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DIFFERENT METHODS FOR MODELLING SEVERE HYPOGLYCAEMIC EVENTS: IMPLICATIONS FOR EFFECTIVENESS AND COST-EFFECTIVENESS ANALYSES

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Severe hypoglycaemia

- Can occur in people with diabetes who take insulin and other anti-diabetic treatments.
- Diabetic emergency which can lead to seizures, coma or death.

Background

- Clinical trials report severe hypoglycaemic events in different ways

Risk

No. of patients experiencing event out of Total number randomised

Rate

No. of events for given total exposure

Background

- NICE guideline on Type 1 Diabetes in adults (NG17, 2015 update)[1]
- Intervention: Basal Insulin Regimens
- Data: 20 trials reporting severe hypoglycaemic events
  - 12 reported both risk and rate of events
  - 4 only reported risk
  - 4 only reported rate

Network Meta-analysis (NMA)

- Combines all available evidence
- Produces estimates of the **relative effects** of each intervention compared to every other in a network
- Different data types modelled in different ways

NMA models for adverse events

Risk
- Binomial with **logit** link
- Binomial with complementary log-log (**clog-log**) link

Rate
- **Poisson** with log link

Based on the approach and code provided in the NICE Decision Support Unit's Technical Support Documents 2 on evidence synthesis[2]

