

# BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email [editorial.bmjopen@bmj.com](mailto:editorial.bmjopen@bmj.com)

# BMJ Open

## A COST EFFECTIVENESS COMPARISON OF THE NICE 2015 AND WHO 2013 DIAGNOSTIC CRITERIA FOR GESTATIONAL DIABETES

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-016621
Article Type:	Research
Date Submitted by the Author:	03-Mar-2017
Complete List of Authors:	Jacklin, Paul; Royal College of Obstetricians and Gynaecologists, National Guideline Alliance Maresh, Michael; Central Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre Patterson, Chris; Queen's University Belfast, Centre for Public Health Stanley, Katharine; Norfolk and Norwich University Hospitals NHS Foundation Trust, Department of Obstetrics and Gynaecology Dornhorst, Anne; Hammersmith Hospital, Department of Investigative Medicine Burman-ROY, Shona; Royal College of Obstetricians and Gynaecologists, National Guideline Alliance Bilous, Rudy; Newcastle University Medicine Malaysia
<b>Primary Subject Heading</b>:	Health economics
Secondary Subject Heading:	Diabetes and endocrinology, Obstetrics and gynaecology, Diagnostics
Keywords:	HEALTH ECONOMICS, DIABETES & ENDOCRINOLOGY, OBSTETRICS

SCHOLARONE™  
Manuscripts

1  
2  
3 **Title:**  
4

5 A COST EFFECTIVENESS COMPARISON OF THE NICE 2015 AND WHO 2013  
6  
7 DIAGNOSTIC CRITERIA FOR GESTATIONAL DIABETES  
8

9  
10  
11 **Authors:** PB Jacklin<sup>1</sup>, MJA Maresh<sup>2</sup>, CC Patterson<sup>3</sup>, KP Stanley<sup>4</sup>, A Dornhorst<sup>5</sup>, S Burman-  
12 Roy<sup>1</sup>, RW Bilous<sup>6</sup>  
13  
14  
15  
16  
17

18 **Institutions:**  
19

- 20 1. Royal College of Obstetricians and Gynaecologists, London NW1 4RG, UK  
21  
22 2. St. Mary's Hospital, Central Manchester University Hospitals NHS Foundation Trust,  
23 Manchester Academic Health Science Centre, Manchester M13 9WL, UK  
24  
25 3. Centre for Public Health, Queen's University Belfast, Room 3.014, ICS Block B, Grosvenor Road,  
26 Belfast BT12 6BJ, UK  
27  
28 4. Department of Obstetrics and Gynaecology, Norfolk and Norwich University Hospitals NHS  
29 Foundation Trust, Colney Ln, Norwich NR4 7UY, UK  
30  
31 5. Faculty of Medicine, Department of Investigative Medicine, Hammersmith Hospital, Imperial  
32 College London, London, UK  
33  
34 6. Newcastle University Medicine Malaysia, Johor, Malaysia  
35  
36  
37  
38

39 **Corresponding author:**  
40

41 Paul Jacklin  
42 e-mail: [pjacklin@rcog.org.uk](mailto:pjacklin@rcog.org.uk)  
43  
44

45  
46 Abstract: 278 words  
47

48 Main text: 4618 words  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 29 **Abstract**  
4

5 30

6 31 **Objectives** To compare the cost effectiveness of The National Institute for Health and Care  
7  
8  
9 32 Excellence (NICE) 2015 and the World Health Organisation (WHO) 2013 diagnostic thresholds  
10  
11 33 for gestational diabetes (GDM).

12  
13 34 **Setting:** The analysis was from the perspective of the National Health Service (NHS) in  
14  
15 35 England and Wales.

16  
17 36 **Participants:** 6,221 patients from 4 of the Hyperglycaemia and Adverse Pregnancy Outcomes  
18  
19 37 (HAPO) study centres (2 UK, 2 Australian), 6,308 patients from the Atlantic Diabetes in  
20  
21 38 Pregnancy (DiP) study and 12,755 patients from UK clinical practice

22  
23 39 **Primary and secondary outcome measures planned:** The incremental cost per quality  
24  
25 40 adjusted life year (QALY), net monetary benefit (NMB) and the probability of being cost-  
26  
27 41 effective at cost-effectiveness thresholds of £20,000 and £30,000 per QALY

28  
29 42 **Results.** In a population of pregnant women from the 4 HAPO study centres, and utilising  
30  
31 43 NICE defined risk factors for GDM, diagnosing GDM using NICE 2015 criteria had an  
32  
33 44 incremental cost effectiveness ratio (ICER) of £23,073 per QALY gained compared to £37,669  
34  
35 45 per QALY gained using WHO 2013 diagnostic criteria. At a cost-effectiveness threshold of  
36  
37 46 £30,000 per QALY the NICE 2015 criteria had a 43.4% probability of being cost-effective  
38  
39 47 compared to the WHO 2013 diagnostic criteria which had a 34.7% probability of being cost-  
40  
41 48 effective (no treatment had a 21.9% probability of being cost-effective). The ICERs for women  
42  
43 49 without NICE risk factors in this population were £43,845 and £220,638 per QALY for NICE  
44  
45 50 and WHO diagnostic criteria, respectively.

46  
47 51 **Conclusion** The NICE 2015 diagnostic criteria for GDM can be considered cost-effective  
48  
49 52 relative to the WHO 2013 alternative at a cost-effectiveness (CE) threshold of £30,000 per  
50  
51 53 QALY. Universal screening for GDM was not found to be cost-effective relative to screening  
52  
53 54 based on NICE risk factors.  
54

1  
2  
3 55  
4  
5 56  
6  
7 57  
8  
9 58  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

**Keywords:** Cost Effectiveness, Gestational Diabetes, Screening, Risk Factors, Diagnosis

For peer review only

1  
2  
3 59 **Strengths and limitations of this study**  
4

- 5 60 • This economic evaluation address an important clinical and policy issue. The existing  
6  
7 61 economic evidence is limited and WHO have stated that studies of this type are needed  
8  
9 62 to inform a future update of their guideline  
10  
11 63 • Our paper has used patient-level data from the influential HAPO study for an economic  
12  
13 64 analysis which has not been previously been published in a peer reviewed journal.  
14  
15 65 • This analysis provides strong evidence that universal screening is not cost-effective in  
16  
17 66 the UK  
18  
19 67 • This analysis suggests that the NICE diagnostic criteria for GDM are more cost-  
20  
21 68 effective than the WHO criteria in the UK context  
22  
23 69 • Model conclusions are sensitive to uncertainties with respect to valuation of health  
24  
25 70 outcomes and the possible long term metabolic consequences for offspring for which the  
26  
27 71 evidence is debated and which are hard to quantify  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## 72 Introduction

73 The diagnostic glycaemic thresholds for GDM remain the subject of considerable debate. The  
74 original definition was based upon maternal risk for developing post partum diabetes, but  
75 subsequent thresholds have concentrated on complications during pregnancy and the health of  
76 the offspring. Since the publication of the HAPO study<sup>1</sup> showing that there was a linear  
77 association between increasing levels of maternal hyperglycaemia and adverse perinatal  
78 outcomes with no obvious threshold, the discussion around the diagnostic criteria that should  
79 define GDM has intensified. New diagnostic thresholds were proposed by the International  
80 Association of Diabetes in Pregnancy Study Group (IADPSG)<sup>2</sup> based upon the HAPO study  
81 levels of plasma glucose when fasting, and at 1 and 2 hours after an oral 75g glucose load that  
82 were associated with covariate adjusted odds ratio of 1.75 relative to the mean glucose value in  
83 the whole HAPO cohort on three offspring outcomes: exceeding the 90<sup>th</sup> centile for birth  
84 weight, for cord serum C-peptide concentration and for percent fetal body fat. These diagnostic  
85 criteria have been subsequently adopted by the WHO.<sup>3</sup> However, they remain controversial, and  
86 have not been supported by bodies such as the National Institutes for Health and the American  
87 College of Obstetricians.<sup>4</sup> Furthermore, WHO has acknowledged that they will have to be  
88 revisited in the near future in the light of new studies reporting their cost-effectiveness.<sup>3</sup>

89  
90 In 2015 the NICE published updated guidance on Diabetes in Pregnancy<sup>5</sup> which included  
91 recommendations on diagnostic thresholds for GDM which differ from those adopted by WHO.  
92 These NICE thresholds were informed by an economic evaluation of the type that WHO  
93 considered important to inform future recommendations, but have attracted criticism in the UK<sup>6</sup>  
94 and elsewhere. Data from a recently published Spanish study<sup>7</sup> have been widely cited<sup>6,8</sup> in  
95 support of the cost effectiveness of the WHO criteria.

96

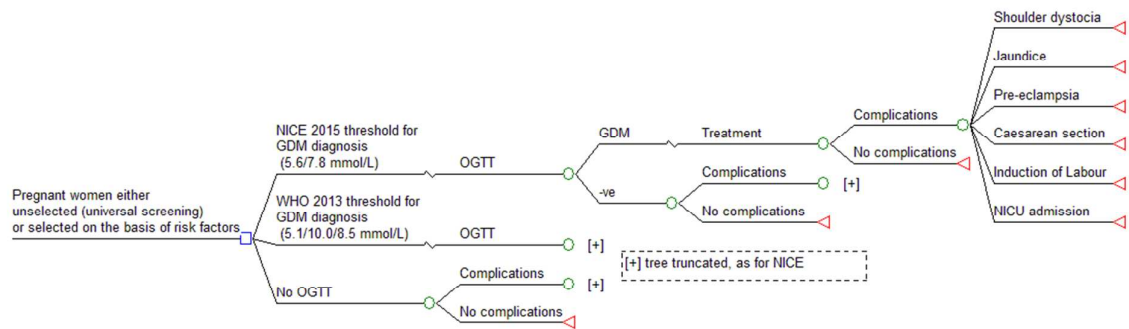
97 In this paper we compared the cost-effectiveness of NICE 2015 and WHO 2013 diagnostic  
 98 thresholds for GDM. The analysis was undertaken using a revised version of the health  
 99 economic model developed for the NICE guideline and was based upon data from the UK and  
 100 Australian HAPO Study centres.

102 **Methods**

103 *Model description*

104 A decision analytic framework was used to evaluate the cost effectiveness of two recently  
 105 proposed diagnostic thresholds for GDM, together with a no diagnosis/no treatment option (See  
 106 Table 1). A schematic of the model is shown in **Error! Reference source not found.** Cost-  
 107 effectiveness was evaluated using both deterministic and probabilistic sensitivity analysis.

109 **Figure 1: Model Schematic**



111



112 **Table 1:** Diagnostic thresholds for plasma glucose evaluated in the economic model

Threshold name	Fasting (mmol/L)	1-hour (mmol/L)	2-hour (mmol/L)
No diagnosis/no treatment	-	-	-
NICE 2015	$\geq 5.6$	-	$\geq 7.8$
WHO 2013	$\geq 5.1$	$\geq 10.0$	$\geq 8.5$

113

114 *Population*

115 The model population comprised women of gestational age 24-28 weeks without pre-existing  
 116 diabetes. The analysis utilised individual patient data from three datasets which, although not  
 117 restricted to the UK, provide a representative cross section of the demographic and patient  
 118 characteristics that would be found in the UK. The analyses were run separately for each dataset  
 119 and, where possible, for subgroups with and without risk factors for GDM within a dataset.

120

121 i. HAPO – a dataset from the two UK (Manchester and Belfast) and two Australian  
 122 (Brisbane and Newcastle) centres of the HAPO Study, referred to as HAPO (4)

123 ii. Norwich – these data were routinely collected between 2008 and February 2014 on  
 124 women who had an oral glucose tolerance test (OGTT) on the basis of the presence of one or  
 125 more risk factors for GDM. The results were obtained from laboratory records with no  
 126 identifiers. Risk factors in addition to those recommended by NICE were used e.g. women with  
 127 polycystic ovary syndrome, previous stillbirth or recurrent glycosuria.

128 iii. Atlantic Diabetes in Pregnancy (Atlantic DiP) – these data were collected between 2007  
 129 and 2013 as part of a research initiative in the Republic of Ireland intended to improve  
 130 pregnancy outcomes for women with diabetes before, during and after pregnancy.

131

1  
2  
3 132 For the HAPO (4) and Atlantic DiP datasets the populations were stratified according to  
4  
5 133 whether or not they had NICE risk factors for GDM (body mass index (BMI) above 30 kg/m<sup>2</sup>,  
6  
7 134 previous baby with birthweight  $\geq 4.5$  kg, previous GDM, first-degree relative with diabetes and  
8  
9 135 minority ethnic family origin with a high prevalence of diabetes). This facilitated a comparison  
10  
11 136 of the cost-effectiveness of universal screening for GDM when compared with a risk factor  
12  
13 137 approach.  
14  
15  
16  
17

18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

138  
139 The NICE risk factor approach could not be replicated exactly because the patient data used in  
140 the model do not include information on previous offspring birth weight, and the HAPO (4)  
141 dataset does not provide information on previous GDM. Therefore, the comparison in the model  
142 was between universal screening and a subset of NICE risk factors.  
143

#### 144 *Clinical outcomes*

145 The agreed outcomes for the economic model were selected prior to model development by the  
146 NICE Guideline Development Group. They were:

- 147 i. Shoulder dystocia (SD) – this was used to estimate serious perinatal complications  
148 (SPC), a broader composite outcome (death, shoulder dystocia and birth trauma) used as  
149 a primary outcome in clinical trials. The estimation of SPC from shoulder dystocia has  
150 been described elsewhere.<sup>5</sup>
- 151 ii. Caesarean section (CS)
- 152 iii. Neo-natal intensive care unit (NICU) admission
- 153 iv. Jaundice requiring phototherapy (Jaund)
- 154 v. Pre-eclampsia (PE)
- 155 vi. Induction of labour (IOL)

1  
2  
3 156 Outcomes were prioritised for inclusion in the model if they had a direct impact on health  
4  
5 157 related quality of life and/or cost. Birth weight was not included because there were few long-  
6  
7 158 term outcome data for modelling any risk benefit of a reduction in birth weight for future  
8  
9 159 diabetes and other health outcomes in the offspring.

10  
11  
12 160

13  
14 161 In addition, outcomes were only included if the relationship with plasma glucose levels had  
15  
16 162 been established in the HAPO study, and also that they had been assessed in intervention  
17  
18 163 studies used to derive treatment effect size estimates. Possible double counting of certain  
19  
20 164 outcomes was taken into account (e.g. preterm birth and NICU admission). The final list of  
21  
22 165 outcomes included in the model was therefore a pragmatic one.

23  
24  
25 166

26  
27 167 *Baseline risk*

28  
29 168 Logistic regression analyses of patient data from HAPO (4) were used to predict a baseline risk  
30  
31 169 for all six outcomes for each woman, based on their characteristics including their OGTT  
32  
33 170 results. In the HAPO study the OGTT was blinded to the carers, unless there was overt diabetes,  
34  
35 171 thus allowing direct comparison of the OGTT with perinatal outcomes without intermediate  
36  
37 172 treatment effects for those meeting the new diagnostic criteria for GDM.

38  
39  
40 173 For each of the six outcomes, 2 logistic analyses to predict risk were assessed:

41  
42  
43 174 i. Prediction based on OGTT plasma glucose results and including the same covariates as  
44  
45 175 used for Model 2 in the original analysis of the HAPO data<sup>1</sup> – this could not be applied  
46  
47 176 to the Norwich and Atlantic DiP datasets as information on all HAPO covariates was not  
48  
49 177 available.

50  
51 178 ii. Prediction based only on OGTT plasma glucose results

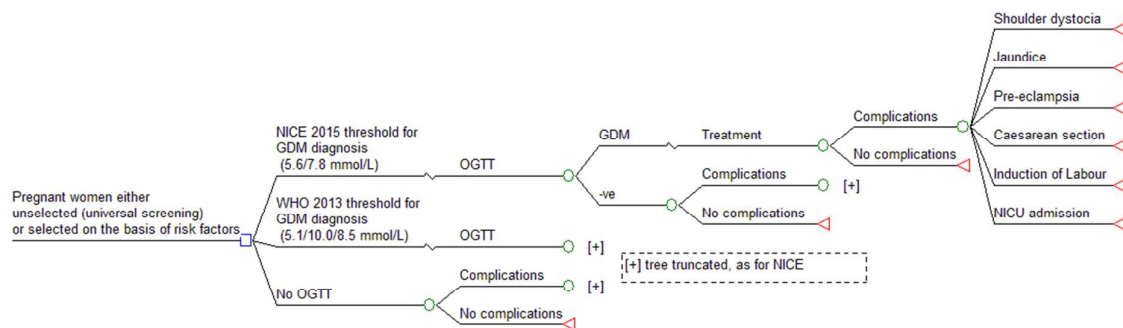
52  
53  
54 179 Backward elimination of plasma glucose variables with non-significant coefficients was  
55  
56 180 undertaken to arrive at a ‘final’ logistic regression analysis to predict baseline risk for each  
57  
58  
59  
60

1  
2  
3 181 outcome for the base case analysis, although a sensitivity analysis is also presented where the  
4  
5 182 model was run with plasma glucose variables with non-significant coefficients retained. The  
6  
7 183 logistic regression analyses used to predict the baseline risk for each outcome are shown in the  
8  
9  
10 184 Supplementary Report, Tables x1 to x6.

11  
12 185

13  
14 186 *Clinical effectiveness*

15  
16  
17 187 For each evaluated diagnostic threshold in



18 188

1  
2  
3 189 Table 1 the model determined whether a woman would be identified as having GDM based on  
4  
5 190 her OGTT. If the woman was not identified as having GDM then outcome probabilities were  
6  
7 191 based on the predicted baseline risk, but for women identified as having GDM the predicted  
8  
9 192 baseline risk was modified to take account of the effects of treatment. Treatment effectiveness  
10  
11 193 for most outcomes was estimated from a random-effects meta-analysis of two studies,  
12  
13 194 Australian Carbohydrate Intolerance Study (ACHOIS) and the Landon et al. trial.<sup>9, 10</sup> Other  
14  
15 195 published studies of treatment for GDM were adjudged to lack adequate randomisation.<sup>11</sup> For  
16  
17 196 the NICU outcome only the Landon et al. trial data were used as it was considered to more  
18  
19 197 closely represent UK practice as they utilised all neonatal nursery admissions. Similarly, the  
20  
21 198 incidence of pre-eclampsia seemed high in ACHOIS in both arms, and again only Landon et al.  
22  
23 199 trial data were utilised. The treatment effects for each of the model's clinical outcomes are  
24  
25 200 shown in Table 2 along with parameters for probabilistic sampling. The model assumes that the  
26  
27 201 relative treatment effect will be the same irrespective of the absolute baseline risk. For  
28  
29 202 deterministic analyses the point estimate of relative risk was used but in order to account for  
30  
31 203 uncertainty in these point estimates, these relative risks were sampled from a log-normal  
32  
33 204 distribution in the simulations undertaken for probabilistic sensitivity analysis (PSA).  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44

206 **Table 2:** Relative treatment effects for model outcomes

Outcome	Relative risk (RR)	Standard error (log RR)	Source
Shoulder dystocia	0.41	0.316	ACHOIS (2005), Landon (2009)
Caesarean section	0.88	0.095	ACHOIS (2005), Landon (2009)

<b>NICU</b>	0.77	0.194	Landon (2009)
<b>Jaundice requiring phototherapy</b>	0.83	0.136	ACHOIS (2005), Landon (2009)
<b>Pre-eclampsia</b>	0.46	0.345	Landon (2009)
<b>Induction of Labour</b>	1.16	0.126	ACHOIS (2005), Landon (2009)

207

208

For peer review only

1  
2  
3 209 *Costs*

4  
5 210 Costing was undertaken from the perspective of the NHS and was calculated for each woman in  
6  
7 211 the dataset being analysed and made up of three components;

- 8  
9  
10 212 • the costs of the diagnostic test – not applied in the *no test/no treat* strategy  
11  
12 213 • the costs of treatment- applied to every woman diagnosed with GDM at a particular  
13  
14 214 threshold  
15  
16 215 • the costs associated with the various outcomes – with the cost for each woman being the  
17  
18 216 expected (or average) cost of the outcome based on her estimated risk

19  
20  
21 217 The costs calculated for each woman were then summed across the entire patient dataset to give  
22  
23 218 a total cost for a particular diagnostic threshold.

24  
25 219

26  
27 220 Costs were taken from published UK sources where possible (cost year 2015) and have not been  
28  
29 221 discounted as they are all assumed to occur within 12 months of diagnosis. Model unit costs are  
30  
31 222 reported in the Supplementary Report, Table x7.

32  
33 223

34  
35 224 *Other event probabilities*

36  
37 225 Probabilities in decision analysis were used to calculate the expected costs and benefits of the  
38  
39 226 various comparators. Many of these probabilities stemmed from relative treatment effects but a  
40  
41 227 few additional event probabilities were included in the model in order to estimate certain costs.

42  
43 228 These probabilities are shown in Table 3 and their source is described elsewhere.<sup>5</sup>

44  
45 229

46  
47 230

48  
49 231

50  
51 232

233 **Table 3:** Model event probability not derived from patient level regression

Event	Probability
Not requiring hypoglycaemic therapy when treated for GDM	36%
Risk of hypoglycaemia if taking hypoglycaemic therapy	20%
Risk of hypoglycaemia being severe (requiring hospitalisation)	5%

234

235 *Quality Adjusted Life Years (QALYs)*

236 Following previous studies<sup>5, 16</sup> a QALY decrement of 2.2 was assigned to serious perinatal  
 237 complications (SPC), defined as per the ACHOIS study as a composite outcome of shoulder  
 238 dystocia, death and birth trauma.<sup>9</sup> More detail on the derivation of this QALY loss is provided  
 239 in the Supplementary Report. The cost-effectiveness of a healthcare intervention is determined  
 240 by the opportunity cost of the health foregone on the basis that with a fixed health budget any  
 241 newly funded intervention would displace the least cost-effective treatment currently provided.  
 242 In the UK, NICE typically uses a threshold of £20,000 to £30,000 per QALY as a benchmark<sup>17</sup>  
 243 for the opportunity cost of health foregone and this paper assesses cost-effectiveness  
 244 accordingly.

245

246 *Sensitivity analysis*

247

248 Probabilistic sensitivity analysis, using Monte Carlo simulation (with 2,000 iterations for each  
 249 analysis), was undertaken in order to assess the impact of sampling uncertainty on model inputs.  
 250 Parameters and distributions for the probabilistic sensitivity analysis are given in Table 2 and  
 251 Table x7 in the supplementary report **Error! Reference source not found.** For the logistic  
 252 regression coefficients used to predict baseline risk, the Cholesky decomposition method<sup>18</sup> was



253 used to sample from a multivariate normal distribution in order to reflect correlations between  
254 the coefficients.

255

## 256 Results

257 Table 4 shows the percentage of women diagnosed with GDM in the three populations using  
258 both of the evaluated diagnostic thresholds. In addition, for the HAPO (4) and Atlantic DiP  
259 datasets this is additionally broken down in the subgroups with and without NICE risk factors  
260 (RF).

261 **Table 4:** Percentage of women identified with GDM by threshold and population

Threshold name	Norwich (n=12,754)	HAPO all (n=6,163)	HAPO RF (n=3,549)	HAPO No RF (n=2,614)	DiP All (n=5,290)	DiP RF (n=1,988)	DiP No RF (n=3,302)
NICE 2015	7.0%	13.6%	17.7%	8.0%	13.1%	25.0%	5.9%
WHO 2013	13.9%	18.9%	25.7%	9.7%	21.2%	37.7%	11.2%

262

263 Detailed deterministic and probabilistic results for HAPO (4) with risk factors are shown in  
264 Table 5, Table 6, Table 7 and

265

266

267

268

1  
2  
3 269 **Figure 2.**

4  
5 270

6  
7 271 **Table 5:** *Clinical outcomes for HAPO (4) population with NICE risk factors (n=3,549)*

Diagnostic threshold	Diagnosed	SD	SPC	CS	NICU	Jaund	PE	IOL
No Treatment	0	49	67	759	345	219	146	974
NICE 2015	629	41	56	739	326	210	123	1,004
WHO 2013	912	39	54	731	321	207	117	1,016

8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21 272

22  
23 273 **Table 6:** *Deterministic analysis for the HAPO (4 centres) population with NICE risk factors*  
24 274 *(n=3,549)*

Diagnostic threshold	Cost	QALY	Incremental cost	Incremental QALY	ICER
No Treatment	£0	0.00	n/a	n/a	n/a
NICE 2015	£546,349	23.68	£546,349	23.68	£23,073
WHO 2013	£778,993	29.86	£232,644	6.18	£37,669

25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37 275

38  
39 276 Table 5 indicates that there was a relatively small difference in clinical outcomes contrasting  
40  
41 277 NICE and WHO diagnostic criteria, despite there being a 45% increase in women diagnosed  
42  
43 278 with GDM. Using the WHO 2013 criteria, instead of the NICE 2015 criteria, an additional 142  
44  
45 279 women would have had to be diagnosed with GDM, and treated in order to prevent 1 case of  
46  
47 280 shoulder dystocia.

48  
49  
50 281

51  
52 282 In the deterministic analysis the NICE 2015 diagnostic criteria would be considered cost-  
53  
54 283 effective at a cost-effectiveness threshold of £30,000 per QALY (Table 6).

55  
56  
57 284  
58  
59  
60

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

285 The probabilistic sensitivity analysis reached a similar conclusion, with the NICE 2015  
286 diagnostic threshold having the highest probability of being the most cost-effective treatment  
287 and the highest NMB using a cost-effectiveness threshold of £30,000 per QALY (Table 7 and  
288  
289  
290  
291

For peer review only

1  
2  
3 292 **Figure 2).** The analysis also suggested that no diagnosis/no treatment might be considered the  
4  
5 293 most likely to be cost-effective when using a lower cost-effectiveness threshold of £20,000 per  
6  
7 294 QALY. The probability of no diagnosis/no treatment being cost-effective falls sharply in the  
8  
9 295 cost-effectiveness threshold range of £20,000 - £30,000 *per* QALY. As shown in the cost-  
10  
11 296 effectiveness acceptability curve of

12  
13  
14 297

15  
16 298

17  
18 299

19  
20  
21 300

For peer review only

1  
2  
3 301 **Figure 2**, the WHO 2013 diagnostic threshold becomes more cost-effective as the cost-  
4  
5 302 effectiveness threshold increases. Nevertheless, this would have to exceed £30,000 per QALY  
6  
7 303 before becoming cost-effective, indicating that the further reduction in adverse outcomes, are  
8  
9 304 achieved at an unacceptably high opportunity cost. The Supplementary Report plots the  
10  
11 305 incremental cost and QALY outcomes of 2,000 simulations from the probabilistic analysis on  
12  
13 306 the cost-effectiveness plane (see Figure x1). Whilst most points fall in the south-western  
14  
15 307 quadrant, suggesting that WHO 2013 diagnostic criteria are likely to lead to additional QALYs  
16  
17 308 when compared with NICE 2015 criteria, all points show that NICE 2015 criteria were  
18  
19 309 associated with markedly lower costs.  
20  
21  
22

310

311

312 **Table 7: Probabilistic sensitivity analysis for HAPO (4) in a population with NICE risk factors**

<b>Diagnostic threshold</b>	<b>NMB CE threshold £30,000 per QALY</b>	<b>Probability cost- effective CE threshold £20,000 per QALY</b>	<b>Probability cost- effective CE threshold WTP = £30,000 per QALY</b>
No Treatment	£391	54.2%	21.9%
NICE 2015	£233,192	40.7%	43.4%
WHO 2013	£200,384	5.2%	34.7%

313

314

315

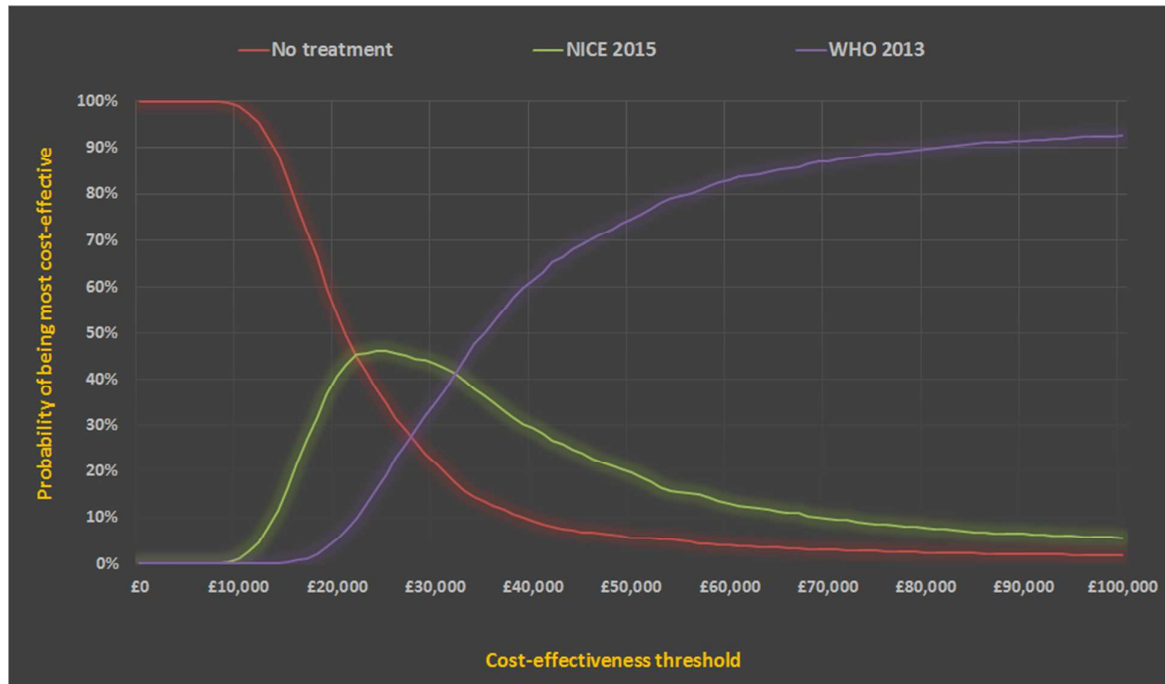
316

317

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

318 **Figure 2**– Cost-effectiveness acceptability curve indicating the probability of a threshold or a  
319 no diagnosis/no treatment strategy being cost-effective at different cost-effectiveness thresholds  
320 for the HAPO 4 centres population with risk factors

321



322

323

324

325 Summaries of results for all of the model populations and more detailed results are provided in  
326 the Supplementary Report.

327

328 Table x9 and Table x10 in the Supplementary Report show that in both the HAPO (4) and  
329 Atlantic DiP populations with NICE risk factors, the NICE diagnostic threshold is the most  
330 cost-effective strategy at a cost-effectiveness threshold of £30,000 per QALY. The NICE 2015  
331 diagnostic threshold has ICERs of less than £30,000 per QALY, and in the probabilistic  
332 sensitivity analysis it has the highest net monetary benefit and the highest probability of being  
333 the most cost-effective. For HAPO (4) the results are similar if baseline risks are estimated  
334 using logistic regression based on all covariates or a logistic regression just using plasma  
335 glucose levels

1  
2  
3 336  
4

5 337 The results also suggested that universal screening would not be cost-effective as, when  
6  
7 338 compared to risk factor screening (as recommended in NICE guidelines), the additional women  
8  
9 339 included in such an approach would be those without risk factors and the model demonstrates  
10  
11 340 that the ICERs for diagnosis and treatment are all well in excess of £30,000 per QALY;  
12  
13 341 markedly so when using WHO 2013 diagnostic thresholds. These conclusions were supported  
14  
15 342 by an analysis of the Norwich dataset (see Supplementary Report).  
16  
17  
18  
19 343

20  
21 344 It was not possible to stratify the Norwich dataset according to risk factors, and therefore the  
22  
23 345 ICERs presented relate to a comparison between no screening/treatment and universal screening  
24  
25 346 and treatment. However, the results were consistent with those for HAPO (4) and Atlantic DiP.  
26  
27 347 First, they showed that universal screening was not cost-effective even when compared to an  
28  
29 348 alternative of no screening/no treatment. Second, the ICERs for the whole population were a  
30  
31 349 weighted average of the populations with and without risk factors. The ICER for the population  
32  
33 350 with risk factors would be lower than the ICER for the entire population, which was not  
34  
35 351 substantially above the £30,000 per QALY threshold.  
36  
37  
38  
39 352

#### 40 353 *One-way sensitivity analysis*

41  
42  
43 354 As part of a sensitivity analysis the deterministic models were re-run using the logistic  
44  
45 355 regression models without backward elimination of glucose variables with non-significant  
46  
47 356 coefficients, and these analyses are summarised in the Supplementary Report.  
48  
49  
50 357

## 51 358 **Discussion**

52  
53  
54 359 In the NICE guideline analysis, 14 alternative diagnostic thresholds were compared and there  
55  
56 360 was no single optimal diagnostic threshold which clearly emerged<sup>5</sup>. This is not surprising given  
57  
58  
59  
60

1  
2  
3 361 the small differences in patient outcomes between them. In that analysis the previous WHO  
4  
5 362 1999 criteria emerged as a relatively cost-effective strategy. However, the Guideline Committee  
6  
7 363 rejected a fasting threshold of 7.0 mmol/L as there was a wide clinical consensus that this was  
8  
9 364 too high, as 6.1-7.0 mmol/L is diagnostic of impaired fasting glycaemia in the non-pregnant  
10  
11 365 population. Intervention studies had used a lower fasting threshold than 7.0 mmol/L as a basis  
12  
13 366 for inclusion, and therefore made a case for intervention at lower levels. Based upon detailed  
14  
15 367 cost effectiveness analysis of all the options, the Guideline Committee ultimately decided on  
16  
17 368 recommending a fasting plasma glucose of 5.6 mmol/L and a 2 hour plasma glucose of 7.8  
18  
19 369 mmol/L. In this paper, we have restricted our analysis of cost effectiveness to the WHO 2013  
20  
21 370 and NICE 2015 criteria (with a no screening/treatment baseline also included) as these two  
22  
23 371 recommendations have the most clinical currency at present.  
24  
25  
26  
27  
28

29 372  
30 373 All of the analyses presented in this paper suggest that, in a population with NICE risk factors,  
31  
32 374 the NICE 2015 diagnostic criteria for GDM could be considered cost-effective relative to no  
33  
34 375 screening/no treatment and to WHO 2013 diagnostic thresholds when using a cost-effectiveness  
35  
36 376 threshold of £30,000 per QALY. The analyses also show that no screening/no treatment is cost-  
37  
38 377 effective in populations without NICE risk factors, suggesting that universal screening does not  
39  
40 378 represent value for money, at least in a UK setting.  
41  
42  
43

44 379  
45 380 One of the limitations of our analysis was that the 2-hour threshold was restricted to the  
46  
47 381 historical WHO 1999 2-hour definition of 7.8mmol/l, or the new WHO 2013 criteria of 8.5  
48  
49 382 mmol/l. It is conceivable that a 2-hour threshold lying between these values might outperform  
50  
51 383 both. Our greater focus, though was on the optimal fasting level as this is where the greatest  
52  
53 384 controversy lies with respect to potentially missed treatment opportunities.  
54  
55  
56

57 385  
58  
59  
60



1  
2  
3 386 As noted by the proponents of WHO 2013 diagnostic criteria for GDM, using a lower fasting  
4  
5 387 plasma glucose threshold would by definition detect more cases. Furthermore, because we  
6  
7 388 assumed in the model that the relative treatment effect would be the same in additionally  
8  
9 389 diagnosed cases, it follows that such a threshold could potentially yield the lowest number of  
10  
11 390 adverse outcomes and the greatest QALY gain. However, our analysis suggests that the  
12  
13 391 relatively small additional gains are not justified by the substantially higher costs that such  
14  
15 392 lower thresholds would require.  
16  
17  
18  
19

393

20  
21 394 A key driver of our results were the logistic regression models which were used to predict  
22  
23 395 baseline risk. For the outcomes included in this study these regression models suggested that the  
24  
25 396 2-hour plasma glucose was a much more important predictor of adverse outcomes than the  
26  
27 397 fasting plasma glucose, something we were unaware of when selecting the model's clinical  
28  
29 398 outcomes.  
30  
31

399

32  
33  
34 400 We consider that our analysis which builds on previous modelling<sup>5, 16</sup> is the most  
35  
36 401 comprehensive assessment of the cost-effectiveness of diagnostic thresholds for GDM yet  
37  
38 402 undertaken, and will hopefully contribute to the WHO's expectation "that a substantial body of  
39  
40 403 new data will emerge in the near future, providing currently scarce health and economic  
41  
42 404 evaluation of the recommended criteria applied to various populations and with different  
43  
44 405 approaches (universal screening, screening only women at high risk, diagnostic testing only)".  
45  
46  
47

406

48  
49 407 A number of commentators<sup>19, 20</sup> have recently advocated universal screening for GDM. The  
50  
51 408 essence of the argument is based upon the number of cases of GDM that would be missed with  
52  
53 409 selective screening, and the subsequent reduced opportunity to prevent a serious perinatal  
54  
55 410 outcome. Of course, it is true that universal screening will detect more cases, although the  
56  
57  
58  
59  
60

1  
2  
3 411 absolute numbers will depend upon the thresholds used to define GDM. Table 5 shows that  
4  
5 412 many more women would need to be diagnosed in order to prevent a single adverse outcome.  
6  
7 413 However, in the context of finite health care resources, it must be accepted that it may be cost-  
8  
9 414 effective to miss some cases. Epidemiological measures such as number needed to treat (or  
10  
11 415 number needed to screen in this case) implicitly recognise that a goal of health care systems  
12  
13 416 cannot be to maximize health gain without any consideration of cost. Identifying missed cases  
14  
15 417 carries an opportunity cost and it may be that those resources would achieve greater benefit if  
16  
17 418 employed elsewhere in the health care system. If a population is divided into those with risk  
18  
19 419 factors and those without risk factors, then the prevalence of GDM must be lower in the group  
20  
21 420 without risk factors (and the number needed to screen higher) with concomitantly lower cost-  
22  
23 421 effectiveness. However, the comparative cost-effectiveness of screening in those with and  
24  
25 422 without risk factors is not only affected by the respective prevalence in the two groups, but also  
26  
27 423 differences in severity. In those diagnosed with GDM and who had risk factors there were, as  
28  
29 424 anticipated, greater levels of hyperglycaemia than in those without risk factors. As shown in  
30  
31 425 Table x24 in the Supplementary Report, **Error! Reference source not found.** **Error! Reference**  
32  
33 426 **source not found.** ‘true positives’ or identified cases (risk factor present and GDM) had higher  
34  
35 427 plasma glucose values than ‘false negatives’ or missed cases (risk factors absent and GDM)  
36  
37 428 when defining GDM positives according to WHO 2013 diagnostic thresholds.  
38  
39  
40  
41  
42  
43  
44

45 430 We would therefore expect the women with risk factors and GDM to be at greater risk of  
46  
47 431 adverse outcomes than the women with GDM without risk factors as a result of their higher  
48  
49 432 plasma glucose levels. So the “cases” missed with selective screening would have, on average,  
50  
51 433 fewer adverse outcomes than in “cases” in a population with risk factors. So the ICER would  
52  
53 434 be greater in the population without risk factors because prevalence is lower and cases have  
54  
55 435 fewer adverse outcomes.  
56  
57  
58  
59  
60

436

437 Our analysis, by splitting the HAPO (4) and Atlantic DiP datasets into those with and without  
438 risk factors, was able to evaluate the cost-effectiveness of moving from risk factor screening to  
439 universal screening. Whilst diagnosis in populations with risk factors was shown to be cost-  
440 effective at a threshold of £30,000 per QALY, it was never cost-effective to diagnose and treat  
441 in those without risk factors. Table 4 indicates the large differences that exist in prevalence  
442 between the populations with and without risk factors. Our analysis suggests that the cost-  
443 effectiveness threshold would have to substantially exceed currently accepted UK norms for  
444 universal screening to be considered cost-effective. Although the NICE risk factor approach  
445 could not be replicated exactly, we felt that the approximation used was acceptable, as the only  
446 women who would be omitted from the model risk factor population were multiparous and  
447 would have had a large baby previously and/or a past history of GDM. This approximation  
448 would over-estimate slightly the benefits of universal screening, as the baseline risk in a group  
449 designated as being without NICE risk factors present would be over-stated.

450

451 A previous study<sup>7</sup> from Spain using WHO 2013 diagnostic criteria suggested cost effectiveness  
452 compared with a two-step protocol using the Carpenter – Coustan thresholds. However, this  
453 was largely based upon estimates of reduction of caesarean section rates of 50% which we find  
454 implausible based upon changes in diagnostic criteria alone, noting that ACHOIS and Landon et  
455 al. found only a 4% and 21% reduction in caesarean section respectively as a result of treating  
456 gestational diabetes. The Spanish study did not consider other alternative thresholds, and was a  
457 retrospective, before and after analysis which has been criticized by the Cochrane Collaboration  
458 as it does not control for possible changes in important variables, such as clinical management,  
459 over time.<sup>21</sup>

460

1  
2  
3 461 Our model has a number of limitations particularly with respect to the valuation of health  
4  
5 462 outcomes. We did not include large for gestational age as an outcome because it was felt that  
6  
7 463 shoulder dystocia was the relevant immediate complication of interest, and that possible long  
8  
9 464 term metabolic consequences for the offspring were hard to quantify and therefore difficult to  
10  
11 465 incorporate within the model. As previously noted, the QALY loss from a serious perinatal  
12  
13 466 complication used in this analysis is likely to be overstated because of the relatively large  
14  
15 467 weight given to death based on the intervention studies.<sup>16</sup> HAPO failed to show an association  
16  
17 468 between perinatal mortality and plasma glucose levels, which may mean that perinatal mortality  
18  
19 469 reduction is less amenable to reduction by treatment than other serious perinatal complications.  
20  
21 470 In this respect the cost-effectiveness of diagnosing and treating GDM may be over-stated. On  
22  
23 471 the other hand, the model does not take account of any potential long term effects on the  
24  
25 472 offspring (e.g. adiposity and the likelihood of subsequent pathology) as these effects are  
26  
27 473 difficult to quantify but may under-estimate the QALY gain from diagnosis and treatment. A  
28  
29 474 US study<sup>22</sup> considered the potential long-term benefits to the mother whereby a diagnosis of  
30  
31 475 GDM averts or delays onset of Type 2 diabetes mellitus, but this was not incorporated into our  
32  
33 476 model as we did not consider that the relationship was sufficiently well established at this time.  
34  
35 477 However, to the extent that such a relationship does exist our model would also underestimate  
36  
37 478 the QALY gain from a diagnosis of GDM. A recent review has, however, questioned the  
38  
39 479 association between maternal glycaemia and subsequent cardio-metabolic outcomes in offspring  
40  
41 480 in humans.<sup>23</sup>  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 486 word on the subject, and that further health economic evaluation is required to either  
4  
5 487 corroborate our findings or to challenge them. Nevertheless, we feel that our analysis represents  
6  
7 488 a constructive and evidence based contribution to establishing cost effective diagnostic  
8  
9  
10 489 thresholds for GDM and will hopefully lead to more research to clarify this important but vexed  
11  
12 490 area of clinical diagnosis.

