Newer agents for blood glucose control in type 2 diabetes: systematic review and economic evaluation

N Waugh,* E Cummins, P Royle, C Clar, M Marien, B Richter and S Philip

University of Aberdeen, Aberdeen, UK

*Corresponding author

Executive summary

Health Technology Assessment 2010; Vol. 14: No. 36
DOI: 10.3310/hta14360

Health Technology Assessment
NIHR HTA programme
www.hta.ac.uk

Executive summary

Background

The National Institute for Health and Clinical Excellence (NICE) issued an updated guideline [clinical guideline 66 (CG 66)] for the management of all aspects of type 2 diabetes in May 2008. However, new drug developments mean that this guideline itself already requires an update. This technology assessment report (TAR) aims to provide information to support the Short Guideline Development Group (GDG) which will produce a 'new drugs update' to the 2008 guideline.

The four classes of drugs that the GDG has been asked to consider are:

- The glucagon-like peptide-1 (GLP-1) analogue, exenatide, in its currently available form, given by injection twice daily. The second drug in that class, liraglutide, was not licensed in time to be included in the guideline update, and nor was the long-acting form of exenatide.
- The dipeptidyl peptidase-4 (DPP-4) inhibitors, sitagliptin and vildagliptin.
- The long-acting insulin analogues, glargine and detemir. Glargine had been the subject of a previous technology appraisal (TA 43) but it was felt that this needed updating. Detemir had not previously been appraised by NICE.
- The thiazolidinediones (TZDs) (hereafter referred to as the glitazones), more from the safety aspects than for glycaemic control.

Methods

Systematic review of clinical effectiveness studies (systematic reviews and new trials) and economic evaluations.

The bibliographic databases searched were MEDLINE (1990–April 2008), EMBASE (1990–April 2008), the Cochrane Library (all sections) Issue 2, 2008, and the Science Citation Index (SCI) and ISI Proceedings (2000–April 2008). The websites of the American Diabetes Association (ADA), the European Association for the Study of Diabetes (EASD), the US Food and Drug Administration (FDA), the European Medicines Evaluation Agency (EMEA) and the Medicines and Healthcare Products Regulatory Agency (MHRA) were searched, as were manufacturers' websites. References cited by retrieved studies were checked for other trials. AutoAlerts were set up so that new studies were identified as they appeared. For the review of the DPP-4 inhibitors, we searched only for studies published since the time of the searches for the 2008 Cochrane review of these drugs, and used data from that review.

Abstracts of retrieved studies were checked for relevant studies by two reviewers, and in cases where there was doubt, copies of full papers were obtained. Only English language studies were obtained.

Data extraction was carried out by one person, and checked by a second, using predefined tables. Studies were assessed for quality using standard methods for reviews of trials as appropriate.

Meta-analyses were carried out using the Cochrane Review Manager (REVMAN) software.

Inclusion and exclusion criteria were based on current standard clinical practice in the UK, as outlined in NICE CG 66. This meant that only studies of the new drugs versus an appropriate comparator, and in an appropriate situation, were used. It was assumed that treatment of type 2 diabetes would start with lifestyle measures, principally diet, followed by metformin monotherapy then by the addition of a sulfonylurea. So the new drugs would be used in addition to metformin and sulfonylurea combination treatment, or as second-line therapy, particularly in those unable to tolerate adequate doses of those drugs. The main implication of this was that trials of the new drugs versus placebo, or as first-line monotherapy, or comparators not relevant to standard practice as laid down in CG 66, were excluded.

The outcomes of most interest for the GLP-1 analogues, DPP-4 inhibitors and the long-acting insulin analogues were:

- glycaemic control, as reflected by glycated haemoglobin (HbA_{1c}), and taken to be an indicator of the risk of long-term complications of diabetes
- hypoglycaemic episodes
- changes in weight
- adverse events
- quality of life (QoL)
- costs.

We did not expect to find any trials that were long enough to have microvascular or macrovascular events as end points.

For the glitazones, the main interest was safety, especially the risk of cardiovascular events.

Cost-effectiveness analysis

Modelling of the cost-effectiveness of the various regimes has used the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model, which models the first occurrence of a variety of downstream complications of diabetes, and estimates the cost and QoL impact of these. This was undertaken first for a representative male patient of body mass index (BMI) 30 kg/m^2, who was assumed to be reaching the 7.5% HbA_{1c} intensification threshold, but was repeated for males with BMI 35, and for females with BMIs 30 and 35.

