How real-world data compensate for scarce evidence in HTA

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NICE

Outline of presentation

- Very brief introduction to NICE
- Value Assessment at NICE
- Use of real world data in Technology Appraisals
- 3 Examples
- Thoughts about the future

What does NICE do?

Guiding quality in health and social care

- London and Manchester
- > 600 staff, operate as network
- 1999: set up to reduce variation in the availability and quality of NHS treatments
- 2005: merged with the Health Development Agency, developing public health guidance.
- 2013: established in primary legislation, placing NICE on a solid statutory footing as set out in the Health and Social Care Act 2012; responsibility for developing guidance and quality standards in social care

What does NICE do? (cont.)

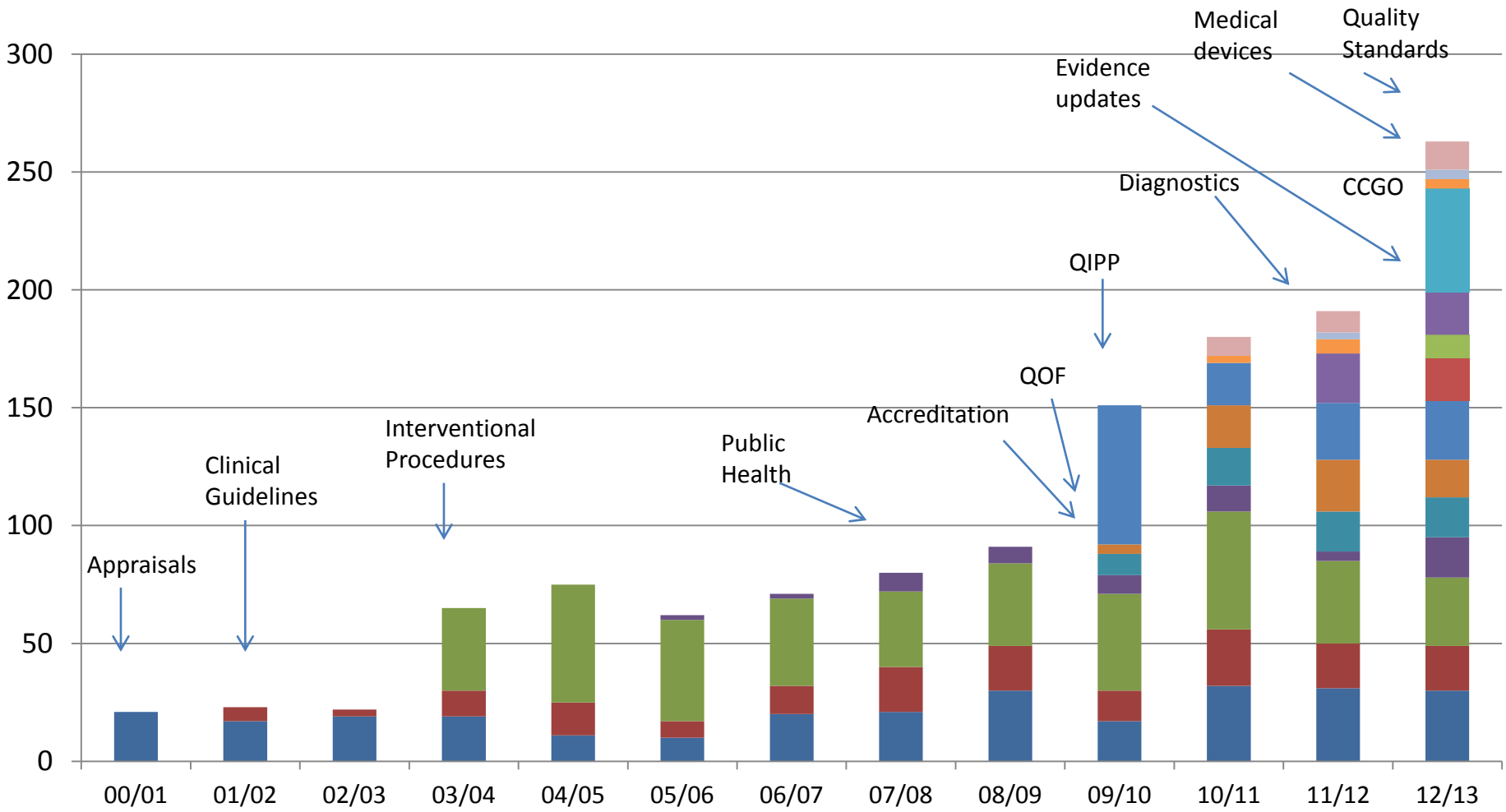
Produce **evidence based guidance** and advice for health, public health and social care practitioners.

- Health technologies (drugs, med tech, interventional procedures)
- Clinical guidelines
- Public health guidance
- Social care guidance

Develop **quality standards** and performance metrics for those providing and commissioning health, public health and social care services.

