

## 7 Blood glucose control and insulin therapy

### 7.1 Clinical monitoring of blood glucose

Q 9 What is the optimum form of self-monitoring of glucose control in adults with Type 1 diabetes?

Author / Title / Reference / Yr	Coster S, Gulliford MC, Seed PT, Guillford MC, Powrie JK, Swaminathan R 2000 Monitoring blood glucose control in diabetes mellitus: a systematic review. Health Technol Assess 4(12)
N=	8 controlled trials (4 in adults) Within trials: largest n = 181, smallest n = 16, rest one study n=68, the rest less than 40
Research Design	Systematic review
Aim	To assess the optimum protocol for self monitoring of blood glucose
Population	Type 1 diabetes
Intervention	Frequencies, blood or urine testing.
Comparison	Varied between studies
Outcome	Clinical and cost effectiveness of different methods for monitoring blood glucose control in diabetes mellitus. Self-monitoring by patients and near-patient or laboratory testing in healthcare settings were considered. A number of outcomes were analysed including intermediate outcomes such as changes in blood glucose control and patient satisfaction, as well as measures of health status and health-related quality of life. Costs, including treatment costs and patient costs.
Characteristics	Varied between studies Some studies included children
Results	Evidence statements Of the controlled trials, only one suggested a benefit of blood testing for GHb. The rest showed no difference between blood or urine testing or different frequencies of testing. Three studies found the frequency of hypoglycaemia was low and not different between blood monitoring and control groups. A meta-analysis of data from studies comparing blood monitoring with urine monitoring in IDDM children or adults suggested a mean difference in GHb of approximately -0.567% (95% CI: -1.073 to -0.061), this result was of borderline significance and was sensitive to two assumptions made in interpreting and analysing the data. Blood testing was more costly than urine, but was preferred by patients, possibly due to the accuracy of the resultant information.

#### Reliability and Validity of self-monitoring:

A convenience sample of papers known to the authors suggests that issues of observer training, interdevice variability, the effects of long-term use and patient acceptability have not usually been addressed. Most studies reported a formal assessment of meter reliability and validity but inappropriate statistical methods were used for method comparison.

The development of memory meters showed that diabetic patients often made incorrect recordings of blood glucose values in their diary records.

Williams et al identified a number of sources of inaccurate readings in 21 patients with type 1 diabetes. These included: rounding values to the nearest whole number, omission of outlying values and reporting of results when no test was recorded in the memory of the meter. Over and under reporting often occurred together and were associated with higher GHb levels. Ziegler et al confirmed these findings in 14 people with diabetes. Mean blood glucose values and the amplitude of blood glucose excursions were lower in logbook records than in meter memories. Addition of phantom values in the logbook and omission of SMBG measurements were common leading to an overall obscuring of the occurrence of hypo- and hyperglycaemia.

Strowig and Raskin found that these problems could be addressed by informing patients of the memory capacity of the meter.

Bolinder et al showed SMBG results may be inaccurate in some patients, compared to continuous microdialysis measurement of glucose in subcutaneous adipose tissue, due to wide variations in glucose levels between SMBG that can go recognised. This was more likely to happen at night and could occur when subjects were testing as frequently as seven times/day. This study concluded that the true diurnal variability in glycaemia of people with Type 1 diabetes is too great to be measured, even by frequent SMBG.

#### Other factors influencing reliability

Patient factors: Kabadi et al showed more accurate blood glucose readings may be obtained by patients following sufficient training. Bernbaum et al reported that older people (aged 65–79 years) could produce results as reliable as those obtained by younger subjects.

Two reports suggested that visually impaired patients might be able to use SMBG with satisfactory results, but only after extensive instruction.

Impairment of colour vision can lead to misinterpretation of visually read strips. Colour vision should be tested formally before self-monitoring with visually read strips is recommended<sup>1</sup>, although this can be overcome by using a meter.

#### Clinical effectiveness of Self monitoring in Type 1 diabetes

Four studies were conducted in adults. Details of these studies are in the table below:

Post hoc calculations of power showed that the study by Starostina et al was the only study with sufficient power to detect a difference in GHb of less than 1% but greater than 0.5%

Drop out rates in the studies were between 10 and 20 %

Studies varied in their instructions for frequencies and timing of monitoring.

The studies by Worth and Starostina gave algorithms to patients to alter insulin dose; Gordon et al encouraged alteration of dose but did not provide algorithms and Terent et al encouraged patients to change their insulin dose in order to achieve FBG

of less than 7 mmol/l or postprandial blood glucose of less than 10 mmol

Study	Setting	Design	intervention	outcome	No of (wk)	N	Power (detectable difference in GHb)	Inclusion criteria
Worth 1982	UK hospital diabetes clinic	RCT	Urine vs. SMBG (visual) vs. SMBG (meter)	GHb Blood glucose Urine glucose	60	38	1.0–2.0 %	Exceptions: pregnancy, oral contraceptives, renal disease, retinopathy
Terent 1985	Sweden	Factorial randomised trial	Education vs. SMBG vs. SMBG + education vs. conventional care	HbA1	78	37	2.0–3.0 %	Age greater than 17, Dm duration ≤ 20 years Exclusions: renal transplant, pregnancy, alcoholic, prisoner
Gordon 1991	UK, general hospital	Random crossover trial	Three different frequencies of SMBG	GHb Fructosamine Blood glucose	25	25	1.0–2.0 %	Age: 18–50 years Diabetes for ≥ 12 months Two insulin injections daily. Previous SMBG for ≥ 6 months
Starostina 1994	Russia, Research centre	Consecutive allocation to treatment	Urine vs. SMBG vs. none	HbA1 Weight Cost	104	181	0.5–1.0 %	Exclusions: chronic conditions not DM related

Effect on blood glucose control

No trial demonstrated effect of SMBG on blood glucose control.

Effect on other outcomes

Hypoglycaemia: One study reported frequency and occurrence of hypoglycaemia was low and not different in SMBG or controls

Patient outcomes: Three studies measured patient outcomes

Worth et al found that on a comprehensive questionnaire greater than 50% of patients thought that blood testing was superior to urine testing for assessing metabolic control

40% felt that a combination of blood and urine testing was better, and No patient thought urine testing superior to blood testing.

No clear preference was expressed for either visual strips or strips with meters

Gordon et al reported that 9/18 patients preferred testing four times daily twice weekly; 6/18 patient preferred four times daily

	<p>once a week; and 3/18 preferred twice daily testing seven days a week.  Neither of these studies evaluated patient preferences before the start of the trial  The third study, testing the effect of monitoring on DM knowledge, showed higher test scores after the intervention. However, this study demonstrates the validity of an overall testing package with great emphasis on education, rather than one specific SMBG technique  A standard protocol for conducting and reporting evaluations of blood glucose monitoring devices should be developed. Further work should be done to develop standard packages of proven effectiveness, to train patients in the use of self-monitoring devices and to provide them with the information needed to adjust their therapy according to self-monitoring results. These packages should form part of the overall approach to patient education in diabetes.  Self-monitoring in Type 1 diabetes  The use of SMBG is well established in Type 1 diabetes and has received support from the results of the DCCT. Unconfounded studies do not provide convincing evidence for an effect of self-monitoring on blood glucose control. The question of whether SMBG is necessary for all patients might best be addressed by carrying out prospective observational studies of groups of patients with Type 1 diabetes in order to characterise those who do not use monitoring or do not use it effectively. These groups might be the subject of intervention studies.  Recommendations for research  Observational studies should be carried out in samples of subjects with Type 1 diabetes to identify groups of patients in whom blood glucose self-monitoring is of benefit and groups in whom it is not.  Studies should also not just include assessment of GHb, but also the occurrence of hypoglycaemia, patients' satisfaction with care and health-related quality of life.</p>
Hierarchy of Evidence Grading	Ia
Comments	<p>Search strategy  The author's personal collections, Diabetes care and Diabetic Medicine (1990–1999), the electronic databases MEDLINE and EMBASE, and the Index and Bibliography of Social Sciences.  Citations from papers retrieved were screened.  Letters were sent to the British Diabetic Association and leading manufacturers.  Retrieved papers were evaluated for quality using a validated checklist, by two independent reviewers.  Data were abstracted and synthesised using meta-analysis where possible, papers were reviewed using a quality checklist.  <i>Keywords:</i> insulin-dependent diabetes; self-care, blood glucose self-monitoring, patient compliance, glucose blood level, urinalysis.  Papers retrieved  24 papers: 8 RCT, 16 non-controlled studies  Mean quality rating 14.4 (SD 1.6)  Only one study had sufficient power to detect differences in GHb of <math>\leq 1.0\%</math>  Objectives  To systematically search for research data on the clinical and cost effectiveness of different methods of monitoring blood</p>

	<p>glucose control in diabetes.</p> <p>To evaluate methods of self monitoring by the patient</p> <p>To evaluate both laboratory-based testing and near patient testing in healthcare settings</p> <p>To consider the separate needs of patients with Type 1 diabetes and to consider age, ethnic group and social factors as possible effect modifiers</p> <p>To synthesise conclusive results to provide protocols for monitoring and to make recommendations for future primary research where existing evidence was insufficient</p> <p>Authors note that meters have improved considerably during the time since the reviewed studies were reported.</p> <p>Trajectory of knowledge base</p> <p>the development of methods of monitoring has been the subject of considerable technical innovation, but the evaluation of the clinical- and cost-effectiveness of the application of these methods has not been the subject of many recent studies. This cannot be considered to be a rapidly developing field, as evidenced by the age of the studies included in this review.</p> <p>There is no standard protocol for evaluating blood glucose monitoring devices. Published evaluations have often only evaluated a limited number of aspects of meter performance and have not always used appropriate methods to analyse the reliability of measurements.</p> <p>Conclusions</p> <p>A standardised protocol should be drawn up for conducting and reporting evaluations of blood glucose monitoring devices. Blood glucose self monitoring is well established in clinical practice but the optimal use of the technique has not been established. Present evidence suggests that it may not be essential for all patients</p>
Trials included	See original study
NCC CC ID	191
Reference / Citation	

Q10 What is the optimum regimen of self-monitoring of glucose control in adults with stable Type 1 diabetes?

Author / Title / Reference / Yr	Lindsey, C. C., Carter, A. W., Mangum, S., Greene, D., Richardson, A., Brown, S., & McCandless, B. 2002, "A prospective, randomized, multicentered controlled trial to compare the annual outcomes of patients with diabetes mellitus monitored with weekly fructosamine testing versus usual care: a 3-month interim analysis", <i>Diabetes Technology &amp; Therapeutics</i> , vol. 4, no. 5, pp. 637-642.
N=	n=60 fructosamine testing =33, normal care =27 USA 3 sites
Research Design	Randomised controlled trial
Aim	Objectives of this study are to compare the quarterly A1c results of subjects who monitor weekly fructosamine with results of those receiving usual care for their diabetes management.
Population	Mixed type 1 and Type 2 diabetes
Intervention	An intervention of weekly test for fructosamine level in addition to daily blood glucose assessment.
Comparison	Monitoring was compared to conventional care with only blood glucose monitoring for three months
Outcome	Mean blood glucose over the 2-week period prior to follow-up visits was recorded for both groups. QOL scores were collected at baseline and will be evaluated at the 12-month follow-up visit. The primary outcome of glucose control was evaluated using an A1c At-Home test, and QOL scores evaluated using the diabetes-39 questionnaire which has been validated in this population
Characteristics	Demographic characteristics not presented in report
Results	No statistically significant differences between mean glucose, fructosamine, and A1c were observed to 3 month follow-up. For A1c the fructosamine testing group then mean value was 7.755% SD (1.408) and for the control group 7.971% SD (1.797) (p=0.676) Mean BMI, compliance with diabetes medication, alcohol intake, tobacco use, dietary regimen, and exercise did not change between groups at the quarterly analysis.
Hierarchy of Evidence Grading	Ib

Comments	Power analysis undertaken The time needed to reflect a statistically significant change in the A1c has yet to develop. A1c values take several weeks to show any significant changes, which may result in a lag time of observable differences greater than 3 months. Not all of the enrolled study subjects have yet reached the 3-month review point and enrolment is still continuing, for the 1 year outcome study
NCC CC ID	1942
Reference / Citation	

Q10 What is the optimum regimen of self-monitoring of glucose control in adults with stable Type 1 diabetes?

Author / Title / Reference / Yr	Gordon D, Semple CG, Paterson KR 1991 Do different frequencies of self-monitoring of blood glucose influence control in type 1 diabetic patients. Diabetic Medicine 8:679–682						
N=	N=25 UK						
Research Design	Randomised controlled trial						
Aim	To evaluate the effectiveness of different monitoring regimens						
Population	Type 1 diabetes						
Intervention	A four-point profile on any two non-consecutive days per week One four-point profile on any day of the week						
Comparison	Two blood glucose measurements on each day for 7 days per week						
Outcome	Blood glucose control, fructosamine control, GHb levels, insulin dose changes and patient preference.						
Characteristics	16 male, 9 female; age= 31.0±10.0 years; duration of diabetes=1.09±7.7 years						
Results	Four patients withdrew during the study, all while undergoing the single day week protocol. The two patients who provided reasons for withdrawal expressed concern about the infrequency of monitoring during this phase.						
	Laboratory measurements						
	No significant differences were found when comparing the three protocols between any of the measures studied:						
		2 days x 4 tests / wk		1 days x 4 tests / wk		7 days x 2 tests / wk	
		Wk 1–6	Wk 7–12	Wk 1–6	Wk 7–12	Wk 1–6	Wk 7–12
	BG from diary cards (mmol/L)	8.3±1.9	8.3±1.9	8.0±1.9	8.2±1.5	8.4±2.0	8.4±1.7
BG at clinic visits (mmol/L)	11.6±5.5	11.7±5.6	10.7±6.3	11.2±5.7	11.4±6.1	11.3±5.8	
GHb (%)	9.5±2.0	9.6±2.0	9.4±1.9	9.6±2.1	9.7±1.8	9.7±2.0	
Fructosamine (µmol/L)	419±84	433±83	429±95	428±89	436±96	440±85	

	<p>Diary card results represent pre-prandial samples while clinic results were taken randomly depending upon time of attendance at the hospital, thus clinic results are higher than those recorded by self-monitoring</p> <p>Insulin dose changes</p> <p>The frequency at which patients altered insulin doses was extremely variable: 3.3 (median; range 0.03–11.8) dosage changes/wk.</p> <p>A significant increase was seen in frequency of changes during the 2 day x 4 tests/week protocol, compared with 1 day x 4 tests/wk (p less than 0.02)</p> <p>No significant relationship was seen between the frequency at which a patient altered insulin dosage and their metabolic control as estimated by mean GHb</p> <p>However, the lack of differences between 1 day x 4 tests/wk and 7 days x 2 tests / wk, fails to demonstrate clearly that alteration in frequency of blood glucose monitoring influences patient practice.</p> <p>Protocol preference</p> <p>At the final visit, of the 21 patients completing the study, 18 expressed a preference:  9/18 patients preferred 2 days x 4 tests / wk; 6/18 preferred 1 days x 4 tests / wk; 3/18 preferred 7 days x 2 tests / wk  These differences were not statistically significant</p>
Hierarchy of Evidence Grading	Ib
Comments	<p>Patients re-educated in insulin dose adjustment in relation to exercise, diet and prevailing blood glucose level at pre-trial visit. Patients instructed in completion of daily record diaries of SMBG, insulin dose adjustments and frequency and severity of hypoglycaemia.</p> <p>All patients required to achieve an accuracy of within 10% of laboratory results before inclusion into study.</p> <p>Patients reviewed at 6 week intervals when glycosylated haemoglobin, fructosamine, and blood glucose were estimated. Effects of exercise or alteration of diet on blood glucose were noted and appropriate alterations to insulin were again suggested.</p> <p>Patients actively encouraged to make further changes to either short- and long-acting insulin doses in response to self-monitored blood glucose, and changes to insulin regimen in anticipation of exercise or changes to diet.</p> <p>Algorithms for altering insulin doses were not distributed as they would contravene routine patient management.</p> <p>Self-monitoring performed with BM-44 or Visidex reagent strips. Laboratory estimation of blood glucose was by the glucose oxidase method using Technicon RA 1000 Analyser. GHb measured by pH-dependent chromatography using Quik-Sep Test System. Fructosamine measured by a nitroso-blue tetrazolium reduction assay.</p> <p>Laboratory variables and mean diary care blood glucose from each 6-week period were compared after 6 and 12 weeks. The three different monitoring regimens were compared irrespective of the order in which they were undertaken.</p> <p>Study contains insufficient power to show clinically important differences in results (n=21 at end of study)</p> <p>Dietary compliance, lifestyle and other factors affecting blood glucose concentrations not standardised across the study. No way of controlling for these confounding factors.</p> <p>Self-reporting of data leaves possibility of patient editing of results.</p> <p>Authors state: we have been unable to identify an optimal frequency for blood glucose self-monitoring in a typical diabetic</p>

	population. There is little or no relationship between the frequency of blood glucose monitoring, the frequency of insulin dose adjustments and the level of metabolic control achieved
NCC CC ID	886
Reference / Citation	

Q 9 What is the optimum form of self-monitoring of glucose control in adults with Type 1 diabetes?

Author / Title / Reference / Yr	Halimi S, Charpentier G, Grimaldi A, Grenier JL, Baut F, Germain B, Magnette J 2001 Effect of compliance, acceptability of blood glucose self-monitoring and HbA1c of a self-monitoring system developed according to patient wishes. Diabetes Metab 27:681-387
N=	N=179: Group A: n=55, Group B: n=60, Group C: n=49 France
Research Design	Randomised controlled trial
Aim	To assess which method of glucose self testing is most convenient to people with diabetes
Population	Type of diabetes not stated
Intervention	Group A: patients continued on original treatment Group B: patients were given the Glucotrend Premium and SoftClix II system Group C: patients were given the One Touch Profile Autolet system
Comparison	No inactive comparison
Outcome	Compliance Also: patient preferences, accuracy of monitoring
Characteristics	Age (years): Group A=35±15; Group B=39.2±16.2, Group C=45±15.1 BMI (kg/m <sup>2</sup> ): Group A=23.3±3.4; Group B=24.4±4.1, Group C=24.6±3.2 Duration diabetes (years): Group A=14±8; Group B=13±9, Group C=16±10
Results	143 patients completed the study. No significant differences were seen at baseline in any of the 179 patients, no serious adverse event was observed during the study. HbA1c (at M0): Group A=9.83±1.44; Group B=9.51.2±1.6, Group C=9.29±1.48 (non significant) Compliance At entry: Group A=29%, Group B=35% and Group C=47% After 3 months: Group A=83%, Group B=75% and Group C=71% After 6 months: Group A=65%, Group B=78% and Group C=68% In the three groups the number of measurements was increased at M3 and then M6 Factors favourably influencing compliance

	<p>Evaluated on the 10-point scale by decreasing order: lack of patient motivation, finger-prick pain, cost of tests amount of blood extracted and the complexity of the test.</p> <p>No differences were seen between the three groups when assessed on this scale.</p> <p><b>HbA1c levels</b></p> <p>Within the three groups HbA1c levels progressively decreased during the 6 months of study.</p> <p>No significant difference in improvement was seen between the three groups although it was significant at the three time periods throughout the study.</p> <p>At three months: 0.3±0.9%, 0.7±1.2% and 0.64±0.9% for groups A, B and C respectively</p> <p>At six months: 0.6±1.1%, 0.9±1.2% and 1.0±0.9% respectively.</p> <p><b>Hypoglycaemic episodes</b></p> <p>The number of hypoglycaemic episodes per week were increased in groups B and C from 2.3±2.5 and 1.89±2.0 respectively at M0 to 7.9±14.0 and 7.6±18.0 respectively after 6 months. No change was seen in the control groups.</p> <p><b>Changes in insulin needs</b></p> <p>Total insulin requirement decreased in group B for both intermediate and rapid acting insulin (10 and 26% respectively) whereas no changes were seen in Groups A and C</p> <p><b>Accuracy of capillary blood glucose determinations</b></p> <p>The best correlation with laboratory (venous) and meter(capillary) measurements were found in group B (Pearson correlation coefficient:0.95 and 0.97 at M0 and M6 respectively). No significant differences were seen between meters at M3.</p>
Hierarchy of Evidence Grading	Ib
Comments	<p>Glucotrend designed from patient suggestions at focus groups, comprising an elaborated mechanism of finger-stick, reshaped lance to reduce pain and to produce a smaller blood drop, culminating in the SoftClix II system adapted to the Glucotrend glucose meter.</p> <p>The One Touch Profile Autolet system was introduced to reduce the ‘protocol effect’ which may otherwise skewed results in favour of the Glucotrend system. This Profile system contained only one of the requested characteristics—a memory function to evaluate compliance</p> <p>Patients randomly allocated by centre, each centre enrolling a multiple of three patients to maintain balance.</p> <p>Patients initially received identical education on the optimal use of glucose meters and finger-lancing devices, to test 4 times daily and to keep a specific diary to record the results.</p> <p>Study duration was for 6 months, HbA1c (determined using HPLC), total and short-acting insulin daily doses (IU/day), hypoglycaemic episodes (number/week), quality of practical determination of capillary blood glucose measurements (nurse assessments) were recorded at entry into the study (M0), and at 3 (M3) and 6 (M6) months.</p> <p>At entry patients filled in an acceptability questionnaire to precisely assess their opinion on the expected qualities of a SMBG system, and key components likely to be responsible for possible changes in compliance and metabolic control were recorded on a 10 point scale (1 unlikely to 10 very important). Patients also used a questionnaire and analogue scales to evaluate their judgement on the system of SMBG they currently used, its size, the fingerprick pain, global practicability, ease of use and time to display results.</p>

	Compliance was assessed from either a blood glucose diary (Group A) or the results memorised in the monitor (B and C) The number of weekly hypoglycaemic episodes was noted and the monitor reading was compared to the result of laboratory venous blood glucose. Patients were analysed on an intention to treat basis
NCC CC ID	874
Reference / Citation	

Q 9 What is the optimum form of self-monitoring of glucose control in adults with Type 1 diabetes?

Author / Title / Reference / Yr	Germer S, Campbell IW 1985 Home monitoring of blood glucose—patient preference for BM-test Glycemic 20-800 strips or glucometer. The British Journal of Clinical Practice
N=	N=32 in crossover design UK
Research Design	Randomised controlled trial
Aim	To assess which method of glucose self testing is most convenient to people with diabetes
Population	Type 1 diabetes
Intervention	Glucometer
Comparison	BM-Test Glycemic 20-800 strips
Outcome	Patient preference
Characteristics	(17 female, 15 male) age: 13–60 years, duration of diabetes: 6 months–32 years 31 insulin treated patients, 1 patient controlled with oral hypoglycaemic drugs
Results	Overall 30/32 patients preferred measuring blood sugar to urine testing and continued with home blood glucose monitoring after the study end. The remaining two patients were uncomfortable with pricking their fingers for blood samples. Average demonstration time: glucometer=30–40 min, for BM Glycemic strips=10 mins Clarity of instructions 31 patients reported that instructions provided with the glucometer as clear. One 13 year old boy required further assistance with using the glucometer all patients reported instructions with the BM Glycemic strips as ‘clear’ Convenience of use 17 subjects reported BM Glycemic strips as more convenient. 14 patients felt the glucometer and strips were equally convenient. One patient found the glucometer more convenient, citing the built in timer as the main reason Number of tests to become confident with the technique BM Glycemic strips= 1–3 tests, Glucometer= 2–12 tests Advantages/disadvantages 12 patients found the built in timer on the glucometer was an advantage compared to using a watch or clock with the BM Glycemic strips

	<p>5 patients recorded difficulties in collaborating the glucometer and felt this was a disadvantage  11 patients had slight difficulties in matching the colours on the strips. Although this was only marked in two patients.  One patient identified as red-green colour blind at the study outset expressed no difficulty in matching colours on the strips.  Overall preference  19 patients preferred the glucometer as a method of choice, 9 patients preferred using the strips and 4 patients had no particular preference  Reasons for preferring glucometer (in order of frequency): more accurate, more confident of result, no decision required to be made to obtain result, could not match colours on BM Glycemic strip test, advantage of timer, not able to cheat with result, easier to put blood on the dextrostix  The main reason for preferring the glucometer was more confidence in the result despite the fact that they were informed that both methods were equally accurate  Reasons for preferring BM Glycemic (in order of frequency): Quicker, More convenient as no water required to clean strip, less complicated, more portable, less blood needed and easier to apply to strip  Preference of own judgement of results rather than that of a machine, which could go wrong.</p>
Hierarchy of Evidence Grading	Ib
Comments	<p>Patients attended training at diabetic clinic in groups of 3, following which patients tested their own blood sugar under supervision  Patients took demonstrated method home for a two week period and tested blood sugar for <math>\geq 3</math> days per week, four times daily  Most patients tested more frequently that required at the outset of the two week period to become experienced with the equipment  After 2 weeks patients returned to the clinic and the alternative method was demonstrated and used for a further 2 weeks.  At the end of the study discussion and a patient questionnaire was completed  Glucometer depends on dextrostix read in a reflectance meter  Method of patient selection not outlined. Source population not defined  Randomisation of patients not outlined.  More time spent educating patients in how to use the glucometer could influence patient confidence in test.  More practice with glucometer in the initial stages of the trial may have lead to more accurate results and a resulting greater confidence in this test.  Slightly more (6%) patients used the glycometer first compared to those testing the BM Glycemic strips first, which could influence patient decision.  Follow-up period is very short  No description provided for the type of questionnaire used, or whether this was a previously validated method of measurement.</p>
NCC CC ID	890
Reference / Citation	



Q 9 What is the optimum form of self-monitoring of glucose control in adults with Type 1 diabetes?

