Practical examples of a good health economic submission

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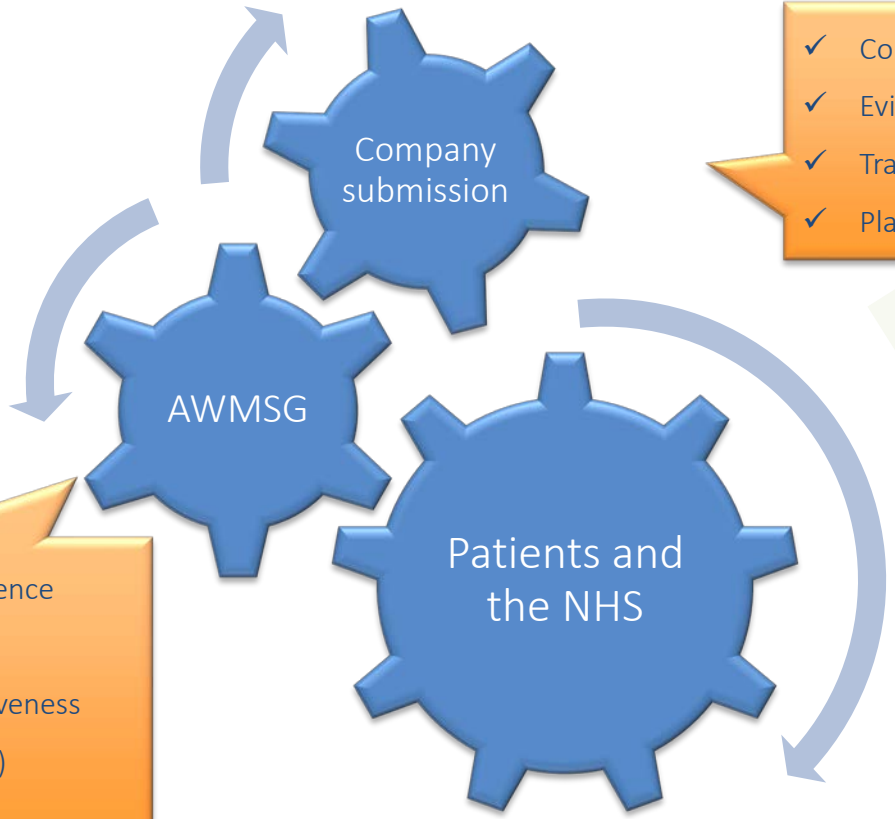
Working with the reimbursement process



- ✓ Content
- ✓ Evidence presentation
- ✓ Transparency
- ✓ Plausibility

CAN INFLUENCE

- ✓ Clinical and cost-effective evidence
- ✓ Decision-making framework
- ✓ Rules and policies (cost-effectiveness thresholds, end-of-life, orphan)
- ✓ Value judgements

Submission – key elements

	Consider:
Indication	Is it appropriate?
Comparator	Most relevant?
Evidence base	Strength of evidence?
Costing approach	Appropriate for Wales?
Utilities	Credible values?
Cost-effectiveness	Modelling approach?
Uncertainty	Sensitivity of results to input values? Alternative plausible scenarios?
End Of Life	Is the AWMSG criteria met?
Orphan medicines /Rare disease	Are AWMSG criteria met?

Beyond the submission

- Draft ASAR
  - Opportunity to comment
  - Address queries and concerns, clarify
  - Challenge interpretation
  - Not a chance to change mind and present different data!
- New Medicines Group meeting
- Public AWMSG meeting

	NMG	AWMSG
Clinical Effectiveness	✓	✓
Cost-effectiveness	✓	✓
Broader Societal Issues	✗	✓
Budget Impact	✗	✓

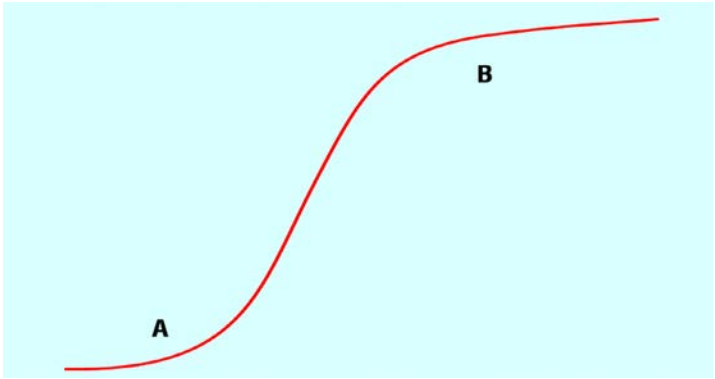
Decision making

- When the ICER < £20,000
  - may not be recommended if AWMSG/NMG are not persuaded by the plausibility of the inputs and/or the certainty around the estimated ICER
- When the ICER falls between £20,000-£30,000
  - The degree of certainty surrounding the calculation of ICERs
  - The innovative nature of the medicine
  - The particular features of the condition and population receiving the medicine
  - Where appropriate, the broader societal impact
- When the ICER is > £30,000, the case for supporting the medicine has to be increasingly strong

