Universitair Ziekenhuis Gent

UNIVERSITEIT GENT

Integration of economic data in clinical trials

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BELGIUM

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
KCE

"Not enough patients for a Belgian Hadron Therapy Centre"

Hadrontherapie

KCE reports vol. 67A

Minister L. Onkelinx

- Eligible indications
- Number of potential patients and sessions
- Technical specifications
- ***Costs calculations, financing issues and health economic evaluations***
- Centre of preference: rational choice

CANCER PLAN

ACTION 30

(FINANCED BY THE FEDERAL PUBLIC SERVICE OF HEALTH, FOOD CHAIN SAFETY AND ENVIRONMENT)

Feasibility study of a Hadron Therapy Centre in Belgium

EXECUTED BY

THE BELGIAN HADRON THERAPY CENTRE (BHTC) FOUNDATION

IN COLLABORATION WITH

BELGIAN UNIVERSITIES, UNIVERSITY HOSPITALS, RESEARCH INSTITUTES, EXPERTS FROM THE BELGIAN SOCIETY OF PAEDIATRIC HEMATOLOGY AND ONCOLOGY

AND

INTERNATIONAL EXPERTS IN HADRON THERAPY

GUIDED BY THE CANCER PLAN UNIT

REVIEWED BY THE STEERING COMMITTEE OF ACTION 30

REPORT PHASE-I, REVISED VERSION - MAY 10TH, 2013

the evidence?

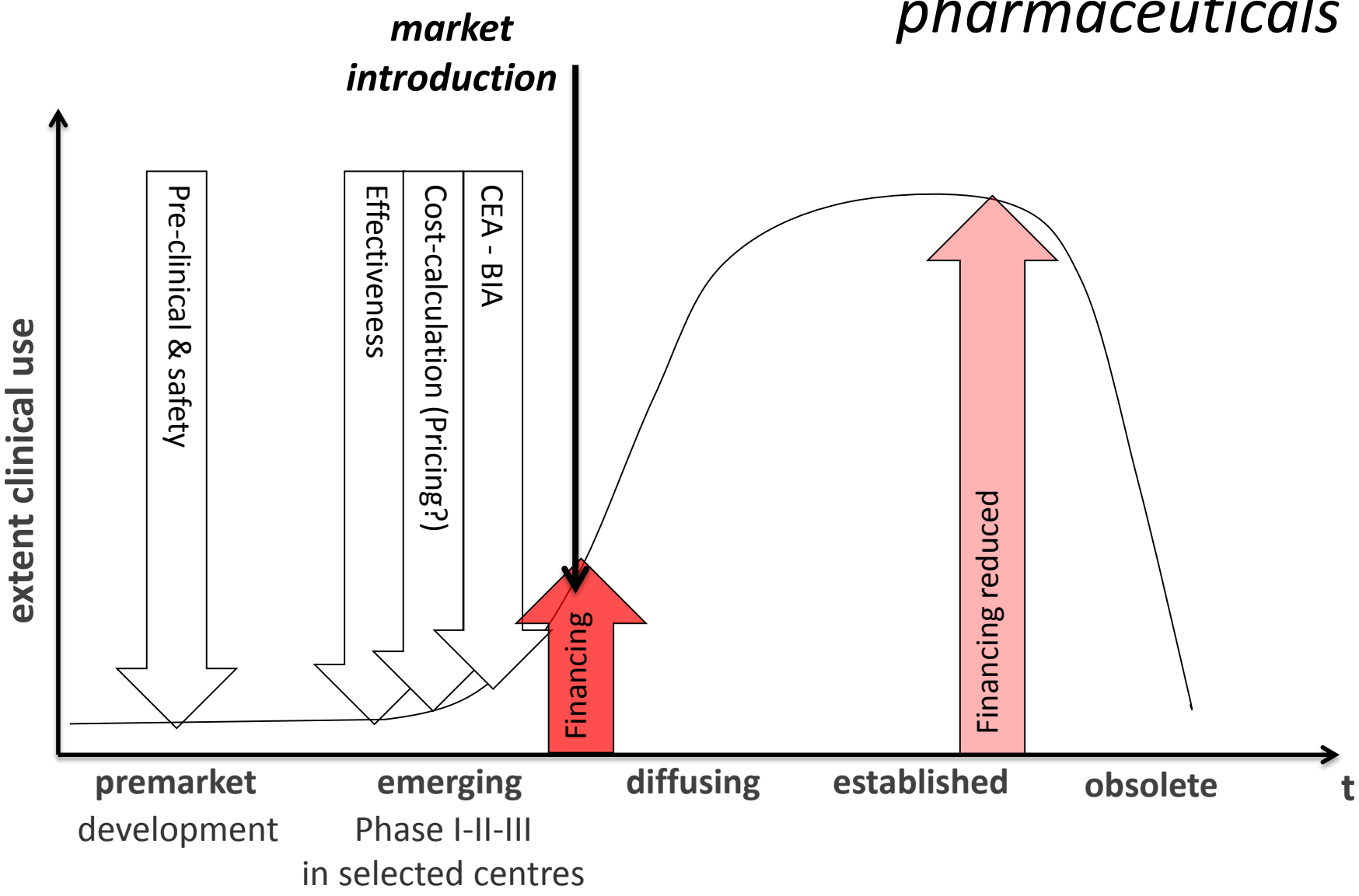
the cost?

the value for money?

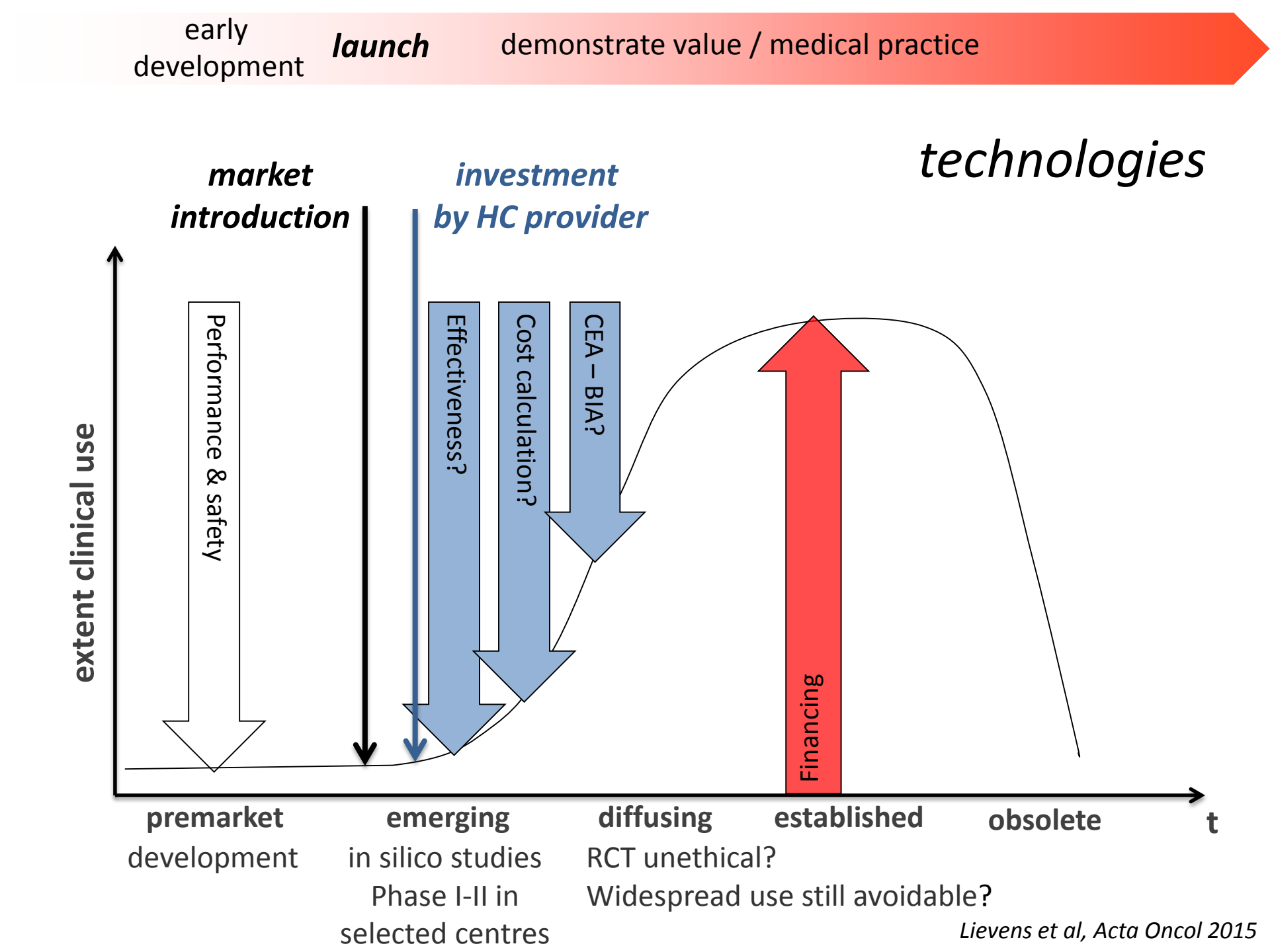
the budgetary impact?