Author / Title / Reference / Yr	Edelman SV, Callahan P, Deeb LC 2000 Multisite evaluation of a new diabetes self-test for glucose and glycated protein (fructosamine). Diabetes Technology and Therapeutics 2 (2):233–238
N=	N=116
Research Design	Diagnostic study
Aim	To evaluate the accuracy of fructosamine testing in glucose self monitoring
Population	Mixed diabetes population
Intervention	Duet glucose test and Duet GlucoProtein (fructosamine) test strip
Comparison	reference standard
Outcome	Confirmation of accuracy of glucose and fructosamine testing
Characteristics	aged: 16–18 years; Gender (M/F): 31/28 (IDDM); 29/28 NIDDM
Results	<p><b>Blood glucose test:</b>            Following a precision study using a low (5.5mM) and high (15mM) control, coefficients of variation observed at each site were 5.7, 3.1 and 2.3% and 3.4, 3.2 and 6.6% for low and high controls respectively.            Combined correlation data show a regression coefficient of 0.97.            Bias analysis of the correlation study yielded a bias of 5%, –4%, –6%, and –8% at 5.5, 11.1, 16.7 and 22.2 mM respectively.            Error Grid Analysis of this data shows that 100% of the test results fall in the A and B region with no results fall in the C, D, or E region where a test result could lead to improper therapeutic adjustment.</p> <p><b>GlucoProtein (fructosamine) test:</b>            Precision studies at each of the three sites using a low (225µmol/L) and high (500µmol/L) controls consisting of glycated human serum albumin provided in the test kit from the manufacturer. Coefficients for variation were 10.3, 11.3 and 1.04% and 9.4, 7.2 and 12.1% for the low and high controls respectively (manufacturer reports 2.2 to 2.5% on labelling)            Combined correlation data from all sites showed a correlation coefficient of 0.72 (manufacturer reports 0.77 on labelling).            Bias analysis of the correlation study yielded a bias of 9%, 4%, –2%, and –5% at fructosamine values of 250, 350, 450 and 550 µmol/L, respectively.            Sensitivity analysis was performed according to the manufacturer provided fructosamine values that indicate poor control and good control, enabling a two-by-two Gaddis analysis to be performed:</p>

	<table border="1"> <tr> <td colspan="2"></td> <td colspan="2">Lab result</td> </tr> <tr> <td colspan="2"></td> <td>Good control</td> <td>Poor control</td> </tr> <tr> <td rowspan="2">Self-test result</td> <td>Good control</td> <td>50 (TN)</td> <td>0 (FN)</td> </tr> <tr> <td>Poor control</td> <td>4 (FP)</td> <td>12 (TP)</td> </tr> </table>					Lab result				Good control	Poor control	Self-test result	Good control	50 (TN)	0 (FN)	Poor control	4 (FP)	12 (TP)
			Lab result															
			Good control	Poor control														
	Self-test result	Good control	50 (TN)	0 (FN)														
Poor control		4 (FP)	12 (TP)															
<p>Sensitivity: <math>TP/(FN+TP) = 100\%</math>; Specificity: <math>TN/(TN+FP) = 92\%</math>  Accuracy: <math>TN+TP/(TN+TP+FN+FP) = 95\%</math>; Positive predicative value: <math>TP/(TP+FN) = 75\%</math> ability to identify poor control;  Negative predicative value: <math>TN/(TN+FN) = 100\%</math> ability to identify good control</p>																		
<p>Overall analysis:  The blood glucose test gave excellent precision and correlation to the laboratory standard method, the error grid analysis showing 97.5% of test results lying within the accurate A zone, and only 2.5% in the clinically neutral or benign errors B zone.  Fructosamine test results confirmed the home test as accurate and appropriate for patient care. The test gave reasonable correlation to the laboratory test with very low bias.  The imprecision of the test is larger than the laboratory test (~10% CV), however, the self test is effective at identifying patients with good versus poor glycaemic control.  The Duet System therefore accurately measures both glucose and fructosamine from fingerstick capillary blood</p>																		
Hierarchy of Evidence Grading	DS																	
Comments	<p>Fingerstick puncture capillary blood glucose was tested in duplicate using the YSI model 1500 and once with the Duet Glucose test. The Duet strip requires 10µL of capillary blood and gives test results in 8 to 30 seconds, depending on the glucose concentration of the sample.  Fingerstick puncture capillary blood was tested once with the GlucoProtein fructosamine test strip. The strip require 25 µL of capillary blood and gives test results in 4 minutes. For comparison a venipuncture blood sample of ECTA plasma was collected and tested in duplicate using the Roche Unimate laboratory test  It is implied that ‘self-tests’ were carried out by clinicians, rather than by the patients themselves.  Authors suggest that self-testing could overcome the problems with lab fructosamine testing because the latter is hampered by the impracticalities of lab testing every two to three w</p>																	
NCC CC ID	901																	
Reference / Citation																		

Q 9 What is the optimum form of self-monitoring of glucose control in adults with Type 1 diabetes?

Author / Title / Reference / Yr	Cefalu WT, Wang ZQ, Redmon E, Bell-Farrow AD, McBride D, King T 1999 Clinical validity of self-test fructosamine in outpatient diabetic management. Diabetes Technology and Therapeutics 1(4):435–441
N=	N=51 USA
Research Design	Diagnostic study
Aim	To assess the usefulness of fructosamine testing in blood glucose management
Population	Mixed diabetes population
Intervention	Fingerstick capillary blood sample tested on the new self-test fructosamine meter
Comparison	Venipuncture for laboratory determination of serum fructosamine
Outcome	Measurement of fructosamine
Characteristics	Age 24–72; average: 53±2 (diabetics); 44 ±3 (controls) Gender (M/F): 18/15 (diabetics); 6/12 (controls) Fasting glucose (mmol/L): 13.1±0.9 (diabetics); 5.5±0.13 (controls) GHb (%): 12.2±0.1 (diabetics) 5.4±0.1 (controls) Fructosamine (µM): 370±14 (diabetics); 257±6 (controls)
Results	The fingerstick fructosamine demonstrated good correlation with laboratory assessment by venipuncture in controls and subjects with diabetes. Correlation of fingerstick fructosamine with laboratory fructosamine: r=0.80, pless than0.001 Correlation of fingerstick fructosamine with glycated haemaglobin: r=0.81, pless than0.001
Hierarchy of Evidence Grading	DS
Comments	Subjects evaluated in a fasting state All patients in normal health assessed with patient history, physical and laboratory evaluation of complete blood counts, liver function, renal and electrolyte evaluations and urinary microalbumin. Meter capable of performing an 8-second glucose test and a measure of glycated protein (fructosamine). The coefficient of variation for the self-test, determined for two levels of glycaemia was less than 5.0% at each level. Glycated protein level is determined on capillary blood and measured in micromoles of fructosamine per litre (µmol/L) of blood. Results ≤ 310 µmol/L

	<p>indicate good control, <math>\geq 380</math> <math>\mu\text{mol/L}</math> indicate poor control  Stats analysed with Pearson coefficient and ANOVA where relevant  Very strict exclusion criteria, thus conclusions may only be applicable to a subsection of the population covered by this guideline.  No description of blinding of investigators  Raw data only provided in abstract  Reference standard test performed prior to 'self-testing', so investigators potentially know outcome of one test prior to testing with the other.  Study implies that fingerstick test was performed by the investigator rather than the patient, therefore not self-test  Prospective study performed in type 2 diabetes patients only</p>
NCC CC ID	913
Reference / Citation	

Q 9 What is the optimum form of self-monitoring of glucose control in adults with Type 1 diabetes?

Author / Title / Reference / Yr	Maran A, Crepaldi C, Tiengo A, Grassi G, Vitali E, Pagano G, Bistoni S, Calabrese G, Santeusanio F, Leonetti F, Ribaldo M, Di Mario U, Annuzzi G, Genovese S, Ricardi G, Previti M, Cucinotta D, Giorgino F, Bellomo A., Giorgino R, Poscia A, Varalli M 2002 Continuous subcutaneous glucose monitoring in diabetic patients. Diabetes Care 25:347–352
N=	N=70 Italy
Research Design	Case series
Aim	To assess the usefulness of continuous glucose monitoring
Population	Mixed diabetes population
Intervention	Continuous glucose monitoring using a subcutaneous glucose sensor (Glucoday)
Comparison	Venous blood glucose measurement
Outcome	Efficacy and accuracy of new glucose sensor
Characteristics	Type 1 diabetes = 43, Type 2 diabetes = 32 Sex M/F: 32/38 Age: 47±17 years; BMI=24.9±3.2 kg/m <sup>2</sup> ; retinopathy in 43%, nephropathy in 15% and neuropathy in 34%
Results	<p>Withdrawals 60/70 patients successfully completed the 24 h monitoring and were analysed by an independent statistician In 1 patient monitoring was interrupted after a few hours due to vagal reaction; in 7 patients data were not correctly transferred to the computer unit and could not be analysed; In 2 patients venous blood samples were not collected.</p> <p>Acceptability Fibre insertion and the wearing of the device were well tolerated by all patients. Just over 50% of patients reported mild pain sensation during fibre insertion, and just under 50% reported mild discomfort during normal daily activities throughout the monitoring period No complications at the site of implantation were observed</p> <p>Blood glucose monitoring Subcutaneous glucose concentrations were well correlated with plasma levels: (r=0.9, r<sup>2</sup>=0.817, p less than 0.001) Venous blood measurement showed 5.5% of values in the hypoglycaemic range Error grid analysis findings showed 97% of values were either totally exact (≤20% deviation) or 20% above or below the</p>

	<p>reference venous blood glucose values. Values that fall within this range are clinically acceptable</p> <p>Only three percent of patients values deviated outside this acceptable range to a point at which they deviated to a level that may be potentially dangerous with the possibility of making clinically significant mistakes.</p> <p>Bias percentage from reference was -2% in the hypoglycaemic range, 6.9% in the euglycaemic range and 11.2% in the hyperglycaemia range.</p> <p>Chi-squared heterogeneity test between the two blood glucose measuring techniques showed good correlation (pless than 0.001) between the two methods</p>
Hierarchy of Evidence Grading	III
Comments	<p>Patients hospitalised for 24 h</p> <p>System takes glucose measurement every second and stores an average value every 3 min. Data can be visualised continuously through an infrared communicating port and downloaded on to a PC to enable observance of glucose profiles over a 24 hour continuous monitoring period.</p> <p>Nine venous blood samples collected during the 24 hour period: 1 hour after insertion (usually in the morning) ; before lunch; 1, 2 and 3 h after lunch; before dinner; 2 h after dinner and at 3 am and 1 am on the next day.</p> <p>At study completion patients completed a questionnaire, ranking discomfort and pain during monitoring on a linear analogue scale</p> <p>Final patient questionnaire not previously validated</p> <p>No details of patient selection, exclusions on account of demographic data, or comparison with available population.</p> <p>Results were analysed by an independent statistician</p>
NCC CC ID	928
Reference / Citation	

Q 9 What is the optimum form of self-monitoring of glucose control in adults with Type 1 diabetes?

Author / Title / Reference / Yr	Gross T, Ter Veer A 2000 Continuous glucose monitoring in previously unstudied population subgroups. Diabetes technology and therapeutics 2: S27–S34
N=	238
Research Design	Case series
Aim	To evaluate the replicability of continuous blood glucose monitoring in a range of population subgroups
Population	Mixed diabetes population
Intervention	Continuous glucose monitoring system (CGMS) patients recorded capillary blood glucose levels
Comparison	Not applicable
Outcome	Accuracy of monitoring system measured by blood glucose values.
Characteristics	Sex (M/F): 102/136; Age (mean): 35.6±16.8 years; IDDM = 83%; duration of diabetes: 15.4±10.7 years; HbA1c:7.9±1.6%
Results	<p>Overall there was excellent agreement between the paired sensor and meter readings (correlation coefficient = 0.91)  Median absolute percent difference = 12.6%</p> <p>Evaluated by demographic subgroups  Correlation coefficient for each demographic subgroup was well above the cut-off criteria used by the CGMS software to identify optimal sensor calibration accuracy. (<math>\geq 0.79</math>)  No statistically significant differences in correlation coefficients were seen when comparing adult to paediatric patients, Caucasian to non-Caucasian patients, or patients with and without chronic illnesses.  Patients with type 2 diabetes had a statistically lower correlation coefficient when compared to patients with type 1 diabetes (<math>r=0.88</math> vs. <math>0.91</math>, <math>p=0.04</math>), as did pregnant vs. non-pregnant subjects (<math>r=0.84</math> vs. <math>0.90</math>, <math>p=0.0001</math>)  Percentage differences in each of the subgroups were well below the 28% cutoff criteria for optimal accuracy.  Statistically significant differences were only seen between patients with type 1 and type 2 diabetes (12.6% vs. 10.6%, <math>p=0.001</math>), and pregnant patients had a statistically higher percentage difference between results compared to nonpregnant females (16.1 vs. 12.6%, <math>p=0.0001</math>)</p>
Hierarchy of Evidence Grading	III
Comments	Physicians and their staff were given an orientation in CGMS and provided with all the necessary equipment.

	<p>Patients were asked to take <math>\geq 4</math> fingersticks/day using their own home blood glucose meters and to enter the readings into the CGMS monitor.</p> <p>Patients wore the CGMS at home for 3 days, at the end of which they returned to the medical office to have the sensor removed and the data downloaded and interpreted.</p> <p>Interpretation of data was performed by the healthcare provider.</p> <p>Each physician then returned the CGMS downloaded data along with anonymous demographic data and sensor insertion records, to the device manufacturer</p> <p>Absolute percent difference between each meter reading and its paired sensor reading for each subject</p> <p>Post marketing study</p> <p>Data evaluated by manufacturer, not by individual physicians.</p> <p>No details of validation of manufacturers results</p> <p>No raw data provided. All statistics are cumulative, no details given of individual patient results</p> <p>Results of CGMS performance statistics can be strongly influenced by the level and range of standard blood glucose meter values used to calculate them.</p> <p>Same meters are used to calibrate and evaluate the CGMS technique.</p> <p>No details given of timing of meter readings taken by the patients.</p> <p>No data given of whether patients continued with CGMS (as they were given the option to) after study completion</p>
NCC CC ID	897
Reference / Citation	

Q 9 What is the optimum form of self-monitoring of glucose control in adults with Type 1 diabetes?

Author / Title / Reference / Yr	Gross TM, Bode BW, Einhorn D, Kayne DM, Reed JH, White NH, Mastrototaro JJ 2000 Performance evaluation of the MiniMed continuous glucose monitoring system during patient home use. Diabetes Technology and Therapeutics 2(1):49–56
N=	N=135 USA
Research Design	Case series
Aim	To evaluate the accuracy of continuous monitoring systems
Population	Mixed diabetes population
Intervention	MiniMed continuous glucose monitoring system
Comparison	Self-monitoring blood glucose
Outcome	Accuracy of CGMS, measured by correlation of blood glucose results
Characteristics	Age: 40.5±14.5 (4–70) years; duration of diabetes: 18.0±9.8 (0.8–42.8 years); IDDM = 87%
Results	On average patients used CGMS for 4.2±2.0 (1–18) days 2726 SMBG readings were available for pairing with sensor readings Blood glucose profiles demonstrated a close agreement between meter readings and the CGMS profile Overall correlation for the CGMS in a home setting was 0.91 Overall bias between the sensor and meter readings were -3.2±33.7mg/dl, mean absolute difference = 18.0±19.8% For SMBG ≤70 mg/dl mean difference = 7.3±24.58, SMBG between 70 and 180 mg/dl mean difference = 0.00±28.26, for SMBG greater than 180 mean difference = -12.83±41.51 96.2% of readings fell within a clinically acceptable error range
Hierarchy of Evidence Grading	III
Comments	Data received from 8 clinical sites Patients wore the CGMS at home for ≤ 3 days Patients took ≥ 4 SMBG measurements each day using their own home blood glucose meters, starting ≥1 h after insertion of the CGMS monitor. Data was downloaded by physicians at the end of 3 days. Each clinical site completed a demographic questionnaire and returned the form along with the CGMS data download to the

	<p>device manufacturer</p> <p>No restrictions were placed on the participating physicians selection of patients, the reason for prescription, not the conditions of use.</p> <p>Study sponsored by MiniMed. Primary author MiniMed employee</p> <p>Authors state that initial orientation on the use of CGMS was given to each clinical site by either clinical research or marketing personnel, however, no formal study procedure was dictated.</p> <p>Demographic form for patient returned to the manufacturer along with CGMS download results</p>
NCC CC ID	878
Reference / Citation	

Q 9 What is the optimum form of self-monitoring of glucose control in adults with Type 1 diabetes?

Author / Title / Reference / Yr	Ellison JM, Stegmann JM, Colner SL, Michael RH, Sharma MK, Ervin KR, Horwitz DL 2002 Rapid changes in postprandial blood glucose produce concentration differences at finger forearm and thigh sampling sites. Diabetes Care 25:961–964
N=	N=42 USA
Research Design	Case series
Aim	An assessment of the replicability of blood glucose testing at various body sites
Population	Type of diabetes not recorded
Intervention	Capillary blood glucose concentrations measured at the forearm and thigh, using a blood glucose monitoring system and technician-obtained samples.
Comparison	Finger samples (verified with a laboratory instrument).
Outcome	Accuracy and reproducibility of testing at different sites.
Characteristics	Sex (M/F): 15/23; Age: 48.1±12.3 years; diabetes type (1/2): 13/25; BMI: 30.7±6.8 kg/m <sup>2</sup>
Results	<p>Laboratory evaluation before the study demonstrated strip-to-strip coefficients of variation of less than 4% at blood glucose concentrations of ~40, 80, 250 and 450 mg/dL</p> <p>In both phases meter finger results at all time points were closely matched with the corresponding YSI plasma results.</p> <p>All sampling sites showed a large increase in blood glucose after the meal, followed by a levelling and a gradual decline thereafter</p> <p>Finger glucose concentrations peaked during the 90 min session, whereas forearm and thigh concentrations peaked at around 120 min and at a lower glucose concentration.</p> <p>In each phase, between subject glucose variations were substantial yet consistent in magnitude across the three sampling sites at each time point.</p> <p>Repeated measures ANOVA for mean glucose showed statistically significant differences (p less than 0.05) among sampling sites at 60 min. Differences for all other sampling sites and time points were not statistically significant.</p> <p>Analyses of covariates</p> <p>Analyses of the covariates of age, BMO, test time (am/pm), diabetes type, and insulin dependence, suggested that site differences were more pronounced in older subjects (greater than 40 years), testing in the morning, and non-insulin treated patients. None of these differences were statistically significant.</p>

	<p>Diabetes type and BMI did not have a consistent effect on site differences.</p> <p>Percentage differences between sites  Data suggests that the sign and magnitude of the forearm and thigh percentage differences might be related to the direction and rate of blood glucose changes  At higher rates of blood glucose change the differences between finger and alternate site blood glucose concentrations became greater.  Linear regression analysis supports the observed relationship for both forearm (<math>r=0.56</math>, <math>p &lt; 0.0001</math>) and thigh (<math>r=0.52</math>, <math>p &lt; 0.0001</math>) percentage differences.</p>
Hierarchy of Evidence Grading	III
Comments	<p>Subjects provided relevant demographic medical, and dietary information; maintained normal diet and medication practices; acted as a source of blood samples for technician-performed tests  Each phase consisted of six testing sessions (premeal and ~60, 90, 120, 150 and 180 min post meal) in which subjects were tested with a glucose monitoring system using finger, forearm and thigh blood samples.  Testing sessions scheduled to minimize impact on daily diabetes management regimes  Items consumed by each subject at each meal were documented. Total carbohydrate content for breakfast ~226g and ~143 g for lunch.  Skin punctures and glucose tests performed by trained technicians. Order of sites tested was varied between subjects, with minimal elapsed time between sites.  Finger and forearm samples were collected from the same arm, the choice of arm varying between sessions.  Meter system accuracy verified by comparing meter finger results with the corresponding Plasma glucose values  Testing sessions were identified as nominal time points however, actual times between testing sessions varied slightly from subject to subject.  Forearm and thigh sites were rubbed vigorously for several seconds to promote adequate blood flow, aided by a warm pad if necessary.  Between-subject mean glucose concentrations at three sampling sites were compared using repeated measures ANOVA  Glucose concentration differences between alternate sites (forearm and thigh) and finger meter measurements were calculated as percentage differences for each subject  No details given of selection of patients  No raw data given in results.  Authors conclusion: Glucose values measured at forearm and thigh sampling sites might lag behind values obtained from the finger when glucose levels are changing rapidly. This lag may produce significant difference in blood glucose concentrations measured at these sites</p>
NCC CC ID	1388
Reference / Citation	



Q 9 What is the optimum form of self-monitoring of glucose control in adults with Type 1 diabetes?

Author / Title / Reference / Yr	Lock PJ, Szuts EZ, Malomo KJ, Anagnostopoulos A 2002 Whole-blood glucose testing at alternate sites. Diabetes Care 25:337–341
N=	N=50 USA
Research Design	Case series
Aim	An assessment of the replicability of blood glucose testing at various body sites
Population	Mixed diabetes population
Intervention	Finger tip testing
Comparison	Forearm testing
Outcome	Accuracy of testing at different sites measured in blood glucose and haemoglobin (Hb) concentration results
Characteristics	Sex (F): 50%; Age: 45.4±11.3 (18–65) years; Duration of diabetes: 17.9±11.4 years; Type 1 diabetes: 52%; % Type 2 diabetes on insulin treatment: 54.2%; BMI: 27.9±5.5 kg/m <sup>2</sup> ; HbA1c:8.2±1.8%
Results	<p>Haemoglobin concentrations</p> <p>Significant variation in Hb concentration was found between the capillary beds of the forearm and fingertip. For all subjects Hb concentration in the arm was 15.7±1.8 g/dl, ~1.7 g/dl higher than in the fingertip (14.0±1.9 g/dl). This difference was not significant because interperson variability masks individual bias. When intraperson differences were calculated, this difference becomes significant. Approximately 90% of subjects had a higher Hb concentration in their arm than their fingertip.</p> <p>Glucose concentrations</p> <p>Mean difference for all participants between arm and finger blood glucose concentrations = -0.1% (measurement errors ~8%)  Mean difference in subjects whose glucose concentrations varied ≤9 mg/dl = -1±6%; ≤18 mg/dl = -0.9±6% and greater than 18 mg/dl = 2±10%</p> <p>Differences between sites was small and insignificant</p>
Hierarchy of Evidence Grading	III

Comments	<p>In each patient the fingertip was lanced for initial assay with YSI; Forearm was lanced twice for consecutive assays of glucose and Hb concentration; Fingertip lanced once and ~100 µl blood collected for glucose and Hb assays/  The second two steps were then repeated twice so each assay was performed in triplicate. Mean of triplicates were used to calculate each subjects percent of glucose difference between arm and finger  A final finger lancing for repeat glucose assay with the YSI analyser  Assays were performed by two trained operators so that interperson variability was minimized.  Control experiments were conducted to evaluate the contribution of various physical factors of equipment that might alter results during vacuum collection. Results indicated no significant effect on the outcome of these experimental techniques.  Assays performed by trained operators  Results taken in triplicate  Because of the order in which replicates were collected, the two sites were equally affected by time-dependent changes, e.g. glucose drift. Thus mean values in these results should reflect the effects of intrinsic factors, if any, that could alter local glucose concentrations.  Analysis was performed using the entire data set, with none of the data removed.  No details given of rationale for recruitment of subjects into the study  No exclusion/inclusion criteria are stated  Neither intraperson differences nor measurement errors are provided for glucose measurements</p>
NCC CC ID	1398
Reference / Citation	

Q 9 What is the optimum form of self-monitoring of glucose control in adults with Type 1 diabetes?