The absolute HbA_{1c} impacts, weight impacts, cholesterol impacts and systolic blood pressure (SBP) impacts for the head-to-head comparisons, as identified within the clinical effectiveness section, were applied as first-line treatment and the UKPDS Outcomes Model was given an initial run to predict the evolution of HbA_{1c}. As treatment would be intensified again once the 7.5% HbA_{1c} intensification threshold was reached, for example intensification from first-line oral treatment to second-line basal insulin at the point the UKPDS Outcomes Model predicted the HbA_{1c} would rise above 7.5%, the effectiveness of the second-line treatment was applied. The UKPDS Outcomes Model was run a second time to predict the sawtooth evolution of HbA_{1c} for these first-line/second-line combination treatments. In a like manner, where a third-line intensification was possible, i.e. switching from second-line basal insulin to third-line basal bolus insulin, the procedure was undertaken once more, with the assumption of a 0.5% improvement in HbA_{1c} level on the switch to third-line basal bolus insulin.

Costs took into account the need for education and support on starting insulin, and the need for home blood glucose testing. This contrasts with exenatide, which has a fixed dose. The UKPDS Outcomes Model predicted the total cost and quality-adjusted life-years (QALYs) arising from routine care, and the microvascular and macrovascular complications of diabetes for each treatment sequence.

However, while the UKPDS Outcomes Model is well validated, it does not directly address aspects of the treatments under consideration, for example the direct utility effects from weight loss or weight gain, severe hypoglycaemic events and the fear of severe hypoglycaemic events. As a consequence, the survival curves of the UKPDS Outcomes Model were used to append these effects to the cost and QALY estimates of the UKPDS Outcomes Model.

Results – clinical effectiveness

GLP-1 analogue – exenatide

We looked first for trials in which exenatide was added to dual therapy with metformin and sulfonylurea, when that combination failed to achieve adequate glycaemia control. Comparators could be placebo, or a glitazone, or insulin.

There were five randomised controlled trials (RCTs) of reasonable quality which addressed our main questions. The main quality problems were insufficient reporting of methods (such as how randomisation was done) and lack of optimisation of other treatments (such as insulin dose). One trial was of exenatide versus insulin in people who were already on insulin. We added two other trials that did not meet our original criteria. One was added in order to provide more data on the insulin-versus-exenatide comparison; it was in patients who had failed only monotherapy with metformin. The other compared metformin monotherapy with metformin plus exenatide, and was added at the request of the NICE GDG to address the question of how to treat patients whose weight was of considerable concern, and in whom adding a sulfonylurea or a glitazone would cause undesirable further weight gain. All trials were sponsored by, and/or had co-authors from, the manufacturer.

HbA_{1c}

In patients with inadequate control on two oral glucose-lowering agents, the addition of exenatide led to a fall in HbA_{1c} level of about 1%.

In trials against insulins, results on HbA_{1c} level were comparable. In one trial in which insulin glargine or exenatide was added to the metformin-plus-sulfonylurea combination, HbA_{1c} level was reduced by 1.1% in both groups. In the trial in which exenatide or glargine was added when metformin monotherapy failed, both groups had a reduction of almost 1.4% in HbA_{1c} level.

Hypoglycaemia

Severe hypoglycaemic events were few in the trials. With oral combinations, most hypoglycaemic events seen with exenatide were when it was used in combination with a sulfonylurea.

Compared with insulin, there was less nocturnal hypoglycaemia with exenatide, but differences were not marked.

Weight

When exenatide is added to dual therapy, patients tend to lose weight – on average about 2 kg. In comparisons with insulin, patients on exenatide lost weight, whereas those on insulin tended to gain it, giving a difference that can be in the order of 5 kg.

Adverse effects

About half of the patients on exenatide suffer from nausea. This is usually more at the start of treatment, and is usually moderate or mild. Vomiting is quite common. In the trials, only a small proportion had to stop exenatide because of nausea. In some observational studies there were higher cessation rates. It is worth noting that the weight loss is not due only to nausea.