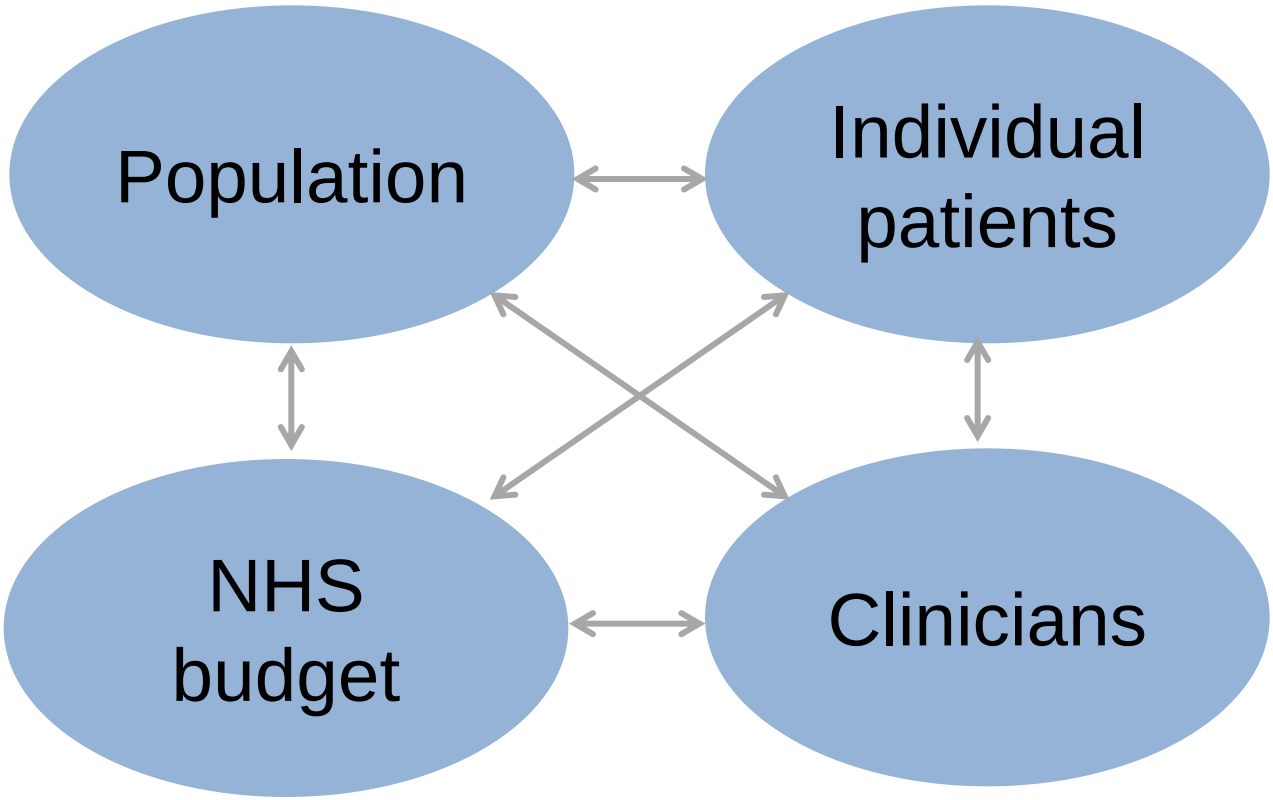
Provide a range of **informational services** for commissioners, practitioners and managers across the spectrum of health and social care.

NICE products by year



Value Assessment

Value of healthcare - for whom?



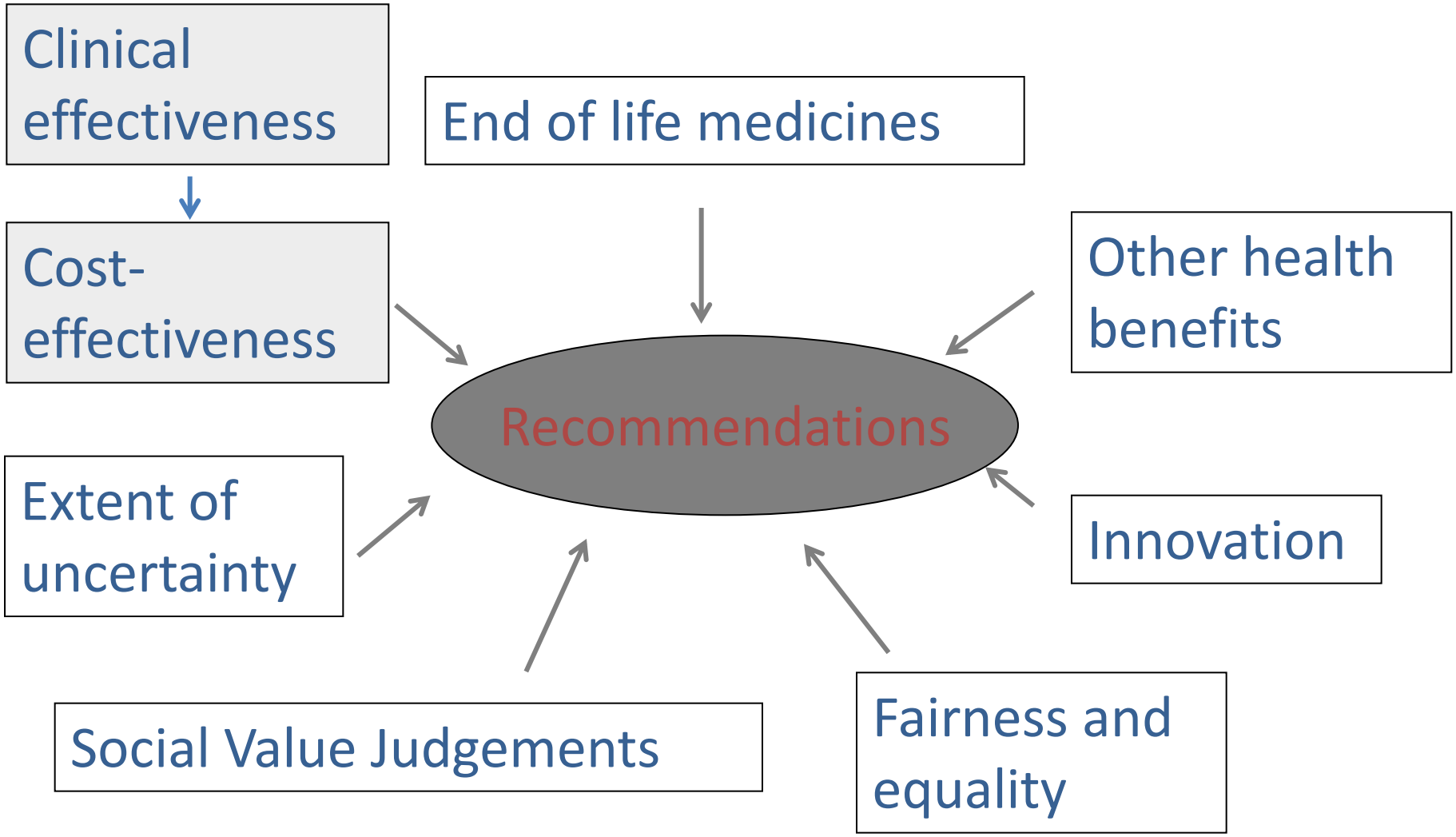
Definition of value at NICE
→ through opportunity cost