Author / Title / Reference / Yr	Jungheim K, Koschinsky T 2002 Glucose monitoring at the arm. Diabetes Care 25:956–960
N=	N=17 Germany
Research Design	Case series
Aim	An assessment of the replicability of blood glucose testing at various body sites
Population	Mixed diabetes population
Intervention	Capillary blood glucose samples analysed with approved SMBG devices in capillary blood taken from the fingertip
Comparison	Samples from the forearm.
Outcome	Accuracy of blood glucose testing
Characteristics	Sex (M/F): 15/2; Age: 20–59 years (median 38); Type 1 diabetes n=13; Duration of diabetes: 2 weeks–28 years (median 13 years); no complications in 12 patients; retinopathy n=5; sensorimotor neuropathy n=2; microalbuminuria n=2, impaired hypoglycaemia awareness n=5
Results	<p>Blood Glucose values</p> <p>No relevant differences between blood glucose values were seen at the finger and forearm at baseline (7.7 vs. 6.5 mmol/l, p=0.06)</p> <p>30–90 min after ingestion of glucose the rate of increase in blood glucose measured at the fingertip = 0.13±0.03 mmol/l/min. The individual maximal difference in blood glucose between the forearm and finger was 4.7 mmol/l.</p> <p>The decrease in blood glucose at the fingertip was also consistently larger than that at the forearm (15.0 vs. 12.0 mmol/l, pless than0.001)</p> <p>An individual maximal difference in blood glucose between forearm and finger of 5.4 mmol/l was observed 15–75 min after administration of insulin.</p> <p>At the first hypoglycaemic fingertip blood glucose value (<math>\leq 3.5</math> mmol/l), 80% of forearm blood glucose values were <math>\geq 5.0</math> mmol/l</p> <p>During the increase and decrease parts, blood glucose at the forearm was lagging behind blood glucose at the fingertip by a median of 27 min (6–91, pless than0.001), 35 min (22–67, pless than0.001) and 34 min (27–35, pless than0.05) at 14.p, 5.5 and 3.5 mmol/l respectively.</p>

	<p>Forearm rubbing</p> <p>A significant difference was seen following rubbing of the forearm in the eight patients in which this was performed. On average the maximal difference between forearm and finger was reduced during the increase part from <math>4.5 \pm 0.7</math> to <math>3.1 \pm 1.1</math> mmol/l (p less than 0.05) and during the decrease part from <math>4.8 \pm 1.1</math> to <math>3.0 \pm 0.9</math> mmol/l (p less than 0.001)</p>
Hierarchy of Evidence Grading	III
Comments	<p>Recruitment of patients for testing was independently made by the caring physicians. Three patients from the original population refused to participate in this study due to the required additional BG sampling.</p> <p>Additional capillary whole blood samples were collected from the fingertip in parallel to the SMBG device and analysed in the laboratory.</p> <p>Laboratory values matched the respective fingertip values measured with the examined SMBG devices.</p> <p>Technical performance of all blood glucose monitors was evaluated and was within the limits expected for all SMBG devices of relative glucose deviation.</p> <p>Blood samples were collected in parallel (within 3 min) from the fingertip and the forearm every 15 min.</p> <p>Forearm skin was not rubbed before BG sampling, as recommended by some manufacturers, to avoid any disturbance of the normal regional blood flow. (except in a subgroup of patients (n=8) in which additional samples were taken from the other forearm after rubbing for 5–10s)</p> <p>Capillary blood samples collected by a trained research nurse</p> <p>No inclusion/exclusion criteria for patients.</p> <p>Very small study sample.</p> <p>Authors conclude that blood glucose testing at the forearm under metabolic steady-state conditions (e.g. fasting/preprandial state) can be a reliable and valuable alternative to blood glucose testing at the finger tip. However during rapid blood glucose changes the forearm should not be used for testing due to risky delays in detection of hypoglycaemia.</p>
NCC CC ID	1390
Reference / Citation	

7.2 Glucose control assessment levels  
Not applicable

### 7.3 Insulin regimens

Q 27 What types of insulin regimens aid optimal diabetic control in adults with stable type I diabetes?

Author / Title / Reference / Yr	NICE 2002 Guidance on the use of long-acting analogues for the treatment of diabetes - insulin glargine. Technology Appraisal Guidance No.53
N=	6 fully published open-label RCTs: four in type 1 diabetes (two in type 2 diabetes) Seven studies published only in abstract form were also reviewed, and one unpublished abstract made available by manufacturer. Three observational studies were also presented by the manufacturer. UK
Research Design	Systematic review / guidelines
Aim	To assess the usefulness of alternative insulin regimens
Population	Mixed diabetes population
Intervention	Once daily insulin glargine
Comparison	Once- or twice-daily NPH Insulin doses were titrated and adjusted in an attempt to achieve target fasting blood glucose (FBG). This phase was followed by a post-titration period in which insulin doses were kept stable for each individual.
Outcome	Primary outcome: All studies used a measure of glycaemic control, either fasting blood glucose (FBG), fasting plasma glucose (FPG) or HbA1c Secondary outcome: The incidence and severity of hypoglycaemic episodes (classified as nocturnal, symptomatic or severe) were also reported)
Characteristics	Varied between studies
Results	Type 1 diabetes Glycaemic control In all four fully published studies, mean change in FPG from baseline was significantly greater in the groups using insulin glargine compared with those using NPH. The difference between mean changes from baseline across the trials ranged from 1.34 mmol/l and 2.23 mmol/litre. In three trials, insulin glargine was significantly superior to NPH in terms of reducing FBG (difference in mean change 0.71-1.50 mmol/litre) The fourth study showed no significant difference between insulin glargine and NPH for this endpoint.

#### Haemoglobin A levels

Three of the four studies reported no statistically significant differences in HbA1c between groups receiving insulin glargine over NPH.

One study showed an overall statistically significant superiority of insulin glargine over NPH in terms of reducing HbA1c; however, the duration of this trial was only 4 weeks.

#### Incidence of nocturnal hypoglycaemic episodes

One study reported a significantly smaller percentage of people experiencing nocturnal hypoglycaemia in the insulin glargine groups taken together compared with the NPH group over the whole duration of the trials (36% vs 56% respectively;  $p < 0.01$ ). However, over the post-titration phase the difference was significant for only one glargine formulation compared with NPH (8% vs 19%,  $p < 0.05$ ). In this study, there was a clear advantage of insulin glargine over NPH once daily in reducing hypoglycaemia, but the percentages of individuals with nocturnal hypoglycaemia were very similar when insulin glargine was compared with NPH twice daily. One study reported fewer episodes of nocturnal hypoglycaemia in the group using insulin glargine compared with the group using NPH in the post-titration phase. One study showed no difference between insulin glargine and NPH in the incidence of nocturnal hypoglycaemia. One study did not distinguish nocturnal hypoglycaemia from other hypoglycaemic episodes.

#### Incidence of symptomatic hypoglycaemic episodes

One study reported a smaller percentage of people experiencing symptomatic hypoglycaemia in the group using insulin glargine compared with the group using NPH for both the whole trial and the post-titration phases (40% vs 49% respectively for the post-titration phase only; figures were not reported for the whole trial). Two studies showed no difference between groups in the incidence of symptomatic hypoglycaemia in either the entire trial period or the post-titration phase. The fourth study did not distinguish symptomatic hypoglycaemia from other hypoglycaemic episodes.

#### Incidence of severe hypoglycaemic episodes

Of the three studies reporting severe hypoglycaemia, only one reported that a significantly smaller percentage of people experienced severe episodes of hypoglycaemia in the insulin glargine group compared with the NPH group in the post-titration phase (1.9% vs 5.6% of the patients respectively;  $p < 0.05$ ). Two studies reported no significant differences between groups in terms of severe hypoglycaemia during either the entire trial period or the post-titration phase.

#### Observational studies

The analysis of a large observational dataset from Germany, which contains data on approximately 10,000 individuals and is managed by the manufacturer, showed a 1.7% reduction in HbA1c levels in people with type 1 diabetes compared with baseline when they were treated with insulin glargine for up to 8 weeks. In the same dataset, 70.3% of people with type 1 diabetes reported fewer hypoglycaemic episode when they were receiving insulin glargine.

Another unpublished observational study using a US database (of 489 people with diabetes) reported a 0.36% reduction in HbA1c levels compared with baseline in people with type I diabetes

	<p>Guidance for type I diabetes On the balance of effectiveness and cost-effectiveness evidence, Insulin glargine is recommended as a treatment option for people with type I diabetes</p> <p>Future research The degree to which individuals' quality of life is affected by increased awareness and uncertainty of their daily blood glucose status and their recognition of the need to achieve a balance between the risk of hypoglycaemic and the benefits of longer-term glycaemic control The duration and severity profile of hypoglycaemic episodes, which may differ between individuals. It is also recommended that the method of documenting hypoglycaemic episodes in future clinical studies in this area is improved (to include the duration of the episode and time of the day in which the episode occurred) to allow the impact on quality of life to be better appreciated. The effectiveness and cost effectiveness of insulin glargine as part of a multiple-daily-injection regimen compared with insulin pump therapy</p>
Hierarchy of Evidence Grading	NICE
Comments	<p>Implications for the NHS The impact of insulin glargine on the NHS budget will depend on the eipdemiology of the target population, the cost of insulin glargine and the expected uptake rates for insulin glargine It is estimated that up to 137,000 individuals would be eligible for insulin glargine treatment (type I and type 2 diabetes) The incremental cost of insulin glargine (based on vial costs) is assumed to be £101 per annum for people with type I diabetes (annual cost of insulin glargine is £203 and annual cost of NPH is £102)</p> <p>Provides evidence-based clinical practice for the National Service Framework Guidance to be considered for review in 2005. Appraisal process involves the manufacturer of the technology for which guidance is being produced and the organisations that represent the healthcare professionals, patients and carers who will be affected by the guidance. Appraisal takes about 12 months to complete. Guidance was peer-reviewed and made available for consultation prior to publication of the final report.</p>
Trials included	See original study
NCC CC ID	1117
Reference / Citation	

Q 27 What types of insulin regimens aid optimal diabetic control in adults with stable type I diabetes?

Author / Title / Reference / Yr	Egger M, Davey G, Stettler SC, Diem P 1997 Risk of adverse effects of intensified treatment in insulin-dependent diabetes mellitus: A meta-analysis. <i>Diabetic Medicine</i> 14:919-928
N=	Fourteen trials identified. N = 1028 type 1 patients allocated to intensified and 1039 allocated to conventional treatment. Most studies were parallel studies. 14 studies included 15 trials and contributed 16 comparisons between intensified and conventional insulin regimens.
Research Design	Meta-Analysis
Aim	To evaluate the risks of alternative insulin regimens
Population	Type 1 diabetes
Intervention	Intensified insulin treatment regimens Patients randomised to intensified treatment either received pump treatment (9 trial arms), multiple daily injections (4 trial arms) or could choose between the two intensified regimens (3 trial arms).
Comparison	Conventional treatment inpatients with type 1 diabetes. Conventional treatment typically consisted of twice-daily injection regimens without frequent blood glucose self-monitoring.
Outcome	Primary outcome: Progression of chronic complications of diabetes - Severe hypoglycaemia, ketoacidosis and death
Characteristics	Varied between studies
Results	Severe hypoglycaemia A total of 846 patients suffered from at least one episode of severe hypoglycaemia, 175 patients experience ketoacidosis and 26 patients died. Combined odds ratio (95% CI) for hypoglycaemia was 2.99 (2.45-3.64), for ketoacidosis 1.74 (1.27-2.38) and for death from all causes 1.4 (0.65-3.01). The risk of severe hypoglycaemia was determined by the degree of normalisation of glycaemia achieved. Ketoacidosis Ketoacidosis risk depended on the type of intensified treatment used – odds ratios were 7.20 (2.95-17.58) for exclusive use of pumps, 1.13 (0.15-8.35) for multiple daily injections and 1.28 (0.9-1.83) for trials offering a choice between the two. Mortality Mortality was significantly (0.007) increased for causes potentially associated with acute complications (7 vs. 0 deaths, 5 deaths attributed to ketoacidosis, and 2 sudden deaths), and non-significantly (p=0.16) decreased for microvascular causes.

Hierarchy of Evidence Grading	Ia
Comments	<p>Each study was graded for its methodological quality. Logistic regression was used for calculation of combined odds ratios and 95% confidence intervals.</p> <p>Statistical analysis was by fixed effects method.</p> <p>Chi-squared test used to test for heterogeneity.</p> <p>Sensitivity analysis performed.</p> <p>The influence of covariates was examined using covariate-by-treatment interaction terms.</p> <p>Methodological study quality was assessed and sensitivity analyses performed.</p> <p>Conclusion – substantial risk of severe adverse effects associated with intensified insulin treatment. Mortality from acute metabolic causes is increased; however, this is largely counterbalance by a reduction in cardiovascular mortality.</p>
Trials included	See original trial
NCC CC ID	283
Reference / Citation	

Q 27 What types of insulin regimens aid optimal diabetic control in adults with stable type I diabetes?

Author / Title / Reference / Yr	Davey P, Grainger D, MacMillan J, Rajan N, Aristides M, Gliksman M 1997 Clinical outcomes with insulin lispro compared with human regular insulin: A meta-analysis. <i>Clinical Therapeutics</i> 19:656-674
N=	(2361 patients) Eight randomised, controlled trials
Research Design	Meta-analysis
Aim	A comparison of insulin types
Population	Type 1 and Type 2 diabetes
Intervention	insulin lispro
Comparison	Compared with human regular insulin
Outcome	Primary outcome: postprandial glycaemia control, including postprandial glucose excursion (therapeutic success = decrease in postprandial glucose levels to less than 8 mmol/L, a 2 hr postprandial blood glucose level within 20% of the pre-meal level, or a decrease from baseline in 2-hour postprandial glucose excursion greater than or equal to 50%. Secondary outcome: Overall glycaemic control and hypoglycaemic episodes
Characteristics	Varied between studies
Results	Pooled studies (patients with type I and type II diabetes) Dichotomous outcomes Insulin lispro was found to offer statistically significant advantages over human regular insulin in terms of risk difference and odds ratios for predefined outcomes related to postprandial glucose control. The number of patients achieving a postprandial glucose levels of less than 8mmol/L showed a statistically significant difference in favour of insulin lispro (p less than 0.00001) No significant differences were seen between the insulins in terms of the number of patients achieving a 2-hour postprandial blood glucose levels within 20% of the pre-meal level or at least a 50% decrease from baseline in 2-hour postprandial glucose excursion. Continuous outcomes Postprandial blood glucose control (1-hour postprandial blood glucose, 2-hour postprandial blood glucose, and 1- and 2-hour glucose excursion) showed statistically significant differences in favour of insulin lispro (p less than 0.02, p less than 0.001, p less than 0.001 and p less than 0.001, respectively)

	<p>No significant differences were seen in the weighted mean differences for measures of long-term glycaemic control (glycated haemoglobin HbA1c), fasting blood glucose, and hypoglycaemic rate per 30 days.</p> <p>Studies in patients with Type 1 diabetes</p> <p>Dichotomous variables</p> <p>Significantly more patients had a decrease in postprandial blood glucose level less than 8mmol/L with insulin Lispro (pless than0.0001).</p> <p>Continuous variables</p> <p>Significant differences in favour of insulin lispro were seen in 2-hour postprandial blood glucose level (pless than0.05) and in 1-hour (pless than0.02) and 2-hour (pless than0.01) glucose excursion.</p> <p>No differences were seen in the weighted mean differences for HbA1c, fasting blood glucose and hypoglycaemic rate per 30 days.</p>
Hierarchy of Evidence Grading	Ia
Comments	<p>Fixed-effects and random-effects methods were used for dichotomous variables.</p> <p>Odds ratios and absolute risk differences were calculated.</p> <p>Chi-square statistic used to test for lack of homogeneity.</p> <p>For continuous variables, weighted least squares estimation with weighting by study precision was used to obtain pooled fixed-effects estimate of the mean difference in response.</p> <p>A 95% confidence interval was give for each treatment difference.</p> <p>Meta-analysis of studies involving 2361 patients demonstrated significant differences in favour of insulin lispro in outcomes related to postprandial glycaemic control.</p> <p>This improvement in glycaemic control was apparently achieved without an increase in the rate of hypoglycaemic episodes.</p>
NCC CC ID	291
Reference / Citation	

Q 27 What types of insulin regimens aid optimal diabetic control in adults with stable type I diabetes?

Author / Title / Reference / Yr	Shukla, VK, Otten, N 1999 Insulin lispro: a critical evaluation. 1895561728. Technology Report Issue 18. Canadian Coordinating Office for Health Technology Assessment (CCOHTA).
N=	n = 2558 people with Type I diabetes
Research Design	Systematic review
Aim	To evaluate the efficacy of insulin Lispro
Population	Type 1 diabetes
Intervention	insulin lispro
Comparison	regular insulin Study duration 2-12 months
Outcome	Glycaemic control as measured by postprandial rise in serum glucose and postprandial glucose excursions (pre-test glucose subtracted from 1 and 2 hour postprandial values) Glycaemic control as measured by the surrogate marker Haemoglobin A1 Incidence and severity of hypoglycaemia
Characteristics	Varied between studies
Results	<p>Glycaemic control</p> <p>Lispro injection significantly decreases the postprandial rise in serum glucose, as well as postprandial glucose excursions compared to regular insulin therapy</p> <p>Lispro controlled the postprandial plasma glucose concentrations significantly better than regular insulin in patients with type I diabetes.</p> <p style="text-align: center;">Haemoglobin A1 levels</p> <p>No consistent effects of Lispro on HbA1c levels have been found in comparison to regular insulin therapy. A number of studies detect no significant difference between groups, whereas other studies have shown significant decreases in HbA1c levels with lispro treatment compared with regular human insulin. Such differences may also be accounted for by a number of other factors, including a change in dietary habits or an increase in total insulin daily dose.</p> <p style="text-align: center;">Hypoglycaemia in intensive insulin therapy</p> <p>In two 3-month studies comparing lispro administered in continuous subcutaneous infusion and regular insulin using an insulin pump no significant difference in the frequency of hypoglycaemic per 30 days was observed.</p>

	<p>In one study the rate of occurrence of very low blood glucose (less than 2mmol/l) was significantly reduced with lispro</p> <p>Hypoglycaemia in regular insulin therapy</p> <p>Lispro significantly reduced hypoglycaemic episodes in patients with type I diabetes</p> <p>No significant difference in the frequency of severe hypoglycaemic episodes was observed between lispro and regular human insulin in individual clinical trials; however, a meta-analysis which included three parallel and five crossover design multicentre clinical trials in patients with type I diabetes concluded that the incidence of severe hypoglycaemic episodes was significantly less in the lispro group compared with regular human insulin group</p>
Hierarchy of Evidence Grading	Ia
Comments	<p>In the individual clinical studies, lispro improved postprandial glucose profiles; however, its role in improving glycaemic control based on HbA1c levels has not been fully established.</p> <p>There is no firm evidence to support a reduced frequency of symptomatic hypoglycaemia by lispro treatment in patients with type I diabetes</p> <p>The long-term safety profile of insulin lispro has not yet been established.</p>
Trials included	See original study
NCC CC ID	1064
Reference / Citation	

Q 27 What types of insulin regimens aid optimal diabetic control in adults with stable type I diabetes?

Author / Title / Reference / Yr	Brunelle RL, Llewelyn J, Anderson JH, Jr., Gale EAM, Koivisto VA 1998 Meta-analysis of the effect of insulin lispro on severe hypoglycemia in patients with type 1 diabetes. Diabetes Care 21:1726-1731
N=	Studies included 2576 type 1 diabetes patients, with 2,327 receiving insulin lispro and 2,339 receiving regular human insulin Eight large multicentre clinical trials, three with parallel and five with crossover designs
Research Design	Meta-analysis
Aim	To evaluate the pooled treatment effect of insulin Lispro
Population	Type I diabetes
Intervention	Insulin lispro
Comparison	Regular human insulin (Humulin R or Actrapid) before each meal
Outcome	Primary outcome: Severe hypoglycaemia, defined as coma or requiring glucagons or intravenous glucose.
Characteristics	Varied between trials
Results	72 patients (3.1%) had a total of 102 severe hypoglycaemic episodes during insulin lispro therapy, compared with 102 (4.4%) patients with a total of 131 episodes during regular human insulin therapy (p = 0.024) In no instance was there a statistically significant difference between the treatments for the incidence of severe hypoglycaemic events within the individual studies. No significant difference in the diurnal distribution of severe hypoglycaemia between the two therapies.
Hierarchy of Evidence Grading	Ia
Comments	Meta-analysis of studies involving 2576 type 1 diabetic patients demonstrated that the frequency of severe hypoglycaemia could be reduced by taking insulin lispro as compared with regular human insulin therapy. Study quality was assessed by reviewing the designs and implementation of each study. Cochran-Matel-Haenszel test was used to compare the treatment groups for the incidence of severe hypoglycaemic events. Sensitivity analysis was performed to examine effects of various studies on overall outcome. Chi-squared test used to compare numbers of patients experiencing at least one severe hypoglycaemic event between study groups. Crossover data was split to make crossover data look like parallel study.

Trials included	See original study
NCC CC ID	44
Reference / Citation	

Q 27 What types of insulin regimens aid optimal diabetic control in adults with stable type I diabetes?

Author / Title / Reference / Yr	Lalli C, Ciofetta M, Del Sindaco P, et al 1999 Long-term intensive treatment of type 1 diabetes with the short-acting insulin analog lispro in variable combination with NPH insulin at mealtime. Diabetes Care 22:468-477
N=	56: lispro = 28, human insulin =28 Italy
Research Design	Randomised Controlled Trial
Aim	To compare effectiveness of human and artificial insulin
Population	Type 1 diabetes
Intervention	Lispro (Humalog) at meals Lispro was injected at mealtime With lispro, NPH was added at breakfast (~70/30), lunch (~60/40), and supper (~80/20) to optimised premeal and bedtime blood glucose
Comparison	Regular human insulin (Hum-R) at meals Hum-R was given 10-40 minutes before meals.
Outcome	Effect on glycaemic control
Characteristics	Type 1 diabetes, treated with intensive insulin therapy at attend clinic at least quarterly every year. C-peptide negative.
Results	<p>Insulin dosage</p> <p>Total daily insulin units were no different in the two treatment groups, but with lispro ~30% less short-acting insulin at meals and ~30% more NPH was needed versus Hum R (p less than 0.05). Bedtime NPH dosage was no different.</p> <p>Glycaemic control</p> <p>With lispro + NPH, the mean daily blood glucose was lower than with Hum R (<math>8.0 \pm 0.1</math> vs. <math>8.8 \pm 0.1</math> mmol/l; p less than 0.05) as a result of lower post meal (<math>8.1 \pm 0.2</math> vs. <math>9.7 \pm 0.2</math> mmol/l; p less than 0.05) and fasting, premeal, bedtime and 0300 blood glucose (<math>8.1 \pm 0.2</math> vs. <math>8.3 \pm 0.2</math>; p = 0.07)</p> <p>With lispro + NPH, the mean HbA1c was lower than in the Hum-R group (<math>6.34 \pm 0.10</math> vs. <math>6.71 \pm 0.11\%</math>, mean value over 1 year, p less than .002) and hypoglycaemia was less frequent (<math>7.4 \pm 0.5</math> vs. <math>11.5 \pm 0.7</math> episodes/patient month) and tended to occur more within 90 min after meals than in the post absorptive state (p less than 0.05)</p> <p>After 1 year, plasma adrenaline and symptoms responses to experimental stepped hypoglycaemia improved with lispro and were closer to the responses of 12 nondiabetic control subjects versus Hum-R both in terms of thresholds and magnitude (p less</p>

	than0.05)
Hierarchy of Evidence Grading	Ib
Comments	<p>1 month run-in period - patients continued their previous model of insulin therapy (Hum R) at breakfast, lunch, dinner and NPH insulin at bedtime.</p> <p>During run-in and treatment periods, patients were seen at 1-2 week intervals.</p> <p>In the Hum-R and lispro groups, 20 and 18 patients, respectively, mixed lispro or Hum-R with NPH insulin in syringes. The remaining patients used separated injections with insulin pens to administer short- and intermediate-acting insulin.</p> <p>Of 56 type 1 patients, 36 added NPH to regular insulin at lunch to optimise predinner glucose.</p> <p>Patients were randomly assigned to two groups and studied for 12 months.</p> <p>Patients aimed at 90 min post meal blood glucose of 9-10 mmol/l and fasting and premeal glucose 7-8 mmol/l</p> <p>Open label as different pharmacokinetics for insulins require different intervals before mealtime.</p> <p>Baseline characteristics of patients similar at start of trial</p> <p>Glycaemic thresholds were defined as the plasma glucose concentration at which the parameter first exceeded the 95% CI limit observed for changes in that parameter at the corresponding time point in normoglycaemic control experiments</p> <p>Euglycaemic control experiments were performed in all 12 volunteers and 12 type 1 diabetic patients, whose results did not differ from those of the nondiabetic patients.</p> <p>Because of difference in units of treatment, results of cognitive tests were transformed to z scores</p> <p>Data were analysed by paired and, when appropriate, unpaired t tests after analysis of variance for crossover</p>
NCC CC ID	1066
Reference / Citation	

Q 27 What types of insulin regimens aid optimal diabetic control in adults with stable type I diabetes?

