Cost-Utility Analysis of Prophylactic Dextrose Gel vs Standard Care for Neonatal Hypoglycemia in At-Risk Infants

Matthew J. Glasgow, MHlthMgt[1], Richard Edlin, PhD[2], and Jane E. Harding, FRACP, DPhil[1]

Objective To evaluate the long-term costs and impact on quality of life of using prophylactic dextrose gel in patients at increased risk of developing neonatal hypoglycemia.

Study design A cost-utility analysis was performed from the perspective of the health system, using a decision tree to model the long-term clinical outcomes of neonatal hypoglycemia, including cerebral palsy, epilepsy, vision disturbances, and learning disabilities, in patients at increased risk of neonatal hypoglycemia who received prophylactic dextrose gel vs standard care. Model parameters including likelihoods of hypoglycemia and admission to a neonatal intensive care unit, were based on the pre-Hypoglycemia Prevention with Oral Dextrose Study. Estimations of the likelihood of long-term condition(s), and their costs, were based on review of published literature.

Results Patients who received prophylactic dextrose gel incurred costs to the health system of around US $14 000 over an 18-year time horizon, accruing 11.25 quality-adjusted life-years, whereas those who did not receive prophylactic treatment incurred cost of around $16 000 and experienced a utility of 11.10 quality-adjusted life-years.

Conclusions A prophylactic strategy of using dextrose gel in infants at increased risk of neonatal hypoglycemia is likely to be cost effective compared with standard care, to reduce the direct costs to the health system over an 18-year time horizon, and improve quality of life. *(J Pediatr 2020;226:80-6)*.

Neonatal hypoglycemia is a common metabolic condition in newborn infants that affects 5%-15% of all newborn infants and 50% of those with risk factors, and is frequently asymptomatic. Hypoglycemia can be associated with later neurologic and neurodevelopmental impairment even when no symptoms are seen.[1,2]

Management of neonatal hypoglycemia involves monitoring of blood glucose concentrations and the administration of supplemental carbohydrate, often initially by increased oral feeding. An infant who responds poorly to initial treatment often requires admission to a neonatal intensive care unit (NICU), which can be costly, interfere with mother-infant bonding, and impair the establishment of breastfeeding. Buccal dextrose gel for treatment of hypoglycemia reduces the risk of admission to the NICU for hypoglycemia, compared with feeding alone.[3] Admission to the NICU constitutes the greatest component of the cost difference between infants who become hypoglycemic and those who do not.[4]

Most clinical guidelines recommend screening of at-risk infants and use of prophylactic measures, predominantly encouraging early initiation of breastfeeding, or supplementary oral formula feeding.[5-9]

The pre-Hypoglycemia Prevention with Oral Dextrose (pre-hPOD Study) was a randomized, placebo-controlled, dose-finding trial of buccal dextrose gel to prevent neonatal hypoglycemia in infants at increased risk.[10] The administration of prophylactic dextrose gel at any trial dose (range, 200-1000 mg/kg) reduced the risk of developing neonatal hypoglycemia, with an overall relative risk of 0.79 (95% CI, 0.64-0.98).[10] A decrease in cases of neonatal hypoglycemia will decrease costs in both the short and long term. However, prophylaxis does not abolish the risk of hypoglycemia and also incurs costs both in those who become hypoglycemic despite prophylaxis and in the 50% of infants who would not have become hypoglycemic despite their increased risk. We therefore undertook a cost-utility analysis using a decision tree to quantify the long-term impact and costs of using prophylactic dextrose gel vs standard care in infants at increased risk of developing neonatal hypoglycemia.

Methods

We created a decision-analytic model to assess the cost effectiveness of using 40% oral dextrose gel to prevent neonatal hypoglycemia in infants at increased risk (late preterm, small or large birthweight, or infant of a diabetic mother).[11] Our analysis builds on an existing model (unpublished data 2019, available on request) that considers the postnatal hospital costs, costs due to long-term

EVPI	Expected value of perfect information
NICU	Neonatal intensive care unit
Pre-hPOD	Pre-Hypoglycemia Prevention with Oral Dextrose
QALY	Quality-adjusted life-year

From the [1]Liggins Institute and the School of Population Health, University of Auckland, Auckland, New Zealand

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clinical outcomes of neonatal hypoglycemia, and impact on quality of life, measured as quality-adjusted life-years (QALYs).