- Health benefit displaced elsewhere in the NHS if a new technology is adopted
- i.e. what the NHS pays on average to generate health benefit (a QALY gained)

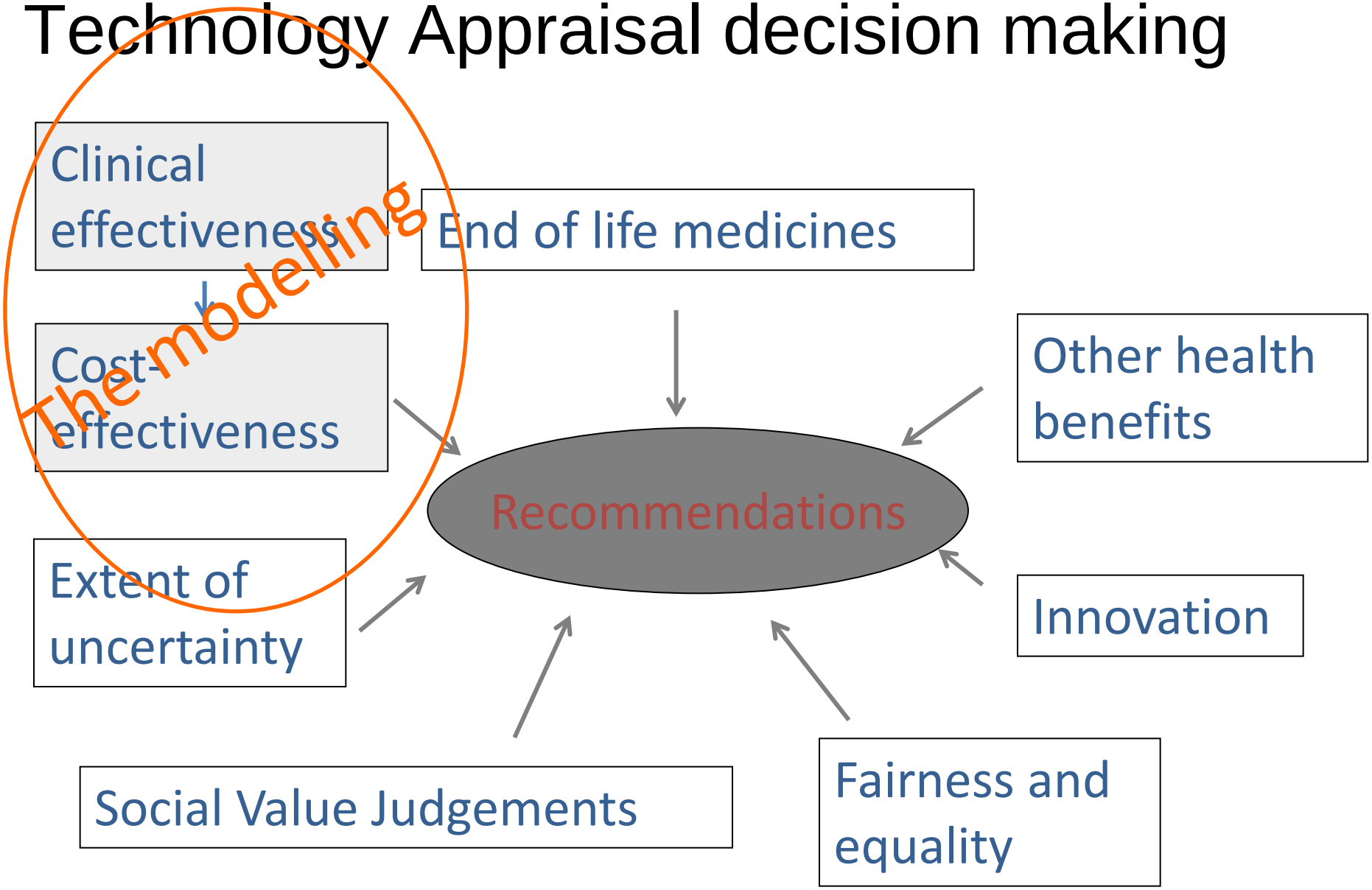
  = maximum acceptable cost per QALY gained
  (£20,000-30,000 per QALY gained)