Author / Title / Reference / Yr	Anderson JH, Brunelle RL, Koivisto VA, Pfozner A, Trautmann ME, Vignati L, DiMarchi R. 1997 Reduction of postprandial hyperglycemia and frequency of hypoglycemia in IDDM patients on insulin-analog treatment. Multicenter Insulin Lispro Study Group. Diabetes 46:265-270
N=	1008
Research Design	Randomised Controlled Trial
Aim	To evaluate the frequency of hypoglycaemia with insulin lispro treatment
Population	Type 1 diabetes
Intervention	Insulin lispro (Humalog U-100)
Comparison	regular human insulin (Humulin R U-100) in the mealtime treatment
Outcome	Glycaemic control
Characteristics	type 1 diabetes according to WHO criteria, between the ages of 12 and 70 years, and had been on human insulin therapy for at least 2 months
Results	<p>Glycaemic control</p> <p>Postprandial rise in serum glucose was significantly lower during lispro therapy</p> <p>At endpoint, postprandial rise in serum glucose was reduced at 1h by 1.3mmol/l and at 2h by 2mmol/l in patients treated with insulin lispro (pless than0.001).</p> <p>HbA1c levels improved significantly and equally in both treatment groups during the study.</p> <p>Hypoglycaemia</p> <p>The rate of hypoglycaemia was 12% less with insulin lispro (<math>6.4 \pm 0.2</math> vs. <math>7.2 \pm 0.3</math> episodes/30 days, pless than0.001), independent of basal insulin regimen or HbA1c level. – The reduction was observed equally in episodes with or without symptoms.</p> <p>Number of hypoglycaemic episodes was less with insulin lispro than with regular human insulin therapy during three of four quarters of the day (pless than0.001).</p> <p>The largest relative improvement was during the night.</p>
Hierarchy of Evidence Grading	Ib

Comments	<p>Insulin lispro injected immediately before the meal, and regular human insulin injected 30-45 minutes before the meal. NPH insulin (Humulin N U-100) or ultralente insulin (Humulin U U-100) were used for basal substitution using a pen.</p> <p>After 2-4 week lead-in period, patients were randomised to one of two treatment sequences</p> <ol style="list-style-type: none"> <li>1) Multiple premeal dose therapy with regular human insulin for 3 months</li> <li>2) Multiple premeal dose therapy with insulin lispro for 3 months</li> </ol> <p>After 3 months the patients groups crossover to the alternative therapy</p> <p>Self-monitoring of glucose was basis for insulin adjustments.</p> <p>One-and two-hour blood glucose values were determined after test meals at baseline and monthly intervals to determine postprandial glucose control.</p> <p>Not blinded to allow both rapid-acting insulins to be given at recommended time intervals before meal.</p> <p>Crossover model used to evaluate carryover and treatment effects</p> <p>No evidence of carryover effect observed.</p> <p>Within-treatment comparisons performed using paired t-test.</p> <p>Data from all patients included in analyses using intent-to-treat methodology.</p> <p>Analyses were performed using endpoint value, and last observation carried forward</p>
NCC CC ID	1062
Reference / Citation	

Q 27 What types of insulin regimens aid optimal diabetic control in adults with stable type I diabetes?

Author / Title / Reference / Yr	Pfutzner A, Kustner E, Forst T, Schulze-Schleppinghoff, Trautmann ME, Haslbeck, Schatz H, Beyer J 1996 Intensive insulin therapy with insulin lispro in patients with type 1 diabetes reduces the frequency of hypoglycemic episodes. <i>Experimental &amp; Clinical Endocrinology &amp; Diabetes</i> 104:25-30
N=	N = 107
Research Design	Randomised Controlled Trial
Aim	Comparing human and artificial insulin
Population	Type 1 diabetes
Intervention	Insulin lispro
Comparison	Regular human insulin
Outcome	Glycaemic control measured by pre-test blood glucose, 1 and 2 hour postprandial glucose excursions, glycated haemoglobin levels, frequency and severity of hypoglycaemic episodes and daily insulin doses, body weight, insulin antibodies and the number and severity of adverse event. A questionnaire was used to measure quality of life aspects. All tests performed in central laboratory
Characteristics	(53 male, 54 female; mean age $32 \pm 9.7$ years, range 18-65 years) Mean duration of diabetes was $9.55 \pm 7.74$ years.
Results	HbA1c values were equal and remained stable with both treatment regimens With insulin lispro the number of hypoglycaemic episodes was significantly lower $8.57 \pm 0.7$ episodes/month vs. $9.61 \pm 0.72$ episodes/month, $p = 0.008$ With insulin lispro the 1 and 2 hour blood glucose excursions decreased to a greater extent compared with the regular human insulin group. With insulin lispro a significant improvement was seen for treatment satisfaction compared with regular human insulin.
Hierarchy of Evidence Grading	Ib
Comments	2-4 week lead-in period treated with regular human insulin and NPH human insulin as basal insulin. Patients were then randomised to received either lispro and human NPH or regular human insulin and human NPH Crossover took place after three months of treatment Study continued for another 3 months Study was not blinded to allow both rapid acting insulins to be given at the optimum time interval before the meal.

	<p>The statistical crossover analysis was performed using both parametric and nonparametric techniques  97 of 107 included patients completed the trial  Reasons for patient discontinuation were patient decision (3 cases), lack of efficacy of insulin lispro as perceived by the investigator (2 cases), violation of entry criteria (1 case) and one adverse event.  Pre-test blood glucose values tended to be lower in the patients treated with insulin lispro (ns)</p>
NCC CC ID	1053
Reference / Citation	

Q 27 What types of insulin regimens aid optimal diabetic control in adults with stable type I diabetes?

Author / Title / Reference / Yr	Renner R, Pfutzner A, Trautmann M, Harzer O, Sauter K, Landgraf R 1999 Use of insulin lispro in continuous subcutaneous insulin infusion treatment: Results of a multicenter trial. <i>Diabetes Care</i> 22:784-788
N=	113 Germany
Research Design	Randomised Controlled Trial
Aim	To evaluate the effects of infused artificial insulin in people with diabetes
Population	Type 1 diabetes
Intervention	Insulin lispro
Comparison	Regular human insulin, both applied with insulin pumps for 4 months each. After treatment period of 4 months, a crossover to the alternative regimen occurred and the study was continued for another 4 months
Outcome	HbA1c, daily and postprandial blood glucose profiles, adverse events, rate of hypoglycaemic (less than 3.5 mmol/l) and hyperglycaemic events, number of catheter obstructions and treatment satisfaction. Basal insulin rate at mealtime, prandial insulin doses, body weight and the number and severity of adverse events were recorded. Hypoglycaemic episodes were recorded by the patient in a self-monitoring diary. A treatment satisfaction questionnaire was completed by the patients at the beginning of the study and at the end of each treatment arm
Characteristics	60 male, 53 female, age $37 \pm 12$ years, duration of diabetes $19 \pm 9$ years
Results	With insulin lispro treatment, postprandial blood glucose excursions were significantly reduced (p less than 0.001), resulting in smaller meal-related blood glucose increases after every meal. With insulin lispro treatment daily blood glucose control was more stable compared with human insulin With insulin lispro mean blood glucose values were significantly less at 10pm (p less than 0.001), whereas no difference was observed at 2 am. With insulin lispro the mean HbA1c value at end point was significantly lower than with regular human insulin. There were no significant differences between groups in the average number of hypoglycaemic episodes per patient. There were no significant differences between groups in insulin doses. The questionnaire used to assess the satisfaction of patients with each therapy (max score 48) showed a statistically significant result in favour of insulin lispro ( $35.16 \pm 4.25$ vs. regular $32.36 \pm 5.87$ , p less than 0.001)

	<p>Side effects</p> <p>The most frequently reported adverse events in both groups were infections (lispro 19.4%, regular 21.1%; mainly common cold) and rhinitis (lispro 15.8%, regular 13.8%)</p> <p>Among adverse events possibly related to study drug, the most frequent was ketosis, reported by five (4.5%) patients receiving lispro and four (3.7%) patients receiving regular human insulin.</p> <p>Four (3.7%) patients during insulin lispro treatment and two (1.8%) patients during regular human insulin treatment reported injection site reactions.</p> <p>No significant difference between insulin lispro and regular human insulin in the rate and number of catheter occlusions.</p>
Hierarchy of Evidence Grading	Ib
Comments	<p>Study was not blinded to allow both insulins to be given at the optimum time interval before the meal</p> <p>During lead-in period of 4 weeks, patients were treated with CSII therapy with regular human insulin allowing basal rates and meal related bolus doses to be optimised.</p> <p>Open label to allow for different action profiles of insulin types.</p> <p>Baseline characteristics between patients not compared</p> <p>No power analysis included</p> <p>Effect of treatment assessed by two-sided analysis of covariance.</p> <p>Dependent variables were treatment period, premeal glucose, insulin dose and basal insulin, all of which were recorded during the run-in period.</p> <p>Differences in secondary parameters were determined by analysis of variance with patient, treatment and period terms.</p> <p>No details of randomisation method.</p> <p>No details for allocation concealment.</p> <p>Treatment and control groups similar at start of trial.</p> <p>No details of patient follow up</p>
NCC CC ID	1048
Reference / Citation	

Q 27 What types of insulin regimens aid optimal diabetic control in adults with stable type I diabetes?

Author / Title / Reference / Yr	Holleman F, Schmitt H, Rottiers R, Rees A, Symanowski S, Anderson JH, Benelux-UK Insulin Lispro study group 1997 Reduced frequency of severe hypoglycemia and coma well-controlled IDDM patients treated with insulin lispro. Diabetes Care 20:1827-1832
N=	199 Lispro-regular sequence n = 96 Regular-lispro sequence n = 103 European
Research Design	Randomised Controlled Trial
Aim	Outcomes of hypoglycaemia are studies following treatment with insulin lispro
Population	People with type I diabetes recruited into trial
Intervention	Insulin lispro in combination with NPH insulin
Comparison	Regular insulin in combination with NPH insulin
Outcome	Glycaemic control as measured by HbA1c, home blood glucose measurement, rate and timing of hypoglycaemic events, evaluation form regarding therapy-related quality of life. Patients noted time, severity, symptoms and therapy of subjective and objective hypoglycaemic events. Study not blinded due to differences in time-action profiles.
Characteristics	(126 men, 73 women) Baseline characteristics for the two groups did not differ significantly
Results	HbA1c levels were similar for both treatments. With insulin lispro treatment meal-related glucose excursions were significantly lowered (mean excursion $-0.8 \pm 1.7$ mmol/l vs. $1.1 \pm 1.6$ mmol/l, p less than 0.001) With insulin lispro treatment predinner glucose was higher (8.7 vs. 7.5 mmol/l, p less than 0.001) With insulin lispro the daily glucose variability was significantly lower. There were no significant differences in overall hypoglycaemia rates. With insulin lispro, severe hypoglycaemia (36 vs. 58 episodes p = 0.037) including coma (3 vs. 16 episodes, p = 0.004) were significantly reduced. With insulin lispro hypoglycaemia occurred earlier compared with regular insulin (4.3h vs. 5.2h, p less than 0.001)

	<p>With insulin lispro, the frequency of nocturnal hypoglycaemia was significantly decreased</p> <p>With insulin lispro, the frequency of morning hypoglycaemia significantly increased</p> <p>With insulin lispro patients expressed more flexibility in their lifestyle in general (86% as easier vs. 2% as more difficult, pless than0.001), timing of meals (70 vs. 3%, pless than0.0001), planning of physical (51 vs. 9%, pless than0.0001) and social activities (60 vs. 8%, pless than0.0001)</p> <p>Of 199 randomised patients, 144 elected to continue treatment with insulin lispro</p>
Hierarchy of Evidence Grading	Ib
Comments	<p>Run-in period of 4 weeks during which treatment with regular insulin in combination with NPH insulin was optimised. Randomised for 12 weeks to be treated with Insulin lispro in combination with NPH insulin vs. regular insulin in combination with NPH insulin</p> <p>Study visits at baseline, after run-in period and after 4 and 12 weeks of each treatment.</p> <p>Patients to inject regular insulin half an hour before meals and to inject insulin lispro immediately before meals.</p> <p>Premeal insulin adjusted to achieve target glucose value of less than10 mmol/l 2 h postprandial</p> <p>NPH insulin dose adjusted to reach target value of less than 7 mmol/l fasting.</p> <p>In last 2 weeks before each study visit, each patient recorded four 7-point home blood glucose monitoring profiles.</p> <p>189 completed both study periods; 6 patients withdrew because of perceived lack of efficacy of insulin lispro, 1 patient died of ischaemic heart disease and 2 patients were discontinued at their own/investigators' decision. One patient had a positive pregnancy test after 29 days use of insulin lispro and was discontinued from the study.</p> <p>Data for the two treatment sequences were pooled</p> <p>Efficacy analyses were performed on intention-to-treat basis and included all available data from all randomised patients</p> <p>Analysis for carryover effects was performed.</p> <p>Quality of life data were assessed using a nonparametric Sign test; however, should be interpreted with caution, as study was not blinded.</p> <p>Rise in preprandial glucose values with insulin lispro may be explained by relative lack of basal insulin between meals.</p> <p>Main problem of intensive therapy with insulin lispro and once-daily NPH insulin seems to be relative lack of basal insulinaemia in the afternoon and evening. Possible solution suggested</p> <p>Increase in evening dosage of NPH insulin</p> <p>Diminish consumption of snacks in afternoon and evening</p> <p>Give additional NPH insulin dosages</p> <p>Most of the severe hypoglycaemic episodes occurred during the night.</p> <p>Despite specific instruction to inject regular insulin half an hour before the meal, a majority of patients indicated they failed to do so (31% of patients injected regular insulin within 10 minutes, 34% injected regular insulin between 10 and 20 minutes and only 27% injected regular insulin between 20 and 30 minutes before their meal)</p>
NCC CC ID	1051
Reference / Citation	



Q 27 What types of insulin regimens aid optimal diabetic control in adults with stable type I diabetes?

Author / Title / Reference / Yr	Ebeling P, Jansson PA, Smith U, Lalli C, Bolli GB, Koivisto VA 1997 Strategies toward improved control during insulin lispro therapy in IDDM. Importance of basal insulin. Diabetes Care 20:1287-1289
N=	N=66 European
Research Design	Before and after study
Aim	A comparison of insulin regimens
Population	Type 1 diabetes
Intervention	insulin lispro as a pre-meal therapy
Comparison	Human regular insulin The premeal and basal insulin regimens were adjusted according to self monitoring of blood glucose during the visits at 2-week to 1-month intervals.
Outcome	Glycaemic control as measured by diurnal glucose profile, hypoglycaemic events, HbA1c and patient satisfactions During each visit at 2-week intervals for the first 2 months and at monthly intervals thereafter, self-monitoring of blood glucose and hypoglycaemic episodes were evaluated. Hypoglycaemia was defined as blood glucose values less than 3.0 mmol/L. Patients self-measured blood glucose at least seven times per day (before and 90 minutes after each breakfast, lunch, dinner and at bedtime) 2 days each week before the visits
Characteristics	41 men, 15 women. Mean age $38.0 \pm 1.1$ years, BMI $23.8 \pm 0.3$ kg/m <sup>2</sup> , and diabetes duration $15.4 \pm 1.0$ years.
Results	Blood glucose profile The mean diurnal blood glucose concentration decreased on average by $0.8 \pm 0.2$ mmol/l during the study (p less than 0.001) All meal-induced increments in blood glucose were less (p less than 0.001) and postprandial glucose values after breakfast and dinner were lower during insulin lispro than during the human regular insulin therapy (p less than 0.01 in all) Hypoglycaemic episodes The frequency of hypoglycaemic values remained unchanged Glycated haemoglobin The mean HbA1c level decreased on average by 0.8% point during the 5 month study and the value was significantly lower than baseline after 2 months At the end of the study, the HbA1c values correlated with the premeal, with the average daily and with the average post meal

	<p>glucose values. In addition, the HbA1c levels correlated inversely with the percentage of NPH insulin from total dose.</p> <p>Patient satisfaction</p> <p>At the end of the study, 86% of the patients considered the insulin lispro regimen either equal (32%) or better (54%) than human regular insulin therapy (p less than 0.001)</p>
Hierarchy of Evidence Grading	III
Comments	<p>Trial preceded by a run-in period of 2 weeks, during which patients received Humulin Regular before the meals and Humulin NPH as basal insulin.</p> <p>After the run-in period, the premeal insulin regimen was transferred to insulin lispro. Insulin lispro was injected immediately before each main meal.</p> <p>Adjustments of the lispro dose were made based on postprandial glycaemia, and the dose and number of NPH injections were based on blood glucose determinations before main meals.</p> <p>Injections were taken either by mixing lispro and NPH insulin in the syringe immediately before injection (n=23) or by taking the two insulins separately with pens (n=43)</p> <p>Baseline characteristics of patients not compared between groups</p> <p>Open label to allow for different action profiles of insulin</p> <p>Because of the uncontrolled nature of the study, it is not possible to estimate how much of the improvement in glycaemia or HbA1c is due to insulin lispro <i>per se</i>, how much is due to associated changes in basal insulin, or how much is due to the intensive attention the patients were given during the study.</p> <p>Total dose of insulin increased by 3U (7%) from baseline to study endpoint (5 months). This was due to an increase in NPH insulin by 8U (43%) and a reduction of short-acting insulin dose by 5U (20%)</p> <p>Three male patients discontinued the study. Two of them complained of headache, which persisted after discontinuation.</p> <p>Frequent visits and blood glucose monitoring irritated the third patient.</p> <p>One patient needed external help to treat hypoglycaemia during the study</p>
NCC CC ID	1032
Reference / Citation	

Q 27 What types of insulin regimens aid optimal diabetic control in adults with stable type I diabetes?

Author / Title / Reference / Yr	Ahmed AB, Home PD 1998 The effect of the insulin analog lispro on nighttime blood glucose control in type 1 diabetic patients. Diabetes Care 21:32-37
N=	N=23 UK
Research Design	Randomised Controlled Trial
Aim	An analysis of the effects of insulin analogue lispro
Population	Type 1 diabetes
Intervention	Lispro
Comparison	Unmodified regular human insulin before evening meal.
Outcome	Primary outcome - Mean blood glucose concentrations in the early part of the night (midnight to 4am) Secondary outcomes - Glycaemic control as measured by blood glucose. Biochemical hypoglycaemic episodes with blood glucose less than 3.5 mmol/l in absence of symptoms before midnight and with or without symptoms between midnight and 4:00am were taken as endpoint.
Characteristics	All patients had been stable on insulin for more than 1 year, with HbA1c of $7.8 \pm 0.9\%$ (normal less than 6.1%) and no serious hypoglycaemic events. All patients had serum C-peptide less than 0.18 nmol/l when blood glucose concentration was greater than 5.0 mmol/l.
Results	Average postprandial (6:00-10:00pm) blood glucose concentrations were significantly lower after lispro therapy compared with human insulin ( $7.1 \pm 0.4$ vs. $8.5 \pm 0.4$ mmol/l, $p=0.0002$ ) Night time blood glucose concentrations were significantly higher after lispro compared with human insulin ( $10.3 \pm 0.4$ vs. $9.1 \pm 0.4$ mmol/l, $p = 0.02$ ). The difference in night time blood glucose concentrations was greatest in patients on the premeal plus basal insulin regimen ( $11.6 \pm 0.5$ vs. $8.7 \pm 0.4$ mmol/l, $p < 0.001$ ). The incidence of nocturnal hypoglycaemia was less with lispro compared with unmodified insulin (1 vs. 6 patients, $p = 0.04$ ).
Hierarchy of Evidence Grading	Ib
Comments	12 patients were using a premeal plus basal insulin regimen, and 11 were using twice daily insulin injections.

	<p>In all cases, the extended acting insulin used was NPH.  Each patient was studied on 2 separate days, at a 1- to 4-week interval.  On each study day, patients were requested to undertake their normal food and insulin up to the time of their admission to the investigation unit at 5:00pm for overnight study.  At 5 minutes before the evening meal, patients received either lispro or unmodified human insulin (Humulin S)  Dose and type of extended-acting insulin were unchanged from patient's usual regimen.  Randomised double-blind  Standard parametric methods of data analysis  Blood glucose level for hypoglycaemia less than 3.5mmol/l</p>
NCC CC ID	1017
Reference / Citation	

Q 27 What types of insulin regimens aid optimal diabetic control in adults with stable type I diabetes?

Author / Title / Reference / Yr	Daniels AR, Bruce R, McGregor L 1997 Lispro insulin as premeal therapy in type 1 diabetes: Comparison with Humulin R. New Zealand Medical Journal 110:435-438
N=	N = 20 N = 11 lispro for 3 months then crossover to Humulin R N = 9 Humulin R for 3 months then crossover to lispro New Zealand
Research Design	Randomised Controlled Trial
Aim	A comparison of insulin lispro and human insulin
Population	Type 1 diabetes
Intervention	Short-acting insulin analogues lispro
Comparison	Regular human insulin, Humulin R as premeal therapy
Outcome	Glycaemic control as measured by blood glucose and HbA1c, insulin dosages, hypoglycaemic episodes and adverse events Blood glucose results recorded in diary with at least 4 tests performed daily. Blood glucose measured fasting at one and two hours postprandial. Hypoglycaemia episodes were recorded if typical symptoms were experienced.
Characteristics	nine females and 11 males; mean duration of diabetes 15 years (range 1-41 years); mean age 33 years.
Results	Glycaemic control No significant differences in HbA1c, fasting blood glucose levels, 1 hour glucose excursion or the two hour postprandial glucose result Insulin dosages When compared to baseline the total insulin dosages U/kg/day were similar during the duration of the trial Hypoglycaemic episodes and adverse events Incidence of hypoglycaemia per 30 days was similar for lispro and Humulin R therapy No difference between the number and type of adverse events during therapy with either lispro or Humulin R Adverse events included upper respiratory infections, pharyngitis, rhinitis, paraesthesia, backache and nausea
Hierarchy of Evidence Grading	Ib

Comments	<p>Lead-in period 2-4 weeks, all patients were treated with Humulin R before meals and wither Humulin N or U as basal insulin.  Insulin doses reviewed by specialist physician.  Lispro injected just before mealtimes, Humulin R injected injected 30-45 minutes before mealtimes.  Basal insulins were Humulin N (n = 18) and Humulin U (n= 2)  Target blood glucose fasting less than 7.8mmol/L and postprandial less than 10mmol/L  20 patients randomised to receive lispro for 3 months and Humulin R for 3 months  Part of international study (n = 1008)  Open label to allow for time interval difference in administration of insulins  No difference baseline characteristics of patients  Treatment groups compared at each visit, using an analysis of variance.  Paired t-test used to compare results at each visit with baseline.  Non parametric tests were performed using a signed rank test.  A crossover analysis was performed to test for carryover and treatment effects.  One patient was withdrawn due to unplanned pregnancy</p>
NCC CC ID	1052
Reference / Citation	

Q 27 What types of insulin regimens aid optimal diabetic control in adults with stable type I diabetes?

Author / Title / Reference / Yr	Vignati L, Anderson JH, Jr., Iversen PW 1997 Efficacy of insulin lispro in combination with NPH human insulin twice per day in patients with insulin-dependent or non-insulin-dependent diabetes mellitus. Multicenter Insulin Lispro Study Group. Clinical Therapeutics 19:1408-1421
N=	N= 379 International
Research Design	Randomised Controlled Trial
Aim	An analysis of the effect of a mixed lispro and human insulin regime
Population	Type 1 diabetes
Intervention	Insulin lispro and NPH human insulin
Comparison	Regular human insulin and NPH human insulin
Outcome	Preprandial and postprandial glucose control, percent of glycated haemoglobin A1c (HbA1c) and incidence and frequency of hypoglycaemia. Patients seen within 2 week period after dose adjustment and monthly thereafter for assessment of HbA1c and adverse events. Patients obtained glucose profile using home monitoring on days 9,6,3 and 1 before clinic visits at baseline and at end of each treatment period. Patients kept a diary of any hypoglycaemic events.
Characteristics	male n = 213 female n = 166, mean age 39.1, mean duration of diabetes 13.1 yr (range 0.2-48.2)
Results	Postprandial glucose control With insulin lispro the mean morning 2-hour postprandial blood glucose level and post meal increase were significantly lower (pless than0.001) The noon 2-hour postprandial glucose level was not statistically different between the two treatments. With insulin lispro the post-meal increase in blood glucose level after the evening meal was significantly lower (p = 0.007) Premeal and bedtime glucose level The premeal glucose levels were similar for each insulin (pgreater than 0.066) At bedtime, blood glucose levels were similar for each treatment (pgreater than0.404) Hypoglycaemia At baseline and at end point, approximately 80% of type 1 diabetes patients had at least one hypoglycaemic episode between visits, regardless of rapid-acting insulin treatment.