We used the input parameters from the base analysis of our preexisting neonatal hypoglycemia model, and expanded it to include an initial decision node that branches between administering prophylactic dextrose gel to the at-risk infant vs standard care without prophylaxis (**Table I**). Subsequent branching is based on the likelihood of developing hypoglycemia in the dextrose and placebo (standard care) groups, from the published pre-hPOD Study results and thereafter for all combinations of expected clinical outcomes for each of the groups that did and did not experience hypoglycemia[10,15,17,22-28] (**Figure 1**). Our initial model (unpublished data, 2019) identified the net benefit of preventing cases of neonatal hypoglycemia, based on a systematic review of the literature for publications addressing neonatal hypoglycemia and either any previously reported adverse outcomes or the assessment tools that have been used to diagnose them.[30-42] Publications were included if they were of low risk of bias and if prevalences were directly reported or able to be calculated. This model included 5 categories of clinical outcomes associated with neonatal hypoglycemia for which prevalence values were available: cerebral palsy, epilepsy (seizures beyond those during the episodes of hypoglycemia), learning disabilities (mild-moderate learning disorders, language development disorders, intellectual disability), severe learning disabilities (severe or global developmental delay), and vision disorders including blindness.[12-14,16,18-21]

We assessed costs from a health care system perspective, and modelled outcomes over an 18-year time horizon. Cost estimates were based on a systematic review of the literature.[24-28] All currencies are presented in 2018 USD unless otherwise specified. Population-level expected value of perfect information (EVPI) was calculated for a single cohort for both the US and New Zealand, with the latter being also presented in 2018 New Zealand dollars, over a 10-year time horizon, using a 3.5% discount rate and a willingness-to-pay value of $100 000.[43] The estimate is based on the cohort expected to benefit from this intervention; that is, neonates at risk of neonatal hypoglycemia, who comprise approximately 30% of annual live births.[11] Currency conversions were performed using purchasing power parities, and costs were inflated using the personal consumption expenditures health-by-function index.[29,44] In our base analysis, a discount rate of 3.5% was applied to both costs and utilities.

Table I. Decision analytic model inputs (base analysis) for the cost-utility of prophylactic dextrose gel in infants at increased risk of neonatal hypoglycemia compared with standard management

