



## Designing Economic Evaluation Alongside Clinical Studies

### Health Economics Short Course

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## Module 5 – Examples & getting projects funded

Centre for Health Policy  
Melbourne School of Population and Global Health



### UKPDS: Case study

- United Kingdom Prospective Diabetes Study was one of the first large RCTs to include economic evaluation
- Reported in September 1998
- Of the 40 publications since publication of the main study results, around 10 have had a health economic focus
- Continued collaboration 15 years on



### Blood Glucose & Blood pressure Study: Aims

To determine the cost per Quality Adjusted Life Year (QALY) gained of three UKPDS policies:

- **Intensive blood glucose control:** Is intensive blood glucose control with sulphonylurea, or insulin, cost-effective in preventing clinical complications in people with Type 2 Diabetes?
- **Metformin:** Is intensive blood glucose control with Metformin in overweight patients cost-effective in preventing complications?
- **Tight blood pressure control:** Is tight blood pressure control cost-effective in preventing complications?



### Main economic evaluation

**Comparison:** Intensive versus conventional blood glucose and blood pressure control policies in Type 2 diabetic patients

**Data:** Patient level data on costs and outcomes from UKPDS

**Outcome measure:** Quality adjusted life years

**Time period:** Within study effects extrapolated over lifetime (median follow-up 10 years for Blood Glucose and 8.4 years for Blood Pressure Trial)

**Perspective:** UK health care system

**Result:** Incremental cost per QALY gained in 2004 £s (£1 = 1.5 Euros)

## Costs and resource use

- **Therapy:**
  - **Drug doses** (antidiabetic, antihypertensive, other)
  - **Tests** (blood glucose, HbA<sub>1c</sub>)
  - **Standard practice** (cost of implementing UKPDS policies in a general health care setting)
- **Complications:**
  - **Hospital admissions** (length of stay, diagnosis)
  - **Non-inpatient services** (home, clinic & telephone contacts with GPs, nurses, dieticians, etc.)
- **Cost of complications is modelled over each patient's lifetime**

## Unit costs

| Item                                                                 | Unit cost £s 2004 | Source                                                                                           |
|----------------------------------------------------------------------|-------------------|--------------------------------------------------------------------------------------------------|
| <b>Therapy costs</b>                                                 |                   |                                                                                                  |
| Metformin (500 mg/850 mg tablet)                                     | 0.03/0.04         | Drug tariff 2004                                                                                 |
| Chlorpropamide (100 mg/250 mg)                                       | 0.09/0.10         | Drug tariff 2004                                                                                 |
| Glibenclamide (2.5 mg/5 mg)                                          | 0.03/0.05         | Drug tariff 2004                                                                                 |
| Glipizide (2.5 mg/5 mg)                                              | 0.05/0.08         | Drug tariff 2004                                                                                 |
| Ultralente insulin 1,000-unit-vial/750-unit cartridge                | 9.80              | Drug tariff 2004                                                                                 |
| Soluble insulin 1,000-unit-vial/750-unit cartridge                   | 9.80/10.20        | Drug tariff 2004                                                                                 |
| Atenolol (25/50/100 mg)                                              | 0.06/0.07/0.09    | Drug tariff 2004                                                                                 |
| Captopril (12.5/25/50 mg)                                            | 0.04/0.06/0.07    | Drug tariff 2004                                                                                 |
| Other drugs                                                          | Cost per item     | Drug tariff 2004                                                                                 |
| <b>Implementation unit costs</b>                                     |                   |                                                                                                  |
| General practitioner (clinic visit)                                  | 23                | Netten and Curtis 2003 [10]                                                                      |
| Practice nurse (home visit/surgery visit)                            | 10/8              |                                                                                                  |
| Dieticians                                                           | 9                 |                                                                                                  |
| Hospital eye clinic                                                  | 42                |                                                                                                  |
| Estimated standard practice costs by treatment                       | 57                | Unit costs multiplied by average resource use reported in Table 3 of UKPDS 63 [11]               |
| Conventional primarily on diet/or tablets                            | 140               |                                                                                                  |
| Intensive on tablets                                                 | 168               |                                                                                                  |
| Intensive on insulin                                                 | 405               |                                                                                                  |
| <b>Immediate (subsequent years) costs of selected complications*</b> |                   |                                                                                                  |
| <b>Hospital costs</b>                                                |                   |                                                                                                  |
| Fatal myocardial infarction                                          | 1,366             | UKPDS 65 [12] adjusted for inflation using the Hospital & Community Services Pay And Price Index |
| Non-fatal myocardial infarction                                      | 4,825 (550)       |                                                                                                  |
| Non-fatal stroke                                                     | 2,806 (295)       |                                                                                                  |
| Amputation                                                           | 10,029 (358)      |                                                                                                  |
| <b>Non-hospital costs</b>                                            |                   |                                                                                                  |
| Macrovascular events                                                 | 373 (306)         |                                                                                                  |
| Microvascular events                                                 | 324 (242)         |                                                                                                  |