Cost-effectiveness threshold

A = <£20,000 per QALY gained
B = >£30,000 per QALY gained

Probability of rejection on grounds of cost infectiveness



Increasing cost/QALY (log scale)

Modelling approach

- Reflect the decision problem at hand

- Base case:
  - **perspective** of NHS in Wales and personal social services
  - **robust, plausible** assumptions and estimates
  - **most relevant analysis** to address decision problem

- a **range of plausible alternatives** (combinations of sensitivity and scenario analyses)

Cost Utility Analysis vs Cost Minimisation Analysis

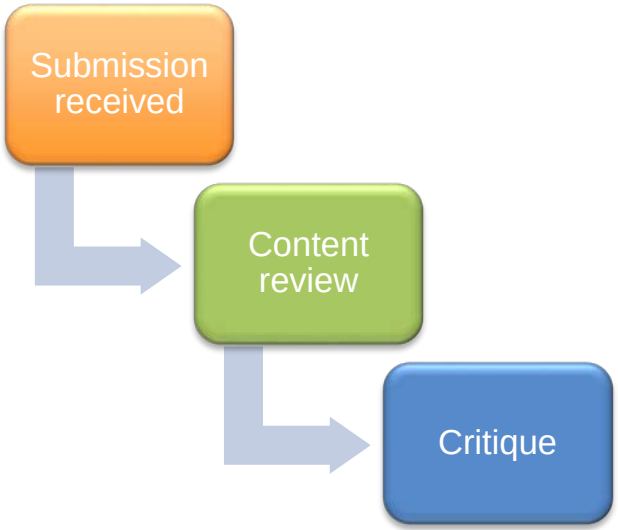
- **CUA is preferred approach**, cost per QALY gained

- CMA *only* acceptable when no clinically meaningful differences in the distribution of effects between the medicine and its comparator(s).
  - include **all dimensions of health**
  - Well designed **equivalence trials** for the evaluation of efficacy and evidence of close comparability of other effects
  - Non-inferiority ≠ equivalence

Working through the case studies

Case Study 1 : Cost-utility analysis, Orphan medicine

Case Study 2 : Cost-minimisation analysis



Case Study 1: Cost-utility Analysis Orphan medicine

Submission indication – Agent R

Adjunctive therapy of refractory seizures in children aged 3-18 with severe myoclonic epilepsy whose seizures are not adequately controlled with Agent S alone.

Once daily administration

Intervention	Comparator
Agent R, plus Agent S	Agent S

Clinical Evidence

- Phase III RCT comparing efficacy of Agent R as add-on therapy to Agent S over a 12-month period in 80 patients in the US
- Post-marketing survey of patients using Agent R for 1-5 years

Clinical outcomes: Percentage of patients with > 50% reduction in seizures during treatment

Agent R 73% vs placebo 3%, p<0.00001

Safety

No major safety concerns identified

Health economic approach	Cost effectiveness analysis
Clinical data	**Markov model** with a three-month cycle length, 15 year time horizon. **Transition probabilities** used in the model were derived from the Phase III RCT study for the first 4 x 3 month cycles and the post-marketing survey thereafter (post-hoc analysis).
Utility values	**Published study** eliciting utilities for severe adult epilepsy using time-trade off interviews among the UK general public.
Resource use source	Pivotal **US study**, a **French economic model**, and **expert opinion**.
Costs applied	Costs of **drug therapy, monitoring, changing therapy, status epilepticus and managing adverse events.**

Basecase results	
Total costs	Intervention: £242,166; comparator £238,655 , *Difference = £3,511*
Total QALYs	Intervention: 6.93; comparator, 6.78 *Difference = 0.15*
ICER	*£23,407*
Sensitivity Analysis	
Scenario analyses	• **Alternative utility values** from an observational study of adjunctive therapy with a range of AEDs. *ICER £41,173* • **Alternative utility values** evaluating AED used to treat focal epilepsies in children. *ICER £39,918*
One Way Sensitivity Analysis	• ICERs in all one-way sensitivity analyses ranged from *dominant to £76,290 per QALY gained.*
Probabilistic Sensitivity Analysis	• Probability cost effective at £20,000/QALY = 44% • Probability cost effective at £30,000/QALY = 69%

AWMSG Orphan Drugs Policy	Criteria
Patient numbers	196 patients in Wales
Degree of severity of the disease as presently managed	The company estimate premature mortality can affect up to 20% of patients.
Unmet need	Another orphan drug is already available, BD administration.
Reverse or cure	No; stabilises
Innovative	No
Added value to the patient which may not be adequately captured in the QALY:	Should result in improved behavioural problems, but no supporting evidence presented
Added value to the patient's family	May prevent or at least limit long-term damage in children, but no supporting evidence presented