13  
14 491

15  
16 492 **Conclusions**

17  
18 493 The results presented in this analysis, based on a UK setting, do not suggest that the diagnostic  
19  
20 494 thresholds for GDM adopted by the WHO are cost-effective. On the other hand they do provide  
21  
22 495 some support for the cost-effectiveness of the diagnostic criteria adopted by NICE when  
23  
24 496 compared to either no screening/treatment and to WHO 2013 diagnostic criteria. Furthermore,  
25  
26 497 according to this analysis, universal screening would seem to offer poor value for money and  
27  
28 498 does not appear cost-effective compared to the current NICE guidance of targeting high risk  
29  
30 499 women.  
31  
32

33  
34 500  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 501 **Acknowledgements**  
4

5 502 We are grateful to Professor DR McCance and Professor HD McIntyre for allowing us to use  
6  
7 503 their local datasets from the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) trial and  
8  
9 504 to Professor F Dunne for allowing us to use her Atlantic DiP dataset  
10

11 505 We are also grateful to Professor David James who provided clinical support during the  
12  
13 506 development of the updated NICE guideline on Diabetes in Pregnancy  
14  
15

16 507

17  
18 508 **Competing interests**  
19

20 509 All authors have completed the ICMJE uniform disclosure form at

21  
22 510 [http://www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) and declare:  
23  
24

25 511

26  
27 512 **Funding:** Some of this work was undertaken by the now defunct National Collaborating Centre  
28  
29 513 for Women's and Children's Health (subsumed within the National Guideline Alliance from 1st  
30  
31 514 April 2016), which received funding from NICE. The views expressed in this publication are  
32  
33 515 those of the authors and not necessarily those of the institute. Revisions to the guideline model  
34  
35 516 after the guideline was published and drafting of the manuscript was done in the author's own  
36  
37 517 time and was not funded  
38  
39

40 518

41  
42  
43 519 National Institute for Health and Care Excellence (2015). Diabetes in pregnancy: management  
44  
45 520 from preconception to the postnatal period. Available from

46  
47 521 <https://www.nice.org.uk/guidance/ng3>  
48

49 522 PBJ and SBR are employees of the National Guideline Alliance (part of the RCOG), which  
50  
51 523 receives its funding from NICE.  
52

53  
54 524 MJAM, KS, AD and RWB received travel expenses from NICE for attending clinical guideline  
55  
56 525 development meetings  
57  
58  
59  
60

1  
2  
3 526 **Author contribution**  
4

5 527 Paul Jacklin designed and developed the health economic model, undertook the health  
6  
7 528 economic analysis, wrote the first draft of the manuscript and incorporated edits from co-  
8  
9  
10 529 authors. Mike Maresh provided clinical input into the design of the health economic model;  
11  
12 530 read, commented and edited various draft of the manuscripts. Katharine Stanley supplied the  
13  
14 531 Norwich dataset, provided clinical input into the design of the health economic model; read,  
15  
16 532 commented and edited various draft of the manuscripts. Anne Dornhorst provided clinical input  
17  
18 533 into the design of the health economic model; read, commented and edited various draft of the  
19  
20  
21 534 manuscripts. Chris Patterson provided statistical advice, undertook statistical analysis of the  
22  
23 535 HAPO dataset; read, commented and edited various drafts of the manuscript. Shona Burman  
24  
25 536 Roy reviewed the clinical literature, contributed to discussions of model design; read,  
26  
27 537 commented and edited various drafts of the manuscript. Rudy Bilous chaired the NICE  
28  
29 538 guideline, provided clinical input into the design of the health economic model; read,  
30  
31 539 commented and edited various draft of the manuscripts  
32

33  
34 540  
35

36 541 **Transparency declaration**  
37

38 542 The lead author, Paul Jacklin, affirms that this manuscript is an honest, accurate, and  
39  
40 543 transparent account of the study being reported; that no important aspects of the study have  
41  
42 544 been omitted; and that any discrepancies from the study as planned (and, if relevant, registered)  
43  
44 545 have been explained.  
45  
46

47 546  
48

49 547 **Exclusive License**  
50

51  
52 548 "I Paul Jacklin The Corresponding Author of this article contained within the original  
53  
54 549 manuscript which includes any diagrams & photographs within and any related or stand alone  
55  
56 550 film submitted (the Contribution") has the right to grant on behalf of all authors and does grant  
57  
58  
59  
60

1  
2  
3 551 on behalf of all authors, a licence to the BMJ Publishing Group Ltd and its licencees, to permit  
4  
5 552 this Contribution (if accepted) to be published in the BMJ and any other BMJ Group products  
6  
7 553 and to exploit all subsidiary rights, as set out in our licence set out at:  
8  
9 554 [http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/copyright-](http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/copyright-open-access-and-permission-reuse)  
10  
11 555 [open-access-and-permission-reuse.](http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/copyright-open-access-and-permission-reuse)”  
12  
13

14 556

15  
16 557 **Data sharing Statement**

17  
18 558 Potential for data sharing (the health economic model) can be discussed with study  
19  
20  
21 559 investigators.  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



560 **References**

- 1  
2  
3  
4  
5  
6 561 1. Metzger BE, Lowe LP, Dyer AR, et al. Hyperglycemia and adverse pregnancy outcomes. *N Engl J*  
7  
8 562 *Med* 2008;358:1991-2002.
- 10 563 2. Metzger BE, Gabbe SG, Persson B, Buchanan TA, Catalano PA, Damm P, et al. International  
11  
12 564 Association of Diabetes and Pregnancy Study Groups recommendations on the diagnosis and  
13  
14 565 classification of hyperglycemia in pregnancy. *Diabetes Care* 2010;33:676-82.
- 17 566 3. WHO Health organisation, 2013. Diagnostic criteria and classification of hyperglycaemia first  
18  
19 567 detected in pregnancy WHO/NMH/MND/13.2  
20  
21 568 [http://apps.who.int/iris/bitstream/10665/85975/1/WHO\\_NMH\\_MND\\_13.2\\_eng.pdf](http://apps.who.int/iris/bitstream/10665/85975/1/WHO_NMH_MND_13.2_eng.pdf).
- 23 569 4. American College of Obstetricians and Gynecologists. *Practice Bulletin 137: Mellitus. Obstet*  
24  
25 570 *Gynecol* 2013; 122: 406-16
- 27 571 5. National Institute for Health and Care Excellence (NICE) (2015) Diabetes in pregnancy:  
28  
29 572 management of diabetes and its complications from preconception to the postnatal period.  
30  
31 573 Clinical guideline NG3 (2015). Available from  
32  
33 574 [www.nice.org.uk/guidance/ng3/resources/diabetes-in-pregnancy-management-of-diabetes-](http://www.nice.org.uk/guidance/ng3/resources/diabetes-in-pregnancy-management-of-diabetes-)  
34  
35 575 [and-itscomplications-from-preconception-to-the-postnatal-period-51038446021](http://www.nice.org.uk/guidance/ng3/resources/diabetes-in-pregnancy-management-of-diabetes-and-itscomplications-from-preconception-to-the-postnatal-period-51038446021), accessed  
36  
37 576 February 2016
- 40 577 6. Meek CL, Lewis HB, Patient C, et al. Diagnosis of gestational diabetes: falling through the net.  
41  
42 578 *Diabetologia* 2015;Sep;58(9):2003-12
- 44 579 7. Duran A, Sáenz S, Torrejón MJ et al. Introduction of IADPSG criteria for the screening and  
45  
46 580 diagnosis of gestational diabetes mellitus results in improved pregnancy outcomes at a lower  
47  
48 581 cost in a large cohort of pregnant women: the St. Carlos Gestational Diabetes Study. *Diabetes*  
49  
50 582 *Care* 2014;37(9):2442–2450. doi: 10.2337/dc14-0179.
- 53 583 8. Herman WH. Insights offered by economic analyses. *Diabetes Care*. 2014 Sep;37(9):2424-6. doi:  
54  
55 584 10.2337/dc14-1232.

- 1  
2  
3 585 9. Crowther CA, Hiller JE, Moss JR, McPhee AJ, Jeffries WS, Robinson JS. Effect of treatment of  
4  
5 586 gestational diabetes mellitus on pregnancy outcomes. *N Engl J Med* 2005;352:2477-86.  
6  
7 587 10. Landon MB, Spong CY, Thom E, Carpenter MW, Ramin SM, Casey B, et al. A multicenter,  
8  
9 588 randomized trial of treatment for mild gestational diabetes. *N Engl J Med* 2009;361:1339-48  
10  
11 589 11. Horvath K, Koch K, Jeitler K et al. Effects of treatment in women with gestational diabetes  
12  
13 590 mellitus: systematic review and meta-analysis. *BMJ (Clin Res Ed)* 2010;340:c1395  
14  
15 591 12. British National Formulary. July 2016. <https://www.medicinescomplete.com/mc/bnf/current/>  
16  
17 592 (accessed 4 Aug 2016).  
18  
19 593 13. Unit Costs of Health and Social Care 2015. Personal Social Services Research Unit, The  
20  
21 594 University of Kent, 2015.  
22  
23 595 14. Department of Health. NHS reference costs: financial year 2014–2015.  
24  
25 596 <https://www.gov.uk/government/publications/nhs-reference-costs-2014-to-2015> ,  
26  
27 597 Department of Health, 2015.  
28  
29 598 15. NHS Electronic Drug Tariff, August 2016. [http://www.drugtariff.nhsbsa.nhs.uk/#/00336026-](http://www.drugtariff.nhsbsa.nhs.uk/#/00336026-DD_1/DD00336022/Home)  
30  
31 599 [DD\\_1/DD00336022/Home](http://www.drugtariff.nhsbsa.nhs.uk/#/00336026-DD_1/DD00336022/Home) (accessed 4 Aug 2016).  
32  
33 600 16. Round, J.A., Jacklin, P., Fraser, R.B., Hughes, R.G., Muggleston, M.A., Holt, R.I., Screening for  
34  
35 601 gestational diabetes mellitus: cost-utility of different screening strategies based on a woman's  
36  
37 602 individual risk of disease, *Diabetologia* 2011,54(2), 256-263. doi: 10.1007/s00125-010-1881-y  
38  
39 603 17. National Institute for Health and Care Excellence. Developing NICE guidelines: the manual.  
40  
41 604 October 2014 ([https://www.nice.org.uk/media/default/about/what-we-do/our-](https://www.nice.org.uk/media/default/about/what-we-do/our-programmes/developing-nice-guidelines-the-manual.pdf)  
42  
43 605 [programmes/developing-nice-guidelines-the-manual.pdf](https://www.nice.org.uk/media/default/about/what-we-do/our-programmes/developing-nice-guidelines-the-manual.pdf))  
44  
45 606 18. Briggs A, Claxton K, Sculpher M. Decision Modelling for Health Economic Evaluation. Oxford:  
46  
47 607 Oxford University Press; 2006  
48  
49 608 19. Avalos GE, Owens LA, Dunne F et al. Applying Current Screening Tools for Gestational Diabetes  
50  
51 609 Mellitus to a European Population: Is It Time for Change? *Diabetes Care*. 2013 Oct;36(10):3040-  
52  
53 610 4. doi: 10.2337/dc12-2669. Epub 2013 Jun 11.  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 611 20. Simmons D, Moses RG. Gestational Diabetes Mellitus: To Screen or Not to Screen? Is this really  
4 still a question? *Diabetes Care*. 2013 Oct;36(10):2877-2878  
5 612  
6  
7 613 21. Armstrong R, Waters E, Doyle J (editors). Chapter 21: Reviews in health promotion and public  
8 health. In Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of*  
9 614 *Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011.  
10 615 Available from [www.cochrane-handbook.org](http://www.cochrane-handbook.org). Accessed June 2015  
11 616  
12  
13  
14  
15  
16 617 22. Werner EF, Pettker CM, Zucrow et al. Screening for gestational diabetes mellitus: are the  
17 618 criteria proposed by the international association of the Diabetes and Pregnancy Study Groups  
18 619 cost-effective? *Diabetes Care*. 2012 Mar;35(3):529-35. doi: 10.2337/dc11-1643.  
19  
20  
21  
22 620 23. Donovan LE, Cundy T. Does exposure to hyperglycaemia in utero increase the risk of obesity  
23 621 and diabetes in the offspring? A critical reappraisal. *Diabetic Medicine*. 2015 Mar;32(3):295-  
24 622 304. doi: 10.1111/dme.12625. Epub 2014 Dec 17.  
25  
26  
27  
28  
29  
30 623  
31  
32  
33 624  
34  
35  
36 625  
37  
38 626  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## 1 **Supplementary Report**

2 This supplementary document provides further details about model parameter estimates and model  
3 results.

### 4 **Multivariable prediction models to estimate baseline risk**

5 Model 1 includes all three blood glucose regression coefficients while Model 2 includes only blood  
6 glucose regression coefficients which remained significant after performing variable selection by  
7 backward elimination.

8

For peer review only

9 **Table x1.** Logistic regression models to predict neonatal shoulder dystocia

Variable	Co-efficient b (Standard error (SE(b)))			
	Model with blood glucose covariates		Model with all covariates	
	Model 1 <sup>a</sup>	Model 2 <sup>b</sup>	Model 1 <sup>a</sup>	Model 2 <sup>b</sup>
Centre (Manchester v Belfast)	-	-	1.151 (0.424)	1.151 (0.423)
(Brisbane v Belfast)	-	-	0.562 (0.491)	0.505 (0.489)
(Newcastle v Belfast)	-	-	1.622 (0.472)	1.604 (0.472)
Age at OGTT (yr)	-	-	-0.022 (0.024)	-0.023 (0.024)
BMI at OGTT (kg/m <sup>2</sup> )	-	-	-0.011 (0.024)	-0.006 (0.023)
Smoker (Yes v No)	-	-	-0.477 (0.409)	-0.480 (0.409)
Drinker (Yes v No)	-	-	-0.107 (0.317)	-0.101 (0.317)
Family history DM (Yes v No)	-	-	-0.008 (0.187)	-0.006 (0.184)
Gestational age at OGTT (wk)	-	-	-0.114 (0.092)	-0.111 (0.091)
Neonate gender (F v M)	-	-	-1.316 (0.292)	-1.321 (0.292)
Family history HBP (Yes v No) <sup>c</sup>	-	-	-	-
Maternal UTI (Yes v No) <sup>c</sup>	-	-	-	-
Mean Blood Pressure (mmHg)	-	-	-0.007 (0.015)	-0.006 (0.015)
Hospital admission before delivery (Yes v No)	-	-	0.175 (0.267)	0.173 (0.266)
Parity (1 v 0)	-	-	-0.108 (0.420)	-0.118 (0.420)
(2+ v 0)	-	-	0.469 (0.414)	0.456 (0.412)
(Unknown v 0)	-	-	-0.013 (0.399)	-0.026 (0.399)
Fasting blood glucose <sup>d</sup>	0.166 (0.110)	-	0.151 (0.112)	-
1-hr blood glucose <sup>d</sup>	-0.152 (0.163)	-	-0.138 (0.165)	-
2-hr blood glucose <sup>d</sup>	0.265 (0.151)	0.267 (0.097)	0.222 (0.152)	0.223 (0.100)
Constant	-4.475 (0.122)	-4.467 (0.122)	1.139 (3.508)	0.925 (3.025)

10 (a) Sensitivity analysis

11 (b) Base case analysis

12 (c) Omitted from HAPO model for shoulder dystocia

13 (d) Blood glucose values are 'standardised' – so the exponential of the coefficient represents the odds ratio for shoulder  
14 dystocia arising from a 1 Standard Deviation (SD) increase in plasma glucose (fasting plasma glucose mean (SD) =  
15 4.60(0.47); 1-hour plasma glucose mean (SD) = 7.57(1.83); 2-hour plasma glucose mean (SD) = 6.21(1.44)

16

17

18

18

19 **Table x2.** Logistic regression models to predict caesarean section

Variable	Co-efficient b (Standard error (SE(b)))			
	Model with blood glucose covariates		Model with all covariates	
	Model 1 <sup>a</sup>	Model 1 <sup>a</sup>	Model 1 <sup>a</sup>	Model 1 <sup>a</sup>
Centre (Manchester v Belfast)	-	-	-0.495 (0.092)	-0.494 (0.092)
(Brisbane v Belfast)	-	-	-0.114 (0.100)	-0.099 (0.098)
(Newcastle v Belfast)	-	-	-0.692 (0.141)	-0.681 (0.140)
Age at OGTT (yr)	-	-	0.034 (0.007)	0.034 (0.007)
BMI at OGTT (kg/m <sup>2</sup> )	-	-	0.039 (0.007)	0.039 (0.007)
Smoker (Yes v No)	-	-	-0.292 (0.106)	-0.304 (0.106)
Drinker (Yes v No)	-	-	-0.025 (0.087)	-0.028 (0.087)
Family history DM (Yes v No)	-	-	0.052 (0.057)	0.050 (0.057)
Gestational age at OGTT (wk)	-	-	0.004 (0.029)	0.004 (0.029)
Neonate gender (F v M)	-	-	-0.205 (0.071)	-0.205 (0.071)
Family history HBP (Yes v No) <sup>c</sup>	-	-	-	-
Maternal UTI (Yes v No) <sup>c</sup>	-	-	-	-
Mean Blood Pressure (mmHg)	-	-	0.003 (0.004)	0.003 (0.004)
Hospital admission before delivery (Yes v No)	-	-	0.510 (0.079)	0.514 (0.079)
Parity (1 v 0) <sup>c</sup>	-	-	-	-
(2+ v 0) <sup>c</sup>	-	-	-	-
(Unknown v 0) <sup>c</sup>	-	-	-	-
Fasting blood glucose <sup>d</sup>	0.053 (0.040)	-	-0.009 (0.044)	-
1-hr blood glucose <sup>d</sup>	0.119 (0.048)	0.138 (0.046)	0.101 (0.051)	0.144 (0.037)
2-hr blood glucose <sup>d</sup>	0.113 (0.046)	0.123 (0.046)	0.071 (0.048)	
Constant	-1.433 (0.035)	-1.435 (0.035)	-3.509 (0.950)	-3.518 (0.947)

20 (a) Sensitivity analysis

21 (b) Base case analysis

22 (c) Omitted from HAPO model for caesarean section

23 (d) Blood glucose values are 'standardised' – so the exponential of the coefficient represents the odds ratio for caesarean  
 24 section arising from a 1 Standard Deviation (SD) increase in plasma glucose (fasting plasma glucose mean (SD) =  
 25 4.60(0.47); 1-hour plasma glucose mean (SD) = 7.57(1.83); 2-hour plasma glucose mean (SD) = 6.21(1.44)

26

27

28 **Table x3.** Logistic regression models to predict neonatal intensive care unit admissions

Variable	Co-efficient b (Standard error (SE(b)))			
	Model with blood glucose covariates		Model with all covariates	
	Model 1 <sup>a</sup>	Model 1 <sup>a</sup>	Model 1 <sup>a</sup>	Model 1 <sup>a</sup>
Centre (Manchester v Belfast)	-	-	0.889 (0.159)	0.894 (0.159)
(Brisbane v Belfast)	-	-	1.400 (0.163)	1.393 (0.161)
(Newcastle v Belfast)	-	-	1.163 (0.191)	1.153 (0.161)
Age at OGTT (yr)	-	-	0.012 (0.009)	0.013 (0.009)
BMI at OGTT (kg/m <sup>2</sup> )	-	-	0.024 (0.009)	0.025 (0.009)
Smoker (Yes v No)	-	-	0.201 (0.130)	0.209 (0.130)
Drinker (Yes v No)	-	-	-0.023 (0.117)	-0.025 (0.117)
Family history DM (Yes v No)	-	-	0.038 (0.069)	0.033 (0.069)
Gestational age at OGTT (wk)	-	-	-0.052 (0.038)	-0.050 (0.038)
Neonate gender (F v M)	-	-	-0.302 (0.094)	-0.304 (0.094)
Family history HBP (Yes v No) <sup>c</sup>	-	-	-	-
Maternal UTI (Yes v No) <sup>c</sup>	-	-	-	-
Mean Blood Pressure (mmHg)	-	-	0.006 (0.006)	0.006 (0.006)
Hospital admission before delivery (Yes v No)	-	-	0.792 (0.097)	0.794 (0.148)
Parity (1 v 0)	-	-	-0.474 (0.148)	-0.474 (0.148)
(2+ v 0)	-	-	-0.493 (0.157)	-0.490 (0.157)
(Unknown v 0)	-	-	-0.086 (0.135)	-0.084 (0.135)
Fasting blood glucose <sup>d</sup>	-0.025 (0.050)	-	-0.003 (0.054)	-
1-hr blood glucose <sup>d</sup>	0.078 (0.064)	-	0.082 (0.067)	-
2-hr blood glucose <sup>d</sup>	0.167 (0.060)	0.208 (0.041)	0.107 (0.063)	0.159
Constant	-2.375 (0.046)	-2.374 (0.046)	-3.061 (1.243)	-3.181 (1.236)

29 (a) Sensitivity analysis

30 (b) Base case analysis

31 (c) Omitted from HAPO model for neonatal intensive care unit admissions

32 (d) Blood glucose values are 'standardised' – so the exponential of the coefficient represents the odds ratio for neonatal  
 33 intensive care unit admissions arising from a 1 Standard Deviation (SD) increase in plasma glucose (fasting plasma glucose  
 34 mean (SD) = 4.60(0.47); 1-hour plasma glucose mean (SD) = 7.57(1.83); 2-hour plasma glucose mean (SD) = 6.21(1.44)

35

36 **Table x4.** Logistic regression models to predict jaundice

37

Variable	Co-efficient b (Standard error (SE(b)))			
	Model with blood glucose covariates		Model with all covariates	
	Model 1 <sup>a</sup>	Model 1 <sup>a</sup>	Model 1 <sup>a</sup>	Model 1 <sup>a</sup>
Centre (Manchester v Belfast)	-	-	0.410 (0.157)	0.407 (0.157)
(Brisbane v Belfast)	-	-	0.420 (0.173)	0.449 (0.171)
(Newcastle v Belfast)	-	-	-0.332 (0.259)	-0.315 (0.259)
Age at OGTT (yr)	-	-	-0.005 (0.011)	0.005 (0.011)
BMI at OGTT (kg/m <sup>2</sup> )	-	-	-0.009 (0.012)	-0.011 (0.011)
Smoker (Yes v No)	-	-	-0.093 (0.162)	0.082 (0.161)
Drinker (Yes v No)	-	-	-0.508 (0.163)	-0.514 (0.163)
Family history DM (Yes v No)	-	-	-0.060 (0.094)	-0.060 (0.094)
Gestational age at OGTT (wk)	-	-	-0.077 (0.047)	-0.078 (0.047)
Neonate gender (F v M)	-	-	-0.115 (0.113)	-0.116 (0.113)
Family history HBP (Yes v No) <sup>c</sup>	-	-	-	-
Maternal UTI (Yes v No) <sup>c</sup>	-	-	-	-
Mean Blood Pressure (mmHg)	-	-	0.018 (0.007)	0.018 (0.007)
Hospital admission before delivery (Yes v No)	-	-	0.865 (0.116)	0.867 (0.116)
Parity (1 v 0)	-	-	-0.380 (0.185)	-0.382 (0.185)
(2+ v 0)	-	-	-0.526 (0.200)	-0.526 (0.200)
(Unknown v 0)	-	-	0.078 (0.165)-	0.078 (0.165)
Fasting blood glucose <sup>d</sup>	-0.063 (0.061)	-	-0.055 (0.066)	-
1-hr blood glucose <sup>d</sup>	0.199 (0.078)	0.237 (0.052)	0.192 (0.079)	0.216 (0.056)
2-hr blood glucose <sup>d</sup>	0.102 (0.072)	-	0.073 (0.074)	
Constant	-2.850 (0.057)	-2.846 (0.057)	-2.014 (1.526)	-1.927 (1.522)

38 (a) Sensitivity analysis

39 (b) Base case analysis

40 (c) Omitted from HAPO model for jaundice

41 (d) Blood glucose values are 'standardised' – so the exponential of the coefficient represents the odds ratio for jaundice  
 42 arising from a 1 Standard Deviation (SD) increase in plasma glucose (fasting plasma glucose mean (SD) = 4.60(0.47); 1-hour  
 43 plasma glucose mean (SD) = 7.57(1.83); 2-hour plasma glucose mean (SD) = 6.21(1.44)

44



45 **Table x5.** Logistic regression models to predict pre-eclampsia

46

Variable	Co-efficient b (Standard error (SE(b)))			
	Model with blood glucose covariates		Model with all covariates	
	Model 1 <sup>a</sup>	Model 1 <sup>a</sup>	Model 1 <sup>a</sup>	Model 1 <sup>a</sup>
Centre (Manchester v Belfast)	-	-	-0.800 (0.193)	-0.794 (0.192)
(Brisbane v Belfast)	-	-	-0.277 (0.202)	-0.308 (0.200)
(Newcastle v Belfast)	-	-	-0.667 (0.278)	-0.685 (0.278)
Age at OGTT (yr)	-	-	-0.011 (0.015)	-0.009 (0.015)
BMI at OGTT (kg/m <sup>2</sup> )	-	-	0.097 (0.012)	0.101 (0.011)
Smoker (Yes v No)	-	-	-0.569 (0.246)	-0.556 (0.245)
Drinker (Yes v No)	-	-	-0.168 (0.194)	-0.170 (0.194)
Family history DM (Yes v No)	-	-	0.006 (0.127)	-0.004 (0.127)
Gestational age at OGTT (wk)	-	-	-0.096 (0.059)	-0.092 (0.059)
Neonate gender (F v M)	-	-	0.174 (0.147)	0.173 (0.147)
Family history HBP (Yes v No)	-	-	0.230 (0.150)	0.233 (0.150)
Maternal UTI (Yes v No)	-	-	0.721 (0.211)	0.734 (0.211)
Mean Blood Pressure (mmHg) <sup>c</sup>	-	-	-	-
Hospital admission before delivery (Yes v No) <sup>c</sup>	-	-	-	-
Parity (1 v 0)	-	-	-0.292 (0.240)	-0.291 (0.240)
(2+ v 0)	-	-	-0.703 (0.271)	-0.701 (0.271)
(Unknown v 0)	-	-	0.023 (0.224)	0.026 (0.224)
Fasting blood glucose <sup>d</sup>	0.183 (0.068)	0.201 (0.065)	0.062 (0.078)	-
1-hr blood glucose <sup>d</sup>	0.083 (0.098)	-	0.065 (0.104)	-
2-hr blood glucose <sup>d</sup>	0.150 (0.090)	0.196 (0.072)	0.195 (0.096)	0.272 (0.067)
Constant	-3.455 (0.075)	-3.453 (0.075)	-3.107 (1.855)	-3.370 (1.842)

47 (a) Sensitivity analysis

48 (b) Base case analysis

49 (c) Omitted from HAPO model for pre-eclampsia

50 (d) Blood glucose values are 'standardised' – so the exponential of the coefficient represents the odds ratio for pre-eclampsia  
 51 arising from a 1 Standard Deviation (SD) increase in plasma glucose (fasting plasma glucose mean (SD) = 4.60(0.47); 1-hour  
 52 plasma glucose mean (SD) = 7.57(1.83); 2-hour plasma glucose mean (SD) = 6.21(1.44)

53

54 **Table x6.** Logistic regression models to predict induction of labour

55

56

Variable	Co-efficient b (Standard error (SE(b)))		
	Model with blood glucose covariates	Model with all covariates	
	Model 1 <sup>a</sup>	Model 1 <sup>a</sup>	Model 1 <sup>a</sup>
Centre (Manchester v Belfast)	-	-0.476 (0.077)	-0.476 (0.077)
(Brisbane v Belfast)	-	-0.333 (0.087)	-0.337 (0.085)
(Newcastle v Belfast)	-	-0.384 (0.110)	-0.387 (0.109)
Age at OGTT (yr)	-	0.006 (0.006)	0.006 (0.006)
BMI at OGTT (kg/m <sup>2</sup> )	-	0.039 (0.006)	0.039 (0.006)
Smoker (Yes v No)	-	0.051 (0.082)	0.051 (0.082)
Drinker (Yes v No)	-	0.079 (0.072)	0.079 (0.072)
Family history DM (Yes v No)	-	0.016 (0.048)	0.016 (0.048)
Gestational age at OGTT (wk)	-	0.011 (0.024)	0.011 (0.024)
Neonate gender (F v M)	-	-0.038 (0.059)	-0.038 (0.059)
Family history HBP (Yes v No) <sup>c</sup>	-	-	-
Maternal UTI (Yes v No) <sup>c</sup>	-	-	-
Mean Blood Pressure (mmHg)	-	0.008 (0.004)	0.008 (0.004)
Hospital admission before delivery (Yes v No)	-	0.608 (0.066)	0.608 (0.066)
Parity (1 v 0)	-	-0.363 (0.101)	-0.363 (0.101)
(2+ v 0)	-	-0.193 (0.105)	-0.193 (0.105)
(Unknown v 0)	-	0.141 (0.094)	0.141 (0.094)
Fasting blood glucose <sup>d</sup>	0.079 (0.033)	0.009 (0.037)	-
1-hr blood glucose <sup>d</sup>	-0.093 (0.041)	-0.111 (0.043)	-0.108 (0.041)
2-hr blood glucose <sup>d</sup>	0.100 (0.040)	0.094 (0.041)	0.096 (0.041)
Constant	-1.032 (0.029)	-3.037 (0.796)	-3.050 (0.794)

57

(a) Sensitivity analysis

58

(b) Base case analysis

59

(c) Omitted from HAPO model for induction of labour

60

(d) Blood glucose values are 'standardised' – so the exponential of the coefficient represents the odds ratio for induction of labour arising from a 1 Standard Deviation (SD) increase in plasma glucose (fasting plasma glucose mean (SD) = 4.60(0.47); 1-hour plasma glucose mean (SD) = 7.57(1.83); 2-hour plasma glucose mean (SD) = 6.21(1.44)

61

62

63

64

65 **Table x7:** Model unit costs

Category	Cost	Standard Error	Distribution	Source
2 sample OGTT	£8.07	n/a	n/a	NICE 2015 <sup>5</sup>
3 sample OGTT	£12.11	n/a	n/a	NICE 2015 <sup>5</sup>
Rapilose OGTT solution	£3.48	n/a	n/a	BNF July 2016 <sup>12</sup>
Health Care Assistant Band 3 (per hour)	£25	n/a	n/a	Unit Costs of Health and Social Care 2015 <sup>13</sup>
Nurse Band 7 (per hour of patient contact)	£147	n/a	n/a	Unit Costs of Health and Social Care 2015 <sup>13</sup>
Dietician	£38	n/a	n/a	Unit Costs of Health and Social Care 2015 <sup>13</sup>
Ante-natal appointment	£96	£9.07	Normal	NHS Reference Costs 2014-15 <sup>14</sup>
Ultrasound scan	£112	£7.65	Normal	NHS Reference Costs 2014-15 <sup>14</sup>
Rapid acting insulin	£0.02	n/a	n/a	BNF June 2016 <sup>12</sup>
Regular insulin	£0.02	n/a	n/a	BNF June 2016 <sup>12</sup>
Needles	£0.10	n/a	n/a	NHS Drugs Tariff June 2016 <sup>15</sup>
Lancets	£0.03	n/a	n/a	NHS Drugs Tariff June 2016 <sup>15</sup>
Strips	£0.18	n/a	n/a	NHS Drugs Tariff June 2016 <sup>15</sup>
Treatment of GDM	£987	n/a	n/a	Calculated
Severe hypoglycaemia	£650	n/a	n/a	NHS Reference Costs 2014-15 <sup>14</sup>
Admission to NICU	£1,176	£38	Normal	NHS Reference Costs 2014-15 <sup>14</sup>
Caesarean section	£982	£80	Normal	NHS Reference Costs 2014-15 <sup>14</sup>
Neonatal death	£777	£39	Normal	NHS Reference Costs 2014-15 <sup>14</sup>
Shoulder dystocia	£1,394	£79	Normal	NHS Reference Costs 2014-15 <sup>14</sup>
Birth trauma	£1,394	£79	Normal	NHS Reference Costs 2014-15 <sup>14</sup>
Serious perinatal complication (death, shoulder dystocia, birth trauma)	£1,347	n/a	n/a	Calculated
Phototherapy	£788	£72	Normal	NHS Reference Costs 2014-15 <sup>14</sup>
Pre-eclampsia	£4,750	n/a	n/a	NICE 2015 <sup>5</sup>

66

67

68 **QALYs**

69 A QALY loss was estimated for each individual component (shoulder dystocia, death and birth trauma)  
 70 of the composite serious perinatal outcome, which was used in the ACHOIS study.<sup>9</sup> A weighting for  
 71 each individual component was derived according to their relative frequency in the selected studies to  
 72 assess treatment effectiveness.<sup>9, 10</sup> These were then used in order to derive a weighted average for a  
 73 serious perinatal complication as shown in Table x8. QALY losses from a serious perinatal complication  
 74 could be experienced over a lifetime and therefore an annual discount rate of 3.5% was applied in line  
 75 with NICE methods.<sup>13</sup> For each patient, an expected QALY decrement is calculated based on their risk of  
 76 serious perinatal complications. These individual patient QALY decrements are then summed across all  
 77 patients to give the total QALY decrement for the patient dataset for each different diagnostic  
 78 threshold.

79 **Table x8:** QALY losses and weights from individual components of the composite outcome of serious  
 80 perinatal complications

Complication	Weight	QALY	Weighted QALY
Death	0.08	25	2.00
Shoulder dystocia	0.73	0.2	0.15
Birth trauma	0.20	0.2	0.04

81

82 The analyses presented in this paper include a maternal health state utility which was estimated from  
 83 quality of life data collected as part of the ACHOIS study. Whilst treatment conferred a small benefit in  
 84 maternal health state utility, this was small in comparison to QALYs derived from infant outcomes. The  
 85 value of the maternal health state utility with and without treatment is the same as has been used  
 86 previously<sup>5</sup>.

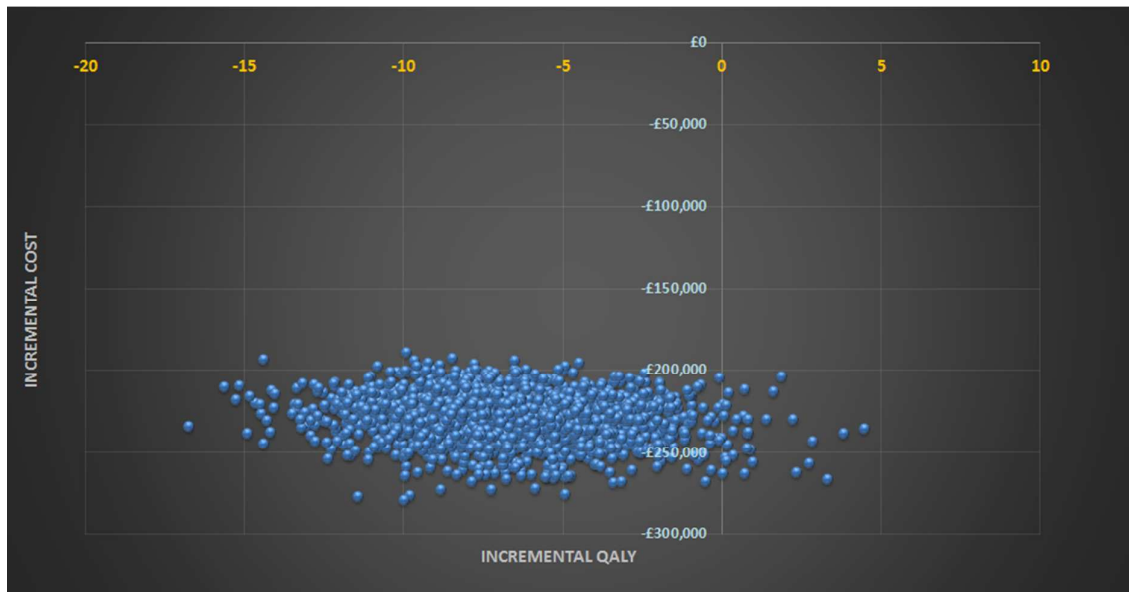
87

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

88 **Results for the HAPO (4) population with risk factors**

89 **Figure x1:** Cost-effectiveness plane for NICE 2015 compared with WHO 2013 for HAPO (4) with risk  
90 factors

91



92

93

94

95 **Summary of Results for each model population**

96 **Table x9:** Summary of deterministic ICERs for each population with backward elimination of plasma  
 97 glucose variables with non-significant coefficients

Diagnostic threshold	All covariates		Plasma glucose covariates				Norwich
	HAPO Risk factor (n=3,549)	HAPO No Risk factor (n=2,614)	HAPO Risk factor (n=3,549)	HAPO No Risk factor (n=2,614)	Atlantic DiP Risk factor (n=1,988)	Atlantic DiP No Risk factor (n=3,302)	
No Treatment	-	-	-	-	-	-	-
NICE 2015	£23,073	£43,845	£25,434	£35,230	£23,755	£35,732	£33,177
WHO 2013	£37,669	£220,638	£41,631	£97,941	£42,457	£45,075	£42,931

98

99

100 **Table x10:** Probability that a threshold is cost-effective at a threshold of £30,000 per QALY and the  
 101 net monetary benefit in each population using regression models with backward elimination of  
 102 plasma glucose variables with non-significant coefficients

Diagnostic threshold	All covariates		Plasma glucose covariates				Norwich
	HAPO Risk factor (NMB)	HAPO No Risk factor (NMB)	HAPO Risk factor (NMB)	HAPO No Risk factor (NMB)	Atlantic DiP Risk factor (NMB)	Atlantic DiP No Risk factor (NMB)	
No Treatment	21.9% (£391)	78.7% (£223)	33.7% (£845)	66.9% (£392)	30.2% (£518)	69.0% (£402)	59.7% (£1,141)
NICE 2015	43.4% (£233,192)	20.9% (-£57,742)	45.6% (£111,502)	31.0% (-£33,767)	50.8% (£116,178)	18.0% (-£36,481)	23.2% (-£76,289)
WHO 2013	34.7% (£201,384)	0.5% (-£94,754)	20.8% (£45,208)	2.2% (-£61,385)	19.1% (£53,129)	13.1% (-£88,283)	17.2% (-£300,254)

103

104 **Results for the HAPO (4) population without risk factors**105 **Table x11:** Clinical outcomes for HAPO (4) population without NICE risk factors (n=2,614)

Diagnostic threshold	Diagnosed	SD	SPC	CS	NICU	Jaund	PE	IOL
No Treatment	0	24	34	466	188	126	55	647
NICE 2015	208	23	31	460	184	124	51	655
WHO 2013	253	23	31	459	184	123	51	657

106

107 **Table x12:** Deterministic analysis for HAPO (4) population without NICE risk factors (n=2,614)

Diagnostic threshold	Cost	QALY	Incremental cost	Incremental QALY	ICER
No Treatment	£0	0.00	n/a	n/a	n/a
NICE 2015	£238,074	5.43	£238,074	5.43	£43,845
WHO 2013	£281,357	5.63	£43,283	0.20	£220,638

108

109 **Table x13:** Probabilistic sensitivity analysis for HAPO (4) in a population without NICE risk factors

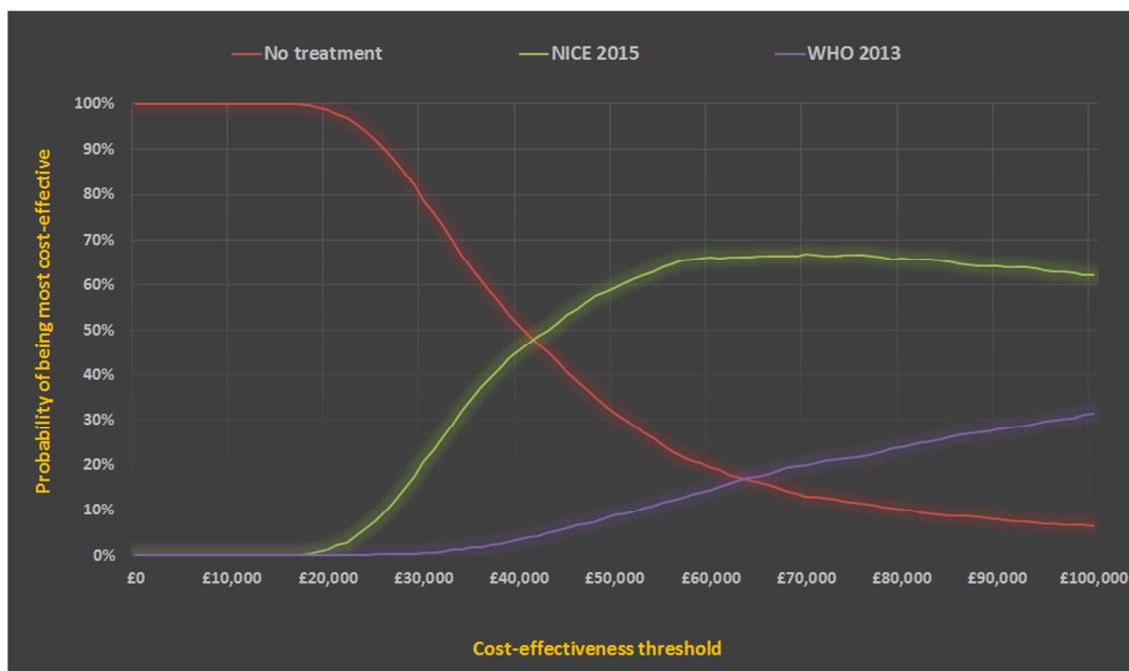
Diagnostic threshold	NMB CE threshold £30,000 per QALY	Probability cost- effective CE threshold £30,000 per QALY
No Treatment	£223	78.9%
NICE 2015	-£57,742	20.9%
WHO 2013	-£94,754	0.5%

110

111

112

113 **Figure x2:** Cost-effectiveness acceptability curve indicating the probability of a threshold or a no  
114 diagnosis/no treatment strategy being cost-effective at different cost-effectiveness thresholds for  
115 HAPO (4) population without risk factors



116  
117

118

review only



119 **Results for the Atlantic DiP population with risk factors**120 **Table 14:** Clinical outcomes for Atlantic DiP population with NICE risk factors (n=1,988)

Diagnostic threshold	Diagnosed	SD	SPC	CS	NICU	Jaund	PE	IOL
No Treatment	0	25	34	408	177	122	73	522
NICE 2015	497	19	26	391	163	116	56	545
WHO 2013	749	17	24	385	158	112	51	555

121

122 **Table x15:** Deterministic analysis for the Atlantic DiP population with NICE risk factors (n=1,988)

Diagnostic threshold	Cost	QALY	Incremental cost	Incremental QALY	ICER
No Treatment	£0	0.00	n/a	n/a	n/a
NICE 2015	£414,714	17.46	£414,714	17.46	£23,755
WHO 2013	£626,417	22.44	£211,703	4.98	£42,457

123

124 **Table x16:** Probabilistic sensitivity analysis for Atlantic in a population with NICE risk factors

Diagnostic threshold	NMB CE threshold £30,000 per QALY	Probability cost- effective CE threshold £30,000 per QALY
No Treatment	£518	30.2%
NICE 2015	£116,178	50.8%
WHO 2013	£53,129	19.1%

125

126

127

128

129 **Figure x3:** Cost-effectiveness acceptability curve indicating the probability of a threshold or a no  
 130 diagnosis/no treatment strategy being cost-effective at different cost-effectiveness thresholds for  
 131 the Atlantic DiP centres population with risk factors



132  
 133

134

135 **Results for the Atlantic DiP population without risk factors**136 **Table x17:** Clinical outcomes for Atlantic DiP population without NICE risk factors (n=3,302)

Diagnostic threshold	Diagnosed	SD	SPC	CS	NICU	Jaund	PE	IOL
No Treatment	0	33	45	575	254	168	84	828
NICE 2015	194	31	42	569	248	166	79	837
WHO 2013	371	30	41	564	245	163	76	844

137

138 **Table x18:** Deterministic analysis for the Atlantic DiP population without NICE risk factors (n=3,302)

Diagnostic threshold	Cost	QALY	Incremental cost	Incremental QALY	ICER
No Treatment	£0	0.00	n/a	n/a	n/a
NICE 2015	£231,633	6.48	£231,633	6.48	£35,732
WHO 2013	£381,795	9.81	£150,162	3.33	£45,075

139

140 **Table x19:** Probabilistic sensitivity analysis for the Atlantic DiP population without NICE risk factors

Diagnostic threshold	NMB CE threshold £30,000 per QALY	Probability cost- effective CE threshold £30,000 per QALY
No Treatment	£402	69.0%
NICE 2015	-£36,481	18.0%
WHO 2013	-£88,283	13.1%