## Costs: Blood pressure study

**Table 4** Mean and SD costs per patient during the trial follow-up period and mean (95% CI) cost differences for tight vs less tight blood pressure control, by cost category (£s 2004)

|                                                | Less tight |        | Tight  |        | Mean cost difference (95% CI) per patient* |
|------------------------------------------------|------------|--------|--------|--------|--------------------------------------------|
|                                                | Mean       | SD     | Mean   | SD     |                                            |
| Antidiabetic treatment                         | 1,027      | 1,028  | 1,119  | 1,163  | 92 (-40, 224)                              |
| Anti-hypertensive treatment                    | 554        | 628    | 1,102  | 720    | 549 (468, 630)                             |
| Cost of implementation                         | 1,332      | 777    | 1,782  | 858    | 450 (351, 548)                             |
| Total cost of treatment                        | 2,913      | 1,605  | 4,003  | 1,931  | 1,090 (867, 1,314)                         |
| Within-trial hospital inpatient costs          | 4,414      | 9,549  | 3,555  | 9,229  | -860 (-2,002, 282)                         |
| Within-trial non-hospital and outpatient costs | 2,116      | 788    | 2,144  | 799    | -28 (-125, 70)                             |
| Projected hospital inpatient costs             | 13,702     | 36,117 | 13,657 | 38,715 | -46 (-6,115, 6,024)                        |
| Projected non-hospital and outpatient costs    | 3,505      | 3,755  | 3,634  | 3,808  | 129 (-425, 684)                            |
| Total cost of complications                    | 23,738     | 40,415 | 22,989 | 42,561 | -749 (-7,371, 5,873)                       |
| Total costs, undiscounted                      | 26,651     | 40,577 | 26,993 | 42,713 | 342 (-6,295, 6,978)                        |
| Total costs, 3.5% discount rate                | 15,786     | 16,378 | 15,895 | 16,025 | 108 (-2,347, 2,563)                        |
| Total costs, 6% discount rate                  | 11,984     | 11,082 | 12,042 | 10,671 | 58 (-1,490, 1,606)                         |

\*Negative cost differences indicate cost-savings associated with more intensive therapies. Sub-totals may not sum exactly due to rounding

## Total discounted costs

### Mean costs per patient over study period, £s, 3.5% discount

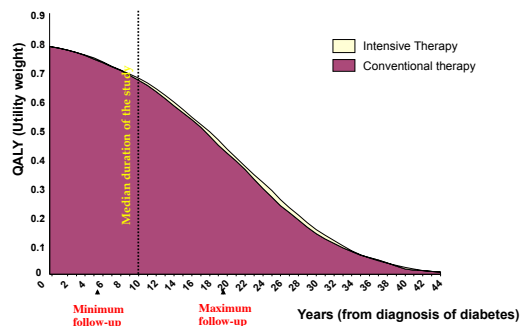
| Item           | Mean (SD) conventional | Mean (SD) intensive | Mean difference (95% C.I.) |
|----------------|------------------------|---------------------|----------------------------|
| Intensive BG   | 14,984 (17,888)        | 15,868 (14,465)     | 884(-483, 2250)            |
| Metformin      | 16,941 (23,193)        | 15,920 (13,678)     | -1021(-4291, 2249)         |
| Blood pressure | 15,786 (16,378)        | 15,895 (16,025)     | 108(-2347, 2563)           |

## Estimating Outcomes

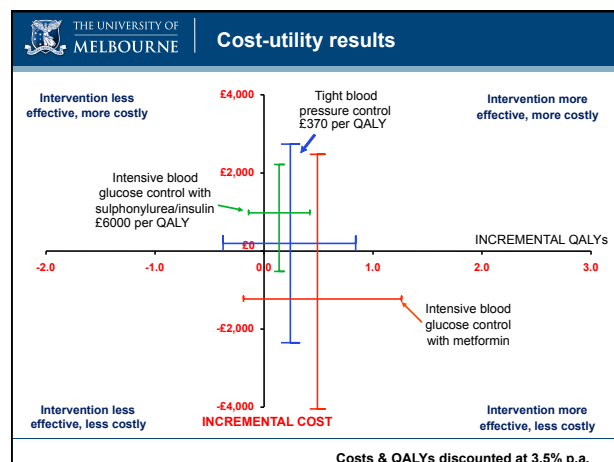
- Estimate QALYs for people with Type 2 diabetes, based on profile of complications of each patient over their remaining lifetime
- Use **UKPDS Outcomes Model** which is based on an integrated set of parametric proportional hazard models to predict absolute risk of first occurrence of seven major diabetes-related complications, using:
  - patients' characteristics (e.g. age and sex)
  - time varying risk factors (e.g. HbA<sub>1c</sub>)