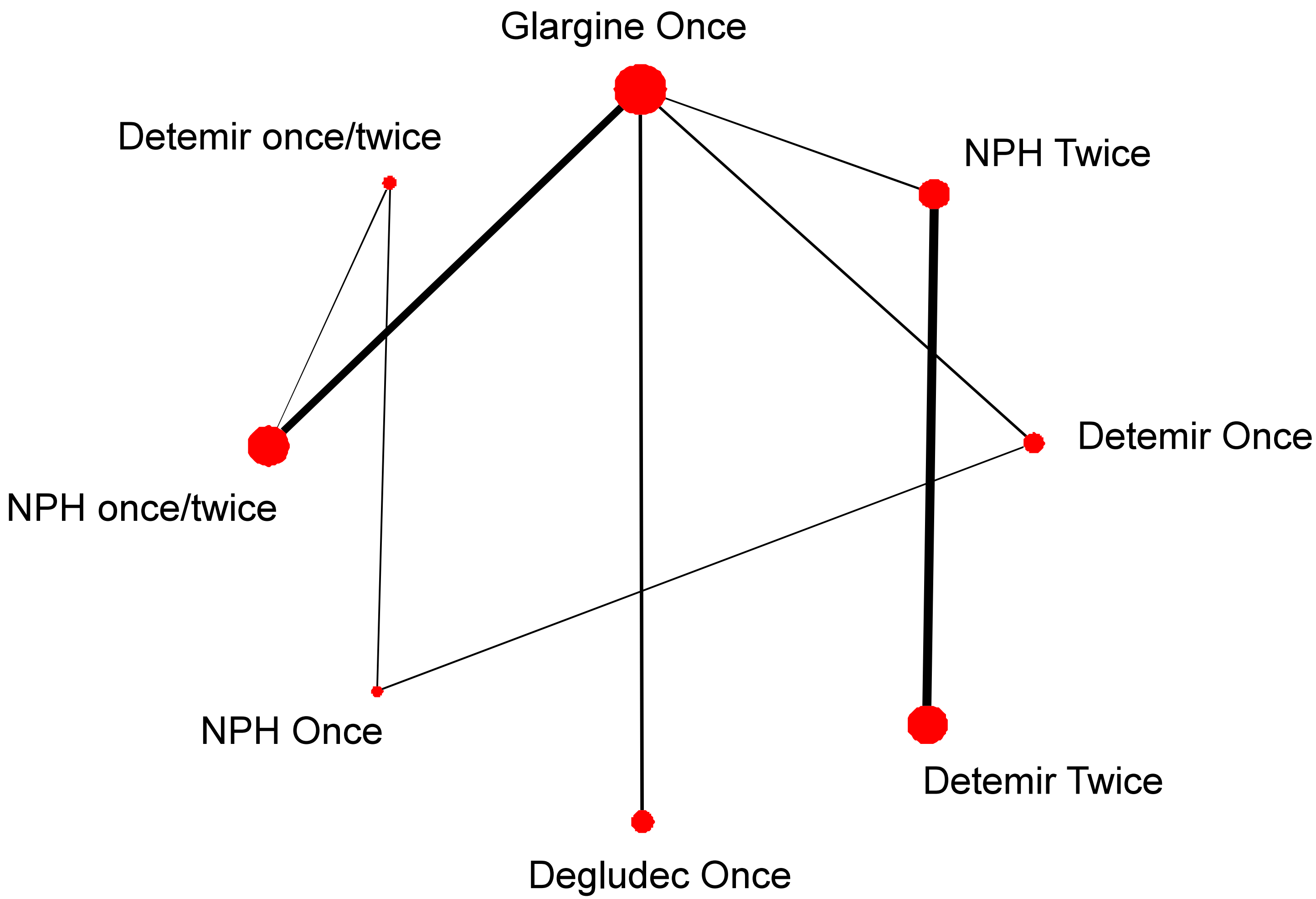
Shared parameter model

- Combines risk and rate data
  - Binomial with **clog-log** link for risk data
  - **Poisson** with log link for rate data

Question No. 1

- 4 models:
  - Binomial with logit link
  - Binomial with clog-log link
  - Poisson with log link
  - Shared parameter model
- What impact does choice of model have on relative effectiveness results?