Variables	Mean	Distribution
Probabilities		
Hypoglycemia (dextrose prophylaxis)[10]	0.4116	Beta (α = 114.00, β = 163.00)
Hypoglycemia (standard care)[10]	0.5217	Beta (α = 72.00, β = 66.00)
NICU admission (dextrose prophylaxis)[10]	0.0650	Beta (α = 18.00, β = 259.00)
NICU admission (standard care)[10]	0.1014	Beta (α = 14.00, β = 124.00)
Cerebral palsy (hypoglycemic)[12-14]	0.0520	Beta (α = 52.94, β = 965.06)
Cerebral palsy (nonhypoglycemic)[15]	0.0021	Beta (α = 751.34, β = 357 030.89)
Epilepsy (hypoglycemia)[13,16]	0.0053	Beta (α = 7535.60, β = 1 414 275.40)
Epilepsy (nonhypoglycemia)[17]	0.0064	Beta (α = 183.56, β = 28 586.88)
Mild-moderate learning disorders (hypoglycemic)[12-14,18-21]	0.1560	Beta (α = 204.67, β = 1107.33)
Learning disorders (nonhypoglycemic)	0.0104	Beta (α = 623.09, β = 59 462.53)
Mild-moderate learning disorders (nonhypoglycemic)[22]	0.0097	Calculated, proportion of all learning disorders
Severe learning disorders (hypoglycemic)[13]	0.0324	Beta (α = 8.94, β = 267.06)
Severe learning disorders (nonhypoglycemic)[22]	0.0006	Calculated, proportion of all learning disorders
Blindness/vision disorders (hypoglycemic)[13]	0.0074	Beta (α = 1.98, β = 266.02)
Blindness/vision disorders (nonhypoglycemic)[23]	0.0171	Calculated, sum of subgroups (beta)
Short-term costs		
Dextrose gel[4]	$10.41	Fixed
Dextrose gel administration[4]	$7.38	Fixed
Postnatal hospital stay (hypoglycemia and NICU)[4]	$7896.86	Calculated, sum of subgroups (lognormal)[4]
Postnatal hospital stay (hypoglycemia, no NICU)[4]	$3312.60	Calculated, sum of subgroups (lognormal)[4]
Postnatal hospital stay (no hypoglycemia, NICU)[4]	$8890.37	Calculated, sum of subgroups (lognormal)[4]
Postnatal hospital stay (no hypoglycemia, no NICU)[4]	$3097.53	Calculated, sum of subgroups (lognormal)[4]
Annual cost related to childhood disability		
Cerebral palsy (per annum)[24]	$21 656	Lognormal (μ = 9.04, σ = 1.37)
Epilepsy[25]	$3605	Lognormal (μ = 7.25, σ = 1.37)
Severe learning disorder[26]	$14 388	Lognormal (μ = 8.63, σ = 1.37)
Blindness/vision disorders[27,28]	$2949	Lognormal (μ = 7.05, σ = 1.37)
Quality of life		
Baseline[29]	0.876	Fixed
Decrement for cerebral palsy[29]	0.528	Beta (α = 99.75, β = 89.17)
Decrement for epilepsy[29]	0.324	Beta (α = 4.37, β = 9.12)
Decrement for mild-moderate learning disorders[29]	0.400	Beta (α = 469.98, β = 704.97)
Decrement for severe learning disorders[29]	0.600	Beta (α = 134.45, β = 89.63)
Decrement for blindness/vision disorders[29]	0.329	Beta (α = 55.02, β = 112.21)