	<p>There was no between-treatment difference in the rate of hypoglycaemic episode for type 1 diabetes (<math>p = 0.677</math>)</p> <p>Five patients on each therapy required glucagon therapy</p> <p>Glycated haemoglobin</p> <p>No difference in HbA1c value at baseline or endpoint</p>
Hierarchy of Evidence Grading	Ib
Comments	<p>4 week run-in period - regular human insulin and NPH human insulin</p> <p>Patients then randomised to receive either</p> <p>Insulin lispro and NPH human insulin for 2 months followed by regular human insulin and NPH insulin for 2 months</p> <p>Regular human insulin and NPH insulin for 2 months followed by insulin lispro and NPH human insulin for 2 months</p> <p>Doses were adjusted by investigator to achieve 2 hour postprandial serum glucose level of less than 8.9mmol/L and a fasting serum glucose level of less than 7.8mmol/L.</p> <p>Patients instructed to inject insulin lispro immediately before the meal, but to inject regular insulin at the same time before the meal as they had done in run-in period.</p> <p>Study could not be blinded due to different timing of administration of lispro insulin and human insulin prior to meals.</p> <p>Parametric and nonparametric analyses of variance appropriate for crossover design were performed.</p> <p>Analyses based on data from all randomised patients using last measurement observed for each patient within each study period.</p> <p>No carryover effects were found.</p> <p>Study was designed to allow detection of a 0.7 mmol/L between-treatment difference in blood glucose measurements with 80% power.</p> <p>Sequence group assignment for each patient was from a central location using a computer-generated scheme.</p> <p>Patient baseline characteristics were not statistically different</p>
NCC CC ID	275
Reference / Citation	

Q 27 What types of insulin regimens aid optimal diabetic control in adults with stable type I diabetes?

Author / Title / Reference / Yr	Del Sindaco P, Ciofetta M, Lalli, Periello, Pampanelli S, Torlone E, Brunetti P, Bolli G. 1998 Use of the short-acting insulin analogue lispro in intensive treatment of type 1 diabetes mellitus: importance of appropriate replacement of basal insulin and time-interval injection-meal. Diabetic Medicine 1998;15:592-600
N=	N = 69 Italy
Research Design	Randomised Controlled Trial
Aim	A study of the effect of timing of insulin regimen in diabetes
Population	Type 1 diabetes
Intervention	Group 1 – Lispro + 1-2 NPH/day vs. soluble insulin + 1-2 NPH/day Group 2 - Lispro + 3-4 NPH/day vs. soluble insulin + 1-2 NPH/day Group 3 - Lispro + 3-4 NPH/day vs. soluble insulin + 3-4 NPH/day
Comparison	Group 4 - Time interval between soluble injection to meal 5 minutes vs. 10-40 minutes
Outcome	Frequency of severe hypoglycaemia and body weight. HbA1c.
Characteristics	Inclusion: patients already established on long-term near-normoglycaemia, with glycosylated haemoglobin A1c levels between 6 and 7.5%. Treated with intensive insulin therapy and attend diabetes clinic at least quarterly. All were C-peptide negative. Free of any detectable microangiopathic complication, and negative at the screening for autonomic neuropathy.
Results	Group 1 - Effects of substitution of regular soluble with lispro insulin and no change in number (but increase in dose) of daily NPH insulin injections. With lispro, mean daily blood glucose concentrations were similar to that with regular soluble insulin ( $8.8 \pm 1.2$ mmol/L vs. $8.6 \pm 0.8$ mmol/L). With lispro, fasting, pre-meal and nocturnal blood glucose were significantly greater than with regular soluble insulin ( $8.9 \pm 1.1$ vs. $8.3 \pm 1.2$ mmol/L pless than0.05) With lispro post-prandial glucose was significantly lower than with lispro compared with regular soluble insulin ( $8.9 \pm 0.7$ vs. $9.2 \pm 1.4$ mmol/L pless than0.05) With lispro, the total insulin dose was significantly increase compared with conventional soluble insulin (total insulin dose increase 23% - due to increase in short-acting insulin at meals of 15% and NPH insulin of 44%) HbA1c was no different after 3 month treatment with lispro and conventional soluble insulin. Hypoglycaemia was more frequent with lispro than with conventional insulin.

	<p>Group 2 - Effects of substitution of regular soluble with lispro insulin and increase in number of daily NPH insulin injections. With lispro + multiple NPH daily blood glucose levels were significantly lower compared with regular soluble insulin (<math>8.1 \pm 0.8</math> vs. <math>8.6 \pm 0.8</math> mmol/L, <math>p &lt; 0.05</math>) associated with significantly lower postprandial blood glucose (<math>8.3 \pm 0.7</math> vs. <math>9.3 \pm 0.8</math> mmol/L) and super imposable pre-meal and nocturnal blood glucose concentrations (<math>8.2 \pm 0.7</math> vs. <math>8.2 \pm 0.7</math> mmol/L) The total daily insulin dose during treatment with lispro + multiple NPH and regular soluble insulin was no different; however, with the former, 33% more NPH and 27% less short-acting insulin was needed. After lispro + multiple NPH the % HbA1c was lower by 0.35% compared with regular soluble insulin, while the frequency of hypoglycaemia was similar. Ratio of lispro/NPH was 65/35 at breakfast, 60/40 at lunch and 10/90 at supper, and the majority of patients required NPH four times daily.</p> <p>Group 3 - Effect of treatment with regular soluble insulin and multiple insulin injections at mealtime  With lispro + multiple NPH, mean daily blood glucose concentrations remained significantly lower compared with conventional soluble insulin  With lispro and multiple NPH, % HbA1c remained significantly lower compared with regular soluble insulin + Insulin dose was no different, but hypoglycaemia was more frequent when multiple NPH doses were combined with conventional soluble insulin</p> <p>Group 4 - Effect of time interval between injection of regular soluble insulin and meal  When conventional soluble insulin was given 10-40 minutes prior to meals, mean blood glucose concentration was significantly lower compared with regular soluble insulin given at mealtime (<math>8.5 \pm 1.1</math> vs. <math>8.9 \pm 1.2</math> mmol/L).  When conventional soluble insulin was given 10-40 minutes prior to meals, percentage of HbA1c was significantly lower compared with regular soluble insulin given at mealtime (<math>0.18 \pm 0.15\%</math> lower).  When conventional soluble insulin was given 10-40 minutes prior to meals, frequency of hypoglycaemia was significantly lower compared with regular soluble insulin given at mealtime.  There was no difference in the total insulin dose between the two treatments</p>
Hierarchy of Evidence Grading	Ib
Comments	<p>1 month run-in period, patients continued their previous insulin therapy i.e. soluble insulin (humulin R) at breakfast, lunch and supper and NPH insulin at bedtime.  34 patients added NPH to soluble insulin at lunch (to a final ratio of 30/70, NPH/soluble) to optimise pre-dinner glucose. Patients were randomly assigned to four groups, and studied for 6 months (each treatment for 3 months followed by crossover)  Lispro was injected immediately prior to meals; regular soluble insulin was injected 10-40 minutes prior to meals.  Patients were instructed to aim for post prandial levels of 9-10mmol/L and fasting 7-8mmol/  Baseline characteristics no difference between groups</p>

	Open label due to different pharmacokinetics of insulin, require administration at different time intervals before meals All analysis was carried out using a single-value for each patient per crossover period. Very small numbers in groups (n = 12 in group III)
NCC CC ID	297
Reference / Citation	

Q 27 What types of insulin regimens aid optimal diabetic control in adults with stable type I diabetes?

Author / Title / Reference / Yr	Roach P, Strack T, Arora V, Zhao Z 2001 Improved glycaemic control with the use of self-prepared mixtures of insulin lispro and insulin lispro protamine suspension in patients with types 1 and 2 diabetes. International Journal of Clinical Practice 55:177-182
N=	N = 102 International
Research Design	Randomised Controlled Trial
Aim	An investigation into the efficacy of a combined insulin regimen
Population	Mixed diabetes population
Intervention	Insulin lispro combined with insulin lispro protamine suspension (NPL), an intermediate-acting formation of lispro
Comparison	Regular human insulin combined with human NPH insulin
Outcome	Glycaemic control measured by weekly self-monitored blood glucose profiles, glycated haemoglobin levels, frequency and severity of hypoglycaemic episodes and patient satisfaction and well-being and patient preference. At baseline and at 1,3,6,9 and 12 months HbA1c measurements were taken. Within 10 days of same visits three BG profiles (before and two hours after breakfast, lunch and evening meal, at bedtime and at 3am) were collected. Patients recorded hypoglycaemic episodes and BG profile in diary. Average blood glucose profile data (e.g. average fasting BG, the average two hour post-breakfast glucose) was averaged across the monitoring days
Characteristics	Type 1 diabetes according to WHO criteria, between ages of 18 and 75 years and had received insulin therapy using mixtures of short-acting or rapid-acting insulin (regular human insulin or insulin lispro) and intermediate- or long-acting insulin twice daily (self-mixed or manufactured pre-mixed) for at least 120 days before enrolment in the study.
Results	Glycaemic control At endpoint, with LP/NPL two hour post-prandial blood glucose measurements were significantly lower following the morning meal and the evening meal. With LP/NPL the morning and evening 2h post prandial blood glucose excursions were significantly smaller. With LP/NPL blood glucose measurements were significantly lower before lunch and at bedtime. With LP/NPL the HbA1c level was significantly lower at endpoint.

	<p>Hypoglycaemia</p> <p>The rate of hypoglycaemia declined significantly in both treatment groups during the study</p> <p>At study endpoint there was no difference in the median hypoglycaemia rates between treatments</p>
Hierarchy of Evidence Grading	Ib
Comments	<p>2-4 week lead-in period treated with regular human insulin combined with NPH before the morning and evening meals. Patients were then randomised to received either a combination of lispro and NPL (LP/NPL) or a combination of HR (Humulin R) and human NPH (Humulin N) (HR/NPH) for 12 months.</p> <p>Patients randomised to LP/NPL were asked to inject their insulin 0-15 minutes before the morning and evening meals</p> <p>Patients randomised to HR/NPH were asked to inject their insulin 30-45 minutes before the same meals.</p> <p>Insulin doses were to be adjusted to meet the glycaemic targets; fasting blood glucose less than 7.8 mmol/L and two post-prandial blood glucose less than 10mmol/L.</p> <p>During initial three months, patients were treated with self-prepared mixtures only before morning and evening meals.</p> <p>After three month visit, patient s and investigators were allowed to alter the treatment regimen as dictated by the results of self-BG monitoring.</p> <p>Hypoglycaemia rate was normalised to 30 day period and expressed as episodes per patient per 30 days</p> <p>Open-label to allow for different pharmacokinetics of insulin.</p> <p>At baseline, no significant differences between the treatment groups with respect to HbA1c levels, self monitored BG profiles, hypoglycaemia rates, insulin doses with exception of significantly lower evening two-hour postprandial BG level in the LP/NPL group (p = 0.004)</p> <p>All comparisons used two-tailed tests.</p> <p>All data from all patients randomised to on of the treatment groups was included in the analysis.</p> <p>Analysis was intent to treat and last observation carried forward.</p> <p>Publication did not discuss individual type 1 and type 2 diabetes results but commented ‘the above results were qualitatively similar in both diabetes type subgroups’</p>
NCC CC ID	1043
Reference / Citation	

Q 27 What types of insulin regimens aid optimal diabetic control in adults with stable type I diabetes?

Author / Title / Reference / Yr	Stades AM, Hoekstra JB, van dT, I, Erkelens DW, Holleman F, STABILITY Study Group 2002 Additional lunchtime basal insulin during insulin lispro intensive therapy in a randomized, multicenter, crossover study in adults : a real-life design. Diabetes Care 25 :712-717
N=	N = 121 The Netherlands
Research Design	Randomised Controlled Trial
Aim	A trial of an additional lunchtime insulin therapy
Population	Type 1 diabetes
Intervention	NPH insulin (1 x NPH)
Comparison	Twice (2 x NPH) daily for 4 months All patients to maintain sc injections of insulin lispro throughout study
Outcome	HbA1c, incidence and timing of hypoglycaemic episodes, and home blood glucose profiles. Body weight and insulin dosages. Patients recorded glucose profiles and hypoglycaemic events in diary
Characteristics	Diagnosis of type 1 diabetes based on C-peptide criteria, an HbA1c less than 8.5%, using insulin lispro intensive therapy for greater than 3 months combined with once or twice daily NPH insulin, age 18-65 years, and the ability and willingness to do regular home blood glucose monitoring Baseline characteristics did not differ significantly except for slight gender difference
Results	HbA1c HbA1c levels were similar for both therapies Blood glucose profiles Pre-dinner glucose values were 0.76 mmol/l lower during the 2 x NPH than during 1 x NPH protocol (p = 0.004) The 2 hour post-dinner glucose values were 0.66 mmol/l lower during the 2 x NPH protocol (p = 0.023) Hypoglycaemia In the evening, the frequency of hypoglycaemia increased significantly during the 2 x NPH daily protocol with a median difference of 0.56 mild episodes/30 days (p = 0.001) and 6.9 severe episodes/patient year (p = 0.007) Body weight and insulin dosage Body weight and total daily insulin dosages were similar in both treatment regimens

Hierarchy of Evidence Grading	Ib
Comments	<p>2 month run-in period using once daily NPH insulin delivered sc at bedtime.  The second dose of NPH was injected at lunchtime, since lunchtime is closer to a 12-h time interval after the bedtime dose than breakfast time  Patients switched to 2 x NPH starting with a lunchtime NPH insulin injection of 40% of their last bedtime NPH dose, with minimum dose of 4 IU.  The lunchtime NPH dose was injected before 1330  Patients asked to continually optimise glycaemic control using targets of; preprandial glucose 4-7 mmol/l, postprandial glucose less than 8mmol/l and bedtime glucose 7-9mmol/l.  Open label due to different time interval required for insulin administration before meals.  No differences in patient baseline characteristics.  Independent person made a block randomisation for each investigator.  The investigator disclosed the assignment of the allocated schedule during the participant's second (baseline) visit to the outpatient clinic  Sample size was calculated on main outcome variable (HbA1c) To detect a significant and clinically relevant intraindividual HbA1c difference of 0.3% with a statistical power of 0.8, 106 patients were needed.  Outcomes of the overall glucose profiles were analysed with overall repeated measures ANOVA.  In all, 138 patients entered the run-in period. The 17 non randomised patients included 9 who did not meet the inclusion criteria, 6 who chose not to enter the study, 1 who was withdrawn at the investigator's discretion and 1 who did not tolerate once daily NPH.  Of the 12 randomised patients, 104 complete both study periods, 3 patients withdrew because of increased hypoglycaemia during the 2 x NPH protocol, 1 did not tolerate the 1 x NPH protocol, 6 did not endure the study load, 5 were noncompliant, 1 moved abroad and 1 became pregnant.</p>
NCC CC ID	1027
Reference / Citation	

Insulin aspart

Q 27 What types of insulin regimens aid optimal diabetic control in adults with stable type I diabetes?

Author / Title / Reference / Yr	Home PD, Lindholm A, Hylleberg B, Round P 1998 Improved glycemic control with insulin aspart: a multicenter randomized double-blind crossover trial in type 1 diabetic patients. UK Insulin Aspart Study Group. Diabetes Care 21:1904-1909
	N=104 UK
Research Design	Randomised controlled trial
Aim	A comparison of a artificial insulin with human insulin
Population	Type 1 diabetes
Intervention	Insulin aspart
Comparison	Soluble human insulin administered before meals, and NPH insulin administered at bedtime as basal therapy.
Outcome	Primary endpoint was fructosamine level at the end of each treatment period. Secondary endpoint were blood glucose levels, frequency and severity of hypoglycaemia, insulin dosage and serum insulin concentration and adverse events Daily four point preprandial glucose profiles were taken Weekly eight point glucose profiles (premeal, post meal, bedtime and 0200)
Characteristics	100% male subjects aged 18-60 years, with BMI less than 29kg/m <sup>2</sup> and an HbA <sub>1c</sub> less than 9%. For at least 1 month before the study, the patients were required to use human unmodified premeal insulin plus NPH insulin as basal insulin administered only at bedtime.
Results	Insulin dosage No significant difference in the bolus to basal insulin ratio between the insulin aspart period and the human insulin period (mean doses given were 40.9 ± 13.6 U/day for insulin aspart, 39.7 ± 13.5 U/day for human insulin, 27.8 ± 11.3 U/day for bedtime NPH insulin during the insulin aspart period, and 26.8 ± 12 U/day during human insulin period. Serum insulin concentration After prebreakfast subcutaneous injection of insulin aspart, the time to C <sub>max</sub> was shorter for insulin aspart than for human insulin (42 ± 58 vs. 88 ± 66min pless than 0.05. Post breakfast insulin C <sub>max</sub> values were higher than after injection with human insulin (pless than 0.05). Insulin concentrations were lower in the early part of the night (pless than 0.01) with insulin aspart than with human insulin (pless than 0.001)

	<p>Blood glucose control Overall 2h glucose control was significantly improve with insulin aspart, with the excursion 78% of that obtained with human insulin pless than0.01. Daytime glucose control was significantly lower with insulin aspart than with human insulin. During the night, Cmin was significantly lower than with insulin aspart. Afternoon and evening postprandial concentrations were significantly improved with insulin aspart. Mid morning and nighttime differences were not significant.</p> <p>Hypoglycaemia There was no significant difference in the number of hypoglycaemic episodes between the two groups. There were significantly fewer major hypoglycaemic episodes in the whole aspart period than in the whole human insulin period pless than0.002</p> <p>Other adverse events There was no significant difference in the number of treatment-emergent adverse events between the two groups. Serious adverse events (vomiting/pyrexia and hypoglycaemia with convulsions) were reported in two subjects using insulin aspart Serious adverse events (confusion and hypoglycaemia and convulsions) were reported in two subjects using human insulin.</p>
Hierarchy of Evidence Grading	Ib
Comments	<p>4 week run-in period in which treatment consisted of unmodified insulin plus bedtime NPH insulin Patients randomised to premeal insulin aspart or human unmodified insulin for 4 weeks Patients then crossed over to treatment with the other premeal insulin for another 4 weeks Patients were asked to take the premeal insulin injections just before eating (bias?) This timing is preferred by patients, is usually used by patients treated with human insulin even when they are advised otherwise, and is safer unless blood glucose is self-monitored before each injection. NPH was taken once daily before bedtime. Targets for premeal and 0200 were 4-7 mmol/l and postprandial blood glucose less than10 mmol/l No description of randomisation 90 completed the trial 1 subject was withdrawn because of an adverse event, 3 violated the protocol, and 10 felt unable to continue with the demands of the protocol. With an inpatient coefficient of variation for fructosamine of 20% and a significance level of 5%, a sample size of 80 would detect a true difference of 0.5 with the required certainty (power greater than 80%) All tests were two-tailed. Efficacy results are presented as intent-to-treat population. For fructosamine, a standard two-way crossover analysis was applied</p>
NCC CC ID	1021
Reference / Citation	



Q 27 What types of insulin regimens aid optimal diabetic control in adults with stable type I diabetes?

Author / Title / Reference / Yr	Nielsen FS, Jorgensen LN, Ipsen M, Voldsgaard AI, Parving HH 1995 Long-term comparison of human insulin analogue B10Asp and soluble human insulin in IDDM patients on a basal/bolus insulin regimen. Diabetologia 38:592-598
N=	N=24 Denmark
Research Design	Randomised controlled trial
Aim	To compare the long term efficacy of a synthetic insulin regimen
Population	Type 1 diabetes
Intervention	Insulin analogue B10 Asp
Comparison	Soluble human insulin (Actrapid) given as mealtime insulin and intermediate acting isophane insulin (Protaphane) at bedtime.
Outcome	Glycaemic control as measured by blood glucose profiles. Number and severity of hypoglycaemic events. Patients then taken to metabolic ward for 24h profiles of blood glucose and plasma free-insulin/analogue and HbA1c.
Characteristics	Age 18 to 40 years, male, duration of diabetes of more than 1 year, treated with a multiple injection regimen for longer than 6 months, haemoglobin A1c less than 10%, body mass index less than 27 kkg/m2 and a stable metabolic control (HbA1c varying less than 1% over the previous 6 months).
Results	Significantly higher plasma insulin/analogue levels after breakfast, lunch and dinner with B10 Asp as compared to Actrapid (pless than0.05). Plasma insulin/analogue levels were significantly lower before lunch and dinner with B10 Asp as compare to Actrapid (pless than0.05). Plasma insulin/analogue level tended to be lower at bedtime when comparing B10Asp to Actrapid. 24 hour glucose profiles showed identical fasting blood glucose, significantly lower blood glucose after breakfast with the analogue (pless than0.05), no differences in blood glucose after lunch and dinner but a significantly higher glucose at midnight using the analogue (pless than0.05) The overall 24h mean blood glucose concentrations, the daily insulin dose, HbA1c, diet, home blood glucose monitoring and frequency of hypoglycaemic were almost identical in the two treatment periods
Hierarchy of Evidence Grading	Ib

Comments	<p>Open 1-month run-in period during which patients were treated with soluble human insulin (Actrapid) less than 5 minutes before breakfast, lunch and dinner and with intermediate acting isophane insulin (Protaphane) at bedtime.</p> <p>Patients randomised to either Actrapid or insulin analogue B10Asp as premeal insulin for 2 months.</p> <p>Patients then changed to the other type of premeal insulin for a further 2 months and then taken to the metabolic ward for repeat measurements.</p> <p>Fasting blood glucose targets were 4-7 mmol/l and postprandial blood glucose levels less than 11 mmol/l. Study was completed by 21 patients;</p> <p>3 were excluded, one patient because of a gastroscopic verified ulcer duodenus at the first visit, a second because his HbA1c rose more than 3% during the run-in period. The third patient had an infected toenail at the first hospitalisation and required antibiotic and surgical treatment.</p> <p>Results from the three excluded patients were not used in the calculations.</p> <p>Comparison of normally distributed parameters was done using ANOVA for two crossover periods.</p> <p>Study was powered to detect a difference of 0.5% in HbA1c with a power of 90% provided 21 patients completed the study.</p>
NCC CC ID	1034
Reference / Citation	

Q 27 What types of insulin regimens aid optimal diabetic control in adults with stable type I diabetes?

Author / Title / Reference / Yr	Home PD, Lindholm A, Riist A 2000 Insulin aspart vs. human insulin in the management of long-term blood glucose control in Type 1 diabetes mellitus: A randomized controlled trial. Diabetic Medicine 17:762-770
N=	N = 1070 European
Research Design	Randomised controlled trial
Aim	A comparison of a artificial insulin with human insulin
Population	Type 1 diabetes
Intervention	6 months treatment with Insulin aspart
Comparison	Soluble human insulin before main meals both with NPH insulin as basal insulin.
Outcome	Blood glucose control as assessed by HbA1c, eight point self monitored blood glucose profiles, insulin dose, quality of life, hypoglycaemia and adverse events, frequency and severity of hypoglycaemic episodes. At each visit measures of efficacy, insulin dose adjustments advised, adverse events recorded and insulin use monitored. BG profiles (preprandial, 90 minutes post prandial, bed time and 0200h were requested before randomisation and after 5 and 6 months treatment. Diabetes Treatment and Satisfaction questionnaire was completed in the UK
Characteristics	adult men and women with type 1 diabetes (WHO criteria), duration of diabetes greater than 2 years and treated with insulin for 1 year. Body mass index less than 35 kg/m and HbA1c less than 11%.
Results	Insulin dose The doses of meal-related insulin did not change from baseline to 6 months No difference between groups at 6 months Baseline dose of NPH was similar for the two study groups At 6 months NPH insulin dose was 8.5% higher in subjects treated with insulin aspart compared to human insulin  Overall blood glucose control With insulin aspart HbA1c was significantly improved compared with soluble human insulin  Eight point blood glucose profiles

	<p>With insulin aspart post-prandial blood glucose control was significantly better than with human insulin. After 6 months, the insulin aspart group had significantly lower blood glucose levels after breakfast, lunch and dinner but higher before breakfast and dinner compared with human insulin.</p> <p>The average prandial blood glucose increment decreased from a baseline of 2.0 (SD 2.4) to 0.6 (2.2) mmol/l in the insulin aspart group while it remained unchanged at 1.7 (2.6 and 2.2) mmol/l in the human insulin group. The baseline adjusted difference between the groups at 6 months was 1.15mmol/l (pless than0.0001)</p> <p>Quality of life The DTSQ showed significant overall improvement in treatment satisfaction with insulin aspart with largest differences related to the convenience, flexibility and satisfaction to continue present treatment items.</p> <p>Hypoglycaemia Significantly fewer patients on insulin aspart (1.3%) experienced nocturnal major B hypoglycaemia compared with human insulin (pless than0.05) Post injection major hypoglycaemia 4-6h after a meal occurred in 1.8% of patients on insulin aspart and in 5% of subjects on human insulin (pless than0.005) No significant differences between groups were observed in the proportion of patients with major hypoglycaemia. No significant difference in the major events requiring parenteral administration of glucose or glucagons (grade B). No significant difference in the number of patients with a major nocturnal event. No significant difference in post-injection major hypoglycaemia within 1 h of starting a meal.</p> <p>Adverse events Adverse events were equally distributed between treatments</p>
Hierarchy of Evidence Grading	Ib
Comments	<p>4 week run in period soluble insulin was administered as meal time insulin and NPH insulin was administered as basal insulin once or twice daily.</p> <p>Patients were randomised between insulin treatments, 1065 received trial agents</p> <p>Study visits were scheduled at screening, 2 weeks into the run-in period, at randomisation (baseline), 2 weeks after randomisation and then monthly.</p> <p>Insulin aspart to be administered immediately before meal and soluble human insulin to be administered 30 minutes before meal.</p> <p>Target blood glucose of 5-8 mmol/L preprandial and at bedtime, and less than 10mmol/L 103h after meals.</p> <p>Large sample (n = 1070). Sample size based on ICH guideline aiming at randomising 1000 patients to treatment. An assumed baseline variance for HbA1c of 1.5% gave a probability of detecting non-inferiority of 0.98, if the true difference in HbA1c was 0.2%</p> <p>Multi-centre, randomised, open label, parallel.</p>

	<p>Open label due to different time interval required prior to meal for different insulins.  For primary endpoint HbA1c at 6 months, data analysed using ANOVA.  Trial was not blinded so that advice on timing of insulin dosage before meals could follow recommendations.  Patients asymmetrically randomised in a 2:1 ratio  Of 1070 patients randomised, 94% completed 6 months.  No difference in baseline characteristics between the two groups.  No differences regarding reasons for withdrawal (insulin aspart 4%, human insulin 6%)  1011 patients completed the trial  1047 patients were included in the intention-to-treat analysis 1006 patients in the per protocol analysis.</p>
NCC CC ID	1067
Reference / Citation	

Q 27 What types of insulin regimens aid optimal diabetic control in adults with stable type I diabetes?