Network plot – Risk data



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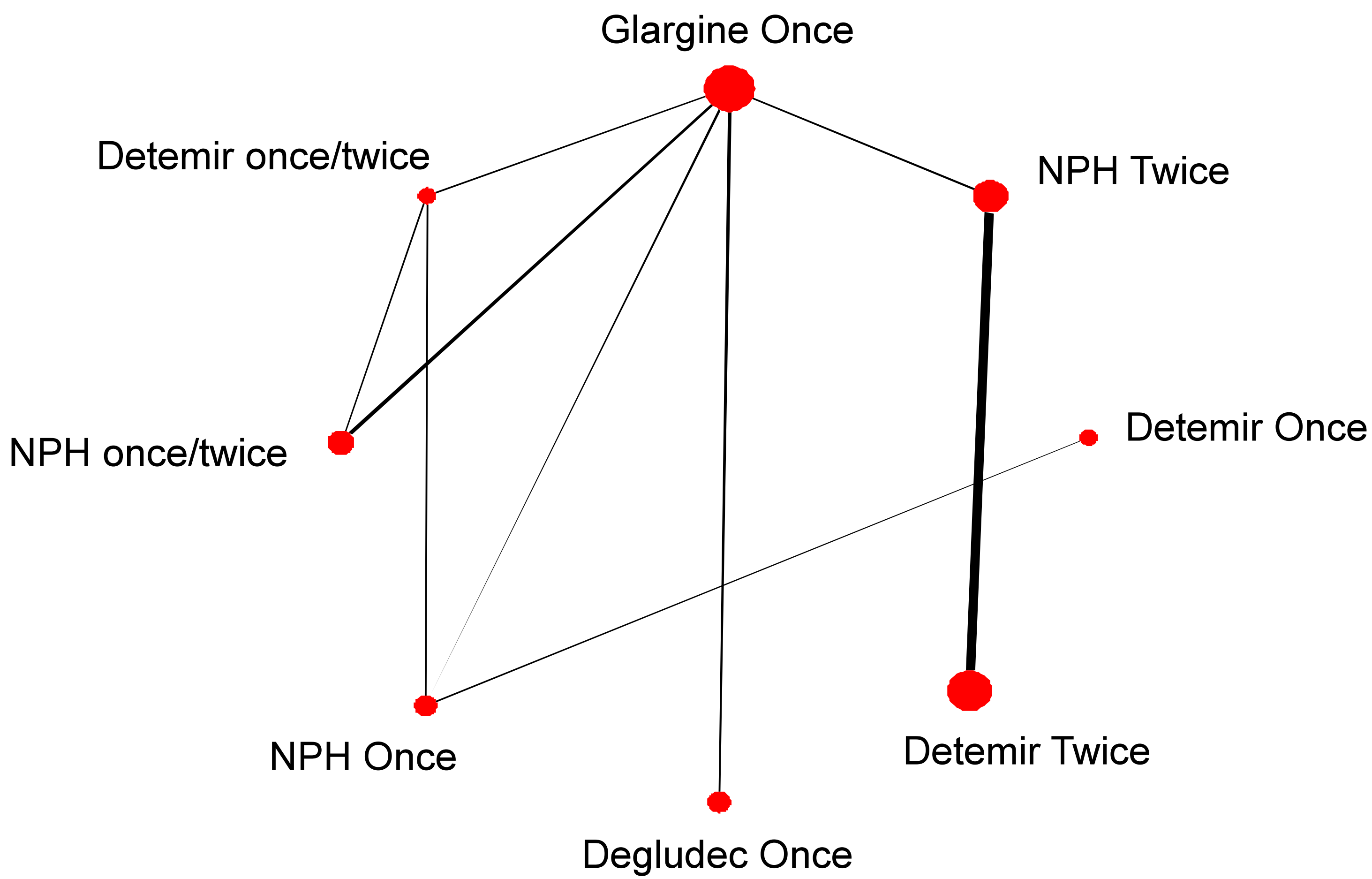