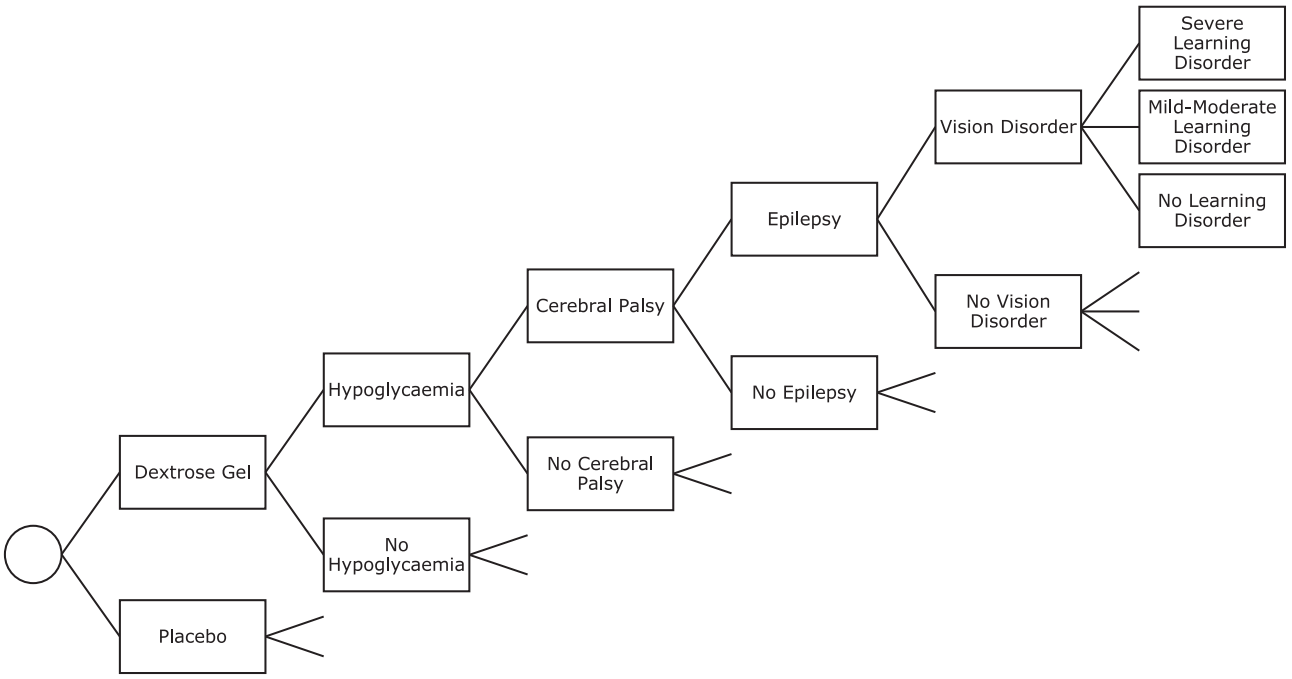

Figure 1. Decision tree for dextrose gel vs standard care in infants at risk of neonatal hypoglycemia. Open-ended branches are duplicates of their respective complementary nodes in the model.

We modelled the short-term costs of neonatal hypoglycemia, including those associated with postnatal ward stay, any NICU bed occupancy, a single dose of dextrose gel, and time for administration of dextrose gel. The component costs are consistent with our previous analysis of treating neonatal hypoglycemia with dextrose gel and assume a prefilled syringe is used.[4] The proportions of infants in the standard care group and dextrose gel groups who experienced hypoglycemia, and who required time in NICU are based on the primary data from the pre-hPOD study.[10] The overall costs are the sum of the short-term (postnatal) and long-term (over an 18-year time horizon) costs.

In our base analysis, we used the utility values for childhood conditions from the published catalogue of Kwon et al.[45]

The base and all sensitivity analyses are stochastic and present results over 100 000 simulated runs. This strategy allows analyses to ascertain the impact of simultaneous uncertainty in each input parameter on our results, presented as mean costs and QALYs, in addition to cost-effectiveness acceptability curves. In addition to assessing the impact of input parameter uncertainties, the stochastic analysis allows for estimation of uncertainties in both output parameters (costs, QALYs) and the confidence with which a cost-effective decision can be identified.

We conducted 1-way sensitivity analyses on the following aspects of our model: discount rates for costs and utilities of 0% and 5%; modelling over an 80-year time horizon; alternative sources of quality-of-life indices for childhood diseases; estimation of utility values in multiple health state outcomes using a multiplicative method; estimating the costs of multiple health state outcomes using the sum of the costs of all of the included outcomes; using only the lowest prevalence available in the literature for each major outcome; using prevalences for epilepsy and vision disorders equivalent to their prevalences in the nonhypoglycemic population; variations in the costs of dextrose gel and the cost of administration of dextrose gel; greater decrease in cases with prophylactic dextrose gel based on those pre-hPOD Study participants who received the optimal dose of dextrose gel (200 mg/kg), and had the lowest relative risk of hypoglycemia; smaller reduction in cases with prophylactic dextrose gel, that is, a greater relative risk than that reported in pre-hPOD.[46,47]

Results

Base Analysis

In our base analysis, patients who received prophylactic dextrose gel incurred costs to the health system of around $14 000 over an 18-year time horizon, and accrued 11.25 QALYs, whereas those who did not receive prophylactic treatment incurred cost of around $16 000 and accrued 11.10 QALYs (**Table II**). Prophylaxis was dominant and was likely to result in better outcomes than no prophylaxis at less cost.