early development | demonstrate value | ***launch*** | medical practice

pharmaceuticals

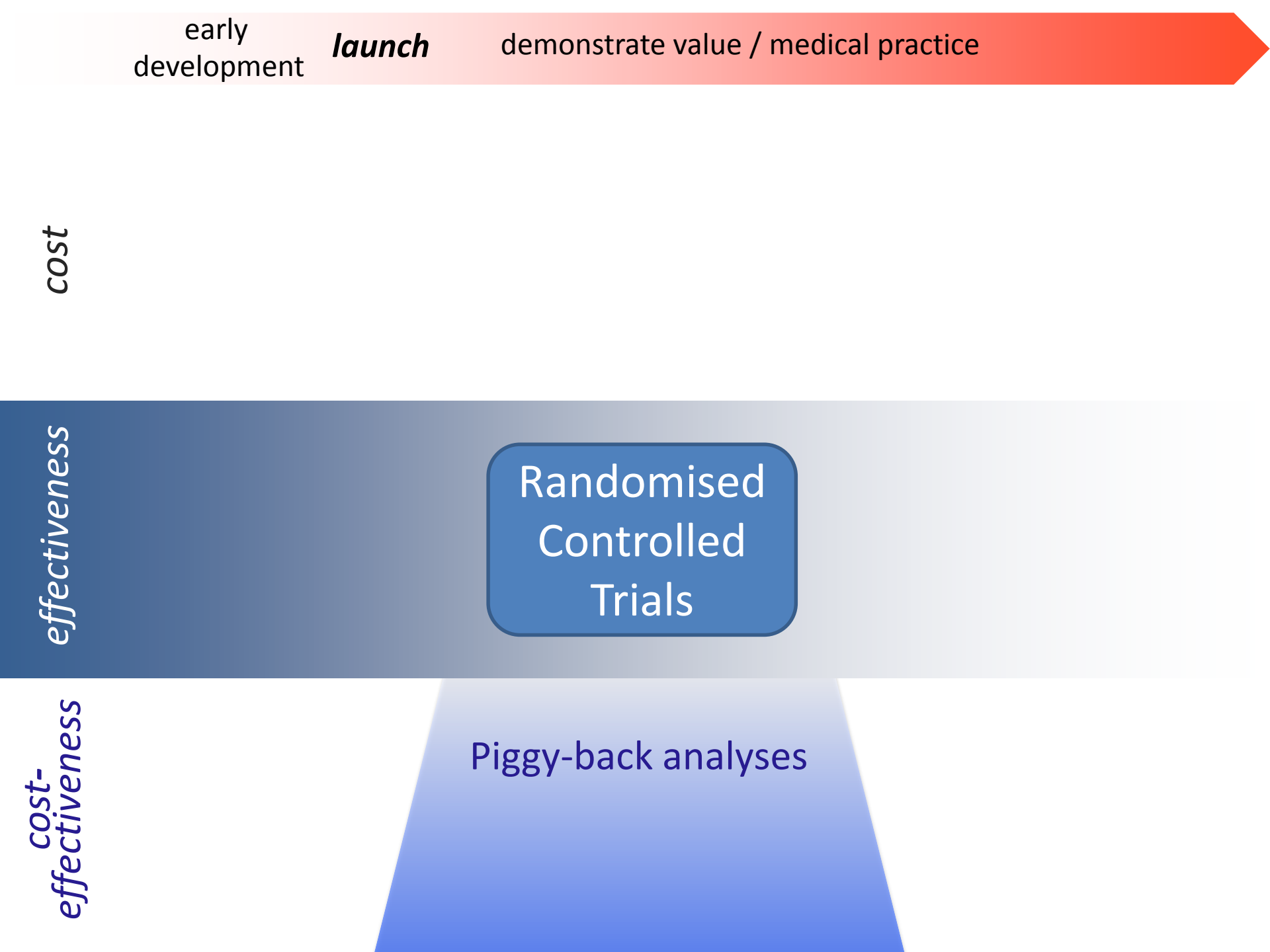


Lievens et al, Acta Oncol 2015



Lievens et al, Acta Oncol 2015

$$\text{cost-effectiveness} = \frac{\text{incremental cost}}{\text{incremental health gain}}$$


early development
launch
demonstrate value / medical practice
cost
effectiveness
Randomised Controlled Trials
cost-effectiveness
Piggy-back analyses

a piggy-back trial

is an economic analysis,
in most cases an economic evaluation study,
which is embedded in a clinical trial.
additional economic cost and outcome data are collected and analyzed,
but the trial itself is designed according to clinical issues.

Encyclopedia of Public Health – Wilhelm Kirch

ongoing trials on proton beam therapy

127 trials registered for proton beam therapy

- 70 trials recruiting
- 21 completed/terminated trials
  - 19 randomised controlled trials

5 trials health economic outcome data in secondary objectives

- 2 RCTs: cost-effectiveness
  - RTOG 1308: PBT vs IMRT in inoperable NSCLC
  - UPenn PARTIQoL: PBT vs IMRT in low/intermediate risk prostate Ca
- 3 nonRCTs: measure utilisation of health services
  - 3 studies by MGH: 2 in pancreatic Ca, 1 in anal Ca

http:// clinicaltrials.gov – assessed 02/2016

clinical trialist's view 	health economist's view 
Purpose = Authorisation	Purpose = Reimbursement
Controlled environment	Real life environment
Strict protocol instructions *Protocol induced resource use* *Protocol induced findings*	"Do what you normally do" *Real resource use* *Real findings*
Exclude confounders *Avoid co-morbidities* *Avoid elderly*	Only exclude if contra-indicated *Include co-morbidities* *Include elderly*
Limited time	Time to include all relevant costs and outcomes
Drop-outs not analysed	Drop-outs crucial
Efficacy (often intermediate endpoint)	**Effectiveness → cost-effectiveness**
Compared to placebo or "golden standard"	Compared to relevant practice ("the most likely to be replaced")

Courtesy L. Annemans

Table I Core recommendations for conducting economic analyses alongside clinical trials

Trial design

Trial design should reflect effectiveness rather than efficacy when possible.
Full follow-up of all patients is encouraged.
Describe power and ability to test hypotheses, given the trial sample size.
Clinical end points used in economic evaluations should be disaggregated.
Direct measures of outcome are preferred to use of intermediate end points.

Data elements

Obtain information to derive health state utilities directly from the study population.
Collect all resources that may substantially influence overall costs; these include those related and unrelated to the intervention.

Database design and management

Collection and management of the economic data should be fully integrated into the clinical data.
Consent forms should include wording permitting the collection of economic data, particularly when it will be gathered from third-party databases and may include pre- and/or post-trial records.

Analysis

The analysis of economic measures should be guided by a data analysis plan and hypotheses that are drafted prior to the onset of the study.
All cost-effectiveness analyses should include the following: an intention-to-treat analysis; common time horizon(s) for accumulating costs and outcomes; a within-trial assessment of costs and outcomes; an assessment of uncertainty; a common discount rate applied to future costs and outcomes; an accounting for missing and/or censored data
Incremental costs and outcomes should be measured as differences in arithmetic means, with statistical testing accounting for issues specific to these data (e.g., skewness, mass at zero, censoring, construction of QALYs).
Imputation is desirable if there is a substantial amount of missing data. Censoring, if present, should also be addressed.
One or more summary measures should be used to characterize the relative value of the intervention.
Examples include ratio measures, difference measures, and probability measures (e.g., cost-effectiveness acceptability curves).
Uncertainty should be characterized. Account for uncertainty that stems from sampling, fixed parameters such as unit costs and the discount rate, and methods to address missing data.
Threats to external validity—including protocol-driven resource use, unrepresentative recruiting centers, restrictive inclusion and exclusion criteria, and artificially enhanced compliance—are best addressed at the design phase.
Multinational trials require special consideration to address intercountry differences in population characteristics and treatment patterns.
When models are used to estimate costs and outcomes beyond the time horizon of the trial, good modeling practices should be followed. Models should reflect the expected duration of the intervention on costs and outcomes.
Subgroup analyses based on prespecified clinical and economic interactions, when found to be significant ex post, are appropriate. Ad hoc subgroup analysis is discouraged.