Author / Title / Reference / Yr	Lindholm A, McEwen J, Riis AP 1999 Improved postprandial glycaemic control with insulin aspart. A randomized double-blind cross-over trial in type 1 diabetes. <i>Diabetes Care</i> 22:801-805
N=	N=24 UK
Research Design	Randomised controlled trial
Aim	An evaluation of the effect of an artificial insulin on glycaemic control
Population	Type 1 diabetes
Intervention	Insulin aspart injected subcutaneously immediately before meal
Comparison	Human insulin injected subcutaneously 30 minutes before the meal or immediately before the meal
Outcome	Primary endpoint: Total baseline-corrected excursion of serum glucose from 0-240 minutes. Secondary endpoints: maximum serum glucose concentration, time of maximum serum glucose concentration, max insulin concentration, time of max insulin concentration.
Characteristics	type 1 diabetes of at least 2 years duration, were currently on a meal-related treatment regimen with a combination of NPH insulin and soluble human insulin, presented with a meal-stimulated C-peptide of less than 0.1 nmol/l at 1-3h post meal, and were reasonably well controlled as assessed by HbA1c of less than 9%.
Results	With insulin aspart the postprandial glucose control was superior compared with that of human insulin injected immediately before or 30 minutes before a meal ( $891 \pm 521$ vs. $1311 \pm 512$ vs. $1106 \pm 571$ mmol/l/min, p less than 0.0001 and p less than 0.02) With insulin aspart, there was a significantly lower glucose maximum concentration than for human insulin injected immediately before the meal ( $13.5 \pm 3.5$ vs. $16.4 \pm 3.4$ mmol/l, p less than 0.001)  Side effects: All side effects were mild or moderate in severity. Of 24 subjects exposed to insulin aspart, 14 had 30 adverse events. Of 23 subjects exposed to human insulin, 15 had 25 adverse events, and of 22 subjects exposed to human insulin t-30 minutes, 11 had 17 adverse events. Most common side effects were hypoglycaemia and headache
Hierarchy of Evidence Grading	Ib

Comments	<p>Single centre double-blind double-dummy randomised three way crossover trial  Three study days separated by a week  On each study day, subjects received two injections, one 30 minutes before and one immediately before a standard breakfast. One injection was placebo and the other injection was insulin aspart 0.15U/kg body weight (only immediately before the meal) or unmodified human insulin 0.15U/kg (30 minutes before the meal or immediately before the meal).  Subjects admitted to clinic evening before test. On that evening, no NPH insulin allowed.  Subjects received overnight euglycaemic clamp to achieve target blood glucose 5-8 mmol/l  Double-blind, double-dummy  Due to pharmacokinetics of the two insulins, they had to be injected at different time intervals before meal; however allocation was concealed by giving two injections prior to the meal – one of which was placebo  22 completed the study  2 withdrew: 1 for personal reasons and 1 for adverse events.  Primary efficacy assessment was postprandial glucose excursion. Assuming inpatients coefficient of variation of up to ~1.67 mmol/l/min, and using significance level of 5%, sample size of 21 would detect a true difference.</p>
NCC CC ID	1065
Reference / Citation	

Insulin velosulin

Q 27 What types of insulin regimens aid optimal diabetic control in adults with stable type I diabetes?

Author / Title / Reference / Yr	Wolffenbittel BH, van Ouwkerk BM, Veldhuyzen BF, Geelhoed-Duijvestijn PH, Jakobsen G, van Doorn LG 1990 Comparative effects of two different multiple injection regimens on blood glucose control and patient acceptance in type 1 diabetes. <i>Diabetic Medicine</i> 7:695-699
N=	N = 43 The Netherlands
Research Design	Randomised controlled trial
Aim	A comparison of insulin regimens
Population	Type 1 diabetes
Intervention	12 week treatment with Group 1) 5 daily injections, comprising short-acting insulin (Velosulin) before meals using the Insuject pen injector, and intermediate-acting insulin (Insulatard) before breakfast and at bedtime using the Insuject-X pen injector
Comparison	Group 2) 4 daily injections, comprising short-acting insulin before the main meals and intermediate-acting insulin at bedtime, given either by means of a pen-injector or by conventional insulin injections using vials and syringes.
Outcome	Bodyweight, dose of short-acting and intermediate-acting insulin and hypoglycaemic episodes were recorded. Prior to each study visit patients measured a blood glucose profile, HbA1c. All patients seen at outpatient clinic after 2,4,8, and 12 weeks of each regimen. Blood glucose taken before and 1.5 after main meals, at 2300 h, at 0300h, and before breakfast the next morning. HbA1c determined at 0,8 and 12 weeks.
Characteristics	Age 37 ± 11 years, duration of diabetes 15 (range 2-48 years, 26 males and 17 females)
Results	Insulin dose No significant differences in insulin dose were detected throughout the study. Glycaemic control No significant differences were found in fasting and mean daily blood glucose values and HbA1c between the two injection regimens. Subgroup analysis of patients in excellent (HbA1c less than6%) and poor control (HbA1c greater than8%) showed no differences in changes of fasting or mean blood glucose or HbA1c The number and severity of hypoglycaemic reactions was not significantly different between the two regimens Patient acceptance

	No difference between treatment acceptance and health belief were found between the two treatment sequences.
Hierarchy of Evidence Grading	Ib
Comments	<p>4 week run-in period, insulin treatment and self-monitoring of glucose were optimised.</p> <p>Patients randomised into 2 groups for first 12 weeks</p> <p>After 12 weeks all patients crossed over to other regimen</p> <p>Patients aim for fasting BG levels of 4-7mmol/L and postprandial values between 5-8mmol/L.</p> <p>Insulin dose was adjusted according to results of home blood glucose monitoring.</p> <p>Questionnaire used to assess patient acceptance and quality of life.</p> <p>Not blinded due to different number of injection and different methods of administration</p> <p>Fasting BG calculated as mean of two measurements made on consecutive days.</p> <p>Patient characteristics at entry were compared by means of Student t-test or non-parametric test.</p> <p>Centres were compared by means of one-way analysis of variance.</p> <p>Significance of differences for measures of blood glucose control were assessed by means of analysis of variance (two period repeated measurements cross-over over time).</p> <p>Tests for period effects and carry-over effects were made.</p>
NCC CC ID	1038
Reference / Citation	

Premixed insulin preparations

Q 27 What types of insulin regimens aid optimal diabetic control in adults with stable type I diabetes?

Author / Title / Reference / Yr	Dunbar JM, Madden PM, Gleeson DT, Fiad TM, McKenna TJ 1994 Premixed insulin preparations in pen syringes maintain glycaemic control and are preferred by patients. Diabetes Care 17:874-878
N=	N=32 Republic of Ireland
Research Design	Randomised controlled trial
Aim	To examine the impact on glycaemic control of substituting a range of premixed insulins for the standard treatment with patient-mixed insulin combinations
Population	Type 1 diabetes
Intervention	Premixed insulin preparation that delivered short-acting and intermediate-acting insulins in the following percentages: Pen Mix (Novo Nordisk) 10/90%, 20/80%, 30/70%, 40/60% and 50/50%. Preparations delivered from cartridges using the Novo Pen II
Comparison	Self-mixed insulin (Human Actrapid and Human Monotard (intermediate-acting insulin, 30% amorphous, 70% crystalline insulin, Novo Nordisk) insulin)
Outcome	Glycaemic control as measured by assessment of glycosylated haemoglobin levels at start of study and after each 2-month study period. In addition, during the 1 month run-in period and during both 2-month study periods, a seven point blood glucose profile was obtained. Seven blood glucose measurements were obtained on at least 1 day in each phase of the study. Total glycated haemoglobin levels were measured at the point of randomisation and after 2 and 4 months. Patients were required to record all hypoglycaemic episodes and to grade them according to severity. At the end of the study, all participants were requested to complete a questionnaire assessing their preference for one of the two regimes used in the study.
Characteristics	Age 18-63 yrs, mean age 34.77. Duration of diabetes ranged from 19 months to 29 years (10.61 ± 8.1)
Results	Glycosylated haemoglobin levels were unchanged throughout the duration of the study (levels obtained at point of randomisation, after 2 months of treatment on premixed insulins, or after 2 months of treatment on patient-mixed insulins). No systematic changes in individual seven point blood glucose profiles before randomisation, while using premixed insulins, or after 2 months of treatment on patient-mixed insulins. Treatment with Pen Mix insulins, 16.9% of blood glucose readings were less than 4mM. Treatment with self-mixed insulins,

	<p>21.7% were less than 4mM. Five patients reported eight instances of grade 3 hypoglycaemic reactions while taking Pen Mix insulins. Three patients experienced a total of 21 grade 3 hypoglycaemic reactions and 1 patient experienced 1 grade 4 reaction while taking patient-mixed insulins.</p> <p>Frequency of hypoglycaemic reactions was similar on patient-mixed and premixed insulins.</p> <p>83% patients expressed a preference for premixed insulins.</p>
Hierarchy of Evidence Grading	Ib
Comments	<p>One month run-in period, patients adjusted insulin dosage to optimise control</p> <p>Patients then randomised either to change to premixed insulins or to continue with self-mixed insulins for 2 months</p> <p>At end of 2 months, patients crossover to other regimen for further 2 months</p> <p>When patients changed from self-mixed to premixed preparations, the premixed preparation chosen was one that gave the closest fit below their previous ratios, i.e., if the patient was using an ~40:60 ratio of Actrapid to Monotard, the 30/70% Pen Mix preparation was used.</p> <p>Aim was to maintain preprandial glucose at 72-144 mg/dl (4-8mM).</p> <p>During study, patients and medical staff were encouraged to adjust insulins to facilitate optimum control.</p> <p>Patients advised to adjust insulins weekly by 2U if relevant dose was less than 20U and by 4U if the dose was greater than 20 U.</p> <p>Patients encouraged to monitor plasma glucose levels on average twice daily to cover the four time points of before breakfast, before lunch, before the evening meal, and before the evening snack over any 24h period.</p> <p>Open label to allow for different time action profiles of insulin.</p> <p>No power calculations.</p> <p>Five patients withdrew from the study for a variety of reasons, including onset of renal failure, concern about the efficacy of the pen syringe, and non-specific deterioration in sense of well-being. One patient was not happy about what was considered more limitations associated with the use of premixed insulins than with patient-mixed insulins.</p> <p>Glycaemic control was similar in patient-mixed and premixed insulins, and patients had a marked preference for premixed insulins delivered in a pen-type syringe over conventional insulin therapy.</p> <p>Statistical analysis only performed on the 27 patients who completed the study.</p> <p>Analysis of variance suitable for studies of crossover design was used when comparing glycosylated haemoglobin levels before the study and in the two treatment groups. The Gart's test was used to compare hypoglycaemic reactions occurring in the two study phases.</p>
NCC CC ID	1054
Reference / Citation	

Q 27 What types of insulin regimens aid optimal diabetic control in adults with stable type I diabetes?

Author / Title / Reference / Yr	Gale EA 2000 A randomized, controlled trial comparing insulin lispro with human soluble insulin in patients with Type 1 diabetes on intensified insulin therapy. The UK Trial Group. Diabetic Medicine 17:209-214
N=	N = 93 UK
Research Design	Randomised controlled trial
Aim	To Compare the efficacy of artificial insulin with human insulin
Population	Type 1 diabetes
Intervention	Mix 50 (50% insulin lispro/50% NPL) given immediately before the morning meal and Mix 25 (25% insulin lispro/75% NPL) given immediately before the evening meal
Comparison	Human insulin 50/50 (50% regular human insulin/50% NPH) given 30-45 minutes before the morning meal and human insulin 30/70 (30% regular human insulin/70% NPH) given 30 to 45 minutes before the evening meal
Outcome	Glycaemic control measured by weekly self-monitored blood glucose profiles, glycated haemoglobin levels, frequency and severity of hypoglycaemic episodes and patient satisfaction and well-being and patient preference. The Diabetes Treatment Satisfaction Questionnaire and the Well Being Questionnaire were used as quality of life measures.
Characteristics	(44 women and 49 men). Median age 35 yrs (range 18-63 yrs), median duration of diabetes 13.1 years (range 1-51 years), and the median body mass index 25.2kg/m <sup>2</sup> (range 20-33.7 kg/m <sup>2</sup> )
Results	Glycaemic control With insulin lispro blood glucose levels were significantly lower after breakfast and lunch compared with Humulin S. With insulin lispro blood glucose levels were significantly higher before breakfast, lunch or supper compared with Humulin S. Levels of HbA1c were not significantly different between groups Hypoglycaemia The overall frequency of symptomatic hypoglycaemia did not differ between the two treatments. With insulin lispro patients were less likely to experience hypoglycaemia between midnight and 6am, and more likely to experience episodes from 6am to midday. Patient satisfaction No significant preference for either treatment emerged Insulin doses The daily dose of short-acting insulin was similar for the two insulin preparations.

	<p>The total dose of basal insulin was the same for the two insulin preparations.</p> <p>Quality of life</p> <p>There were no differences between the two treatments for any of the quality of life scores</p>
Hierarchy of Evidence Grading	Ib
Comments	<p>At study entry all patients were on multiple injection therapy, and those not using Humulin S (soluble) as their short acting insulin and Humulin I (isophane) as their basal insulin were converted to this regimen before entering the study.</p> <p>The majority injected Humulin S three times daily before meals and Humulin I with their bed-time snack.</p> <p>Run-in period of 6 weeks during which control was optimised with above regimen.</p> <p>Patients then randomly allocated to treatment with Humulin S or insulin lispro before meals, with unchanged basal insulin.</p> <p>Each patient received either</p> <p>3 months treatment with Humulin S before meals, with Humulin I as basal insulin</p> <p>3 months treatment with insulin lispro before meals, with Humulin I as basal insulin</p> <p>Patients were then changed to the alternative regimen for a further 3 months.</p> <p>Insulin for injection was supplied in double-blind pens.</p> <p>Patients and investigators were instructed to adjust insulin doses in the light of home blood glucose tests, with target glucose level less than 7mmol/L fasting and less than 10mmol/L post prandial.</p> <p>Insulin supplied in double-blind fashion as 1.5ml cartridges for use in pen devices.</p> <p>Study was powered at 80% level to detect a difference in HbA1c of 0.27%.</p> <p>Student's t-test was used for comparisons between treatments.</p> <p>For efficacy and safety measurement an analysis for a crossover design was used to test for both treatment and carryover effects.</p> <p>An intention to treat analysis using the last observation carried forward for each patient within the crossover periods was employed.</p> <p>Six out of 93 patients dropped out.</p> <p>Two patients withdrew because of potential serious adverse events – hypoglycaemic coma and increasing emotional lability.</p> <p>Both patients were taking Humulin S at the time. One patient was withdrawn at the discretion of the local physician owing to difficulties in compliance. One patient withdrew because of personal problems, and two (both on insulin lispro) withdrew because of difficulties with glucose control.</p> <p>Patient inclusion criteria may have biased the comparison in favour of lispro, since post-prandial control is less good when soluble insulin is given shortly before meals.</p> <p>Comparison of the rates of nocturnal hypoglycaemia may be misleading, since fasting glucose levels were higher on insulin lispro and overnight glucose control was therefore not equivalent</p>
NCC CC ID	1060
Reference / Citation	

Q 27 What types of insulin regimens aid optimal diabetic control in adults with stable type I diabetes?

Author / Title / Reference / Yr	Roach P, Trautmann M, Arora V, Sun B, Anderson JH, Jr. 1999 Improved postprandial blood glucose control and reduced nocturnal hypoglycemia during treatment with two novel insulin lispro-protamine formulations, insulin lispro mix25 and insulin lispro mix50. Mix50 Study Group. Clinical Therapeutics 1999;21:523-534
N=	N = 37 European
Research Design	Randomised controlled trial
Aim	To evaluate the efficacy of premixed insulin therapy
Population	Type 1 diabetes
Intervention	Mix 50 (50% insulin lispro/50% NPL) given immediately before the morning meal and Mix 25 (25% insulin lispro/75% NPL) given immediately before the evening meal
Comparison	Human insulin 50/50 (50% regular human insulin/50% NPH) given 30-45 minutes before the morning meal and human insulin 30/70 (30% regular human insulin/70% NPH) given 30 to 45 minutes before the evening meal
Outcome	Glycaemic control as measured by blood glucose profiles, HbA1c and frequency and severity of hypoglycaemic episodes. Patients seen on monthly basis Blood glucose measurement were taken by the patient before and 2 hours after morning, midday and evening meals, at bedtime and at 3am. HbA1c was measured at baseline and at the end of each 3-month treatment period. Patients were instructed to record all hypoglycaemic episodes in study diary.
Characteristics	12 females, 25 males; mean age 39.4 years; mean duration of diabetes 12.9 years
Results	Insulin dosages Mean insulin doses were similar or identical between treatments (0.35 U/kg) Mean evening insulin doses for insulin lispro mixtures and human insulin mixtures were 0.29 and 0.27 U/kg. Blood glucose control Treatment with Mix 50 resulted in a mean morning BG excursion that was significantly smaller than during treatment with human insulin 50/50 (-3.38 vs. -0.51; p = 0.002) No significant difference was seen in evening BG excursion between groups. Fasting blood glucose levels did not differ between groups. Treatment with insulin lispro mixtures resulted in significantly lower BG levels 2 hours after the morning meal (p less than

	<p>0.001) and before lunch (p = 0.037)</p> <p>Human insulin and insulin lispro mixtures achieved comparable overnight glycaemic control.</p> <p>HbA1c measurements did not differ significantly between treatments at end point</p> <p>Hypoglycaemia</p> <p>No difference between treatments with respect to the incidence of hypoglycaemia</p> <p>No difference between the numbers of nocturnal hypoglycaemic episodes.</p> <p>No difference between treatments with respect to severe hypoglycaemia. Five patients with type 1 diabetes experienced a total of 6 episodes of severe hypoglycaemia. Two episodes occurred during treatment with insulin lispro mixtures, and 4 episodes occurred during treatment with human insulin mixtures</p>
Hierarchy of Evidence Grading	Ib
Comments	<p>4 week run-in period – patients were treated with human insulin 50/50 before the morning meal and human insulin 30/70 before the evening meal.</p> <p>Patients then randomly assigned to the two treatment groups</p> <p>To allow optimal intervals between insulin injections and meals, the study was not masked</p> <p>Insulin lispro mixtures were to be given immediately before morning and evening meals, and human insulin mixtures were to be given 30-45 minutes before meals.</p> <p>Investigators were instructed to adjust insulin to achieve treatment goals of fasting BG less than 7.8mmol/L and 2 hour postprandial BG less than 10mmol/L</p> <p>Open label to allow different time intervals of administration before meals.</p> <p>No difference in patient baseline characteristics.</p> <p>Data was analysed on intent to treat basis and last observation carried forward.</p> <p>All comparisons were performed using two tailed tests.</p> <p>Three patients elected not to continue the study after 1 month of treatment with Mix50/Mix25 during period 1</p>
NCC CC ID	1029
Reference / Citation	

Q 27 What types of insulin regimens aid optimal diabetic control in adults with stable type I diabetes?

Author / Title / Reference / Yr	Hermansen K, Vaaler S, Madsbad S, Dalgaard M, Zander M, Begtrup K, Soendergaard 2002 Postprandial glyceemic control with biphasic insulin aspart in patients with type 1 diabetes. <i>Metabolism-Clinical and Experimental</i> 51:896-900
N=	N=50 European
Research Design	Randomised controlled trial
Aim	To compare mixed insulin regimens
Population	Type 1 diabetes
Intervention	Biphasic insulin aspart 30 (Novomix 30 – 30% soluble insulin aspart and 70% protamine insulin aspart)
Comparison	BHI 30 (Mixtard 30)
Outcome	Glucose, lipids, insulin, adverse events and hypoglycaemic episodes. During period from –30 to 240 minutes relative to the time of starting breakfast, 16 blood samples were drawn at regular intervals for measuring glucose and insulin
Characteristics	Patients diagnosed with type 1 diabetes for at least 2 years and treated with human insulin for at least 12 months. Age greater than 18 years, BMI less than 30kg/m <sup>2</sup> , and HbA <sub>1c</sub> less than 11%
Results	Glucose BiAsp 30 reduced the postprandial serum glucose AUC by 23% compared with BHI 30 taken immediately before meal (p less than 0.001) and by 9% compared with BHI 30 taken 30 minutes before meal (p = 0.013) Insulin Pharmacokinetics of BiAsp 30 differed from those of BHI 30: the insulin AUC 0-4h observed for BiAsp 30 was larger by 24% compared with BHI taken immediately before food and 16% compared with BHI 30 taken 30 minutes before food. Hypoglycaemia 16 minor hypoglycaemic events occurred with BiAsp 30, 9 events with BHI 30 injected immediately before the meal and 9 events with BHI injected 30 minutes before the meal
Hierarchy of Evidence Grading	Ib
Comments	Three trials separated by 5 to 21 days. Following 3 treatments given in random order:

	<p>1) Biphasic insulin aspart 30 injected immediately before a standard breakfast  2) BHI 30 (Mixtard 30) injected 30 minutes before breakfast  3) BHI 30 injected immediately before breakfast  Insulin dose was 0.4U/kg body weight for all 3 treatments  Subjects on their usual insulin regimen between visits but were instructed not to inject intermediate- or long-acting insulin after breakfast on the day preceding trial days.  During night preceding trial days and until 15 minutes before meals, they were given human insulin (Actrapid) by intravenous infusion to stabilise blood glucose concentration between 5 and 8 mmol/l.  Three trial days where interventions given  Of the 50 enrolled patients, 6 completed the trial and 4 were withdrawn: 3 because they wished to discontinue.</p>
NCC CC ID	1163
Reference / Citation	

Q 27 What types of insulin regimens aid optimal diabetic control in adults with stable type I diabetes?

Author / Title / Reference / Yr	Small M, MacRury S, Boal A, Paterson KR, MacCuish AC 1988 Comparison of conventional twice daily subcutaneous insulin administration and a multiple injection regimen (using the NovoPen) in insulin-dependent diabetes mellitus. Diabetes Research 1988;8:85-89
N=	N=37 human Actrapid group =19, conventional therapy =18 UK
Research Design	Randomised controlled trial
Aim	To compare mixed insulin regimens
Population	Type 1 diabetes
Intervention	Human Actrapid insulin given 30 min preprandial with Human Ultratard as basal insulin
Comparison	Conventional therapy 2 dose (with mixtard (30% short acting, 70% isophane) or Initard (50% short acting 50% isophane)
Outcome	HbA1c, blood glucose profiles, insulin dosage, frequency and severity of hypoglycaemic episodes
Characteristics	diabetes for over one year, performed regular glucose monitoring, were taking CT with Mixtard (30% short acting, 70% isophane) insulin and were willing to transfer to a multiple injection regimen The groups were well matched with respect to age, sex, BMI and duration of diabetes
Results	Glycaemic control During the 6 month study period no significant improvement in HbA1c levels were noted in either group, and at no time point were there any difference in HbA1c levels between the two groups The Novo Pen group had lower mean glucose profiles at three and five months (pless than0.05); however no differences between groups were seen at other time points Insulin dosage and weight No significant difference in weight and insulin dosages during the study Frequency of hypoglycaemia No significant differences between the groups were found Novo Pen - patient assessment The majority 15/19 said four injections per day suited their lifestyle 16/18 said four injections per day gave them greater flexibility of lifestyle

Hierarchy of Evidence Grading	Ib
Comments	<p>Run-in period of 2 months to optimise glycaemic control on CT  Glucose profile times were before and 90 minutes after breakfast, lunch and dinner and at bedtime.  After 2 months (baseline), patients were randomised to continue on their present therapy (n= 18) or to change to three injections of Human Actrapid Insulin, using the Novo pen  Initially, patients were given 40% of their previous total insulin dose in the form of Ultratard with the remaining 60% divided before their main meals  All patients were seen monthly for six months when glycaemic control was assessed and insulin dosage adjusted  Open label with no allocation concealment due to different methods of administration (subcutaneous vs. pen)  During the run-in period there were slight, but significant changes in the following variables: weight, evening insulin dosage, and fasting glucose.  Three patients failed to complete the study but were included in the analysis. One patient in the CT group failed to attend after the three month visit. In the Novo Pen group, one patient transferred back to CT after the two month visit as he had a strong dislike for multiple injections, and one further patient stopped using the Novo Pen after the four month visit due to a dislike of multiple injections and lack of improvement in her glycaemic control.</p>
NCC CC ID	1070
Reference / Citation	

Basal insulin

Q 27 What types of insulin regimens aid optimal diabetic control in adults with stable type I diabetes?