141

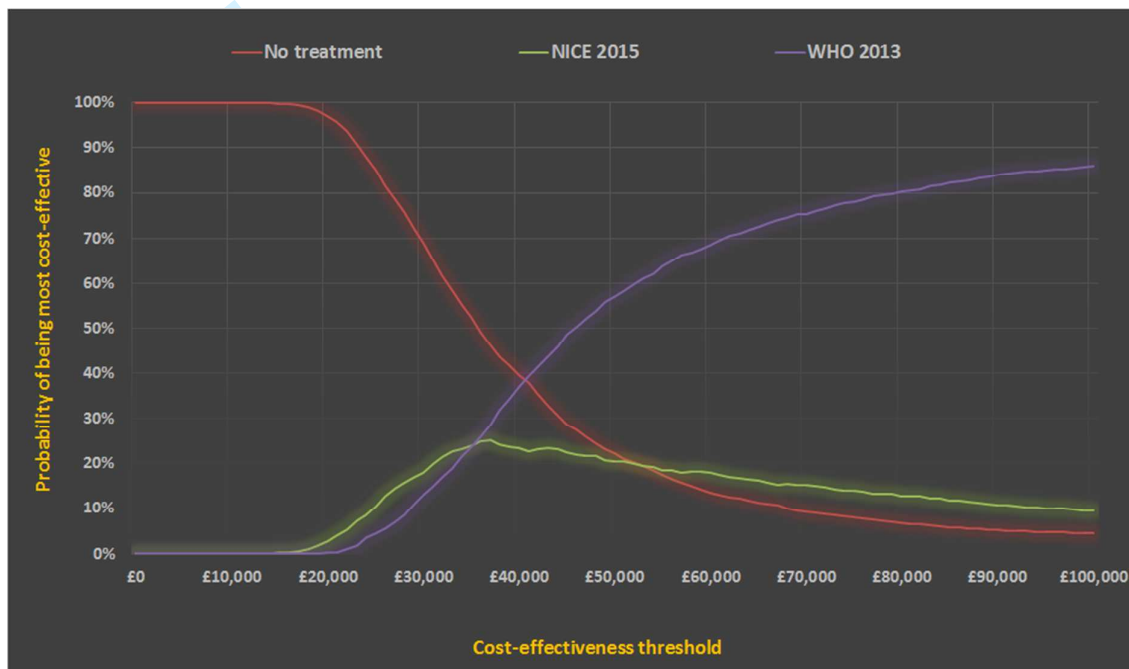
142

143

144

145 **Figure x4:** Cost-effectiveness acceptability curve indicating the probability of a threshold or a no  
146 diagnosis/no treatment strategy being cost-effective at different cost-effectiveness thresholds for  
147 the Atlantic DiP centres population without risk factors

148



149

150

151 **Results for the Norwich population**152 **Table x20:** Clinical outcomes for Norwich population (n=12,754)

Diagnostic threshold	Diagnosed	SD	SPC	CS	NICU	Jaund	PE	IOL
No Treatment	0	132	182	2,333	1,005	699	346	3,173
NICE 2015	888	122	168	2,305	981	687	318	3,214
WHO 2013	1,771	117	161	2,283	965	676	301	3,248

153

154 **Table x21:** Deterministic analysis for the Norwich population (n=12,754)

Diagnostic threshold	Cost	QALY	Incremental cost	Incremental QALY	ICER
No Treatment	£0	0.00	n/a	n/a	n/a
NICE 2015	£979,903	29.54	£979,903	29.54	£33,177
WHO 2013	£1,725,098	46.89	£745,195	17.35	£42,931

155

156 **Table x22:** Probabilistic sensitivity analysis for the Norwich population

Diagnostic threshold	NMB CE threshold £30,000 per QALY	Probability cost- effective CE threshold £30,000 per QALY
No Treatment	£1,141	59.7%
NICE 2015	-£76,289	23.2%
WHO 2013	-£300,524	17.2%

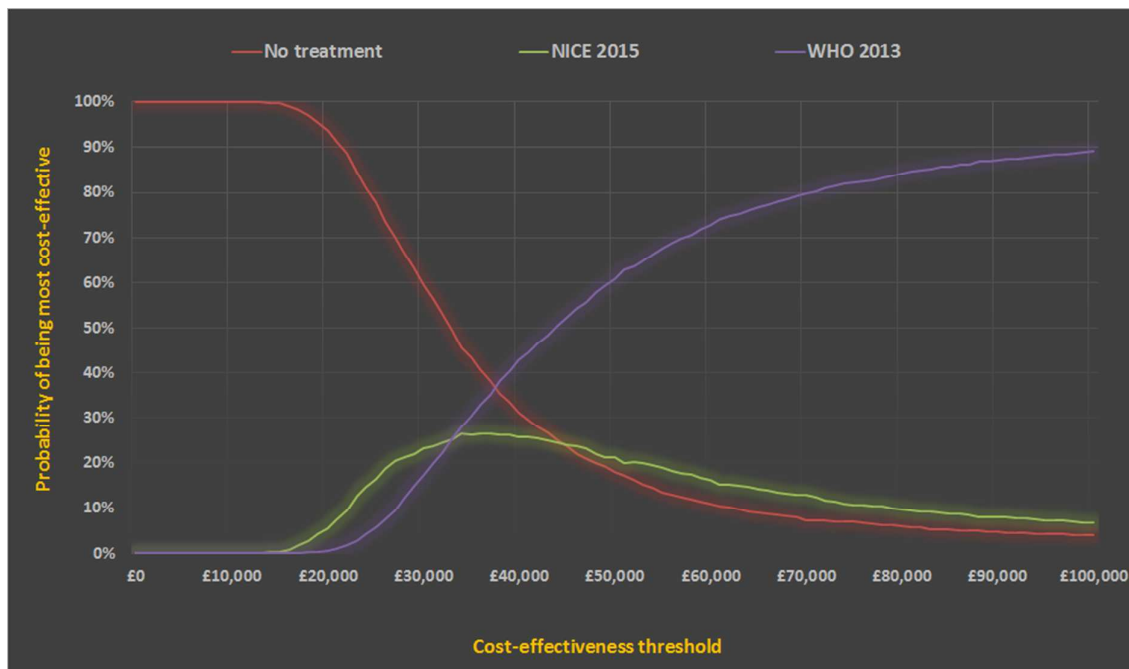
157

158

159

160

161 **Figure x5:** Cost-effectiveness acceptability curve indicating the probability of a threshold or a no  
162 diagnosis/no treatment strategy being cost-effective at different cost-effectiveness thresholds for  
163 the Norwich population



164

165

166

167

1  
2  
3 **168 One-way sensitivity analysis**  
4

5  
6 169 The cost-effectiveness of universal screening was not generally affected when the model was re-run  
7  
8 170 using the regression models without backward elimination of non-significant variables with no  
9  
10 171 screening/no treatment continuing to be the cost-effective option in populations not selected on the  
11  
12 172 basis of NICE risk factors (see Table x23). In the Norwich population, universal screening was  
13  
14 173 borderline cost-effective compared to no screening/no treatment at £30,000 per QALY but the same  
15  
16 174 point remains that a risk factor subset in this population would have a lower ICER than that  
17  
18 175 reported, and that a subset without risk factors, (i.e. those additionally incorporated as a result of  
19  
20 176 universal screening compared to risk factor screening), would have a higher ICER. In populations  
21  
22 177 with NICE risk factors the NICE 2015 diagnostic thresholds were still found to be cost-effective at a  
23  
24 178 threshold of £30,000 per QALY, with broadly similar ICERs as previously. Similarly, the WHO 2013  
25  
26 179 diagnostic threshold was never found to be cost effective even in a population with risk factors.  
27  
28  
29

30 **180 Table x23:** Summary of deterministic ICERs for each population without backward elimination of  
31 non-significant coefficients  
32

Diagnostic threshold	All covariates		Plasma glucose covariates				Norwich (n=12,754)
	HAPO Risk factor (n=3,549)	HAPO No Risk factor (n=2,614)	HAPO Risk factor (n=3,549)	HAPO No Risk factor (n=2,614)	Atlantic DiP Risk factor (n=1,988)	Atlantic DiP No Risk factor (n=3,302)	
No Treatment	-	-	-	-	-	-	-
NICE 2015	£22,786	£46,677	£24,802	£39,338	£22,126	£37,887	£31,191
WHO 2013	£33,876	£107,247	£35,852	£54,288	£41,652	£43,106	£43,694

33  
34  
35  
36  
37  
38 182

39  
40  
41  
42  
43 183  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 184 **Mean plasma glucose values according to risk factor status**  
4  
5

6 185 | **Table x241:** Mean plasma glucose values in HAPO (4) and Atlantic DiP population according to their  
7 186 risk factor status  
8

9 187

	HAPO 4			Atlantic DiP		
	Fasting	1-hour	2-hour	Fasting	1-hour	2-hour
True Positives	5.24	9.90	7.89	5.21	10.21	7.61
False Positives	4.50	7.20	5.95	4.33	6.75	5.33
True Negatives	4.44	6.95	5.78	3.92	5.99	4.76
False Negatives	4.89	9.52	7.41	4.90	9.51	7.12

10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25 188  
26  
27

28 189  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



## CHEERS Statement

CHEERS checklist—Items to include when reporting economic evaluations of health interventions

Section/item	Item No	Recommendation	Reported on page No/ line No
<b>Title and abstract</b>			
Title	1	Identify the study as an economic evaluation or use more specific terms such as “cost-effectiveness analysis”, and describe the interventions compared.	Yes Page 1 Line 2
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	Yes Page 2 Lines 29-47
<b>Introduction</b>			
Background and objectives	3	Provide an explicit statement of the broader context for the study.	Yes Page 3-4 Lines 70-80
		Present the study question and its relevance for health policy or practice decisions.	Yes Page 3 Lines 53-68
<b>Methods</b>			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Yes Page 5 Lines 94-122
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Yes Page 5 Lines 94-99
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Yes Page 9 Line 189
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Yes Page 4 Line 77-78; 84-85
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Yes Page 10 Line 200  Supp. Report Page 9 Line 74

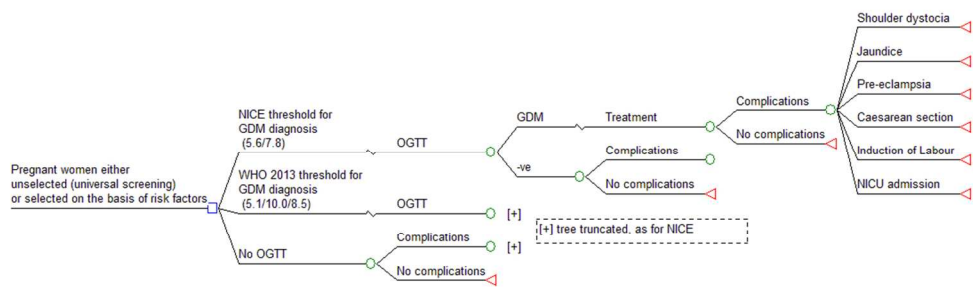
Section/item	Item No	Recommendation	Reported on page No/ line No
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	Yes Page 10 Line 200  Supp. Report Page 9 Line 74
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Yes Pages 6-7 Lines 124-145
Measurement of effectiveness	11a	<i>Single study-based estimates:</i> Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	Yes Pages 8 Lines 174-177
	11b	<i>Synthesis-based estimates:</i> Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	Yes Pages 8 Lines 171-174
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	
Estimating resources and costs	13a	<i>Single study-based economic evaluation:</i> Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
	13b	<i>Model-based economic evaluation:</i> Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Yes Page 10-11 Lines 188-213  Supp. Report Page 8 Line 65
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Yes Page 10 Lines 199

Section/item	Item No	Recommendation	Reported on page No/ line No
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	Yes Page 4 Lines 84-85; 89-91
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	Yes Page 6-7 Lines 124-145  Yes Page 11 Lines 214-218  Supp. Report Page 2-7  Supp. Report Page 9 Lines 68-86  +References to other sources
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	Yes Page 7 Lines 147-164  Yes Page 11 Lines 225-232  Supp. Report Page 2-7
<b>Results</b>			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Yes Page 9 Lines 185-186  Page 11 Lines 212-213

Section/item	Item No	Recommendation	Reported on page No/ line No
			Supp. Report Page 2-9
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Yes Page 13 Lines 246-248  Supp. Report Page 11-19
Characterising uncertainty	20a	<i>Single study-based economic evaluation:</i> Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	
	20b	<i>Model-based economic evaluation:</i> Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Yes Supp. Report Page 11 Lines 95-103  Supp. Report Page 20 Lines 181-182
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	Yes Supp. Report Page 11 Lines 95-103
<b>Discussion</b>			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Yes Pages 16-22
<b>Other</b>			
Source of funding	23	Describe how the study was funded and the role	Yes

Section/item	Item No	Recommendation	Reported on page No/ line No
		of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	Page 23 Lines 476-489
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Yes Page 23 Lines 472-474

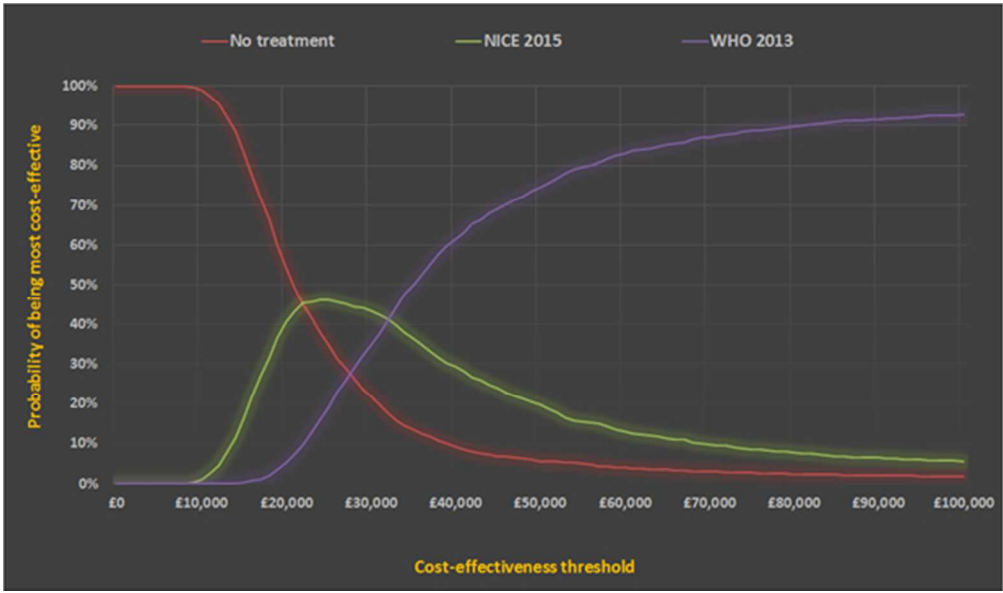
1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



Model Schematic

peer review only

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



Cost-effectiveness acceptability curve indicating the probability of a threshold or a no diagnosis/no treatment strategy being cost-effective at different cost-effectiveness thresholds for the HAPO 4 centres population with risk factors

Review only

# BMJ Open

## A COST EFFECTIVENESS COMPARISON OF THE NICE 2015 AND WHO 2013 DIAGNOSTIC CRITERIA FOR WOMEN WITH GESTATIONAL DIABETES WITH AND WITHOUT RISK FACTORS

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-016621.R1
Article Type:	Research
Date Submitted by the Author:	28-Apr-2017
Complete List of Authors:	Jacklin, Paul; Royal College of Obstetricians and Gynaecologists, National Guideline Alliance Maresh, Michael; Central Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre Patterson, Chris; Queen's University Belfast, Centre for Public Health Stanley, Katharine; Norfolk and Norwich University Hospitals NHS Foundation Trust, Department of Obstetrics and Gynaecology Dornhorst, Anne; Hammersmith Hospital, Department of Investigative Medicine Burman-ROY, Shona; Royal College of Obstetricians and Gynaecologists, National Guideline Alliance Bilous, Rudy; Newcastle University Medicine Malaysia
<b>Primary Subject Heading</b>:	Health economics
Secondary Subject Heading:	Diabetes and endocrinology, Obstetrics and gynaecology, Diagnostics
Keywords:	HEALTH ECONOMICS, DIABETES & ENDOCRINOLOGY, OBSTETRICS

SCHOLARONE™  
Manuscripts



1  
2  
3 **Title:**  
4

5 A COST EFFECTIVENESS COMPARISON OF THE NICE 2015 AND WHO 2013  
6  
7 DIAGNOSTIC CRITERIA FOR WOMEN WITH GESTATIONAL DIABETES WITH AND  
8  
9  
10 WITHOUT RISK FACTORS  
11

12  
13  
14 **Authors:** PB Jacklin<sup>1</sup>, MJA Maresh<sup>2</sup>, CC Patterson<sup>3</sup>, KP Stanley<sup>4</sup>, A Dornhorst<sup>5</sup>, S Burman-  
15  
16 Roy<sup>1</sup>, RW Bilous<sup>6</sup>  
17  
18

19  
20  
21 **Institutions:**  
22

- 23 1. Royal College of Obstetricians and Gynaecologists, London NW1 4RG, UK  
24 2. St. Mary's Hospital, Central Manchester University Hospitals NHS Foundation Trust,  
25 Manchester Academic Health Science Centre, Manchester M13 9WL, UK  
26  
27 3. Centre for Public Health, Queen's University Belfast, Room 3.014, ICS Block B, Grosvenor Road,  
28 Belfast BT12 6BJ, UK  
29  
30 4. Department of Obstetrics and Gynaecology, Norfolk and Norwich University Hospitals NHS  
31 Foundation Trust, Colney Ln, Norwich NR4 7UY, UK  
32  
33 5. Faculty of Medicine, Department of Investigative Medicine, Hammersmith Hospital, Imperial  
34 College London, London, UK  
35  
36 6. Newcastle University Medicine Malaysia, Johor, Malaysia  
37  
38

39  
40  
41 **Corresponding author:**  
42

43 Paul Jacklin  
44 e-mail: [pjacklin@rcog.org.uk](mailto:pjacklin@rcog.org.uk)  
45  
46

47  
48 Abstract: 278 words  
49

50 Main text: 4618 words  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 30 **Abstract**  
4

5 31

6 32 **Objectives** To compare the cost effectiveness of The National Institute for Health and Care  
7  
8 33 Excellence (NICE) 2015 and the World Health Organisation (WHO) 2013 diagnostic thresholds  
9  
10 34 for gestational diabetes (GDM).  
11

12  
13 35 **Setting:** The analysis was from the perspective of the National Health Service (NHS) in  
14  
15 36 England and Wales.  
16

17  
18 37 **Participants:** 6,221 patients from four of the Hyperglycaemia and Adverse Pregnancy  
19  
20 38 Outcomes (HAPO) study centres (2 UK, 2 Australian), 6,308 patients from the Atlantic  
21  
22 39 Diabetes in Pregnancy (DiP) study and 12,755 patients from UK clinical practice  
23

24 40 **Primary and secondary outcome measures planned:** The incremental cost per quality  
25  
26 41 adjusted life year (QALY), net monetary benefit (NMB) and the probability of being cost-  
27  
28 42 effective at cost-effectiveness thresholds of £20,000 and £30,000 per QALY  
29

30  
31 43 **Results.** In a population of pregnant women from the four HAPO study centres, and utilising  
32  
33 44 NICE defined risk factors for GDM, diagnosing GDM using NICE 2015 criteria had an  
34  
35 45 incremental cost effectiveness ratio (ICER) of £20,400 per QALY gained (relative to no  
36  
37 46 treatment) compared to £33,596 per QALY gained (relative to NICE 2015 criteria) using WHO  
38  
39 47 2013 diagnostic criteria. At a cost-effectiveness threshold of £30,000 per QALY the NICE 2015  
40  
41 48 criteria had a 53.5% probability of being cost-effective compared to the WHO 2013 diagnostic  
42  
43 49 criteria which had a 26.8% probability of being cost-effective (no treatment had a 19.8%  
44  
45 50 probability of being cost-effective). The ICERs for women without NICE risk factors in this  
46  
47 51 population were £36,878 and £141,812 per QALY for NICE and WHO diagnostic criteria,  
48  
49 52 respectively.  
50

51  
52  
53 53 **Conclusion** The NICE 2015 diagnostic criteria for GDM can be considered cost-effective  
54  
55 54 relative to the WHO 2013 alternative at a cost-effectiveness (CE) threshold of £30,000 per  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

55 QALY. Universal screening for GDM was not found to be cost-effective relative to screening  
56 based on NICE risk factors.

57

58 **Keywords:** Cost Effectiveness, Gestational Diabetes, Screening, Risk Factors, Diagnosis

59

60

For peer review only

1  
2  
3 61 **Strengths and limitations of this study**  
4

- 5 62 • This economic evaluation addresses an important clinical and policy issue. The existing  
6  
7 63 economic evidence is limited and WHO have stated that studies of this type are needed  
8  
9 64 to inform a future update of their guideline  
10  
11 65 • Our paper has used patient-level data from the influential HAPO study for an economic  
12  
13 66 analysis which has not been previously been published in a peer reviewed journal  
14  
15  
16 67 • This analysis provides clear evidence that universal screening is not cost-effective in the  
17  
18 68 UK  
19  
20  
21 69 • This analysis suggests that the NICE diagnostic criteria for GDM are more cost-  
22  
23 70 effective than the WHO criteria in the UK context  
24  
25  
26 71 • Model conclusions are sensitive to uncertainties with respect to valuation of health  
27  
28 72 outcomes and the possible long term metabolic consequences for offspring for which the  
29  
30 73 evidence is debated and which are hard to quantify  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## 74 **Introduction**

75 The diagnostic glycaemic thresholds for GDM remain the subject of considerable debate. The  
76 original definition was based upon maternal risk for developing postpartum diabetes, but  
77 subsequent thresholds have concentrated on complications during pregnancy and the health of  
78 the offspring. The publication of the HAPO study<sup>1</sup> demonstrated a linear association between  
79 increasing levels of maternal hyperglycaemia and adverse perinatal outcomes with no obvious  
80 threshold, an association that has also been observed in subsequent analyses.<sup>2</sup> The discussion  
81 around the diagnostic criteria that should define GDM has intensified. New diagnostic  
82 thresholds were proposed by the International Association of Diabetes in Pregnancy Study  
83 Group (IADPSG)<sup>3</sup> based upon the HAPO study levels of plasma glucose when fasting, and at 1  
84 and 2 hours after an oral 75g glucose load that were associated with covariate adjusted odds  
85 ratio of 1.75 relative to the mean glucose value in the whole HAPO cohort on three offspring  
86 outcomes: exceeding the 90<sup>th</sup> centile for birth weight, for cord serum C-peptide concentration  
87 and for percent fetal body fat. These diagnostic criteria have been subsequently adopted by the  
88 WHO.<sup>4</sup> However, they remain controversial and have not been supported by bodies such as the  
89 National Institutes for Health and the American College of Obstetricians.<sup>5</sup> Furthermore, WHO  
90 has acknowledged that they will have to be revisited in the near future in the light of new  
91 studies reporting their cost-effectiveness.<sup>4</sup>

92  
93 In 2015 NICE published updated guidance on Diabetes in Pregnancy<sup>6</sup> which included  
94 recommendations on diagnostic thresholds for GDM which differ from those adopted by WHO.  
95 These NICE thresholds were informed by an economic evaluation of the type that WHO  
96 considered important to inform future recommendations, but have attracted criticism in the UK<sup>7</sup>  
97 and elsewhere. Data from a published Spanish study<sup>8</sup> have been widely cited<sup>7,9</sup> in support of the

1  
2  
3 98 cost effectiveness of the WHO criteria, although a UK analysis has more recently suggested that  
4  
5 99 it is not cost-effective to identify gestational diabetes for treatment.<sup>10</sup>  
6  
7  
8  
9

100

101 In this paper we compared the cost-effectiveness of NICE 2015 and WHO 2013 diagnostic  
102 thresholds for GDM, as these are new thresholds proposed by national and international bodies.

103 The analysis was undertaken using a revised version of the health economic model developed  
104 for the NICE guideline and was based upon data from the UK and Australian HAPO Study  
105 centres.  
106

107

## 107 **Methods**

### 108 *Model description*

109 A decision analytic framework was used to evaluate the cost effectiveness of two recently  
110 proposed diagnostic thresholds for GDM, together with a no diagnosis/no treatment option (See  
111 Table 1). A schematic of the model is shown in Figure 1. Cost-effectiveness was evaluated  
112 using both deterministic and probabilistic sensitivity analysis.  
113

114

114 **Table 1:** Diagnostic thresholds for plasma glucose evaluated in the economic model

Threshold name	Fasting (mmol/L)	1-hour (mmol/L)	2-hour (mmol/L)
No diagnosis/no treatment	-	-	-
NICE 2015	≥5.6	-	≥7.8
WHO 2013	≥5.1	≥10.0	≥8.5

115

### 116 *Population*

117 The model population comprised women of gestational age 24-28 weeks without pre-existing  
118 diabetes. The analysis utilised individual patient data from three datasets which, although not  
119  
120

1  
2  
3 119 restricted to the UK, provide a representative cross section of the demographic and patient  
4  
5 120 characteristics that would be found in the UK (Table x1 in the Supplementary Report provides a  
6  
7 121 breakdown of ethnic groups in each of our datasets) . The analyses were run separately for each  
8  
9 122 dataset and, where possible, for subgroups with and without risk factors for GDM within a  
10  
11 123 dataset.  
12  
13  
14

15  
16 125 i. HAPO – a dataset from the two UK (Manchester and Belfast) and two Australian  
17  
18 126 (Brisbane and Newcastle) centres of the HAPO Study, referred to as HAPO (4)

19  
20  
21 127 ii. Norwich – these data were routinely collected between 2008 and February 2014 on  
22  
23 128 women who had an oral glucose tolerance test (OGTT) on the basis of the presence of one or  
24  
25 129 more risk factors for GDM. The results were obtained from laboratory records with no  
26  
27 130 identifiers. Risk factors in addition to those recommended by NICE were used e.g. women with  
28  
29 131 polycystic ovary syndrome, previous stillbirth or recurrent glycosuria.

30  
31  
32 132 iii. Atlantic Diabetes in Pregnancy (Atlantic DiP) – these data were collected between 2007  
33  
34 133 and 2013 as part of a research initiative in the Republic of Ireland intended to improve  
35  
36 134 pregnancy outcomes for women with diabetes before, during and after pregnancy.  
37  
38  
39

40  
41 136 For the HAPO (4) and Atlantic DiP datasets the populations were stratified according to  
42  
43 137 whether or not they had NICE risk factors for GDM (body mass index (BMI) above 30 kg/m<sup>2</sup>,  
44  
45 138 previous baby with birthweight  $\geq 4.5$  kg, previous GDM, first-degree relative with diabetes and  
46  
47 139 minority ethnic family origin with a high prevalence of diabetes). This facilitated a comparison  
48  
49 140 of the cost-effectiveness of universal screening for GDM when compared with a risk factor  
50  
51 141 approach.  
52  
53  
54

55  
56  
57  
58  
59  
60

1  
2  
3 143 The NICE risk factor approach could not be replicated exactly because the patient data used in  
4  
5 144 the model do not include information on previous offspring birth weight, and the HAPO (4)  
6  
7 145 dataset does not provide information on previous GDM. Similarly the Atlantic DIP dataset does  
8  
9 146 not include data on previous macrosomia or previous GDM. Therefore, the comparison in the  
10  
11 147 model was between universal screening and a subset of NICE risk factors. Our Norwich dataset  
12  
13 148 only included the plasma glucose values from a three point (fasting, 1 and 2 hour) OGTT and  
14  
15 149 therefore it was not possible to assess cost-effectiveness according to the presence of risk  
16  
17 150 factors in this group.  
18  
19  
20  
21

22 151

### 23 152 *Clinical outcomes*

24  
25 153 The agreed outcomes for the economic model were selected prior to model development by the  
26  
27 154 NICE Guideline Development Group. They were:

- 28  
29 155 i. Shoulder dystocia (SD) – this was used to estimate serious perinatal complications  
30  
31 156 (SPC), a broader composite outcome (death, shoulder dystocia and birth trauma) used as  
32  
33 157 a primary outcome in clinical trials. The estimation of SPC from shoulder dystocia has  
34  
35 158 been described elsewhere.<sup>6</sup>  
36  
37  
38 159 ii. Caesarean section (CS)  
39  
40  
41 160 iii. Neonatal intensive care unit (NICU) admission  
42  
43 161 iv. Jaundice requiring phototherapy (Jaund)  
44  
45 162 v. Pre-eclampsia (PE)  
46  
47 163 vi. Induction of labour (IOL)

48  
49 164 Outcomes were prioritised for inclusion in the model if they had a direct impact on health  
50  
51 165 related quality of life and/or cost. Birth weight was not included because there were few long-  
52  
53 166 term outcome data for modelling any risk benefit of a reduction in birth weight for future  
54  
55 167 diabetes and other health outcomes in the offspring.  
56  
57  
58  
59  
60



1  
2  
3 168

4  
5 169 In addition, outcomes were only included if the relationship with plasma glucose levels had  
6  
7 170 been established in the HAPO study, and also that they had been assessed in intervention  
8  
9 171 studies used to derive treatment effect size estimates. Possible double counting of certain  
10  
11 172 outcomes was taken into account (e.g. preterm birth and NICU admission). The final list of  
12  
13 173 outcomes included in the model was therefore a pragmatic one.  
14

15  
16  
17 174

18  
19 175 *Baseline risk*

20  
21 176 Logistic regression analyses of patient data from HAPO (4) were used to predict a baseline risk  
22  
23 177 for all six outcomes for each woman, based on their characteristics including their OGTT  
24  
25 178 results. In the HAPO study the OGTT was blinded to the carers, unless there was overt diabetes,  
26  
27 179 thus allowing direct comparison of the OGTT with perinatal outcomes without intermediate  
28  
29 180 treatment effects for those meeting the new diagnostic criteria for GDM.

30  
31  
32 181 For each of the six outcomes, 2 logistic analyses to predict risk were assessed:

33  
34 182 i. Prediction based on OGTT plasma glucose results and including the same covariates as  
35  
36 183 used for Model 2 in the original analysis of the HAPO data<sup>1</sup> – this could not be applied  
37  
38 184 to the Norwich and Atlantic DiP datasets as information on all HAPO covariates was not  
39  
40 185 available

41  
42  
43 186 ii. Prediction based only on OGTT plasma glucose results

44  
45 187 Backward elimination of plasma glucose variables with non-significant coefficients was  
46  
47 188 undertaken to arrive at a ‘final’ logistic regression analysis to predict baseline risk for each  
48  
49 189 outcome for the base case analysis, although a sensitivity analysis is also presented where the  
50  
51 190 model was run with plasma glucose variables with non-significant coefficients retained. The  
52  
53 191 logistic regression analyses used to predict the baseline risk for each outcome are shown in the  
54  
55 192 Supplementary Report, Tables x2 to x7.  
56  
57  
58  
59  
60

193

194 *Clinical effectiveness*

195 For each evaluated diagnostic threshold in Table 1 the model determined whether a woman  
 196 would be identified as having GDM based on her OGTT. If the woman was not identified as  
 197 having GDM then outcome probabilities were based on the predicted baseline risk, but for  
 198 women identified as having GDM the predicted baseline risk was modified to take account of  
 199 the effects of treatment. Treatment effectiveness for most outcomes was estimated from a  
 200 random-effects meta-analysis of two studies, the Australian Carbohydrate Intolerance Study  
 201 (ACHOIS) and the Landon et al. trial.<sup>11, 12</sup> Other published studies of treatment for GDM were  
 202 adjudged to lack adequate randomisation.<sup>13</sup> For the NICU outcome only the Landon et al. trial  
 203 data were used as it was considered to more closely represent UK practice as all neonatal  
 204 nursery admissions were utilised. Similarly, the incidence of pre-eclampsia seemed high in  
 205 ACHOIS in both arms, and again only Landon et al. trial data were utilised. The treatment  
 206 effects for each of the model's clinical outcomes are shown in Table 2 along with parameters  
 207 for probabilistic sampling. The model assumes that the relative treatment effect will be the same  
 208 irrespective of the absolute baseline risk. For deterministic analyses the point estimate of  
 209 relative risk was used but in order to account for uncertainty in these point estimates, these  
 210 relative risks were sampled from a log-normal distribution in the simulations undertaken for  
 211 probabilistic sensitivity analysis (PSA).

212

213 **Table 2:** Relative treatment effects for model outcomes

Outcome	Relative risk (RR)	Standard error (log RR)	Source
---------	-----------------------	----------------------------	--------

<b>Shoulder dystocia</b>	0.41	0.316	ACHOIS (2005), Landon (2009)
<b>Caesarean section</b>	0.88	0.095	ACHOIS (2005), Landon (2009)
<b>NICU</b>	0.77	0.194	Landon (2009)
<b>Jaundice requiring phototherapy</b>	0.83	0.136	ACHOIS (2005), Landon (2009)
<b>Pre-eclampsia</b>	0.46	0.345	Landon (2009)
<b>Induction of Labour</b>	1.16	0.126	ACHOIS (2005), Landon (2009)

214

215

1  
2  
3 216 *Costs*

4  
5 217 Costing was undertaken from the perspective of the NHS, was calculated for each woman in the  
6  
7 218 dataset being analysed and was made up of three components;

- 8  
9  
10 219 • the costs of the diagnostic test – not applied in the *no test/no treat* strategy  
11  
12 220 • the costs of treatment- applied to every woman diagnosed with GDM at a particular  
13  
14 221 threshold  
15  
16 222 • the costs associated with the various outcomes – with the cost for each woman being the  
17  
18 223 expected (or average) cost of the outcome based on her estimated risk

19  
20  
21 224 The costs calculated for each woman were then summed across the entire patient dataset to give  
22  
23 225 a total cost for a particular diagnostic threshold.

24  
25  
26 226

27  
28 227 Costs are presented in pounds sterling and were taken from published UK sources where  
29  
30 228 possible (cost year 2015). They have not been discounted as they are all assumed to occur  
31  
32 229 within 12 months of diagnosis. Model unit costs are reported in the Supplementary Report,  
33  
34 230 Table x14. The costing methodology and assumptions are described in greater detail elsewhere.<sup>6</sup>

35  
36  
37 231

38  
39 232 *Other event probabilities*

40  
41 233 Probabilities in decision analysis were used to calculate the expected costs and benefits of the  
42  
43 234 various comparators. Many of these probabilities stemmed from relative treatment effects but a  
44  
45 235 few additional event probabilities were included in the model in order to estimate certain costs.

46  
47 236 These probabilities are shown in Table 3 and their source is described elsewhere.<sup>6</sup>

48  
49  
50 237

51  
52  
53 238

54  
55  
56 239

57  
58  
59 240

241 **Table 3:** Model event probability not derived from patient level regression

Event	Probability
Not requiring hypoglycaemic therapy when treated for GDM	36%
Risk of hypoglycaemia if taking hypoglycaemic therapy	20%
Risk of hypoglycaemia being severe (requiring hospitalisation)	5%

242  
243 *Quality Adjusted Life Years (QALYs)*

244 Following previous studies<sup>6, 14</sup> a QALY decrement of 2.2 was assigned to serious perinatal  
245 complications (SPC), defined as per the ACHOIS study as a composite outcome of shoulder  
246 dystocia, death and birth trauma.<sup>11</sup> More detail on the derivation of this QALY loss is provided  
247 in the Supplementary Report. The cost-effectiveness of a healthcare intervention is determined  
248 by the opportunity cost of the health foregone on the basis that with a fixed health budget any  
249 newly funded intervention would displace the least cost-effective treatment currently provided.  
250 In the UK, NICE typically uses a threshold of £20,000 to £30,000 per QALY as a benchmark<sup>15</sup>  
251 for the opportunity cost of health foregone and this paper assesses cost-effectiveness  
252 accordingly.

253  
254 *Sensitivity analysis*

255  
256 Probabilistic sensitivity analysis, using Monte Carlo simulation (with 2,000 iterations for each  
257 analysis), was undertaken in order to assess the impact of sampling uncertainty on model inputs.  
258 Parameters and distributions for the probabilistic sensitivity analysis are given in Table 2 and  
259 Table x14 in the supplementary report. For the logistic regression coefficients used to predict  
260 baseline risk, the Cholesky decomposition method<sup>16</sup> was used to sample from a multivariate  
261 normal distribution in order to reflect correlations between the coefficients. The Cholesky

decomposition of the variance covariance matrices from the regression analyses used in the base case probabilistic sensitivity analysis are given in Table x8 to x13 in the Supplementary Report.

264

## 265 Results

266 Table 4 shows the percentage of women diagnosed with GDM in the three populations using  
267 both of the evaluated diagnostic thresholds. In addition, for the HAPO (4) and Atlantic DiP  
268 datasets this is additionally broken down in the subgroups with and without NICE risk factors  
269 (RF).

270 **Table 4:** Percentage of women identified with GDM by threshold and population

Threshold name	Norwich (n=12,754)	HAPO all (n=6,163)	HAPO RF (n=3,549)	HAPO No RF (n=2,614)	DiP All (n=5,290)	DiP RF (n=1,988)	DiP No RF (n=3,302)
NICE 2015	7.0%	13.6%	17.7%	8.0%	13.1%	25.0%	5.9%
WHO 2013	13.9%	18.9%	25.7%	9.7%	21.2%	37.7%	11.2%

271

272 Detailed deterministic and probabilistic results for HAPO (4) with risk factors are shown in  
273 Table 5, Table 6, Table 7 and Figure 2.

274

275 **Table 5:** Clinical outcomes for HAPO (4) population with NICE risk factors (n=3,549)

Diagnostic threshold	Diagnosed	SD	SPC	CS	NICU	Jaund	PE	IOL
No Treatment	0	49	67	759	345	219	146	974
NICE 2015	629	41	56	739	326	210	123	1,004
WHO 2013	912	39	54	731	321	207	117	1,016

276

277 **Table 6:** Deterministic analysis for the HAPO (4 centres) population with NICE risk factors  
 278 (n=3,549)

Diagnostic threshold	Cost <sup>a</sup>	QALY <sup>a</sup>	Incremental cost	Incremental QALY	ICER
No Treatment	£0	0.00	n/a	n/a	n/a
NICE 2015	£546,349	26.78	£546,349	26.78	£23,073
WHO 2013	£778,993	34.35	£254,376	7.57	£37,669

279 a) Costs and QALYs are measured relative to a baseline of No Treatment

280

281 Table 5 indicates that there was a relatively small difference in clinical outcomes contrasting  
 282 NICE and WHO diagnostic criteria, despite there being a 45% increase in women diagnosed  
 283 with GDM. Using the WHO 2013 criteria, instead of the NICE 2015 criteria, an additional 142  
 284 women would have been diagnosed with GDM, and treated in order to prevent 1 case of  
 285 shoulder dystocia.

286

287 In the deterministic analysis the NICE 2015 diagnostic criteria would be considered cost-  
 288 effective at a cost-effectiveness threshold of £30,000 per QALY (Table 6).

289

290 The probabilistic sensitivity analysis reached a similar conclusion, with the NICE 2015  
 291 diagnostic threshold having the highest probability of being the most cost-effective treatment  
 292 and the highest NMB using a cost-effectiveness threshold of £30,000 per QALY (Table 7 and  
 293 Figure 2). The analysis also suggested that no diagnosis/no treatment might be considered the  
 294 most likely to be cost-effective when using a lower cost-effectiveness threshold of £20,000 per  
 295 QALY. The probability of no diagnosis/no treatment being cost-effective falls sharply in the  
 296 cost-effectiveness threshold range of £20,000 - £30,000 *per* QALY. As shown in the cost-  
 297 effectiveness acceptability curve in Figure 2, the WHO 2013 diagnostic threshold becomes

298 more cost-effective as the cost-effectiveness threshold increases. Nevertheless, this would have  
 299 to exceed £30,000 per QALY before becoming cost-effective, indicating that the further  
 300 reduction in adverse outcomes, are achieved at an unacceptably high opportunity cost. The  
 301 Supplementary Report plots the incremental cost and QALY outcomes of 2,000 simulations  
 302 from the probabilistic analysis on the cost-effectiveness plane (see Figure x1). Whilst most  
 303 points fall in the south-western quadrant, suggesting that WHO 2013 diagnostic criteria are  
 304 likely to lead to additional QALYs when compared with NICE 2015 criteria, all points show  
 305 that NICE 2015 criteria were associated with markedly lower costs.

306

307

308 **Table 7: Probabilistic sensitivity analysis for HAPO (4) in a population with NICE risk factors**

<b>Diagnostic threshold</b>	<b>NMB<sup>a</sup> CE threshold £30,000 per QALY</b>	<b>Probability cost- effective CE threshold £20,000 per QALY</b>	<b>Probability cost- effective CE threshold WTP = £30,000 per QALY</b>
No Treatment	£486	55.5%	19.8%
NICE 2015	£230,798	42.1%	53.5%
WHO 2013	£178,231	2.4%	26.8%

309 a) NMB is measured relative to the least costly and least effective strategy in each simulation

310 Summaries of results for all of the model populations and more detailed results are provided in  
 311 the Supplementary Report.

312

313 Tables x16 and x17 in the Supplementary Report show that in both the HAPO (4) and Atlantic  
 314 DiP populations with NICE risk factors, the NICE diagnostic threshold is the most cost-  
 315 effective strategy at a cost-effectiveness threshold of £30,000 per QALY. The NICE 2015



1  
2  
3 316 diagnostic threshold has ICERs of less than £30,000 per QALY, and in the probabilistic  
4  
5 317 sensitivity analysis it has the highest net monetary benefit and the highest probability of being  
6  
7 318 the most cost-effective. For HAPO (4) the results are similar if baseline risks are estimated  
8  
9  
10 319 using logistic regression based on all covariates or a logistic regression just using plasma  
11  
12 320 glucose levels.

13  
14 321  
15  
16 322 The results also suggested that universal screening would not be cost-effective as, when  
17  
18 323 compared to risk factor screening (as recommended in NICE guidelines), the additional women  
19  
20 324 included in such an approach would be those without risk factors and the model demonstrates  
21  
22 325 that the ICERs for diagnosis and treatment are all well in excess of £30,000 per QALY;  
23  
24  
25 326 markedly so when using WHO 2013 diagnostic thresholds. These conclusions were supported  
26  
27 327 by an analysis of the Norwich dataset (see Supplementary Report).

28  
29 328  
30  
31  
32 329 It was not possible to stratify the Norwich dataset according to risk factors, and therefore the  
33  
34 330 ICERs presented relate to a comparison between no screening/treatment and universal screening  
35  
36 331 and treatment. However, the results were consistent with those for HAPO (4) and Atlantic DiP.  
37  
38 332 First, they showed that universal screening was not cost-effective even when compared to an  
39  
40 333 alternative of no screening/no treatment. Second, the ICERs for the whole population were a  
41  
42 334 weighted average of the populations with and without risk factors. The ICER for the population  
43  
44 335 without risk factors would be higher than the ICER for the entire population, which was only  
45  
46 336 marginally below the £30,000 per QALY threshold.

47  
48  
49 337

50  
51  
52 338 *Deterministic sensitivity analysis*

1  
2  
3 339 As part of a sensitivity analysis the deterministic models were re-run using the logistic  
4  
5 340 regression models without backward elimination of glucose variables with non-significant  
6  
7 341 coefficients, and these analyses are summarised in the Supplementary Report.  
8  
9  
10 342

### 11 343 **Discussion**

12  
13  
14 344 In the NICE guideline analysis, 14 alternative diagnostic thresholds were compared and there  
15  
16 345 was no single optimal diagnostic threshold which clearly emerged<sup>6</sup>. This is not surprising given  
17  
18 346 the small differences in patient outcomes between them. In that analysis the previous WHO  
19  
20 347 1999 criteria emerged as a relatively cost-effective strategy. However, the Guideline  
21  
22 348 Development Group rejected a fasting threshold of 7.0 mmol/L as there was a wide clinical  
23  
24 349 consensus that this was too high, as 6.1-7.0 mmol/L is diagnostic of impaired fasting glycaemia  
25  
26 350 in the non-pregnant population. Intervention studies had used a lower fasting threshold than 7.0  
27  
28 351 mmol/L as a basis for inclusion, and therefore made a case for intervention at lower levels.  
29  
30 352 Based upon detailed cost effectiveness analysis of all the options, the Guideline Development  
31  
32 353 Group ultimately decided on recommending a fasting plasma glucose of 5.6 mmol/L and a 2  
33  
34 354 hour plasma glucose of 7.8 mmol/L. In this paper, we have restricted our analysis of cost-  
35  
36 355 effectiveness to the WHO 2013 and NICE 2015 criteria (with a no screening/treatment baseline  
37  
38 356 also included) as these two recommendations have the most clinical currency at present.  
39  
40  
41  
42  
43  
44

45 358 All of the analyses presented in this paper suggest that, in a population with NICE risk factors,  
46  
47 359 the NICE 2015 diagnostic criteria for GDM could be considered cost-effective relative to no  
48  
49 360 screening/no treatment and to WHO 2013 diagnostic thresholds when using a cost-effectiveness  
50  
51 361 threshold of £30,000 per QALY. The analyses also show that no screening/no treatment is cost-  
52  
53 362 effective in populations without NICE risk factors, suggesting that universal screening does not  
54  
55 363 represent value for money, at least in a UK setting.  
56  
57  
58  
59  
60

364

365 One of the limitations of our analysis was that the 2-hour threshold was restricted to the  
366 historical WHO 1999 2-hour definition of 7.8mmol/l, or the new WHO 2013 criteria of 8.5  
367 mmol/l. It is conceivable that a 2-hour threshold lying between these values might outperform  
368 both. Our greater focus, though was on the optimal fasting level as this is where the greatest  
369 controversy lies with respect to potentially missed treatment opportunities.