Reporting the results

Minimum reporting standards for cost-effectiveness analyses should be adhered to for those conducted alongside clinical trials.
The cost-effectiveness report should include a general description of the clinical trial and key clinical findings.
Reporting should distinguish economic data collected as part of the trial vs. data not collected as part of the trial.
The amount of missing data should be reported. If imputation methods are used, the method should be described.
Methods used to construct and compare costs and outcomes, and to project costs and outcomes beyond the trial period should be described.
The results section should include summaries of resource use, costs, and outcome measures, including point estimates and measures of uncertainty. Results should be reported for the time horizon of the trial, and for projections beyond the trial (if conducted).
Graphical displays are recommended for results not easily reported in tabular form (e.g., cost-effectiveness acceptability curves, joint density of incremental costs and outcomes).

Ramsey et al. Value in Health 2005
The ISPOR RCT-CEA Task Force Report

EDITORIALS

Clinical Trials Provide Essential Evidence, but Rarely Offer a Vehicle for Cost-Effectiveness Analysis

How often are the characteristics in a RCT consistent with the key criteria for evidence-based decision making?

Limited external validity !

Sculpher M. Value in Health 2015

need for additional modeling

additional assumptions & sensitivity analysis

→ to compare all relevant options

→ to incorporate all appropriate evidence

→ to translate intermediate endpoints into final consequences

→ to extrapolate over the appropriate time horizon

→ to generalize to other settings or populations

A Systematic Review of the Cost and Cost-Effectiveness Studies of Proton Radiotherapy

Vivek Verma MD[1]; Mark V. Mishra MD[2]; and Minesh P. Mehta MBChB[2]

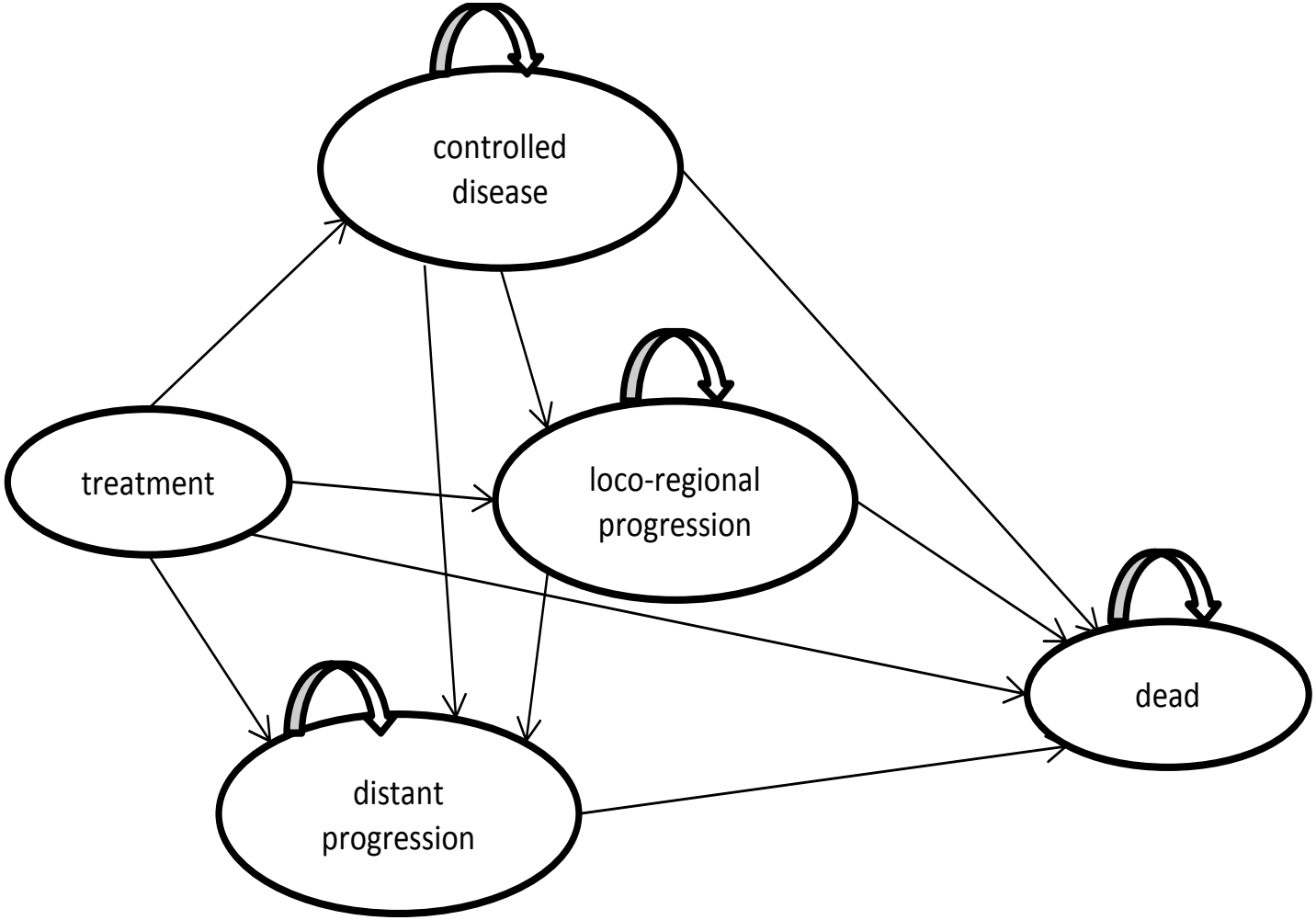
BACKGROUND: Economic analyses of new technologies, such as proton-beam radiotherapy (PBT), are a public health priority. To date, no systematic review of the cost-effectiveness of PBT has been performed. **METHODS:** Systematic searches of PubMed, EMBASE, abstracts from American Society for Radiation Oncology and American Society of Clinical Oncology meetings, and the Cost-Effectiveness Analysis Registry were conducted (2000-2015) along with abstracts from the Particle Therapy Co-Operative Group of North America for both years of existence (2014-2015). Eighteen original investigations were analyzed. **RESULTS:** The cost-effectiveness for prostate cancer—the single most common diagnosis currently treated with PBT—was suboptimal. PBT was the most cost-effective option for several pediatric brain tumors. PBT costs for breast cancer were increased but were favorable for appropriately selected patients with left-sided cancers at high risk of cardiac toxicity and compared with brachytherapy for accelerated partial breast irradiation. For non-small cell lung cancer (NSCLC), the greatest cost-effectiveness benefits using PBT were observed for locoregionally advanced—but not early stage—tumors. PBT offered superior cost-effectiveness in selected head/neck cancer patients at higher risk of acute mucosal toxicities. Similar cost-effectiveness was observed for PBT, enucleation, and plaque brachytherapy in patients with uveal melanoma. **CONCLUSIONS:** With greatly limited amounts of data, PBT offers promising cost-effectiveness for pediatric brain tumors, well-selected breast cancers, locoregionally advanced NSCLC, and high-risk head/neck cancers. Heretofore, it has not been demonstrated that PBT is cost-effective for prostate cancer or early stage NSCLC. Careful patient selection is absolutely critical to assess cost-effectiveness. Together with increasing PBT availability, clinical trial evidence, and ongoing major technological improvements, cost-effectiveness data and conclusions from this analysis could change rapidly. ***Cancer* 2016;000:000–000.** © *2016 American Cancer Society.*

KEYWORDS: cost-effectiveness, health care economics, operational costs, proton radiation therapy.

