An Roinn Sláinte
Department of Health

Adult type 1 diabetes mellitus

National Clinical Guideline No. 17

Annex 1: Economic evidence review

National Patient Safety Office
Oifig Náisiúnta um Shábháilteacht Othar

NATIONAL CLINICAL EFFECTIVENESS COMMITTEE

HRB Health Research Board

CICER Collaboration in Ireland for Clinical Effectiveness Reviews

Membership of the Evaluation Team

The members of the Health Research Board-Collaboration in Ireland for Clinical Effectiveness Reviews (HRB-CICER) and Health Information and Quality Authority (HIQA) Evaluation Team were: Mr Paul Carty, Ms Michelle O'Neill, Dr Patricia Harrington and Professor Susan Smith.

About HRB-CICER

In 2016, the Department of Health requested that the Health Research Board (HRB) fund an evidence synthesis service called HRB-CICER (Collaboration in Ireland for Clinical Effectiveness Reviews) to support the activities of the Ministerial appointed National Clinical Effectiveness Committee (NCEC). Following a competitive process, the Health Information and Quality Authority (HIQA) was awarded the contract for the five-year period from 2017 to 2022. The HRB-CICER team comprises a dedicated multidisciplinary research team supported by staff from the Health Technology Assessment (HTA) team in HIQA and the HRB Centre for Primary Care Research at the Royal College of Surgeons in Ireland (RCSI), as well as national and international clinical and methodological experts.

With regard to clinical guidelines, the role of the HRB-CICER team is to independently review evidence and provide scientific support for the development, by guideline development groups, of National Clinical Guidelines for the NCEC. The HRB-CICER team undertakes systematic reviews of the clinical effectiveness and cost-effectiveness of interventions included in the guidelines as well as estimating the budget impact of implementing the guidelines. The HRB-CICER team also works closely with the guideline development groups; provides tailored training sessions; assists in the development of clinical questions and search strategies; performs systematic reviews of international clinical guidelines and supports the assessment of their suitability for adaption to Ireland; and supports the development of evidence-based recommendations informed by the evidence produced by HRB-CICER within the National Clinical Guidelines.

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CICER
Collaboration in Ireland for Clinical Effectiveness Reviews

Economic evidence review –

Adult type 1 diabetes mellitus

August 2017

Health Information and Quality Authority
An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

HRB Health Research Board

NATIONAL CLINICAL EFFECTIVENESS COMMITTEE

RCSI

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List of abbreviations

CBA	Cost-benefit analysis
CBT	Cognitive behavioural therapy
CGM	Real-time continuous glucose monitoring
CMA	Cost minimisation analysis
CPI	Consumer Price Index
CRD	Centre for Reviews and Dissemination
CUA	Cost utility analysis
DAFNE	Dose Adjusted for Normal Eating
EQ-5D	EuroQol five dimensions questionnaire
GDG	Guideline development group
GMS	General medical services
HEED	Health Economic Evaluation Database
HIQA	Health Information and Quality Authority
HRB-CICER	Health Research Board-Collaboration in Ireland for Clinical Effectiveness Reviews
HSE	Health Service Executive
HTA	Health technology assessment
HTD	High tech drugs
ICER	Incremental cost-effectiveness ratio
LTI	Long-term illness scheme
MET	Motivational enhancement therapy
MMP	Medicines Management Programme
NCPE	National Centre for Pharmacoeconomics
NHS	National Health Service
NHS EED	National Health Service Economic Evaluations Database
NICE	National Institute for Health and Care Excellence
NMB	Net monetary benefit
NPH	Neutral protamine hagedorn
PCRS	Primary Care Reimbursement Service
PICO	Population, intervention, comparison and outcome

QALY	Quality-adjusted life year
RCT	Randomised-controlled trials
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
SMBG	Standard monitoring of blood glucose
SMS	Self-management support
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
WTP	Willingness to pay

1. Introduction

1.1 Scope of work

The diabetes guideline development group (GDG) was tasked with developing a clinical guideline, *Type I diabetes in adults guideline,* for the Irish healthcare system. Developing a new clinical guideline (de novo development) or adapting an existing clinical guideline is a resource-intensive process. With this in mind, the GDG identified a recent high-quality clinical guideline that was considered applicable to the Irish healthcare setting: the *Clinical guideline NG17 Type 1 diabetes in adults: diagnosis and management*,[(1)] which was informed by a systematic literature review up to 28 August 2014, and published by the National Institute for Health and Care Excellence (NICE) in the United Kingdom (UK) in 2015. Given its availability, the GDG decided to pilot NICE contextualisation as the methodology by which the *Adult type I diabetes mellitus* guideline would be developed. Contextualisation is a process designed to streamline the development of high-quality clinical guidelines and is an alternative to adaption or de novo developmentAs part of the contextualisation process, HRB-CICER (Health Research Board-Collaboration in Ireland for Clinical Effectiveness Reviews) reviewed the economic evidence underpinning NICE's *Clinical guideline NG17 Type 1 diabetes in adults: diagnosis and management*.[(1)]

The purpose of this review was to ensure that the economic evidence could be applied to the Irish healthcare setting. The review encompassed a systematic appraisal of the literature identified in the NICE guideline, including reviews of the economic evidence tables, and the de novo cost-effectiveness modelling of health interventions in Appendices H, N, O and P of the 2015 guideline. It also included the excluded economic studies contained in Appendix L of the 2015 guideline. Consistent with the NICE contextualisation process, the systematic review of the cost-effectiveness literature underpinning the NICE guideline was not updated. However, a targeted literature review was conducted and completed to identify economic literature made available since August 2014 within the Irish context that could substantiate the evidence-base for contextualisation to Ireland. Nonetheless, the recommendations are principally based on the evidence identified during the systematic review conducted in 2014.

2. Economic evidence

2.1 Methodology

The NICE (2015) guideline identified and considered 30 review questions defined in line with the population, intervention, comparison and outcome (PICO) framework based on the key clinical areas identified in the scope of the guideline. A full systematic literature review of the economic and clinical evidence to August 2014 was completed for each of the review questions. In compiling the evidence for its 2015 guideline, NICE critically appraised the applicability of relevant studies using the economic evaluations checklist in its guidelines manual.[(2)] Given the strength and relevance of the evidence within the NICE guideline, the scope of the contextualised guideline stated that the review questions for the Irish context would be consistent with those presented in the NICE guideline.

This review examined the economic evidence contained in Appendices H, N, O and P of the NICE guideline. The appendices consisted of evidence tables, which summarised the published economic literature identified for inclusion in the systematic review of the literature, and de novo cost-effectiveness models developed by NICE that assessed the interventions designated as priority areas for economic analysis. The assessment of quality and relevance by HRB-CICER was conducted in accordance with the HIQA guidelines for retrieval and interpretation of economic evaluations of health technologies.[(3)] The HIQA guidelines specify the use of an appropriate checklist for assessing the quality and applicability of the economic evaluations, such as the Consensus on Health Economics (CHEC)-List, the *British Medical Journal* (*BMJ*) Checklist or the Philips Checklist.[(4-6)] As such, the applicability of the evidence in the NICE guideline to the Irish context was evaluated in terms of its:

- relevance to the healthcare setting
- study perspective
- time horizon
- health outcome measures and
- methodological limitations.

Where clarification beyond the evidence contained in the NICE guideline was required, this review

consulted the original publication of the relevant study.

The costs presented were updated to 2016 euros to aid interpretation of the cost-effectiveness of the health interventions within the Irish context. The process for updating costs followed the procedure for historical cost adjustment outlined in the HIQA guidelines for economic evaluation.[3] Online national statistics websites were consulted to access relevant consumer price indices for health to inflate the costs to 2016; costs were then transferred to Ireland using purchasing power parities (PPPs) for cost adjustment.[8-16] These updated costs are presented in brackets as 2016 euros alongside the costs presented by NICE. Two reviewers independently performed data extraction with any disagreement resolved through discussion. Cost calculations were undertaken by one reviewer and quality assured by a second reviewer. Costs were not updated where the base year was either not clearly reported or was inconsistent in the original publication. In Ireland, the cost-effectiveness threshold for pharmaceuticals is €45,000 per quality-adjusted life year (QALY) gained.[17] There is no explicit cost-effectiveness threshold for health technologies other than pharmaceuticals; however, a value of €45,000 is often used for reporting purposes.[3]

As part of the contextualisation process, economic evidence within the context of the Irish healthcare setting was identified in addition to a review of the economic evidence supplied by NICE. This evidence was identified by updating the systematic search contained in Appendix F of the NICE guideline, reviewing the publications of key authors and hand searching the bibliographies of relevant economic evaluations of the treatment of diabetes in Ireland. The health economic search (contained in Appendix F of the NICE guideline) was updated for the period from August 2014 to August 2017 in the Embase, MEDLINE and Cochrane Library databases. The results of these searches were screened to identify economic evidence in the Irish healthcare setting published during this period. The search terms and results are detailed in Appendices A to C of this review.

In addition, the following grey literature sources were consulted:

- published recommendations by the National Centre for Pharmacoeconomics (NCPE) relating to company submissions for pharmaceuticals
- relevant health technology assessments (HTAs) conducted by HIQA
- the approved medications list of the Health Service Executive (HSE) to confirm whether a drug had been reimbursed under the long-term illness scheme (LTI)

- the HSE's Medicines Management Programme (MMP) to obtain position papers and to identify drugs listed on the Preferred Drugs Initiative that may serve to inform recommendations for the treatment of diabetes in Ireland[18]
- the Rian and Lenus health repositories to identify relevant Irish publications.

2.2 Results

The results of the review are outlined in section 2.2.1 to section 2.2.10. The results comprise an appraisal of the economic evidence presented by NICE and a summary and appraisal of Irish economic evidence identified in the targeted literature review conducted by HRB-CICER. The evidence is categorised according to the intervention type assessed. On the whole, the economic literature described below was relatively poor with only a limited number of high-quality and applicable economic analyses identified. Moreover, the economic literature on occasion reported conflicting findings on the cost-effective nature of interventions. Finally, there was no Irish economic evidence included in the evidence compiled by NICE. In general, however, the conclusions of HRB-CICER were consistent with the recommendations provided by NICE. Studies from the UK were generally considered to be highly applicable to the Irish healthcare setting given the similarities between the Type 1 diabetes populations and the comparability of the respective healthcare systems and delivery of healthcare.