Author / Title / Reference / Yr	Zinman B, Ross S, Campos RV, Strack T 1999 Effectiveness of human ultralente versus NPH insulin in providing basal insulin replacement for an insulin lispro multiple daily injection regimen: A double-blind randomized prospective trial. Diabetes Care 22:603-608.
N=	N=178: Ultralente insulin =87, human NPH =91
Research Design	Randomised controlled trial
Aim	A comparison of basal insulin types
Population	Type 1 diabetes
Intervention	ultralente insulin once daily at bedtime
Comparison	Human NPH
Outcome	Glycaemic control as measured by HbA1c, blood glucose and frequency and severity of hypoglycaemic episodes Eight-point blood glucose profiles were collected once monthly in the first 4 months, then every two months for the remainder of the study. Patients asked to perform premeal blood glucose measurements every day throughout the study.
Characteristics	age 35 ± 1 years, BMI 25 ± 1 kg/m <sup>2</sup>
Results	<p>Insulin doses</p> <p>Insulin doses before meals and basal insulin doses were similar at baseline.</p> <p>At the end of the study, meal doses remained the same, while basal requirements were somewhat higher for the ultralente groups than in the NPH group (P less than 0.05).</p> <p>Hypoglycaemia</p> <p>Overall hypoglycaemia rates were comparable in both groups and fell continuously towards the end of the study.</p> <p>Rates of severe hypoglycaemia were similar for patients on NPH and for ultralente insulin.</p> <p>Glycaemic control</p> <p>Compared with baseline, patients in both groups were able to markedly reduce their endpoint postprandial blood glucose levels (p less than 0.004 at post breakfast)</p> <p>There was no significant difference for glycaemic control between the NPH and UL groups overall and by the end of the study a similar number of patients in the NPH and ultralente groups needed to be switched to twice daily basal insulin (21 and 24%, respectively).</p> <p>Of the patients switched to twice daily injection of NPH or UL insulin, NPH patients had a lower level of glycaemia from</p>

	<p>bedtime until the prelunch reference time point</p> <p>Patients requiring twice daily injections of basal insulin had a longer duration of diabetes, and a higher baseline HbA1c and were significantly older.</p> <p>Glycosylated haemoglobin</p> <p>HbA1c levels decreased by 0.6% (NPH) and 0.7% (UL) compared with baseline after 4 months, and were maintained at the lower level for the remainder of the study (pless than0.001).</p> <p>No significant differences in HbA1c between groups</p>
Hierarchy of Evidence Grading	Ib
Comments	<p>Of the 178 patients, 78 had been on multiple injections while the remainder had been on twice-daily treatment.</p> <p>Patients received regular human insulin (Humulin R) together with their previous basal insulin in an open-label 2 week run-in period.</p> <p>Randomised to NPH (Humulin N) or UL (Humulin U) insulin plus insulin lispro administered three times daily before each meal for a 12-month double-blind treatment period.</p> <p>Patients were asked to inject insulin lispro administered three times daily before each meal for 12 month double blind period.</p> <p>Basal insulin was administered by syringe only to maintain masking.</p> <p>Target range for premeal glucose levels 6-8mmol/l.</p> <p>Of 178 patients enrolled, 162 (90%) completed the 1year study: seven patients in the NPH group discontinued before the last visit, and nine in the UL group.</p> <p>Reasons for discontinuation were relocation of patients (5 patients), adverse events (two patients), and non-compliance with study procedures (two patients). Three patients decided to withdraw from the study for perceived lack of efficacy (one and two patients from the UL and NPH groups, respectively) and four for other personal reasons.</p> <p>Significant adverse drug-related events (serious hypoglycaemia requiring assistance and/or hospitalisation in two patients) and non-study drug-related events (surgery for three patients and car accident not related to hypoglycaemia for two patients).</p> <p>All efficacy results presented as intent-to-treat analysis.</p>
NCC CC ID	176
Reference / Citation	

Q 27 What types of insulin regimens aid optimal diabetic control in adults with stable type I diabetes?

Author / Title / Reference / Yr	Hermansen K, Madsbad S, Perrild H, Kristensen A, Axelsen M 2001 Comparison of the soluble basal insulin analog insulin detemir with NPH insulin: A randomized open crossover trial in type 1 diabetic subjects on basal-bolus therapy. Diabetes Care 24:296-301
N=	N=59 Denmark
Research Design	Randomised controlled trial
Aim	To compare the efficacy of basal insulin preparations
Population	Type 1 diabetes
Intervention	Insulin detemir 100 U/ml
Comparison	NPH insulin (Insulatard 100 IU/ml) as basal insulin
Outcome	Glycaemic control as measured by blood glucose, incidence and severity of hypoglycaemic, dose of insulin and safety Primary endpoint was area under serum glucose curve in time interval 23:00 to 08:00. Two glucose profiles each week (before each meal, 90 min after each meal, at bedtime and one at 03:00) Fasting blood glucose taken during last 4 days of each treatment period
Characteristics	46 men and 10 women between 19-52 years of age; mean duration of diabetes a14.8 years
Results	Serum glucose and glycaemic control The area under the curve, in the time interval 23:00-8:00, derived from 24h serum glucose profiles was not statistically significantly different for the two treatment periods The intrasubject variation in fasting blood glucose during the last 4 days of treatment was lower for insulin detemir compared with NPH (pless than0.001) Insulin doses Mean dose requirements of insulin detemir were 2.35 times higher compared with NPH. Hypoglycaemic episodes During the last week of treatment, fewer subjects experience hypoglycaemic episodes on insulin detemir compared with NPH treatment. Adverse events Approximately 30% of subjects had adverse events during either treatment period.

Hierarchy of Evidence Grading	Ib
Comments	<p>Run-in period of 2 weeks – subjects administered an evening NPH injection in addition to HIS (Actrapid 100 IU/ml) before each meal.</p> <p>Subjects randomised symmetrically in blocks of four to a treatment sequence  Insulin detemir or NPH between 21:00 and 23:00 and HIS 30 minutes before each main meal.  Blood glucose targets fasting 4-7mmol/l and postprandial 5-9mmol/l, 03.00 4-7 mmol/l  Two 6 week treatment periods  Filed for approval in Europe 12/11/02. UK license not expected until early 2004  To obtain a power of 80%, 49 subjects were needed to detect a difference in the primary endpoint of 10% with a significance level of 5%.  7 investigation sites (total 56 patients)  Analysis undertaken using ANOVA.  Two subjects discontinued prematurely because of excessive C-peptide levels at inclusion and the concern over volume of injected insulin detemir.  56 completed trial and were included in efficacy analysis</p>
NCC CC ID	1045
Reference / Citation	

Q 27 What types of insulin regimens aid optimal diabetic control in adults with stable type I diabetes?

Author / Title / Reference / Yr	Fanelli CG, Pampanelli S, Porcellati F, Rossetti P, Brunetti P, Bolli GB 2002 Administration of neutral protamine Hagedorn insulin at bedtime versus with dinner in type 1 diabetes mellitus to avoid nocturnal hypoglycemia and improve control. A randomized, controlled trial. Annals of Internal Medicine.136(7):504-14
N=	N=22 Italy
Research Design	Randomised controlled trial
Aim	To compare the efficacy of basal insulin preparations
Population	Type 1 diabetes
Intervention	Mixed treatment – a mixture of human regular and neutral protamine hagedorn (NPH) insulin administered before dinner
Comparison	Split treatment – human regular insulin administered before dinner and NPH insulin administered at bedtime
Outcome	Frequency of nocturnal hypoglycaemic. Secondary endpoints were levels of fasting blood glucose and HbA1c and responses to experimental hypoglycaemia
Characteristics	C-peptide negative persons with type 1 diabetes mellitus (10 women, 12 men) type 1 diabetes mellitus, receiving long-term intensive insulin treatment (multiple insulin injections with regular human insulin before meals and NPH insulin at bedtime)
Results	During split regimen treatment period, patients had fewer episodes of nocturnal hypoglycaemia ( $0.10 \pm 0.02$ episode/patient-day vs. $0.28 \pm 0.04$ episode/patient-day; $p = 0.002$ ) During split regimen patients had a lower fasting blood glucose level ( $7.6 \pm 0.2$ mmol/l vs. $8.3 \pm 0.5$ mmol/l; $p = 0.03$ ) During split regimen patients had less variable fasting blood glucose levels ( $2 \pm 0.4$ vs. $3.5 \pm 0.6$ ; $p = 0.001$ ) and lower haemoglobin A1c levels ( $7.0\% \pm 0.11\%$ vs. $7.5\% \pm 0.15\%$ ; $p = 0.004$ ) Responses to experimental hypoglycaemia were better preserved with the split regimen than with the mixed regimen. Insulin doses did not differ between groups
Hierarchy of Evidence Grading	Ib
Comments	1 month run-in period, during which patients continued usual regimen of multiple daily insulin injections Patients randomly assigned to two treatment groups for 4 months Patients then switched to alternative group for further 4 months.

	<p>Target fasting blood glucose of 5-6.7 mmol/l before meals and at bedtime</p> <p>Sample-size power calculations indicated that 20 patients would be required to detect a 50% decrease in primary end point with power of 80% at 5% significance</p> <p>All patients completed the study</p>
NCC CC ID	1019
Reference / Citation	

Q 27 What types of insulin regimens aid optimal diabetic control in adults with stable type I diabetes?

Author / Title / Reference / Yr	Tunbridge F, Newen A, Home PD, Davis SN, Murphy M, Burrin JM, Alberti KG, Jensen I 1989 Double-blind crossover trial of isophane (NPH)- and lente-based insulin regimens. Diabetes Care 12:115-119
N=	N=82 UK
Research Design	Randomised controlled trial
Aim	A study to compare the efficacy of two insulin regimens
Population	Diagnosed type 1 diabetes
Intervention	lente (Monotard) insulin
Comparison	NPH (Protaphane)
Outcome	Glycaemic control as measured by glycosylated haemoglobin and fructosamine concentrations and blood glucose measurements. Incidence and severity of hypoglycaemia. On day before each visit patients collected a 7 point blood glucose profile (before and after breakfast, lunch and dinner and before bed)
Characteristics	Not recorded – crossover design
Results	Glycaemic control Glycaemic control as assessed by glycosylated haemoglobin (NPH $9.2 \pm 0.1\%$ , lente $9.3 \pm 0.1\%$ ) and fructosamine ( $1.55 \pm 0.02$ and $157 \pm 0.02$ mM) concentrations were identical for the two regimens. No differences between groups was observed in fasting blood glucose (NPH $8.8 \pm 0.5$ mM, lente $9.0 \pm 0.5$ mM) and mean blood glucose ( $8.2 \pm 0.3$ and $7.6 \pm 0.3$ mM) Insulin doses For both groups, insulin dosage was similar (NPH $56.3 \pm 0.6$ U/day, lente $57.2 \pm 0.6$ U/day) with no tendency for a difference in the evening intermediate acting dose (NPH $17 \pm 0.3$ U/day, lente $17 \pm 0.3$ U/day) to counter fasting hyperglycaemia. Conclusion Lente and NPH-based twice daily human insulin regimens give indistinguishable metabolic control
Hierarchy of Evidence Grading	Ib
Comments	2 month run-in period. Patients encouraged to change to high carbohydrate/fibre modified low-fat diet.

	<p>Patients randomised to NPH (Protaphane) or lente (Monotard) insulin preparations given together with Actrapid as a twice daily injection regimen</p> <p>Patients seen monthly and crossed over after 5 months</p> <p>Power calculations suggested 80 patients would have a 95% chance of detecting a 1% difference in glycosylated haemoglobin and a 2 mM difference in fasting BG concentration.</p> <p>77 patients completed the study; the five dropouts were due to pregnancy (2 subjects), failure to attend (1 subject on each insulin type), and moving away from area (1 subject).</p> <p>Five dropout patients are included in intent-to-treat analysis</p> <p>Crossover analysis performed.</p>
NCC CC ID	248
Reference / Citation	

Q 27 What types of insulin regimens aid optimal diabetic control in adults with stable type I diabetes?

Author / Title / Reference / Yr	Tunbridge FK, Newens A, Home PD, Davis S, Murphy M, Burrin J, Alberti K, Jensen I 1989 A comparison of human ultralente- and lente-based twice-daily injection regimens. Diabetic Medicine 1989;6:496-501
N=	N=66 UK
Research Design	Randomised controlled trial
Aim	A comparison of the effectiveness of different insulin preparations
Population	Type 1 diabetes
Intervention	Human ultralente
Comparison	Human lente insulin given together with human soluble insulin in twice daily injection regimen.
Outcome	Glycaemic control as measured by blood glucose levels, insulin dosage, hypoglycaemic events and glycosylated Haemoglobin (HbA1c) Day before each monthly visit patients performed 8 point glucose profile (before and after each main meal, before bed, and during the night at 0300h)
Characteristics	age 18-62 years; 37 male and 29 female
Results	<p>Insulin dose The evening extended acting insulin dose for the ultralente based insulin regimen was slightly but significantly lower than that for the lente-based regimen (<math>14.9 \pm 0.8</math> vs. <math>15.5 \pm 0.8</math> U, <math>p &lt; 0.05</math>)</p> <p>Blood glucose profiles Fasting blood glucose concentration on the ultralente regimen was lower than on the lente regimen (<math>6.6 \pm 0.5</math> vs. <math>8.2 \pm 0.5</math> mmol/l, <math>p &lt; 0.05</math>) No significant difference in other values tested. Patients with mean fasting blood glucose concentrations below the median (as measured over previous 10 months), this measure was significantly improved on the ultralente –based compared with the lente-based regimen (<math>5.3 \pm 0.5</math> vs. <math>7.6 \pm 0.8</math> mmol/l, <math>p &lt; 0.05</math>)</p> <p>Hypoglycaemic events No differences were found between the frequencies of grades 1,2 and 4 events. There were more grade 3 events (day and night), requiring third party assistance, on the ultralente regimen (<math>0.38 \pm 0.10</math> events/patient/month) than on the lente regimen (<math>0.09 \pm 0.04</math> events/patient/month)</p>

	Of these grade 3 events a large proportion occurred during the night ( $0.28 \pm 0.09$ events/patient/month on the ultralente vs. $0.06 \pm 0.03$ events/patient/month on the lente regimen pless than0.05), with 60% occurring after 0500h on the ultralente regimen, compared with 14% on the lente regimen
Hierarchy of Evidence Grading	Ib
Comments	<p>Run-in period of 1 year on similar study</p> <p>Short and extended-acting insulin doses were not changed on entry to study.</p> <p>Patients randomised to</p> <p>Human ultralente insulin (Human ultratard) given together with human soluble insulin (Human Actrapid)</p> <p>Human lente insulin (Human monotard), given together with human soluble insulin (Human Actrapid)</p> <p>Extended acting insulin and soluble insulin were mixed in the syringe immediately before each injection, given twice daily 15-30 minutes before breakfast and the evening meal</p> <p>Double-blind crossover</p> <p>Human ultralente insulin is of longer duration than human lente</p> <p>Blinding carried out by pharmacy staff</p> <p>Labelling with patient record numbers was according to a randomisation code prepared elsewhere</p> <p>65 of 66 patients completed the 6 month study,</p> <p>Single drop out due to non-compliance</p> <p>All patients subjected to intention to treat analysis</p> <p>Data analysis was by standard parametric and nonparametric techniques</p> <p>Main crossover analysis was performed using ANOVA to exclude any effect of duration of study..</p>
NCC CC ID	1039
Reference / Citation	

Q 27 What types of insulin regimens aid optimal diabetic control in adults with stable type I diabetes?

Author / Title / Reference / Yr	Haakens K, Hanssen KF, Dahl-Jorgensen K, Vaaler S, Torjesen P, Try K 1989 Early morning glycaemia and the metabolic consequences of delaying breakfast/morning insulin. A comparison of continuous subcutaneous insulin infusion and multiple injection therapy with human isophane or human ultralente insulin at bedtime in insulin-dependent diabetics. Scandinavian Journal of Clinical & Laboratory Investigation 49:653-659
N=	N=54
Research Design	Randomised controlled trial
Aim	A study into alternative insulin therapy regimens
Population	Type 1 diabetes
Intervention	Delay of morning insulin/breakfast in type 1 diabetics on the following regimens 1) Continuous subcutaneous insulin infusion (CSII). 2) Multiple injection therapy (MI) with human isophane insulin at bedtime (MI/human isophane) (Protophane human))
Comparison	3) MI with human ultralente insulin at bedtime (MI/human ultralente) (Ultratard human)
Outcome	Morning glycaemia and metabolic control as measured by blood glucose, serum free insulin and serum betahydroxybutyrate
Characteristics	C-peptide negative
Results	At all times blood glucose was lowest on CSII, intermediate on MI/human ultralente and lowest on MI/human isophane Serum hydroxybutyrate was lowest on CSII, intermediate on MI/human ultralente and highest on MI/human isophane Blood glucose rose significantly on MI/human isophane (pless than0.001) and CSII (pless than0.02); serum free insulin declined significantly on MI/human isophane (pless than0.001), and betahydroxybutyrate rose significantly on all regimens.  Conclusion Morning metabolic control is better with CSII than MI. Human isophane insulin is preferable to human ultralente insulin overnight in MI. Delaying morning insulin is not advisable on intensified insulin regimens, being most unfavourable on MI/human isophane
Hierarchy of Evidence Grading	Ib
Comments	After overnight fast, food and insulin (except for basal infusion on CSII) were withheld Blood glucose, serum free insulin and serum betahydroxybutyrate followed from 0800 hours to 1300 hours

	Standardised test for paired and unpaired data
NCC CC ID	1057
Reference / Citation	

Human vs animal insulin

Q 27 What types of insulin regimens aid optimal diabetic control in adults with stable type I diabetes?

Author / Title / Reference / Yr	Richter B, Neises G, Bergerhoff K 2002 Human versus animal insulin in people with diabetes mellitus: A systematic review. <i>Endocrinology &amp; Metabolism Clinics of North America</i> 31:723-749
N=	45 randomised controlled clinical trials that studied the effects of human versus animal insulin n = 2156 participants (NB diagnosis of type 1 or type 2 diabetes). 58% of crossover and parallel studies investigated type 1 diabetes
Research Design	Systematic review
Aim	to assess effects of different insulin species by evaluating their efficacy (in particular glycaemic control) and adverse effects profile (mainly hypoglycaemia)
Population	Both Type 1 diabetes and mixed diabetes populations
Intervention	Any type and preparation of animal insulin therapy. Purified porcine and semi-synthetic insulin were most often investigated
Comparison	Comparisons of any type and preparation of human insulin treatment
Outcome	Primary outcome: Glycaemic control (glycated haemoglobin), frequency, severity and symptoms of hypoglycaemia and diabetic complications (for example diabetic retinopathy, diabetic nephropathy, diabetic neuropathy) Secondary outcome: Fasting plasma glucose, any other adverse event other than hypoglycaemia, diabetes-related mortality, health-related quality of life, compliance, costs, socio-economic effects. All studies reported on metabolic control and insulin dosage, some on insulin antibodies and adverse effects in general, and many on hypoglycaemic episodes.
Characteristics	Varied between studies
Results	No significant differences in glycaemic control or hypoglycaemic episodes between various insulin species could be found
Hierarchy of Evidence Grading	Ia
Comments	Highly sensitive search combined with key terms for identifying was performed using Cochrane, Medline and Embase. Reference lists and databases of ongoing trials were also searched. 86% of the studies did not define a primary endpoint, only three studies provided a power calculation. None of the crossover studies used a washout period in between two crossover phases, and only three analysed data for carryover and period effects. Inclusion criteria were described in 73% and exclusion criteria in 55% of trials.

	<p>No meta-analysis undertaken due to heterogeneity of outcomes</p> <p>Review is in accordance with the findings of previous systematic review with respect to absence of significant differences between animals and human insulin, indicating that human insulin may have been introduced without proof of being superior to animal insulin.</p> <p>Studies have not assessed patient-centred outcomes like patient satisfaction, health-related quality of life and diabetes-related morbidity.</p> <p>Randomised trials did not report on qualitative assessments of patients' experiences when using difference insulin species.</p>
Trials included	See original paper
NCC CC ID	1041
Reference / Citation	

Q 27 What types of insulin regimens aid optimal diabetic control in adults with stable type I diabetes?

Author / Title / Reference / Yr	Richter B, Neises G, Bergerhoff K 2002 Human versus animal insulin in people with diabetes mellitus: A systematic review. Endocrinology & Metabolism Clinics of North America 31:723-749
N=	Eighteen studies (11 used crossover design, 7 used a parallel study design) studied 700 patients
Research Design	Systematic review
Aim	A comparison of animal and human insulin regimens
Population	Mixed diabetes population
Intervention	Any type and preparation of animal insulin
Comparison	Any type and preparation of human insulin treatment
Outcome	Primary outcome: Glycaemic control (glycosylated haemoglobin and fasting blood glucose levels), frequency, severity and symptoms of hypoglycaemic, diabetic complications (e.g. diabetic retinopathy, diabetic nephropathy) Secondary outcomes: Any other adverse effect apart from hypoglycaemia, diabetes-related mortality, health related quality of life, compliance, costs and socio-economic effects.
Characteristics	Varied between trials
Results	Metabolic control Parallel studies Five studies reported no significant differences between insulin species in glycosylated haemoglobin (HbA1c) and fasting plasma glucose outcomes. One study described a significant increase in HbA of 1.9% after porcine insulin administration. Another trial reported a significant increase in fasting plasma glucose after human insulin administration and a decrease after porcine insulin administration. Crossover studies HbA1, HbA1c, fructosamine, and fasting plasma glucose measurements generally indicated no significant differences between insulin species. Hypoglycaemic episodes Parallel studies Studies do not mention severe hypoglycaemic events and report no differences in the risk of hypoglycaemia associated with the insulin preparations. One trial mentioned one to two mild to moderate hypoglycaemic events per week in both insulin groups. Crossover studies

	Two studies described hunger and sweating as initial warning symptoms significantly more often during porcine insulin therapy. Other studies could not detect significant differences in autonomic and neuroglycopenic symptom scores. No study found a significant difference in severe hypoglycaemic events, the total number of hypoglycaemic episodes, the number of events per patients, hypoglycaemic coma, frequency or time of occurrence, and unexplained or nocturnal hypoglycaemic episodes
Hierarchy of Evidence Grading	Ia
Comments	<p>Search of Cochrane library and Medline for randomised trials.</p> <p>All participants were ambulatory patients. Trial duration from 3 months to 5 years for parallel studies and 1.5 to 3 months for crossover trials.</p> <p>Numbers of participants ranged from 20 to 103 in parallel studies to 15 to 88 in crossover studies.</p> <p>Almost all participants received animal insulin in the purified porcine form; only three randomised, double blind studies investigated bovine insulin.</p> <p>All of the crossover and most of the parallel studies were of high quality.</p> <p>Pharmaceutical studies sponsored almost all studies.</p> <p>Two reviewers.</p> <p>Interobserver agreement.</p> <p>Validated quality criteria – assessment of randomisation, allocation concealment, blinding, description of withdrawals and dropouts, and intention-to-treat analysis.</p> <p>Outcome measures could not be converted into standard measure, therefore no meta-analysis performed.</p> <p>The overall picture with regard to hypoglycaemic events and glycaemic control does not indicate any substantial difference between insulin species.</p>
Trials included	See original study
NCC CC ID	1041
Reference / Citation	

Q 27 What types of insulin regimens aid optimal diabetic control in adults with stable type I diabetes?