Verma et al, Cancer 2016

Markov modeling

Cost-effectiveness of PBT vs 3D-CRT or IMRT



Verhaeghe et al. Submitted

Table 1: Standard and PBT treatments: transition probabilities per 3-month Markov cycle

Transition	Probability	Source
Chemotherapy + 3D-CRT		
treatment→locoregional progression	0.057058	[5]
treatment→distant progression	0.105464	[5]
treatment→dead	0.050991	Adjusted from [5,13,16]
controlled disease→locoregional progression	0.057058	[5].
controlled disease→distant progression	0.105464	[5]
controlled disease→dead	0.016572	Adjusted from [13]
locoregional progression→distant progression	0.210927	Adjusted for model calibration
locoregional progression→dead	0.259917	[14]
distant progression→dead	0.259917	[14]
Chemotherapy + IMRT		
treatment→locoregional progression	0.057058	[5]
treatment→distant progression	0.105464	[5]
treatment→dead	0.050991	Adjusted from [5,13,16]
controlled disease→locoregional progression	0.057058	[5]
controlled disease→distant progression	0.105464	[5]
controlled disease→dead	0.013895	Adjusted from [13]
locoregional progression→distant progression	0.210927	Adjusted for model calibration
locoregional progression→dead	0.217931	Adjusted from [14]
distant progression→dead	0.217931	Adjusted from [14]
Chemotherapy + PBT		
treatment→locoregional progression	0.012944	[15]
treatment→distant progression	0.074327	[15]
treatment→dead	0.050991	Adjusted from [5,13,16]
controlled disease→locoregional progression	0.012944	[15]
controlled disease→distant progression	0.074327	[15]
controlled disease→dead	0.013003	Adjusted from [13]
locoregional progression→distant progression	0.148653	Adjusted for model calibration
locoregional progression→dead	0.217931	Adjusted from [14]
distant progression→dead	0.217931	Adjusted from [14]

3D-CRT, Three-dimensional conformal photon radiotherapy; IMRT, intensity-modulated photon radiotherapy; PBT, proton-beam therapy

Verhaeghe et al. Submitted

Table 2: Treatment-induced toxicity, health utilities and costs in the Markov model.

Variable	Input value	Source
Treatment-induced toxicity (%)		
3D-CRT		
esophagitis	31.6	[8,18]
pneumonitis	30.0	[8,18]
fibrosis	8.3	[8,18]
IMRT		
esophagitis	31.6	[8,17]
pneumonitis	9.0	[8,17]
fibrosis	7.6	[8,17]
PBT		
esophagitis	5.0	[6,8]
pneumonitis	2.0	[6,8]
fibrosis	4.5	[6,8]
Health utilities		
treatment	0.58	[19]
controlled disease	0.63	[19]
loco-regional progression	0.46	[14]
distant progression	0.46	[14]
acute pneumonitis grade ≥3	0.46	[20]
acute esophagitis grade ≥3	0.46	[20]
dyspnoea grade ≥3	0.46	[20]
dead	0	
Costs (€)		
treatment costs		
3D-CRT	6,177	[23]
IMRT	7,699	[22]
PBT	28,399	[22]
toxicity costs/cycle		
esophagitis		[20,24]
3D-CRT	451	
IMRT	451	
PBT	71	
pneumonitis		[20,24]
3D-CRT	1,361	
IMRT	408	
PBT	91	
fibrosis		[20,24]
3D-CRT	26	
IMRT	24	
PBT	14	
follow-up cost/cycle	192	[25]
progression cost/cycle	10,628	[26]

3D-CRT, Three-dimensional conformal photon radiotherapy; IMRT, intensity-modulated photon radiotherapy; PBT, proton-beam therapy

Verhaeghe et al. Submitted

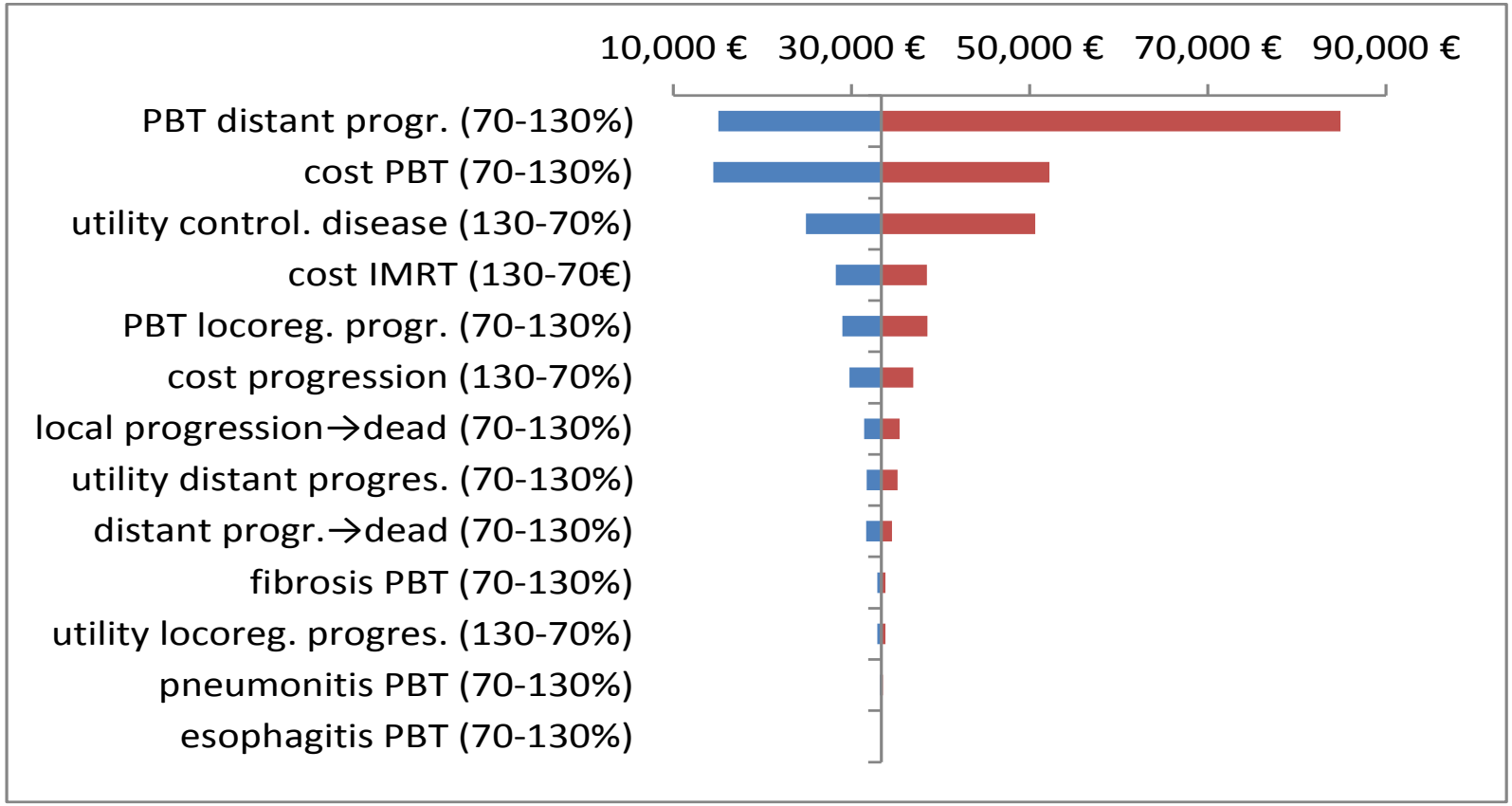
base case incremental cost-effectiveness ratio (ICER)