A number of different discount rates were applied to the costs and benefits evaluated in the studies identified. It should be noted that the incorporation of different discount rates in economic evaluations may have a considerable impact on the incremental cost-effectiveness ratio (ICER) of interventions where the intervention is associated with future costs and benefits. For instance, diabetic retinopathy screening will have immediate costs and projected future benefits. Therefore, if considering the transferability of a study that uses a discount rate that is lower than the 5% rate specified by Irish national HTA guidelines, then the estimated benefits will be inflated. This may lead to an underestimate of the ICER (that is, the technology would be considered more cost-effective) in the Irish setting. However, the benefits in most of the interventions considered here are mainly accrued in the short term — meaning that changes in the discount rate will only have a marginal effect.

2.2.1 Diagnosis (Recommendations 3.1.1 to 3.2.8)

No economic evidence was identified for inclusion in the NICE guideline. No additional economic evidence was identified for inclusion in this targeted review.

2.2.2 Education programmes and self-care (Recommendations 3.3.1 to 3.5.2)

One UK-based study by Kruger et al.[19] was included in the economic evidence of the NICE guideline for education programmes and self-care. A deterministic decision analytic model was developed based on the Sheffield Type 1 Diabetes Policy Model to assess the cost-effectiveness of the Dose Adjusted for Normal Eating (DAFNE) programme in comparison to receiving no DAFNE education programme. The analysis adopted the perspective of the National Health Service (NHS) and was modelled over a lifetime time horizon. This took the form of a cost-utility analysis (CUA) where a quality adjusted life-year (QALY) was the health outcome of interest. Discounting of costs and benefits was applied at a rate of 3.5%, which is lower than the 5% discount rate specified in the Irish national HTA guidelines for the reference case, while unit costs were reported in 2011/12 GBP (Great British pound). The patient population consisted of adults with Type 1 diabetes in whom HbA1c (haemoglobin A1c or glycated haemoglobin) was used as the key surrogate outcome predicting long-term diabetes-related complications. The new intervention (DAFNE) was found to be slightly more costly and effective than receiving no DAFNE, and the ICER of £14,475 per QALY gained was considered cost-effective in the UK setting (threshold of £20,000 to £30,000 per QALY gained). However, NICE reported some significant limitations, including:

- the historical nature of data incorporated in the model that restricts the accuracy of the incidence of complications in the UK DAFNE population
- extrapolation and assumptions on HbA1c levels
- and that not all relevant costs were included within the model.

In addition to the evidence identified by NICE relating to structured education programmes, another UK-based study was identified in the targeted review. The study by Heller et al.[20] was deemed to be applicable to the Irish healthcare setting. In this study, the authors used the Sheffield Type 1 Diabetes Policy Model to assess the cost-effectiveness of the DAFNE programme in comparison with no training programme. The CUA adopted the perspective of the NHS, was modelled over a lifetime time horizon with discounting of costs and benefits applied at a rate of 3.5%, while unit costs were reported as 2012/13 GBP. The cohort consisted of patients with Type 1

diabetes in whom HbA1c was used as the key surrogate outcome predicting long-term diabetes-related complications. The authors found that receiving DAFNE training dominated receiving no training over the patient's lifetime (that is, DAFNE was less costly and more effective). This was despite the higher cost of insulin (as patients who received DAFNE used more) and the cost of the DAFNE programme itself due to cost savings associated with a reduction in long-term complications and adverse events.

The Heller study reported on the cost-effectiveness of delivery methods comparing a five-week versus one-week DAFNE programme. The authors reported that the five-week delivery method was slightly more cost-effective in the short term (one year), but that the one-week programme was marginally favoured in the lifetime analysis. The differences between the delivery methods, in terms of projected utilities, costs and incidence rates, were negligible. However, there were a number of limitations to the analysis. The model incorporated data from non-UK sources to define the risk of long-term complications, some of which were over 20 years old, which restricts the accuracy of the incidence of complications in the UK population; the risk of long-term macrovascular complications primarily depended on HbA1c levels with the effect of other risk factors not captured. The model also failed to incorporate uncertainty surrounding some of the parameters.

In December 2015, HIQA completed a HTA that examined the clinical- and cost-effectiveness of self-management support (SMS) interventions for both Type 1 and Type 2 diabetes.[21] Within the confines of the HTA, a self-management support intervention was broadly defined as any intervention that helps patients to manage portions of their chronic disease through education, training and support.[21] Cost-effectiveness was assessed through a systematic review of the literature. A journal article of the systematic review of the costs and cost-effectiveness of SMS interventions was subsequently published in 2016.[22] The advice provided by HIQA to the HSE reported that education programmes may be cost-effective relative to usual care, but that the evidence was limited and undermined by the limited number and quality of studies.[21] The applicability of these results were noted to depend on the extent to which the effect sizes estimated in trials, which typically involve no more than 18 months' follow-up, persist over a patient's lifetime. A limiting factor within several of the evaluations was the use of randomised-controlled trials (RCTs) where the observed benefit was not found to be statistically significant. It was recommended that the results of these studies should therefore be interpreted with caution,

although the general finding is of potential cost-effectiveness.

HIQA's systematic review retrieved 38 economic evaluations of chronic disease self-management interventions for the treatment of diabetes. Of these, 19 studies concerned cohorts with Type 2 diabetes only, 15 studies included all adult patients with diabetes and four studies specified a population of adult patients with Type 1 diabetes only. The review found three evaluations of SMS education programmes where the population was restricted to adults with Type 1 diabetes and all three studies found structured education to be cost-effective relative to usual care.[23-25] HIQA's review identified two studies that were not included in NICE's review.[23, 26]

Gillespie et al.,[23] developed a trial-based analysis to estimate the cost-effectiveness of group follow-up compared to individual follow-up after participation in the DAFNE programme for adults with Type 1 diabetes in Ireland. The CUA assumed an 18-month time horizon, adopted the perspective of the HSE and did not apply discounting. The authors noted that group follow-up post-structured education using DAFNE is less costly and less beneficial than individual follow-up (although the difference in effect was marginal and not statistically significant in the base-case analysis) and concluded that there was little evidence to support the implementation of group care as the sole means of follow-up after structured education. A number of limitations were highlighted by the authors. The study design lacked blinding, thus there was a risk of performance bias, and the data were collected via retrospective structured questionnaires at baseline and at three follow-up points: six months, 12 months and 18 months; thus there was a risk of participant recall bias. Additionally, there was a lack of available Irish cost and utility data which led to the incorporation of assumptions regarding generalisability of cost inputs, while other costs items, such as diabetic retinopathy screening, were not captured in the analysis. As the analysis was modelled over an 18-month time horizon, medium- and longer-term differences in benefits were not considered.

Ismail et al.[26] evaluated motivational enhancement therapy (MET) and cognitive behavioural therapy (CBT) in order to improve glycaemic control when delivered by general nurses with additional training in these techniques. The cohort consisted of adults with Type 1 diabetes for a minimum duration of two years and a current HbA1c value between 8.2% and 15%. The study conducted a CUA from the perspective of the NHS using data generated by an randomised controlled trial (RCT) modelled over a one-year time horizon. Compared to usual care, neither MET alone nor MET in combination with CBT were found to be cost-effective according to conventional UK or Irish thresholds. A number of limitations applied to the analysis. Firstly, the cost data were

potentially subject to participant recall bias due to data collection via questionnaire. Secondly, there was a risk of over-counting of costs where the intervention group participants could have mistakenly reported therapy sessions as part of their routine diabetes care, in which case the analysis would underestimate the cost saving. Finally, the time horizon may have been insufficient to accurately identify longer-term outcomes for the patient cohort. The authors stressed that the cost-effectiveness results should be interpreted with caution given a failure to account for uncertainty in the analysis.

Table 1. Summary of educational and self-care interventions

Study	Applicability	Quality	ICER	Findings
Gillespie et al. (2014, Ireland)[23]	Very relevant	Potentially serious limitations	ICERs not reported	Group follow-up post DAFNE was less costly and less beneficial versus individual follow-up
Heller et al. (2014, United Kingdom)[24]	Very relevant	Potentially serious limitations	Receiving the DAFNE programme was cost-saving and more effective versus receiving no structured education	DAFNE dominated receiving no formal education programme
Ismail et al. (2010, United Kingdom)[26]*	Very relevant	Serious limitations	£48,636 (€64,742) per QALY gained (CBT versus usual care); £311,970 (€415,282) per QALY gained (CBT and MET versus usual care)	Neither CBT nor CBT and MET were cost-effective versus usual care.
Kruger et al. (2013, United Kingdom) [19]	Very relevant	Potentially serious limitations	£14,475 per QALY gained	DAFNE was cost-effective versus standard practice.

CBT — cognitive behavioural therapy; DAFNE — dose adjustment for normal eating; ICER — incremental cost-effectiveness ratio; MET — motivational enhancement therapy.

*Denotes that the figures presented in GBP (Great British pound) are the incremental cost-effectiveness ratios (ICERs) presented in the original publication and have not been adjusted by NICE.

The adjusted ICER for Ireland is presented in parenthesis ( ).

Cost-effectiveness threshold in the UK is £20,000 to £30,000 per QALY gained.

Cost-effectiveness threshold in Ireland is €45,000 per QALY gained.