370

371 As noted by the proponents of WHO 2013 diagnostic criteria for GDM, using a lower fasting  
372 plasma glucose threshold would by definition detect more cases. Furthermore, because we  
373 assumed in the model that the relative treatment effect would be the same in additionally  
374 diagnosed cases, it follows that such a threshold could potentially yield the lowest number of  
375 adverse outcomes and the greatest QALY gain. However, our analysis suggests that the  
376 relatively small additional gains are not justified by the substantially higher costs that such  
377 lower thresholds would require.

378

379 A key driver of our results were the logistic regression models which were used to predict  
380 baseline risk. For the outcomes included in this study these regression models suggested that the  
381 2-hour plasma glucose was a much more important predictor of adverse outcomes than the  
382 fasting plasma glucose, something we were unaware of when selecting the model's clinical  
383 outcomes. For the regression models fitted to predict baseline risk in the HAPO (4) dataset with  
384 covariates and backward elimination of the OGTT plasma glucose variables (Model 1 base case  
385 analysis regressions in Supplementary Tables x2 to x7), the Hosmer-Lemeshow Goodness of  
386 Fit Test did not indicate evidence of poor fit ( $p > 0.05$ ). However, there was evidence of poor fit  
387 ( $p < 0.05$ ) for the regression models of caesarean section and NICU admission where the  
388 prediction was based only on OGTT plasma glucose results (Model 2 base case analysis

1  
2  
3 389 regressions in Supplementary Tables x2 to x7). Nevertheless, as indicated in Supplementary  
4  
5 390 Table x16 and x17, the choice of prediction model did not have a large bearing on cost-  
6  
7 391 effectiveness.

8  
9 392

10  
11 393 We consider that our analysis which builds on previous modelling<sup>6, 14</sup> is one of the most  
12  
13 394 comprehensive assessments of the cost-effectiveness of diagnostic thresholds for GDM yet  
14  
15 395 undertaken, and will hopefully contribute to the WHO's expectation "that a substantial body of  
16  
17 396 new data will emerge in the near future, providing currently scarce health and economic  
18  
19 397 evaluation of the recommended criteria applied to various populations and with different  
20  
21 398 approaches (universal screening, screening only women at high risk, diagnostic testing only)".<sup>4</sup>  
22  
23  
24

25 399

26  
27 400 A number of commentators<sup>17, 18</sup> have recently advocated universal screening for GDM. The  
28  
29 401 essence of the argument is based upon the number of cases of GDM that would be missed with  
30  
31 402 selective screening, and the subsequent reduced opportunity to prevent a serious perinatal  
32  
33 403 outcome. Of course it is true that universal screening will detect more cases, although the  
34  
35 404 absolute numbers will depend upon the thresholds used to define GDM. Table 5 shows that  
36  
37 405 many more women would need to be diagnosed in order to prevent a single adverse outcome.  
38  
39 406 However, in the context of finite health care resources, it must be accepted that it may be cost-  
40  
41 407 effective to miss some cases. Epidemiological measures such as number needed to treat (or  
42  
43 408 number needed to screen in this case) implicitly recognise that a goal of health care systems  
44  
45 409 cannot be to maximize health gain without any consideration of cost. Identifying missed cases  
46  
47 410 carries an opportunity cost and it may be that those resources would achieve greater benefit if  
48  
49 411 employed elsewhere in the health care system. If a population is divided into those with risk  
50  
51 412 factors and those without risk factors, then the prevalence of GDM must be lower in the group  
52  
53 413 without risk factors (and the number needed to screen higher) with concomitantly lower cost-  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 414 effectiveness. However, the comparative cost-effectiveness of screening in those with and  
4  
5 415 without risk factors is not only affected by the respective prevalence in the two groups, but also  
6  
7 416 differences in severity. In those diagnosed with GDM and who had risk factors there were, as  
8  
9 417 anticipated, greater levels of hyperglycaemia than in those without risk factors. As shown in  
10  
11 418 Table x31 in the Supplementary Report, ‘true positives’ or identified cases (risk factor present  
12  
13 419 and GDM) had higher plasma glucose values than ‘false negatives’ or missed cases (risk factors  
14  
15 420 absent and GDM) when defining GDM positives according to WHO 2013 diagnostic  
16  
17 421 thresholds.  
18  
19  
20  
21 422

22  
23 423 We would therefore expect the women with risk factors and GDM to be at greater risk of  
24  
25 424 adverse outcomes than the women with GDM without risk factors as a result of their higher  
26  
27 425 plasma glucose levels. So the “cases” missed with selective screening would have, on average,  
28  
29 426 fewer adverse outcomes than in “cases” in a population with risk factors. So the ICER would be  
30  
31 427 greater in the population without risk factors because prevalence is lower and cases have fewer  
32  
33 428 adverse outcomes.  
34  
35  
36 429

37  
38 430 Our analysis, by splitting the HAPO (4) and Atlantic DiP datasets into those with and without  
39  
40 431 risk factors, was able to evaluate the cost-effectiveness of moving from risk factor screening to  
41  
42 432 universal screening. Whilst diagnosis in populations with risk factors was shown to be cost-  
43  
44 433 effective at a threshold of £30,000 per QALY, it was never cost-effective to diagnose and treat  
45  
46 434 in those without risk factors. Table 4 indicates the large differences that exist in prevalence  
47  
48 435 between the populations with and without risk factors. Our analysis suggests that the cost-  
49  
50 436 effectiveness threshold would have to substantially exceed currently accepted UK norms for  
51  
52 437 universal screening to be considered cost-effective. Although the NICE risk factor approach  
53  
54 438 could not be replicated exactly, we felt that the approximation used was acceptable, as the only  
55  
56  
57  
58  
59  
60

1  
2  
3 439 women who would be omitted from the model risk factor population were multiparous and  
4  
5 440 would have had a large baby previously and/or a past history of GDM. This approximation  
6  
7 441 would over-estimate slightly the benefits of universal screening, as the baseline risk in a group  
8  
9 442 designated as being without NICE risk factors present would be over-stated.  
10

11 443

12  
13  
14 444 A previous study<sup>8</sup> from Spain using WHO 2013 diagnostic criteria suggested cost effectiveness  
15  
16 445 compared with a two-step protocol using the Carpenter – Coustan thresholds. However, this  
17  
18 446 was largely based upon estimates of reduction of caesarean section rates of 50% which we find  
19  
20 447 implausible based upon changes in diagnostic criteria alone, noting that ACHOIS and Landon et  
21  
22 448 al. found only a 4% and 21% reduction in caesarean section respectively as a result of treating  
23  
24 449 gestational diabetes. The Spanish study did not consider other alternative thresholds, and was a  
25  
26 450 retrospective, before and after analysis which has been criticised by the Cochrane Collaboration  
27  
28 451 as it does not control for possible changes in important variables, such as clinical management,  
29  
30 452 over time.<sup>19</sup>  
31

32 453

33  
34  
35  
36 454 A recently published UK Health Technology Assessment (HTA)<sup>10</sup> suggested that the  
37  
38 455 identification of gestational diabetes for treatment is not cost-effective, in which case finding a  
39  
40 456 cost-effective threshold becomes somewhat redundant. Although the HTA followed a similar  
41  
42 457 approach to our analysis there were some differences which could explain the different  
43  
44 458 conclusions. In our analysis, jaundice was included as an outcome and the relative treatment  
45  
46 459 effect would have tended to lower the incremental costs of intervention as a result of reduced  
47  
48 460 rates of phototherapy. This was not included as an outcome in the HTA. Instrumental delivery  
49  
50 461 was included as an outcome in the HTA but not in our analysis. While instrumental delivery  
51  
52 462 rates could in theory be increased by treatment, as there will be more vaginal births, this could  
53  
54 463 be counteracted by those mothers not treated delivering larger babies vaginally requiring  
55  
56  
57  
58  
59  
60

1  
2  
3 464 assistance; this would be in accord with the HTA meta-analysis which failed to demonstrate a  
4  
5 465 treatment effect on instrumental delivery rates. In addition the HTA reported smaller treatment  
6  
7 466 effects for NICU admission and pre-eclampsia. Unlike our analysis, the HTA did not assume  
8  
9  
10 467 100% uptake of the OGTT and that may also have led to a smaller estimate of treatment benefit.  
11  
12 468 However, the differences should not be over-emphasised. Like the HTA our results would not  
13  
14 469 support the identification and treatment of gestational diabetes if a cost-effectiveness threshold  
15  
16 470 of £20,000 per QALY was used. However, it was the view of the Guideline Development  
17  
18 471 Group that the clinical benefit of identifying and treating women with GDM is widely practiced,  
19  
20  
21 472 and that a no identification/no treat policy would not be acceptable to patients or health care  
22  
23 473 providers. As such, the Group felt that the higher cost threshold of £30,000 was justified.  
24  
25 474  
26  
27 475 Our model has a number of limitations particularly with respect to the valuation of health  
28  
29 476 outcomes. We did not include large for gestational age as an outcome because it was felt that  
30  
31 477 shoulder dystocia was the relevant immediate complication of interest, and that possible long  
32  
33 478 term metabolic consequences for the offspring were hard to quantify and therefore difficult to  
34  
35 479 incorporate within the model. As previously noted, the QALY loss from a serious perinatal  
36  
37 480 complication used in this analysis is likely to be overstated because of the relatively large  
38  
39 481 weight given to death based on the intervention studies.<sup>14</sup> HAPO failed to show an association  
40  
41 482 between perinatal mortality and plasma glucose levels, which may mean that perinatal mortality  
42  
43 483 reduction is less amenable to reduction by treatment than other serious perinatal complications.  
44  
45 484 In this respect the cost-effectiveness of diagnosing and treating GDM may be over-stated. On  
46  
47 485 the other hand, the model does not take account of any potential long term effects on the  
48  
49 486 offspring (e.g. adiposity and the likelihood of subsequent pathology) as these effects are  
50  
51 487 difficult to quantify but may under-estimate the QALY gain from diagnosis and treatment. A  
52  
53 488 US study<sup>20</sup> considered the potential long-term benefits to the mother whereby a diagnosis of  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 489 GDM averts or delays onset of Type 2 diabetes mellitus, but this was not incorporated into our  
4  
5 490 model as we did not consider that the relationship was sufficiently well established at this time.  
6  
7 491 However, to the extent that such a relationship does exist our model would also underestimate  
8  
9 492 the QALY gain from a diagnosis of GDM. A recent review has, however, questioned the  
10  
11 493 association between maternal glycaemia and subsequent cardio-metabolic outcomes in offspring  
12  
13 494 in humans<sup>21</sup> and a recent follow-up study failed to find evidence of a reduction in childhood  
14  
15 495 obesity or metabolic dysfunction at five years in the offspring of women treated for mild  
16  
17 496 gestational diabetes in the study of Landon et al<sup>12, 22</sup>.  
18  
19  
20

21 497  
22  
23 498 Despite these caveats, we feel our analysis represents a robust analysis of the cost-effectiveness  
24  
25 499 of the NICE versus the WHO 2013 diagnostic thresholds for GDM based upon our current  
26  
27 500 understanding of the impact of intervention in women with GDM in the UK population. We  
28  
29 501 acknowledge completely that this analysis cannot be the final word on the subject, and that  
30  
31 502 further health economic evaluation is required to either corroborate our findings or to challenge  
32  
33 503 them. Nevertheless, our analysis represents a constructive and evidence based contribution to  
34  
35 504 establishing cost effective diagnostic thresholds for GDM and will hopefully lead to more  
36  
37 505 research to clarify this important but vexed area of clinical diagnosis.  
38  
39  
40

41 506

## 42 507 **Conclusions**

43  
44  
45 508 The results presented in this analysis, based on a UK setting, do not suggest that the diagnostic  
46  
47 509 thresholds for GDM adopted by the WHO are cost-effective. On the other hand they do provide  
48  
49 510 some support for the cost-effectiveness of the diagnostic criteria adopted by NICE when  
50  
51 511 compared to either no screening/treatment and to WHO 2013 diagnostic criteria. Furthermore,  
52  
53 512 according to this analysis, universal screening would seem to offer poor value for money and  
54  
55  
56  
57  
58  
59  
60



1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

513 does not appear cost-effective compared to the current NICE guidance of targeting high risk  
514 women.  
515

For peer review only

1  
2  
3 516 **Acknowledgements**  
4

5 517 We are grateful to Professor DR McCance and Professor HD McIntyre for allowing us to use  
6  
7 518 their local datasets from the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) trial and  
8  
9 519 to Professor F Dunne for allowing us to use her Atlantic DiP dataset.

10  
11 520 We are also grateful to Professor David James who provided clinical support during the  
12  
13 521 development of the updated NICE guideline on Diabetes in Pregnancy.  
14  
15

16 522

17  
18 523 **Competing interests**  
19

20 524 All authors have completed the ICMJE uniform disclosure form at

21  
22 525 [http://www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) and declare:  
23  
24

25 526

26  
27 527 **Funding:** Some of this work was undertaken by the now defunct National Collaborating Centre  
28  
29 528 for Women's and Children's Health (subsumed within the National Guideline Alliance from 1st  
30  
31 529 April 2016), which received funding from NICE. The views expressed in this publication are  
32  
33 530 those of the authors and not necessarily those of the institute. Revisions to the guideline model  
34  
35 531 after the guideline was published and drafting of the manuscript was done in the author's own  
36  
37 532 time and was not funded.  
38  
39

40 533

41  
42 534 National Institute for Health and Care Excellence (2015). Diabetes in pregnancy: management  
43  
44 535 from preconception to the postnatal period. Available from

45  
46 536 <https://www.nice.org.uk/guidance/ng3>  
47  
48

49 537 PBJ and SBR are employees of the National Guideline Alliance (part of the RCOG), which  
50  
51 538 receives its funding from NICE.  
52

53  
54 539 MJAM, KS, AD and RWB received travel expenses from NICE for attending clinical guideline  
55  
56 540 development meetings  
57  
58  
59  
60

1  
2  
3 541 **Author contribution**  
4

5 542 Paul Jacklin designed and developed the health economic model, undertook the health  
6  
7 543 economic analysis, wrote the first draft of the manuscript and incorporated edits from co-  
8  
9 544 authors. Mike Maresh provided clinical input into the design of the health economic model;  
10  
11 545 read, commented and edited various draft of the manuscripts. Katharine Stanley supplied the  
12  
13 546 Norwich dataset, provided clinical input into the design of the health economic model; read,  
14  
15 547 commented and edited various draft of the manuscripts. Anne Dornhorst provided clinical input  
16  
17 548 into the design of the health economic model; read, commented and edited various draft of the  
18  
19 549 manuscripts. Chris Patterson provided statistical advice, undertook statistical analysis of the  
20  
21 550 HAPO dataset; read, commented and edited various drafts of the manuscript. Shona Burman-  
22  
23 551 Roy reviewed the clinical literature, contributed to discussions of model design; read,  
24  
25 552 commented and edited various drafts of the manuscript. Rudy Bilous chaired the NICE  
26  
27 553 guideline, provided clinical input into the design of the health economic model; read,  
28  
29 554 commented and edited various draft of the manuscripts.  
30  
31  
32  
33

34 555

35  
36 556 **Transparency declaration**  
37

38 557 The lead author, Paul Jacklin, affirms that this manuscript is an honest, accurate, and  
39  
40 558 transparent account of the study being reported; that no important aspects of the study have  
41  
42 559 been omitted; and that any discrepancies from the study as planned (and, if relevant, registered)  
43  
44 560 have been explained.  
45  
46  
47

48 561

49 562 **Exclusive License**  
50

51 563 "I Paul Jacklin The Corresponding Author of this article contained within the original  
52  
53 564 manuscript which includes any diagrams & photographs within and any related or stand alone  
54  
55 565 film submitted (the Contribution") has the right to grant on behalf of all authors and does grant  
56  
57  
58  
59  
60

1  
2  
3 566 on behalf of all authors, a licence to the BMJ Publishing Group Ltd and its licencees, to permit  
4  
5 567 this Contribution (if accepted) to be published in the BMJ and any other BMJ Group products  
6  
7 568 and to exploit all subsidiary rights, as set out in our licence set out at:  
8  
9 569 [http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/copyright-](http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/copyright-open-access-and-permission-reuse)  
10  
11 [open-access-and-permission-reuse.](http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/copyright-open-access-and-permission-reuse)”  
12  
13

14 571

15  
16 572 **Data sharing Statement**  
17

18 573 Potential for data sharing (the health economic model) can be discussed with study  
19  
20  
21 574 investigators.  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

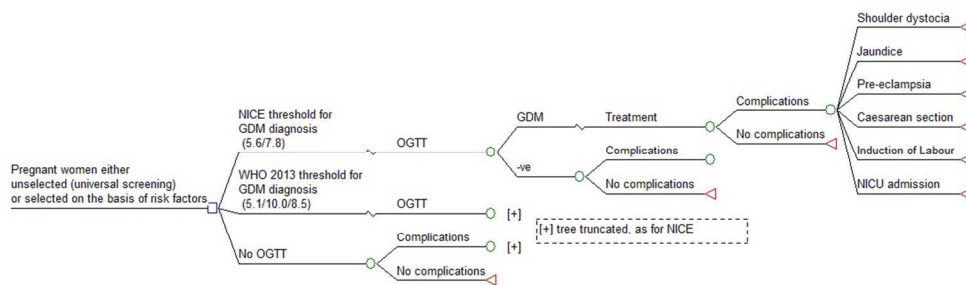
575 **References**

- 576 1. Metzger BE, Lowe LP, Dyer AR, et al. Hyperglycemia and adverse pregnancy outcomes. *N Engl J*  
577 *Med* 2008;358:1991-2002.
- 578 2. Farrar D, Simmonds M, Bryant M, et al. Hyperglycaemia and risk of adverse perinatal  
579 outcomes: systematic review and meta-analysis. *BMJ*. 2016;354:i4694. doi: 10.1136/bmj.i4694.
- 580 3. Metzger BE, Gabbe SG, Persson B, et al. International Association of Diabetes and Pregnancy  
581 Study Groups recommendations on the diagnosis and classification of hyperglycemia in  
582 pregnancy. *Diabetes Care* 2010;33:676-82.
- 583 4. WHO Health organisation, 2013. Diagnostic criteria and classification of hyperglycaemia first  
584 detected in pregnancy WHO/NMH/MND/13.2  
585 [http://apps.who.int/iris/bitstream/10665/85975/1/WHO\\_NMH\\_MND\\_13.2\\_eng.pdf](http://apps.who.int/iris/bitstream/10665/85975/1/WHO_NMH_MND_13.2_eng.pdf).
- 586 5. American College of Obstetricians and Gynecologists. *Practice Bulletin 137: Mellitus. Obstet*  
587 *Gynecol* 2013; 122: 406-16
- 588 6. National Institute for Health and Care Excellence (NICE) (2015) Diabetes in pregnancy:  
589 management of diabetes and its complications from preconception to the postnatal period.  
590 Clinical guideline NG3 (2015). Available from  
591 [www.nice.org.uk/guidance/ng3/resources/diabetes-in-pregnancy-management-of-diabetes-](http://www.nice.org.uk/guidance/ng3/resources/diabetes-in-pregnancy-management-of-diabetes-and-itscomplications-from-preconception-to-the-postnatal-period-51038446021)  
592 [and-itscomplications-from-preconception-to-the-postnatal-period-51038446021](http://www.nice.org.uk/guidance/ng3/resources/diabetes-in-pregnancy-management-of-diabetes-and-itscomplications-from-preconception-to-the-postnatal-period-51038446021), accessed  
593 February 2016
- 594 7. Meek CL, Lewis HB, Patient C, Murphy HR, Simmons D. Diagnosis of gestational diabetes: falling  
595 through the net. *Diabetologia* 2015;Sep;58(9):2003-12
- 596 8. Duran A, Sáenz S, Torrejón MJ et al. Introduction of IADPSG criteria for the screening and  
597 diagnosis of gestational diabetes mellitus results in improved pregnancy outcomes at a lower  
598 cost in a large cohort of pregnant women: the St. Carlos Gestational Diabetes Study. *Diabetes*  
599 *Care* 2014;37(9):2442–2450. doi: 10.2337/dc14-0179.

- 1  
2  
3 600 9. Herman WH. Insights offered by economic analyses. *Diabetes Care*. 2014 Sep;37(9):2424-6. doi:  
4  
5 601 10.2337/dc14-1232.  
6  
7 602 10. Farrar D, Simmonds M, Griffin S et al. The identification and treatment of women with  
8  
9 603 hyperglycaemia in pregnancy: an analysis of individual participant data, systematic reviews,  
10  
11 604 meta-analyses and an economic evaluation. *Health Technol Assess*. 2016 Nov;20(86):1-348.  
12  
13 605 11. Crowther CA, Hiller JE, Moss JR, McPhee AJ, Jeffries WS, Robinson JS. Effect of treatment of  
14  
15 606 gestational diabetes mellitus on pregnancy outcomes. *N Engl J Med* 2005;352:2477-86.  
16  
17 607 12. Landon MB, Spong CY, Thom E, et al. A multicenter, randomized trial of treatment for mild  
18  
19 608 gestational diabetes. *N Engl J Med* 2009;361:1339-48  
20  
21 609 13. Horvath K, Koch K, Jeitler K et al. Effects of treatment in women with gestational diabetes  
22  
23 610 mellitus: systematic review and meta-analysis. *BMJ (Clin Res Ed)* 2010;340:c1395  
24  
25 611 14. Round, J.A., Jacklin, P., Fraser, R.B., Hughes, R.G., Muggleston, M.A., Holt, R.I. Screening for  
26  
27 612 gestational diabetes mellitus: cost-utility of different screening strategies based on a woman's  
28  
29 613 individual risk of disease, *Diabetologia* 2011,54(2), 256-263. doi: 10.1007/s00125-010-1881-y  
30  
31 614 15. National Institute for Health and Care Excellence. Developing NICE guidelines: the manual.  
32  
33 615 October 2014 ([https://www.nice.org.uk/media/default/about/what-we-do/our-](https://www.nice.org.uk/media/default/about/what-we-do/our-programmes/developing-nice-guidelines-the-manual.pdf)  
34  
35 616 [programmes/developing-nice-guidelines-the-manual.pdf](https://www.nice.org.uk/media/default/about/what-we-do/our-programmes/developing-nice-guidelines-the-manual.pdf))  
36  
37 617 16. Briggs A, Claxton K, Sculpher M. Decision Modelling for Health Economic Evaluation. Oxford:  
38  
39 618 Oxford University Press; 2006  
40  
41 619 17. Avalos GE, Owens LA, Dunne F. Applying Current Screening Tools for Gestational Diabetes  
42  
43 620 Mellitus to a European Population: Is It Time for Change? *Diabetes Care*. 2013 Oct;36(10):3040-  
44  
45 621 4. doi: 10.2337/dc12-2669. Epub 2013 Jun 11.  
46  
47 622 18. Simmons D, Moses RG. Gestational Diabetes Mellitus: To Screen or Not to Screen? Is this really  
48  
49 623 still a question? *Diabetes Care*. 2013 Oct;36(10):2877-2878  
50  
51 624 19. Armstrong R, Waters E, Doyle J (editors). Chapter 21: Reviews in health promotion and public  
52  
53 625 health. In Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of*  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 626 Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011.  
4  
5 627 Available from [www.cochrane-handbook.org](http://www.cochrane-handbook.org). Accessed June 2015  
6  
7 628 20. Werner EF, Pettker CM, Zucерwise et al. Screening for gestational diabetes mellitus: are the  
8  
9 629 criteria proposed by the international association of the Diabetes and Pregnancy Study Groups  
10  
11 630 cost-effective? *Diabetes Care*. 2012 Mar;35(3):529-35. doi: 10.2337/dc11-1643.  
12  
13  
14 631 21. Donovan LE, Cundy T. Does exposure to hyperglycaemia in utero increase the risk of obesity  
15  
16 632 and diabetes in the offspring? A critical reappraisal. *Diabetic Medicine*. 2015 Mar;32(3):295-  
17  
18 633 304. doi: 10.1111/dme.12625. Epub 2014 Dec 17.  
19  
20 634 22. Landon MB, Rice MM, Varner MW et al. Mild gestational diabetes mellitus and long-term child  
21  
22 635 health. *Diabetes Care*. 2015 Mar;38(3):445-52. doi: 10.2337/dc14-2159. Epub 2014 Nov 20.  
23  
24  
25 636  
26  
27  
28 637  
29  
30  
31 638  
32  
33  
34 639  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



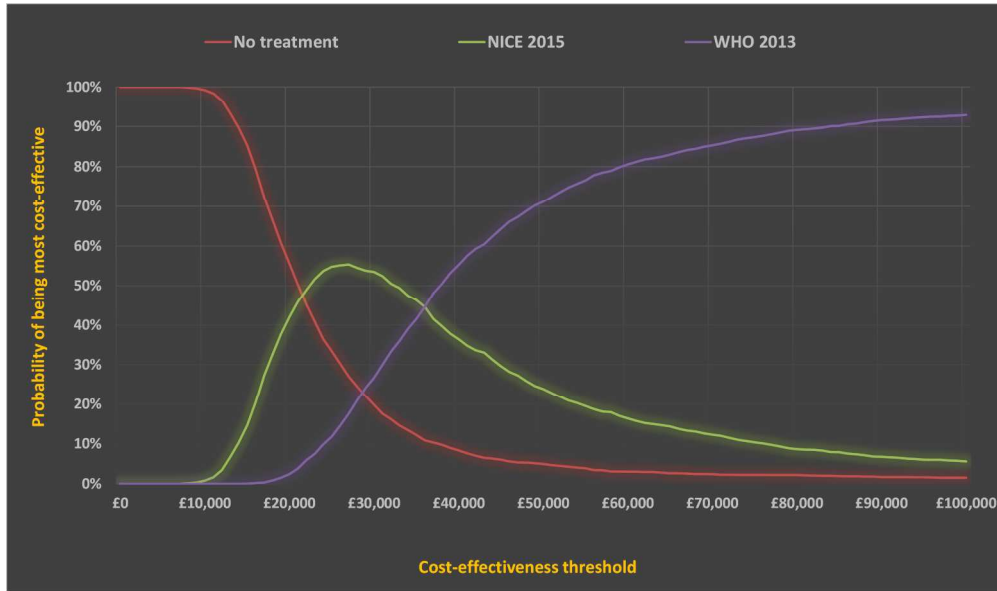
Model Schematic

95x31mm (300 x 300 DPI)

peer review only



1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



Cost-effectiveness acceptability curve indicating the probability of a threshold or a no diagnosis/no treatment strategy being cost-effective at different cost-effectiveness thresholds for the HAPO (4) centres population with risk factors

267x157mm (300 x 300 DPI)

Review only

## 1 Supplementary Report

2 This supplementary document provides further details about model parameter estimates and model  
3 results.

4 **Table x1.** Ethnicity of women in patient datasets and of UK

Ethnic group	HAPO (4) centres	Atlantic DiP	Norfolk <sup>a</sup>	UK <sup>b</sup>
White	79%	93%	96.5%	87%
Black	2%	2%	0.5%	3%
Asian	13%	4%	1.6%	7%
Other	6%	1%	1.6%	3%

5 (a) Our Norwich dataset did not include data on ethnicity and the values presented here are census data for Norfolk  
6 (Estimated from 2011 Census: Ethnic group, local authorities in the United Kingdom. Office for National Statistics. 11  
7 October 2013)

8 (b) Included for comparative purposes (2011 Census: Ethnic group, local authorities in the United Kingdom. Office for National  
9 Statistics. 11 October 2013)

### 11 Multivariable prediction models to estimate baseline risk

12 Model 1 includes the covariates used in the original analysis of the HAPO data whilst Model 2 is  
13 restricted to plasma glucose variables (Tables x2 to Tables x7). In the base case analysis, backward  
14 elimination of plasma glucose variables with non-significant coefficients from the prediction models  
15 was undertaken. A sensitivity analysis was undertaken retaining all plasma glucose variables. For each  
16 model Hosmer-Lemeshow goodness-of-fit statistics are presented and predicted probabilities are used  
17 to derive the area under the receiver-operating characteristic (ROC) curve as an indicator of the  
18 model's discriminatory ability.

20 **Table x2.** Logistic regression models to predict neonatal shoulder dystocia

Variable	Co-efficient b (Standard error (SE(b)))			
	Model 1 (all covariates)		Model 2 (blood glucose covariates)	
	Base case analysis	Sensitivity analysis	Base case analysis	Sensitivity analysis
Centre (Manchester v Belfast)	1.151 (0.423)	1.151 (0.424)	-	-
(Brisbane v Belfast)	0.505 (0.489)	0.562 (0.491)	-	-
(Newcastle v Belfast)	1.604 (0.472)	1.622 (0.472)	-	-
Age at OGTT (yr)	-0.023 (0.024)	-0.022 (0.024)	-	-
BMI at OGTT (kg/m <sup>2</sup> )	-0.006 (0.023)	-0.011 (0.024)	-	-
Smoker (Yes v No)	-0.480 (0.409)	-0.477 (0.409)	-	-
Drinker (Yes v No)	-0.101 (0.317)	-0.107 (0.317)	-	-
Family history DM (Yes v No)	-0.006 (0.184)	-0.008 (0.187)	-	-
Gestational age at OGTT (wk)	-0.111 (0.091)	-0.114 (0.092)	-	-
Neonate gender (F v M)	-1.321 (0.292)	-1.316 (0.292)	-	-
Family history HBP (Yes v No) <sup>a</sup>	-	-	-	-
Maternal UTI (Yes v No) <sup>a</sup>	-	-	-	-
Mean Blood Pressure (mmHg)	-0.006 (0.015)	-0.007 (0.015)	-	-
Hospital admission before delivery (Yes v No)	0.173 (0.266)	0.175 (0.267)	-	-
Parity (1 v 0)	-0.118 (0.420)	-0.108 (0.420)	-	-
(2+ v 0)	0.456 (0.412)	0.469 (0.414)	-	-
(Unknown v 0)	-0.026 (0.399)	-0.013 (0.399)	-	-
Fasting blood glucose <sup>b</sup>	-	0.151 (0.112)	-	0.166 (0.110)
1-hr blood glucose <sup>b</sup>	-	-0.138 (0.165)	-	-0.152 (0.163)
2-hr blood glucose <sup>b</sup>	0.223 (0.100)	0.222 (0.152)	0.267 (0.097)	0.265 (0.151)
Constant	0.925 (3.025)	1.139 (3.508)	-4.467 (0.122)	-4.475 (0.122)
Hosmer-Lemeshow goodness- of-fit test	$\chi^2 = 2.94,$ df=8; P=0.94	$\chi^2 = 6.36,$ df=8; P=0.61	$\chi^2 = 4.99,$ df=8; P=0.76	$\chi^2 = 11.51,$ df=8; P=0.18
Area under the ROC curve (95% CI)	0.75 (0.70, 0.80)	0.76 (0.70, 0.81)	0.58 (0.51, 0.65)	0.60 (0.53, 0.67)

21 (a) Omitted from HAPO model for shoulder dystocia

22 (b) Blood glucose values are 'standardised' – so the exponential of the coefficient represents the odds ratio for shoulder  
23 dystocia arising from a 1 Standard Deviation (SD) increase in plasma glucose (fasting plasma glucose mean (SD) =  
24 4.60(0.47); 1-hour plasma glucose mean (SD) = 7.57(1.83); 2-hour plasma glucose mean (SD) = 6.21(1.44)

27

28 **Table x3.** Logistic regression models to predict caesarean section

Variable	Co-efficient b (Standard error (SE(b)))			
	Model 1 (all covariates)		Model 2 (blood glucose covariates)	
	Base case analysis	Sensitivity analysis	Base case analysis	Sensitivity analysis
Centre (Manchester v Belfast)	-0.494 (0.092)	-0.495 (0.092)	-	-
(Brisbane v Belfast)	-0.099 (0.098)	-0.114 (0.100)	-	-
(Newcastle v Belfast)	-0.681 (0.140)	-0.692 (0.141)	-	-
Age at OGTT (yr)	0.034 (0.007)	0.034 (0.007)	-	-
BMI at OGTT (kg/m <sup>2</sup> )	0.039 (0.007)	0.039 (0.007)	-	-
Smoker (Yes v No)	-0.304 (0.106)	-0.292 (0.106)	-	-
Drinker (Yes v No)	-0.028 (0.087)	-0.025 (0.087)	-	-
Family history DM (Yes v No)	0.050 (0.057)	0.052 (0.057)	-	-
Gestational age at OGTT (wk)	0.004 (0.029)	0.004 (0.029)	-	-
Neonate gender (F v M)	-0.205 (0.071)	-0.205 (0.071)	-	-
Family history HBP (Yes v No) <sup>a</sup>	-	-	-	-
Maternal UTI (Yes v No) <sup>a</sup>	-	-	-	-
Mean Blood Pressure (mmHg)	0.003 (0.004)	0.003 (0.004)	-	-
Hospital admission before delivery (Yes v No)	0.514 (0.079)	0.510 (0.079)	-	-
Parity (1 v 0) <sup>a</sup>	-	-	-	-
(2+ v 0) <sup>a</sup>	-	-	-	-
(Unknown v 0) <sup>a</sup>	-	-	-	-
Fasting blood glucose <sup>b</sup>	-	-0.009 (0.044)	-	0.053 (0.040)
1-hr blood glucose <sup>b</sup>	0.144 (0.037)	0.101 (0.051)	0.138 (0.046)	0.119 (0.048)
2-hr blood glucose <sup>b</sup>	-	0.071 (0.048)	0.123 (0.046)	0.113 (0.046)
Constant	-3.518 (0.947)	-3.509 (0.950)	-1.435 (0.035)	-1.433 (0.035)
Hosmer-Lemeshow goodness-of-fit test	$\chi^2 = 1.88,$ df=8; P=0.99	$\chi^2 = 5.11,$ df=8; P=0.75	$\chi^2 = 16.56,$ df=8; P=0.04	$\chi^2 = 17.66,$ df=8; P=0.02
Area under the ROC curve (95% CI)	0.65 (0.63, 0.66)	0.65 (63, 0.66)	0.58 (0.56, 0.60)	0.58 (0.57, 0.60)

29 (a) Omitted from HAPO model for caesarean section

30 (b) Blood glucose values are 'standardised' – so the exponential of the coefficient represents the odds ratio for caesarean  
 31 section arising from a 1 Standard Deviation (SD) increase in plasma glucose (fasting plasma glucose mean (SD) =  
 32 4.60(0.47); 1-hour plasma glucose mean (SD) = 7.57(1.83); 2-hour plasma glucose mean (SD) = 6.21(1.44)

33

34

35

36 **Table x4.** Logistic regression models to predict neonatal intensive care unit admissions

Variable	Co-efficient b (Standard error (SE(b)))			
	Model 1 (all covariates)		Model 2 (blood glucose covariates)	
	Base case analysis	Sensitivity analysis	Base case analysis	Sensitivity analysis
Centre (Manchester v Belfast)	0.894 (0.159)	0.889 (0.159)	-	-
(Brisbane v Belfast)	1.393 (0.161)	1.400 (0.163)	-	-
(Newcastle v Belfast)	1.153 (0.190)	1.163 (0.191)	-	-
Age at OGTT (yr)	0.013 (0.009)	0.012 (0.009)	-	-
BMI at OGTT (kg/m <sup>2</sup> )	0.025 (0.009)	0.024 (0.009)	-	-
Smoker (Yes v No)	0.209 (0.130)	0.201 (0.130)	-	-
Drinker (Yes v No)	-0.025 (0.117)	-0.023 (0.117)	-	-
Family history DM (Yes v No)	0.033 (0.069)	0.038 (0.069)	-	-
Gestational age at OGTT (wk)	-0.050 (0.038)	-0.052 (0.038)	-	-
Neonate gender (F v M)	-0.304 (0.094)	-0.302 (0.094)	-	-
Family history HBP (Yes v No) <sup>a</sup>	-	-	-	-
Maternal UTI (Yes v No) <sup>a</sup>	-	-	-	-
Mean Blood Pressure (mmHg)	0.006 (0.006)	0.006 (0.006)	-	-
Hospital admission before delivery (Yes v No)	0.794 (0.097)	0.792 (0.097)	-	-
Parity (1 v 0)	-0.474 (0.148)	-0.474 (0.148)	-	-
(2+ v 0)	-0.490 (0.157)	-0.493 (0.157)	-	-
(Unknown v 0)	-0.084 (0.135)	-0.086 (0.135)	-	-
Fasting blood glucose <sup>b</sup>	-	-0.003 (0.054)	-	-0.025 (0.050)
1-hr blood glucose <sup>b</sup>	-	0.082 (0.067)	-	0.078 (0.064)
2-hr blood glucose <sup>b</sup>	0.159 (0.045)	0.107 (0.063)	0.208 (0.041)	0.167 (0.060)
Constant	-3.181 (1.236)	-3.061 (1.243)	-2.374 (0.046)	-2.375 (0.046)
Hosmer-Lemeshow goodness- of-fit test	$\chi^2 = 14.18,$ df=8; P=0.08	$\chi^2 = 11.41,$ df=8; P=0.18	$\chi^2 = 22.16,$ df=8; P=0.005	$\chi^2 = 12.72,$ df=8; P=0.12
Area under the ROC curve (95% CI)	0.71 (0.69, 0.73)	0.71 (0.69, 0.73)	0.57 (0.55, 0.60)	0.57 (0.55, 0.60)

37 (a) Omitted from HAPO model for neonatal intensive care unit admissions

38 (b) Blood glucose values are 'standardised' – so the exponential of the coefficient represents the odds ratio for neonatal  
39 intensive care unit admissions arising from a 1 Standard Deviation (SD) increase in plasma glucose (fasting plasma glucose  
40 mean (SD) = 4.60(0.47); 1-hour plasma glucose mean (SD) = 7.57(1.83); 2-hour plasma glucose mean (SD) = 6.21(1.44)

41

42

43 **Table x5.** Logistic regression models to predict jaundice

44

	Co-efficient b (Standard error (SE(b)))			
	Model 1 (all covariates)		Model 2 (blood glucose covariates)	
Variable	Base case analysis	Sensitivity analysis	Base case analysis	Sensitivity analysis
Centre (Manchester v Belfast)	0.407 (0.157)	0.410 (0.157)	-	-
(Brisbane v Belfast)	0.449 (0.171)	0.420 (0.173)	-	-
(Newcastle v Belfast)	-0.315 (0.259)	-0.332 (0.259)	-	-
Age at OGTT (yr)	0.005 (0.011)	0.005 (0.011)	-	-
BMI at OGTT (kg/m <sup>2</sup> )	-0.011 (0.011)	-0.009 (0.012)	-	-
Smoker (Yes v No)	0.082 (0.161)	0.093 (0.162)	-	-
Drinker (Yes v No)	-0.514 (0.163)	-0.508 (0.163)	-	-
Family history DM (Yes v No)	-0.060 (0.094)	-0.060 (0.094)	-	-
Gestational age at OGTT (wk)	-0.078 (0.047)	-0.077 (0.047)	-	-
Neonate gender (F v M)	-0.116 (0.113)	-0.115 (0.113)	-	-
Family history HBP (Yes v No) <sup>a</sup>	-	-	-	-
Maternal UTI (Yes v No) <sup>a</sup>	-	-	-	-
Mean Blood Pressure (mmHg)	0.018 (0.007)	0.018 (0.007)	-	-
Hospital admission before delivery (Yes v No)	0.867 (0.116)	0.865 (0.116)	-	-
Parity (1 v 0)	-0.382 (0.185)	-0.380 (0.185)	-	-
(2+ v 0)	-0.526 (0.200)	-0.526 (0.200)	-	-
(Unknown v 0)	0.078 (0.165)	0.078 (0.165)	-	-
Fasting blood glucose <sup>b</sup>	-	-0.055 (0.066)	-	-0.063 (0.061)
1-hr blood glucose <sup>b</sup>	0.216 (0.056)	0.192 (0.079)	0.237 (0.052)	0.199 (0.078)
2-hr blood glucose <sup>b</sup>	-	0.073 (0.074)	-	0.102 (0.072)
Constant	-1.927 (1.522)	-2.014 (1.526)	-2.846 (0.057)	-2.850 (0.057)
Hosmer-Lemeshow goodness-of-fit test	$\chi^2 = 8.42,$ df=8; P=0.39	$\chi^2 = 7.96,$ df=8; P=0.44	$\chi^2 = 2.47,$ df=8; P=0.96	$\chi^2 = 10.40,$ df=8; P=0.24
Area under the ROC curve (95% CI)	0.68 (0.65, 0.71)	0.68 (0.65, 0.71)	0.57 (0.54, 0.60)	0.58 (0.55, 0.61)

45 (a) Omitted from HAPO model for jaundice

46 (b) Blood glucose values are 'standardised' – so the exponential of the coefficient represents the odds ratio for jaundice  
 47 arising from a 1 Standard Deviation (SD) increase in plasma glucose (fasting plasma glucose mean (SD) = 4.60(0.47); 1-hour  
 48 plasma glucose mean (SD) = 7.57(1.83); 2-hour plasma glucose mean (SD) = 6.21(1.44)

49

50

51 **Table x6.** Logistic regression models to predict pre-eclampsia

52

Variable	Co-efficient b (Standard error (SE(b)))			
	Model 1 (all covariates)		Model 2 (blood glucose covariates)	
	Base case analysis	Sensitivity analysis	Base case analysis	Sensitivity analysis
Centre (Manchester v Belfast)	-0.784 (0.192)	-0.800 (0.193)	-	-
(Brisbane v Belfast)	-0.308 (0.200)	-0.277 (0.202)	-	-
(Newcastle v Belfast)	-0.685 (0.278)	-0.667 (0.278)	-	-
Age at OGTT (yr)	-0.009 (0.015)	-0.011 (0.015)	-	-
BMI at OGTT (kg/m <sup>2</sup> )	0.101 (0.011)	0.097 (0.012)	-	-
Smoker (Yes v No)	-0.556 (0.245)	-0.569 (0.246)	-	-
Drinker (Yes v No)	-0.170 (0.194)	-0.168 (0.194)	-	-
Family history DM (Yes v No)	-0.004 (0.127)	0.006 (0.127)	-	-
Gestational age at OGTT (wk)	-0.092 (0.059)	-0.096 (0.059)	-	-
Neonate gender (F v M)	0.173 (0.147)	0.174 (0.147)	-	-
Family history HBP (Yes v No)	0.233 (0.150)	0.230 (0.150)	-	-
Maternal UTI (Yes v No)	0.734 (0.211)	0.721 (0.211)	-	-
Mean Blood Pressure (mmHg) <sup>a</sup>	-	-	-	-
Hospital admission before delivery (Yes v No) <sup>a</sup>	-	-	-	-
Parity (1 v 0)	-0.291 (0.240)	-0.292 (0.240)	-	-
(2+ v 0)	-0.701 (0.271)	-0.703 (0.271)	-	-
(Unknown v 0)	0.026 (0.224)	0.023 (0.224)	-	-
Fasting blood glucose <sup>b</sup>	-	0.062 (0.078)	0.201 (0.065)	0.183 (0.068)
1-hr blood glucose <sup>b</sup>	-	0.065 (0.104)	-	0.083 (0.098)
2-hr blood glucose <sup>b</sup>	0.272 (0.067)	0.195 (0.096)	0.196 (0.072)	0.150 (0.090)
Constant	-3.370 (1.842)	-3.107 (1.855)	-3.453 (0.075)	-3.455 (0.075)
Hosmer-Lemeshow goodness- of-fit test	$\chi^2 = 5.46,$ df=8; P=0.71	$\chi^2 = 8.02,$ df=8; P=0.43	$\chi^2 = 12.00,$ df=8; P=0.15	$\chi^2 = 15.98,$ df=8; P=0.04
Area under the ROC curve (95% CI)	0.75 (0.72, 0.78)	0.75 (0.72, 0.79)	0.65 (0.61, 0.68)	0.65 (0.61, 0.68)