Issues

At present, exenatide has to be given by injection, twice daily. A long-acting form is under development, which can be given once weekly. It has been suggested, based on animal experiments, that the GLP-1 agonists may preserve beta-cell function. This is unproven in humans. Some studies show that the effect of exenatide wears off after it has been stopped, suggesting that there is no significant effect on beta-cell capacity.

Cases of pancreatitis have been reported in people taking exenatide. Most of the early reports were in people with other possible causes of pancreatitis, but with more cases being reported, it looks as if pancreatitis may be a real but rare side-effect of exenatide treatment. The FDA and the MHRA have asked for heightened vigilance and reporting, but have not suggested that exenatide should not be used. If the link is confirmed, the balance of risks between occasional pancreatitis and poorly controlled diabetes will need to be considered.

Summary on exenatide

Exenatide is effective in improving glycaemic control by 1% or a little more, and has the added benefit of modest but useful weight loss. The downside is that it causes frequent nausea (although usually not major and tending to wear off with time), it has to be given by (at present) twice-daily injections, and there may be a small risk of pancreatitis.

DPP-4 inhibitors (gliptins)

The licences for these drugs at the time of the review were only for dual therapy with metformin, a glitazone, or (vildagliptin only) a sulfonylurea. However, we thought that triple therapy with a metformin, sulfonylurea and a gliptin would be a logical use of the drugs, and looked for trials of that as well. We also looked for trials in which a gliptin was used in combination therapy as an alternative to adding insulin to (usually) metformin.

Only four published trials met our inclusion criteria. All were sponsored by, and had co-authors from, the manufacturers. Two trials compared a gliptin plus metformin with a glitazone plus metformin. One trial examined the effect of adding sitagliptin to dual therapy with metformin and sulfonylurea (glimepiride or glipizide). The fourth trial took patients who were failing on metformin and added a gliptin or glipizide.

HbA_{1c}

In combination with metformin, the gliptins reduced HbA_{1c} level by similar amounts (about 0.8%) to a glitazone. When added to dual therapy with metformin and glimepiride, sitagliptin reduced HbA_{1c} level by about 0.8% compared with the placebo group. When compared with glipizide in dual therapy with metformin, both reduced HbA_{1c} level by 0.7%. Reductions are higher in those whose baseline HbA_{1c} level is higher, for example a drop of 1.3% in those with a baseline HbA_{1c} level of over 9%.

Hypoglycaemia

No severe hypoglycaemic episodes were reported in patients in the trials. In the wider Cochrane review, severe hypoglycaemia was not reported in any patient on sitagliptin or vildagliptin. Hypoglycaemia was rare in the dual therapy combinations.

Weight

The DPP-4 inhibitors did not seem to have the same weight loss effect as exenatide. In the trials against glitazones there was less weight gain in the DPP-4 groups, but that reflected weight gain on glitazones rather than loss on a DPP-4 inhibitor. However, absence of significant weight gain is a useful benefit, compared with sulfonylureas and glitazones.

Adverse events

In the short term, the gliptins were very well tolerated. Nausea was not increased. Longer-term data are needed to ensure that there are no adverse effects mediated by the immune system. Data from the Cochrane review show a statistically significant increase in infections with sitagliptin [relative risk (RR) 1.29, 95% confidence interval (CI) 1.1 to 1.5, $p = 0.003$] but not with vildagliptin (RR 1.04, 95% CI 0.87 to 1.24).

Other studies

The Cochrane review found 29 comparisons from 25 trials, most of which did not meet our inclusion criteria, usually because they were of gliptin monotherapy versus placebo, or against metformin monotherapy. However, these trials suggest that, compared with placebo, the gliptins reduce HbA_{1c} level by 0.6–0.7%. When compared with monotherapy with other agents, neither drug showed any advantage in HbA_{1c} level.

Summary

The gliptins are effective in glycaemia control, reducing HbA_{1c} level by about 0.8% in the included trials. Hypoglycaemia was not a problem, and nor was weight gain. Data are required on long-term safety.

Exenatide versus the gliptins

There are no published head-to-head trials comparing exenatide with either of the gliptins. The main differences are that the DPP-4 inhibitors are given orally, are less expensive, cause fewer side effects in the short-term, and are weight neutral rather than giving rise to the weight loss seen with exenatide. They may be a little less potent in lowering HbA_{1c} level, but that impression is based on indirect comparison and should be treated with caution.