36,602€/QALY for PBT vs. 3D-CRT

33,379€/QALY for PBT vs. IMRT

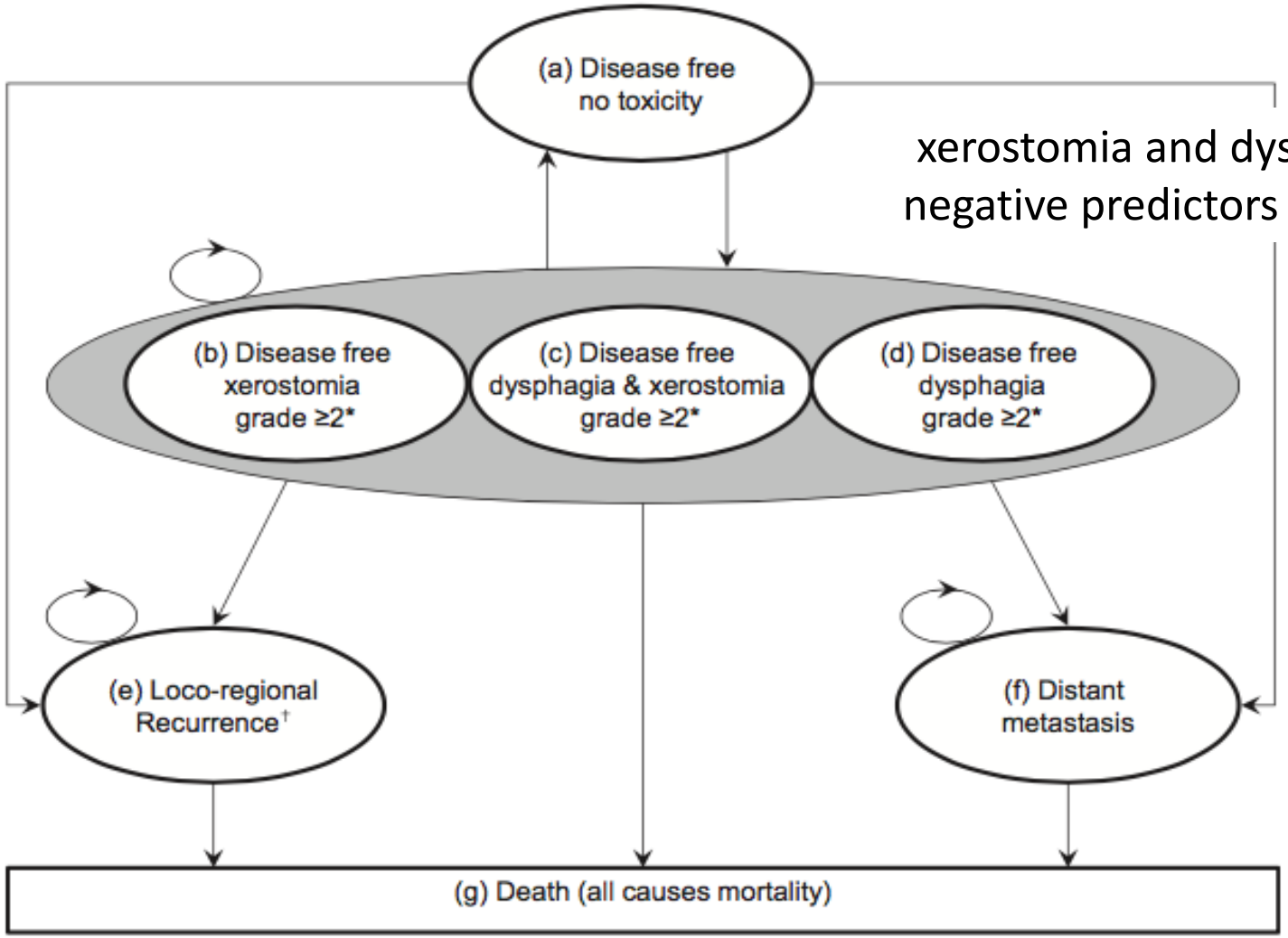
Belgian Health Care context!

sensitivity analysis for PBT vs. IMRT



Verhaeghe et al. Submitted

Normal Tissue Complication Probability models and comparative planning studies



xerostomia and dysphagia:
negative predictors of utility

Ramaekers et al. IJROBP 2013

Table 1 Method to calculate toxicity for the *IMPT if efficient* strategy: Illustrated for xerostomia 6 months after radiation therapy

Patient	Probability of xerostomia (%)		ICER	Preferred	Probability of xerostomia (%)
	IMPT	IMRT	IMPT vs IMRT (€)	IMPT/IMRT	*IMPT if efficient**
1	25.5	41.3	93,302	IMRT	41.3
2	18.9	36.6	169,448	IMRT	36.6
3	23.6	55.2	44,358	IMPT	23.6
4	26.7	37.2	150,041	IMRT	37.2
↓	↓	↓	↓	↓	↓
25	25.8	45.1	89,593	IMRT	45.1
Mean probability of xerostomia for the IMPT if efficient strategy					37.1%

Abbreviations: ICER = incremental cost-effectiveness ratio; IMPT = intensity modulated proton radiation therapy; IMRT = intensity modulated radiation therapy with photons.

* Patients will only receive IMPT in this scenario if IMPT is expected to be cost-effective compared with IMRT (grey fields), thus if the ICER is below the threshold of 80,000 per QALY gained.

Table 2 Base case results of the cost-effectiveness analyses (sorted by QALY)

Treatment strategy	Expected outcomes (95% CI*)		Comparator	Increments (95% CI*)		ICER
	QALY/DTFLY†	Costs (€)		Incremental QALY/DTFLY†	Incremental costs (€)	€ per QALY/DTFLY†
IMRT for all patients	6.520 (5.781 to 7.018)	41,038 (38,878 to 44,158)				
IMPT if efficient	6.563 (5.818 to 7.059)	43,650 (41,523 to 46,949)	IMRT for all patients	0.043 (0.014 to 0.073)	2612 (2008 to 3306)	60,278
IMPT for all patients	6.620 (5.869 to 7.115)	50,989 (48,227 to 54,852)	IMPT if efficient	0.057 (0.016 to 0.102)	7339 (6001 to 8744)	127,946

Ramaekers et al. IJROPB 2013

there is no “perfect” CE analysis!

→ Unavoidable assortment of assumptions: outcomes, QoL, costs

→ Impossible to incorporate all relevant evidence, options, events

→ Limited amount of prospectively-collected data

→ Insufficient capture of evolving technology

→ Various time points

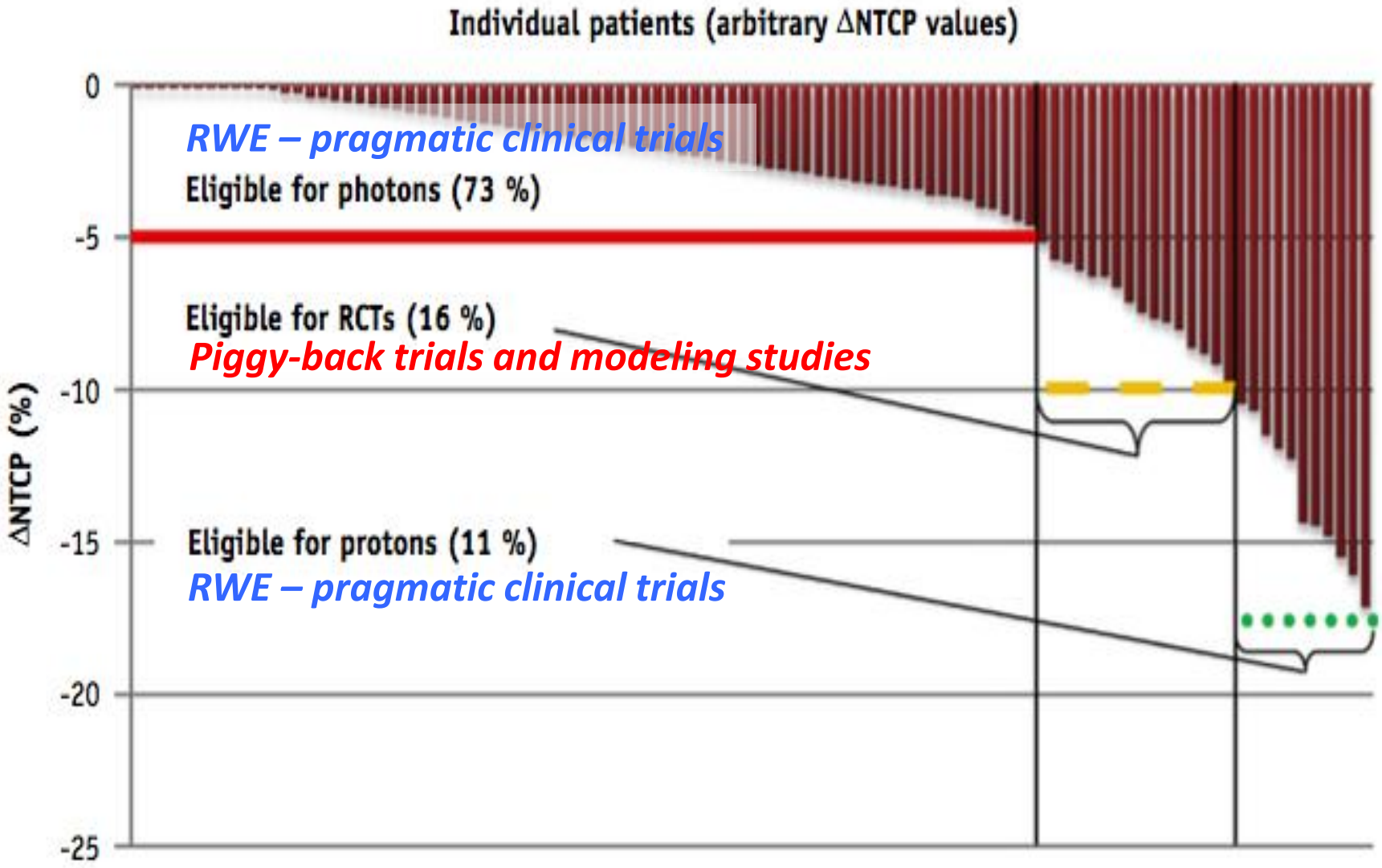
→ Various economic environments

critically evaluate the scope of included variables in each study
practical applicability in own technical and economic environment