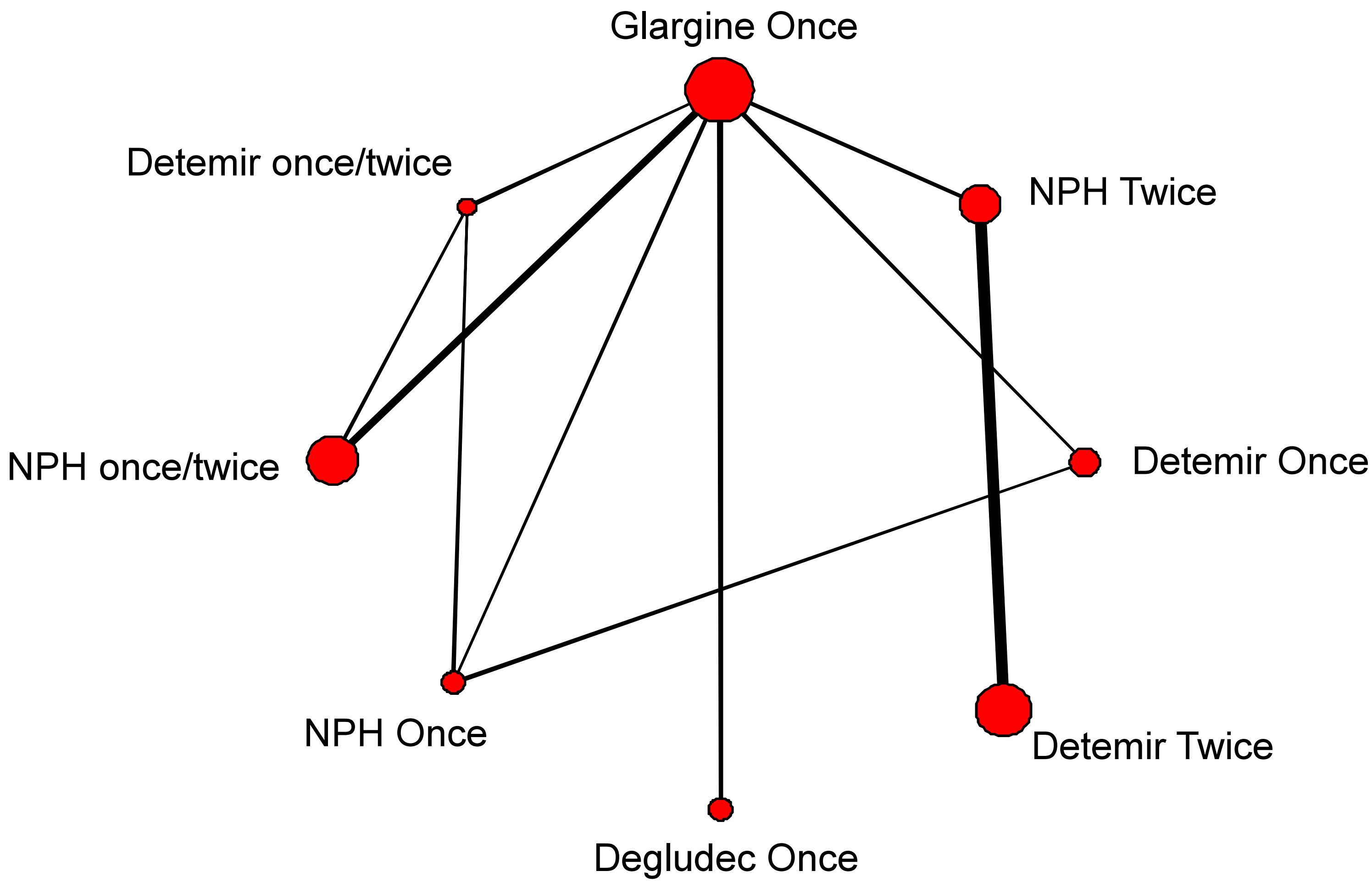
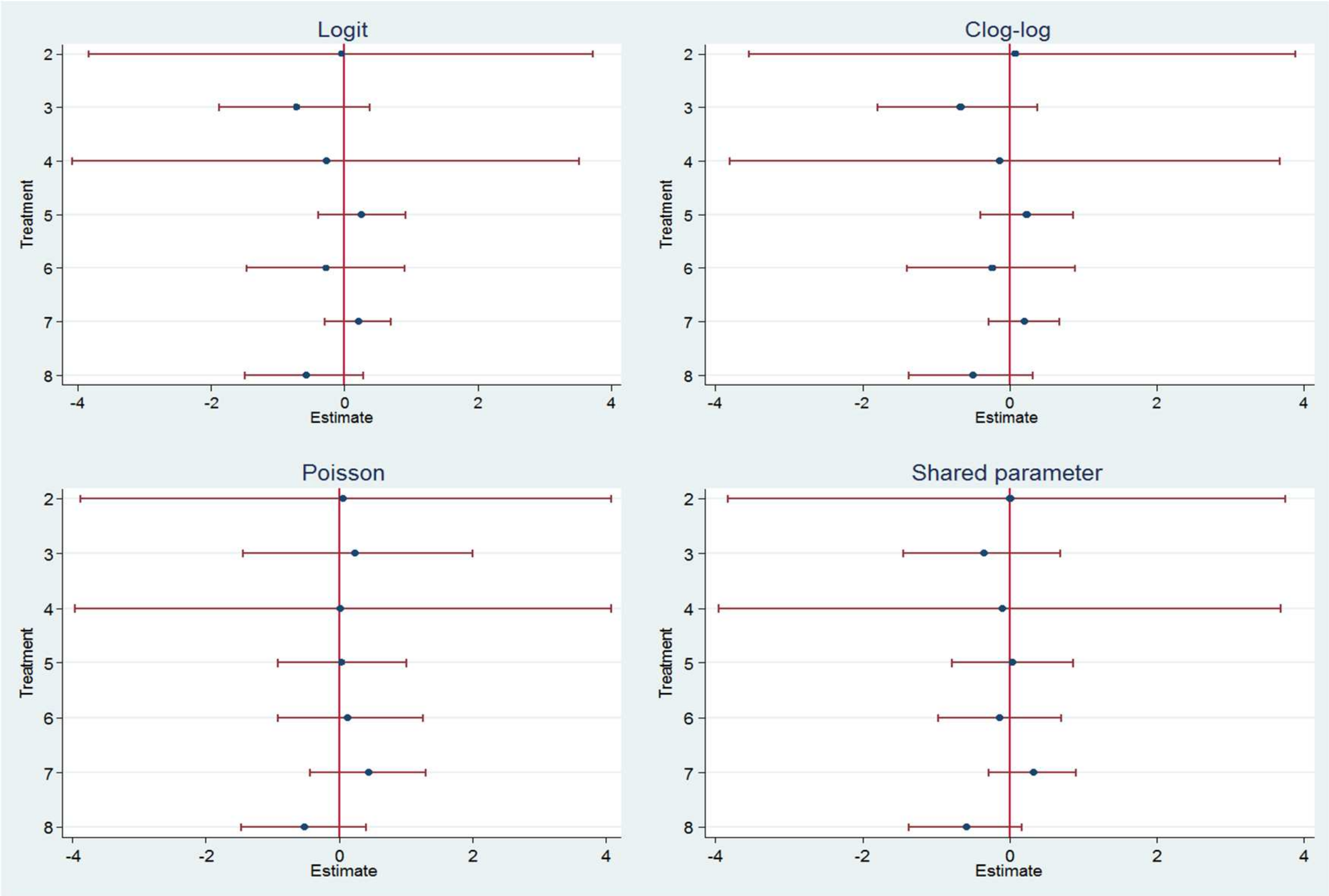
Network plot – Rate data