NHS

Technology Appraisal decision making



Technology Appraisal decision making



The modelling

- Disease modelling → cost effectiveness modelling
- How well does the drug work in relation to how much it costs compared to standard practice in the NHS ?

$$\frac{\text{cost}_{new} - \text{cost}_{current}}{\text{Health benefit}_{new} - \text{health benefit}_{current}}$$

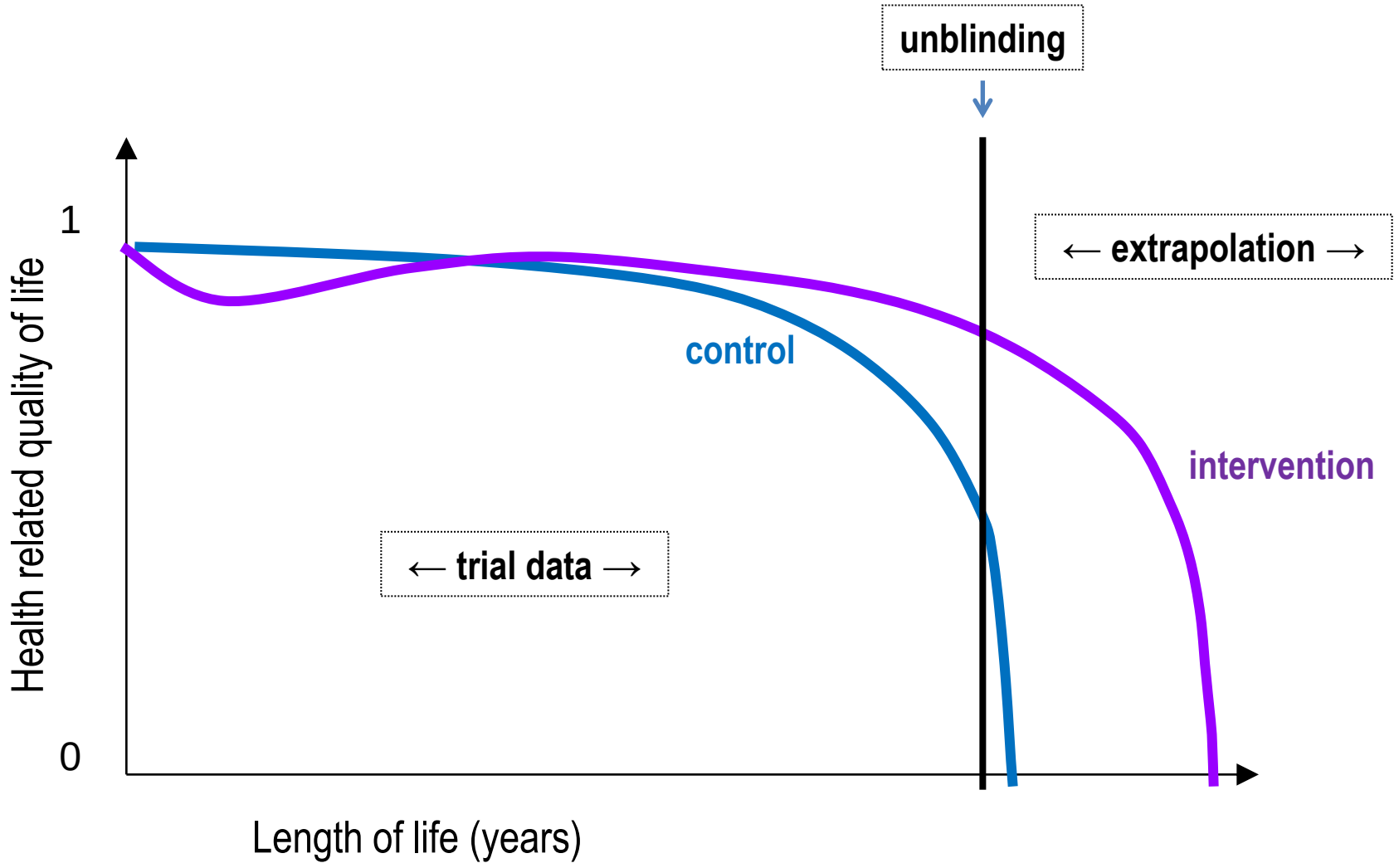
- QALYs → length of life x quality of life index
- Enables consistency and fairness across all decisions for all therapeutic areas
- Cost per QALY gained (=cost utility analysis)

Clinical parameters required for modelling

- Clinical effect sizes, adverse events and complications
- Baseline clinical data
- Epidemiology/ natural history of disease
- Quality of life data
- Compliance/ adherence data
- Extrapolation
  - beyond trial period
  - of intermediate/ surrogate to final outcomes
  - of trial results to relevant settings, for example by incorporating country-specific data

Cooper et al 2005

Example for a cancer drug



Health related quality of life

- The EQ-5D is the preferred measure of HRQL in adults
- Changes in HRQL should be reported directly from patients
- Value of changes in patients' HRQL should be based on preferences expressed by the public

➢ Often included in clinical trials, but not necessarily used!