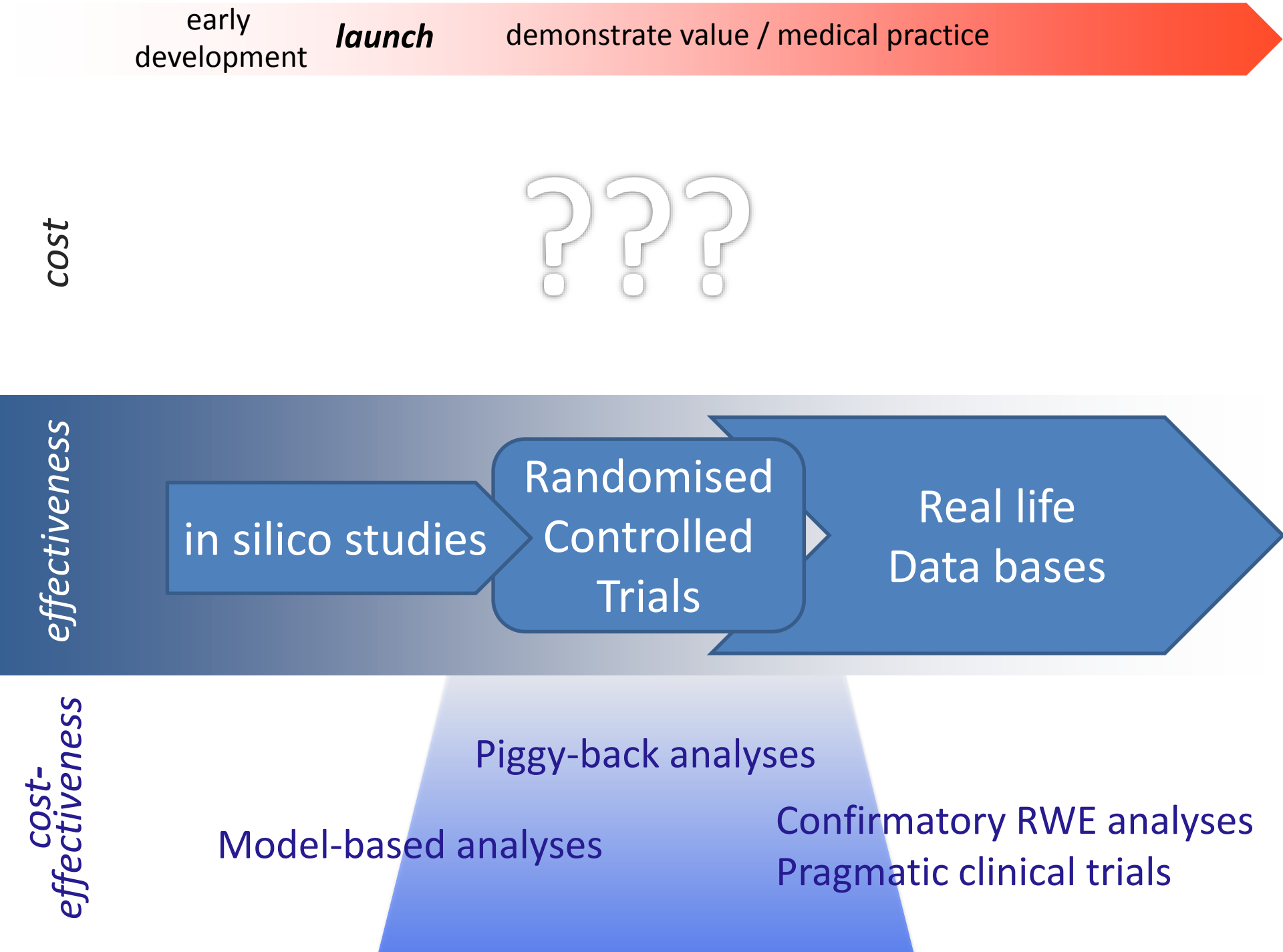
need for prospective real life evidence

What is real world evidence?

- Databases: cross-sectional & longitudinal, retro- & prospective
- Extensions and long-term follow-up of RCTs
- QoL questionnaires, surveys alongside RCTs
- Observational data from cohort studies
- Pragmatic clinical trials
- Patient chart reviews
- (Disease-specific) Patient Registries
- Population health data and surveys
- Administrative data
- Electronic health records
- Health care claims and costs
- Resource utilization data
- …



Widder et al, IJROBP 2016


early development
launch
demonstrate value / medical practice
cost
???
effectiveness
in silico studies
Randomised Controlled Trials
Real life Data bases
cost-effectiveness
Piggy-back analyses
Model-based analyses
Confirmatory RWE analyses
Pragmatic clinical trials

How to Solve The Cost Crisis In Health Care

The biggest problem with health care isn't with insurance or politics. It's that we're measuring the wrong things the wrong way.

by Robert S. Kaplan and Michael E. Porter

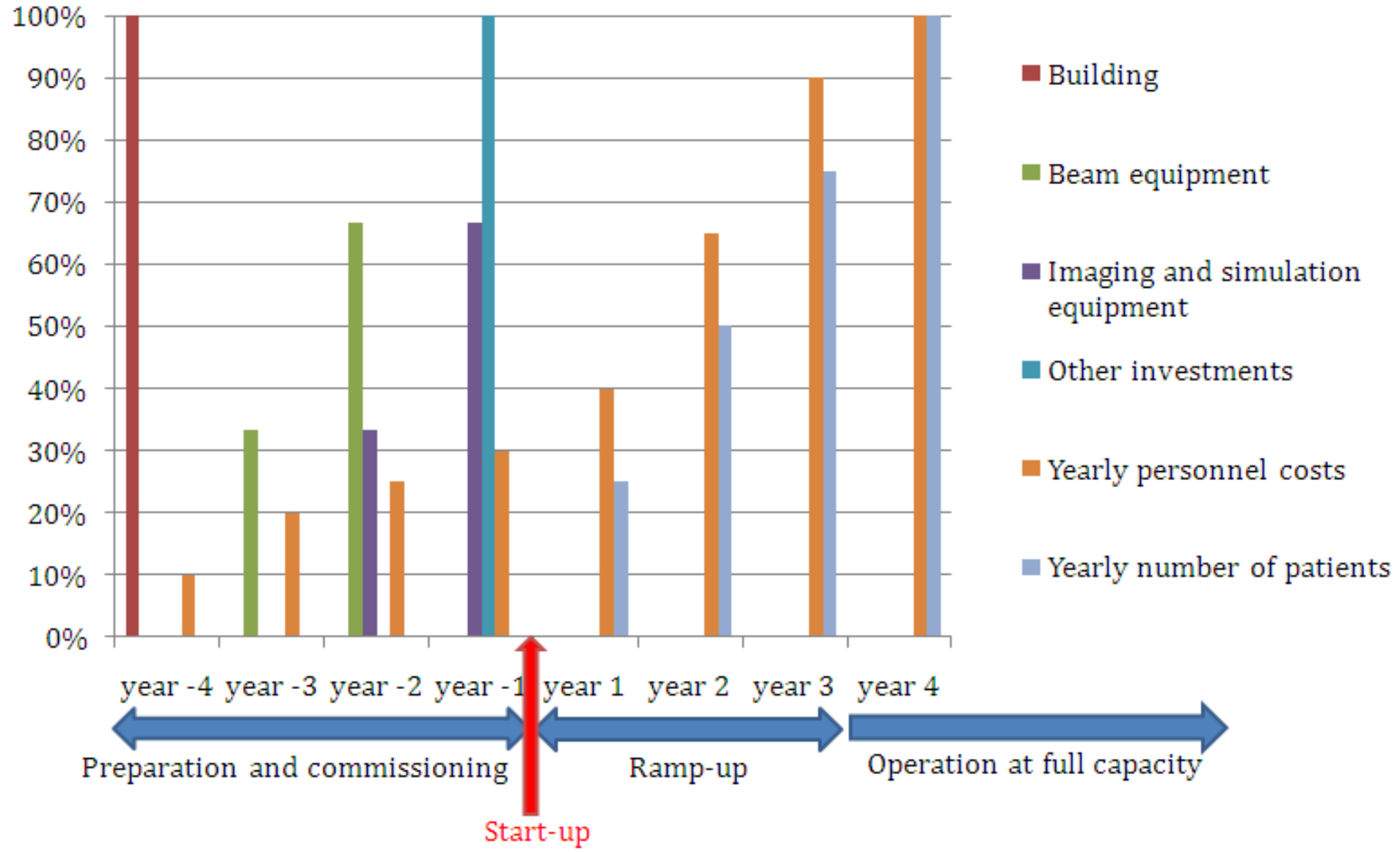
accurately measure costs and compare them with outcomes
charges are not a good surrogate for provider costs