53 (a) Omitted from HAPO model for pre-eclampsia

54 (b) Blood glucose values are 'standardised' – so the exponential of the coefficient represents the odds ratio for pre-eclampsia  
55 arising from a 1 Standard Deviation (SD) increase in plasma glucose (fasting plasma glucose mean (SD) = 4.60(0.47); 1-hour  
56 plasma glucose mean (SD) = 7.57(1.83); 2-hour plasma glucose mean (SD) = 6.21(1.44)

57

58

59 **Table x7.** Logistic regression models to predict induction of labour

60

Variable	Co-efficient b (Standard error (SE(b)))		
	Model 1 (all covariates)		Model 2 (blood glucose covariates)
	Base case analysis	Sensitivity analysis	Base case analysis
Centre (Manchester v Belfast)	-0.476 (0.077)	-0.476 (0.077)	-
(Brisbane v Belfast)	-0.337 (0.085)	-0.333 (0.087)	-
(Newcastle v Belfast)	-0.387 (0.109)	-0.384 (0.110)	-
Age at OGTT (yr)	0.006 (0.006)	0.006 (0.006)	-
BMI at OGTT (kg/m <sup>2</sup> )	0.039 (0.006)	0.039 (0.006)	-
Smoker (Yes v No)	0.051 (0.082)	0.051 (0.082)	-
Drinker (Yes v No)	0.079 (0.072)	0.079 (0.072)	-
Family history DM (Yes v No)	0.016 (0.048)	0.016 (0.048)	-
Gestational age at OGTT (wk)	0.011 (0.024)	0.011 (0.024)	-
Neonate gender (F v M)	-0.038 (0.059)	-0.038 (0.059)	-
Family history HBP (Yes v No) <sup>a</sup>	-	-	-
Maternal UTI (Yes v No) <sup>a</sup>	-	-	-
Mean Blood Pressure (mmHg)	0.008 (0.004)	0.008 (0.004)	-
Hospital admission before delivery (Yes v No)	0.608 (0.066)	0.608 (0.066)	-
Parity (1 v 0)	-0.363 (0.101)	-0.363 (0.101)	-
(2+ v 0)	-0.193 (0.105)	-0.193 (0.105)	-
(Unknown v 0)	0.141 (0.094)	0.141 (0.094)	-
Fasting blood glucose <sup>b</sup>	-	0.009 (0.037)	0.079 (0.033)
1-hr blood glucose <sup>b</sup>	-0.108 (0.041)	-0.111 (0.043)	-0.093 (0.041)
2-hr blood glucose <sup>b</sup>	0.096 (0.041)	0.094 (0.041)	0.100 (0.040)
Constant	-3.050 (0.794)	-3.037 (0.796)	-1.032 (0.029)
Hosmer-Lemeshow goodness-of-fit test	$\chi^2 = 9.08$ , df=8; P=0.34	$\chi^2 = 9.42$ df=8; P=0.31	$\chi^2 = 9.83$ df=8; P=0.28
Area under the ROC curve (95% CI)	0.63 (0.61, 0.65)	0.63 (0.61, 0.65)	0.53 (0.51, 0.55)

61 (a) Omitted from HAPO model for induction of labour

62 (b) Blood glucose values are 'standardised' – so the exponential of the coefficient represents the odds ratio for induction of  
63 labour arising from a 1 Standard Deviation (SD) increase in plasma glucose (fasting plasma glucose mean (SD) = 4.60(0.47);  
64 1-hour plasma glucose mean (SD) = 7.57(1.83); 2-hour plasma glucose mean (SD) = 6.21(1.44)



65 **Table x8.** Cholesky decomposition of shoulder dystocia variance covariance matrix (Model 1, base case)

	Constant	Centre (Manchester r v Belfast)	Centre (Manchester r v Belfast)	Centre (Manchester r v Belfast)	Age at OGTT (yr)	BMI AT OGTT (kg/m <sup>2</sup> )	Smoker	Drinker	Family History DM	Gestational age at OGTT (wk)	Neonatal gender	Mean Blood Pressure	Parity (1 v 0)	Parity (2+ v 0)	Parity (Unknown v 0)	Hospital admission before	2-hr blood glucose
Constant	3.025																
Centre (Manchester v Belfast)	-0.104	0.410															
(Brisbane v Belfast)	-0.129	0.335	0.331														
(Newcastle v Belfast)	-0.135	0.334	0.074	0.295													
Age at OGTT (yr)	-0.005	-0.001	0.000	0.000	0.024												
BMI AT OGTT (kg/m <sup>2</sup> )	-0.001	-0.001	-0.001	-0.001	0.001	0.023											
Smoker	-0.012	0.031	0.001	-0.003	0.047	0.006	0.404										
Drinker	0.001	0.014	-0.006	-0.020	-0.051	0.008	-0.018	0.311									
Family History DM	-0.023	0.012	-0.022	-0.018	-0.005	0.000	-0.009	-0.012	0.179								
Gestational age at OGTT (wk)	-0.080	-0.009	-0.001	0.006	-0.017	-0.007	-0.002	-0.001	-0.008	0.037							
Neonatal gender (F v M)	-0.037	-0.010	-0.006	-0.010	-0.002	0.009	0.003	-0.001	-0.005	-0.080	0.278						
Mean Blood Pressure (mmHg)	-0.004	-0.001	0.000	-0.002	-0.002	-0.006	0.000	0.000	-0.001	-0.011	-0.004	0.004					
Parity (1 v 0)	-0.038	0.014	0.011	-0.029	-0.024	-0.017	0.009	-0.013	0.006	-0.084	-0.020	-0.318	0.253				
(2+ v 0)	-0.026	0.007	0.025	-0.018	-0.082	-0.043	0.000	0.006	0.011	-0.072	-0.027	-0.317	0.021	0.229			
(Unknown v 0)	-0.052	0.019	0.005	-0.020	0.028	0.004	0.015	0.001	0.006	-0.090	-0.026	-0.311	0.020	0.026	0.219		
Hospital admission before delivery	-0.008	-0.007	-0.016	-0.006	0.005	-0.033	-0.006	0.007	-0.002	-0.002	0.004	-0.063	-0.061	-0.071	-0.079	0.225	
2-hr blood glucose	0.012	-0.003	-0.003	0.005	-0.016	-0.015	0.009	0.006	0.013	0.004	0.004	-0.003	-0.007	-0.021	-0.002	-0.015	0.091

66

67

68

69 **Table x9.** Cholesky decomposition of caesarean section variance covariance matrix (Model 1, base case)

	Constant	Centre (Manchester v Belfast)	Centre (Manchester v Belfast)	Centre (Manchester v Belfast)	Age at OGTT (yr)	BMI AT OGTT (kg/m <sup>2</sup> )	Smoker	Drinker	Family History DM	Gestational age at OGTT	Neonatal gender	Mean Blood Pressure	Hospital admission	1-hr blood glucose
Constant	0.947													
Centre (Manchester v Belfast)	-0.020	0.089												
(Brisbane v Belfast)	-0.028	0.047	0.082											
(Newcastle v Belfast)	-0.028	0.048	0.025	0.126										
Age at OGTT (yr)	-0.001	0.000	0.000	0.000	0.007									
BMI AT OGTT (kg/m <sup>2</sup> )	-0.001	-0.001	0.000	0.000	0.000	0.007								
Smoker	-0.004	0.010	0.004	0.001	0.013	0.000	0.104							
Drinker	0.001	0.004	0.000	-0.002	-0.011	0.004	-0.006	0.086						
Family History DM	-0.006	0.006	-0.005	-0.002	-0.003	0.000	-0.003	-0.003	0.056					
Gestational age at OGTT (wk)	-0.026	-0.001	0.000	0.001	-0.005	-0.002	-0.001	-0.001	-0.003	0.011				
Neonate gender	-0.009	-0.001	-0.002	0.000	-0.002	0.002	0.002	-0.001	-0.001	-0.020	0.067			
Mean Blood Pressure (mmHg)	-0.001	0.000	0.000	0.000	-0.001	-0.002	0.000	0.000	0.000	-0.003	-0.001	0.001		
Hospital admission before delivery	-0.003	-0.004	-0.007	-0.001	0.004	-0.009	-0.003	0.004	-0.001	0.000	0.000	-0.042	0.065	
1-hr blood glucose	0.005	-0.001	0.002	0.002	-0.006	-0.006	0.000	0.001	0.005	0.003	0.002	-0.003	-0.003	0.035

70

71

72 **Table x10.** Cholesky decomposition of neonatal intensive care admission variance covariance matrix (Model 1, base case)

	Constant	Centre (Manchester v Belfast)	Centre (Manchester v Belfast)	Centre (Manchester v Belfast)	Age at OGTT (yr)	BMI AT OGTT (kg/m <sup>2</sup> )	Smoker	Drinker	Family History DM	Gestational age at OGTT (wk)	Neonatal gender	Mean Blood Pressure	Parity (1 v 0)	Parity (2+ v 0)	Parity (Unknown v 0)	Hospital admission	2-hr blood glucose
Constant	1.236																
Centre (Manchester v Belfast)	-0.037	0.154															
(Brisbane v Belfast)	-0.047	0.115	0.102														
(Newcastle v Belfast)	-0.050	0.115	0.042	0.137													
Age at OGTT (yr)	-0.002	0.000	0.000	0.000	0.009												
BMI AT OGTT (kg/m <sup>2</sup> )	-0.001	0.000	0.000	0.000	0.000	0.009											
Smoker	-0.007	0.012	0.002	-0.001	0.018	-0.001	0.128										
Drinker	0.002	0.004	-0.002	-0.004	-0.017	0.006	-0.007	0.115									
Family History DM	-0.008	0.004	-0.008	-0.003	-0.003	0.000	-0.004	-0.003	0.068								
Gestational age at OGTT (wk)	-0.034	-0.003	-0.001	0.002	-0.007	-0.002	-0.001	-0.001	-0.004	0.015							
Neonatal gender (F v M)	-0.012	-0.003	-0.004	-0.002	-0.002	0.003	0.000	-0.001	-0.001	-0.025	0.090						
Mean Blood Pressure (mmHg)	-0.002	0.000	0.000	-0.001	-0.001	-0.002	0.000	0.000	0.000	-0.004	-0.001	0.001					
Parity (1 v 0)	-0.011	0.006	0.004	-0.009	-0.009	-0.005	0.002	-0.003	0.002	-0.024	-0.004	-0.103	0.102				
(2+ v 0)	-0.006	0.002	0.011	-0.005	-0.032	-0.015	-0.002	0.003	0.003	-0.021	-0.006	-0.102	0.012	0.111			
(Unknown v 0)	-0.016	0.008	0.003	-0.005	0.010	0.002	0.006	0.001	0.002	-0.025	-0.006	-0.101	0.011	0.011	0.081		
Hospital admission before delivery	-0.005	-0.001	-0.005	0.000	0.004	-0.012	-0.003	0.005	0.000	-0.001	0.000	-0.033	-0.028	-0.025	-0.032	0.075	
2-hr blood glucose	0.004	0.000	0.000	0.001	-0.007	-0.006	0.004	0.002	0.005	0.003	0.002	-0.002	-0.002	-0.006	0.000	-0.006	0.042

73

74 **Table x11.** Cholesky decomposition of jaundice variance covariance matrix (Model 1, base case)

	Constant	Centre (Manchester v Belfast)	Centre (Brisbane v Belfast)	Centre (Newcastle v Belfast)	Age at OGTT (yr)	BMI AT OGTT (kg/m2)	Smoker	Drinker	Family History DM	Gestational age at OGTT (wk)	Neonatal gender	Mean Blood Pressure	Parity (1 v 0)	Parity (2+ v 0)	Parity (Unknown v 0)	Hospital admission	1-hr blood glucose
Constant	1.522																
Centre (Manchester v Belfast)	-0.038	0.153															
(Brisbane v Belfast)	-0.049	0.102	0.128														
(Newcastle v Belfast)	-0.055	0.102	0.041	0.228													
Age at OGTT (yr)	-0.002	0.000	0.000	0.000	0.011												
BMI AT OGTT (kg/m2)	-0.001	-0.001	-0.001	0.000	0.000	0.011											
Smoker	-0.011	0.017	0.003	-0.001	0.023	0.000	0.158										
Drinker	0.003	0.004	0.000	-0.002	-0.020	0.006	-0.011	0.161									
Family History DM	-0.011	0.010	-0.010	-0.003	-0.005	-0.001	-0.004	-0.005	0.092								
Gestational age at OGTT (wk)	-0.042	-0.003	0.000	0.002	-0.008	-0.004	-0.001	-0.001	-0.005	0.018							
Neonatal gender (F v M)	-0.014	-0.003	-0.003	-0.002	-0.002	0.004	0.002	-0.001	0.000	-0.031	0.108						
Mean Blood Pressure (mmHg)	-0.002	0.000	0.000	0.000	-0.001	-0.003	0.000	0.000	0.000	-0.005	-0.002	0.002					
Parity (1 v 0)	-0.016	0.010	0.008	-0.006	-0.011	-0.007	0.001	-0.001	0.003	-0.032	-0.007	-0.128	0.126				
(2+ v 0)	-0.008	0.002	0.014	-0.004	-0.039	-0.016	-0.003	0.005	0.006	-0.030	-0.009	-0.127	0.016	0.144			
(Unknown v 0)	-0.021	0.013	0.006	-0.004	0.012	0.003	0.005	0.002	0.002	-0.034	-0.008	-0.126	0.015	0.013	0.094		
Hospital admission before delivery	-0.006	-0.003	-0.008	-0.002	0.005	-0.016	-0.004	0.003	-0.001	-0.002	0.001	-0.040	-0.034	-0.028	-0.042	0.089	
1-hr blood glucose	0.007	-0.001	0.004	0.003	-0.008	-0.009	0.003	0.001	0.008	0.004	0.003	-0.004	-0.004	-0.009	-0.001	-0.008	0.051

75

76 **Table x12.** Cholesky decomposition of pre-clampsia variance covariance matrix (Model 1, base case)

	Constant	Centre (Manchester v Belfast)	Centre (Manchester v Belfast)	Centre (Manchester v Belfast)	Age at OGTT (yr)	BMI AT OGTT (kg/m <sup>2</sup> )	Smoker	Drinker	Family History DM	Gestational age at OGTT (wk)	Neonatal gender (F v M)	Parity (1 v 0)	Parity (2+ v 0)	Parity (Unknown v 0)	Family History HBP	Maternal UTI	2-hr blood glucose
Constant	1.842																
Centre (Manchester v Belfast)	-0.045	0.187															
(Brisbane v Belfast)	-0.059	0.083	0.173														
(Newcastle v Belfast)	-0.072	0.085	0.053	0.249													
Age at OGTT (yr)	-0.004	0.000	0.000	0.000	0.015												
BMI AT OGTT (kg/m <sup>2</sup> )	-0.002	-0.001	-0.001	-0.002	0.000	0.010											
Smoker	-0.010	0.019	0.002	0.001	0.026	0.001	0.243										
Drinker	0.002	0.007	-0.002	-0.004	-0.023	0.007	-0.009	0.192									
Family History DM	-0.017	0.013	-0.009	-0.006	-0.009	-0.001	-0.004	-0.004	0.124								
Gestational age at OGTT (wk)	-0.054	-0.003	0.000	0.002	-0.013	-0.012	-0.001	-0.001	-0.008	0.011							
Neonatal gender (F v M)	-0.023	-0.004	-0.006	-0.007	-0.003	0.009	0.001	-0.002	-0.001	-0.106	0.099						
Parity (1 v 0)	-0.020	0.013	0.016	-0.006	-0.014	-0.011	0.003	-0.001	0.001	-0.121	-0.123	0.163					
(2+ v 0)	-0.011	-0.001	0.020	-0.005	-0.047	-0.030	0.000	0.000	0.007	-0.117	-0.120	0.042	0.199				
(Unknown v 0)	-0.029	0.014	0.013	-0.004	0.017	0.002	0.006	0.001	0.000	-0.122	-0.125	0.036	0.025	0.127			
Family History HBP	-0.009	0.000	0.006	-0.005	-0.017	-0.014	0.001	-0.001	0.023	-0.034	-0.037	-0.060	-0.038	-0.048	0.108		
Maternal UTI	-0.004	-0.012	0.031	0.002	0.015	-0.001	-0.014	0.004	0.009	-0.021	-0.022	-0.030	-0.018	-0.028	-0.052	0.193	
2-hr blood glucose	0.006	-0.004	0.002	0.001	-0.012	-0.009	0.005	0.004	0.008	-0.006	-0.004	-0.006	-0.011	-0.002	-0.012	-0.009	0.061

77

78 **Table x13.** Cholesky decomposition of induction of labour variance covariance matrix (Model 1, base case)

	Constant	Centre (Manchester r v Belfast)	Centre (Manchester r v Belfast)	Centre (Manchester r v Belfast)	Age at OGTT (yr)	BMI AT OGTT (kg/m2)	Smoker	Drinker	Family History DM	Gestational age at OGTT	Neonatal gender (F v M)	Mean Blood Pressure	Parity (1 v 0)	Parity (2+ v 0)	Parity (Unknown v 0)	Hospital admission	1-hr blood glucose	2-hr blood glucose
Constant	0.794																	
Centre (Manchester v Belfast)	-0.018	0.074																
(Brisbane v Belfast)	-0.024	0.039	0.072															
(Newcastle v Belfast)	-0.024	0.039	0.020	0.097														
Age at OGTT (yr)	-0.001	0.000	0.000	0.000	0.006													
BMI AT OGTT (kg/m2)	0.000	0.000	0.000	0.000	0.000	0.006												
Smoker	-0.005	0.008	0.002	0.001	0.013	0.001	0.081											
Drinker	0.001	0.003	0.000	-0.002	-0.010	0.003	-0.006	0.071										
Family History DM	-0.006	0.005	-0.004	-0.002	-0.002	0.000	-0.002	-0.003	0.047									
Gestational age at OGTT (wk)	-0.021	-0.001	0.000	0.001	-0.004	-0.002	-0.001	0.000	-0.003	0.010								
Neonatal gender (F v M)	-0.007	-0.002	-0.002	-0.001	-0.001	0.002	0.001	-0.001	-0.001	-0.016	0.056							
Mean Blood Pressure (mmHg)	-0.001	0.000	0.000	0.000	-0.001	-0.001	0.000	0.000	0.000	-0.003	-0.001	0.001						
Parity (1 v 0)	-0.008	0.008	0.005	-0.004	-0.006	-0.004	0.000	-0.002	0.001	-0.020	-0.005	-0.075	0.061					
(2+ v 0)	-0.004	0.004	0.008	-0.002	-0.020	-0.010	-0.002	0.001	0.002	-0.019	-0.006	-0.075	0.005	0.067				
(Unknown v 0)	-0.012	0.007	0.003	-0.002	0.006	0.001	0.002	0.001	0.001	-0.021	-0.005	-0.075	0.005	0.004	0.050			
Hospital admission before delivery	-0.004	-0.004	-0.005	-0.001	0.002	-0.007	-0.002	0.003	0.000	-0.001	0.000	-0.017	-0.017	-0.016	-0.020	0.055		
1-hr blood glucose	0.004	0.000	0.004	0.002	-0.004	-0.003	-0.001	0.000	0.003	0.001	0.001	0.000	0.001	-0.001	0.001	0.000	0.040	
2-hr blood glucose	0.001	0.000	-0.003	-0.001	-0.001	-0.002	0.004	0.001	0.001	0.002	0.000	-0.001	0.000	-0.002	0.001	-0.001	-0.027	0.030

79

80 **Table x14:** Model unit costs

Category	Cost	Standard Error	Distribution <sup>a</sup>	Source
2 sample OGTT	£8.07	n/a	n/a	NICE 2015 <sup>b</sup>
3 sample OGTT	£12.11	n/a	n/a	NICE 2015 <sup>b</sup>
Rapilose OGTT solution	£3.48	n/a	n/a	BNF July 2016 <sup>c</sup>
Health Care Assistant Band 3 (per hour)	£25	n/a	n/a	Unit Costs of Health and Social Care 2015 <sup>d</sup>
Nurse Band 7 (per hour of patient contact)	£147	n/a	n/a	Unit Costs of Health and Social Care 2015 <sup>d</sup>
Dietician	£38	n/a	n/a	Unit Costs of Health and Social Care 2015 <sup>d</sup>
Antenatal appointment	£96	£9.07	Normal	NHS Reference Costs 2014-15 <sup>e</sup>
Ultrasound scan	£112	£7.65	Normal	NHS Reference Costs 2014-15 <sup>e</sup>
Rapid acting insulin	£0.02	n/a	n/a	BNF June 2016 <sup>c</sup>
Regular insulin	£0.02	n/a	n/a	BNF June 2016 <sup>c</sup>
Needles	£0.10	n/a	n/a	NHS Drugs Tariff June 2016 <sup>f</sup>
Lancets	£0.03	n/a	n/a	NHS Drugs Tariff June 2016 <sup>f</sup>
Strips	£0.18	n/a	n/a	NHS Drugs Tariff June 2016 <sup>f</sup>
Treatment of GDM	£987	n/a	n/a	Calculated
Severe hypoglycaemia	£650	n/a	n/a	NHS Reference Costs 2014-15 <sup>e</sup>
Admission to NICU	£1,176	£38	Normal	NHS Reference Costs 2014-15 <sup>e</sup>
Caesarean section	£982	£80	Normal	NHS Reference Costs 2014-15 <sup>e</sup>
Neonatal death	£777	£39	Normal	NHS Reference Costs 2014-15 <sup>e</sup>
Shoulder dystocia	£1,394	£79	Normal	NHS Reference Costs 2014-15 <sup>e</sup>
Birth trauma	£1,394	£79	Normal	NHS Reference Costs 2014-15 <sup>e</sup>
Serious perinatal complication (death, shoulder dystocia, birth trauma)	£1,347	n/a	n/a	Calculated
Phototherapy	£788	£72	Normal	NHS Reference Costs 2014-15 <sup>e</sup>
Pre-eclampsia	£4,750	n/a	n/a	NICE 2015 <sup>b</sup>

81 (a) The method used to obtain standard errors and the choice of a normal distribution for probabilistic sampling is described in  
82 detail in the NICE 2015 guideline<sup>6</sup>

- 83 (b) National Institute for Health and Care Excellence (NICE) (2015) *Diabetes in pregnancy: management of diabetes and its*  
 84 *complications from preconception to the postnatal period. Clinical guideline NG3 (2015).*  
 85 (c) *British National Formulary. July 2016. <https://www.medicinescomplete.com/mc/bnf/current/> (accessed 4 Aug 2016).*  
 86 (d) *Unit Costs of Health and Social Care 2015. Personal Social Services Research Unit, The University of Kent, 2015.*  
 87 (e) *Department of Health. NHS reference costs: financial year 2014–2015. [https://www.gov.uk/government/publications/nhs-](https://www.gov.uk/government/publications/nhs-reference-costs-2014-to-2015)*  
 88 *reference-costs-2014-to-2015*, Department of Health, 2015.  
 89 (f) *NHS Electronic Drug Tariff, August 2016. [http://www.drugtariff.nhsbsa.nhs.uk/#/00336026-DD\\_1/DD00336022/Home](http://www.drugtariff.nhsbsa.nhs.uk/#/00336026-DD_1/DD00336022/Home)*  
 90 *(accessed 4 Aug 2016).*  
 91

## 92 QALYs

93 A QALY loss was estimated for each individual component (shoulder dystocia, death and birth trauma)  
 94 of the composite serious perinatal outcome, which was used in the ACHOIS study.<sup>11</sup> A weighting for  
 95 each individual component was derived according to their relative frequency in the selected studies to  
 96 assess treatment effectiveness.<sup>11, 12</sup> These were then used in order to derive a weighted average for a  
 97 serious perinatal complication as shown in Table x15. QALY losses from a serious perinatal complication  
 98 could be experienced over a lifetime and therefore an annual discount rate of 3.5% was applied in line  
 99 with NICE methods.<sup>19</sup> For each patient, an expected QALY decrement is calculated based on their risk of  
 100 serious perinatal complications. These individual patient QALY decrements are then summed across all  
 101 patients to give the total QALY decrement for the patient dataset for each different diagnostic  
 102 threshold.

103 **Table x15:** QALY losses and weights from individual components of the composite outcome of serious  
 104 perinatal complications

Complication	Weight	QALY	Weighted QALY
Death	0.08	25	2.00
Shoulder dystocia	0.73	0.2	0.15
Birth trauma	0.20	0.2	0.04

105

106 The analyses presented in this paper include a maternal health state utility which was estimated from  
 107 quality of life data collected as part of the ACHOIS study. Whilst treatment conferred a small benefit in  
 108 maternal health state utility, this was small in comparison to QALYs derived from infant outcomes. The



1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

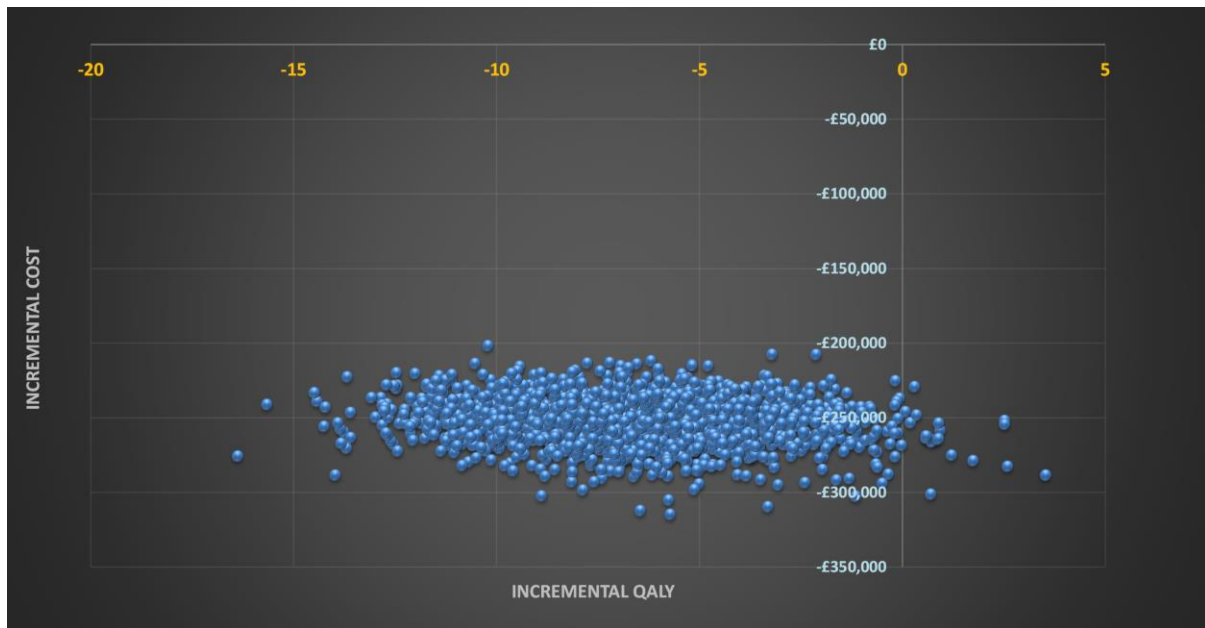
109 value of the maternal health state utility with and without treatment is the same as has been used  
110 previously.<sup>6</sup>

For peer review only

111 **Results for the HAPO (4) population with risk factors**

112 **Figure x1:** Cost-effectiveness plane for NICE 2015 compared with WHO 2013 for HAPO (4) with risk  
 113 factors

114



115

116

117

review only

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

118 **Summary of results for each model population**

119 **Table x16:** Summary of deterministic ICERs for each population with backward elimination of plasma  
 120 glucose variables with non-significant coefficients

Diagnostic threshold	All covariates		Plasma glucose covariates				Norwich (n=12,754)
	HAPO Risk factor (n=3,549)	HAPO No Risk factor (n=2,614)	HAPO Risk factor (n=3,549)	HAPO No Risk factor (n=2,614)	Atlantic DiP Risk factor (n=1,988)	Atlantic DiP No Risk factor (n=3,302)	
No Treatment	-	-	-	-	-	-	-
NICE 2015	£20,400	£36,878	£22,281	£30,449	£20,830	£31,136	£28,893
WHO 2013	£33,596	£141,812	£36,473	£88,661	£35,941	£40,526	£37,918

121

122

123 **Table x17:** Probability that a threshold is cost-effective at a threshold of £30,000 per QALY and the  
 124 net monetary benefit in each population using regression models with backward elimination of  
 125 plasma glucose variables with non-significant coefficients

Diagnostic threshold	All covariates		Plasma glucose covariates				Norwich (NMB)
	HAPO Risk factor (NMB)	HAPO No Risk factor (NMB)	HAPO Risk factor (NMB)	HAPO No Risk factor (NMB)	Atlantic DiP Risk factor (NMB)	Atlantic DiP No Risk factor (NMB)	
No Treatment	19.8% (£486)	78.0% (£203)	34.4% (£361)	66.5% (£235)	27.6% (£326)	68.6% (£268)	59.7% (£938)
NICE 2015	53.5% (£230,798)	22.0% (-£57,048)	53.3% (£108,074)	33.4% (-£32,878)	58.3% (£123,600)	25.3% (-£34,626)	29.6% (-£78,394)
WHO 2013	26.8% (£178,231)	0.1% (-£110,895)	12.4% (£18,317)	0.2% (-£76,674)	14.2% (£48,384)	6.2% (-£106,298)	10.8% (-£380,299)

126

127 **Results for the HAPO (4) population without risk factors**128 **Table x18:** Clinical outcomes for HAPO (4) population without NICE risk factors (n=2,614)

Diagnostic threshold	Diagnosed	SD	SPC	CS	NICU	Jaund	PE	IOL
No Treatment	0	24	34	466	188	126	55	647
NICE 2015	208	23	31	460	184	124	51	655
WHO 2013	253	23	31	459	184	123	51	657

129

130 **Table x19:** Deterministic analysis for HAPO (4) population without NICE risk factors (n=2,614)

Diagnostic threshold	Cost <sup>a</sup>	QALY <sup>a</sup>	Incremental cost	Incremental QALY	ICER
No Treatment	£0	0.00	n/a	n/a	n/a
NICE 2015	£238,074	6.46	£238,074	6.46	£36,878
WHO 2013	£297,364	6.87	£59,290	0.41	£141,812

131 a) Costs and QALYs are measured relative to a baseline of No Treatment

132

133 **Table x20:** Probabilistic sensitivity analysis for HAPO (4) in a population without NICE risk factors

Diagnostic threshold	NMB <sup>a</sup>	Probability cost-effective
	CE threshold £30,000 per QALY	CE threshold £30,000 per QALY
No Treatment	£203	78.0%
NICE 2015	-£57,048	22.0%
WHO 2013	-£110,895	0.1%

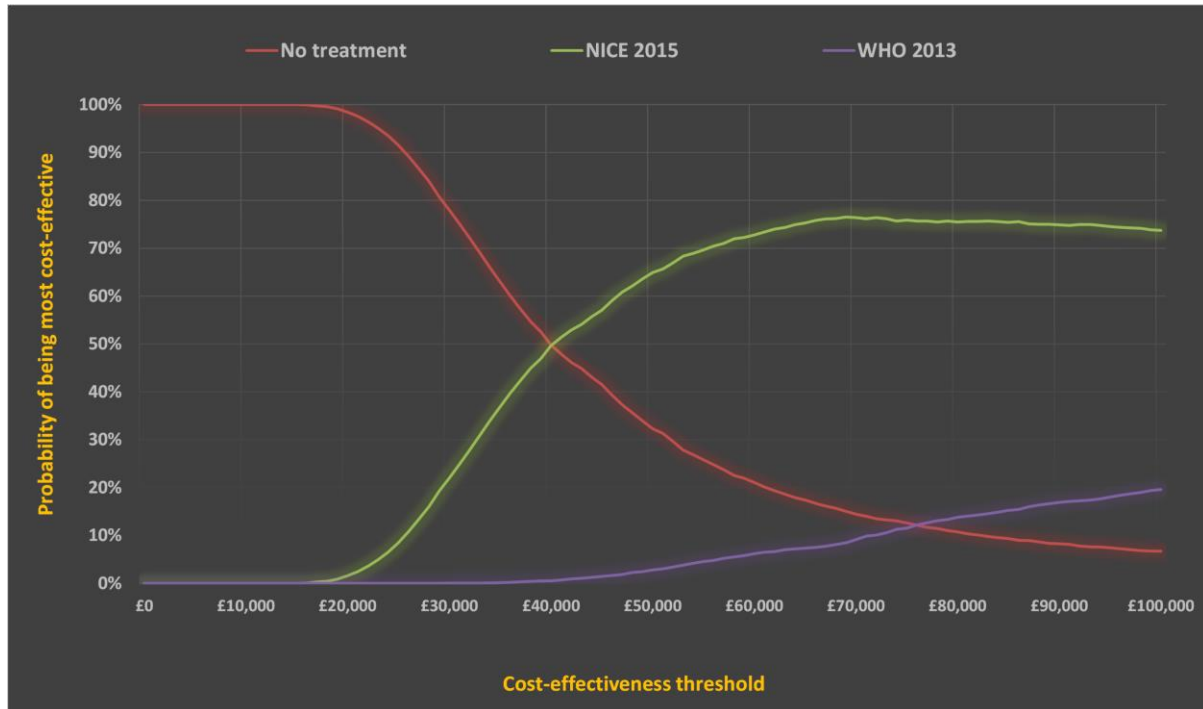
134 a) NMB is measured relative to the least costly and least effective strategy in each simulation

135

136

137

1  
2  
3  
4 138 **Figure x2:** Cost-effectiveness acceptability curve indicating the probability of a threshold or a no  
5 139 diagnosis/no treatment strategy being cost-effective at different cost-effectiveness thresholds for  
6 140 HAPO (4) population without risk factors  
7  
8  
9 141



142

143

144 **Results for the Atlantic DiP population with risk factors**

145 **Table 21:** Clinical outcomes for Atlantic DiP population with NICE risk factors (n=1,988)

Diagnostic threshold	Diagnosed	SD	SPC	CS	NICU	Jaund	PE	IOL
No Treatment	0	25	34	408	177	122	73	522
NICE 2015	497	19	26	391	163	116	56	545
WHO 2013	749	17	24	385	158	112	51	555

146

147

148

149

150

151 **Table x22:** Deterministic analysis for the Atlantic DiP population with NICE risk factors (n=1,988)

Diagnostic threshold	Cost <sup>a</sup>	QALY <sup>a</sup>	Incremental cost	Incremental QALY	ICER
No Treatment	£0	0.00	n/a	n/a	n/a
NICE 2015	£414,714	19.91	£414,714	17.46	£20,830
WHO 2013	£638,590	26.14	£223,876	6.23	£35,941

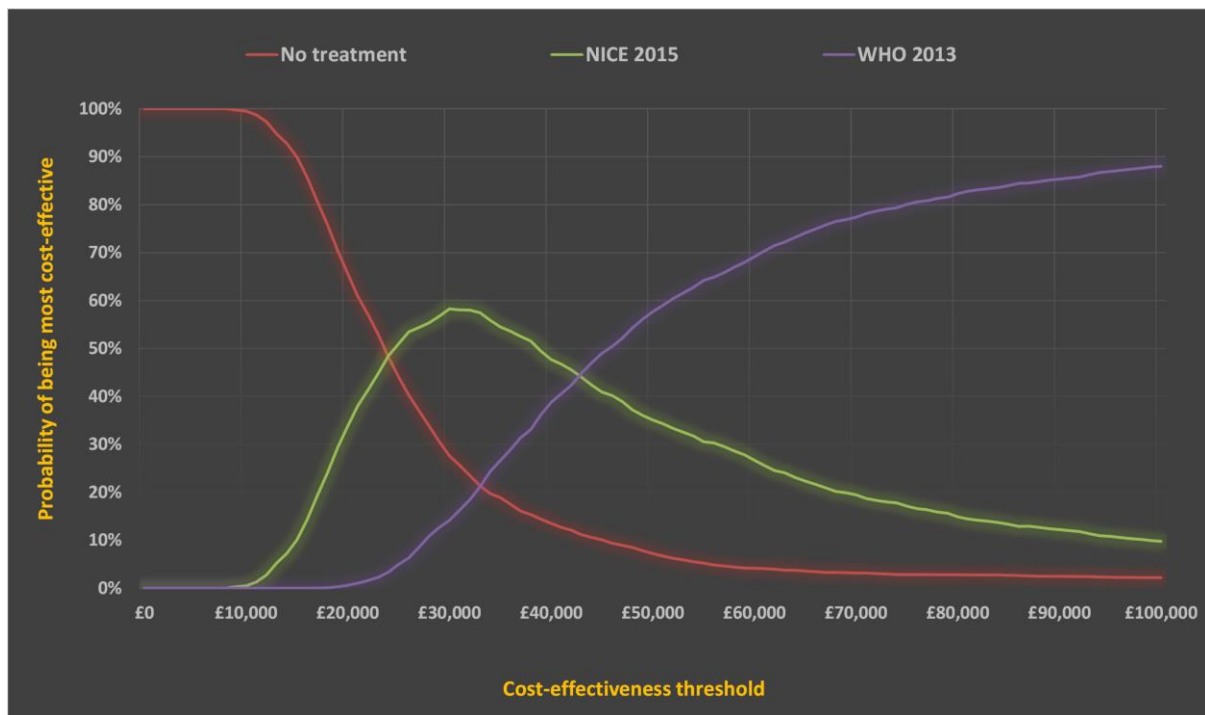
152 a) Costs and QALYs are measured relative to a baseline of No Treatment

153  
154 **Table x23:** Probabilistic sensitivity analysis for Atlantic in a population with NICE risk factors

Diagnostic threshold	NMB <sup>a</sup> CE threshold £30,000 per QALY	Probability cost-effective CE threshold £30,000 per QALY
No Treatment	£326	27.6%
NICE 2015	£123,600	58.3%
WHO 2013	£48,384	14.2%

155 a) NMB is measured relative to the least costly and least effective strategy in each simulation

167 **Figure x3:** Cost-effectiveness acceptability curve indicating the probability of a threshold or a no  
 168 diagnosis/no treatment strategy being cost-effective at different cost-effectiveness thresholds for  
 169 the Atlantic DiP centres population with risk factors



170

171

172 **Results for the Atlantic DiP population without risk factors**

173 **Table x24:** Clinical outcomes for Atlantic DiP population without NICE risk factors (n=3,302)

Diagnostic threshold	Diagnosed	SD	SPC	CS	NICU	Jaund	PE	IOL
No Treatment	0	33	45	575	254	168	84	828
NICE 2015	194	31	42	569	248	166	79	837
WHO 2013	371	30	41	564	245	163	76	844

174

175

176

177

178

179

180

181 **Table x25:** Deterministic analysis for the Atlantic DiP population without NICE risk factors (n=3,302)

Diagnostic threshold	Cost <sup>a</sup>	QALY <sup>a</sup>	Incremental cost	Incremental QALY	ICER
No Treatment	£0	0.00	n/a	n/a	n/a
NICE 2015	£231,633	7.44	£231,633	7.44	£31,136
WHO 2013	£402,014	11.64	£170,381	4.20	£40,526

182 a) Costs and QALYs are measured relative to a baseline of No Treatment

183

184 **Table x26:** Probabilistic sensitivity analysis for the Atlantic DiP population without NICE risk factors

Diagnostic threshold	NMB <sup>a</sup>	Probability cost-effective
	CE threshold £30,000 per QALY	CE threshold £30,000 per QALY
No Treatment	£268	68.6%
NICE 2015	-£34,626	25.3%
WHO 2013	-£106,298	6.2%

185 a) NMB is measured relative to the least costly and least effective strategy in each simulation

186

187

188

189

190

191

192

193

194

195

196



1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

197 **Figure x4:** Cost-effectiveness acceptability curve indicating the probability of a threshold or a no  
198 diagnosis/no treatment strategy being cost-effective at different cost-effectiveness thresholds for  
199 the Atlantic DiP centres population without risk factors

200



201

202

Review only

203 **Results for the Norwich population**204 **Table x27:** Clinical outcomes for Norwich population (n=12,754)

Diagnostic threshold	Diagnosed	SD	SPC	CS	NICU	Jaund	PE	IOL
No Treatment	0	132	182	2,333	1,005	699	346	3,173
NICE 2015	888	122	168	2,305	981	687	318	3,214
WHO 2013	1,771	117	161	2,283	965	676	301	3,248

205

206 **Table x28:** Deterministic analysis for the Norwich population (n=12,754)

Diagnostic threshold	Cost <sup>a</sup>	QALY <sup>a</sup>	Incremental cost	Incremental QALY	ICER
No Treatment	£0	0.00	n/a	n/a	n/a
NICE 2015	£979,903	33.91	£979,903	33.91	£28,893
WHO 2013	£1,803,196	55.63	£823,293	21.72	£37,918

207 a) *Costs and QALYs are measured relative to a baseline of No Treatment*

208

209 **Table x29:** Probabilistic sensitivity analysis for the Norwich population

Diagnostic threshold	NMB <sup>a</sup> CE threshold £30,000 per QALY	Probability cost-effective CE threshold £30,000 per QALY
No Treatment	£938	59.7%
NICE 2015	-£78,394	29.6%
WHO 2013	-£380,299	10.8%

210 a) *NMB is measured relative to the least costly and least effective strategy in each simulation*

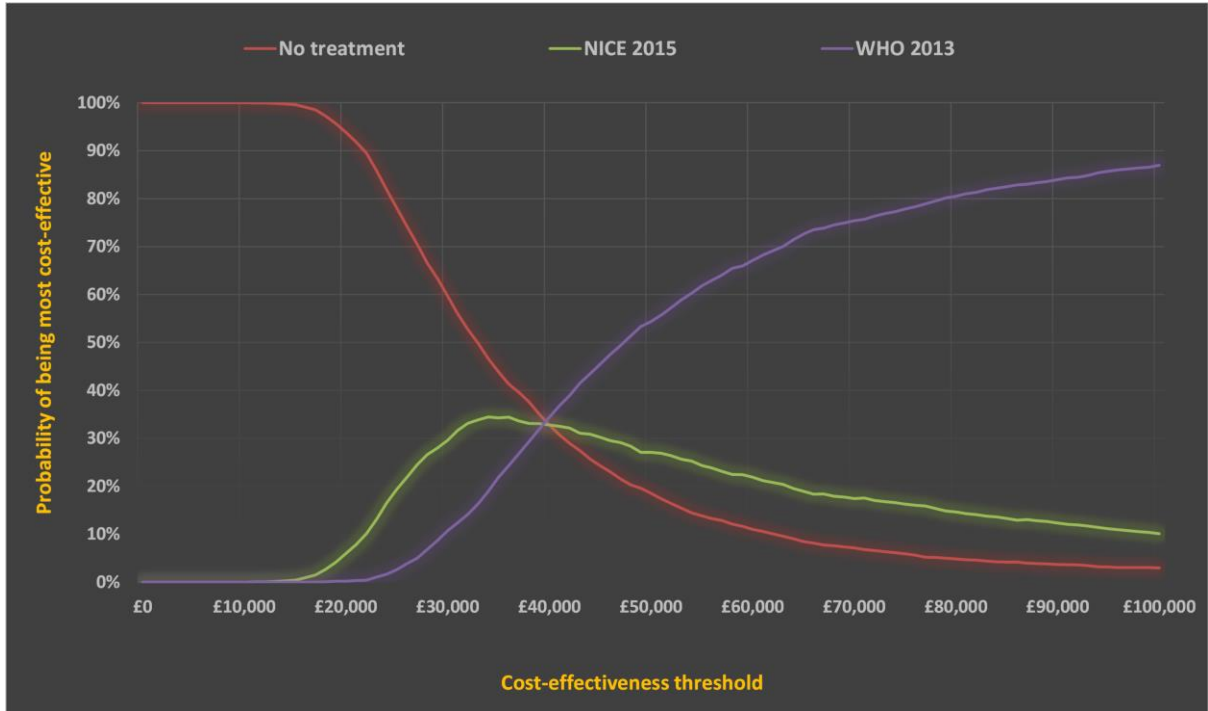
211

212

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

213 **Figure x5:** Cost-effectiveness acceptability curve indicating the probability of a threshold or a no  
214 diagnosis/no treatment strategy being cost-effective at different cost-effectiveness thresholds for  
215 the Norwich population

216



217

218

219

review only

## 220 Deterministic sensitivity analysis

221 The cost-effectiveness of universal screening was not generally affected when the model was re-run  
 222 using the regression models without backward elimination of non-significant variables with no  
 223 screening/no treatment continuing to be the cost-effective option in populations not selected on the  
 224 basis of NICE risk factors (see Table x30). In the Norwich population, universal screening was  
 225 borderline cost-effective compared to no screening/no treatment at £30,000 per QALY but the same  
 226 point remains that a risk factor subset in this population would have a lower ICER than that  
 227 reported, and that a subset without risk factors, (i.e. those additionally incorporated as a result of  
 228 universal screening compared to risk factor screening), would have a higher ICER. In populations  
 229 with NICE risk factors the NICE 2015 diagnostic thresholds were still found to be cost-effective at a  
 230 threshold of £30,000 per QALY, with broadly similar ICERs as previously. Similarly, the WHO 2013  
 231 diagnostic threshold was never found to be cost effective even in a population with risk factors.