Critique – next steps

Critique	Comments
Are the comparators appropriate?	Only one comparator included in the model. *Feedback: this is the most relevant comparator for Wales*
Is the clinical evidence robust and relevant?	Data is from a **12-month RCT** based in the US and a long-term 5 year post-marketing safety survey. *There is no comparative data beyond the 12 month RCT data*

Critique	Comments
Is the health economic approach valid?	The model time horizon of 15 years is based on treatment for patients from age 3 to 18 years. **Long-term transition probabilities** source: *post-hoc analysis of a post-marketing survey* using 5 year data. Transition probabilities *assumed to be the same in both arms* and applied over the full 15-year time horizon
Are the utilities credibly valued?	**Utility values** were for *severe adult epilepsy* among the UK general public Impact of using different utility scores? *ICER increased from £23k to £40k/£41k*
Is the costing evidence robust and relevant?	**Resource utilisation** based on the *RCT conducted in US,* the *French epilepsy model assumptions* and *expert opinion,* one of whom was based in Wales.

Critique	Comments
Is the basecase ICER plausible?	Based on: ▪ *short-term efficacy data* ▪ *small group of patients* ▪ *longer-term data using a post-hoc analysis of a post-marketing safety survey* ▪ *utilities which are not consistent with other utility scores for similar condition.*
Interpreting OWSA	*From dominant to ICER of £76k*
Interpreting PSA	*44% cost-effective at £20k threshold, and 69% at £30k threshold*
Orphan drug criteria	*Generally met*

Consider – approve or reject?

Case Study 2: Cost Minimisation Analysis

Submission indication	
Treatment of diabetes mellitus (type 1 and type 2) in children >2 years and adults	
Intervention: Agent P	**Comparator:** Agent D
long-acting human insulin analogue twice daily s/c administration pen or cartridge formulation	long-acting human insulin analogue twice daily s/c administration; pen, cartridge, or *vial* formulation
Clinical Evidence	
Study 1: Agent P vs Agent D Non-inferiority double-blind phase III RCT study in **T1DM,** in adults for 52 weeks	**Study 2:** Agent P vs Agent D Non-inferiority open-label phase III RCT study in **T2DM,** in adults for 26 weeks

Agent P is an EMA approved biosimilar of Agent D

Clinical outcomes: LSM difference (95% CI) change from baseline mean HbA1c (%)

Study 1:

0.09 (−0.003 to 0.190) at 52 weeks

Study 2:

0.06 (−0.060 to 0.185) at 26 weeks

Agent P was found to be non-inferior to Agent D at the pre-specified non-inferiority margin of 0.25% for both studies

Safety

Overall, the safety profile of Agent P was *similar* to that of Agent D and in line with the safety characteristics expected from an insulin product.

There were *no differences* in the rates of serious adverse events (SAEs) and deaths.

Health economic approach	
Cost minimisation analysis	**Cost comparison only**
Costing approach	
Costs of pens and cartridges compared	Average daily dose (HTA appraisal on long-acting insulins)
Sub-group analysis	Costs for T1DM and T2DM
Base case results	
Average annual medicines acquisition cost	Agent P: £243.55; Agent D £298.46, *Difference −£54.91*
Average annual monitoring and administration cost	Agent P: £133.20; Agent D £133.20, *Difference −£0.00*
Sensitivity Analysis	
	None

Critique points	For consideration
Is the comparator appropriate?	*Based on current practice in Wales*
AWMSG CMA criteria met?	*Equivalence in efficacy demonstrated? Close comparability of AEs, QoL, patient preference and adherence?*
Does the trial data reflect the proposed indication?	*Adults and children with TIDM and T2DM*
Is the trial data open to bias?	*Study 2 Open-label design*
Has a full costing comparison been undertaken against all formulations?	*Pens, cartridges, vials*
Is the model time horizon and perspective appropriate?	*1 year – appropriate?*
Is the sensitivity analysis appropriate?	*No SA*

Consider – approve or reject?

Budget impact

- Not considered by NMG, is considered by AWMSG
- *Is* important
- Needs to be as relevant and robust as the cost effectiveness model
  - Use AWTTC Budget Impact Template
  - Use Welsh data where possible
  - Costs are separated into medicines costs, and resource use costs
  - Justify assumptions
  - Model alternative scenarios

So what makes a successful submission?

- No magic formula
  - Individual drugs appraised on individual basis using a common framework

- Best chance of successful submission is to present
  - *most plausible, transparent, robust case,*
  - *using established best practices,*
  - *in line with the process guidance*

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Housekeeping

- Align
  - Form B Pharmacoeconomics and Resource Implications section
  - Cost-effectiveness model
  - Budget Impact model
- Model
  - Ensure transparency and robustness
  - Make sure the macros run
- References
  - Complete
  - Web links working

Diolch yn fawr - Thank you

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PAMS Patient Access to Medicines Service
WNPU Welsh National Poisons Unit
WeMeReC Welsh Medicines Resource Centre
Yellowcard Centre Wales
WAPSU Welsh Analytical Prescribing Support Unit