Kaplan and Porter, Harvard Business Review 2011

TABLE 1. Overview of Costing Methods Available to US Researchers

Method	Description of Method	Advantage	Disadvantage	Issues for Concern
Microcosting	Enumerate staff time, supplies, and items used to provide a specific service and estimate their cost.	Accurate, often needed to find a cost of a service intervention.	Method is labor intensive and not useful for finding overhead cost. It cannot be used to find total health care cost.	Need to include all costs: nonwage labor cost, person-level and institutional overhead, cost of development, set-up, screening, supplies, and space.
Activity-based cost allocation system.	Multistep cost allocation system. Assign cost of staff time, supplies, and equipment to production departments. Distribute overhead. Use relative values to find cost of specific products and assign cost to specific stays or encounters.	The best available estimate of economic costs of health services.	Used by relatively few hospitals, data may not be available to the researcher. Costing system unlikely to capture costs of a novel intervention tested in a research study.	Quality must be evaluated. Cost estimates may not be generalizable.
Cost-adjusted charges or total reimbursement.	Billed charges are adjusted by the ratio of cost-to-charges in a hospital cost report.	Charges routinely created for most of US health care. Hospital cost reports are available from Medicare.	Requires strong assumptions that charge is proportional to economic cost. Charges difficult to obtain for care received at other sites. Difficult to use to cost ambulatory care.	Use of unadjusted charge. Exclusion of cost of physician services to inpatients. Exclusion of patient copayments and deductibles from reimbursement amount.
Gross costing	Quantities of different services are determined, and cost estimated using service specific unit cost.	Relative ease of implementation.	Strong assumptions about homogeneity of services.	Data on characteristics of service may be inadequate. Use of appropriate unit costs.

Barnett PG. Medical Care 2009



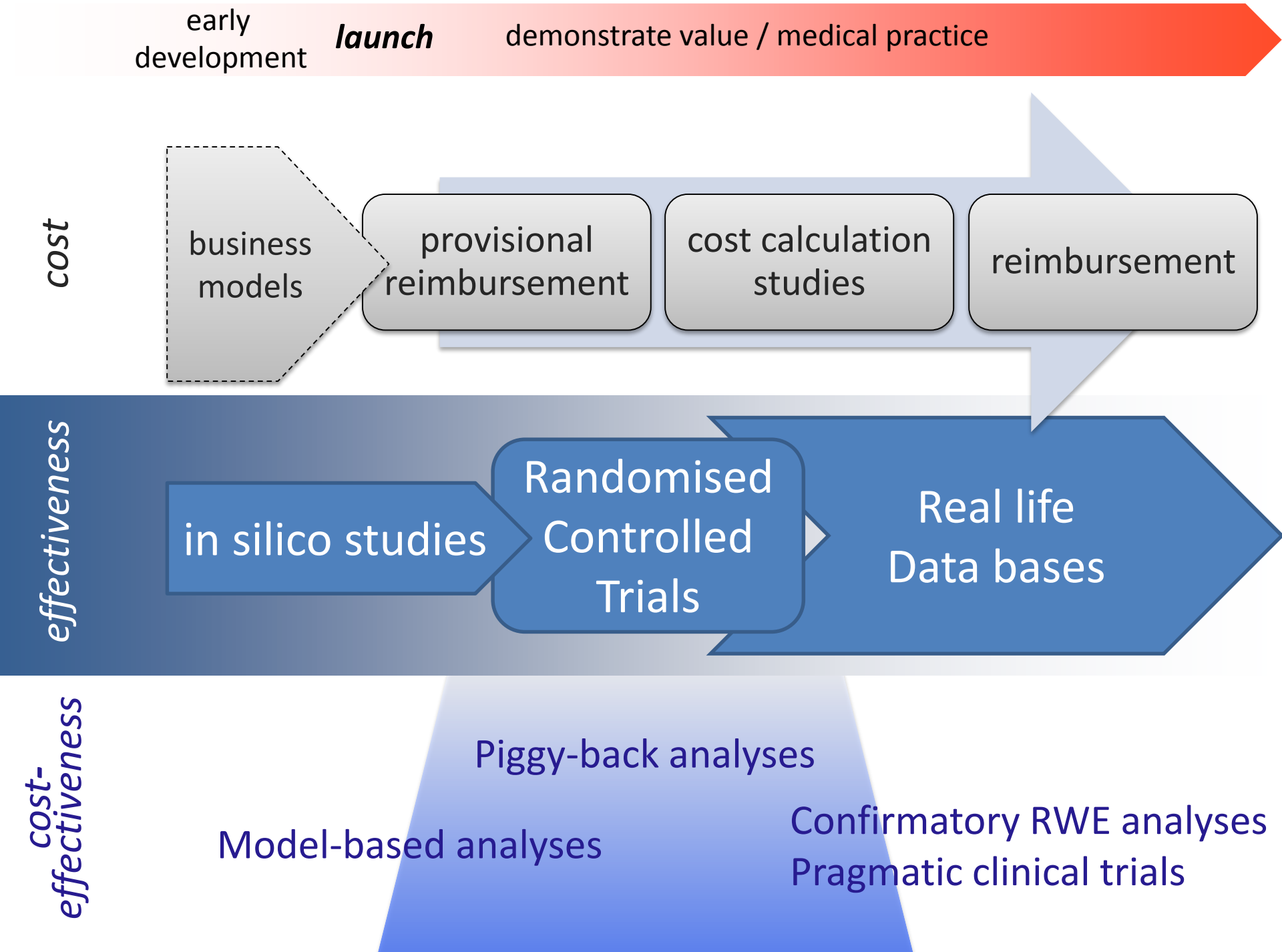
Vanderstraeten et al. IJROBP 2014

Table 2 Required reimbursement rates calculated with the BM for the different technical solutions and both financing methods

Type of technical solution and financing	Required reimbursement rate (€/patient)									
		SA total investment cost					SA total personnel cost	SA delay in commissioning and ramp-up		
	Baseline	−25%	+25%	+50%	+75%	+100%	−30%	1 y	2 y	3 y
CC										
Private financing	51,150	42,800	59,500	67,850	76,200	84,550	47,791	55,650	60,900	67,200
Public sponsoring	27,550	24,750	30,350	33,150	35,950	38,750	24,191	29,950	32,750	36,000
COC										
Private financing	32,400	27,400	37,400	42,400	47,400	52,400	30,040	35,250	38,600	42,500
Public sponsoring	18,400	16,750	20,050	21,700	23,350	25,000	16,040	19,950	21,800	23,950
POC										
Private financing	51,200	44,400	58,000	64,800	71,600	78,400	46,384	55,750	61,100	67,300
Public sponsoring	32,300	30,000	34,600	36,900	39,200	41,500	22,484	35,150	38,450	42,350

Abbreviations: BM = business model; SA = sensitivity analysis. Other abbreviations as in Table 1.