232 **Table x30:** Summary of deterministic ICERs for each population without backward elimination of  
 233 non-significant coefficients

36 Diagnostic threshold	37 All covariates		38 Plasma glucose covariates				39 Norwich (n=12,754)
	40 HAPO Risk factor (n=3,549)	41 HAPO No Risk factor (n=2,614)	42 HAPO Risk factor (n=3,549)	43 HAPO No Risk factor (n=2,614)	44 Atlantic DiP Risk factor (n=1,988)	45 Atlantic DiP No Risk factor (n=3,302)	
46 No Treatment	-	-	-	-	-	-	-
47 NICE 2015	£20,162	£38,869	£21,786	£33,473	£19,557	£32,762	£27,354
48 WHO 2013	£30,734	£94,585	£32,267	£58,604	£35,285	£39,076	£38,402

234

235

236 **Mean plasma glucose values according to risk factor status**

237 **Table x311:** Mean plasma glucose values in HAPO (4) and Atlantic DiP population according to their  
 238 risk factor status

239

	HAPO (4)			Atlantic DiP		
	Fasting	1-hour	2-hour	Fasting	1-hour	2-hour
True Positives	5.24	9.90	7.89	5.21	10.21	7.61
False Positives	4.50	7.20	5.95	4.33	6.75	5.33
True Negatives	4.44	6.95	5.78	3.92	5.99	4.76
False Negatives	4.89	9.52	7.41	4.90	9.51	7.12

240

241

## CHEERS Statement

CHEERS checklist—Items to include when reporting economic evaluations of health interventions

Section/item	Item No	Recommendation	Reported on page No/ line No
<b>Title and abstract</b>			
Title	1	Identify the study as an economic evaluation or use more specific terms such as “cost-effectiveness analysis”, and describe the interventions compared.	Yes Page 1 Line 2
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	Yes Page 2 Lines 30-56
<b>Introduction</b>			
Background and objectives	3	Provide an explicit statement of the broader context for the study.	Yes Page 5-6 Lines 93-105
		Present the study question and its relevance for health policy or practice decisions.	Yes Page 5 Lines 75-91
<b>Methods</b>			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Yes Page 7-8 Lines 120-153
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Yes Page 7 Lines 120-127
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Yes Page 12 Line 220
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Yes Page 6 Line 101-102; 109-110
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Yes Page 12 Line 231  Supp. Report

Section/item	Item No	Recommendation	Reported on page No/ line No
			Page 15 Line 90
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	Yes Page 12 Line 231  Supp. Report Page 15 Line 90
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Yes Pages 8-9 Lines 155-176
Measurement of effectiveness	11a	<i>Single study-based estimates:</i> Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	Yes Pages 10 Lines 205-208
	11b	<i>Synthesis-based estimates:</i> Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	Yes Pages 10 Lines 202-204
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	
Estimating resources and costs	13a	<i>Single study-based economic evaluation:</i> Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
	13b	<i>Model-based economic evaluation:</i> Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Yes Page 12-13 Lines 219-245  Supp. Report Page 14 Line 80
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for	Yes Page 12 Lines 231

Section/item	Item No	Recommendation	Reported on page No/ line No
		converting costs into a common currency base and the exchange rate.	
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	Yes Page 6 Lines 109-112; 114-116
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	Yes Page 8-9 Lines 155-176  Yes Page 13 Lines 247-250  Supp. Report Page 2-7  Supp. Report Page 15 Lines 84-102  +References to other sources
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	Yes Page 9-10 Lines 178-195  Yes Page 13-14 Lines 259-266  Supp. Report Page 2-7
<b>Results</b>			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Yes Page 11 Lines 216-217  Page 13



Section/item	Item No	Recommendation	Reported on page No/ line No
			Lines 244-245  Supp. Report Page 2-15
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Yes Page 15 Lines 280-282  Supp. Report Page 17-25
Characterising uncertainty	20a	<i>Single study-based economic evaluation:</i> Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	
	20b	<i>Model-based economic evaluation:</i> Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Yes Supp. Report Page 17 Lines 116-119  Supp. Report Page 26 Lines 225-227
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	Yes Supp. Report Page 17 Lines 111-114
<b>Discussion</b>			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the	Yes Pages 18-25

Section/item	Item No	Recommendation	Reported on page No/ line No
		findings and how the findings fit with current knowledge.	
<b>Other</b>			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	Yes Page 26 Lines 541-546
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Yes Page 26 Lines 537-539

# BMJ Open

## A COST EFFECTIVENESS COMPARISON OF THE NICE 2015 AND WHO 2013 DIAGNOSTIC CRITERIA FOR WOMEN WITH GESTATIONAL DIABETES WITH AND WITHOUT RISK FACTORS

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-016621.R2
Article Type:	Research
Date Submitted by the Author:	09-Jun-2017
Complete List of Authors:	Jacklin, Paul; Royal College of Obstetricians and Gynaecologists, National Guideline Alliance Maresh, Michael; Central Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre Patterson, Chris; Queen's University Belfast, Centre for Public Health Stanley, Katharine; Norfolk and Norwich University Hospitals NHS Foundation Trust, Department of Obstetrics and Gynaecology Dornhorst, Anne; Hammersmith Hospital, Department of Investigative Medicine Burman-ROY, Shona; Royal College of Obstetricians and Gynaecologists, National Guideline Alliance Bilous, Rudy; Newcastle University Medicine Malaysia
<b>Primary Subject Heading</b>:	Health economics
Secondary Subject Heading:	Diabetes and endocrinology, Obstetrics and gynaecology, Diagnostics
Keywords:	HEALTH ECONOMICS, DIABETES & ENDOCRINOLOGY, OBSTETRICS

SCHOLARONE™  
Manuscripts

1  
2  
3 **Title:**  
4

5 A COST EFFECTIVENESS COMPARISON OF THE NICE 2015 AND WHO 2013  
6  
7 DIAGNOSTIC CRITERIA FOR WOMEN WITH GESTATIONAL DIABETES WITH AND  
8  
9  
10 WITHOUT RISK FACTORS  
11

12  
13  
14 **Authors:** PB Jacklin<sup>1</sup>, MJA Maresh<sup>2</sup>, CC Patterson<sup>3</sup>, KP Stanley<sup>4</sup>, A Dornhorst<sup>5</sup>, S Burman-  
15  
16 Roy<sup>1</sup>, RW Bilous<sup>6</sup>  
17  
18

19  
20  
21 **Institutions:**  
22

- 23 1. Royal College of Obstetricians and Gynaecologists, London NW1 4RG, UK  
24 2. St. Mary's Hospital, Central Manchester University Hospitals NHS Foundation Trust,  
25 Manchester Academic Health Science Centre, Manchester M13 9WL, UK  
26  
27 3. Centre for Public Health, Queen's University Belfast, Room 3.014, ICS Block B, Grosvenor Road,  
28 Belfast BT12 6BJ, UK  
29  
30 4. Department of Obstetrics and Gynaecology, Norfolk and Norwich University Hospitals NHS  
31 Foundation Trust, Colney Ln, Norwich NR4 7UY, UK  
32  
33 5. Faculty of Medicine, Department of Investigative Medicine, Hammersmith Hospital, Imperial  
34 College London, London, UK  
35  
36 6. Newcastle University Medicine Malaysia, Johor, Malaysia  
37  
38

39  
40  
41 **Corresponding author:**  
42

43 Paul Jacklin  
44 e-mail: [pjacklin@rcog.org.uk](mailto:pjacklin@rcog.org.uk)  
45  
46

47  
48 Abstract: 287 words  
49

50 Main text: 5420 words  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 30 **Abstract**  
4

5 31

6 32 **Objectives** To compare the cost effectiveness of The National Institute for Health and Care  
7  
8  
9 33 Excellence (NICE) 2015 and the World Health Organisation (WHO) 2013 diagnostic thresholds  
10  
11 34 for gestational diabetes (GDM).

12  
13 35 **Setting:** The analysis was from the perspective of the National Health Service (NHS) in  
14  
15 36 England and Wales.

16  
17 37 **Participants:** 6,221 patients from four of the Hyperglycaemia and Adverse Pregnancy  
18  
19 38 Outcomes (HAPO) study centres (2 UK, 2 Australian), 6,308 patients from the Atlantic  
20  
21 39 Diabetes in Pregnancy (DiP) study and 12,755 patients from UK clinical practice

22  
23 40 **Primary and secondary outcome measures planned:** The incremental cost per quality  
24  
25 41 adjusted life year (QALY), net monetary benefit (NMB) and the probability of being cost-  
26  
27 42 effective at cost-effectiveness thresholds of £20,000 and £30,000 per QALY

28  
29 43 **Results.** In a population of pregnant women from the four HAPO study centres, and utilising  
30  
31 44 NICE defined risk factors for GDM, diagnosing GDM using NICE 2015 criteria had a NMB of  
32  
33 45 £239,902 (relative to no treatment) at a cost-effectiveness threshold of £30,000 per QALY  
34  
35 46 compared to WHO 2013 criteria which had a NMB of £186,675. NICE 2015 criteria had a  
36  
37 47 51.5% probability of being cost-effective compared to the WHO 2013 diagnostic criteria which  
38  
39 48 had a 27.6% probability of being cost-effective (no treatment had a 21.0% probability of being  
40  
41 49 cost-effective). For women without NICE risk factors in this population the NMB for NICE  
42  
43 50 2015 and WHO 2013 criteria were both negative relative to no treatment, and no treatment had  
44  
45 51 a 78.1% probability of being cost effective.

46  
47 52 **Conclusion** The NICE 2015 diagnostic criteria for GDM can be considered cost-effective  
48  
49 53 relative to the WHO 2013 alternative at a cost-effectiveness (CE) threshold of £30,000 per  
50  
51 54 QALY. Universal screening for GDM was not found to be cost-effective relative to screening  
52  
53 55 based on NICE risk factors.  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 56  
4  
5 57  
6  
7 58  
8  
9 59  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

**Keywords:** Cost Effectiveness, Gestational Diabetes, Screening, Risk Factors, Diagnosis

For peer review only

1  
2  
3 60 **Strengths and limitations of this study**  
4

- 5 61 • This economic evaluation addresses an important clinical and policy issue. The existing  
6 economic evidence is limited and WHO have stated that studies of this type are needed  
7  
8 62 to inform a future update of their guideline  
9  
10 63  
11 64 • Our paper has used patient-level data from the influential HAPO study for an economic  
12 analysis which has not been previously been published in a peer reviewed journal  
13  
14 65  
15  
16 66 • This analysis provides clear evidence that universal screening is not cost-effective in the  
17 UK  
18  
19 67  
20  
21 68 • This analysis suggests that the NICE diagnostic criteria for GDM are more cost-  
22 effective than the WHO criteria in the UK context  
23  
24 69  
25 70 • Model conclusions are sensitive to uncertainties with respect to valuation of health  
26 outcomes and the possible long term metabolic consequences for offspring for which the  
27 evidence is debated and which are hard to quantify  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## 73 Introduction

74 The diagnostic glycaemic thresholds for GDM remain the subject of considerable debate. The  
75 original definition was based upon maternal risk for developing postpartum diabetes, but  
76 subsequent thresholds have concentrated on complications during pregnancy and the health of  
77 the offspring. The publication of the HAPO study<sup>1</sup> demonstrated a linear association between  
78 increasing levels of maternal hyperglycaemia and adverse perinatal outcomes with no obvious  
79 threshold, an association that has also been observed in subsequent analyses.<sup>2</sup> The discussion  
80 around the diagnostic criteria that should define GDM has intensified. New diagnostic  
81 thresholds were proposed by the International Association of Diabetes in Pregnancy Study  
82 Group (IADPSG)<sup>3</sup> based upon the HAPO study levels of plasma glucose when fasting, and at 1  
83 and 2 hours after an oral 75g glucose load that were associated with covariate adjusted odds  
84 ratio of 1.75 relative to the mean glucose value in the whole HAPO cohort on three offspring  
85 outcomes: exceeding the 90<sup>th</sup> centile for birth weight, for cord serum C-peptide concentration  
86 and for percent fetal body fat. These diagnostic criteria have been subsequently adopted by the  
87 WHO.<sup>4</sup> However, they remain controversial and have not been supported by bodies such as the  
88 National Institutes for Health and the American College of Obstetricians.<sup>5</sup> Furthermore, WHO  
89 has acknowledged that they will have to be revisited in the near future in the light of new  
90 studies reporting their cost-effectiveness.<sup>4</sup>

91  
92 In 2015 NICE published updated guidance on Diabetes in Pregnancy<sup>6</sup> which included  
93 recommendations on diagnostic thresholds for GDM which differ from those adopted by WHO.  
94 These NICE thresholds were informed by an economic evaluation of the type that WHO  
95 considered important to inform future recommendations, but have attracted criticism in the UK<sup>7</sup>  
96 and elsewhere. Data from a published Spanish study<sup>8</sup> have been widely cited<sup>7,9</sup> in support of the



97 cost effectiveness of the WHO criteria, although a UK analysis has more recently suggested that  
98 it is not cost-effective to identify gestational diabetes for treatment.<sup>10</sup>

99

100 In this paper we compared the cost-effectiveness of NICE 2015 and WHO 2013 diagnostic  
101 thresholds for GDM, as these are new thresholds proposed by national and international bodies.

102 The analysis was undertaken using a revised version of the health economic model developed  
103 for the NICE guideline and was based upon data from the UK and Australian HAPO Study  
104 centres.

105

## 106 **Methods**

### 107 *Model description*

108 A decision analytic framework was used to evaluate the cost effectiveness of two recently  
109 proposed diagnostic thresholds for GDM, together with a no diagnosis/no treatment option (See  
110 Table 1). A schematic of the model is shown in Figure 1. Cost-effectiveness was evaluated  
111 using both deterministic and probabilistic sensitivity analysis.

112

113 **Table 1:** Diagnostic thresholds for plasma glucose evaluated in the economic model

Threshold name	Fasting (mmol/L)	1-hour (mmol/L)	2-hour (mmol/L)
No diagnosis/no treatment	-	-	-
NICE 2015	≥5.6	-	≥7.8
WHO 2013	≥5.1	≥10.0	≥8.5

114

### 115 *Population*

116 The model population comprised women of gestational age 24-28 weeks without pre-existing  
117 diabetes. The analysis utilised individual patient data from three datasets which, although not

1  
2  
3 118 restricted to the UK, provide a representative cross section of the demographic and patient  
4  
5 119 characteristics that would be found in the UK (Table x1 in the Supplementary Report provides a  
6  
7 120 breakdown of ethnic groups in each of our datasets) . The analyses were run separately for each  
8  
9 121 dataset and, where possible, for subgroups with and without risk factors for GDM within a  
10  
11 122 dataset.  
12  
13

14  
15  
16 124 i. HAPO – a dataset from the two UK (Manchester and Belfast) and two Australian  
17  
18 125 (Brisbane and Newcastle) centres of the HAPO Study, referred to as HAPO (4)

19  
20  
21 126 ii. Norwich – these data were routinely collected between 2008 and February 2014 on  
22  
23 127 women who had an oral glucose tolerance test (OGTT) on the basis of the presence of one or  
24  
25 128 more risk factors for GDM. The results were obtained from laboratory records with no  
26  
27 129 identifiers. Risk factors in addition to those recommended by NICE were used e.g. women with  
28  
29 130 polycystic ovary syndrome, previous stillbirth or recurrent glycosuria.

30  
31  
32 131 iii. Atlantic Diabetes in Pregnancy (Atlantic DiP) – these data were collected between 2007  
33  
34 132 and 2013 as part of a research initiative in the Republic of Ireland intended to improve  
35  
36 133 pregnancy outcomes for women with diabetes before, during and after pregnancy.  
37

38  
39 134

40  
41 135 For the HAPO (4) and Atlantic DiP datasets the populations were stratified according to  
42  
43 136 whether or not they had NICE risk factors for GDM (body mass index (BMI) above 30 kg/m<sup>2</sup>,  
44  
45 137 previous baby with birthweight  $\geq 4.5$  kg, previous GDM, first-degree relative with diabetes and  
46  
47 138 minority ethnic family origin with a high prevalence of diabetes). This facilitated a comparison  
48  
49 139 of the cost-effectiveness of universal screening for GDM when compared with a risk factor  
50  
51 140 approach.  
52

53  
54 141  
55  
56  
57  
58  
59  
60

1  
2  
3 142 The NICE risk factor approach could not be replicated exactly because the patient data used in  
4  
5 143 the model do not include information on previous offspring birth weight, and the HAPO (4)  
6  
7 144 dataset does not provide information on previous GDM. Similarly the Atlantic DIP dataset does  
8  
9 145 not include data on previous macrosomia or previous GDM. Therefore, the comparison in the  
10  
11 146 model was between universal screening and a subset of NICE risk factors. Our Norwich dataset  
12  
13 147 only included the plasma glucose values from a three point (fasting, 1 and 2 hour) OGTT and  
14  
15 148 therefore it was not possible to assess cost-effectiveness according to the presence of risk  
16  
17 149 factors in this group.  
18  
19  
20  
21

22 150

23 151 Permission was obtained from the relevant Caldecott Guardian to use anonymised patient  
24  
25 152 OGTT data from the Norfolk and Norwich University Hospitals NHS Foundation Trust for the  
26  
27 153 analysis. The principle investigators from the Australian (Professor HD McIntyre) and British  
28  
29 154 (Professor DR McCance) centres of the HAPO study and the principle investigator of the  
30  
31 155 Atlantic DiP (Professor F Dunne) study gave permission for anonymised patient data from their  
32  
33 156 studies to be used in the analysis.  
34  
35  
36  
37

38 157

39 158 *Clinical outcomes*

40  
41 159 The agreed outcomes for the economic model were selected prior to model development by the  
42  
43 160 NICE Guideline Development Group. They were:

- 44  
45 161 i. Shoulder dystocia (SD) – this was used to estimate serious perinatal complications  
46  
47 162 (SPC), a broader composite outcome (death, shoulder dystocia and birth trauma) used as  
48  
49 163 a primary outcome in clinical trials. The estimation of SPC from shoulder dystocia has  
50  
51 164 been described elsewhere.<sup>6</sup>  
52  
53 165 ii. Caesarean section (CS)  
54  
55 166 iii. Neonatal intensive care unit (NICU) admission  
56  
57  
58  
59  
60

1  
2  
3 167 iv. Jaundice requiring phototherapy (Jaund)

4  
5 168 v. Pre-eclampsia (PE)

6  
7 169 vi. Induction of labour (IOL)

8  
9  
10 170 Outcomes were prioritised for inclusion in the model if they had a direct impact on health  
11  
12 171 related quality of life and/or cost. Birth weight was not included because there were few long-  
13  
14 172 term outcome data for modelling any risk benefit of a reduction in birth weight for future  
15  
16 173 diabetes and other health outcomes in the offspring.

17  
18  
19 174

20  
21 175 In addition, outcomes were only included if the relationship with plasma glucose levels had  
22  
23 176 been established in the HAPO study, and also that they had been assessed in intervention  
24  
25 177 studies used to derive treatment effect size estimates. Possible double counting of certain  
26  
27 178 outcomes was taken into account (e.g. preterm birth and NICU admission). The final list of  
28  
29 179 outcomes included in the model was therefore a pragmatic one.

30  
31  
32 180

33  
34 181 *Baseline risk*

35  
36 182 Logistic regression analyses of patient data from HAPO (4) were used to predict a baseline risk  
37  
38 183 for all six outcomes for each woman, based on their characteristics including their OGTT  
39  
40 184 results. In the HAPO study the OGTT was blinded to the carers, unless there was overt diabetes,  
41  
42 185 thus allowing direct comparison of the OGTT with perinatal outcomes without intermediate  
43  
44 186 treatment effects for those meeting the new diagnostic criteria for GDM.

45  
46  
47 187 For each of the six outcomes, 2 logistic analyses to predict risk were assessed:

48  
49 188 i. Prediction based on OGTT plasma glucose results and including the same covariates as  
50  
51 189 used for Model 2 in the original analysis of the HAPO data<sup>1</sup> – this could not be applied  
52  
53 190 to the Norwich and Atlantic DiP datasets as information on all HAPO covariates was not  
54  
55 191 available

1  
2  
3 192 ii. Prediction based only on OGTT plasma glucose results  
4

5 193 Backward elimination of plasma glucose variables with non-significant coefficients was  
6  
7 194 undertaken to arrive at a 'final' logistic regression analysis to predict baseline risk for each  
8  
9 195 outcome for the base case analysis, although a sensitivity analysis is also presented where the  
10  
11 196 model was run with plasma glucose variables with non-significant coefficients retained. The  
12  
13 197 logistic regression analyses used to predict the baseline risk for each outcome are shown in the  
14  
15 198 Supplementary Report, Tables x2 to x7.  
16  
17  
18  
19

20  
21 200 *Clinical effectiveness*  
22

23  
24 201 For each evaluated diagnostic threshold in Table 1 the model determined whether a woman  
25  
26 202 would be identified as having GDM based on her OGTT. If the woman was not identified as  
27  
28 203 having GDM then outcome probabilities were based on the predicted baseline risk, but for  
29  
30 204 women identified as having GDM the predicted baseline risk was modified to take account of  
31  
32 205 the effects of treatment. Treatment effectiveness for most outcomes was estimated from a  
33  
34 206 random-effects meta-analysis of two studies, the Australian Carbohydrate Intolerance Study  
35  
36 207 (ACHOIS) and the Landon et al. trial.<sup>11, 12</sup> Other published studies of treatment for GDM were  
37  
38 208 adjudged to lack adequate randomisation.<sup>13</sup> For the NICU outcome only the Landon et al. trial  
39  
40 209 data were used as it was considered to more closely represent UK practice as all neonatal  
41  
42 210 nursery admissions were utilised. Similarly, the incidence of pre-eclampsia seemed high in  
43  
44 211 ACHOIS in both arms, and again only Landon et al. trial data were utilised. The treatment  
45  
46 212 effects for each of the model's clinical outcomes are shown in Table 2 along with parameters  
47  
48 213 for probabilistic sampling. The model assumes that the relative treatment effect will be the same  
49  
50 214 irrespective of the absolute baseline risk. For deterministic analyses the point estimate of  
51  
52 215 relative risk was used but in order to account for uncertainty in these point estimates, these  
53  
54  
55  
56  
57  
58  
59  
60

216 relative risks were sampled from a log-normal distribution in the simulations undertaken for  
 217 probabilistic sensitivity analysis (PSA).

218

219

220

221

222 **Table 2:** Relative treatment effects for model outcomes

<b>Outcome</b>	<b>Relative risk (RR)</b>	<b>Standard error (log RR)</b>	<b>Source</b>
<b>Shoulder dystocia</b>	0.41	0.316	ACHOIS (2005), Landon (2009)
<b>Caesarean section</b>	0.88	0.095	ACHOIS (2005), Landon (2009)
<b>NICU</b>	0.77	0.194	Landon (2009)
<b>Jaundice requiring phototherapy</b>	0.83	0.136	ACHOIS (2005), Landon (2009)
<b>Pre-eclampsia</b>	0.46	0.345	Landon (2009)
<b>Induction of Labour</b>	1.16	0.126	ACHOIS (2005), Landon (2009)

223

224

1  
2  
3 225 *Costs*

4  
5 226 Costing was undertaken from the perspective of the NHS, was calculated for each woman in the  
6  
7 227 dataset being analysed and was made up of three components;

- 8  
9  
10 228 • the costs of the diagnostic test – not applied in the *no test/no treat* strategy  
11  
12 229 • the costs of treatment- applied to every woman diagnosed with GDM at a particular  
13  
14 230 threshold  
15  
16 231 • the costs associated with the various outcomes – with the cost for each woman being the  
17  
18 232 expected (or average) cost of the outcome based on her estimated risk

19  
20  
21 233 The costs calculated for each woman were then summed across the entire patient dataset to give  
22  
23 234 a total cost for a particular diagnostic threshold.

24  
25 235

26  
27 236 Costs are presented in pounds sterling and were taken from published UK sources where  
28  
29 237 possible (cost year 2015). They have not been discounted as they are all assumed to occur  
30  
31 238 within 12 months of diagnosis. Model unit costs are reported in the Supplementary Report,  
32  
33 239 Table x14. The costing methodology and assumptions are described in greater detail elsewhere.<sup>6</sup>

34  
35 240

36  
37  
38 241 *Other event probabilities*

39  
40  
41 242 Probabilities in decision analysis were used to calculate the expected costs and benefits of the  
42  
43 243 various comparators. Many of these probabilities stemmed from relative treatment effects but a  
44  
45 244 few additional event probabilities were included in the model in order to estimate certain costs.

46  
47 245 These probabilities are shown in Table 3 and their source is described elsewhere.<sup>6</sup>

48  
49 246

50  
51 247

52  
53 248

54  
55 249

250 **Table 3:** Model event probability not derived from patient level regression

Event	Probability
Not requiring hypoglycaemic therapy when treated for GDM	36%
Risk of hypoglycaemia if taking hypoglycaemic therapy	20%
Risk of hypoglycaemia being severe (requiring hospitalisation)	5%

251

252 *Quality Adjusted Life Years (QALYs)*

253 Following previous studies<sup>6, 14</sup> a QALY decrement of 2.2 was assigned to serious perinatal  
 254 complications (SPC), defined as per the ACHOIS study as a composite outcome of shoulder  
 255 dystocia, death and birth trauma.<sup>11</sup> More detail on the derivation of this QALY loss is provided  
 256 in the Supplementary Report. The cost-effectiveness of a healthcare intervention is determined  
 257 by the opportunity cost of the health foregone on the basis that with a fixed health budget any  
 258 newly funded intervention would displace the least cost-effective treatment currently provided.  
 259 In the UK, NICE typically uses a threshold of £20,000 to £30,000 per QALY as a benchmark<sup>15</sup>  
 260 for the opportunity cost of health foregone and this paper assesses cost-effectiveness  
 261 accordingly.

262

263 *Sensitivity analysis*

264

265 Probabilistic sensitivity analysis, using Monte Carlo simulation (with 2,000 iterations for each  
 266 analysis), was undertaken in order to assess the impact of sampling uncertainty on model inputs.  
 267 Parameters and distributions for the probabilistic sensitivity analysis are given in Table 2 and  
 268 Table x14 in the supplementary report. For the logistic regression coefficients used to predict  
 269 baseline risk, the Cholesky decomposition method<sup>16</sup> was used to sample from a multivariate  
 270 normal distribution in order to reflect correlations between the coefficients. The Cholesky



271 decomposition of the variance covariance matrices from the regression analyses used in the base  
272 case probabilistic sensitivity analysis are given in Table x8 to x13 in the Supplementary Report.

273

## 274 Results

275 Table 4 shows the percentage of women diagnosed with GDM in the three populations using  
276 both of the evaluated diagnostic thresholds. In addition, for the HAPO (4) and Atlantic DiP  
277 datasets this is additionally broken down in the subgroups with and without NICE risk factors  
278 (RF).

279 **Table 4:** Percentage of women identified with GDM by threshold and population

Threshold name	Norwich (n=12,754)	HAPO all (n=6,163)	HAPO RF (n=3,549)	HAPO No RF (n=2,614)	DiP All (n=5,290)	DiP RF (n=1,988)	DiP No RF (n=3,302)
NICE 2015	7.0%	13.6%	17.7%	8.0%	13.1%	25.0%	5.9%
WHO 2013	13.9%	18.9%	25.7%	9.7%	21.2%	37.7%	11.2%

280

281 Detailed deterministic and probabilistic results for HAPO (4) with risk factors are shown in  
282 Table 5, Table 6, Table 7 and Figure 2.

283

284 **Table 5:** Clinical outcomes for HAPO (4) population with NICE risk factors (n=3,549)

Diagnostic threshold	Diagnosed	SD	SPC	CS	NICU	Jaund	PE	IOL
No Treatment	0	49	67	759	345	219	146	974
NICE 2015	629	41	56	739	326	210	123	1,004
WHO 2013	912	39	54	731	321	207	117	1,016

285

286 **Table 6:** Deterministic analysis for the HAPO (4 centres) population with NICE risk factors  
 287 (n=3,549)

Diagnostic threshold	Cost <sup>a</sup>	QALY <sup>a</sup>	Incremental cost	Incremental QALY	ICER
No Treatment	£0	0.00	n/a	n/a	n/a
NICE 2015	£546,349	26.78	£546,349	26.78	£23,073
WHO 2013	£778,993	34.35	£254,376	7.57	£37,669

288 a) Costs and QALYs are measured relative to a baseline of No Treatment

289

290 Table 5 indicates that there was a relatively small difference in clinical outcomes contrasting  
 291 NICE and WHO diagnostic criteria, despite there being a 45% increase in women diagnosed  
 292 with GDM. Using the WHO 2013 criteria, instead of the NICE 2015 criteria, an additional 142  
 293 women would have been diagnosed with GDM, and treated in order to prevent 1 case of  
 294 shoulder dystocia.

295

296 In the deterministic analysis the NICE 2015 diagnostic criteria would be considered cost-  
 297 effective at a cost-effectiveness threshold of £30,000 per QALY (Table 6).

298

299 The probabilistic sensitivity analysis reached a similar conclusion, with the NICE 2015  
 300 diagnostic threshold having the highest probability of being the most cost-effective treatment  
 301 and the highest NMB using a cost-effectiveness threshold of £30,000 per QALY (Table 7 and  
 302 Figure 2). The analysis also suggested that no diagnosis/no treatment might be considered the  
 303 most likely to be cost-effective when using a lower cost-effectiveness threshold of £20,000 per  
 304 QALY. The probability of no diagnosis/no treatment being cost-effective falls sharply in the  
 305 cost-effectiveness threshold range of £20,000 - £30,000 *per* QALY. As shown in the cost-  
 306 effectiveness acceptability curve in Figure 2, the WHO 2013 diagnostic threshold becomes

307 more cost-effective as the cost-effectiveness threshold increases. Nevertheless, this would have  
 308 to exceed £30,000 per QALY before becoming cost-effective, indicating that the further  
 309 reduction in adverse outcomes, are achieved at an unacceptably high opportunity cost. The  
 310 Supplementary Report plots the incremental cost and QALY outcomes of 2,000 simulations  
 311 from the probabilistic analysis on the cost-effectiveness plane (see Figure x1). Whilst most  
 312 points fall in the south-western quadrant, suggesting that WHO 2013 diagnostic criteria are  
 313 likely to lead to additional QALYs when compared with NICE 2015 criteria, all points show  
 314 that NICE 2015 criteria were associated with markedly lower costs.

315

316

317 **Table 7: Probabilistic sensitivity analysis for HAPO (4) in a population with NICE risk factors**

<b>Diagnostic threshold</b>	<b>NMB<sup>a</sup> CE threshold £30,000 per QALY</b>	<b>Probability cost- effective CE threshold £20,000 per QALY</b>	<b>Probability cost- effective CE threshold WTP = £30,000 per QALY</b>
No Treatment	£0	54.1%	21.0%
NICE 2015	£239,902	43.3%	51.5%
WHO 2013	£186,675	2.7%	27.6%

318 a) NMB is measured relative to a baseline of no treatment

319 Summaries of results for all of the model populations and more detailed results are provided in  
 320 the Supplementary Report.

321

322 Tables x16 and x17 in the Supplementary Report show that in both the HAPO (4) and Atlantic  
 323 DiP populations with NICE risk factors, the NICE diagnostic threshold is the most cost-  
 324 effective strategy at a cost-effectiveness threshold of £30,000 per QALY. The NICE 2015

1  
2  
3 325 diagnostic threshold has ICERs of less than £30,000 per QALY, and in the probabilistic  
4  
5 326 sensitivity analysis it has the highest net monetary benefit and the highest probability of being  
6  
7 327 the most cost-effective. For HAPO (4) the results are similar if baseline risks are estimated  
8  
9 328 using logistic regression based on all covariates or a logistic regression just using plasma  
10  
11 329 glucose levels.

12  
13  
14 330

15  
16 331 The results also suggested that universal screening would not be cost-effective as, when  
17  
18 332 compared to risk factor screening (as recommended in NICE guidelines), the additional women  
19  
20 333 included in such an approach would be those without risk factors and the model demonstrates  
21  
22 334 that the ICERs for diagnosis and treatment are all well in excess of £30,000 per QALY;  
23  
24 335 markedly so when using WHO 2013 diagnostic thresholds. These conclusions were supported  
25  
26 336 by an analysis of the Norwich dataset (see Supplementary Report).

27  
28  
29 337

30  
31  
32 338 It was not possible to stratify the Norwich dataset according to risk factors, and therefore the  
33  
34 339 ICERs presented relate to a comparison between no screening/treatment and universal screening  
35  
36 340 and treatment. However, the results were consistent with those for HAPO (4) and Atlantic DiP.  
37  
38 341 First, they showed that universal screening was not cost-effective even when compared to an  
39  
40 342 alternative of no screening/no treatment. Second, the ICERs for the whole population were a  
41  
42 343 weighted average of the populations with and without risk factors. The ICER for the population  
43  
44 344 without risk factors would be higher than the ICER for the entire population, which was only  
45  
46 345 marginally below the £30,000 per QALY threshold.

47  
48  
49 346

50  
51 347 *Deterministic sensitivity analysis*

52  
53 348 As part of a sensitivity analysis the deterministic models were re-run using the logistic  
54  
55 349 regression models without backward elimination of glucose variables with non-significant  
56  
57  
58  
59  
60

1  
2  
3 350 coefficients, and these analyses are discussed in the Supplementary Report with the results  
4  
5 351 summarised in Table x30.  
6

7 352  
8

9  
10 353 **Discussion**

11 354 In the NICE guideline analysis, 14 alternative diagnostic thresholds were compared and there  
12  
13  
14 355 was no single optimal diagnostic threshold which clearly emerged<sup>6</sup>. This is not surprising given  
15  
16 356 the small differences in patient outcomes between them. In that analysis the previous WHO  
17  
18 357 1999 criteria emerged as a relatively cost-effective strategy. However, the Guideline  
19  
20  
21 358 Development Group rejected a fasting threshold of 7.0 mmol/L as there was a wide clinical  
22  
23 359 consensus that this was too high, as 6.1-7.0 mmol/L is diagnostic of impaired fasting glycaemia  
24  
25 360 in the non-pregnant population. Intervention studies had used a lower fasting threshold than 7.0  
26  
27 361 mmol/L as a basis for inclusion, and therefore made a case for intervention at lower levels.  
28  
29 362 Based upon detailed cost effectiveness analysis of all the options, the Guideline Development  
30  
31 363 Group ultimately decided on recommending a fasting plasma glucose of 5.6 mmol/L and a 2  
32  
33 364 hour plasma glucose of 7.8 mmol/L. In this paper, we have restricted our analysis of cost-  
34  
35 365 effectiveness to the WHO 2013 and NICE 2015 criteria (with a no screening/treatment baseline  
36  
37 366 also included) as these two recommendations have the most clinical currency at present.  
38  
39

40 367  
41

42  
43 368 All of the analyses presented in this paper suggest that, in a population with NICE risk factors,  
44  
45 369 the NICE 2015 diagnostic criteria for GDM could be considered cost-effective relative to no  
46  
47 370 screening/no treatment and to WHO 2013 diagnostic thresholds when using a cost-effectiveness  
48  
49 371 threshold of £30,000 per QALY. The analyses also show that no screening/no treatment is cost-  
50  
51 372 effective in populations without NICE risk factors, suggesting that universal screening does not  
52  
53 373 represent value for money, at least in a UK setting. The slight differences in the costs and  
54  
55 374 QALYs in the current analysis compared to the original NICE guideline are due to a  
56  
57  
58  
59  
60

1  
2  
3 375 combination of using updated cost data and a modification of the statistical analysis utilising the  
4  
5 376 Cholesky decomposition (see methods).  
6

7 377  
8

9 378 One of the limitations of our analysis was that the 2-hour threshold was restricted to the  
10  
11 379 historical WHO 1999 2-hour definition of 7.8mmol/l, or the new WHO 2013 criteria of 8.5  
12  
13 380 mmol/l. It is conceivable that a 2-hour threshold lying between these values might outperform  
14  
15 381 both. Our greater focus, though was on the optimal fasting level as this is where the greatest  
16  
17 382 controversy lies with respect to potentially missed treatment opportunities.  
18  
19

20 383  
21

22  
23 384 As noted by the proponents of WHO 2013 diagnostic criteria for GDM, using a lower fasting  
24  
25 385 plasma glucose threshold would by definition detect more cases. Furthermore, because we  
26  
27 386 assumed in the model that the relative treatment effect would be the same in additionally  
28  
29 387 diagnosed cases, it follows that such a threshold could potentially yield the lowest number of  
30  
31 388 adverse outcomes and the greatest QALY gain. However, our analysis suggests that the  
32  
33 389 relatively small additional gains are not justified by the substantially higher costs that such  
34  
35 390 lower thresholds would require.  
36  
37

38 391  
39

40 392 A key driver of our results were the logistic regression models which were used to predict  
41  
42 393 baseline risk. For the outcomes included in this study these regression models suggested that the  
43  
44 394 2-hour plasma glucose was a much more important predictor of adverse outcomes than the  
45  
46 395 fasting plasma glucose, something we were unaware of when selecting the model's clinical  
47  
48 396 outcomes. For the regression models fitted to predict baseline risk in the HAPO (4) dataset with  
49  
50 397 covariates and backward elimination of the OGTT plasma glucose variables (Model 1 base case  
51  
52 398 analysis regressions in Supplementary Tables x2 to x7), the Hosmer-Lemeshow Goodness of  
53  
54 399 Fit Test did not indicate evidence of poor fit ( $p > 0.05$ ). However, there was evidence of poor fit  
55  
56  
57  
58  
59  
60

1  
2  
3 400 (p < 0.05) for the regression models of caesarean section and NICU admission where the  
4  
5 401 prediction was based only on OGTT plasma glucose results (Model 2 base case analysis  
6  
7 402 regressions in Supplementary Tables x2 to x7). Nevertheless, as indicated in Supplementary  
8  
9 403 Table x16 and x17, the choice of prediction model did not have a large bearing on cost-  
10  
11 404 effectiveness.

12  
13 405  
14  
15 406 We consider that our analysis which builds on previous modelling<sup>6, 14</sup> is, together with another  
16  
17 407 recently published UK analysis<sup>10</sup>, one of the most comprehensive assessments of the cost-  
18  
19 408 effectiveness of diagnostic thresholds for GDM yet undertaken, and will hopefully contribute to  
20  
21 409 the WHO's expectation "that a substantial body of new data will emerge in the near future,  
22  
23 410 providing currently scarce health and economic evaluation of the recommended criteria applied  
24  
25 411 to various populations and with different approaches (universal screening, screening only  
26  
27 412 women at high risk, diagnostic testing only)".<sup>4</sup>

28  
29 413  
30  
31 414 A number of commentators<sup>17, 18</sup> have recently advocated universal screening for GDM. The  
32  
33 415 essence of the argument is based upon the number of cases of GDM that would be missed with  
34  
35 416 selective screening, and the subsequent reduced opportunity to prevent a serious perinatal  
36  
37 417 outcome. Of course it is true that universal screening will detect more cases, although the  
38  
39 418 absolute numbers will depend upon the thresholds used to define GDM. Table 5 shows that  
40  
41 419 many more women would need to be diagnosed in order to prevent a single adverse outcome.  
42  
43 420 However, in the context of finite health care resources, it must be accepted that it may be cost-  
44  
45 421 effective to miss some cases. Epidemiological measures such as number needed to treat (or  
46  
47 422 number needed to screen in this case) implicitly recognise that a goal of health care systems  
48  
49 423 cannot be to maximize health gain without any consideration of cost. Identifying missed cases  
50  
51 424 carries an opportunity cost and it may be that those resources would achieve greater benefit if  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 425 employed elsewhere in the health care system. If a population is divided into those with risk  
4  
5 426 factors and those without risk factors, then the prevalence of GDM must be lower in the group  
6  
7 427 without risk factors (and the number needed to screen higher) with concomitantly lower cost-  
8  
9 428 effectiveness. However, the comparative cost-effectiveness of screening in those with and  
10  
11 429 without risk factors is not only affected by the respective prevalence in the two groups, but also  
12  
13 430 differences in severity. In those diagnosed with GDM and who had risk factors there were, as  
14  
15 431 anticipated, greater levels of hyperglycaemia than in those without risk factors. As shown in  
16  
17 432 Table x31 in the Supplementary Report, ‘true positives’ or identified cases (risk factor present  
18  
19 433 and GDM) had higher plasma glucose values than ‘false negatives’ or missed cases (risk factors  
20  
21 434 absent and GDM) when defining GDM positives according to WHO 2013 diagnostic  
22  
23 435 thresholds.  
24  
25  
26  
27  
28

29 436  
30 437 We would therefore expect the women with risk factors and GDM to be at greater risk of  
31  
32 438 adverse outcomes than the women with GDM without risk factors as a result of their higher  
33  
34 439 plasma glucose levels. So the “cases” missed with selective screening would have, on average,  
35  
36 440 fewer adverse outcomes than in “cases” in a population with risk factors. So the ICER would be  
37  
38 441 greater in the population without risk factors because prevalence is lower and cases have fewer  
39  
40 442 adverse outcomes.  
41  
42  
43

44 443  
45 444 Our analysis, by splitting the HAPO (4) and Atlantic DiP datasets into those with and without  
46  
47 445 risk factors, was able to evaluate the cost-effectiveness of moving from risk factor screening to  
48  
49 446 universal screening. Whilst diagnosis in populations with risk factors was shown to be cost-  
50  
51 447 effective at a threshold of £30,000 per QALY, it was never cost-effective to diagnose and treat  
52  
53 448 in those without risk factors. Table 4 indicates the large differences that exist in prevalence  
54  
55 449 between the populations with and without risk factors. Our analysis suggests that the cost-  
56  
57  
58  
59  
60



1  
2  
3 450 effectiveness threshold would have to substantially exceed currently accepted UK norms for  
4  
5 451 universal screening to be considered cost-effective. Although the NICE risk factor approach  
6  
7 452 could not be replicated exactly, we felt that the approximation used was acceptable, as the only  
8  
9 453 women who would be omitted from the model risk factor population were multiparous and  
10  
11 454 would have had a large baby previously and/or a past history of GDM. This approximation  
12  
13 455 would over-estimate slightly the benefits of universal screening, as the baseline risk in a group  
14  
15 456 designated as being without NICE risk factors present would be over-stated.  
16  
17  
18  
19

457

20  
21 458 A previous study<sup>8</sup> from Spain using WHO 2013 diagnostic criteria suggested cost effectiveness  
22  
23 459 compared with a two-step protocol using the Carpenter – Coustan thresholds. However, this  
24  
25 460 was largely based upon estimates of reduction of caesarean section rates of 50% which we find  
26  
27 461 implausible based upon changes in diagnostic criteria alone, noting that ACHOIS and Landon et  
28  
29 462 al. found only a 4% and 21% reduction in caesarean section respectively as a result of treating  
30  
31 463 gestational diabetes. The Spanish study did not consider other alternative thresholds, and was a  
32  
33 464 retrospective, before and after analysis which has been criticised by the Cochrane Collaboration  
34  
35 465 as it does not control for possible changes in important variables, such as clinical management,  
36  
37 466 over time.<sup>19</sup>  
38  
39  
40

467

41  
42  
43 468 A recently published UK Health Technology Assessment (HTA)<sup>10</sup> suggested that the  
44  
45 469 identification of gestational diabetes for treatment is not cost-effective, in which case finding a  
46  
47 470 cost-effective threshold becomes somewhat redundant. Although the HTA followed a similar  
48  
49 471 approach to our analysis there were some differences which could explain the different  
50  
51 472 conclusions. In our analysis, jaundice was included as an outcome and the relative treatment  
52  
53 473 effect would have tended to lower the incremental costs of intervention as a result of reduced  
54  
55 474 rates of phototherapy. This was not included as an outcome in the HTA. Instrumental delivery  
56  
57  
58  
59  
60

1  
2  
3 475 was included as an outcome in the HTA but not in our analysis. While instrumental delivery  
4  
5 476 rates could in theory be increased by treatment, as there will be more vaginal births, this could  
6  
7 477 be counteracted by those mothers not treated delivering larger babies vaginally requiring  
8  
9 478 assistance; this would be in accord with the HTA meta-analysis which failed to demonstrate a  
10  
11 479 treatment effect on instrumental delivery rates. In addition the HTA reported smaller treatment  
12  
13 480 effects for NICU admission and pre-eclampsia. Unlike our analysis, the HTA did not assume  
14  
15 481 100% uptake of the OGTT and that would have led to a smaller estimate of treatment benefit.  
16  
17 482 We made the simplifying assumption of 100% OGTT uptake because the view of the Guideline  
18  
19 483 Development Group was that uptake would be much higher in a group screened on the basis of  
20  
21 484 risk factors. The HTA also assumed higher uptake of OGTT with risk factor screening  
22  
23 485 compared to universal screening but less than 100%. As we do not find universal screening to  
24  
25 486 be cost-effective then relaxing the assumption of 100% OGTT uptake would only re-inforce  
26  
27 487 that result. We investigated the impact of relaxing the assumption of 100% uptake in groups  
28  
29 488 screened on the basis of risk factors but found that it made a negligible difference to the results.  
30  
31 489 For example, in a deterministic analysis of the HAPO (4) with NICE risk factors, the ICER of  
32  
33 490 NICE 2015 relative to no screening/no treatment only increased from £20,400 per QALY with  
34  
35 491 100% OGTT uptake to £20,585 per QALY with 90% test uptake.  
36  
37  
38 492  
39  
40 493 However, the differences between this analysis and the HTA should not be over-stated. Neither  
41  
42 494 analysis suggests that universal screening for GDM is cost-effective and, like the HTA, our  
43  
44 495 results would not support the identification and treatment of gestational diabetes if a cost-  
45  
46 496 effectiveness threshold of £20,000 per QALY was used. However, it was the view of the  
47  
48 497 Guideline Development Group that the clinical benefit of identifying and treating women with  
49  
50 498 GDM is widely practiced, and that a no identification/no treat policy would not be acceptable to  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 499 patients or health care providers. As such, the Group felt that the higher cost threshold of  
4  
5 500 £30,000 was justified.  
6

7 501

9 502 Our model has a number of limitations particularly with respect to the valuation of health  
10  
11 503 outcomes. We did not include large for gestational age as an outcome because it was felt that  
12  
13 504 shoulder dystocia was the relevant immediate complication of interest, and that possible long  
14  
15 505 term metabolic consequences for the offspring were hard to quantify and therefore difficult to  
16  
17 506 incorporate within the model. As previously noted, the QALY loss from a serious perinatal  
18  
19 507 complication used in this analysis is likely to be overstated because of the relatively large  
20  
21 508 weight given to death based on the intervention studies.<sup>14</sup> HAPO failed to show an association  
22  
23 509 between perinatal mortality and plasma glucose levels, which may mean that perinatal mortality  
24  
25 510 reduction is less amenable to reduction by treatment than other serious perinatal complications.  
26  
27 511 In this respect the cost-effectiveness of diagnosing and treating GDM may be over-stated. On  
28  
29 512 the other hand, the model does not take account of any potential long term effects on the  
30  
31 513 offspring (e.g. adiposity and the likelihood of subsequent pathology) as these effects are  
32  
33 514 difficult to quantify but may under-estimate the QALY gain from diagnosis and treatment. A  
34  
35 515 US study<sup>20</sup> considered the potential long-term benefits to the mother whereby a diagnosis of  
36  
37 516 GDM averts or delays onset of Type 2 diabetes mellitus, but this was not incorporated into our  
38  
39 517 model as we did not consider that the relationship was sufficiently well established at this time.  
40  
41 518 However, to the extent that such a relationship does exist our model would also underestimate  
42  
43 519 the QALY gain from a diagnosis of GDM. A recent review has, however, questioned the  
44  
45 520 association between maternal glycaemia and subsequent cardio-metabolic outcomes in offspring  
46  
47 521 in humans<sup>21</sup> and a recent follow-up study failed to find evidence of a reduction in childhood  
48  
49 522 obesity or metabolic dysfunction at five years in the offspring of women treated for mild  
50  
51 523 gestational diabetes in the study of Landon et al<sup>12, 22</sup>.