Dextrose gel prophylaxis was dominant in the cost-utility plane across the majority of runs in our stochastic analysis (**Figure 2**; available at www.jpeds.com). There was more than a 98% probability that prophylactic dextrose gel was more cost effective than standard care, irrespective of the willingness to pay threshold (ie, the hypothetical value that a society will pay for an increment in quality of life[48]) (**Figure 2**). **Figure 3** displays a scatterplot on the cost-

Table II. Results of the base case and sensitivity analyses for modified input parameters/distributions (18-year time horizon unless otherwise stated)

Analyses	Cost, dextrose (US$)	Utility, dextrose (QALYs)	Cost, standard care (US$)	Utility, standard care (QALYs)	ICER
Base analysis	$13 651.19	11.25	$16 076.97	11.10	−$16 889.68
Sensitivity analyses					
80-year time horizon	$24 038.82	22.81	$28 766.13	22.52	−$16 229.83
80-year time horizon; optimal (minimum) dextrose gel cost	$23 921.86	22.81	$28 636.01	22.51	−$16 180.34
Sum of long-term outcome costs	$13 759.90	11.25	$16 224.09	11.10	−$17 145.89
Multiplication of outcome utilities	$13 717.98	11.23	$16 165.51	11.08	−$16 671.91
Petrou et al[47] catalog for outcome utilities	$13 658.09	11.80	$16 076.95	11.63	−$14 228.39
Carrol et al[46] catalog for outcome utilities, TTO method of estimation	$13 582.03	13.04	$15 992.84	12.91	−$19 266.45
Carrol et al[46] catalog for outcome utilities, SG method of estimation	$13 651.42	13.04	$16 064.29	12.92	−$19 330.92
Optimal (minimum) dextrose gel cost	$13 588.78	11.25	$16 013.06	11.10	−$16 874.74
Low dextrose gel administration costs (75% of base analysis)	$13 775.10	11.25	$16 222.54	11.10	−$17 066.49
High dextrose gel administration costs (125% of base analysis)	$13 694.20	11.25	$16 120.55	11.10	−$16 875.90
0% discount rate	$16 832.02	14.83	$19 971.46	14.64	−$16 604.65
5.0% discount rate	$12 719.75	10.11	$14 945.22	9.98	−$17 227.75
Minimum prevalence value from selected sources	$7854.09	11.66	$8734.68	11.63	−$26 893.63
Variations on epilepsy and visual disorder prevalences	$13 803.91	11.23	$16 268.67	11.08	−$16 693.00
Lower relative risk of neonatal hypoglycemia with dextrose gel (68.0%) using data for 200 mg/kg dosing	$12 809.45	11.29	$16 925.21	11.06	−$17 741.49
Higher relative risk of neonatal hypoglycemia with dextrose gel (99.9%)	$16 108.56	11.10	$16 101.97	11.10	$9690.39

ICER, incremental cost-effectiveness ratio; *SG*, standard gamble; *TTO*, time trade-off.

effectiveness plane, in which most points fall in the southeast quadrant of the diagram.

Our model estimated an overall EVPI, which represents the cost of uncertainty in our model due to input parameter uncertainty, or the maximum potential value of additional research to resolve that uncertainty, of $42.80 per person.[48,49] In the US, where there are approximately 3 855 500 live births per year, of whom 1 156 650 are born at risk of neonatal hypoglycemia, the population-level EVPI is $430 000 000; in New Zealand, where there are approximately 58 000 live births per year with 17 400 at risk of neonatal hypoglycemia, the population-level EVPI is $6 400 000 (New Zealand $9 400 000).[50,51]

Sensitivity Analyses

The ICER estimated over an 80-year time horizon (with the model otherwise identical to our base analysis) favored dextrose gel prophylaxis, as did the ICER over an 18-year time horizon in all of our univariate sensitivity analyses

