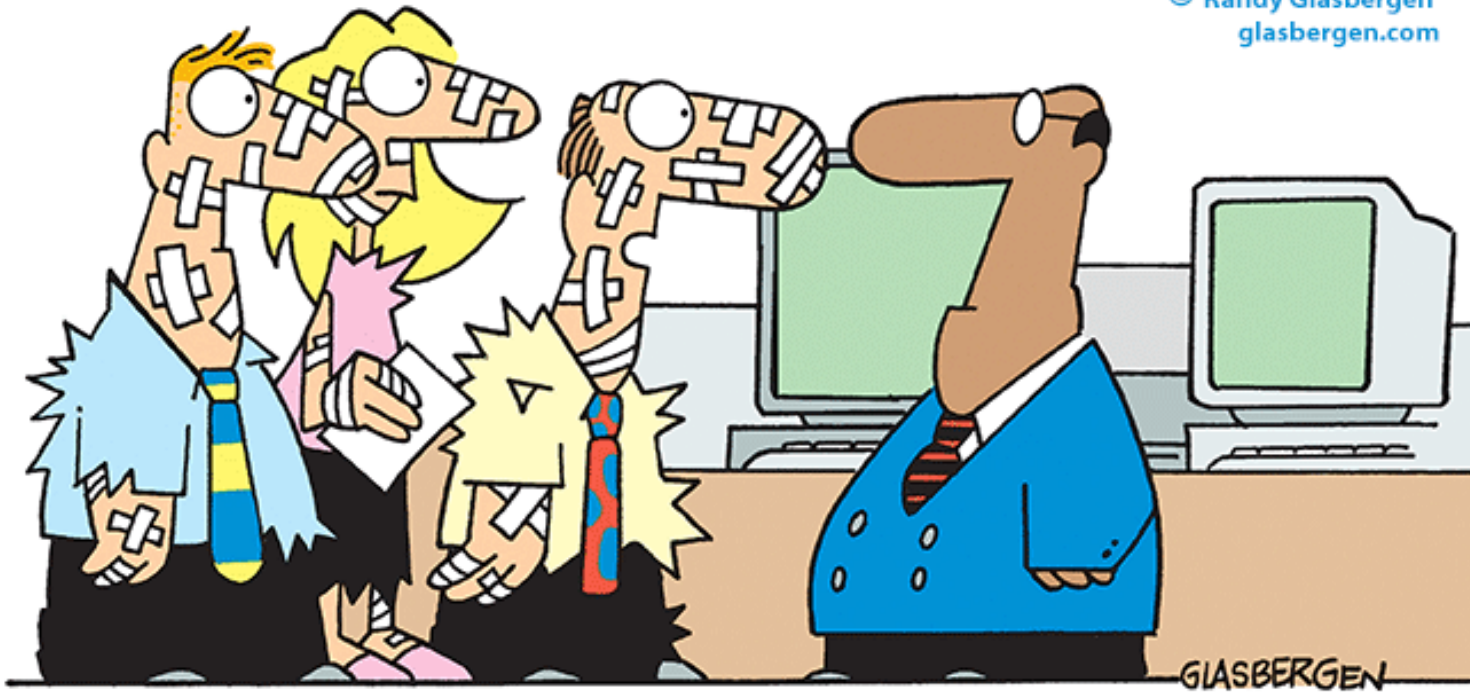


Collect input from patients on endpoints and feasibility



Identify other expertise needed and work with a CTU

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glasbergen.com



**“Frankly sir, we’re tired of being on the cutting edge of technology.”**



eunethta  
EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT



**INAHTA**