Long-acting insulin analogues

Given the number of previous reviews, we started by identifying good-quality systematic reviews, and then looked for new trials published since the reviews. We drew on three good-quality reviews, which included 14 trials of glargine and two of detemir. Three new trials were found, one of glargine and two of detemir. We combined the new trials with the relevant older ones in updated meta-analyses. We also noted one trial of glargine versus detemir.

HbA_{1c}

There was no difference in HbA_{1c} level between glargine and Neutral Protamine Hagedorn (NPH) insulin, and only a small non-significant difference in trials of detemir versus NPH (HbA_{1c} level was higher with detemir by 0.08%; 95% CI –0.03 to 0.19).

Hypoglycaemia

There were no differences in the frequency of severe hypoglycaemia between the analogues and NPH, but, overall, hypoglycaemia was less frequent with both glargine [odds ratio (OR) 0.74, 95% CI 0.63 to 0.89] and detemir (OR 0.51, 95% CI 0.35 to 0.76). Many of the hypoglycaemic episodes were nocturnal, and the ORs for those were 0.47 (95% CI 0.37 to 0.59) for glargine and 0.48 (95% CI 0.37 to 0.63) for detemir.

Weight

The meta-analyses showed that those on glargine gained slightly less weight than those on NPH (0.28 kg; 95% CI –0.72 to 0.15) but this was neither clinically nor statistically significant. On detemir, the difference was a little greater (1.2 kg; 95% CI –1.6 to –0.8). In the head-to-head trial of glargine versus detemir, those on glargine gained 3.5 kg on average, compared with a gain of 2.7 kg on detemir, but the difference of 0.8 kg is of doubtful clinical significance. The difference applied only to those on once-daily detemir; those on two injections daily gained 3.7 kg.

Insulin dose

In the head-to-head trial, the mean daily dose was higher for detemir (0.52 units/kg with once-daily injections; 1.0 units/kg with twice-daily injections) than for glargine (0.44 units/kg with once-daily injections).

Summary

Glargine and detemir are equivalent to NPH (and to each other) in terms of glycaemic control as reflected in HbA_{1c} level, but have modest advantages in terms of hypoglycaemia, especially nocturnal. There is little to choose between the two analogues. Detemir, when used only once daily, appears to have slightly less weight gain than glargine, but the difference in the head-to-head trial was under 1 kg and is probably not clinically significant. Detemir requires a slightly larger daily dose, at higher cost with present prices.

Glitazones

Little new information has emerged since the last guideline was produced. Pioglitazone and rosiglitazone appear to have similar effectiveness in controlling hyperglycaemia, and similar toxicity in terms of oedema, heart failure and fractures (in women only). However, the current evidence suggests that rosiglitazone increases the risk of heart attacks and cardiovascular mortality but that pioglitazone reduces it. The statistical significance of the increased risk for rosiglitazone is still debated. Most analyses show an increase in RR but some find that this is not statistically significant. This is partly because in most of the trials the absolute risk of cardiovascular events was low. Most trials were short-term, with HbA_{1c} level as the main outcome.

Most of the regulatory and prescribing advisory bodies have asked for warnings on rosiglitazone but have allowed its continued use. Some have suggested that, in future, pioglitazone be used in preference. Recent prescribing data from the USA shows a marked drop in the use of rosiglitazone, but suggest a shift to gliptins rather than a straight switch to pioglitazone.

Pioglitazone added to insulin

Pioglitazone is licensed for use with insulin when metformin is contraindicated or not tolerated. We included eight trials that examined the benefits of adding pioglitazone to an insulin regimen. In our meta-analysis, the mean reduction in HbA_{1c} level was 0.54% (95% CI –0.70 to –0.38). Hypoglycaemia was marginally more frequent in the pioglitazone arms (RR 1.27, 95% CI 0.99 to 1.63). In most studies, those on pioglitazone

gained more weight than those who were not, with an average difference of almost 3 kg.

Results – costs and cost-effectiveness

The comparisons below are based on evidence from trials of direct comparisons, and so we are limited in what can be done. Costs were changing during the review. The analysis was bedevilled by very small differences in QALYs amongst the drugs, leading to fluctuations in incremental cost-effectiveness ratios (ICERs) even with 250,000 iterations. All costs given here will almost certainly be out of date by publication time.