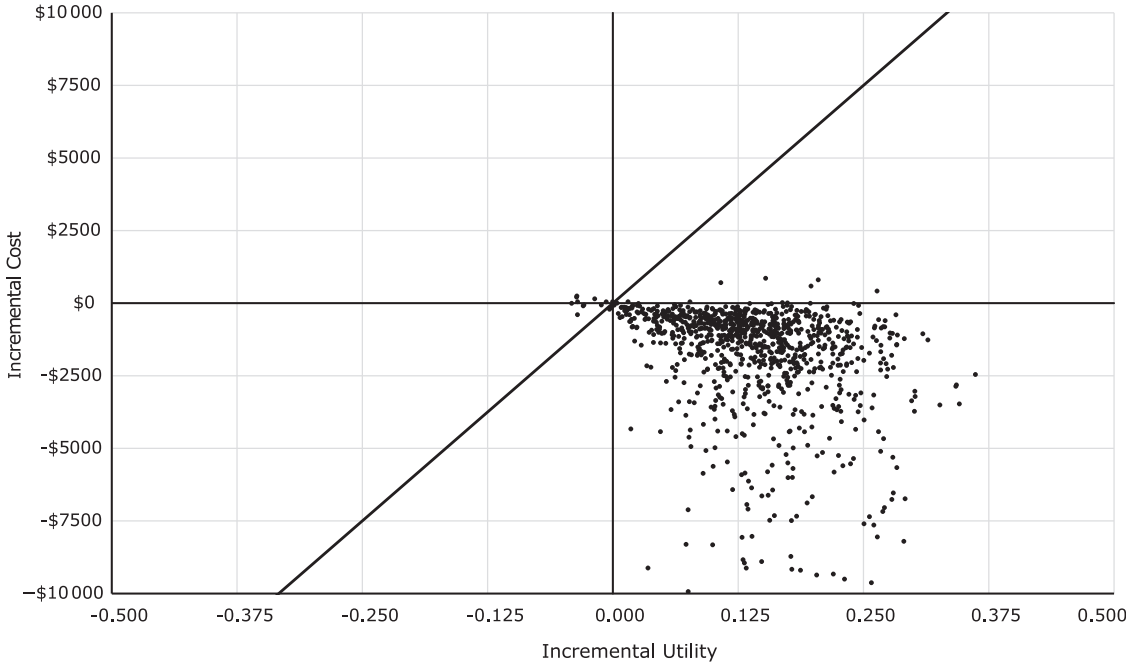

Figure 3. Cost-utility plane for dextrose gel vs standard care (first 2000 runs, 18-year time horizon). Diagonal line represents a willingness-to-pay threshold of $30 000 per QALY.

(Table II). Using alternative methods to estimate the long-term costs (sum of all of the relevant long-term outcome costs) and outcome utilities of multiple health state outcomes (multiplication of relevant long-term outcome utilities) preserved the original result that dextrose gel prophylaxis dominated the comparator of standard care. Using alternative catalogues of quality of life indices for childhood conditions resulted in higher cumulative QALYs at 18 years for both dextrose gel and standard care groups, and ICERs of –$14 000 and –$19 000 per QALY using the catalogues of Petrou and Kupek and Carrol and Downs (both standard gamble and time trade-off estimation methods), respectively.[46,47] The greatest difference in overall cost estimations, and increase in the magnitude of the ICER to approximately –$27 000, came from reducing the hypoglycemia-associated outcome prevalence input parameter to the lowest level found in any of the sources included in our initial systematic review.

Varying the estimations of dextrose gel cost to the lowest cost option of using a single 1.5-mL dose from a 100-mL multidose container of gel and of administration costs to 125% and 75% of that estimated in our base analysis resulted in overall costs and ICERs that approximate those of our base analysis (Table II).

In the additional sensitivity analyses (Table II), prophylaxis remained likely to dominate. Alternative discount rates applied to costs and outcomes (0% and 5%), and using prevalence values for epilepsy and visual disorders that equate to those of the nonhypoglycemic population each resulted in ICERs of approximately –$17 000. Assuming dextrose gel prophylaxis is either more effective (decrease relative risk of hypoglycemia to 0.68 based on the optimal dose of 200 mg/kg[10]) or less effective (increase relative risk to 0.999) the ICERs were approximately –$18 000 and $9 700, respectively.[10] Thus, even in the hypothetical situation where prophylactic dextrose gel only marginally decreased the likelihood of neonatal hypoglycemia, dextrose gel provided outcomes at sufficiently low cost that it would normally be considered cost effective.