NICE methods guide

Resource use/ costs parameters required for modelling

- Resource use in trials is protocol-driven (e.g. regular CT scans or clinical appointments
- Resource use may depend on setting
  - reflects health system service delivery patterns
    - higher admission rates/duration
    - Community-based care
- Sources of data
  - NHS-based observational studies
  - Administrative data, chart reviews
  - Expert opinion
- Need UK specific costs
  - Current official listing published by the Department of Health
  - National data based on healthcare resource groups (HRGs), such as the Payment by Results tariff
  - British National Formulary
  - Administrative data

Sources of non-RCT model parameters

Supplements/extensions of RCTs
Pragmatic clinical trials
Observational data from cohort studies
Early clinical trials/ phase IV trials
Databases
Administrative data
Surveys – patient/population
Chart reviews (data abstraction)
Registries (prospective)
Adverse effect reporting
Tariffs, routine cost data
Expert judgements

Study-based

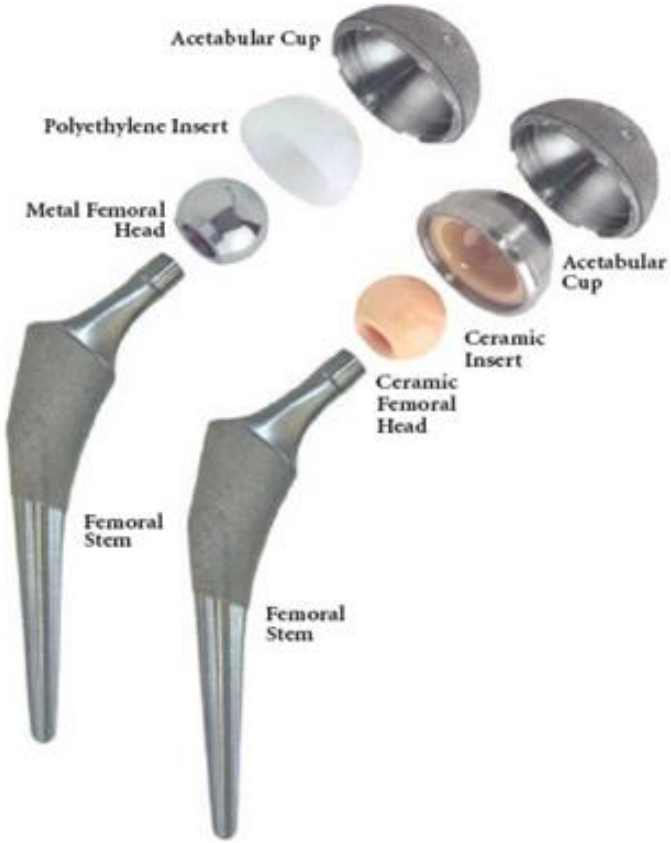
Routine data

⟶ Use of non-RCT data in NICE technology appraisals is the norm

- Modelling is data hungry, data often not available from RCTs
- Non-RCT efficacy/ clinical data evidence frequently used, most common for
  - Devices (eg insulin pumps, cochlear implants, endovascular stents)
  - Interventions where RCTs are difficult (Anti-D or venom prophylaxis)
  - Conditions with poor prognosis where single arm studies are often used (sarcomas, GIST, resistant leukaemias)
- Pragmatic approach to available evidence
- 3 Examples

Example 1
Total hip replacement and resurfacing arthroplasty for end-stage arthritis of the hip

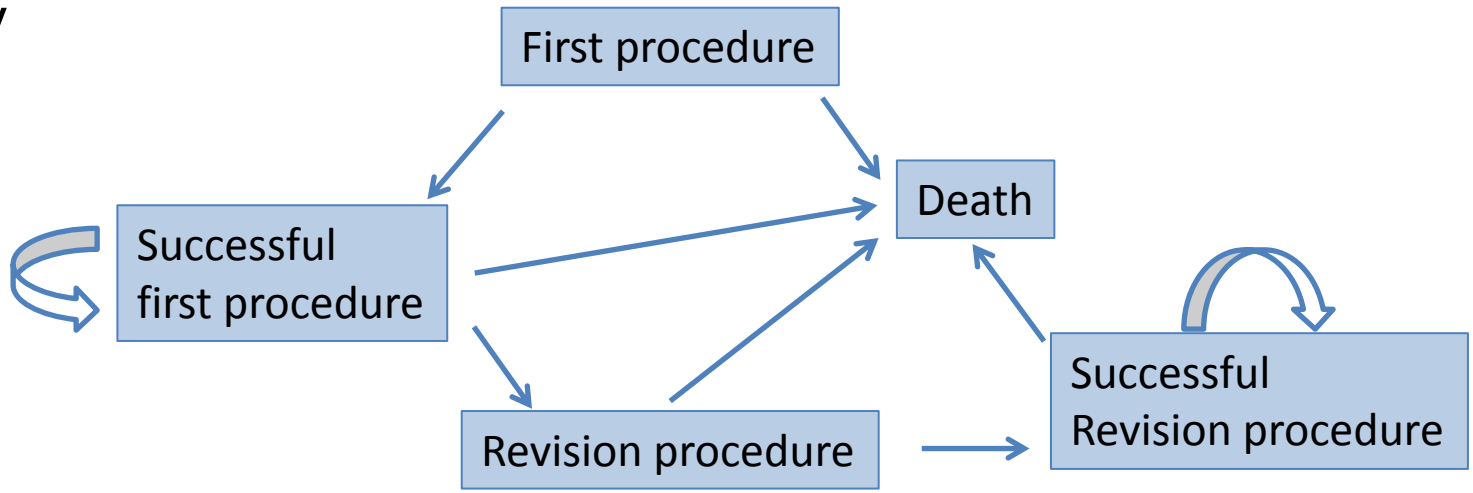
- TA304 Guidance: Prostheses for total hip replacement and resurfacing arthroplasty are recommended as treatment options for people with end-stage arthritis of the hip only if the prostheses have rates (or projected rates) of revision of 5% or less at 10 years.