Overall, notwithstanding the limitations identified, there is strong evidence to suggest that the DAFNE education programme would be a cost-effective means of improving health outcomes for adults with Type 1 diabetes in Ireland. Although the DAFNE programme has not been examined

within an Irish economic evaluation, the analyses by Kruger et al. and Heller et al. both reported cost-effectiveness in the UK setting, while HIQA's analysis suggested that SMS programmes were likely to be cost-effective within the Irish setting. In addition, an Irish-based study assessed the cost-effectiveness of group versus individual follow-up after participation in DAFNE. This study served to demonstrate that group care would not be cost-effective as the sole means of follow-up after DAFNE participation. However, there may presently be insufficient robust evidence to inform a decision regarding the optimal follow-up (group or individual) following participation in DAFNE. Finally, neither MET nor MET in combination with CBT delivered by nurses with additional training in these techniques can be recommended as a means of improving glycaemic control in Ireland on the basis of the cost-effectiveness evidence identified and presented.

2.2.3 Blood glucose monitoring (Recommendations 3.6.1 to 3.6.26)

Two US-based studies were included in the economic evidence for blood glucose monitoring underpinning the NICE guideline.[27, 28] Huang et al.[27] developed a discrete simulation model that assessed the cost-effectiveness of real-time continuous glucose monitoring (CGM) in comparison to standard monitoring of blood glucose (SMBG). The model allowed for the simultaneous progression of diabetes through a number of major complications. The analysis adopted the perspective of the US healthcare system, was modelled over a lifetime time horizon and took the form of a CUA where health outcomes were measured in QALYs. Discounting of costs and benefits was applied at a lower rate of 3% than the 5% discount rate required in the reference case in the Irish national HTA guidelines. The analysis compared two cohorts of patients:

- adults aged 25 and older with an HbA1c≥7% and
- those with an HbA1c≤7% in age groups of patients aged 8 to 24 years.

Unit costs were assumed to be modelled as 2010 US dollars (same year as publication), since the cost year was not reported, and was presented by NICE as 2010 GBP. HRB-CICER did not adjust these costs to the Irish healthcare setting due to the ambiguity around the cost base year.

Huang et al. found that CGM would cost £63,828 per QALY gained. NICE noted that this would not be considered cost-effective at the £20,000 to £30,000 cost-effectiveness threshold in the UK setting. The authors did not conduct a probabilistic sensitivity analysis, although a univariate sensitivity analysis was performed. There was considerable uncertainty around the ICER, which

could be the result of the effectiveness data being derived from a single trial, but the probability of CGM being cost-effective was not reported. NICE reported significant limitations, including the failure to model hypoglycaemia — despite the reduction in hypoglycaemic events being one of the main benefits of CGM. Inclusion of hypoglycaemia may have increased the benefits of CGM and reduced its associated costs versus SMBG which would lead to a more favourable ICER. The study was funded by the Juvenile Diabetes Research Foundation which receives funding from the pharmaceutical and medical devices industry.

NICE developed an original economic model using the IMS CORE Diabetes Model[29] to compare the cost-effectiveness of CGM versus SMBG. The cohort represented adult patients with Type 1 diabetes in the UK. The CUA adopted the perspective of the NHS and was modelled over an 80-year time horizon. Discounting was applied at a rate of 3.5% with unit costs in 2013 GBP. The model compared CGM and five different frequencies of SMBG: (1) SMBG twice daily; (2) SMBG four times daily; (3) SMBG six times daily; (4) SMBG eight times daily; (5) SMBG 10 times daily; and (6) CGM (real time). Overall, SMBG eight times daily was found to be the most cost-effective strategy while SMBG 10 times daily was just above the £20,000 threshold at £23,426 (€28,114) per QALY gained.

There were a number of limitations in the analysis:

- clinical effectiveness data on alternative frequencies of SMBG were obtained from a cross-sectional study
- a higher frequency of testing could lead to a decrease in hypoglycaemic events, but these data could not be obtained from the available study
- the cohort may not adequately represent individuals with Type 1 diabetes who have problems controlling their HbA1c level with SMBG and self-injection only
- the analysis did not assess the cost-effectiveness of CGM in combination with insulin pumps, but this could be more cost-effective in people with glycaemic control issues
- some of the parameters incorporated in the model are not specific to Type 1 diabetes
- the model used HbA1c as one of the two main clinical outcome measures, but HbA1c is an intermediate outcome measure (although a reliable proxy of disease progression and complications)
- and the model did not explicitly include disutility due to hypoglycaemia.

NICE also undertook an original economic analysis, using the IMS Core Diabetes Model to compare the current HbA1c target of 7.5% with a target of 6.5%, in order to determine the optimum target HbA1c level that should be achieved to reduce the risk of complications. The CUA adopted the perspective of the NHS and was modelled over an 80-year time horizon. The patient population consisted of individuals with Type 1 diabetes in the UK and discounting of costs and benefits was applied at a rate of 3.5%. Costs to achieve different HbA1c target levels were not considered as it was noted that changes in HbA1c could be a result of a range of interventions, thus costs could not be reliably estimated. ICERs were not estimated as a result. The economic analysis found that achieving a target of 6.5% HbA1c compared to a 7.5% target is associated with a gain of 0.554 QALYs and a reduction in healthcare costs of £3,524. These consequences considered only the HbA1c reduction in terms of reduction of complications. The actual costs of implementing the strategies to reach the 6.5% HbA1c target were not considered and could offset the cost savings. The analysis did not provide information about which interventions would be cost-effective in achieving the 6.5% target. Of note, the IMS Core Diabetes Model is not specific to Type 1 diabetes and HbA1c is used as one of the main clinical outcomes despite being an intermediate outcome measure. Additionally, disutility due to fear of hypoglycaemia was not explicitly included in the model; and the analysis did not control for the potential increase of risk of hypoglycaemic events associated with a lower HbA1c target level, which may have led to an overestimation of the QALY gain and cost savings.

McQueen et al.[28] developed a probabilistic decision analytic model that assessed the cost-effectiveness of CGM in comparison to SMBG. The authors modelled progression of 12 different diabetes disease states, using a cycle length of one year, allowing for up to four co-existing medical conditions. The CUA adopted a US societal perspective and was modelled over a 33-year time horizon. The patient cohort consisted of adults with Type 1 diabetes who had a mean HbA1c level greater than 7%. Discounting was applied at a rate of 3% and unit costs were reported as 2007 US dollars but presented by NICE as 2007 GBP. Compared with SMBG, it was found that CGM would cost £29,029 (€48,119) per QALY gained. NICE reported potentially significant limitations, including the failure to model hypoglycaemia outcome rates which may have increased the benefits of CGM and reduced the costs compared to SMBG; this would have produced a more favourable ICER. The model assumes that there is a constant probability of diabetes complications over the patient's lifetime — which is unlikely to be the case. There was no evidence of a systematic review to identify evidence of effectiveness, and funding sources were not reported.

Table 2. Summary of blood glucose monitoring interventions

Study	Applicability	Quality	ICER	Findings
Huang et al. (2010, United States)[27]	Relevant	Potentially serious limitations	£63,828 per QALY gained	CGM was not cost-effective versus SMBG
NICE[1] (2015, United Kingdom)	Very relevant	Potentially serious limitations	Full ICERs not reported as interventions ranked according to NMB, but SMBG eight times daily was the optimal strategy; the ICER of SMBG 10 times daily versus SMBG eight times daily was £23,426 (€28,114) per QALY gained	SMBG eight times daily was found to be the most cost-effective strategy; SMBG 10 times daily was just above the £20,000 per QALY gained threshold
NICE[1] (2015, United Kingdom)	Very relevant	Potentially serious limitations	Incremental analysis not conducted	HbA1c target of 6.5% was associated with a QALY gain and a reduction in healthcare costs versus the 7.5% target
McQueen et al. (2011, United States)[28]	Partially relevant	Potentially serious limitations	£29,029 (€48,119) per QALY gained	CGM was cost-effective versus SMBG in the UK setting, but not in the Irish setting

CGM — real time continuous glucose monitoring; ICER — incremental cost-effectiveness ratio; NMB — net monetary benefit; SMBG —standard monitoring of blood glucose.

The adjusted ICER for Ireland is presented in parenthesis.

Cost-effectiveness threshold in the UK is £20,000 to £30,000 per QALY gained.

Cost-effectiveness threshold in Ireland is €45,000 per QALY gained.

Overall, the literature presents conflicting results regarding the cost-effectiveness of interventions for monitoring blood glucose. This is likely to be a consequence of contrasting methodological approaches undertaken in the analyses, such as differences in the perspective adopted. As such, the de novo analyses conducted by NICE are likely to be the most applicable and transferrable to Ireland given the similarities between the target populations and that they adopted the perspective of the healthcare payer in line with Irish national HTA guidelines.[3] The results indicate that SMBG (standard monitoring of blood glucose) eight times daily is the most cost-effective strategy for monitoring blood glucose.

While the de novo analysis by NICE suggests that using an HbA1c target of 6.5% or less is associated with a cost-saving and improvement in QALYs gained, it is noted that the analysis did not consider the potential costs and consequences of an increased incidence of hypoglycaemia events associated with use of a lower target. However, these results must be interpreted with caution given that the analyses were subject to a number of limitations. No Irish studies, in relation to the economic evaluation of blood glucose monitoring interventions, were identified for inclusion in the original NICE guideline or in the targeted search by HRB-CICER.

2.2.4 Insulin therapy (Recommendations 3.7.1 to 3.8.7)

In total, 11 studies were included in the economic evidence for insulin therapy interventions.[30-40] Cameron et al.[30] developed a probabilistic decision analytic model that compared the cost-effectiveness of six interventions:

- regular human insulin (0.68 IU/kg);
- insulin aspart (0.52 IU/kg);
- insulin lispro (0.52 IU/kg);
- neutral protamine Hagedorn (0.34 IU/kg);
- insulin glargine (0.28 IU/kg); and
- insulin detemir (0.28 IU/kg).