Vanderstraeten et al. IJROBP 2014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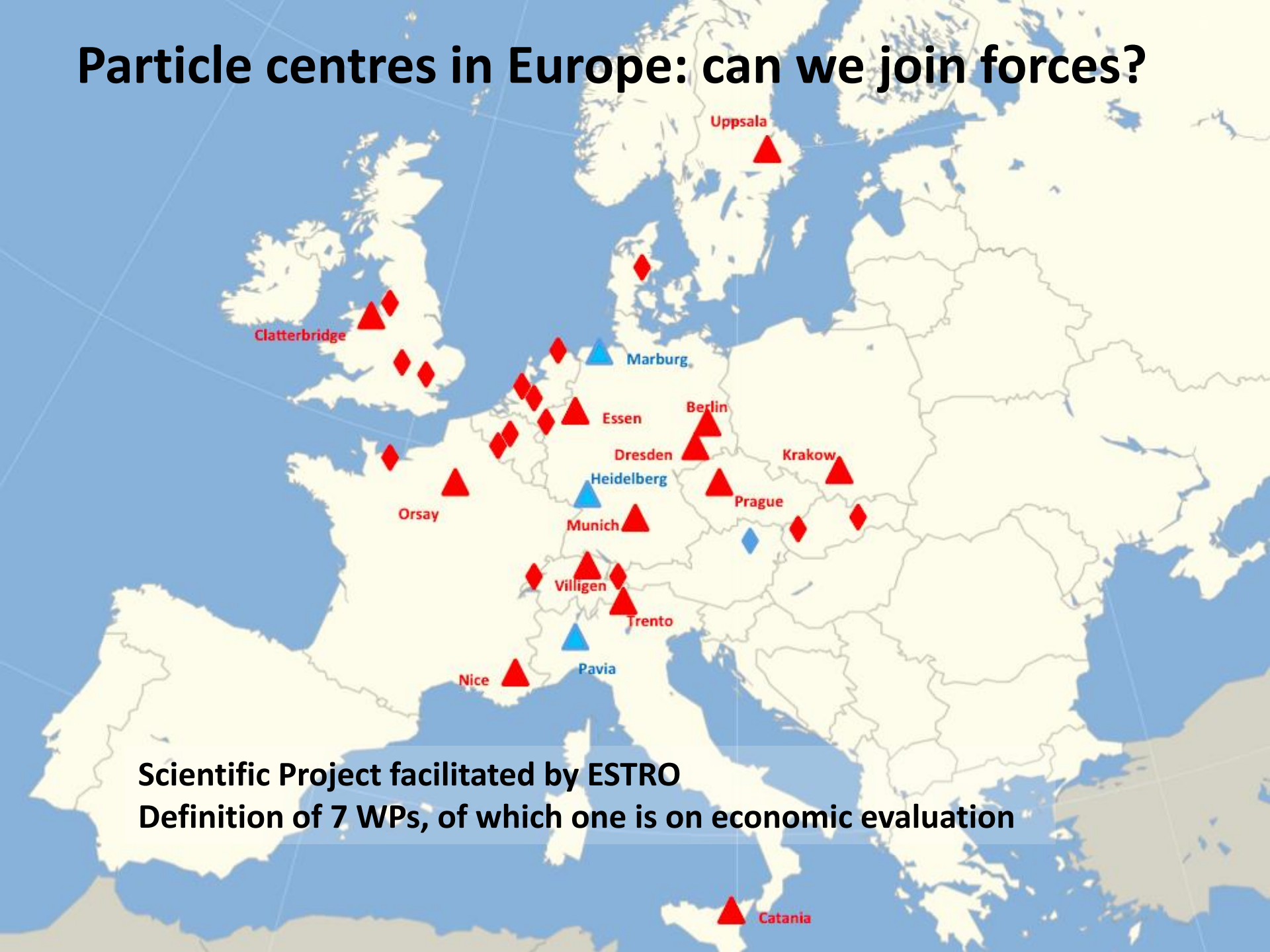
Particle centres in Europe: can we join forces?



Scientific Project facilitated by ESTRO
Definition of 7 WPs, of which one is on economic evaluation

Work Package 7 on Health Economics

Chairs: Klaus Nagels & Yolande Lievens

Project objectives

- Establish a research platform that allows for health economic assessment of particle therapy, including:
  - Cost calculation
  - Cost effectiveness
  - HTA
  - Comparative Effectiveness Research (CER)

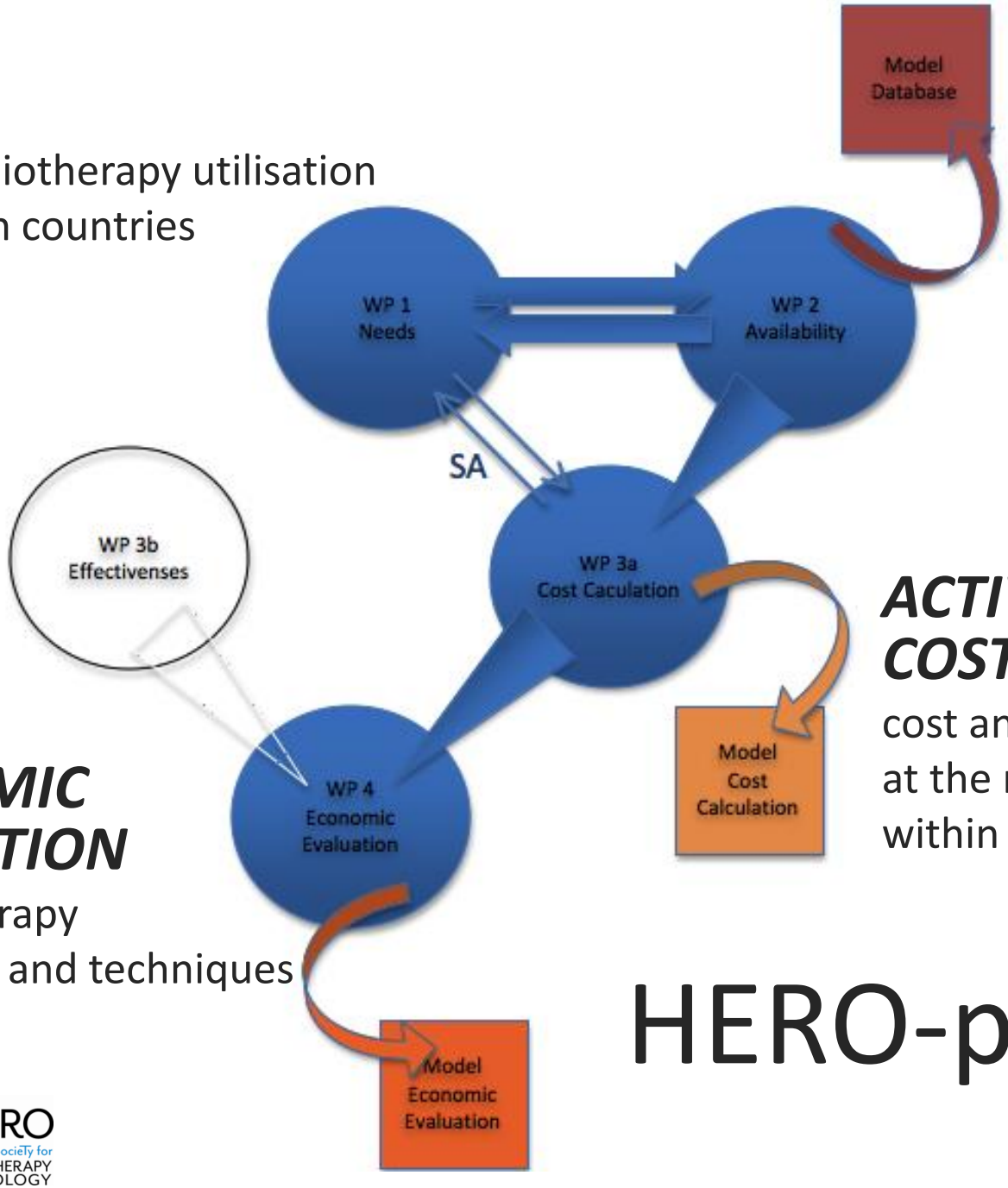
Build a health economic platform on a sound clinical and outcome-oriented database at a high evidence level

- Perform health economic assessment of particle therapy across Europe using the data provided by operational and non-operational centers

- Establish a research approach integrating clinical and health economic parameters that
  - aligns with existing knowledge and experience
  - can be used for other radiation modalities

NEEDS

optimal radiotherapy utilisation
in European countries



AVAILABILITY

equipment & staffing
guidelines
reimbursement
in Europe

ACTIVITY-BASED COSTING

cost and productivity
at the national level
within European countries

ECONOMIC EVALUATION

of radiotherapy
treatments and techniques
in Europe

HERO-project

ESTRO
European Society for
RADIOTHERAPY
& ONCOLOGY

Lievens & Grau. R&O 2012

There is a dearth of evidence in particle therapy.

More prospective data are urgently needed, clinical as well as economical.

There is more than one approach to economical evaluation, the methodology used should be streamlined with the clinical evidence generation.

Particle therapy is here to stay.
If we want to guarantee its long-term sustainability, it's our responsibility to create evidence.
We should not loose the momentum!

thank you for your attention !

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