Outcomes included in the analysis

- Functional result
- Pain
- Bone conservation
- Revision rates
- Prosthesis movement
- Dislocation rates
- Adverse effects of treatment
- Health-related quality of life
- Mortality

Model structure



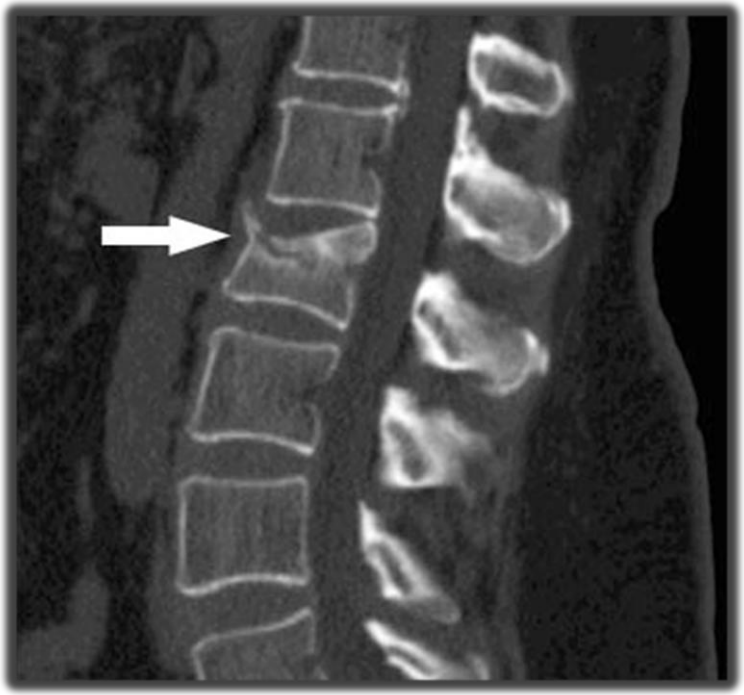
TA304 - Hip prostheses - Key driver

- Revision rate was the key driver of costs and QALYs
  - ➢ Prostheses become more cost effective the lower the revision rates.
- Revision rates not available from RCTs
- Sourced from the National Joint Registry (UK)

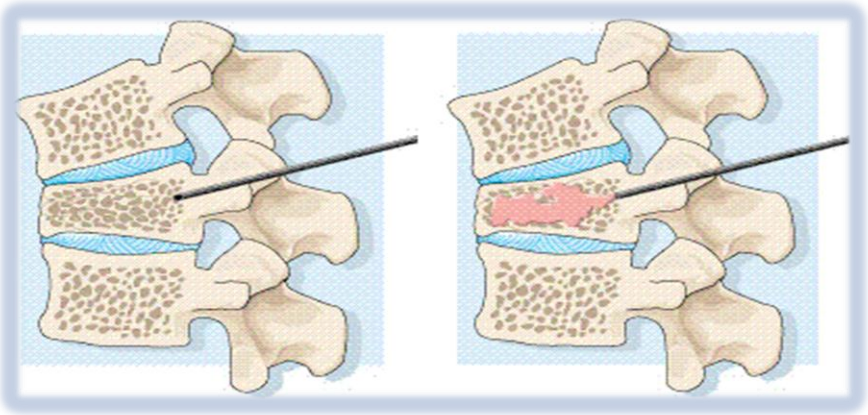
- NJR set up by the Department of Health and Welsh Assembly Government for the mandatory collection of information on all hip, knee, ankle, elbow and shoulder replacement operations from NHS organisations and private practice, and to monitor the performance of joint replacement prostheses. Since 2009, all NHS patients who are having hip replacement surgery are invited to fill in Patient Reported Outcome Measures (PROMs) questionnaires about their health and quality of life before and after their surgery

Example 2
Percutaneous vertebroplasty and percutaneous balloon kyphoplasty for treating osteoporotic vertebral compression fractures

- TA 279 guidance: Percutaneous vertebroplasty, and percutaneous balloon kyphoplasty without stenting, are recommended as options for treating osteoporotic vertebral compression fractures only in people:
  - who have severe ongoing pain after a recent, unhealed vertebral fracture despite optimal pain management and
  - in whom the pain has been confirmed to be at the level of the fracture by physical examination and imaging.