The CUA adopted the Canadian third-party payer perspective and was modelled over a 60-year time horizon. The patient population consisted of adults with Type 1 diabetes. Discounting was applied

at a rate of 5% and unit costs were reported in 2007 Canadian dollars, but presented by NICE as 2005 GBP. Cameron et al.[30] found that insulin aspart dominated regular human insulin (that is it was more effective and less costly), while insulin lispro was cost-effective at £15,442 (€21,036) per QALY gained and that long-acting insulin therapies were not cost-effective at the £20,000 to £30,000 UK threshold. A notable limitation is that although treatment effectiveness was assumed to be maintained over the lifetime of the patient, the trials included short follow-up times. NICE also reported discrepancies between the effectiveness data in the clinical review and economic review, but the authors explained that this was due to the meta-analysis being updated over time. Finally, NICE reported that if a full incremental analysis had been performed where insulin detemir had been compared to neutral protamine Hagedorn (NPH), instead of reporting the results of four pair-wise simulations, then insulin detemir would have been dominated by NPH.

Grima et al.[31] developed a Markov model that compared the cost-effectiveness of insulin glargine (22.16IU daily dose) versus NPH (27.17IU daily dose) and estimated the number and risk of microvascular and macrovascular complications and deaths dependent on HbA1c levels. The CUA adopted the Canadian public payer perspective and was modelled over a 36-year time horizon. The patient population consisted of adults with Type 1 diabetes who did not reach the recommended target (HbA1c ≤[less than or equal to]7%) with multiple daily injections of NPH insulin. Discounting was applied at a rate of 5% and unit costs were reported in 2005 Canadian dollars, but presented by NICE as 2005 GBP. The authors found that it would cost £10,903 (€15,478) per QALY gained; using the NICE threshold of £20,000 per QALY gained, insulin glargine would therefore be considered cost-effective.

The ICER was observed to be most sensitive to changes in efficacy of insulin glargine. NICE identified some significant limitations in the study that included:

- a lack of detail on the cohort's characteristics;
- the source of the utilities data being derived from the UKPDS (United Kingdom Prospective Diabetes Study) trial which focused exclusively on Type 2 diabetes;
- the source of the cost for insulin glargine (being provided by the manufacturer); and
- a failure to explore uncertainty around key clinical parameters.

McEwan et al.[32] developed a deterministic decision analytic model to assess the cost-effectiveness of insulin glargine versus NPH within five different scenarios. The model incorporated seven independent complications in either fatal or non-fatal states; or in ascending severity to consider five scenarios. The CUA adopted the UK NHS payer perspective and was modelled over a 40-year time horizon. The patient population consisted of adults with Type 1 diabetes and discounting was applied at a rate of 3.5% with unit costs in 2005 GBP. The authors found that it would cost from £3,189 (€4,237) to £9,767 (€17,205) per QALY gained, and therefore insulin glargine was cost-effective at the £20,000 threshold. A number of limitations were observed. One meta-analysis used for the clinical data was unpublished and thus its quality could not be appraised; the effectiveness data were derived from non-inferiority trials and therefore were not adequately powered to detect differences between the regimens; and the source of the utilities data were derived from the UKPDS trial which had limited applicability as noted previously. Finally, a number of the cost inputs were conservatively estimated which may have led to an underestimate of the true cost-effectiveness of the intervention.

NICE[1] conducted a de novo analysis, using the IMS Core Diabetes Model, to evaluate the cost-effectiveness of seven basal insulin regimens:

- insulin detemir (once daily);
- insulin detemir (twice daily);
- insulin glargine (once daily);
- insulin degludec (once daily);
- insulin NPH (once daily);
- insulin NPH (twice daily);
- insulin NPH (four times daily).

The analysis was based on the benefits of improved HbA1c levels which is likely to reduce the occurrence of short-term and long-term complications. The CUA adopted the perspective of the NHS and was modelled over an 80-year time horizon. The patient population consisted of

individuals with Type 1 diabetes in the UK and discounting was applied at a rate of 3.5% with unit costs from 2013 GBP. The analysis found that insulin detemir twice daily was the most cost-effective of the seven interventions modelled. Additionally, insulin glargine once daily or detemir once daily were found to be cost-effective for patients for whom insulin detemir twice daily is not an option. One study aside,[30] the authors found that this finding was in line with that of the published literature.[31-33, 37-40] NPH four times daily was dominated by the once and twice daily regimens of insulin NPH. A number of limitations applied to this analysis. Firstly, many of the parameters were not specific to Type 1 diabetes. Secondly, HbA1c was one of the main clinical outcome measures in the analysis, but this is an intermediate outcome measure (although a reliable proxy of disease progression and complications). Thirdly, the model did not explicitly include utility decrements due to fear of hypoglycaemia. Lastly, the model did not control for patient adherence and disutility due to multiple daily injections.

Palmer et al.[33] developed a simulation model, in which insulin detemir plus insulin aspart was compared to NPH plus human soluble insulin, to assess the impact of HbA1c levels on the complications of diabetes. The CUA adopted the perspective of the NHS and was modelled over a lifetime time horizon. The patient population consisted of adults with Type 1 diabetes and discounting was applied at a rate of 3.5% with unit costs from 2003 GBP. The authors found that it would cost from £19,285 per QALY gained and therefore insulin detemir plus insulin aspart was cost-effective at the £20,000 to £30,000 threshold. Sensitivity analysis did not address the uncertainty surrounding key clinical parameters such as the effectiveness of treatments in reducing hypoglycaemic events. In addition, the sources of clinical data may have been selectively included due to the absence of a systematic review, and the results of an unpublished meta-analysis, from which the clinical data were sourced, may be unrepresentative given its high proportion of male participants. Treatment effectiveness was assumed to be maintained over the patient's lifetime, although trial data were for between 16 weeks and six months; utilities were derived from the UKPDS trial; insulin doses were not reported; and QALY gains were not attributed to a reduction in hypoglycaemic events which may have reduced the overall benefits of insulin detemir. The starting age (39.9 years) of the cohort also appeared to be high.

In an update to their previous model, Palmer et al.[34] developed a probabilistic decision analytic model to compare insulin detemir plus insulin aspart (28.2 and 26.3 internation units (IU) daily) versus NPH plus human soluble insulin (32.1 and 26.4 IU daily). The CUA adopted the perspective of

the NHS and was modelled over a lifetime time horizon. The patient population consisted of adults with Type 1 diabetes and discounting was applied at a rate of 3.5% with unit costs in 2004 GBP. Consistent with the previous analysis, insulin detemir plus aspart was found to be cost-effective at the £20,000 threshold with each additional QALY gained costing £2,500. However, the baseline event and clinical effectiveness data were derived from a single trial, which demonstrated a larger reduction in HbA1c and hypoglycaemic events for insulin detemir than seen in either previous trials. Treatment effectiveness was assumed to be maintained over the lifetime of the patient, although the trial was for 18 weeks only. Utilities were again derived from the UKPDS trial and the starting age (39.1 years) of the cohort appeared to be high.

Pfohl et al.[35] developed a discrete event simulation model to assess insulin glargine (24.5 IU daily – 1.1 injection per day) versus NPH (29.1 IU daily – 2.1 injections per day). The CUA adopted a German third-party payer perspective and was modelled over a 40-year time horizon. The patient population consisted of adults with Type 1 diabetes and discounting was applied at a rate of 3%; unit costs were in 2009/10 Euro, but were presented by NICE as 2010 GBP. The authors found that insulin glargine dominated NPH. Effectiveness data were sourced from a meta-regression that included studies which were excluded from NICE's clinical review. Utilities were derived from the UKPDS trial and the sensitivity analysis appeared to be limited. It was noted that the study was funded by a pharmaceutical company, Sanofi.

Pratoomsoot et al.[36] developed a simulation model to assess the impact of HbA1c levels on the complications of diabetes in which the cost-effectiveness of insulin lispro, 32.25 IU (plus basal NPH, 20.25 IU) versus regular human insulin, 32.25 IU (plus basal NPH, 20.25 IU) was compared. The CUA adopted the perspective of the NHS and was modelled over a 50-year time horizon. The patient population consisted of adults with Type 1 diabetes specific to a UK setting and discounting was applied at a rate of 3.5% with unit costs from 2007 GBP. Insulin lispro was found to dominate regular human insulin. However, treatment effectiveness was assumed to be maintained over the lifetime of the patient although trial data had short-term follow-up; utilities were derived from the UKPDS trial; and the starting age (37.8 years) of the cohort appeared to be quite high. It was noted that the study was supported by a research grant from Eli Lily, manufacturers of insulin lispro.

Tunis et al.[37] also developed a simulation model to assess the impact of HbA1c levels on the complications of diabetes in which the cost-effectiveness of insulin detemir plus insulin aspart (39.9 and 30.6 IU daily) was compared with NPH plus insulin aspart (32.6 and 26.9 IU daily). The CUA

adopted the perspective of the Canadian provincial government and was modelled over a 60-year time horizon. The patient population consisted of adults with Type 1 diabetes and discounting was applied at a rate of 5% with unit costs from 2007 Canadian dollars and presented by NICE as 2007 GBP. Tunis et al.[37] found that it would cost £12,989per QALY gained; treatment with insulin detemir plus insulin aspart would therefore be cost-effective at the £20,000 threshold. Uncertainty in the effectiveness of treatments in reducing HbA1c and the cost of insulin treatments were not reported. Sources of clinical data may have been selectively included as a systematic review of clinical evidence was not performed by the authors, baseline characteristics were compiled from a source that is over 20 years old[42] and treatment effectiveness was assumed to be maintained over the lifetime of the patient, although trial data had follow-up of 24 months only. It was noted by NICE that the authors received research funding from the pharmaceutical firm Novo Nordisk.

Valentine et al.[38] developed a simulation model to assess the impact of HbA1c levels on the complications of diabetes and compared the cost-effectiveness of NPH (twice daily plus human soluble insulin), insulin detemir (twice daily plus insulin aspart) and insulin glargine (once daily plus insulin aspart). The CUA adopted the perspective of the US healthcare payer and was modelled over a 35-year time horizon. The patient population consisted of adults with Type 1 diabetes and discounting was applied at a rate of 3% with unit costs in 2005 US dollars and presented by NICE as 2005 GBP. The authors found that treating patients with insulin detemir would cost £9,526 per QALY gained relative to NPH, and that insulin detemir dominated glargine. Sources of clinical data may have been selectively included due to the absence of a systematic review, insulin doses used in the analysis were not reported, utilities were derived from the UKPDS trial and treatment effectiveness was assumed to be maintained over the patient's lifetime despite trial data being for 18 months. It was noted by NICE that the authors of the study also received research funding from Novo Nordisk.