Discussion

Prophylactic oral dextrose gel has previously been shown to decrease the incidence of neonatal hypoglycemia among infants at increased risk.[10] The gel itself, and the staff time taken for its administration, incur costs whether or not hypoglycemia and its complications are avoided. However, our stochastic analysis shows that this prophylactic strategy, compared with standard care, is cost effective and is likely to decrease the direct costs to the health system over an 18-year time horizon, and improve the quality of life of the individual, with an ICER (the incremental cost to achieve an improvement in quality of life) of $17 000 per QALY. This cost per QALY is well below the commonly used cost-effectiveness threshold of $50 000 per QALY gained to determine if an intervention is cost effective.[52,53]

Missing or undertreating cases of neonatal hypoglycemia will impact on short- and long-term clinical outcomes, and incur direct health-related costs. Even when screening detects asymptomatic hypoglycemia, treatment has a financial and quality-of-life cost. The risk of neonatal hypoglycemia is notably higher in an identifiable subset of the newborn population, and in this group, prophylactic strategies may be considered. Buccal dextrose gel has been shown to be well tolerated as a treatment agent, and as a preventive strategy it reduces the risk of neonatal hypoglycemia.[3,10] We have shown that, despite knowledge gaps pertaining to the long-term consequences of neonatal hypoglycemia, this decrease in risk seems to be a cost-effective approach to improve the outcomes of at risk infants based on the existing, published evidence.

Our base analysis considered a very conservative scenario, with inflated values for the costs of dextrose gel and its administration. Despite this, dextrose gel remained cost effective. The direct costs of dextrose gel and its administration are minimal in the context of our overall model, so wide variations in these parameters are unlikely to alter our conclusions. We also considered alternative approaches to assessing quality of life of the population, and to estimating the prevalences of long-term outcomes in our sensitivity analyses. An advantage of our model is that it can be revised to reflect additional follow-up data coming from future trial cohorts, including that of the hPOD Study.[54]

In the context of uncertainties inherent in our model owing to, in particular, the paucity of data about the prevalences of long-term hypoglycemia-associated outcomes, the EVPI is high when calculated for the US ($430 000 000), but more moderate for New Zealand ($6 400 000). This finding represents the monetary value of eliminating uncertainty related to the use of prophylactic dextrose gel in this population.[48,49] Although an EVPI of greater than zero is a necessary condition for additional research, whether such research will be cost effective will depend on how much uncertainty will be decreased by that research and whether this exceeds the costs of the research. Depending on the nature of this research, the expected value of sample information may be a useful measure here, although given the long time period required before such research is likely to inform decision making, a measure incorporating time such as the expected net present value of sample information may be more appropriate.[55] Additional research that decreases uncertainty in the model by elucidating, for example, the prevalence of the long-term outcomes of neonatal hypoglycemia, may be justified if its overall cost reduces the EVPI by more than the research costs.

The limitations of our model largely pertain to uncertainty about probabilities and costs of the long-term clinical outcomes of neonatal hypoglycemia. Methodologic uncertainties in outcome prevalence estimates may stem from the fact that prevalences have been collected across different countries and populations, and from disparate sources that

do not robustly account for the impact of patients who have more than one outcome of interest. Although we have sought to reflect this uncertainty, it may not be fully represented in our model, and our parameter uncertainty may therefore underestimate the true uncertainty in the outcome prevalences. This means that the cost-effectiveness acceptability curve may give a number that is misleadingly high and the EVPI may be too low. Correlations between the components of multiple health state outcomes, which we have not specifically modelled, mean that our estimations of their prevalences have greater uncertainties than those of single health state outcomes. However, the combined prevalences of all of the multiple health state outcome combinations appear to be small compared with the likelihood of the single health state outcomes, mitigating the impact of their uncertainties on our model and estimations.

We have not specifically examined the possible costs of adverse effects of dextrose gel prophylaxis, but when used for the treatment of hypoglycemia, the gel does not increase the risk of recurrent or rebound hypoglycemia, and is not associated with any adverse effects either in the short term or up to 2 years of age.[3,56] Dextrose gel prophylaxis has also been shown to not impact on breastfeeding rates at discharge or 6 weeks.[10] On this basis, we have assumed that it will not negatively impact the long-term clinical outcomes, including of patients who would not have become hypoglycemic even without prophylaxis.