Vertebroplasty



- Under fluoroscopy
- High or low viscosity cements

Balloon Kyphoplasty

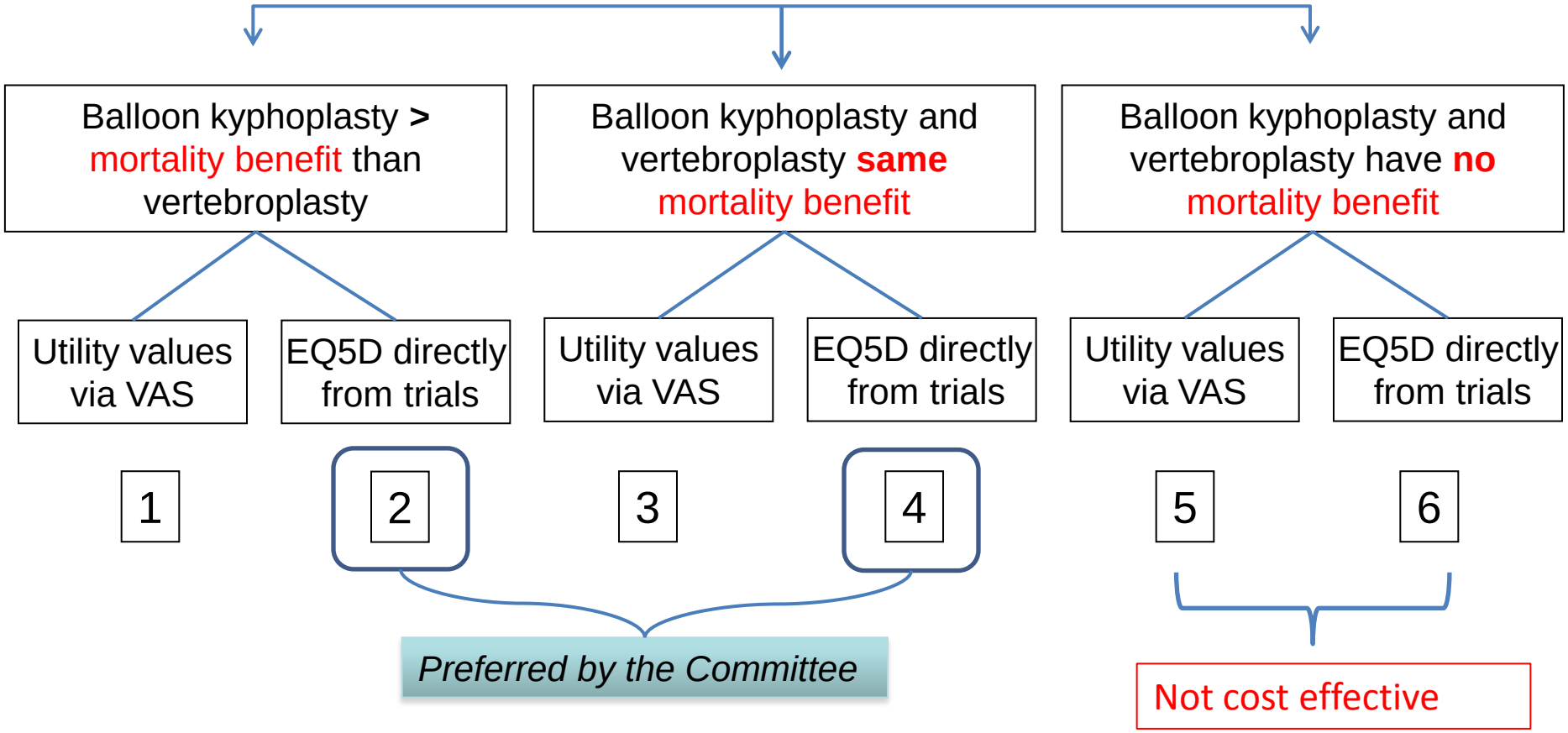
- Balloon inflated to achieve vertebral height
- Deflated – fill space with cement
- Stent may remain

TA279 RCT evidence

- 9 RCTs - outcomes: pain, functional status, quality of life, longest follow up 36 months

	Study	n	Intervention	Comparator	Crossover permitted	Powered for primary outcome?
1	INVEST	131	Vertebroplasty	**Operative placebo**	Yes	Yes
2	Buchbinder	78	Vertebroplasty		No	
3	Farrokhi	82	Vertebroplasty	Optimal pain management	Yes	
4	VERTOS	43	Vertebroplasty		Yes	
5	VERTOS II	202	Vertebroplasty		Yes	
6	Blasco	125	Vertebroplasty	Conservative	Yes	Yes
7	Rousing	50	Vertebroplasty		No	
8	FREE	300	Kyphoplasty		No	Yes
9	Liu	100	Vertebroplasty	Kyphoplasty	No	

TA279 Modelling scenarios - Mortality etc



TA279 Mortality – Trials and Observational Studies

Comparison	Hazard ratio (95% CI)
Assessment Group meta-analysed 3 trials mortality at 12 months	
Intervention (n=90) vs. no intervention (n=186)	0.68 (0.30 to 1.57)
US Medicare Registry n=858979	
Intervention vs. no intervention	0.63 (0.62 to 0.64)
Kyphoplasty vs. no intervention	0.56 (0.55 to 0.57)
Vertebroplasty vs. no intervention	0.76 (0.75 to 0.77)
Kyphoplasty vs. vertebroplasty	0.77 (0.75 to 0.78)
German Health Insurance Fund* n=3607	
Intervention vs. no intervention	(academic in confidence)
Kyphoplasty vs. vertebroplasty	(academic in confidence)

Clinical plausibility that improving spine curvature has an effect on monrtality (improved lung function, digestion, mobility, less opioid analgesics)

Example 3
Pharmalgen for the treatment of bee and wasp venom allergy

TA 246 Guidance: Pharmalgen is recommended as an option for the treatment of IgE-mediated bee and wasp venom allergy in people who have had:

- a severe systemic reaction to bee or wasp venom
  or
- a moderate systemic reaction to bee or wasp venom and who have one or more of the following: a raised baseline serum tryptase, a high risk of future stings or anxiety about future stings.