Valentine et al.[39] then developed a simulation model to assess the impact of HbA1c levels on the complications of diabetes and compared the cost-effectiveness of NPH plus insulin aspart (32.6 and 26.9 IU daily) versus insulin detemir plus insulin aspart (39.9 and 30.6 IU daily). The CUA adopted the perspective of the Swedish healthcare payer and was modelled over a 50-year time horizon. The patient population consisted of adults with Type 1 diabetes while discounting was applied at a rate of 3% with unit costs in 2006 Swedish kronor and presented by NICE as 2006 GBP. Valentine et al. found that it would cost £3,433 per QALY gained, and thus NPH plus insulin aspart was cost-

effective at the £20,000 threshold. However, sources of clinical data may have been selectively included as a systematic review of clinical evidence was not performed by the authors; treatment effectiveness was assumed to be maintained over the patient's lifetime despite trial data being for 24 months only; insulin doses used in the analysis were not reported; and utilities were derived from the UKPDS trial. It was noted by NICE that the authors of the study received research funding from Novo Nordisk.

Warren et al.[40] developed a deterministic decision analytic model that compared the cost-effectiveness of insulin glargine versus NPH. The CUA adopted the perspective of the NHS and was modelled over a nine-year time horizon. The patient population consisted of adults with Type 1 diabetes and unit costs were 2001 GBP. Discounting rates were not reported. The authors found that each additional QALY gained would cost from £3,496 to £4,978 and thus insulin glargine was cost-effective at the £20,000 threshold. However, the sensitivity analysis appeared to be very limited, discount rates were not reported and the time horizon was very short. The baseline event data were derived from a source which was excluded in NICE's clinical review and the cost inputs included were limited. Due to confidentiality restrictions, some data relating to the assessment group were not reported by Warren et al.

Table 3. Summary of insulin therapy interventions

Study	Applicability	Quality	ICER	Findings
Cameron (2009, Canada) [30]	Partially relevant	Minor limitations	Insulin aspart was cost-saving versus regular human insulin (intervention 2 versus 1); £15,442 (€21,036) per QALY gained (intervention 3 versus 1); £46,829 (€63,792) per QALY gained (intervention 5 versus 4); per £206,48 (€281,284) QALY gained (intervention 6 versus 4)	Insulin aspart dominated regular human insulin; insulin lispro was also cost-effective versus regular human insulin; long-acting insulin therapies were not cost-effective.
Grima (2007, Canada) [31]	Partially relevant	Serious limitations	£10,903 (€15,478) per QALY gained	Insulin glargine was cost-effective versus

Study	Applicability	Quality	ICER	Findings
				NPH.
McEwan (2007, United Kingdom) [32]	Partially relevant	Serious limitations	£3,189 (€4,237) to £9,767 (€17,205) per QALY gained	Insulin glargine was cost-effective versus NPH.
NICE (2015, United Kingdom)[1]	Very relevant	Potentially serious limitations	Excluding the dominated strategies, the ICER of insulin detemir (twice daily) versus NPH was £9,986 (€11,985) per QALY gained; the other ICERs were not reported but ranked according to NMB	Insulin detemir (twice daily) was most cost-effective; insulin glargine or detemir (both once daily) were also cost-effective.
Palmer (2004, United Kingdom) [33]	Very relevant	Potentially serious limitations	£19,285 per QALY gained	Insulin detemir plus insulin aspart versus NPH plus human soluble insulin was cost-effective.
Palmer (2007, United Kingdom) [34]	Very relevant	Potentially serious limitations	£2,500 per QALY gained	Insulin detemir plus insulin aspart versus NPH plus human soluble insulin was cost-effective.
Pfohl (2012, Germany) [35]	Partially relevant	Potentially serious limitations	Insulin glargine was cost-saving versus NPH	Insulin glargine was cost-effective versus NPH.
Pratoomsoot (2009, United Kingdom) [36]	Very relevant	Minor limitations	Insulin lispro was cost-saving versus regular human insulin	Insulin lispro plus basal NPH was cost-effective versus regular human insulin.

Study	Applicability	Quality	ICER	Findings
Tunis (2009, Canada) [37]	Partially relevant	Potentially serious limitations	£12,989 per QALY gained	Insulin detemir plus insulin aspart was cost-effective versus NPH plus insulin aspart.
Valentine (2006, United States) [38]	Partially relevant	Potentially serious limitations	£9,526 per QALY gained	Insulin detemir was cost-effective versus NPH and versus glargine.
Valentine (2011, Sweden) [39]	Partially relevant	Potentially serious limitations	£3,433 per QALY gained	NPH plus insulin aspart was cost-effective versus insulin detemir plus insulin aspart.
Warren (2004, United Kingdom) [40]	Relevant	Serious limitations	£3,496 to £4,978 per QALY gained	Insulin glargine was cost-effective versus NPH.

ICER — incremental cost-effectiveness ratio; NMB — net monetary benefit; NPH — neutral protamine Hagedorn.

The adjusted ICER for Ireland is presented in parenthesis ( ).

Cost-effectiveness threshold in the UK is £20,000 to £30,000 per QALY gained.

Cost-effectiveness threshold in Ireland is €45,000 per QALY gained.

*The ICER was not adjusted for the results of Huang et al.[27] as the base year for unit costs was not reported. NICE assumed that the base year was the same as the publication year, however, this is unlikely to be the case

The search of the NCPE database retrieved 14 economic evaluations relating to diabetes. Of these, six pharmacoeconomic assessments were submitted for insulin therapies indicated for treatment of Type 1 diabetes. The remainder of the search results were not considered to be relevant to this analysis. The results of the search are presented in Table 4.

Table 4. Reimbursement status of insulin medications for treatment of Type 1 diabetes in Ireland

Intervention	NCPE recommendation	Date of recommendation (day/month/year)	Reimbursed through PCRS
Insulin aspart (Fiasp®)	Not recommended for full HTA after rapid review.	14/06/17	Yes
Insulin glargine (Abasaglar®)	Not recommended for full HTA after rapid review.	12/10/15	Yes
Insulin glargine U300 (Toujeo®)	Recommended for full HTA at the submitted price.	02/07/15	Yes
Insulin degludec (Tresiba®)	Not recommended for reimbursement at the submitted price. Therefore, insulin degludec (Tresiba®) is not considered cost-effective versus insulin glargine for the treatment of diabetes mellitus in adults, adolescents and children aged greater than one year. However, the HSE approved reimbursement following confidential price negotiation.	04/05/15	Yes
Insulin aspart (NovoRapid® FlexTouch®)	Recommended for full HTA but could not be assessed in terms of cost-effectiveness as a HTA dossier was not received from the manufacturer to support cost-effectiveness. Hence, the intervention was not reimbursed.	28/08/14	No
Inhaled insulin (Exubera®)	Report regarding cost-effectiveness and budget impact was submitted by the manufacturer to support application for reimbursement under the Community Drugs Scheme. NCPE summary report	April 2006	No

Intervention	NCPE recommendation	Date of recommendation (day/month/year)	Reimbursed through PCRS
	indicated that the drug was borderline cost-effective under the GMS scheme but not under the LTI scheme, while the budget impact analysis suggested reimbursement under the HTD scheme.		

GMS — general medical services; HSE — Health Service Executive; HTA — health technology assessment; HTD — high tech drugs; ICER — incremental cost-effectiveness ratio; LTI — long-term illness scheme; NCPE — National Centre for Pharmacoeconomics; PCRS — Primary Care Reimbursement Service.

The evidence surrounding the cost-effectiveness of insulin glargine was quite strong with five studies finding glargine to be cost-effective while the NCPE also issued two positive recommendations regarding its cost-effectiveness.[1, 31, 32, 35, 40] Therefore, the evidence indicates treatment of Type 1 diabetes with insulin glargine is cost-effective. One study found insulin aspart to be cost-effective versus insulin lispro.[30] This finding is reinforced by the NCPE's positive recommendation. Two studies[1, 38] found insulin detemir to be cost-effective while three studies[33, 34, 37] found combined insulin detemir plus insulin aspart therapy to be cost-effective versus combinations of NPH, regular human insulin and glargine. One study each found insulin lispro plus NPH and NPH plus insulin aspart to be cost-effective.[36, 39] The 2015 NICE guideline did not identify any Irish studies for inclusion in its economic evaluation of insulin therapy interventions. Similarly, no additional Irish studies were identified in the targeted search by HRB-CICER with the exception of the NCPE appraisals of company submissions.

In the following areas, no economic evidence was identified for inclusion in the NICE guideline. No additional economic evidence was identified from this targeted review for inclusion in these areas:

2.2.5 Pancreas transplant and islet cell transplantation (Recommendations 3.9.1 to 3.9.2)

2.2.6 Awareness and management of hypoglycaemia (Recommendations 3.10.1 to 3.10.15)

2.2.7 Ketone monitoring and management of DKA (Recommendations 3.11.1 to 3.11.12)

2.2.8 Associated illness and control of cardiovascular risk (Recommendations 3.12.1 to 3.13.13)

2.2.9 Care of adults with type 1 diabetes in hospital (Recommendations 3.14.1 to 3.14.11)

2.2.10 Complications (Recommendations 3.16.1 to 3.16.46)

3. Excluded economic studies

3.1 Methodology

The final step in conducting a review of the economic evidence identified by NICE for the treatment of Type 1 diabetes was to find out whether any relevant literature for the Irish setting had been excluded from the evidence base that was used to inform the recommendations of the 2015 guideline. The purpose of the review of excluded literature was to determine if NICE had excluded economic studies that were directly applicable to the Irish context, such as studies of Irish origin. For obvious reasons, such studies may carry greater weight in terms of applicability to the Irish context than that of the UK.