Network plot – Shared parameter model



Relative effects



Question No. 2

What impact does modelling the risk or the rate have on the costs and QoL outputs of economic models?

Risk

Rate

Cost-effectiveness analysis

- Requires **absolute probabilities** of events

Relative effects from NMA

combined with

probability of event on reference arm

gives

absolute probabilities

Baseline probability

- Probability of having a hypoglycaemic event on baseline treatment (Glargine once) calculated separately in single-arm meta-analyses using three different models
  - Binomial with logit link
  - Binomial with cloglog link
  - Poisson with log link

Baseline Probability

Model	Mean Baseline Probability	95% CrI
Logit	0.07	0.04 – 0.13
Clog-log	0.17	0.06 – 0.34
Poisson	0.29	0.07 – 0.7

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Absolute probabilities of having a hypoglycaemic event (at one year)

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	Logit		Cloglog		Poisson	
	Mean	95% CrIs	Mean	95% CrIs	Mean	95% CrIs
Detemir Once	0.04	(0.01 - 0.11)	0.1	(0.02 - 0.29)	0.37	(0.04 - 0.97)
Detemir Once/Twice	0.04	(0.01 - 0.1)	0.11	(0.03 - 0.29)	0.2	(0.03 - 0.61)
NPH Once	0.06	(0.01 - 0.17)	0.15	(0.03 - 0.43)	0.33	(0.05 - 0.86)
Glargine (Once)	0.07	(0.04 - 0.12)	0.17	(0.07 - 0.34)	0.29	(0.07 - 0.7)
NPH Once/twice	0.08	(0.04 - 0.16)	0.2	(0.07 - 0.43)	0.4	(0.08 - 0.91)
Degludec Once	0.09	(0.03 - 0.18)	0.21	(0.07 - 0.47)	0.31	(0.05 - 0.81)
Detemir Twice	0.12	(0 - 0.71)	0.26	(0 - 1)	0.38	(0 - 1)
NPH (Twice)	0.14	(0 - 0.75)	0.29	(0 - 1)	0.39	(0 - 1)

Expected costs (£)*

Treatment	Logit		Cloglog		Poisson	
	Mean	95% CrIs	Mean	95% CrIs	Mean	95% CrIs
Detemir Once	13.29	(2.97 - 36.83)	34.21	(6.88 - 97.52)	123.8	(13.21 - 323)
Detemir once/twice	14.41	(4.17 - 34.16)	38.16	(9.81 - 97.26)	66.91	(10.31 - 201.7)
NPH Once	20.42	(4.38 - 57.71)	51.11	(10.14 - 145)	110.4	(18.24 - 287.6)
Glargine Once	22.65	(11.76 - 39.04)	56.14	(22.35 - 112.6)	95.59	(22.34 - 233.5)
NPH once/twice	28.08	(12.17 - 53.85)	68.36	(24.27 - 144.5)	134.6	(27.28 - 302.8)
Degludec Once	29.63	(11.53 - 61.19)	71.1	(23.44 - 156.8)	102.7	(18.24 - 287.6)
Detemir Twice	41.67	(0.35 - 237.9)	87.82	(1.13 - 332.8)	126.7	(1.43 - 333)
NPH Twice	47.37	(0.44 - 251.1)	97.82	(1.43 - 333)	128.3	(1.55 - 333)

*Assuming a cost of £333 per severe hypoglycaemic event, estimated from Hammer et al[3]

Expected disutilites*

Treatment	Logit		Cloglog		Poisson	
	Mean	**95% CrIs**	***Mean***	**95% CrIs**	***Mean***	**95% CrIs**
Glargine Once	**-0.001**	(-0.001, 0)	**-0.002**	(-0.004, -0.001)	**-0.003**	(-0.008, -0.001)
NPH Twice	**-0.002**	(-0.009, 0)	**-0.004**	(-0.012, 0)	**-0.005**	(-0.012, 0)
Detemir Once	**0.000**	(-0.001, 0)	**-0.001**	(-0.004, 0)	**-0.004**	(-0.012, 0)
Detemir Twice	**-0.001**	(-0.009, 0)	**-0.003**	(-0.012, 0)	**-0.005**	(-0.012, 0)
Degludec Once	**-0.001**	(-0.002, 0)	**-0.003**	(-0.006, -0.001)	**-0.004**	(-0.01, -0.001)
NPH Once	**-0.001**	(-0.002, 0)	**-0.002**	(-0.005, 0)	**-0.004**	(-0.01, -0.001)
NPH once/twice	**-0.001**	(-0.002, 0)	**-0.002**	(-0.005, -0.001)	**-0.005**	(-0.011, -0.001)
Detemir once/twice	**-0.001**	(-0.001, 0)	**-0.001**	(-0.004, 0)	**-0.002**	(-0.007, 0)

*Assuming a disutility of -0.012 taken from NICE guideline on Diabetes[1]

Conclusion

- Important to ensure absolute probabilities of events are not being underestimated, particularly in health economic models where small differences can have a considerable impact on results.
- Care should be taken to choose an appropriate outcome measure when synthesizing data on repeated events for use in an economic model.

References

1. National Institute for Health and Care Excellence. Type 1 diabetes in adults: diagnosis and management. 2015 update. Clinical guideline NG17. London 2015
2. Dias S, Ades A, Sutton A, Welton N. Evidence Synthesis for Decision Making 2: A Generalized Linear Modeling Framework for Pairwise and Network Meta-analysis of Randomized Controlled Trials. Medical Decision Making. 2013;33:607-17.
3. Hammer M, Lammert M, Mejias SM, Kern W, Frier BM. Costs of managing severe hypoglycaemia in three European countries. Journal of Medical Economics. 2009; 12(4):281-290

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