In terms of annual acquisition costs, among the non-insulin regimes for a representative patient with a BMI of around 30 kg/m^2 the gliptins are the cheapest of the new drugs, with costs of between £386 and £460. The glitazone costs are similar, with a total annual cost for pioglitazone of around £437 and for rosiglitazone of around £482 (although this is expected to fall shortly), but this situation may change as these drugs come off patent and generic varieties become available. Exenatide is somewhat more expensive, with an annual cost of around £830. Regimens containing insulin fall between the gliptins and exenatide in terms of their direct costs (including all costs), with a NPH-based regimen having an annual cost of around £468 for the representative patient, whereas the glargine and detemir regimens are considerably more expensive, at around £634 and £716, respectively. Also, insulin dose increases with patient weight, and, for a BMI of 35 kg/m^2, the annual cost of the NPH regime rises to £576, whereas the cost of glargine rises to £806. But it should be noted that this is for an insulin regime containing only basal insulin. As beta-cell function declines and control worsens, mealtime insulin will be required, increasing annual costs, for example, to around £617 for NPH and £783 for glargine for the representative patient with BMI of 30 kg/m^2.

For the comparison of exenatide with glargine it is anticipated that the net lifetime cost difference will be between a little over £1000 more costly for exenatide. (Note: It is assumed that patients will only stay on exenatide for a few years before insulin is required because of disease progression.) Given an anticipated QALY gain of around 0.057, this results in an estimated cost-effectiveness of around £20,000 per QALY. This improves to a cost-effectiveness estimate of around £1600 per QALY for a patient with a BMI of 35 kg/m^2, due mainly to the increased cost of the glargine regime. The dose of glargine increases with weight, whereas that of exenatide is fixed. However, these cost-effectiveness estimates are sensitive to the direct utility gain assumed for weight loss and weight gain, and if this effect is excluded, the anticipated cost-effectiveness of exenatide relative to glargine increases to between £9000 and £21,000 per QALY for the no-complications and with-complications scenarios, respectively. The term 'direct utility gain' refers to the fact that people feel happier if they lose weight, and is in contrast with the indirect gain achieved when weight loss favourably affects variables such as cholesterol or blood pressure. The UKPDS model already allows for indirect gains from weight loss.

So what this analysis is telling us is that over a lifetime there is little difference in costs of using exenatide for a few years instead of going straight to insulin; there is a slight benefit in QALY terms, mostly due to the weight loss with exenatide. If patients did not lose sufficient weight, exenatide would not be cost-effective.

In summary, taking into account effects, side effects, costs and expected time to progression, and assuming sufficient weight is lost, then exenatide, when compared with glargine, appears to give ICERs within the range usually regarded as cost-effective. Provided that the effect of exenatide on BMI is reasonably consistent across the weight range, the cost-effectiveness of exenatide relative to glargine improves as BMI worsens, due in large part to the increasing cost of the required total glargine dose.

Comparing sitagliptin and rosiglitazone, the anticipated net QALY gain from sitagliptin is only 0.02–0.03, which is marginal and well within the bounds of error. However, sitagliptin is anticipated to be less expensive. If the direct utility effects of weight changes are excluded from this, sitagliptin is associated with a very small utility loss of –0.006 QALYs, although this does not affect the anticipated cost saving. Hence, the two drugs could be regarded as clinically equivalent but with sitagliptin marginally less costly at current prices.

For vildagliptin compared with pioglitazone the differences are again slight, with vildagliptin being associated with an insignificant QALY difference of between –0.011 and –0.007. Hence the two drugs could be regarded as clinically equivalent, but vildagliptin is anticipated to be around £600 less expensive than pioglitazone (at current prices – a fall of 22% in the cost of pioglitazone would equalise costs).

In summary, the gliptins and the glitazones appear roughly equivalent in glycaemic effect, but the former have an advantage in avoidance of weight gain, which, together with their lower (at present) costs, gives them an edge. However, given the uncertainties around the ICER estimate, it would be inappropriate to say that the glitazones were definitely less cost-effective than the gliptins. The cost-effectiveness hangs heavily on the benefits of weight differentials. This does not

take into account the side effects of the glitazones. Both have problems with fractures (in women only) and heart failure, but rosiglitazone also appears to increase the risk of cardiovascular disease. However, until we have longer follow-up we will not know whether the gliptins have, as yet, unreported side effects.