## Simulating lifetime outcomes

### Average QALY for UKPDS patients by blood glucose policy



| Total outcomes                       |                           |                        |                               |
|--------------------------------------|---------------------------|------------------------|-------------------------------|
| Mean QALYs per patient, undiscounted |                           |                        |                               |
| Item                                 | Mean (SD)<br>conventional | Mean (SD)<br>intensive | Mean difference<br>(95% C.I.) |
| Intensive BG                         | 16.35 (8.36)              | 16.62 (8.35)           | 0.27 (-0.48, 1.03)            |
| Metformin                            | 16.44 (8.49)              | 17.32 (7.94)           | 0.88 (-0.54, 2.29)            |
| Blood pressure                       | 13.71 (8.00)              | 14.16 (7.81)           | 0.45 (-0.70, 1.60)            |



### Initial outputs

Three economic evaluations alongside the RCT:

- Two in BMJ
- One in Diabetologia

Cost effectiveness of an intensive blood glucose control policy in patients with type 2 diabetes: economic analysis alongside randomised controlled trial (UKPDS 41)

Alastair Gray, Maria Raskou, Alastair McGuire, Paul Fenn, Richard Stevens, Carole Cull, Irene Stratton, Amanda Adler, Rury Holman, and Robert Turner on behalf of the United Kingdom Prospective Diabetes Study Group

**Abstract**  
**Objective** To estimate the cost effectiveness of conventional versus intensive blood glucose control in outpatients with recent 2 diabetes.

type 2 diabetes, and the cost effectiveness of this policy has been reported using data from the diabetes control and complications trial. Without information on clinical treatments and their long term impact on disease

Health Economics Research Centre, Department of Public Health, University of Oxford Institute of

### Policy paper: Cost of implementation

- Cost of implementation of the program in the UK
- Published in the BMJ 2002

Implementing intensive control of blood glucose concentration and blood pressure in type 2 diabetes in England: cost analysis (UKPDS 63)

Alastair Gray, Philip Clarke, Andrew Farmer, Rury Holman, on behalf of the United Kingdom Prospective Diabetes Study (UKPDS) Group

### Effect of complications on costs & quality of life

- Two papers: 1 on costs (Diabetic Medicine) and 1 utility (Medical Decision Making)
- Trying to capture the degree to which complications contribute to the burden of the disease
- Widely used by other researchers as inputs into their own evaluations

**Estimating Utility Values for Health States of Type 2 Diabetic Patients Using the EQ-5D (UKPDS 62)**

Philip Clarke, PhD, Alastair Gray, PhD, Rury Holman, FRCP

**The impact of diabetes-related complications on healthcare costs: results from the United Kingdom Prospective Diabetes Study (UKPDS Study No. 65)**

P. Clarke, A. Gray, R. Legood, A. Briggs and R. Holman\*

### Building a Simulation Model

UKPDS – describes a simulation model for projecting QALYs for people with diabetes

- Used over 150 research groups world-wide
- 270 citations
- Used by more 180 other research groups

The flowchart illustrates the UKPDS simulation model. It starts with baseline data (Age, Sex, Duration of Diabetes, etc.) and branches into various health events and mortality outcomes. Key events include:
 

- Diabetes-related mortality:** Includes events like stroke, heart failure, and other diabetes-related complications.
- Other mortality:** Includes events like cancer, heart disease, and other non-diabetes-related complications.
- Healthcare costs:** Includes costs for various events and treatments.
- Quality of Life (QALYs):** Includes QALYs for various health states and events.