The evidence review involved screening the table in Appendix L of the 2015 guideline to determine:

1. the studies that were excluded; and
2. the reason for their exclusion.

The title and abstract of each study was screened in order to validate or reject the reason for exclusion. It was possible to determine the origin, date and applicability of the studies to the GDG's review questions in the Irish context. This information was used to decide whether the study should be considered for inclusion in the evidence-base supporting the contextualised guideline. The HRB-CICER review team made a recommendation on the merits of the exclusion or inclusion of each study.

3.2 Results

The results of the review of excluded economic studies are presented in Table 5. Only one of the excluded studies analysed the impact of interventions in the context of the Irish population; however, the study was excluded due to significant limitations regarding the study design which incorporated a within-group comparison where the authors reviewed the case notes of four study participants in isolation.

Table 5. Results of review of excluded economic studies

Reference	NICE reason for exclusion	HRB-CICER conclusion
Davey[43] (1998, Australia)*	This was included in the previous guideline but does not look at the correct intervention for this review question. This study has been selectively excluded due to the methodological limitations of willingness to pay studies and the availability of superior evidence from the UK.	This study has been selectively excluded. Although insulin lispro is primarily used for treatment T2DM, it is also used to treat T1DM and therefore HRB-CICER does not agree that the study looks at the wrong intervention. However, the study involved a mixed sample (n=83) of patients with T1DM and T2DM, is 20 years old, not of Irish origin and incorporated a willingness-to-pay analysis which is associated with methodological limitations.
DCCT Group[42] (1996, United States)	This was included in the previous guideline but does not look at the correct intervention.	This study has been selectively excluded because it is over 20 years old and does not analyse the Irish setting. However, the study does not necessarily look at the wrong intervention – it examines the cost-effectiveness of conventional and intensive insulin therapy for management of insulin-dependent diabetes mellitus (T1DM).
DeWeerdt[44] (1991, United Kingdom)	Selectively excluded on the basis of the availability of a UK CUA.	This study has been selectively excluded due to the availability of a more recent UK-based CUA.
Dranitsaris[45] (2000, Canada)	This was included in the previous guideline but does not look at the correct intervention for this review question.	This study has been selectively excluded because it is over 17 years old and does not analyse the Irish setting. Furthermore, the study adopted a WTP framework which is associated with methodological limitations and analysed a relatively small sample (n=80) of taxpayers that were not diagnosed with diabetes.

Reference	NICE reason for exclusion	HRB-CICER conclusion
Elliott[25] (2014, United Kingdom)	Selectively excluded as it was less applicable and had more limitations compared to the included study.	This study has been selectively excluded. Although the study examines the DAFNE programme, it has more limitations than those that were included in the examination of structured educational programmes.
Ericsson[46] (2013, Sweden)	This study assesses the short-term effects of hypoglycaemia event reduction. As such, it does not include all important health effects in the long term.	This study has been selectively excluded because it was conducted from the societal perspective rather than that of the healthcare payer and it failed to model the long-term effects of treatment (time horizon was one year).
Glasgow[47] (1997, United States)	Selectively excluded as it was less applicable and had more limitations compared to the included study.	This study has been selectively excluded because it is over 20 years old and there was more recent evidence available.
Guillermin[48] (2011, Canada)	This study was excluded due to methodological limitations as the study analysed the cost difference between insulin glargine and insulin detemir and did not consider quality-of-life.	This study was selectively excluded as the analysis incorporated a CMA framework which assumes equivalence between the health interventions.
Hannon[49] (2011, Ireland)	This study was assessed as partially applicable with very serious limitations. It was a within-group comparison where admission costs were assessed for four patients before and after they had the intervention. The comparator is unclear. The cost of the intervention itself was not reported and/or not included.	This study was potentially applicable given its Irish context. However, the analysis contains a number of serious limitations with regards to study design. Firstly, the within-group comparison failed to clarify the comparator incorporated in the analysis. Secondly, the sample size was very small as the authors reviewed the case notes of only four participants. Thirdly, the study employed a CBA framework rather than CUA where the

Reference	NICE reason for exclusion	HRB-CICER conclusion
		methods and cost of the intervention were unclear. As such, the study was selectively excluded.
Herman[50] (1997, United States)	This was included in the previous guideline but is only a cost analysis and does not look at the correct intervention for this review question.	Although the study (which analyses intensive versus conventional therapy) does not necessarily look at the wrong intervention, it was selectively excluded because it is over 20 years old.
Newman[51] (2009, United Kingdom)	This study was excluded as it was a cost-analysis that was performed alongside a trial of a mixed population of patients with Type 1 and Type 2 diabetes, with an 18-month time horizon.	This study has been selectively excluded because it studied a mixed cohort of patients with Type 1 and Type 2 diabetes analysed over a short-time horizon. Although an ICER was not calculated, the study did take into account utility scores based on the EQ-5D and thus was not simply a cost-analysis.
Palmer[41] (2000, Switzerland)	This was included in the previous guideline but does not look at the correct intervention for this review and contains a mixed population of Type 1 and Type 2 diabetes patients.	This study has been selectively excluded because it focused exclusively on the cost-effectiveness of management of overweight patients with T2DM.
Reviriego[52] (2008, Spain)	This study has been selectively excluded as it only considers the impact on hypoglycaemia and as such does not take all health outcomes into account.	This study has been selectively excluded because the data relates only to the prevention of hypoglycaemic events.
Shearer[24] (2004, United Kingdom)	Selectively excluded as this was updated by a more recent analysis.	This study has been selectively excluded due to the availability of a more recent CUA.
Stern[53] (1996, United Kingdom)	This was included in the previous guideline but does not look at the correct intervention for this review question.	The study has been selectively excluded because it is over 20 years old and did not take the form of a CUA. However, the study does not necessarily analyse the wrong intervention; it examined intensive versus conventional insulin therapy in

Reference	NICE reason for exclusion	HRB-CICER conclusion
		terms of direct costs and complications.
Trento[54] (2005, Italy)	Selectively excluded on the basis of the availability of a UK CUA.	This study has been selectively excluded due to the availability of a more recent UK-based CUA.
Valentine[55] (2012, Denmark, Sweden, Finland and Netherlands)	This study was excluded due to methodological limitations as this study assesses the short-term effects of mild hypoglycaemia event reduction. As such, it does not include all important health effects in the long term.	This study has been selectively excluded as it fails to model the long-term effects of treatment.
Wu[56] (1998, Hong Kong)	This was included in the previous guideline but does not look at the correct intervention for this review and contains a mixed population of Type 1 and Type 2 diabetes patients.	This study has been selectively excluded because it is almost 20 years old and the cost-analysis fails to distinguish between patients with T1DM and T2DM within the cohort.

CBA — cost-benefit analysis; CMA — cost minimisation analysis; CUA — cost utility analysis; DAFNE — dose adjustment for normal eating; EQ-5D — EuroQol five dimensions questionnaire; ICER — incremental cost-effectiveness analysis; T1DM — Type 1 diabetes mellitus; T2DM — Type 2 diabetes mellitus; WTP — willingness to pay.

*This study was included and referenced twice with alternative reasons for exclusion in NICE's (2015) guideline. It was unclear whether one of these studies had been incorrectly referenced to Davey et al. Consequently, both reasons for exclusion have been included.

As demonstrated by the results contained in Table 5, no additional studies were identified for inclusion from the list of excluded studies.

4. Conclusion

The purpose of this review was (1) to evaluate the applicability of studies identified by NICE to the Irish healthcare setting; and (2) identify additional studies or evidence relevant to the Irish healthcare setting through targeted review in order to inform the guideline development group's pilot contextualisation of the National Institute for Health and Care Excellence's (NICE's) *Clinical guideline NG17 Type 1 diabetes in adults: diagnosis and management.*[(1)] Overall, a complex picture of the cost-effectiveness of interventions for treatment of Type 1 diabetes is presented due to limitations of the literature in terms of both quantity and quality. Furthermore, there is an evidential lack of literature that is specific to the Irish context.

According to both national and international literature, it was found that structured education was potentially cost-effective compared to routine care, although there is a scarcity of economic literature on this topic within the Irish context. Conflicting results were found regarding the cost-effectiveness of alternative blood glucose monitoring schedules and insulin therapy interventions. The balance of evidence indicates that self-monitoring of blood glucose at specific daily frequencies is cost-effective compared with continuous blood glucose monitoring, while insulin glargine and insulin detemir appeared to be the most cost-effective long-acting insulin therapies, with insulin aspart the most cost-effective rapid-acting insulin.

The conflicting nature of the literature and associated limitations means that the results must be interpreted with caution. Furthermore, it should be noted that the incorporation of different discount rates in economic evaluations may have a considerable impact on the ICER (incremental cost-effectiveness ratio) of interventions where the intervention is associated with future costs and benefits. For example, diabetic retinopathy screening will have immediate costs but projected future savings. Therefore, if considering the transferability of a study that uses a discount rate which is lower than the 5% rate specified by Irish national HTA (health technology assessment) guidelines — as was the case in the majority of studies identified in this review — then the estimated benefits will be inflated. This may lead to an underestimate of the incremental cost-effectiveness analysis (that is, the technology would be considered more cost-effective) in the Irish setting.

Finally, it must be noted that the process of contextualisation is limited by the absence of an update to the systematic review to identify relevant literature (the systematic review is current to 28

August 2014 only), and therefore, there is a risk of missing recent relevant economic evaluations.

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Appendices

Appendix A — Literature search

The aim of the search strategy for the targeted review was to identify economic evidence from the Irish setting. This was undertaken by updating the systematic search conducted by NICE. The updated inclusion criteria specified studies which analysed the Irish setting. The updated search included a grey literature search of relevant Irish sources.