524

525 Despite these caveats, we feel our analysis represents a robust analysis of the cost-effectiveness  
526 of the NICE versus the WHO 2013 diagnostic thresholds for GDM based upon our current  
527 understanding of the impact of intervention in women with GDM in the UK population. We  
528 acknowledge completely that this analysis cannot be the final word on the subject, and that  
529 further health economic evaluation is required to either corroborate our findings or to challenge  
530 them. Nevertheless, our analysis represents a constructive and evidence based contribution to  
531 establishing cost effective diagnostic thresholds for GDM and will hopefully lead to more  
532 research to clarify this important but vexed area of clinical diagnosis.

533

### 534 **Conclusions**

535 The results presented in this analysis, based on a UK setting, do not suggest that the diagnostic  
536 thresholds for GDM adopted by the WHO are cost-effective. On the other hand they do provide  
537 some support for the cost-effectiveness of the diagnostic criteria adopted by NICE when  
538 compared to either no screening/treatment and to WHO 2013 diagnostic criteria. Furthermore,  
539 according to this analysis, universal screening would seem to offer poor value for money and  
540 does not appear cost-effective compared to the current NICE guidance of targeting high risk  
541 women.

542

1  
2  
3 543 **Acknowledgements**  
4

5 544 We are grateful to Professor DR McCance and Professor HD McIntyre for allowing us to use  
6  
7 545 their local datasets from the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) trial and  
8  
9 546 to Professor F Dunne for allowing us to use her Atlantic DiP dataset.

10  
11 547 We are also grateful to Professor David James who provided clinical support during the  
12  
13 548 development of the updated NICE guideline on Diabetes in Pregnancy.  
14

15  
16 549

17  
18 550 **Competing interests**  
19

20 551 All authors have completed the ICMJE uniform disclosure form at

21  
22 552 [http://www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) and declare:  
23

24  
25 553

26  
27 554 **Funding:** Some of this work was undertaken by the now defunct National Collaborating Centre  
28  
29 555 for Women's and Children's Health (subsumed within the National Guideline Alliance from 1st  
30  
31 556 April 2016), which received funding from NICE. The views expressed in this publication are  
32  
33 557 those of the authors and not necessarily those of the institute. Revisions to the guideline model  
34  
35 558 after the guideline was published and drafting of the manuscript was done in the author's own  
36  
37 559 time and was not funded.  
38

39  
40 560

41  
42 561 National Institute for Health and Care Excellence (2015). Diabetes in pregnancy: management  
43  
44 562 from preconception to the postnatal period. Available from

45  
46 563 <https://www.nice.org.uk/guidance/ng3>  
47

48  
49 564 PBJ and SBR are employees of the National Guideline Alliance (part of the RCOG), which  
50  
51 565 receives its funding from NICE.  
52

53  
54 566 MJAM, KS, AD and RWB received travel expenses from NICE for attending clinical guideline  
55  
56 567 development meetings  
57  
58  
59  
60

1  
2  
3 568 **Author contribution**  
4

5 569 Paul Jacklin designed and developed the health economic model, undertook the health  
6  
7 570 economic analysis, wrote the first draft of the manuscript and incorporated edits from co-  
8  
9  
10 571 authors. Mike Maresh provided clinical input into the design of the health economic model;  
11  
12 572 read, commented and edited various draft of the manuscripts. Katharine Stanley supplied the  
13  
14 573 Norwich dataset, provided clinical input into the design of the health economic model; read,  
15  
16 574 commented and edited various draft of the manuscripts. Anne Dornhorst provided clinical input  
17  
18 575 into the design of the health economic model; read, commented and edited various draft of the  
19  
20 576 manuscripts. Chris Patterson provided statistical advice, undertook statistical analysis of the  
21  
22 577 HAPO dataset; read, commented and edited various drafts of the manuscript. Shona Burman-  
23  
24 578 Roy reviewed the clinical literature, contributed to discussions of model design; read,  
25  
26 579 commented and edited various drafts of the manuscript. Rudy Bilous chaired the NICE  
27  
28 580 guideline, provided clinical input into the design of the health economic model; read,  
29  
30 581 commented and edited various draft of the manuscripts.  
31  
32

33  
34 582  
35

36 583 **Transparency declaration**  
37

38 584 The lead author, Paul Jacklin, affirms that this manuscript is an honest, accurate, and  
39  
40 585 transparent account of the study being reported; that no important aspects of the study have  
41  
42 586 been omitted; and that any discrepancies from the study as planned (and, if relevant, registered)  
43  
44 587 have been explained.  
45  
46  
47

48 588  
49

50 589 **Exclusive License**  
51

52 590 "I Paul Jacklin The Corresponding Author of this article contained within the original  
53  
54 591 manuscript which includes any diagrams & photographs within and any related or stand alone  
55  
56 592 film submitted (the Contribution") has the right to grant on behalf of all authors and does grant  
57  
58  
59  
60

1  
2  
3 593 on behalf of all authors, a licence to the BMJ Publishing Group Ltd and its licencees, to permit  
4  
5 594 this Contribution (if accepted) to be published in the BMJ and any other BMJ Group products  
6  
7 595 and to exploit all subsidiary rights, as set out in our licence set out at:  
8  
9 596 [http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/copyright-  
11 open-access-and-permission-reuse.](http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/copyright-<br/>10 open-access-and-permission-reuse)”  
12  
13

14 598

15  
16 599 **Data sharing Statement**

17  
18 600 Potential for data sharing (the health economic model) can be discussed with study  
19  
20 601 investigators.  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

602 **References**

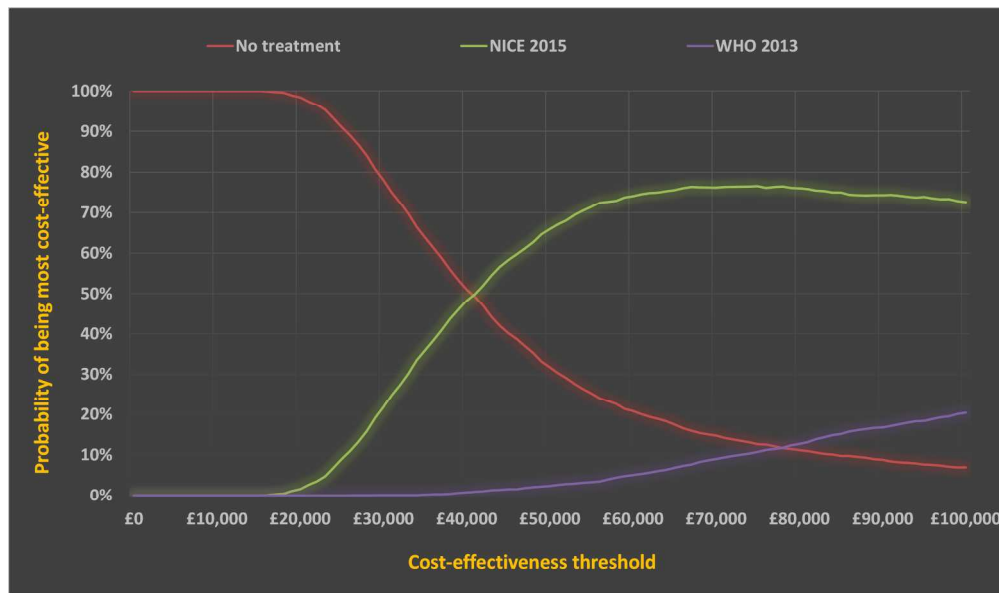
- 603 1. Metzger BE, Lowe LP, Dyer AR, et al. Hyperglycemia and adverse pregnancy outcomes. *N Engl J*  
604 *Med* 2008;358:1991-2002.
- 605 2. Farrar D, Simmonds M, Bryant M, et al. Hyperglycaemia and risk of adverse perinatal  
606 outcomes: systematic review and meta-analysis. *BMJ*. 2016;354:i4694. doi: 10.1136/bmj.i4694.
- 607 3. Metzger BE, Gabbe SG, Persson B, et al. International Association of Diabetes and Pregnancy  
608 Study Groups recommendations on the diagnosis and classification of hyperglycemia in  
609 pregnancy. *Diabetes Care* 2010;33:676-82.
- 610 4. WHO Health organisation, 2013. Diagnostic criteria and classification of hyperglycaemia first  
611 detected in pregnancy WHO/NMH/MND/13.2  
612 [http://apps.who.int/iris/bitstream/10665/85975/1/WHO\\_NMH\\_MND\\_13.2\\_eng.pdf](http://apps.who.int/iris/bitstream/10665/85975/1/WHO_NMH_MND_13.2_eng.pdf).
- 613 5. American College of Obstetricians and Gynecologists. *Practice Bulletin 137: Mellitus. Obstet*  
614 *Gynecol* 2013; 122: 406-16
- 615 6. National Institute for Health and Care Excellence (NICE) (2015) Diabetes in pregnancy:  
616 management of diabetes and its complications from preconception to the postnatal period.  
617 Clinical guideline NG3 (2015). Available from  
618 [www.nice.org.uk/guidance/ng3/resources/diabetes-in-pregnancy-management-of-diabetes-](http://www.nice.org.uk/guidance/ng3/resources/diabetes-in-pregnancy-management-of-diabetes-and-itscomplications-from-preconception-to-the-postnatal-period-51038446021)  
619 [and-itscomplications-from-preconception-to-the-postnatal-period-51038446021](http://www.nice.org.uk/guidance/ng3/resources/diabetes-in-pregnancy-management-of-diabetes-and-itscomplications-from-preconception-to-the-postnatal-period-51038446021), accessed  
620 February 2016
- 621 7. Meek CL, Lewis HB, Patient C, Murphy HR, Simmons D. Diagnosis of gestational diabetes: falling  
622 through the net. *Diabetologia* 2015;Sep;58(9):2003-12
- 623 8. Duran A, Sáenz S, Torrejón MJ et al. Introduction of IADPSG criteria for the screening and  
624 diagnosis of gestational diabetes mellitus results in improved pregnancy outcomes at a lower  
625 cost in a large cohort of pregnant women: the St. Carlos Gestational Diabetes Study. *Diabetes*  
626 *Care* 2014;37(9):2442–2450. doi: 10.2337/dc14-0179.



- 1  
2  
3 627 9. Herman WH. Insights offered by economic analyses. *Diabetes Care*. 2014 Sep;37(9):2424-6. doi:  
4 10.2337/dc14-1232.  
5 628  
6  
7 629 10. Farrar D, Simmonds M, Griffin S et al. The identification and treatment of women with  
8 hyperglycaemia in pregnancy: an analysis of individual participant data, systematic reviews,  
9 630 meta-analyses and an economic evaluation. *Health Technol Assess*. 2016 Nov;20(86):1-348.  
10 631  
11 632 11. Crowther CA, Hiller JE, Moss JR, McPhee AJ, Jeffries WS, Robinson JS. Effect of treatment of  
12 gestational diabetes mellitus on pregnancy outcomes. *N Engl J Med* 2005;352:2477-86.  
13 633  
14 634 12. Landon MB, Spong CY, Thom E, et al. A multicenter, randomized trial of treatment for mild  
15 gestational diabetes. *N Engl J Med* 2009;361:1339-48  
16 635  
17 636 13. Horvath K, Koch K, Jeitler K et al. Effects of treatment in women with gestational diabetes  
18 mellitus: systematic review and meta-analysis. *BMJ (Clin Res Ed)* 2010;340:c1395  
19 637  
20 638 14. Round, J.A., Jacklin, P., Fraser, R.B., Hughes, R.G., Muggleston, M.A., Holt, R.I. Screening for  
21 gestational diabetes mellitus: cost-utility of different screening strategies based on a woman's  
22 individual risk of disease, *Diabetologia* 2011,54(2), 256-263. doi: 10.1007/s00125-010-1881-y  
23 639  
24 640 15. National Institute for Health and Care Excellence. Developing NICE guidelines: the manual.  
25 October 2014 ([https://www.nice.org.uk/media/default/about/what-we-do/our-](https://www.nice.org.uk/media/default/about/what-we-do/our-programmes/developing-nice-guidelines-the-manual.pdf)  
26 [programmes/developing-nice-guidelines-the-manual.pdf](https://www.nice.org.uk/media/default/about/what-we-do/our-programmes/developing-nice-guidelines-the-manual.pdf))  
27 641  
28 642  
29 643  
30 644 16. Briggs A, Claxton K, Sculpher M. Decision Modelling for Health Economic Evaluation. Oxford:  
31 Oxford University Press; 2006  
32 645  
33 646 17. Avalos GE, Owens LA, Dunne F. Applying Current Screening Tools for Gestational Diabetes  
34 Mellitus to a European Population: Is It Time for Change? *Diabetes Care*. 2013 Oct;36(10):3040-  
35 4. doi: 10.2337/dc12-2669. Epub 2013 Jun 11.  
36 647  
37 648  
38 649 18. Simmons D, Moses RG. Gestational Diabetes Mellitus: To Screen or Not to Screen? Is this really  
39 still a question? *Diabetes Care*. 2013 Oct;36(10):2877-2878  
40 650  
41 651 19. Armstrong R, Waters E, Doyle J (editors). Chapter 21: Reviews in health promotion and public  
42 health. In Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of*  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 653 Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011.  
4  
5 654 Available from [www.cochrane-handbook.org](http://www.cochrane-handbook.org). Accessed June 2015  
6  
7 655 20. Werner EF, Pettker CM, Zucерwise et al. Screening for gestational diabetes mellitus: are the  
8  
9 656 criteria proposed by the international association of the Diabetes and Pregnancy Study Groups  
10  
11 657 cost-effective? *Diabetes Care*. 2012 Mar;35(3):529-35. doi: 10.2337/dc11-1643.  
12  
13  
14 658 21. Donovan LE, Cundy T. Does exposure to hyperglycaemia in utero increase the risk of obesity  
15  
16 659 and diabetes in the offspring? A critical reappraisal. *Diabetic Medicine*. 2015 Mar;32(3):295-  
17  
18 660 304. doi: 10.1111/dme.12625. Epub 2014 Dec 17.  
19  
20 661 22. Landon MB, Rice MM, Varner MW et al. Mild gestational diabetes mellitus and long-term child  
21  
22 662 health. *Diabetes Care*. 2015 Mar;38(3):445-52. doi: 10.2337/dc14-2159. Epub 2014 Nov 20.  
23  
24  
25 663  
26  
27  
28 664  
29  
30  
31 665  
32  
33  
34 666  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



Cost-effectiveness acceptability curve indicating the probability of a threshold or a no diagnosis/no treatment strategy being cost-effective at different cost-effectiveness thresholds for the HAPO (4) centres population with risk factors

267x157mm (300 x 300 DPI)

Review only

## 1 Supplementary Report

2 This supplementary document provides further details about model parameter estimates and model  
3 results.

4 **Table x1.** Ethnicity of women in patient datasets and of UK

Ethnic group	HAPO (4) centres	Atlantic DiP	Norfolk <sup>a</sup>	UK <sup>b</sup>
White	79%	93%	96.5%	87%
Black	2%	2%	0.5%	3%
Asian	13%	4%	1.6%	7%
Other	6%	1%	1.6%	3%

5 (a) Our Norwich dataset did not include data on ethnicity and the values presented here are census data for Norfolk  
6 (Estimated from 2011 Census: Ethnic group, local authorities in the United Kingdom. Office for National Statistics. 11  
7 October 2013)

8 (b) Included for comparative purposes (2011 Census: Ethnic group, local authorities in the United Kingdom. Office for National  
9 Statistics. 11 October 2013)

### 11 Multivariable prediction models to estimate baseline risk

12 Model 1 includes the covariates used in the original analysis of the HAPO data whilst Model 2 is  
13 restricted to plasma glucose variables (Tables x2 to Tables x7). In the base case analysis, backward  
14 elimination of plasma glucose variables with non-significant coefficients from the prediction models  
15 was undertaken. A sensitivity analysis was undertaken retaining all plasma glucose variables. For each  
16 model Hosmer-Lemeshow goodness-of-fit statistics are presented and predicted probabilities are used  
17 to derive the area under the receiver-operating characteristic (ROC) curve as an indicator of the  
18 model's discriminatory ability.

20 **Table x2.** Logistic regression models to predict neonatal shoulder dystocia

Variable	Co-efficient b (Standard error (SE(b)))			
	Model 1 (all covariates)		Model 2 (blood glucose covariates)	
	Base case analysis	Sensitivity analysis	Base case analysis	Sensitivity analysis
Centre (Manchester v Belfast)	1.151 (0.423)	1.151 (0.424)	-	-
(Brisbane v Belfast)	0.505 (0.489)	0.562 (0.491)	-	-
(Newcastle v Belfast)	1.604 (0.472)	1.622 (0.472)	-	-
Age at OGTT (yr)	-0.023 (0.024)	-0.022 (0.024)	-	-
BMI at OGTT (kg/m <sup>2</sup> )	-0.006 (0.023)	-0.011 (0.024)	-	-
Smoker (Yes v No)	-0.480 (0.409)	-0.477 (0.409)	-	-
Drinker (Yes v No)	-0.101 (0.317)	-0.107 (0.317)	-	-
Family history DM (Yes v No)	-0.006 (0.184)	-0.008 (0.187)	-	-
Gestational age at OGTT (wk)	-0.111 (0.091)	-0.114 (0.092)	-	-
Neonate gender (F v M)	-1.321 (0.292)	-1.316 (0.292)	-	-
Family history HBP (Yes v No) <sup>a</sup>	-	-	-	-
Maternal UTI (Yes v No) <sup>a</sup>	-	-	-	-
Mean Blood Pressure (mmHg)	-0.006 (0.015)	-0.007 (0.015)	-	-
Hospital admission before delivery (Yes v No)	0.173 (0.266)	0.175 (0.267)	-	-
Parity (1 v 0)	-0.118 (0.420)	-0.108 (0.420)	-	-
(2+ v 0)	0.456 (0.412)	0.469 (0.414)	-	-
(Unknown v 0)	-0.026 (0.399)	-0.013 (0.399)	-	-
Fasting blood glucose <sup>b</sup>	-	0.151 (0.112)	-	0.166 (0.110)
1-hr blood glucose <sup>b</sup>	-	-0.138 (0.165)	-	-0.152 (0.163)
2-hr blood glucose <sup>b</sup>	0.223 (0.100)	0.222 (0.152)	0.267 (0.097)	0.265 (0.151)
Constant	0.925 (3.025)	1.139 (3.508)	-4.467 (0.122)	-4.475 (0.122)
Hosmer-Lemeshow goodness- of-fit test	$\chi^2 = 2.94,$ df=8; P=0.94	$\chi^2 = 6.36,$ df=8; P=0.61	$\chi^2 = 4.99,$ df=8; P=0.76	$\chi^2 = 11.51,$ df=8; P=0.18
Area under the ROC curve (95% CI)	0.75 (0.70, 0.80)	0.76 (0.70, 0.81)	0.58 (0.51, 0.65)	0.60 (0.53, 0.67)

21 (a) Omitted from HAPO model for shoulder dystocia

22 (b) Blood glucose values are 'standardised' – so the exponential of the coefficient represents the odds ratio for shoulder  
23 dystocia arising from a 1 Standard Deviation (SD) increase in plasma glucose (fasting plasma glucose mean (SD) =  
24 4.60(0.47); 1-hour plasma glucose mean (SD) = 7.57(1.83); 2-hour plasma glucose mean (SD) = 6.21(1.44)

27

28 **Table x3.** Logistic regression models to predict caesarean section

Variable	Co-efficient b (Standard error (SE(b)))			
	Model 1 (all covariates)		Model 2 (blood glucose covariates)	
	Base case analysis	Sensitivity analysis	Base case analysis	Sensitivity analysis
Centre (Manchester v Belfast)	-0.494 (0.092)	-0.495 (0.092)	-	-
(Brisbane v Belfast)	-0.099 (0.098)	-0.114 (0.100)	-	-
(Newcastle v Belfast)	-0.681 (0.140)	-0.692 (0.141)	-	-
Age at OGTT (yr)	0.034 (0.007)	0.034 (0.007)	-	-
BMI at OGTT (kg/m <sup>2</sup> )	0.039 (0.007)	0.039 (0.007)	-	-
Smoker (Yes v No)	-0.304 (0.106)	-0.292 (0.106)	-	-
Drinker (Yes v No)	-0.028 (0.087)	-0.025 (0.087)	-	-
Family history DM (Yes v No)	0.050 (0.057)	0.052 (0.057)	-	-
Gestational age at OGTT (wk)	0.004 (0.029)	0.004 (0.029)	-	-
Neonate gender (F v M)	-0.205 (0.071)	-0.205 (0.071)	-	-
Family history HBP (Yes v No) <sup>a</sup>	-	-	-	-
Maternal UTI (Yes v No) <sup>a</sup>	-	-	-	-
Mean Blood Pressure (mmHg)	0.003 (0.004)	0.003 (0.004)	-	-
Hospital admission before delivery (Yes v No)	0.514 (0.079)	0.510 (0.079)	-	-
Parity (1 v 0) <sup>a</sup>	-	-	-	-
(2+ v 0) <sup>a</sup>	-	-	-	-
(Unknown v 0) <sup>a</sup>	-	-	-	-
Fasting blood glucose <sup>b</sup>	-	-0.009 (0.044)	-	0.053 (0.040)
1-hr blood glucose <sup>b</sup>	0.144 (0.037)	0.101 (0.051)	0.138 (0.046)	0.119 (0.048)
2-hr blood glucose <sup>b</sup>	-	0.071 (0.048)	0.123 (0.046)	0.113 (0.046)
Constant	-3.518 (0.947)	-3.509 (0.950)	-1.435 (0.035)	-1.433 (0.035)
Hosmer-Lemeshow goodness- of-fit test	$\chi^2 = 1.88,$ df=8; P=0.99	$\chi^2 = 5.11,$ df=8; P=0.75	$\chi^2 = 16.56,$ df=8; P=0.04	$\chi^2 = 17.66,$ df=8; P=0.02
Area under the ROC curve (95% CI)	0.65 (0.63, 0.66)	0.65 (0.63, 0.66)	0.58 (0.56, 0.60)	0.58 (0.57, 0.60)

29 (a) Omitted from HAPO model for caesarean section

30 (b) Blood glucose values are 'standardised' – so the exponential of the coefficient represents the odds ratio for caesarean  
31 section arising from a 1 Standard Deviation (SD) increase in plasma glucose (fasting plasma glucose mean (SD) =  
32 4.60(0.47); 1-hour plasma glucose mean (SD) = 7.57(1.83); 2-hour plasma glucose mean (SD) = 6.21(1.44)

33

34

35

36 **Table x4.** Logistic regression models to predict neonatal intensive care unit admissions

Variable	Co-efficient b (Standard error (SE(b)))			
	Model 1 (all covariates)		Model 2 (blood glucose covariates)	
	Base case analysis	Sensitivity analysis	Base case analysis	Sensitivity analysis
Centre (Manchester v Belfast)	0.894 (0.159)	0.889 (0.159)	-	-
(Brisbane v Belfast)	1.393 (0.161)	1.400 (0.163)	-	-
(Newcastle v Belfast)	1.153 (0.190)	1.163 (0.191)	-	-
Age at OGTT (yr)	0.013 (0.009)	0.012 (0.009)	-	-
BMI at OGTT (kg/m <sup>2</sup> )	0.025 (0.009)	0.024 (0.009)	-	-
Smoker (Yes v No)	0.209 (0.130)	0.201 (0.130)	-	-
Drinker (Yes v No)	-0.025 (0.117)	-0.023 (0.117)	-	-
Family history DM (Yes v No)	0.033 (0.069)	0.038 (0.069)	-	-
Gestational age at OGTT (wk)	-0.050 (0.038)	-0.052 (0.038)	-	-
Neonate gender (F v M)	-0.304 (0.094)	-0.302 (0.094)	-	-
Family history HBP (Yes v No) <sup>a</sup>	-	-	-	-
Maternal UTI (Yes v No) <sup>a</sup>	-	-	-	-
Mean Blood Pressure (mmHg)	0.006 (0.006)	0.006 (0.006)	-	-
Hospital admission before delivery (Yes v No)	0.794 (0.097)	0.792 (0.097)	-	-
Parity (1 v 0)	-0.474 (0.148)	-0.474 (0.148)	-	-
(2+ v 0)	-0.490 (0.157)	-0.493 (0.157)	-	-
(Unknown v 0)	-0.084 (0.135)	-0.086 (0.135)	-	-
Fasting blood glucose <sup>b</sup>	-	-0.003 (0.054)	-	-0.025 (0.050)
1-hr blood glucose <sup>b</sup>	-	0.082 (0.067)	-	0.078 (0.064)
2-hr blood glucose <sup>b</sup>	0.159 (0.045)	0.107 (0.063)	0.208 (0.041)	0.167 (0.060)
Constant	-3.181 (1.236)	-3.061 (1.243)	-2.374 (0.046)	-2.375 (0.046)
Hosmer-Lemeshow goodness- of-fit test	$\chi^2 = 14.18,$ df=8; P=0.08	$\chi^2 = 11.41,$ df=8; P=0.18	$\chi^2 = 22.16,$ df=8; P=0.005	$\chi^2 = 12.72,$ df=8; P=0.12
Area under the ROC curve (95% CI)	0.71 (0.69, 0.73)	0.71 (0.69, 0.73)	0.57 (0.55, 0.60)	0.57 (0.55, 0.60)

37 (a) Omitted from HAPO model for neonatal intensive care unit admissions

38 (b) Blood glucose values are 'standardised' – so the exponential of the coefficient represents the odds ratio for neonatal  
39 intensive care unit admissions arising from a 1 Standard Deviation (SD) increase in plasma glucose (fasting plasma glucose  
40 mean (SD) = 4.60(0.47); 1-hour plasma glucose mean (SD) = 7.57(1.83); 2-hour plasma glucose mean (SD) = 6.21(1.44)

41

42

43 **Table x5.** Logistic regression models to predict jaundice

44

Variable	Co-efficient b (Standard error (SE(b)))			
	Model 1 (all covariates)		Model 2 (blood glucose covariates)	
	Base case analysis	Sensitivity analysis	Base case analysis	Sensitivity analysis
Centre (Manchester v Belfast)	0.407 (0.157)	0.410 (0.157)	-	-
(Brisbane v Belfast)	0.449 (0.171)	0.420 (0.173)	-	-
(Newcastle v Belfast)	-0.315 (0.259)	-0.332 (0.259)	-	-
Age at OGTT (yr)	0.005 (0.011)	0.005 (0.011)	-	-
BMI at OGTT (kg/m <sup>2</sup> )	-0.011 (0.011)	-0.009 (0.012)	-	-
Smoker (Yes v No)	0.082 (0.161)	0.093 (0.162)	-	-
Drinker (Yes v No)	-0.514 (0.163)	-0.508 (0.163)	-	-
Family history DM (Yes v No)	-0.060 (0.094)	-0.060 (0.094)	-	-
Gestational age at OGTT (wk)	-0.078 (0.047)	-0.077 (0.047)	-	-
Neonate gender (F v M)	-0.116 (0.113)	-0.115 (0.113)	-	-
Family history HBP (Yes v No) <sup>a</sup>	-	-	-	-
Maternal UTI (Yes v No) <sup>a</sup>	-	-	-	-
Mean Blood Pressure (mmHg)	0.018 (0.007)	0.018 (0.007)	-	-
Hospital admission before delivery (Yes v No)	0.867 (0.116)	0.865 (0.116)	-	-
Parity (1 v 0)	-0.382 (0.185)	-0.380 (0.185)	-	-
(2+ v 0)	-0.526 (0.200)	-0.526 (0.200)	-	-
(Unknown v 0)	0.078 (0.165)	0.078 (0.165)	-	-
Fasting blood glucose <sup>b</sup>	-	-0.055 (0.066)	-	-0.063 (0.061)
1-hr blood glucose <sup>b</sup>	0.216 (0.056)	0.192 (0.079)	0.237 (0.052)	0.199 (0.078)
2-hr blood glucose <sup>b</sup>	-	0.073 (0.074)	-	0.102 (0.072)
Constant	-1.927 (1.522)	-2.014 (1.526)	-2.846 (0.057)	-2.850 (0.057)
Hosmer-Lemeshow goodness- of-fit test	$\chi^2 = 8.42,$ df=8; P=0.39	$\chi^2 = 7.96,$ df=8; P=0.44	$\chi^2 = 2.47,$ df=8; P=0.96	$\chi^2 = 10.40,$ df=8; P=0.24
Area under the ROC curve (95% CI)	0.68 (0.65, 0.71)	0.68 (0.65, 0.71)	0.57 (0.54, 0.60)	0.58 (0.55, 0.61)

45 (a) Omitted from HAPO model for jaundice

46 (b) Blood glucose values are 'standardised' – so the exponential of the coefficient represents the odds ratio for jaundice  
 47 arising from a 1 Standard Deviation (SD) increase in plasma glucose (fasting plasma glucose mean (SD) = 4.60(0.47); 1-hour  
 48 plasma glucose mean (SD) = 7.57(1.83); 2-hour plasma glucose mean (SD) = 6.21(1.44)

49

50



51 **Table x6.** Logistic regression models to predict pre-eclampsia

52

Variable	Co-efficient b (Standard error (SE(b)))			
	Model 1 (all covariates)		Model 2 (blood glucose covariates)	
	Base case analysis	Sensitivity analysis	Base case analysis	Sensitivity analysis
Centre (Manchester v Belfast)	-0.784 (0.192)	-0.800 (0.193)	-	-
(Brisbane v Belfast)	-0.308 (0.200)	-0.277 (0.202)	-	-
(Newcastle v Belfast)	-0.685 (0.278)	-0.667 (0.278)	-	-
Age at OGTT (yr)	-0.009 (0.015)	-0.011 (0.015)	-	-
BMI at OGTT (kg/m <sup>2</sup> )	0.101 (0.011)	0.097 (0.012)	-	-
Smoker (Yes v No)	-0.556 (0.245)	-0.569 (0.246)	-	-
Drinker (Yes v No)	-0.170 (0.194)	-0.168 (0.194)	-	-
Family history DM (Yes v No)	-0.004 (0.127)	0.006 (0.127)	-	-
Gestational age at OGTT (wk)	-0.092 (0.059)	-0.096 (0.059)	-	-
Neonate gender (F v M)	0.173 (0.147)	0.174 (0.147)	-	-
Family history HBP (Yes v No)	0.233 (0.150)	0.230 (0.150)	-	-
Maternal UTI (Yes v No)	0.734 (0.211)	0.721 (0.211)	-	-
Mean Blood Pressure (mmHg) <sup>a</sup>	-	-	-	-
Hospital admission before delivery (Yes v No) <sup>a</sup>	-	-	-	-
Parity (1 v 0)	-0.291 (0.240)	-0.292 (0.240)	-	-
(2+ v 0)	-0.701 (0.271)	-0.703 (0.271)	-	-
(Unknown v 0)	0.026 (0.224)	0.023 (0.224)	-	-
Fasting blood glucose <sup>b</sup>	-	0.062 (0.078)	0.201 (0.065)	0.183 (0.068)
1-hr blood glucose <sup>b</sup>	-	0.065 (0.104)	-	0.083 (0.098)
2-hr blood glucose <sup>b</sup>	0.272 (0.067)	0.195 (0.096)	0.196 (0.072)	0.150 (0.090)
Constant	-3.370 (1.842)	-3.107 (1.855)	-3.453 (0.075)	-3.455 (0.075)
Hosmer-Lemeshow goodness-of-fit test	$\chi^2 = 5.46,$ df=8; P=0.71	$\chi^2 = 8.02,$ df=8; P=0.43	$\chi^2 = 12.00,$ df=8; P=0.15	$\chi^2 = 15.98,$ df=8; P=0.04
Area under the ROC curve (95% CI)	0.75 (0.72, 0.78)	0.75 (0.72, 0.79)	0.65 (0.61, 0.68)	0.65 (0.61, 0.68)

53 (a) Omitted from HAPO model for pre-eclampsia

54 (b) Blood glucose values are 'standardised' – so the exponential of the coefficient represents the odds ratio for pre-eclampsia  
 55 arising from a 1 Standard Deviation (SD) increase in plasma glucose (fasting plasma glucose mean (SD) = 4.60(0.47); 1-hour  
 56 plasma glucose mean (SD) = 7.57(1.83); 2-hour plasma glucose mean (SD) = 6.21(1.44)

57

58

59 **Table x7.** Logistic regression models to predict induction of labour

60

Variable	Co-efficient b (Standard error (SE(b)))		
	Model 1 (all covariates)		Model 2 (blood glucose covariates)
	Base case analysis	Sensitivity analysis	Base case analysis
Centre (Manchester v Belfast)	-0.476 (0.077)	-0.476 (0.077)	-
(Brisbane v Belfast)	-0.337 (0.085)	-0.333 (0.087)	-
(Newcastle v Belfast)	-0.387 (0.109)	-0.384 (0.110)	-
Age at OGTT (yr)	0.006 (0.006)	0.006 (0.006)	-
BMI at OGTT (kg/m <sup>2</sup> )	0.039 (0.006)	0.039 (0.006)	-
Smoker (Yes v No)	0.051 (0.082)	0.051 (0.082)	-
Drinker (Yes v No)	0.079 (0.072)	0.079 (0.072)	-
Family history DM (Yes v No)	0.016 (0.048)	0.016 (0.048)	-
Gestational age at OGTT (wk)	0.011 (0.024)	0.011 (0.024)	-
Neonate gender (F v M)	-0.038 (0.059)	-0.038 (0.059)	-
Family history HBP (Yes v No) <sup>a</sup>	-	-	-
Maternal UTI (Yes v No) <sup>a</sup>	-	-	-
Mean Blood Pressure (mmHg)	0.008 (0.004)	0.008 (0.004)	-
Hospital admission before delivery (Yes v No)	0.608 (0.066)	0.608 (0.066)	-
Parity (1 v 0)	-0.363 (0.101)	-0.363 (0.101)	-
(2+ v 0)	-0.193 (0.105)	-0.193 (0.105)	-
(Unknown v 0)	0.141 (0.094)	0.141 (0.094)	-
Fasting blood glucose <sup>b</sup>	-	0.009 (0.037)	0.079 (0.033)
1-hr blood glucose <sup>b</sup>	-0.108 (0.041)	-0.111 (0.043)	-0.093 (0.041)
2-hr blood glucose <sup>b</sup>	0.096 (0.041)	0.094 (0.041)	0.100 (0.040)
Constant	-3.050 (0.794)	-3.037 (0.796)	-1.032 (0.029)
Hosmer-Lemeshow goodness-of-fit test	$\chi^2 = 9.08$ , df=8; P=0.34	$\chi^2 = 9.42$ df=8; P=0.31	$\chi^2 = 9.83$ df=8; P=0.28
Area under the ROC curve (95% CI)	0.63 (0.61, 0.65)	0.63 (0.61, 0.65)	0.53 (0.51, 0.55)

61 (a) Omitted from HAPO model for induction of labour

62 (b) Blood glucose values are 'standardised' – so the exponential of the coefficient represents the odds ratio for induction of  
63 labour arising from a 1 Standard Deviation (SD) increase in plasma glucose (fasting plasma glucose mean (SD) = 4.60(0.47);  
64 1-hour plasma glucose mean (SD) = 7.57(1.83); 2-hour plasma glucose mean (SD) = 6.21(1.44)

65 **Table x8.** Cholesky decomposition of shoulder dystocia variance covariance matrix (Model 1, base case)

	Constant	Centre (Manchester r v Belfast)	Centre (Manchester r v Belfast)	Centre (Manchester r v Belfast)	Age at OGTT (yr)	BMI AT OGTT (kg/m <sup>2</sup> )	Smoker	Drinker	Family History DM	Gestational age at OGTT (wk)	Neonatal gender	Mean Blood Pressure	Parity (1 v 0)	Parity (2+ v 0)	Parity (Unknown v 0)	Hospital admission before	2-hr blood glucose
Constant	3.025																
Centre (Manchester v Belfast)	-0.104	0.410															
(Brisbane v Belfast)	-0.129	0.335	0.331														
(Newcastle v Belfast)	-0.135	0.334	0.074	0.295													
Age at OGTT (yr)	-0.005	-0.001	0.000	0.000	0.024												
BMI AT OGTT (kg/m <sup>2</sup> )	-0.001	-0.001	-0.001	-0.001	0.001	0.023											
Smoker	-0.012	0.031	0.001	-0.003	0.047	0.006	0.404										
Drinker	0.001	0.014	-0.006	-0.020	-0.051	0.008	-0.018	0.311									
Family History DM	-0.023	0.012	-0.022	-0.018	-0.005	0.000	-0.009	-0.012	0.179								
Gestational age at OGTT (wk)	-0.080	-0.009	-0.001	0.006	-0.017	-0.007	-0.002	-0.001	-0.008	0.037							
Neonatal gender (F v M)	-0.037	-0.010	-0.006	-0.010	-0.002	0.009	0.003	-0.001	-0.005	-0.080	0.278						
Mean Blood Pressure (mmHg)	-0.004	-0.001	0.000	-0.002	-0.002	-0.006	0.000	0.000	-0.001	-0.011	-0.004	0.004					
Parity (1 v 0)	-0.038	0.014	0.011	-0.029	-0.024	-0.017	0.009	-0.013	0.006	-0.084	-0.020	-0.318	0.253				
(2+ v 0)	-0.026	0.007	0.025	-0.018	-0.082	-0.043	0.000	0.006	0.011	-0.072	-0.027	-0.317	0.021	0.229			
(Unknown v 0)	-0.052	0.019	0.005	-0.020	0.028	0.004	0.015	0.001	0.006	-0.090	-0.026	-0.311	0.020	0.026	0.219		
Hospital admission before delivery	-0.008	-0.007	-0.016	-0.006	0.005	-0.033	-0.006	0.007	-0.002	-0.002	0.004	-0.063	-0.061	-0.071	-0.079	0.225	
2-hr blood glucose	0.012	-0.003	-0.003	0.005	-0.016	-0.015	0.009	0.006	0.013	0.004	0.004	-0.003	-0.007	-0.021	-0.002	-0.015	0.091

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47

69 **Table x9.** Cholesky decomposition of caesarean section variance covariance matrix (Model 1, base case)

	Constant	Centre (Manchester v Belfast)	Centre (Manchester v Belfast)	Centre (Manchester v Belfast)	Age at OGTT (yr)	BMI AT OGTT (kg/m <sup>2</sup> )	Smoker	Drinker	Family History DM	Gestational age at OGTT	Neonatal gender	Mean Blood Pressure	Hospital admission	1-hr blood glucose
Constant	0.947													
Centre (Manchester v Belfast)	-0.020	0.089												
(Brisbane v Belfast)	-0.028	0.047	0.082											
(Newcastle v Belfast)	-0.028	0.048	0.025	0.126										
Age at OGTT (yr)	-0.001	0.000	0.000	0.000	0.007									
BMI AT OGTT (kg/m <sup>2</sup> )	-0.001	-0.001	0.000	0.000	0.000	0.007								
Smoker	-0.004	0.010	0.004	0.001	0.013	0.000	0.104							
Drinker	0.001	0.004	0.000	-0.002	-0.011	0.004	-0.006	0.086						
Family History DM	-0.006	0.006	-0.005	-0.002	-0.003	0.000	-0.003	-0.003	0.056					
Gestational age at OGTT (wk)	-0.026	-0.001	0.000	0.001	-0.005	-0.002	-0.001	-0.001	-0.003	0.011				
Neonate gender	-0.009	-0.001	-0.002	0.000	-0.002	0.002	0.002	-0.001	-0.001	-0.020	0.067			
Mean Blood Pressure (mmHg)	-0.001	0.000	0.000	0.000	-0.001	-0.002	0.000	0.000	0.000	-0.003	-0.001	0.001		
Hospital admission before delivery	-0.003	-0.004	-0.007	-0.001	0.004	-0.009	-0.003	0.004	-0.001	0.000	0.000	-0.042	0.065	
1-hr blood glucose	0.005	-0.001	0.002	0.002	-0.006	-0.006	0.000	0.001	0.005	0.003	0.002	-0.003	-0.003	0.035