## Other ways to collaborate

## DiGEM Study

- RCT of blood glucose monitoring in people with Type 2 diabetes not using insulin
- Conclusion of main study: "At 12 months the differences in HbA1c level between the three groups (adjusted for baseline HbA1c level) were not statistically significant ( $P=0.12$ )."
- EQ5D administered at baseline & 12 months

Table 4 | Mean (standard error) utility values and utility differences (95% confidence intervals) per patient with non-insulin treated type 2 diabetes receiving standardised usual care, less intensive self monitoring of blood glucose, or more intensive self monitoring of blood glucose

| Intervention                         | No  | Utility       |                    |                            | Difference                                     |                                                |
|--------------------------------------|-----|---------------|--------------------|----------------------------|------------------------------------------------|------------------------------------------------|
|                                      |     | Baseline      | 12 month follow-up | Change                     | Less intensive group v standardised usual care | More intensive group v standardised usual care |
| Standardised usual care group        | 152 | 0.799 (0.023) | 0.798 (0.034)      | -0.001 (-0.060 to 0.059)   | —                                              | —                                              |
| Less intensive self monitoring group | 150 | 0.781 (0.022) | 0.755 (0.024)      | -0.027 (-0.069 to 0.015)   | -0.029 (-0.084 to 0.025)                       | -0.072 (-0.127 to -0.017)*                     |
| More intensive self monitoring group | 151 | 0.807 (0.024) | 0.733 (0.024)      | -0.075 (-0.119 to -0.031)* | —                                              | —                                              |

\* $P<0.05$ .

## LDS study

- Large RCT of statins/ fibrates in people with Type 2 diabetes, ended early due to withdrawal of Cerivastatin
- SF-36 items administered to 4,051 individuals at baseline alongside clinical measure include assessment of visual acuity
- Examined the association between visual acuity and quality of life
- Only paper ever published using the trial data

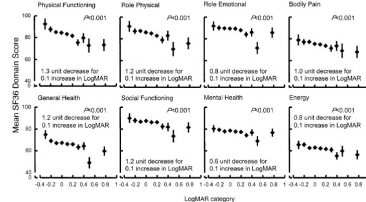


Figure 1—Associations between SF-36 domains and LogMAR score categories in the better eye.

## FIELD study

- Large RCT of the use of Fibrates to lower cholesterol in people with diabetes
- Non-significant primary outcomes
- Looked at relationship between EQ-5D scores predicting events
- Demonstrated that scores further stratified risk over and above that used in CVD risk prediction equations

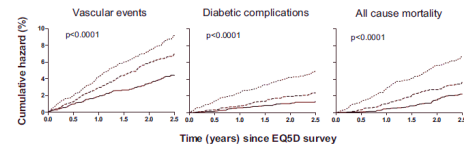
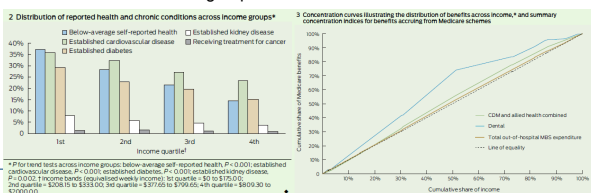


FIGURE 1. Estimated cumulative hazard curves showing proportion having events by EQ-5D index score level. Key: index score < 0.75 dotted line, index score 0.75-1.0 dashed line, index score > 1.0 unbroken line.

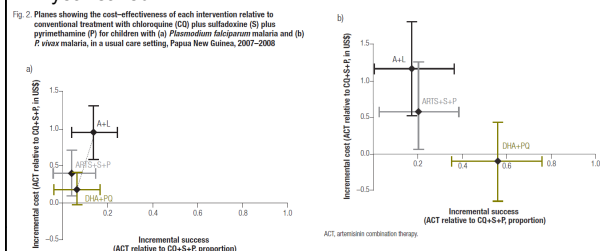
## AusHeart

- Australian Hypertension and Absolute Risk Study involving 322 general practitioners who each collected clinical data on 15–20 patients aged 55 year
- Consented to have their information linked with Medicare data
- Also collected income data & household structure
- First Australian study to combine socio-economic data with clinical & MBS/PBS information
- Showed large health inequality, but even use of out-of-hospital Medicare benefits across income groups

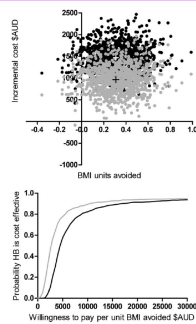


## Developing country application

- Approached by investigators of RCT of Malaria treatments in PNG
- Extrapolated to get estimate in terms of life years saved
- The most cost-effective treatment option was \$58 per life year saved



- To determine the costs and cost-effectiveness of an early childhood home visiting program delivered to families in socio-economically disadvantaged areas of Sydney, Australia during 2007-2010.
- The cost of HB intervention in the clinical study over 2 years was \$1309 per child (2012 AUD).
- The incremental cost-effectiveness ratio was \$4230 per unit BMI avoided



Hayes A, Lung T, Wen LM, Baur L, Rissel C, Howard K. Economic evaluation of “healthy beginnings” an early childhood intervention to prevent obesity. *Obesity* (Silver Spring). 2014 Jul; 22(7):1709-15.