The updated search strategy employed in the 2015 NICE guideline included searches for economic evidence in MEDLINE, Embase, the NHS Economic Evaluations Database (NHS EED), the Health Technology Assessment (HTA) database and the Health Economic Evaluation Database (HEED). NHS EED and HTA were searched via the Cochrane (Wiley) or Centre for Reviews and Dissemination (CRD) interfaces. The search terms are presented alongside the relevant databases in Appendix B. Where possible, searches were run from 28 August 2014 to 24 August 2017 and limited to journal articles and abstracts published in English. In accordance with NICE's search, an economic filter (see B.1) was added to the standard populations (see B.2) for Medline and Embase. All other searches were conducted using only population terms.

A grey literature search was also undertaken. Searches were undertaken using the search terms "diabetes" and "diabetic" to identify Irish economic evidence via the Rian and Lenus health repositories and the website of the National Centre for Pharmacoeconomics (NCPE).

The grey literature search included searches in the following:

- *published recommendations by the National Centre for Pharmacoeconomics (NCPE) relating to company submissions for pharmaceuticals*
- *relevant health technology assessments (HTAs) conducted by HIQA*
- *the approved medications list of the Health Service Executive (HSE) to confirm whether a drug had been reimbursed under the long-term illness scheme (LTI)*
- *the HSE's Medicines Management Programme (MMP) to obtain position papers and drugs listed on the Preferred Drugs Initiative that may serve to inform recommendations for the treatment of diabetes in Ireland*[17]

- *the Rian and Lenus health repositories to identify relevant Irish publications.*

Figure 1 in Appendix C illustrates the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow chart of the cumulative search results.

Appendix B — Study filter search terms

B.1 Health economic search terms

MEDLINE

1.	economics/
2.	value of life/
3.	exp "costs and cost analysis"/
4.	exp economics, hospital/
5.	exp economics, medical/
6.	exp resource allocation/
7.	economics, nursing/
8.	economics, pharmaceutical/
9.	exp "fees and charges"/
10.	exp budgets/
11.	budget*.ti,ab.
12.	cost*.ti,ab.
13.	(economic* or pharmaco?economic*).ti,ab.
14.	(price* or pricing*).ti,ab.
15.	(financ* or fee or fees or expenditure* or saving*).ti,ab.
16.	(value adj2 (money or monetary)).ti,ab.
17.	resourc* allocat*.ti,ab.
18.	(fund or funds or funding* or funded).ti,ab.
19.	(ration or rations or rationing* or rationed).ti,ab.
20.	or/1-19

Embase

1.	health economics/
2.	exp economic evaluation/
3.	exp health care cost/

4.	exp fee/
5.	budget/
6.	funding/
7.	resource allocation/
8.	budget*.ti,ab.
9.	cost*.ti,ab.
10.	(economic* or pharmaco?economic*).ti,ab.
11.	(price* or pricing*).ti,ab.
12.	(financ* or fee or fees or expenditure* or saving*).ti,ab.
13.	(value adj2 (money or monetary)).ti,ab.
14.	resourc* allocat*.ti,ab.
15.	(fund or funds or funding* or funded).ti,ab.
16.	(ration or rations or rationing* or rationed).ti,ab.
17.	or/1-16

B.2 Population search terms

MEDLINE

1.	diabetes mellitus, type 1/
2.	diabetic ketoacidosis /
3.	((diabet* or dm) adj4 (type 1 or type1 or type i or type one)).ti,ab.
4.	(diabet* adj2 (autoimmun* or auto immun*)).ti,ab.
5.	lada.ti,ab.
6.	(diabet* adj2 (brittle or labile)).ti,ab.
7.	(diabet* adj2 (sudden onset or juvenile or childhood)).ti,ab.
8.	(diabet* adj3 (keto* or acido* or gastropare*)).ti,ab.
9.	(dm1 or iddm or t1d* or dka).ti,ab.
10.	((diabet* adj2 (insulin depend* or insulin deficien*)) not non insulin depend*).ti,ab.
11.	diabetes mellitus.ti.
12.	(diabet* adj3 (type 2 or type ii)).ti.
13.	11 not 12
14.	or/1-10,13
15.	((children or adolescen* or school* or infant* or teenage* or paediatric* or pediatric*) not (adult* or onset)).ti.
16.	(pregnan* or gestation*).ti.
17.	14 not (15 or 16)
18.	letter/
19.	editorial/
20.	news/
21.	exp historical article/
22.	anecdotes as topic/
23.	comment/
24.	case report/
25.	(letter or comment*).ti.

26.	or/18-25
27.	26 not (randomized controlled trial/ or random*.ti,ab.)
28.	animals/ not humans/
29.	exp animals, laboratory/
30.	exp animal experimentation/
31.	exp models, animal/
32.	exprodentia/
33.	(rat or rats or mouse or mice).ti.
34.	or/27-33
35.	17 not 34

Embase

1.	insulin dependent diabetes mellitus/
2.	juvenile diabetes mellitus/
3.	diabetic ketoacidosis
4.	((diabet* or dm) adj4 (type 1 or type1 or type i or type one)).ti,ab.
5.	(diabet* adj2 (autoimmun* or auto immun*)).ti,ab.
6.	lada.ti,ab.
7.	(diabet* adj2 (brittle or labile)).ti,ab.
8.	(diabet* adj2 (sudden onset or juvenile or childhood)).ti,ab.
9.	(diabet* adj3 (keto* or acido* or gastropare*)).ti,ab.
10.	(dm1 or iddm or t1d* or dka).ti,ab.
11.	((diabet* adj2 (insulin depend* or insulin deficien*)) not non insulin depend*).ti,ab.
12.	diabetes mellitus.ti.
13.	(diabet* adj3 (type 2 or type ii)).ti.
14.	12 not 13
15.	or/1-11,14
16.	((children or adolescen* or school* or infant* or teenage* or paediatric* or

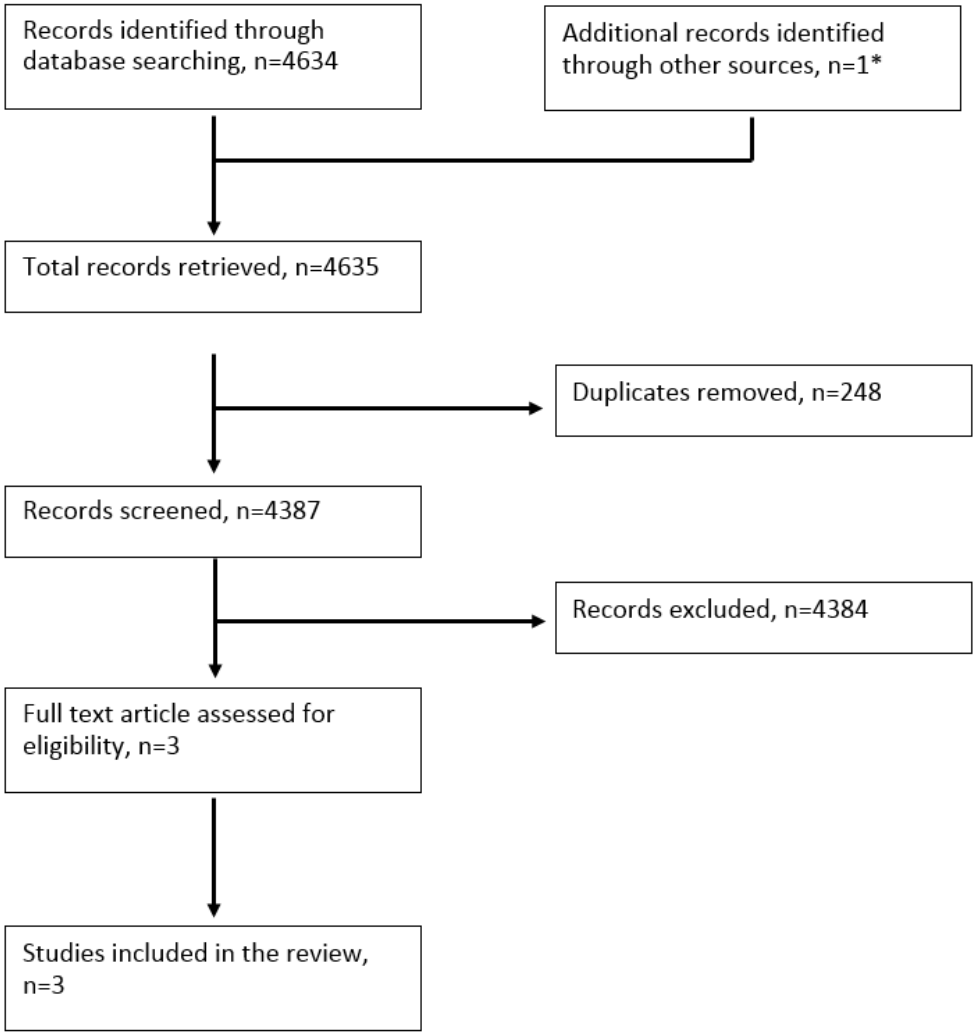
	pediatric*) not (adult* or onset)).ti.
17.	(pregnan* or gestation*).ti.
18.	15 not (16 or 17)
19.	letter.pt. or letter/
20.	note.pt.
21.	editorial.pt.
22.	case report/ or case study/
23.	(letter or comment*).ti.
24.	or/19-23
25.	24 not (randomized controlled trial/ or random*.ti,ab.)
26.	animal/ not human/
27.	nonhuman/
28.	exp animal experiment/
29.	exp experimental animal/
30.	animal model/
31.	exp rodent/
32.	rat or rats or mouse or mice).ti.
33.	or/25-32
34.	18 not 33

Cochrane

1.	MeSH descriptor diabetes mellitus, type 1 explode all trees
2.	MeSH descriptor diabetic ketoacidosis, this term only

Appendix C — Economic article selection

Figure 1. PRISMA flow chart of economic article selection for the targeted review



* Additional record identified through HIQA HTA of SMS interventions for Type 1 and Type 2 diabetes.[26]

Glossary of terms

Some of the terms in this glossary will not be found within the body of these guidelines. They have been included here to make the glossary a more complete resource for users.