TA 246 Appraisal Scope

Population	History of type 1 IgE-mediated systemic allergic reactions to bee or wasp venom
Intervention	Pharmalgen – subcutaneous Initial phase – 'up-dosing' or 'rush' Maintenance phase
Comparison	Standard care w/o venom immunotherapy: 1. High-dose antihistamines (HDA), 2. Adrenaline auto-injector (AAI) + training 3. Advice on avoiding bee or wasp venom
Outcomes	1. Number and severity of type 1 IgE-mediated, systemic allergic reactions 2. Anxiety related to future reactions 3. Mortality 4. Adverse effects of treatment 5. Health-related quality of life.
Subgroup	1. Risk future stings 2. Risk severe reactions to future stings 3. Contraindication to adrenaline 4. Children

The impact of reduced anxiety about stings on cost effectiveness

- No evidence on quality of life using a validated utility measure → in the base case analysis no change in utility associated with anxiety assumed

	Pharmalgen vs. HDA + AAI + Advice
Base case analysis	
Incremental costs	£2,028,808
Incremental QALYs	0.11
Cost per QALY gained	£18,065,527
People at high risk of stings	
Incremental costs (£)	- £1,057,682
Incremental QALYs	5.91
Cost per QALY gained	- £179,020 (cost saving)

Estimation of utility associated with anxiety through the standard EQ5D questionnaire

Mobility	
I have no problems in walking about	☑
I have some problems in walking about	☐
I am confined to bed	☐
Self-care	
I have no problems with self care	☑
I have some problems washing or dressing myself	☐
I am unable to wash or dress myself	☐
Usual activities	
I have no problems with performing my usual activities	☐
I have some problems with performing my usual activities	☑
I am unable to perform my usual activities	☐
Pain/discomfort	
I have no pain or discomfort	☑
I have moderate pain or discomfort	☐
I have extreme pain or discomfort	☐
Anxiety/depression	
I am not anxious or depressed	☐
I am moderately anxious or depressed	☑
I am extremely anxious or depressed	☐

Health state 11212

Utility decrease using standard tariff: 0.16

Estimating utility of reduced anxiety

- Conservative assumptions
  - Anxiety about stings reduces utility by 25% of 0.16 (that is, a reduction in utility of 0.04 associated with venom allergy)
  - Treatment with Pharmalgen increases utility by 25% of that value (that is, 0.01 per person per year)

	Pharmalgen vs. HDA + AAI + Advice
People who benefit by lower anxiety	
Incremental costs (£)	2,028,808
Incremental QALYs	85.00
Cost per QALY gained	£23,868

Real World Data

Problems

- Confounders and bias
- Changes over time
- Uncertain accuracy
- Missing data
- Aggregated at level of provider unit or disease - not patient-level data
- Risk adjustment requires data on well-defined prognostic factors
- Definitions may vary from trials

Improvements

- Ability of identify cases and link data sources
- Procedures for validation of data - audit
- Routinely capture HRQL and patient preferences
- Routinely include important patient variables
  - socio-demographic
  - disease severity
  - comorbidities
- Use of explicit definitions of variables including coding system
- Limit missing data

Adopted from Williams et al 2003, Raftery et al 2005

IMI GetReal

- EU public-private consortium consisting of pharmaceutical companies, SMEs, academia, HTA agencies and regulators, patient organisations
- First time that a public-private partnership has been used to consider options for the use of real-world evidence in a ‘save-harbour’ environment.
- 3 year project, 1 year remaining
- Comprehensive stakeholder inclusion (HTA, regulators, pharma, patients, clinicians, academics etc).
- A key deliverable is a ‘framework’ which is intended to provide guidance on the available options for use of real world evidence to support effectiveness estimates

IMI GetReal (cont.)

- **WP1** Framework Policies Processes (NICE co-leading) - 5 case studies in different disease areas. Focus on effectiveness challenges experienced in past regulatory assessments and HTA, propose potential solutions using RWE, and get stakeholder reactions on the acceptability and usefulness of these solutions for decision making
- **WP2 -** Understanding what drives any differences between efficacy and effectiveness, understand when RWE is needed; improve design of RW studies
- **WP3** Overcoming operational, legal and ethical challenges to the design of RW studies
- **WP4** Scientific methods for evidence synthesis and predictive modelling, including RWE in NMA

http://www.imi-getreal.eu/

ADAPT SMART

- Coordination of Medicines Adaptive Pathways to Patients (MAPPs) activities. MAPPs seeks to foster access to beneficial treatments for the right patient groups at the earliest appropriate time in the product life-span in a sustainable fashion
- ADAPT SMART will support IMI2 projects investigating MAPPs tools and methodologies
- Engage in a dialogue with all relevant stakeholders to prove and develop workable MAPPs concepts

- WP1 - Evidence generation throughout the entire product life cycle
- WP 2 - Designing the MAPPs pathway
- WP 3 - Decision-making, sustainability and their implications
- WP 4 - Operational Project Management

- http://adaptsmart.eu/

The future….

- Earlier licensing with less evidence
  - Not ‘reasonable’/ fair to say no to use in clinical practice just because of the evidence base
  - Handling uncertainty through managed access agreements (‘recommendations with research’), that is, data collection on the back of routine care = real world data
- Adaptive licensing/ MAPPs - development of one strategy for product development and access

The future….

- Concern about ‘lowering evidence standards’ by using observational studies
- Need to use the right tool for different questions
- Opportunity to strengthen the evidence standards/ evidence generation through the life cycle of technologies
- RCTs and real world evidence complement each other
- Amendments to NICE methods guide to cover advice on observational study design and analysis/ Project on accreditation of registers

- A plea: Please engage with GetReal and ADAPT SMART to help develop approaches that are broadly acceptable and work