Figure 8 Incremental cost-effectiveness plane and cost-effectiveness acceptability curves for reducing BMI by 1 unit. Crosses=point estimates of ICERs. Black dots= bootstrapped replicates of incremental costs and outcomes from RCT. Grey dots= bootstrapped replicates of incremental costs and outcomes from scenario analysis. Black line= probability cost-effective in RCT; grey line= probability cost-effective in practice.

## Collaboration & Funding

- Collaboration represents trade between researchers
- Clear gains as it allows people to specialize, but there must be gains from trade
- Only four reasons to collaborate and so each party must be exchanging:
  - Data
  - Money
  - Skills
  - Enjoyment of academic interaction

1. In theory grant collaborations should work as both parties have a common goal – high quality publications
2. Clear understanding of roles and responsibilities on project
3. If you want people to do a hard day’s work – you need to pay them!
4. If things become difficult - try to think of it from the other researcher’s perspective

- Chief investigator usually required for a typical economic evaluation alongside a clinical study (0.05 to 0.1FTE)
- Smaller applications may be fine with an AI (many health economists are already on maximum number NHMRC grants)
- Role as CI for economics is specific so don’t rule out more junior economists (i.e. Senior Research Fellows/ Associate Professors)
  - Can always use more junior economist as CI with Professor as AI
  - Can use AI with named researcher

- Economic evaluation alongside a clinical study
  - PSP4 Experienced postdoctoral researcher (i.e. a researcher who would normally be considered as a named investigator on the research application and/or approaching the NHMRC CDA scheme or equivalent
  - \$82,551 p.a.
  - Occasionally a salary for CI economist if relatively junior (RF/SRF) and not on fellowship
  - Could justify PSP3 if simple application

## Examples of role for CI

"CIX has made a major contribution to the planning and design of the health economic evaluation of this program. In doing so CIX has also provided input into overall research design, outcome measures and follow-up periods. CIX will be primarily responsible for overseeing and supervising the economic evaluation/modelling and associated manuscripts, with contributions to the overall study management"

## Role/justification of funding for PSP4

- "A research fellow with significant experience in economic evaluation and modelling is required to for this project. They will be required to coordinate appropriate collection of both clinical study data on key outcomes related to the economic modelling and to translate and prepare this data in a format suitable for the economic modelling. They will take the lead in the design and collection of cost data through embedding processes within the study conduct and administrative databases. They will coordinate the capture of downstream health costs associated with the relevant disease states. They will be responsible with direction from CIX for the economic modelling. Model validation and calibration will be required to ensure model outputs are consistent with known patterns of mortality and disease progression in Australia. Extensive one-way and multiway including probabilistic sensitivity analyses will be conducted by the research fellow and with oversight and direction from CIX and they will be responsible for the presentation of results and preparation of manuscripts."

## Example budgets- salary

### Salary

|        | Simple (PSP3) |           | Standard (PSP4) |           | Complex (PSP4) |            |
|--------|---------------|-----------|-----------------|-----------|----------------|------------|
|        | Fraction      | Cost      | Fraction        | Cost      | Fraction       | Cost       |
| Year 1 | 0.1           | \$ 6,989  | 0.2             | \$ 16,510 | 0.4            | \$ 33,020  |
| Year 2 | 0.1           | \$ 6,989  | 0.2             | \$ 16,510 | 0.4            | \$ 33,020  |
| Year 3 | 0.5           | \$ 34,946 | 0.6             | \$ 49,531 | 0.8            | \$ 66,041  |
| Total  |               | \$ 48,924 |                 | \$ 82,551 |                | \$ 132,082 |

\*Illustrative examples only- requirements may change significantly depending on specifics of a research proposal

## Other possible budget items

- Access costs for PBS/MBS data
  - Varies from \$5000 to \$10,000
- Travel to investigator meetings
- Specialist software e.g. TreeAge for economic modelling

## Greatest challenges

- Appropriate match of CI/AI and finding one who has not filled all their NHMRC project places
- Engaging economist early increases chances of finding one with capacity
- Looking to set up a "Health Economics/ Clinical researchers eHarmony" website
- Long-term collaborations work best.

## Final observations

- Need to engage early with a health economist to scope the task and help design the study
- Focus on collecting data where there are likely to be differences between groups
- Be true to the data when undertaking the analysis and adopt "conservative assumptions" when required.
- Be prepared to change your beliefs if evidence disproves your hypothesis