Although future longitudinal trials to assess the relationship between neonatal hypoglycemia and neurodevelopment out to at least school age may decrease uncertainties in the outcome prevalence model inputs, the complexities and heterogeneity of the long-term costs of neurologic and neurodevelopmental impairment will likely remain a challenge. However, we have shown, by way of sensitivity analyses that test modelling assumptions and uncertainties, that prophylactic dextrose gel appears to be cost effective even if it reduces cases of neonatal hypoglycemia by only a small amount.

Our economic analysis supports the use of prophylactic dextrose gel to prevent neonatal hypoglycemia in infants at increased risk, on the basis that it will improve the average quality of life of that population, and that any reduction in cases will decrease hypoglycemia-related costs to the health system. Given the overall prevalence of neonatal hypoglycemia, and the size of the at-risk infant population, the cost savings are likely to be significant. ■

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Reprint requests: Jane E. Harding, FRACP, DPhil, Liggins Institute, Private Bag 92019, Grafton, Auckland 1142, New Zealand. E-mail: j.harding@auckland.ac.nz

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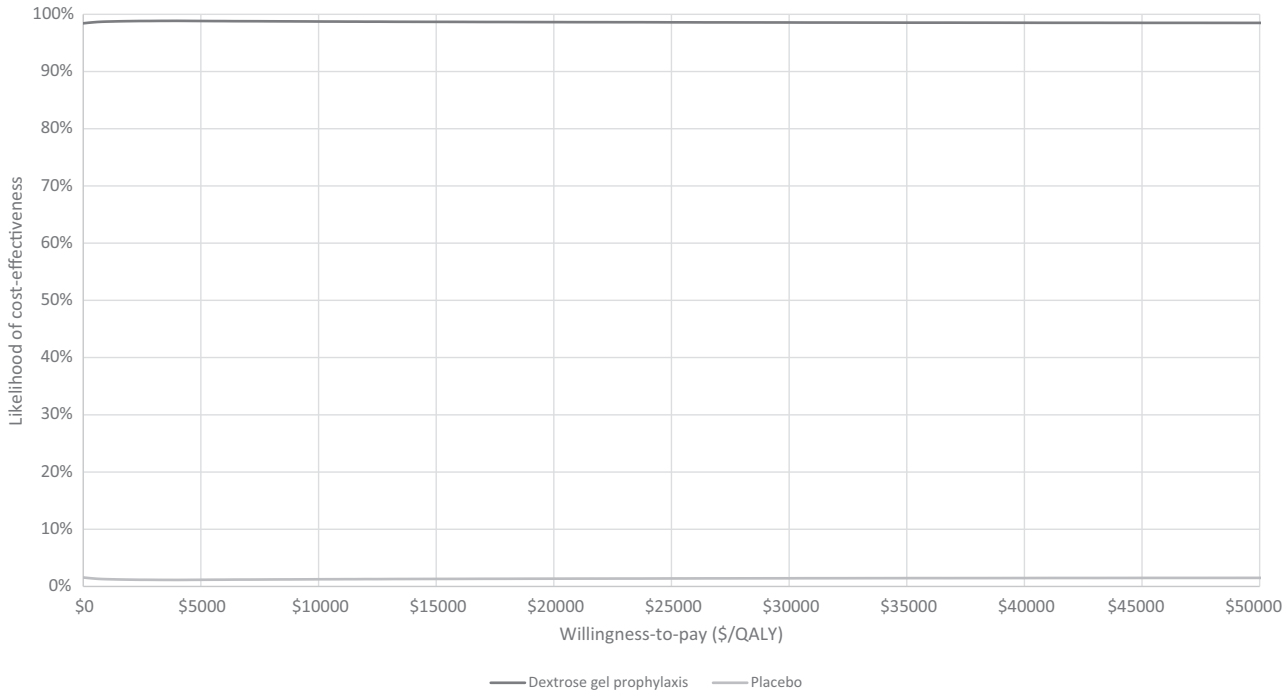

Figure 2. Cost-effectiveness acceptability curve for dextrose gel vs standard care.