For the comparison of glargine with NPH, the additional anticipated cost of around £1800 is associated with an insignificant QALY gain: yielding cost-effectiveness estimates of between £280,000 and £320,000 per QALY.

Within the comparison of detemir and NPH, the overall treatment costs from detemir are slightly higher, being between £2700 and £2600. QALY gains are again slight – about 0.015–0.006. Cost per QALY ranges from £188,000 to £412,000.

Hence on cost-effectiveness grounds, NPH should be the first-choice insulin in type 2 diabetes. However, some patients will have more trouble with hypoglycaemia than others and will potentially have more to gain.

In summary, as in CG 66, NPH should be preferred as first-line insulin, rather than a long-acting analogue. The analogues have modest advantages but, at present, much higher cost.

In some patients, the benefits of the analogues relative to NPH may be greater and cost-effectiveness correspondingly better.

Discussion

The main weaknesses in the evidence base at present are:

- long-term data on the safety of exenatide and the gliptins
- a lack of trials directly comparing exenatide and the gliptins
- lack of data on the effects of exenatide and the gliptins on cardiovascular outcomes
- a lack of head-to-head trials of exenatide and NPH.

Research needs

We need long-term follow-up studies of exenatide and the gliptins, although it is likely that exenatide will in future be used as the long-acting form, once weekly or even less often, and trials should use that form. Preliminary data from trials suggests that it will be more effective than the twice-daily form.

Data on combined insulin and exenatide treatment would be useful. The combination appears logical, but practice appears to be running ahead of evidence.

In routine care, how much does compliance fall off as complexity of regimens increases?

More economic analysis is required, undertaken independently of the manufacturers, including:

- looking at when it becomes cost-effective to switch from NPH to a long-acting analogue
- strengthening the evidence for the direct utility of weight gain, or of avoiding weight loss.

Conclusion

The new drugs – exenatide, the gliptins – and the 'not so new' detemir are all clinically effective.

In the authors' opinion, the long-acting insulin analogues, glargine and detemir, have only slight clinical advantages over NPH, but have much higher costs, and hence very high ICERs. They do not appear cost-effective as first-line insulins compared with NPH insulin in type 2 diabetes.

Exenatide, when used as third drug instead of progressing immediately to insulin therapy after failure of dual oral combination therapy, appears cost-effective relative to glargine, the current market leader, with most ICERs around £20,000, acceptable by current NICE standards. However, exenatide appears to be unlikely to be cost-effective compared with NPH.

The gliptins are comparable to the glitazones in glycaemic control and costs, but, at present, appear to have fewer long-term side effects.

Publication

Waugh N, Cummins E, Royle P, Clar C, Marien M, Richter B, *et al.* Newer agents for blood glucose control in type 2 diabetes: systematic review and economic evaluation. *Health Technol Assess* 2010;**14**(36).

NIHR Health Technology Assessment programme

The Health Technology Assessment (HTA) programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The research findings from the HTA programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the 'National Knowledge Service'.

The HTA programme is needs led in that it fills gaps in the evidence needed by the NHS. There are three routes to the start of projects.

First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, from the public and consumer groups and from professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA programme then commissions the research by competitive tender.

Second, the HTA programme provides grants for clinical trials for researchers who identify research questions. These are assessed for importance to patients and the NHS, and scientific rigour.

Third, through its Technology Assessment Report (TAR) call-off contract, the HTA programme commissions bespoke reports, principally for NICE, but also for other policy-makers. TARs bring together evidence on the value of specific technologies.

Some HTA research projects, including TARs, may take only months, others need several years. They can cost from as little as £40,000 to over £1 million, and may involve synthesising existing evidence, undertaking a trial, or other research collecting new data to answer a research problem.

The final reports from HTA projects are peer reviewed by a number of independent expert referees before publication in the widely read journal series *Health Technology Assessment*.

Criteria for inclusion in the HTA journal series

Reports are published in the HTA journal series if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this issue of the journal was commissioned and funded by the HTA programme on behalf of NICE as project number 08/05/01. The protocol was agreed in May 2008. The assessment report began editorial review in September 2008 and was accepted for publication in January 2010. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

ISSN 1366-5278

Published by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk), on behalf of NETSCC, HTA.

Printed on acid-free paper in the UK by the Charlesworth Group.