Adverse event	An undesirable effect of a health technology.
Baseline	A term used to describe the initial set of measurements taken at the beginning of a study (after a run-in period, when applicable).
Bias	Systematic (as opposed to random) deviation of the results of a study from the 'true' results.
Budget impact analysis (BIA)	A procedure for comparing only the financial costs and cost offsets of competing options, rather than comparing their clinical and economic costs and benefits.
Comorbidity	The coexistence of a disease, or more than one disease, in a person in addition to the disease being studied or treated.
Comparator	The alternative against which the intervention is compared.
Confidence interval (CI)	The computed interval with a specified probability (by convention, 95%) that the true value of a variable such as mean, proportion, or rate is contained within the interval.
Consumer Price Index (CPI)	This index measures the change in the average price levels (including all indirect taxes) paid for consumer goods and services by all private households in the country and by foreign tourists holidaying in the country.
Cost	The value of opportunity forgone, as a result of engaging resources in an activity (see opportunity cost); there can be a cost without the exchange of money; range of costs (and benefits) included in a particular economic evaluation depends on perspective taken; average costs are average cost per unit of output (that is, total costs divided by total number of units produced); incremental costs are extra costs associated with intervention compared to alternative; marginal cost is cost of producing one extra unit of output.
Cost benefit analysis (CBA)	An economic evaluation that compares the proposed technology with its main comparator(s) in which both costs and benefits are measured in monetary terms to compute a net monetary gain or loss or benefit gain or loss

Cost-effective (value for money)	A proposed technology is considered cost-effective for a specified main indication if the incremental benefits of the proposed technology versus its main comparator(s) justify its incremental costs and harms.
Cost-effectiveness analysis (CEA)	An economic evaluation in which costs are measured in monetary terms and clinical or health outcomes are measured in natural units, for example, reduced mortality or morbidity.
Cost-minimisation analysis (CMA)	An economic evaluation that finds the least costly alternative technology. For example, after the proposed technology has been demonstrated to be no worse than its main comparator(s) in terms of effectiveness and adverse events.
Cost-utility analysis (CUA)	An economic evaluation that compares the proposed technology with its main comparator(s) in which costs are measured in monetary terms and outcomes are measured in terms of extension of life and the utility value of that extension, for example, using qualityadjusted life years (QALYs).
Critical appraisal	A strict process to assess the validity, results and relevance of evidence.
Deterministic decision analytic model	A method of decision analysis where the output of the model is fully determined by the parameter values without any room for random variation.
Direct costs	The fixed and variable costs of all resources (goods, services, and so on) consumed in the provision of a technology as well as any consequences of the intervention such as adverse effects or goods or services induced by the intervention. These include direct medical costs and direct non-medical costs such as transportation or child care.
Discount rate	The interest rate used to discount or adjust future costs and benefits so as to arrive at their present values, for example 5%. This is also known as the opportunity cost of capital investment.
Discounting	The process used in economic analyses to convert future costs or benefits to present values using a discount rate. Discounting costs reflects societal preference for costs to be experienced in the future rather than the present. Discounting benefits reflects a preference for benefits to be realised in the present rather than at a later date.

Economic evaluation	Application of analytical methods to identify, measure, value, and compare costs and consequences of alternatives being considered; addresses issue of efficiency to aid decision-making for resource allocation. It is an umbrella term covering CBA, CEA, CMA and CUA.
Economic model	Economic models provide a means of bringing together different types of data from a range of sources and provide a framework for decision making under conditions of uncertainty. Modelling may be used to combine different data sets changing the information collected from a clinical trial into a form that can be used, to extrapolate short-term clinical data to longer term, to link intermediate with final endpoints, to generalise from clinical trial settings to routine practice and to estimate the relative effectiveness of technologies where these have not been directly compared in clinical trials.
Effectiveness	The extent to which a technology produces an overall health benefit (taking into account adverse and beneficial effects) in routine clinical practice. (Contrast with efficacy.)
Efficacy	The extent to which a technology produces an overall health benefit (taking into account adverse and beneficial effects) when studied under controlled research conditions. (Contrast with effectiveness.)
Epidemiology	The study of the distribution and determinants of healthrelated conditions or events in defined populations.
Extrapolation	Prediction of value of model parameter outside measured range or inference of value of parameter of related outcome (for example, extrapolation of reduction in rate of progression to AIDS from improvement in HIV viral load).
Generalisability	The problem of whether one can apply or extrapolate results obtained in one setting or population to another; term may also be referred to as 'transferability', 'transportability', 'external validity', 'relevance', or 'applicability'.
Grey literature	Research that is either unpublished or has been published in non-commercial form, such as government reports.
Health outcome	A change (or lack of change) in health status caused by a therapy or factor when compared with a previously documented health status using disease-specific measures, general quality of life measures or utility measures.

Health technology	The application of scientific or other organised knowledge – including any tool, technique, product, process, method, organisation or system – in healthcare and prevention. In healthcare, technology includes drugs, diagnostics, indicators and reagents, devices, equipment, and supplies, medical and surgical procedures, support systems and organisational and managerial systems used in prevention, screening diagnosis, treatment and rehabilitation.
Heterogeneity	In the context of meta-analysis, clinical heterogeneity means dissimilarity between studies. It can be because of the use of different statistical methods (statistical heterogeneity), or evaluation of people with different characteristics, treatments or outcomes (clinical heterogeneity). Heterogeneity may render pooling of data in meta-analysis unreliable or inappropriate. Finding no significant evidence of heterogeneity is not the same as finding evidence of no heterogeneity. If there are a small number of studies, heterogeneity may affect results but not be statistically significant.
Health technology assessment (HTA)	This is a multidisciplinary process that summarises information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, robust manner. Its aim is to inform the formulation of safe, effective health policies that are patient-focused and seek to achieve best value.
Incidence	The number of new cases of a disease or condition that develop within a specific time frame in a defined population at risk. It is usually expressed as a ratio of the number of affected people to the total population.
Incremental costs	The absolute difference between the costs of alternative management strategies of the same medical condition, disease or disorder.
Indirect costs	The cost of time lost from work and decreased productivity due to disease, disability, or death. (In cost accounting, it refers to the overhead or fixed costs of producing goods or services.)
Meta-analysis	Systematic methods that use statistical techniques for combining results from different studies to obtain a quantitative estimate of the overall effect of a particular intervention or variable on a defined outcome. This combination may

	produce a stronger conclusion than can be provided by any individual study. Also known as data synthesis or quantitative overview
Opportunity cost	The value of the forgone benefits because the resource is not available for its best alternative use.
Outcome	Consequence of condition or intervention; in economic guidelines, outcomes most often refer to health outcomes, such as surrogate outcomes or patient outcomes.
Perspective	This is the viewpoint from which an economic evaluation is conducted. Viewpoints that may be adopted include that of the patient, the public healthcare payer or society.
PPP	This theory states that in an efficient market, the exchange rate of two currencies results in equal purchasing power. The purchasing power indices are currency conversion rates that both convert to a common currency and equalise the purchasing power of different currencies. In other words, they eliminate the differences in price levels between countries in the process of conversion.
QALY	A unit of healthcare outcomes that adjusts gains (or losses) in years of life subsequent to a healthcare intervention by the quality of life during those years. QALYs can provide a common unit for comparing costutility across different technologies and health problems. Analogous units include disability-adjusted life years (DALYs) and healthy-years equivalents (HYEs).
Scenario analysis	A method of decision analysis that considers future events by considering possible alternative scenarios. It can use both one-way (variation of one variable at a time) and multi-way (two or more parameters varied at the same time) to capture the level of uncertainty in the results.
Sensitivity analysis	A means to determine the robustness of a mathematical model or analysis by examining the extent to which results are affected by changes in methods, parameters or assumptions.
Surrogate endpoint	A measure that is used in place of a primary endpoint (outcome). Examples are decrease in blood pressure as a predictor of decrease in strokes and heart attacks in hypertensive patients, and increase in T-cell (a type of white blood cell) counts as an indicator of improved survival of patients with AIDS. Use of a surrogate endpoint assumes that it is a reliable predictor of the primary endpoint(s) of

	interest.
Target population	In the context of a budget impact analysis the individuals with a given condition or disease who might avail of the technology being assessed within the defined time horizon.
Technology	The application of scientific or other organised knowledge –including any tool, technique, product, process, method, organisation or system–to practical tasks. In healthcare, technology includes drugs; diagnostics, indicators and reagents; devices, equipment and supplies; medical and surgical procedures; support systems; and organisational and managerial systems used in prevention, screening, diagnosis, treatment and rehabilitation.
Time horizon or Time frame	The time span used in the assessment that captures the period over which meaningful differences between costs and outcomes between competing technologies would be expected to accrue.
Tornado diagram	Diagrammatic display of the results of one-way sensitivity analysis; each bar represents the range of change in model results when the parameter is varied from its minimum to maximum values.
Transferability	A trial, study or model has transportability if it can produce unbiased inferences to another specified healthcare system (for example, from overseas to Ireland).
Uncertainty	Where the true value of a parameter or the structure of a process is unknown
Usual care	This is the most common or most widely used alternative in clinical practice for a specific condition. This is also referred to as 'routine care' or 'current practice' or 'typical care'.
Utility	In economic evaluation, utilities are used to represent the strength of individuals' preferences for different health states. When utility values are averaged over a population of responders they can be considered to be valuations of health states. Conventionally the valuations fall between 0 and 1, with 1 representing the valuation of a state of perfect health and 0 representing the valuation of death (non-existence).
Validity	The extent to which technique measures what it is intended to measure.
Value Added	This is a tax on consumer spending. It is collected by VAT-registered traders on

Tax	their supplies of goods and services to customers. Each such trader in the chain of supply from manufacturer through to retailer charges VAT on his or her sales and is entitled to deduct from this amount the VAT paid on his or her purchases, that is, the tax is on the added value. For the final consumer, not being VAT-registered, VAT is simply part of the purchase price.
Variability	This reflects known differences in parameter values arising out of inherent differences in circumstances or conditions. It may arise due to differences in patient population (for example, patient heterogeneity – baseline risk, age, gender), differences in clinical practice by treatment setting or geographical location.