70

71

72 **Table x10.** Cholesky decomposition of neonatal intensive care admission variance covariance matrix (Model 1, base case)

	Constant	Centre (Manchester r v Belfast)	Centre (Manchester r v Belfast)	Centre (Manchester r v Belfast)	Age at OGTT (yr)	BMI AT OGTT (kg/m2)	Smoker	Drinker	Family History DM	Gestational age at OGTT (wk)	Neonatal gender	Mean Blood Pressure	Parity (1 v 0)	Parity (2+ v 0)	Parity (Unknown v 0)	Hospital admission	2-hr blood glucose
Constant	1.236																
Centre (Manchester v Belfast)	-0.037	0.154															
(Brisbane v Belfast)	-0.047	0.115	0.102														
(Newcastle v Belfast)	-0.050	0.115	0.042	0.137													
Age at OGTT (yr)	-0.002	0.000	0.000	0.000	0.009												
BMI AT OGTT (kg/m2)	-0.001	0.000	0.000	0.000	0.000	0.009											
Smoker	-0.007	0.012	0.002	-0.001	0.018	-0.001	0.128										
Drinker	0.002	0.004	-0.002	-0.004	-0.017	0.006	-0.007	0.115									
Family History DM	-0.008	0.004	-0.008	-0.003	-0.003	0.000	-0.004	-0.003	0.068								
Gestational age at OGTT (wk)	-0.034	-0.003	-0.001	0.002	-0.007	-0.002	-0.001	-0.001	-0.004	0.015							
Neonatal gender (F v M)	-0.012	-0.003	-0.004	-0.002	-0.002	0.003	0.000	-0.001	-0.001	-0.025	0.090						
Mean Blood Pressure (mmHg)	-0.002	0.000	0.000	-0.001	-0.001	-0.002	0.000	0.000	0.000	-0.004	-0.001	0.001					
Parity (1 v 0)	-0.011	0.006	0.004	-0.009	-0.009	-0.005	0.002	-0.003	0.002	-0.024	-0.004	-0.103	0.102				
(2+ v 0)	-0.006	0.002	0.011	-0.005	-0.032	-0.015	-0.002	0.003	0.003	-0.021	-0.006	-0.102	0.012	0.111			
(Unknown v 0)	-0.016	0.008	0.003	-0.005	0.010	0.002	0.006	0.001	0.002	-0.025	-0.006	-0.101	0.011	0.011	0.081		
Hospital admission before delivery	-0.005	-0.001	-0.005	0.000	0.004	-0.012	-0.003	0.005	0.000	-0.001	0.000	-0.033	-0.028	-0.025	-0.032	0.075	
2-hr blood glucose	0.004	0.000	0.000	0.001	-0.007	-0.006	0.004	0.002	0.005	0.003	0.002	-0.002	-0.002	-0.006	0.000	-0.006	0.042

73

74 Table x11. Cholesky decomposition of jaundice variance covariance matrix (Model 1, base case)

	Constant	Centre (Manchester v Belfast)	Centre (Brisbane v Belfast)	Centre (Newcastle v Belfast)	Age at OGTT (yr)	BMI AT OGTT (kg/m2)	Smoker	Drinker	Family History DM	Gestational age at OGTT (wk)	Neonatal gender	Mean Blood Pressure	Parity (1 v 0)	Parity (2+ v 0)	Parity (Unknown v 0)	Hospital admission	1-hr blood glucose
Constant	1.522																
Centre (Manchester v Belfast)	-0.038	0.153															
(Brisbane v Belfast)	-0.049	0.102	0.128														
(Newcastle v Belfast)	-0.055	0.102	0.041	0.228													
Age at OGTT (yr)	-0.002	0.000	0.000	0.000	0.011												
BMI AT OGTT (kg/m2)	-0.001	-0.001	-0.001	0.000	0.000	0.011											
Smoker	-0.011	0.017	0.003	-0.001	0.023	0.000	0.158										
Drinker	0.003	0.004	0.000	-0.002	-0.020	0.006	-0.011	0.161									
Family History DM	-0.011	0.010	-0.010	-0.003	-0.005	-0.001	-0.004	-0.005	0.092								
Gestational age at OGTT (wk)	-0.042	-0.003	0.000	0.002	-0.008	-0.004	-0.001	-0.001	-0.005	0.018							
Neonatal gender (F v M)	-0.014	-0.003	-0.003	-0.002	-0.002	0.004	0.002	-0.001	0.000	-0.031	0.108						
Mean Blood Pressure (mmHg)	-0.002	0.000	0.000	0.000	-0.001	-0.003	0.000	0.000	0.000	-0.005	-0.002	0.002					
Parity (1 v 0)	-0.016	0.010	0.008	-0.006	-0.011	-0.007	0.001	-0.001	0.003	-0.032	-0.007	-0.128	0.126				
(2+ v 0)	-0.008	0.002	0.014	-0.004	-0.039	-0.016	-0.003	0.005	0.006	-0.030	-0.009	-0.127	0.016	0.144			
(Unknown v 0)	-0.021	0.013	0.006	-0.004	0.012	0.003	0.005	0.002	0.002	-0.034	-0.008	-0.126	0.015	0.013	0.094		
Hospital admission before delivery	-0.006	-0.003	-0.008	-0.002	0.005	-0.016	-0.004	0.003	-0.001	-0.002	0.001	-0.040	-0.034	-0.028	-0.042	0.089	
1-hr blood glucose	0.007	-0.001	0.004	0.003	-0.008	-0.009	0.003	0.001	0.008	0.004	0.003	-0.004	-0.004	-0.009	-0.001	-0.008	0.051

75

76 **Table x12.** Cholesky decomposition of pre-clampsia variance covariance matrix (Model 1, base case)

	Constant	Centre (Manchester v Belfast)	Centre (Manchester v Belfast)	Centre (Manchester v Belfast)	Age at OGTT (yr)	BMI AT OGTT (kg/m2)	Smoker	Drinker	Family History DM	Gestational age at OGTT (wk)	Neonatal gender (F v M)	Parity (1 v 0)	Parity (2+ v 0)	Parity (Unknown v 0)	Family History HBP	Maternal UTI	2-hr blood glucose
Constant	1.842																
Centre (Manchester v Belfast)	-0.045	0.187															
(Brisbane v Belfast)	-0.059	0.083	0.173														
(Newcastle v Belfast)	-0.072	0.085	0.053	0.249													
Age at OGTT (yr)	-0.004	0.000	0.000	0.000	0.015												
BMI AT OGTT (kg/m2)	-0.002	-0.001	-0.001	-0.002	0.000	0.010											
Smoker	-0.010	0.019	0.002	0.001	0.026	0.001	0.243										
Drinker	0.002	0.007	-0.002	-0.004	-0.023	0.007	-0.009	0.192									
Family History DM	-0.017	0.013	-0.009	-0.006	-0.009	-0.001	-0.004	-0.004	0.124								
Gestational age at OGTT (wk)	-0.054	-0.003	0.000	0.002	-0.013	-0.012	-0.001	-0.001	-0.008	0.011							
Neonatal gender (F v M)	-0.023	-0.004	-0.006	-0.007	-0.003	0.009	0.001	-0.002	-0.001	-0.106	0.099						
Parity (1 v 0)	-0.020	0.013	0.016	-0.006	-0.014	-0.011	0.003	-0.001	0.001	-0.121	-0.123	0.163					
(2+ v 0)	-0.011	-0.001	0.020	-0.005	-0.047	-0.030	0.000	0.000	0.007	-0.117	-0.120	0.042	0.199				
(Unknown v 0)	-0.029	0.014	0.013	-0.004	0.017	0.002	0.006	0.001	0.000	-0.122	-0.125	0.036	0.025	0.127			
Family History HBP	-0.009	0.000	0.006	-0.005	-0.017	-0.014	0.001	-0.001	0.023	-0.034	-0.037	-0.060	-0.038	-0.048	0.108		
Maternal UTI	-0.004	-0.012	0.031	0.002	0.015	-0.001	-0.014	0.004	0.009	-0.021	-0.022	-0.030	-0.018	-0.028	-0.052	0.193	
2-hr blood glucose	0.006	-0.004	0.002	0.001	-0.012	-0.009	0.005	0.004	0.008	-0.006	-0.004	-0.006	-0.011	-0.002	-0.012	-0.009	0.061

77

78 **Table x13.** Cholesky decomposition of induction of labour variance covariance matrix (Model 1, base case)

	Constant	Centre (Manchester v Belfast)	Centre (Manchester v Belfast)	Centre (Manchester v Belfast)	Age at OGTT (yr)	BMI AT OGTT (kg/m <sup>2</sup> )	Smoker	Drinker	Family History DM	Gestational age at OGTT	Neonatal gender (F v M)	Mean Blood Pressure	Parity (1 v 0)	Parity (2+ v 0)	Parity (Unknown v 0)	Hospital admission	1-hr blood glucose	2-hr blood glucose
Constant	0.794																	
Centre (Manchester v Belfast)	-0.018	0.074																
(Brisbane v Belfast)	-0.024	0.039	0.072															
(Newcastle v Belfast)	-0.024	0.039	0.020	0.097														
Age at OGTT (yr)	-0.001	0.000	0.000	0.000	0.006													
BMI AT OGTT (kg/m <sup>2</sup> )	0.000	0.000	0.000	0.000	0.000	0.006												
Smoker	-0.005	0.008	0.002	0.001	0.013	0.001	0.081											
Drinker	0.001	0.003	0.000	-0.002	-0.010	0.003	-0.006	0.071										
Family History DM	-0.006	0.005	-0.004	-0.002	-0.002	0.000	-0.002	-0.003	0.047									
Gestational age at OGTT (wk)	-0.021	-0.001	0.000	0.001	-0.004	-0.002	-0.001	0.000	-0.003	0.010								
Neonatal gender (F v M)	-0.007	-0.002	-0.002	-0.001	-0.001	0.002	0.001	-0.001	-0.001	-0.016	0.056							
Mean Blood Pressure (mmHg)	-0.001	0.000	0.000	0.000	-0.001	-0.001	0.000	0.000	0.000	-0.003	-0.001	0.001						
Parity (1 v 0)	-0.008	0.008	0.005	-0.004	-0.006	-0.004	0.000	-0.002	0.001	-0.020	-0.005	-0.075	0.061					
(2+ v 0)	-0.004	0.004	0.008	-0.002	-0.020	-0.010	-0.002	0.001	0.002	-0.019	-0.006	-0.075	0.005	0.067				
(Unknown v 0)	-0.012	0.007	0.003	-0.002	0.006	0.001	0.002	0.001	0.001	-0.021	-0.005	-0.075	0.005	0.004	0.050			
Hospital admission before delivery	-0.004	-0.004	-0.005	-0.001	0.002	-0.007	-0.002	0.003	0.000	-0.001	0.000	-0.017	-0.017	-0.016	-0.020	0.055		
1-hr blood glucose	0.004	0.000	0.004	0.002	-0.004	-0.003	-0.001	0.000	0.003	0.001	0.001	0.000	0.001	-0.001	0.001	0.000	0.040	
2-hr blood glucose	0.001	0.000	-0.003	-0.001	-0.001	-0.002	0.004	0.001	0.001	0.002	0.000	-0.001	0.000	-0.002	0.001	-0.001	-0.027	0.030

79



80 **Table x14:** Model unit costs

Category	Cost	Standard Error	Distribution <sup>a</sup>	Source
2 sample OGTT	£8.07	n/a	n/a	NICE 2015 <sup>b</sup>
3 sample OGTT	£12.11	n/a	n/a	NICE 2015 <sup>b</sup>
Rapilose OGTT solution	£3.48	n/a	n/a	BNF July 2016 <sup>c</sup>
Health Care Assistant Band 3 (per hour)	£25	n/a	n/a	Unit Costs of Health and Social Care 2015 <sup>d</sup>
Nurse Band 7 (per hour of patient contact)	£147	n/a	n/a	Unit Costs of Health and Social Care 2015 <sup>d</sup>
Dietician	£38	n/a	n/a	Unit Costs of Health and Social Care 2015 <sup>d</sup>
Antenatal appointment	£96	£9.07	Normal	NHS Reference Costs 2014-15 <sup>e</sup>
Ultrasound scan	£112	£7.65	Normal	NHS Reference Costs 2014-15 <sup>e</sup>
Rapid acting insulin	£0.02	n/a	n/a	BNF June 2016 <sup>c</sup>
Regular insulin	£0.02	n/a	n/a	BNF June 2016 <sup>c</sup>
Needles	£0.10	n/a	n/a	NHS Drugs Tariff June 2016 <sup>f</sup>
Lancets	£0.03	n/a	n/a	NHS Drugs Tariff June 2016 <sup>f</sup>
Strips	£0.18	n/a	n/a	NHS Drugs Tariff June 2016 <sup>f</sup>
Treatment of GDM	£987	n/a	n/a	Calculated
Severe hypoglycaemia	£650	n/a	n/a	NHS Reference Costs 2014-15 <sup>e</sup>
Admission to NICU	£1,176	£38	Normal	NHS Reference Costs 2014-15 <sup>e</sup>
Caesarean section	£982	£80	Normal	NHS Reference Costs 2014-15 <sup>e</sup>
Neonatal death	£777	£39	Normal	NHS Reference Costs 2014-15 <sup>e</sup>
Shoulder dystocia	£1,394	£79	Normal	NHS Reference Costs 2014-15 <sup>e</sup>
Birth trauma	£1,394	£79	Normal	NHS Reference Costs 2014-15 <sup>e</sup>
Serious perinatal complication (death, shoulder dystocia, birth trauma)	£1,347	n/a	n/a	Calculated
Phototherapy	£788	£72	Normal	NHS Reference Costs 2014-15 <sup>e</sup>
Pre-eclampsia	£4,750	n/a	n/a	NICE 2015 <sup>b</sup>

81 (a) The method used to obtain standard errors and the choice of a normal distribution for probabilistic sampling is described in  
82 detail in the NICE 2015 guideline<sup>6</sup>

- 1  
2  
3 83 (b) National Institute for Health and Care Excellence (NICE) (2015) *Diabetes in pregnancy: management of diabetes and its*  
4 84 *complications from preconception to the postnatal period. Clinical guideline NG3 (2015).*  
5 85 (c) *British National Formulary. July 2016. <https://www.medicinescomplete.com/mc/bnf/current/> (accessed 4 Aug 2016).*  
6 86 (d) *Unit Costs of Health and Social Care 2015. Personal Social Services Research Unit, The University of Kent, 2015.*  
7 87 (e) *Department of Health. NHS reference costs: financial year 2014–2015. [https://www.gov.uk/government/publications/nhs-](https://www.gov.uk/government/publications/nhs-reference-costs-2014-to-2015)*  
8 88 *reference-costs-2014-to-2015*, Department of Health, 2015.  
9 89 (f) *NHS Electronic Drug Tariff, August 2016. [http://www.drugtariff.nhsbsa.nhs.uk/#/00336026-DD\\_1/DD00336022/Home](http://www.drugtariff.nhsbsa.nhs.uk/#/00336026-DD_1/DD00336022/Home)*  
10 90 *(accessed 4 Aug 2016).*  
11 91

## 12 13 92 QALYs

14  
15  
16 93 A QALY loss was estimated for each individual component (shoulder dystocia, death and birth trauma)  
17  
18 94 of the composite serious perinatal outcome, which was used in the ACHOIS study.<sup>11</sup> A weighting for  
19  
20 95 each individual component was derived according to their relative frequency in the selected studies to  
21  
22 96 assess treatment effectiveness.<sup>11, 12</sup> These were then used in order to derive a weighted average for a  
23  
24 97 serious perinatal complication as shown in Table x15. QALY losses from a serious perinatal complication  
25  
26 98 could be experienced over a lifetime and therefore an annual discount rate of 3.5% was applied in line  
27  
28 99 with NICE methods.<sup>19</sup> For each patient, an expected QALY decrement is calculated based on their risk of  
29  
30 100 serious perinatal complications. These individual patient QALY decrements are then summed across all  
31  
32 101 patients to give the total QALY decrement for the patient dataset for each different diagnostic  
33  
34 102 threshold.  
35  
36  
37  
38  
39

40 103 **Table x15:** QALY losses and weights from individual components of the composite outcome of serious  
41 104 perinatal complications

Complication	Weight	QALY	Weighted QALY
Death	0.08	25	2.00
Shoulder dystocia	0.73	0.2	0.15
Birth trauma	0.20	0.2	0.04

52  
53 105

54  
55 106 The analyses presented in this paper include a maternal health state utility which was estimated from  
56  
57 107 quality of life data collected as part of the ACHOIS study. Whilst treatment conferred a small benefit in  
58  
59 108 maternal health state utility, this was small in comparison to QALYs derived from infant outcomes. The  
60

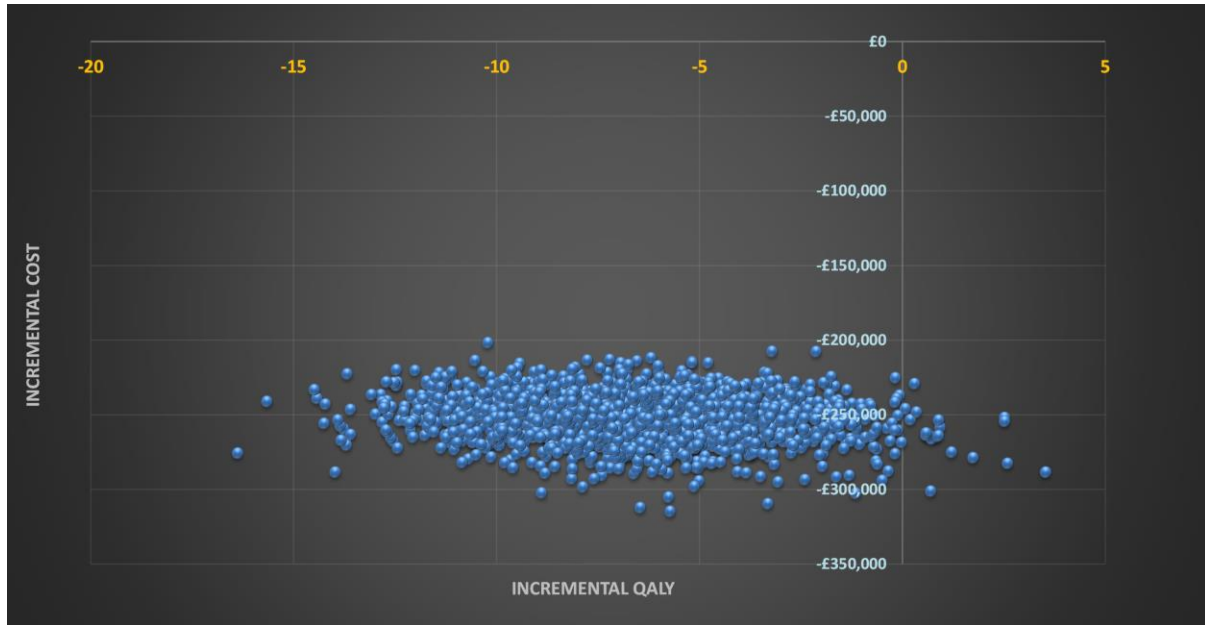
1  
2  
3 109 value of the maternal health state utility with and without treatment is the same as has been used  
4  
5 110 previously.<sup>6</sup>  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

111 **Results for the HAPO (4) population with risk factors**

112 **Figure x1:** Cost-effectiveness plane for NICE 2015 compared with WHO 2013 for HAPO (4) with risk  
113 factors

114



115

116

117

review only

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

118 **Summary of results for each model population**

119 **Table x16:** Summary of deterministic ICERs for each population with backward elimination of plasma  
120 glucose variables with non-significant coefficients

Diagnostic threshold	All covariates		Plasma glucose covariates				Norwich (n=12,754)
	HAPO Risk factor (n=3,549)	HAPO No Risk factor (n=2,614)	HAPO Risk factor (n=3,549)	HAPO No Risk factor (n=2,614)	Atlantic DiP Risk factor (n=1,988)	Atlantic DiP No Risk factor (n=3,302)	
No Treatment	-	-	-	-	-	-	-
NICE 2015	£20,400	£36,878	£22,281	£30,449	£20,830	£31,136	£28,893
WHO 2013	£33,596	£141,812	£36,473	£88,661	£35,941	£40,526	£37,918

121  
122  
123 **Table x17:** Probability that a threshold is cost-effective at a threshold of £30,000 per QALY and the  
124 net monetary benefit in each population using regression models with backward elimination of  
125 plasma glucose variables with non-significant coefficients

Diagnostic threshold	All covariates		Plasma glucose covariates				Norwich (NMB)
	HAPO Risk factor (NMB)	HAPO No Risk factor (NMB)	HAPO Risk factor (NMB)	HAPO No Risk factor (NMB)	Atlantic DiP Risk factor (NMB)	Atlantic DiP No Risk factor (NMB)	
No Treatment	21.0% (£0)	78.1% (£0)	33.7% (£0)	69.3% (£0)	30.6% (£0)	70.0% (£0)	61.2% (£0)
NICE 2015	51.5% (£239,902)	21.9% (-£57,790)	53.2% (£104,075)	30.7% (£36,652)	54.6% (£113,042)	23.5% (-£37,716)	29.3% (-£96,248)
WHO 2013	27.6% (£186,675)	0.1% (-£111,179)	13.2% (£13,836)	0.1% (£79,581)	14.9% (£36,377)	6.6% (-£109,809)	9.6% (-£414,428)

127 **Results for the HAPO (4) population without risk factors**128 **Table x18:** Clinical outcomes for HAPO (4) population without NICE risk factors (n=2,614)

Diagnostic threshold	Diagnosed	SD	SPC	CS	NICU	Jaund	PE	IOL
No Treatment	0	24	34	466	188	126	55	647
NICE 2015	208	23	31	460	184	124	51	655
WHO 2013	253	23	31	459	184	123	51	657

129

130 **Table x19:** Deterministic analysis for HAPO (4) population without NICE risk factors (n=2,614)

Diagnostic threshold	Cost <sup>a</sup>	QALY <sup>a</sup>	Incremental cost	Incremental QALY	ICER
No Treatment	£0	0.00	n/a	n/a	n/a
NICE 2015	£238,074	6.46	£238,074	6.46	£36,878
WHO 2013	£297,364	6.87	£59,290	0.41	£141,812

131 a) *Costs and QALYs are measured relative to a baseline of No Treatment*

132

133 **Table x20:** Probabilistic sensitivity analysis for HAPO (4) in a population without NICE risk factors

Diagnostic threshold	NMB <sup>a</sup>	Probability cost-effective
	CE threshold £30,000 per QALY	CE threshold £30,000 per QALY
No Treatment	£0	78.1%
NICE 2015	-£57,790	21.9%
WHO 2013	-£111,179	0.1%

134 a) *NMB is measured relative to a baseline of no treatment*

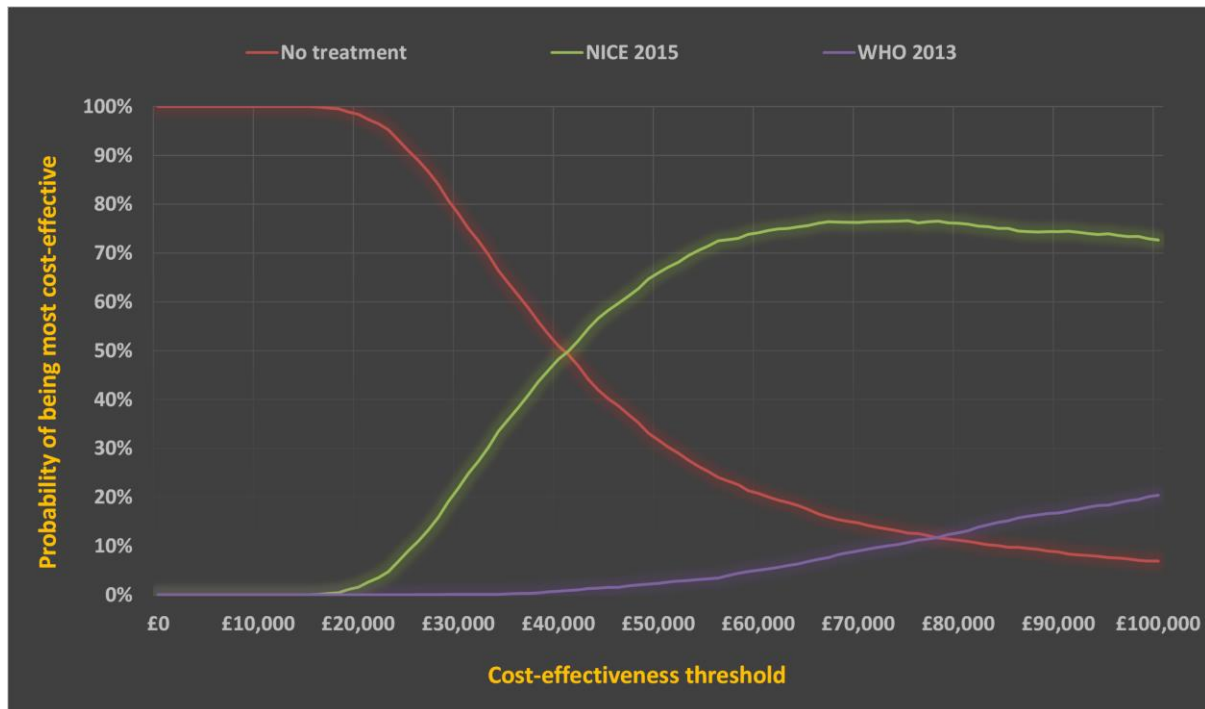
135

136

137

138 **Figure x2:** Cost-effectiveness acceptability curve indicating the probability of a threshold or a no  
 139 diagnosis/no treatment strategy being cost-effective at different cost-effectiveness thresholds for  
 140 HAPO (4) population without risk factors

141



142

143

144 **Results for the Atlantic DiP population with risk factors**

145 **Table 21:** Clinical outcomes for Atlantic DiP population with NICE risk factors (n=1,988)

Diagnostic threshold	Diagnosed	SD	SPC	CS	NICU	Jaund	PE	IOL
No Treatment	0	25	34	408	177	122	73	522
NICE 2015	497	19	26	391	163	116	56	545
WHO 2013	749	17	24	385	158	112	51	555

146

147

148

149

150

151 **Table x22:** Deterministic analysis for the Atlantic DiP population with NICE risk factors (n=1,988)

Diagnostic threshold	Cost <sup>a</sup>	QALY <sup>a</sup>	Incremental cost	Incremental QALY	ICER
No Treatment	£0	0.00	n/a	n/a	n/a
NICE 2015	£414,714	19.91	£414,714	17.46	£20,830
WHO 2013	£638,590	26.14	£223,876	6.23	£35,941

152 a) Costs and QALYs are measured relative to a baseline of No Treatment

153

154 **Table x23:** Probabilistic sensitivity analysis for Atlantic in a population with NICE risk factors

Diagnostic threshold	NMB <sup>a</sup> CE threshold £30,000 per QALY	Probability cost-effective CE threshold £30,000 per QALY
No Treatment	£0	30.6%
NICE 2015	£113,042	54.3%
WHO 2013	£36,377	14.9%

155 a) NMB is measured relative to a baseline of no treatment

156

157

158

159

160

161

162

163

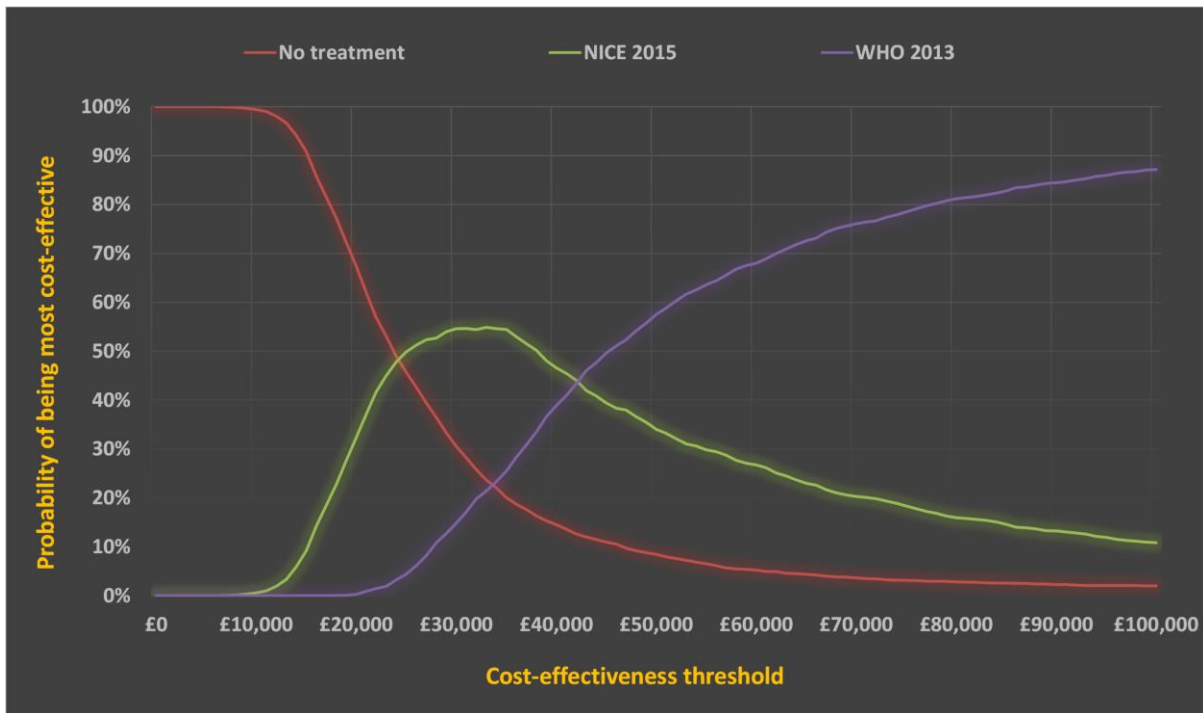
164

165

166



167 **Figure x3:** Cost-effectiveness acceptability curve indicating the probability of a threshold or a no  
 168 diagnosis/no treatment strategy being cost-effective at different cost-effectiveness thresholds for  
 169 the Atlantic DiP centres population with risk factors



170

171

172 **Results for the Atlantic DiP population without risk factors**

173 **Table x24:** Clinical outcomes for Atlantic DiP population without NICE risk factors (n=3,302)

Diagnostic threshold	Diagnosed	SD	SPC	CS	NICU	Jaund	PE	IOL
No Treatment	0	33	45	575	254	168	84	828
NICE 2015	194	31	42	569	248	166	79	837
WHO 2013	371	30	41	564	245	163	76	844

174

175

176

177

178

179

180

181 **Table x25:** Deterministic analysis for the Atlantic DiP population without NICE risk factors (n=3,302)

<b>Diagnostic threshold</b>	<b>Cost<sup>a</sup></b>	<b>QALY<sup>a</sup></b>	<b>Incremental cost</b>	<b>Incremental QALY</b>	<b>ICER</b>
No Treatment	£0	0.00	n/a	n/a	n/a
NICE 2015	£231,633	7.44	£231,633	7.44	£31,136
WHO 2013	£402,014	11.64	£170,381	4.20	£40,526

182 a) *Costs and QALYs are measured relative to a baseline of No Treatment*

183

184 **Table x26:** Probabilistic sensitivity analysis for the Atlantic DiP population without NICE risk factors

<b>Diagnostic threshold</b>	<b>NMB<sup>a</sup></b>	<b>Probability cost-effective</b>
	<b>CE threshold £30,000 per QALY</b>	<b>CE threshold £30,000 per QALY</b>
No Treatment	£0	70.0%
NICE 2015	-£37,716	23.5%
WHO 2013	-£109,809	6.6%

185 a) *NMB is measured relative to a baseline of no treatment*

186

187

188

189

190

191

192

193

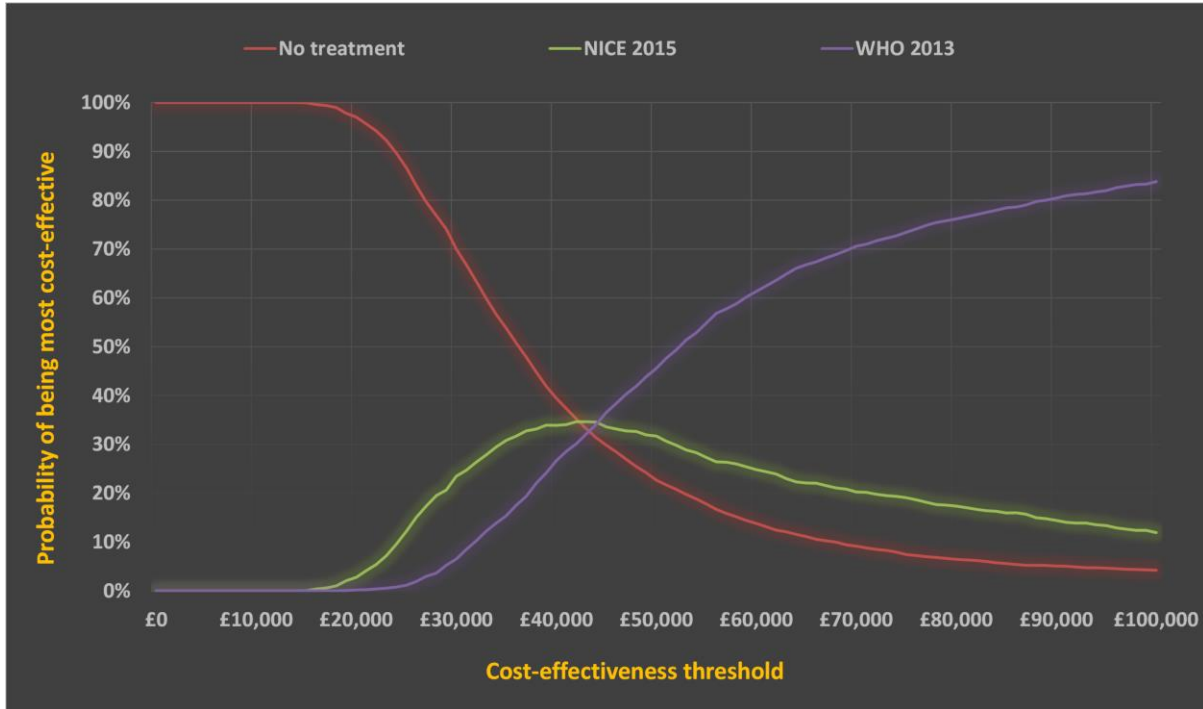
194

195

196

197 **Figure x4:** Cost-effectiveness acceptability curve indicating the probability of a threshold or a no  
 198 diagnosis/no treatment strategy being cost-effective at different cost-effectiveness thresholds for  
 199 the Atlantic DiP centres population without risk factors

200



201

202

Review only

203 **Results for the Norwich population**204 **Table x27:** Clinical outcomes for Norwich population (n=12,754)

Diagnostic threshold	Diagnosed	SD	SPC	CS	NICU	Jaund	PE	IOL
No Treatment	0	132	182	2,333	1,005	699	346	3,173
NICE 2015	888	122	168	2,305	981	687	318	3,214
WHO 2013	1,771	117	161	2,283	965	676	301	3,248

205

206 **Table x28:** Deterministic analysis for the Norwich population (n=12,754)

Diagnostic threshold	Cost <sup>a</sup>	QALY <sup>a</sup>	Incremental cost	Incremental QALY	ICER
No Treatment	£0	0.00	n/a	n/a	n/a
NICE 2015	£979,903	33.91	£979,903	33.91	£28,893
WHO 2013	£1,803,196	55.63	£823,293	21.72	£37,918

207 a) *Costs and QALYs are measured relative to a baseline of No Treatment*

208

209 **Table x29:** Probabilistic sensitivity analysis for the Norwich population

Diagnostic threshold	NMB <sup>a</sup> CE threshold £30,000 per QALY	Probability cost-effective CE threshold £30,000 per QALY
No Treatment	£0	61.2%
NICE 2015	-£96,248	29.3%
WHO 2013	-£414,428	9.6%

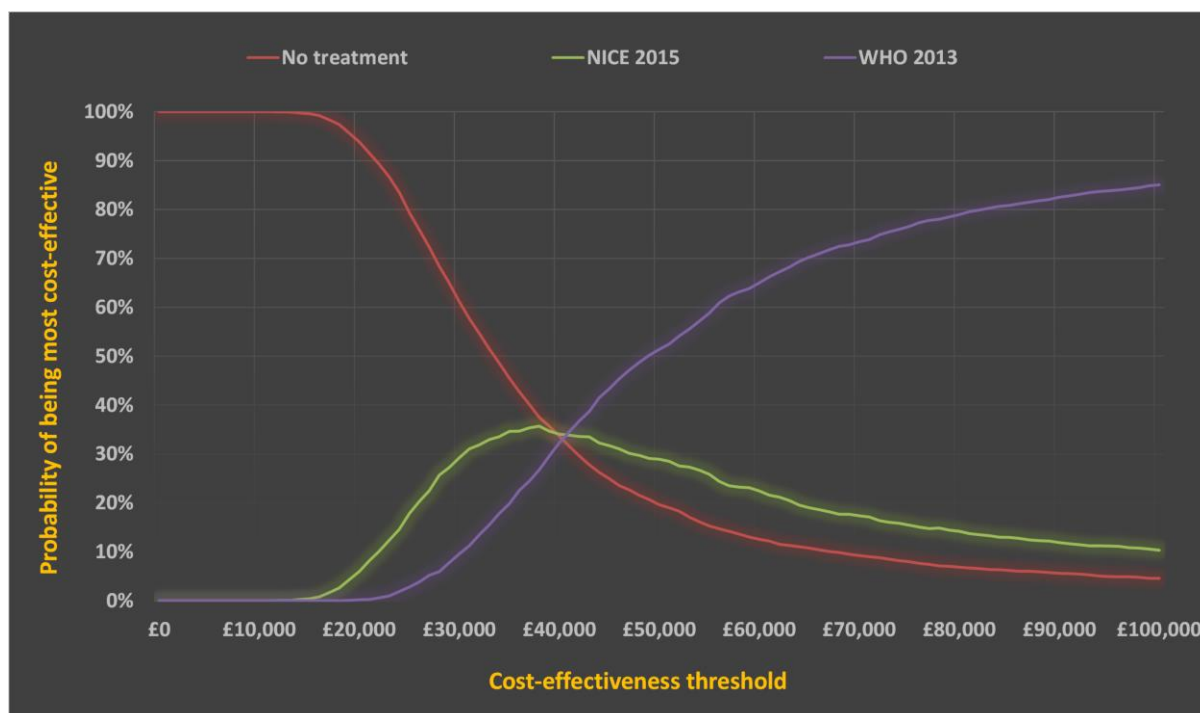
210 a) *NMB is measured relative to a baseline of no treatment*

211

212

213 **Figure x5:** Cost-effectiveness acceptability curve indicating the probability of a threshold or a no  
 214 diagnosis/no treatment strategy being cost-effective at different cost-effectiveness thresholds for  
 215 the Norwich population

216



217

218

219

review only

220 **Deterministic sensitivity analysis**

221 The cost-effectiveness of universal screening was not generally affected when the model was re-run  
 222 using the regression models without backward elimination of non-significant variables with no  
 223 screening/no treatment continuing to be the cost-effective option in populations not selected on the  
 224 basis of NICE risk factors (see Table x30). In the Norwich population, universal screening was  
 225 borderline cost-effective compared to no screening/no treatment at £30,000 per QALY but the same  
 226 point remains that a risk factor subset in this population would have a lower ICER than that  
 227 reported, and that a subset without risk factors, (i.e. those additionally incorporated as a result of  
 228 universal screening compared to risk factor screening), would have a higher ICER. In populations  
 229 with NICE risk factors the NICE 2015 diagnostic thresholds were still found to be cost-effective at a  
 230 threshold of £30,000 per QALY, with broadly similar ICERs as previously. Similarly, the WHO 2013  
 231 diagnostic threshold was never found to be cost effective even in a population with risk factors.

232 **Table x30:** Summary of deterministic ICERs for each population without backward elimination of  
 233 non-significant coefficients

Diagnostic threshold	All covariates		Plasma glucose covariates				Norwich (n=12,754)
	HAPO Risk factor (n=3,549)	HAPO No Risk factor (n=2,614)	HAPO Risk factor (n=3,549)	HAPO No Risk factor (n=2,614)	Atlantic DiP Risk factor (n=1,988)	Atlantic DiP No Risk factor (n=3,302)	
No Treatment	-	-	-	-	-	-	-
NICE 2015	£20,162	£38,869	£21,786	£33,473	£19,557	£32,762	£27,354
WHO 2013	£30,734	£94,585	£32,267	£58,604	£35,285	£39,076	£38,402

234

235

236 **Mean plasma glucose values according to risk factor status**

237 **Table x311:** Mean plasma glucose values in HAPO (4) and Atlantic DiP population according to their  
 238 risk factor status

239

	HAPO (4)			Atlantic DiP		
	Fasting	1-hour	2-hour	Fasting	1-hour	2-hour
True Positives	5.24	9.90	7.89	5.21	10.21	7.61
False Positives	4.50	7.20	5.95	4.33	6.75	5.33
True Negatives	4.44	6.95	5.78	3.92	5.99	4.76
False Negatives	4.89	9.52	7.41	4.90	9.51	7.12

240

241

## CHEERS Statement

CHEERS checklist—Items to include when reporting economic evaluations of health interventions

Section/item	Item No	Recommendation	Reported on page No/ line No
<b>Title and abstract</b>			
Title	1	Identify the study as an economic evaluation or use more specific terms such as “cost-effectiveness analysis”, and describe the interventions compared.	Yes Page 1 Line 2
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	Yes Page 2 Lines 30-55
<b>Introduction</b>			
Background and objectives	3	Provide an explicit statement of the broader context for the study.	Yes Page 5-6 Lines 92-104
		Present the study question and its relevance for health policy or practice decisions.	Yes Page 5 Lines 74-90
<b>Methods</b>			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Yes Page 6-8 Lines 116-149
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Yes Page 6-7 Lines 116-122
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Yes Page 12 Line 219
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Yes Page 6 Line 100-104; 108-111
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Yes Page 12 Line 230  Supp. Report



Section/item	Item No	Recommendation	Reported on page No/ line No
			Page 15 Line 90
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	Yes Page 12 Line 230  Supp. Report Page 15 Line 90
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Yes Pages 8-9 Lines 152-172
Measurement of effectiveness	11a	<i>Single study-based estimates:</i> Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	Yes Pages 10 Lines 202-205
	11b	<i>Synthesis-based estimates:</i> Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	Yes Pages 10 Lines 199-201
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	
Estimating resources and costs	13a	<i>Single study-based economic evaluation:</i> Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
	13b	<i>Model-based economic evaluation:</i> Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Yes Page 12-13 Lines 218-243  Supp. Report Page 14 Line 80
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for	Yes Page 12 Lines 230

Section/item	Item No	Recommendation	Reported on page No/ line No
		converting costs into a common currency base and the exchange rate.	
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	Yes Page 6 Lines 108-111; 113-114
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	Yes Page 8-9 Lines 151-172  Yes Page 13 Lines 245-248  Supp. Report Page 2-7  Supp. Report Page 15 Lines 84-102  +References to other sources
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	Yes Page 9-10 Lines 174-191  Yes Page 13-14 Lines 259-266  Supp. Report Page 2-7
<b>Results</b>			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Yes Page 11 Lines 215-216  Page 13

Section/item	Item No	Recommendation	Reported on page No/ line No
			Lines 243-244  Supp. Report Page 2-15
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Yes Page 15 Lines 279-281  Supp. Report Page 17-25
Characterising uncertainty	20a	<i>Single study-based economic evaluation:</i> Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	
	20b	<i>Model-based economic evaluation:</i> Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Yes Supp. Report Page 17 Lines 116-119  Supp. Report Page 26 Lines 225-227
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	Yes Supp. Report Page 17 Lines 111-114
<b>Discussion</b>			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the	Yes Pages 18-25

Section/item	Item No	Recommendation	Reported on page No/ line No
		findings and how the findings fit with current knowledge.	
<b>Other</b>			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	Yes Page 26 Lines 547-552
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Yes Page 26 Lines 557-560