Author / Title / Reference / Yr	George E, Bedford C, Peacey SR, Hardisty CA, Heller SR 1997 Further evidence for a high incidence of nocturnal hypoglycaemia in IDDM: no effect of dose for dose transfer between human and porcine insulins. Diabetic Medicine 14:442-448
N=	N=20 human insulin = 10 , porcine = 10 UK
Research Design	Randomised controlled trial
Aim	A comparison of human and animal insulin therapy
Population	Type 1 diabetes
Intervention	NPH (Insulatard) (intermediate-acting porcine insulin)
Comparison	Velosulin (short-acting human insulin) Twice daily dosing for 12 weeks – crossover to alternative treatment occurring every 4 weeks
Outcome	Insulin doses, glycaemic control as measured by blood glucose. Frequency and severity of hypoglycaemic episodes, HbA1c measured at screening, first day of transfer and end of trial
Characteristics	Type 1 diabetes. Sixteen had used animal insulins in the past but all had been using human insulin for at least 3 years. Sixteen had been using a bolus regimen, 3 twice-daily mixtures of short- and long-acting insulin and 1 twice daily long-acting insulin only, men insulin dosage being $0.66 \pm 0.05$ units/kg/day. Mean total HbA1 was $10.3 \pm 0.3\%$ . Five patients had evidence of background retinopathy; six had evidence of peripheral neuropathy.
Results	Glycaemic control HbA1c fell significantly during the study from $10.3 \pm 0.3\%$ at screening to $9.9 \pm 0.3\%$ at completion HbA1c values fell significantly during the first 4 weeks on human insulin (from $10.2 \pm 0.3\%$ to $9.8 \pm 0.3\%$ , p less than 0.02) HbA1c levels were not significantly different during the first 4 weeks on porcine insulin ( $10 \pm 0.3\%$ to $10 \pm 0.3\%$ ) No difference in HbA1 at the end of each phase. Insulin doses Total daily insulin dosage was similar in all phases of the study Reported episodes of hypoglycaemia Episodes of hypoglycaemia were not significantly different Nocturnal studies The episodes of hypoglycaemia seen on each night were similar in number and duration

	<p>The total number of interventions with food or intravenous dextrose to correct hypoglycaemia were not significantly different</p> <p>The time of onset of hypoglycaemia did not differ between nights</p> <p>There was a significant difference in the overnight glucose profiles between nights 1 and 8 following transfer to human insulin (AUC night 1 <math>82.3 \pm 7.8</math> vs. night 8 <math>61.4 \pm 5.3</math> mmol/h, <math>p &lt; 0.05</math>)</p> <p>No differences in glucose profile were seen following transfer to porcine insulin (AUC night 1 <math>70.7 \pm 7.2</math> vs. night 8 <math>70.1 \pm 7.5</math> mmol/h, <math>p = 0.74</math>)</p> <p>Comparison of glucose values from all 4 nights revealed no overall differences in AUC.</p> <p>Glucose values at 10 pm on nights 1 and 8 on human insulin and porcine insulin were similar</p>
Hierarchy of Evidence Grading	Ib
Comments	<p>4 week run in period, encouraging patients to optimise glycaemic control.</p> <p>All patients underwent two transfers of insulin species</p> <p>Patients were encouraged to alter insulin doses as usual except on first day of each transfer of insulin species when patients used the same doses of insulin as on the previous day, i.e. insulin species was transferred on a unit for unit basis.</p> <p>Patients were admitted to hospital on first night of transfer to have nocturnal glucose measurements taken.</p> <p>No comparison between baseline characteristics of patients</p> <p>Blinding and dispensing of insulins was performed by the Pharmacy at the hospital.</p> <p>High rates of nocturnal hypoglycaemia were seen (35% on the first night after transfer to human insulin to 55% on the eighth night after transfer to porcine insulin)</p> <p>Study had 80% power to detect a doubling of asymptomatic hypoglycaemia from 20-40 %; however because frequency of overnight hypoglycaemia was greater than anticipated at 50%, the power to detect an increase of 20% was only 50% - possible type 2 error.</p>
NCC CC ID	1033
Reference / Citation	

Q 27 What types of insulin regimens aid optimal diabetic control in adults with stable type I diabetes?

Author / Title / Reference / Yr	Karlson B, Agardh CD 1994 Influence of intensified insulin regimen on quality of life and metabolic control in insulin-dependent diabetes mellitus. Diabetes Research & Clinical Practice - Supplement 25:111-115
N=	N = 78 Sweden
Research Design	Cohort study
Aim	To assess the efficacy of a changed insulin regimen in diabetes
Population	Type 1 diabetes
Intervention	Treatment mode using 4 injections per day with a pen injector
Comparison	A 3-dose insulin regimen using conventional syringes
Outcome	Metabolic control Perceived distress from diabetes on everyday life and Correspondence between expectations and experiences of treatment
Characteristics	Aged $33.8 \pm 9.6$ years, with a duration of diabetes of $16.6 \pm 9.5$ years and an HbA1c level of $8\% \pm 1.5$ at baseline
Results	Neither the metabolic control nor the BMI or rate of hypoglycaemic episodes changed during the study period. Patients did experience a decreased distress from diabetes, which appeared during the first 3 months and remained unchanged thereafter. Expectations of advantages from the intensified insulin therapy were generally high and were mostly either fulfilled or exceeded by experiences.  Conclusion No positive effects on metabolic control were noted following the change to a more intensified insulin regimen; however, an improvement in quality of life was shown.
Hierarchy of Evidence Grading	Iia
Comments	Existing treatment consisted of a 3-dose insulin regimen using conventional syringes.

	<p>Patients were switched to using an injection pen (Insuject) with at least three primal boluses of short-acting insulin (Velosulin Human) and with one injection of intermediate-acting insulin (NPH - Insulatard Human) by means of conventional syringes and insulin vials at bedtime.</p> <p>When needed, Insulatard Human was also given before breakfast.</p> <p>Experience measures were registered at baseline and after 3 and 12 months, respectively.</p> <p>HbA1c levels were measured every 3 months.</p> <p>A questionnaire covering 13 aspects of treatment was designed; however some centres only started the study with preliminary version, response to which were excluded leaving only 54 out of 73 patients.</p> <p>Questionnaire not validated</p> <p>Repeated measures of analysis of variance was used, t-tests and chi squared test for heterogeneity</p>
NCC CC ID	1035
Reference / Citation	

Q 33 Can combination therapy (oral glucose lowering drugs and insulin) improve blood glucose control compared to insulin therapy alone in adults with Type 1 diabetes?

Author / Title / Reference / Yr	Hollander, P., Pi, S., X, & Coniff, R. F. 1997, "Acarbose in the treatment of type I diabetes. [see comments.]", <i>Diabetes Care</i> , vol. 20, pp. 248-253.
N=	n=264, acarbose =132, placebo =132 USA Multi-centre study, number of sites not stated
Research Design	Randomised controlled trial
Aim	<b>A study to assess the safety and efficacy of acarbose in conjunction with diet and insulin therapy</b>
Operational Definition	Not stated
Population	Type 1 diabetics
Intervention	An intervention of acarbose three times daily (orally) with doses titrated up from 50mg to 300mg at 6 weeks periods for a total of 24 weeks in combination with insulin therapy.
Comparison	Intervention compared to insulin therapy and placebo
Outcome	Outcome measurements were change from baseline in HbA1c, and change in daily insulin requirements, and the number of hypoglycaemic episodes. Secondary outcomes included meal tolerance variables, serum lipid levels, and an analysis of changes in HbA1c and insulin as improving or worsening, as well as safety parameters with a complete physical examination, at 6 weeks to 24 weeks. For each assessment visit a full meal tolerance test was performed, other information gathered included body weight and other vital signs, HbA1c, fasting blood chemistry, HDL cholesterol was measured at start and end of study. All measurements were made at central laboratory, except for plasma glucose values
Characteristics	Age =37yrs, Male =67%, BMI =25 kg/m <sup>2</sup> , duration of diabetes =14.5 yrs, Type 1 diabetes =100%
Results	Treatment with acarbose was associated with a statistically significant reduction in mean HbA1c levels compared with placebo $-0.30 \pm 0.08\%$ decrease Vs $0.18 \pm 0.08\%$ increase ( $p<0.05$ ) There were significant decreases in fasting plasma glucose levels and postprandial glucose levels at 60, 90, and 120 minutes ( $p<0.05$ for all) There were significant reductions in plasma glucose Cmax and glucose rise ( $p<0.05$ for both) There were no significant differences noted between acarbose and placebo groups in daily insulin dose or in the number of hypoglycaemic episodes. For other variables measured including body weight, fasting triglyceride, and total and HDL cholesterol there were no significant differences between the groups 49% of the placebo patients and 84% of the acarbose population reported one or more adverse event while taking study medication ( $p<0.01$ ) these were predominantly gastrointestinal symptoms

	There were significantly greater incidence of abdominal pain, overall pain, diarrhoea, and flatulence, (p<0.05 for all) Treatment was discontinued in 19% of the acarbose group that was significantly greater than the 5% of the placebo group that withdrew.
Hierarchy of Evidence Grading	Ib
Comments	Stabilisation of insulin was achieved during a 6 week run in period. Following randomisation insulin adjustments were made at the discretion of the attending physician based on hypoglycaemic events, changes in therapy were not documented Doses of intervention drug were variable and dose response analysis not stated Compared with the results of the DCCT trial the present study would have expected to reduce the risk of sustained progression of retinopathy by roughly 25% In this trial patients received a variety of different insulin regimens. Despite this variability, acarbose significantly improved glycaemic control in these patients Most of the patients who dropped out of the study did so at the lower dosage level of 50 mg
NCC CC ID	Ref ID: 1651
Reference / Citation	

Q 33 Can combination therapy (oral glucose lowering drugs and insulin) improve blood glucose control compared to insulin therapy alone in adults with Type 1 diabetes?

Author / Title / Reference / Yr	Riccardi, G., Giacco, R., Parillo, M., Turco, S., Rivellese, A. A., Ventura, M. R., Contadini, S., Marra, G., Monteduro, M., Santeusano, F., Brunetti, P., Librenti, M. C., Pontiroli, A. E., Vedani, P., Pozza, G., Bergamini, L., & Bianchi, C. 1999, "Efficacy and safety of acarbose in the treatment of Type 1 diabetes mellitus: a placebo-controlled, double-blind, multicentre study", <i>Diabetic Medicine</i> , vol. 16, pp. 228-232.
N=	n=121, acarbose =61, placebo =60 Italy 3 sites
Research Design	Randomised controlled trial
Aim	A study to evaluate the efficacy and safety of acarbose in patients with type 1 diabetes
Operational Definition	Not stated
Population	Type 1 diabetics
Intervention	An intervention of 50mg acarbose (orally) three times daily for 2 weeks rising to 100mg 3 times daily for 24 weeks with concurrent insulin.
Comparison	Intervention compared with insulin and placebo
Outcome	Outcomes of HbA1c, blood glucose (fasting and postprandial), and other blood and plasma parameters were measured up to the 24 week time point. Safety and tolerability in terms of heart rate, blood pressure, bodyweight, adverse events and withdrawals are studies to the same time. Fasting samples for the evaluation of metabolic and safety parameters were taken after the run-in and at the end of the study. HbA1c was measured using the same high performance liquid chromatography in each centre with variability <10%. Plasma glucose, cholesterol, triglyceride, and HDL cholesterol were measured by standard colorimetric methods
Characteristics	Age =34 yrs, Male =44%. BMI =24.7 kg/m <sup>2</sup> , HbA1c =9.1%, Insulin dose 40 U/day, Type 1 diabetics =100%
Results	The adjusted mean HbA1c values at the end of study were not significantly different between the study groups, 8.67 ± 0.14 % Vs 8.90 ± 0.14 % for acarbose and placebo groups respectively There was a significant decrease in the 2 hrs post prandial plasma glucose level with acarbose 12.23 ± 0.83 mmol/l compared with people on placebo 14.93 ± 0.87 mmol/l (p<0.02) Stratifying people according to carbohydrate intake there was found no significant difference in either HbA1c or postprandial glucose level reduction between those who had a higher (>54%) or lower (<54%) carbohydrate consumption There were no significant differences between groups between acarbose and placebo for the outcomes of daily insulin dose, fasting glycaemia, total cholesterol, or triglycerides.

	<p>HDL cholesterol levels were significantly lower in people on acarbose compared to placebo <math>1.39 \pm 0.03</math> mmol/l Vs <math>1.50 \pm 0.03</math> mmol/l (<math>p &lt; 0.02</math>)</p> <p>75% of the acarbose group reported at least one adverse event compared to 39% of the placebo group, these were mostly mild and confined to the gastrointestinal tract.</p> <p>The total number of hypoglycaemic episodes was similar in the acarbose and placebo groups</p> <p>There were no clinically significant differences in laboratory parameters of bodyweight, vital signs, or ECG measurements in any of the study population</p> <p>One patient withdrew from the placebo group due to a gastrointestinal adverse event, while five patients withdrew from the acarbose group four from gastrointestinal effects</p>
Hierarchy of Evidence Grading	Ib
Comments	<p>Every effort was made to avoid increasing the dose of insulin during the treatment period, however doses could be adjusted if blood glucose levels exceeded 11.1 mmol/l and reduced with hypoglycaemic episodes</p> <p>Type 1 diabetes confirmed by a glucagon test to exclude the possibility of residual insulin secretion (C-peptide <math>&gt; 0.6</math> mmol/l at 6 min)</p> <p>Apart from the effects on postprandial blood glucose, acarbose was not associated with a significant decrease in HbA1c</p> <p>Acarbose may find a role as an adjuvant to diet and insulin as an additional therapeutic option</p>
NCC CC ID	Ref ID: 1654
Reference / Citation	

Q 33 Can combination therapy (oral glucose lowering drugs and insulin) improve blood glucose control compared to insulin therapy alone in adults with Type 1 diabetes?

Author / Title / Reference / Yr	Viviani, G. L., Camogliano, L., Borgoglio, M. G., & et, a. 1987, "Acarbose treatment in insulin-dependent diabetics. A double-blind crossover study", <i>CURR THER RES, CLIN EXP</i> , vol. 42, pp. 1-11.
N=	n=30 in crossover design
Research Design	Randomised controlled trial
Aim	To investigate the effectiveness of acarbose in lowering postprandial hyperglycaemia in an insulin dependant population following an experimental low carbohydrate diet
Operational Definition	Not stated
Population	Type 1 diabetics
Intervention	An intervention of 100 mg acarbose (orally) three times a day with continuing insulin for 4 weeks.
Comparison	Intervention compared to insulin and placebo in a cross over design
Outcome	Outcomes of glucose profiles were determined at baseline and at 2 week intervals. Haematological and biochemical tests and glycosylated haemoglobin determination were evaluated at baseline and at 4 and 8 weeks (at the end of each intervention period). Plasma glucose was determined using glucose-oxidase method. HbA1c was evaluated by isoelectric focusing. Other blood and plasma characteristics were measured using standard procedures
Characteristics	Age =38yrs, Male =50%, Duration of diabetes =12.4 yrs, daily dose of insulin = 30.9 units
Results	Glucose patterns were not significantly different at baseline. While acarbose significantly lowered the plasma glucose values compared to baseline (p<0.05 to p<0.001 depending on time of day of sampling). Glycaemic control worsened in the two groups during placebo treatment (p<0.05 to p<0.001). No comparisons between groups were made No variations were registered in body weight, arterial blood pressure, or routine and haematological parameters at the end of each treatment period With acarbose treatment there was a slightly higher incidence of intestinal disturbances, and hypoglycaemic symptoms were observed (incidence rates stated and up to 17%)
Hierarchy of Evidence Grading	Ib
Comments	Subjects were randomised to treatment with acarbose or placebo first, method not stated The low intake of sugar in the people included in the study with the experimental diet might have contributed to the low incidence of side effects reported.
NCC CC ID	Ref ID: 1652
Reference / Citation	



Q 33 Can combination therapy (oral glucose lowering drugs and insulin) improve blood glucose control compared to insulin therapy alone in adults with Type 1 diabetes?

Author / Title / Reference / Yr	Marena, S., Tagliaferro, V., Cavallero, G., Pagani, A., Montegrosso, G., Bianchi, W., Zaccarini, P., & Pagano, G. 1991, "Double-blind crossover study of acarbose in type 1 diabetic patients", <i>Diabetic Medicine</i> , vol. 8, pp. 674-678.
N=	n=14 in cross over design Italy One site only
Research Design	Randomised controlled trial
Aim	A study to determine efficacy and safety of acarbose in type 1 diabetics, no hypothesis provided
Operational Definition	Definition of Type 1 diabetics according to the USA National Diabetes Data Group criteria
Population	Type 1 diabetics
Intervention	An intervention of 100 acarbose three times daily (orally) at the beginning of each meal with normal insulin therapy for 6 weeks
Comparison	Compared to insulin therapy and placebo
Outcome	Outcome measures of blood glucose levels, HbA1c and cholesterol markers are determined along with frequency of side effects and tolerability to the end of each 6 week intervention period. A complete blood glucose profile (fasting, pre-prandial and postprandial) was determined, with blood glucose measured by reagent strip. Laboratory test were performed on a venous blood sample. HbA1c was evaluated by HPLC, total cholesterol and HDL cholesterol and triglyceride were also measured. Haematology and liver function tests were also performed.
Characteristics	Age =35 yrs, BMI =22.5 kg/m <sup>2</sup> , duration of diabetes =7.9 yrs, HbA1c =9.6 %, fasting plasma C-peptide =0.08 nmol/l
Results	Fasting and mean daily blood glucose levels were decreased with acarbose compared to placebo 7.4 ± 0.5 nmom/l Vs 10.7 ±0.5 nmol/l (p<0.001) and 8.5 ±0.3 nmol/l Vs 9.7 ± 0.3 nmol/l (p<0.002) respectively for each outcome HbA1c was significantly lower when on acarbose (8.3 ± 0.2 %) than on placebo (9.4 ± 0.3 %) (p<0.001) Analysis of plasma triglycerides showed these to be lower on acarbose (1.2 ±0.2 mmol/l) than on placebo (1.4 ±0.2 mmol/l) (p<0.006) There were no significant differences between the groups in any other recorded laboratory measure During the acarbose period two people complained of abdominal discomfort and two developed asymptomatic fasting hypoglycaemia. One case of mild flatulence occurred to a patient on placebo
Hierarchy of Evidence Grading	Ib
Comments	There was no indication of additional interventions being offered to either study group. It is not clear if insulin regimens were altered in any patients during the study prior to withdrawal and artificial B-cell analysis

	<p>Both patients and investigators unaware of the treatment allocation</p> <p>No washout during cross over study, although authors state the effects of acarbose were not dependant on the order of study</p> <p>Adherence to treatment was evaluated by tablet count and was good in both groups</p> <p>Outcomes and study duration are relatively short</p> <p>Additional analysis carried out on insulin requirement after withdrawal not reported here</p>
NCC CC ID	Ref ID: 1653
Reference / Citation	

Q 33 Can combination therapy (oral glucose lowering drugs and insulin) improve blood glucose control compared to insulin therapy alone in adults with Type 1 diabetes?

Author / Title / Reference / Yr	Gums, J. G., Curry Jr, R. W., De Oca, G. M., Skluth, H. A., & Reynolds, L. R. 1992, "Treatment of type I diabetes with a combination of glyburide and insulin", <i>Annals of Pharmacotherapy</i> , vol. 26, no. 6, pp. 757-762.
N=	Per protocol n=40, glyburide =20, placebo =20 USA One site only
Research Design	Randomised controlled trial
Aim	A study to assess the ability of a combination of insulin and an oral hypoglycaemic agent to improve the overall glycaemic control in Type 1 diabetics
Operational Definition	None stated
Population	Type 1 diabetics
Intervention	An intervention of 5mg glyburide (oral) for 12 weeks after a 12 week baseline evaluation period and open label insulin run-in
Comparison	A control of placebo with normal insulin regimen
Outcome	Outcomes blood glucose concentration, daily insulin dose, glycosylated haemoglobin, and plasma lipids were reported to the end of the 12 week study period, and certain measures at 4 week intervals in between. All outcomes are biochemical measurements made using standard methods. Evaluations of HbA1c were performed at weeks 0, 4, 8, and 12. Serum C-peptide concentrations were measured by radioimmunoassay, glycosylated haemoglobin concentrations were measured by column chromatography, fasting plasma glucose measurements were determined by enzymatic assay, Self blood glucose monitoring was conducted using the Glucometer M blood glucose meter, and levels determined from machine memory
Characteristics	Age =34yrs, Male =63%, Duration of diabetes =12 yrs, HbA1c 10.7 %, Fasting blood glucose =10 mmol/l Type 1 diabetics =100%
Results	Fasting blood glucose significantly declined from baseline on glyburide (p=0.0150) by week 4 although no comparison made to placebo group No significant changes in glucose concentrations before supper were noted at any point in either the glyburide or placebo groups No difference was noted between the groups in terms of daily insulin dose, or glycosylated haemoglobin levels at any stage up to 12 weeks Average total cholesterol did not change in either group over the duration of the study
Hierarchy of Evidence Grading	Ib
Comments	There were no differences in baseline demographic characteristics between the two study groups however patients in the

	<p>glyburide group had a longer duration of diabetes than those in the control group (<math>15.60 \pm 1.79</math> yrs Vs <math>8.90 \pm 1.65</math> yrs respectively) (<math>p &lt; 0.01</math>)</p> <p>Both investigators and patients were blind to treatment allocation using identical placebo</p> <p>The insulin dependant nature of the patients was confirmed by a documented lack of endogenous insulin secretion (postprandial C-peptide response <math>&lt; 1.5</math> ng/ml)</p> <p>Study failed to find a consistent trend of improvement in glycaemic control</p> <p>More significant results may have been found with a more homogeneous population or with a higher dose of glyburide.</p> <p>Effects of oral glyburide might not become apparent in the 12 week follow up employed</p>
NCC CC ID	Ref ID: 1689
Reference / Citation	

Q 33 Can combination therapy (oral glucose lowering drugs and insulin) improve blood glucose control compared to insulin therapy alone in adults with Type 1 diabetes?

Author / Title / Reference / Yr	Goldman, J., Tamayo, R. C., Whitehouse, F. W., & Kahkonen, D. M. 1984, "Effect of glyburide on metabolic control and insulin binding in insulin-dependent diabetes mellitus", <i>Diabetes Care</i> , vol. 7 Suppl 1, pp. 106-112.
N=	n=28, glyburide =14, placebo =14 USA One site only
Research Design	Randomised controlled study
Aim	The study set out to assess efficacy of glyburide as dual therapy with insulin to aid metabolic control, but no hypothesis stated
Operational Definition	Not stated
Population	Type I diabetics
Intervention	An intervention of 5mg glyburide (orally) to be taken before breakfast in addition to normal insulin regimen fro 24 weeks
Comparison	Intervention compared to insulin with placebo for a 24 week period
Outcome	Outcomes of C-peptide levels, insulin antibody tiers and plasma glucose concentrations were studied at 6 week intervals to 24 weeks. In addition HbA1c and blood plasma cholesterol parameters were evaluated. Plasma C-peptide levels and insulin antibodies were assayed by previously reported methods. Glycosylated haemoglobin levels were measured by liquid chromatography. Standard automated methods were used to assay plasma glucose, triglycerides, BUN, creatinine, liver function tests and cell blood counts.
Characteristics	Age =48yrs, Male =64%, Duration of diabetes =12.5 yrs, Daily insulin dose =41.5 U, Type 1 diabetes =100%
Results	There were no significant differences in plasma C-peptide levels between the glyburide and placebo groups, nor was there a difference in insulin antibody tiers Plasma glucose concentrations were not significantly different between groups at any time point up to 24 weeks. There was a significantly larger change in HbA1c from baseline between glyburide and placebo groups at 6 weeks (p<0.05) but no differences were found at any other time points There were no significant differences in plasma cholesterol and triglyceride concentrations between study groups Similarly plasma cholesterol lipoprotein fractions did not change significantly change between the groups at ant time point
Hierarchy of Evidence Grading	Ib
Comments	Only a small and transient improvement in diabetes control No details of baseline comparisons makes outcomes hard to evaluate No power calculation or definition of primary endpoints and with small sample size it is unsurprising that few significant

	outcomes were found
NCC CC ID	Ref ID: 306
Reference / Citation	

Q 33 Can combination therapy (oral glucose lowering drugs and insulin) improve blood glucose control compared to insulin therapy alone in adults with Type 1 diabetes?

Author / Title / Reference / Yr	Fallucca, F., Sciuillo, E., & Maldonato, A. 1996, "Combined therapy with insulin and sulfonylurea for the treatment of new-onset insulin-dependent diabetes mellitus", <i>Hormone &amp; Metabolic Research</i> , vol. 28, no. 2, pp. 86-88.
N=	n=22, gliclazide =11, placebo =11 Italy One site only
Research Design	Randomised controlled trial
Aim	No clear definition of intent or hypothesis set
Operational Definition	Not stated
Population	Type 1 diabetics
Intervention	An intervention of gliclazide at 80mg twice daily in addition to insulin as a continuous therapy
Comparison	Intervention compared to insulin and placebo
Outcome	Outcomes measured included changes in insulin dose required, glycosylated haemoglobin, plasma glucose and C peptide levels at fasting and 60 minutes after a standard breakfast are all measured to 18 months. The methods for determining outcomes are reported in a separate publication
Characteristics	Age =19.4 yrs, Male =55%, Type I diabetes =100%, HbA1c =9.0%, Plasma glucose =166 mg/dl
Results	Insulin requirement was similar between groups at baseline but by month 18 it was $15 \pm 2.0$ U/24hrs in the gliclazide group and $51 \pm 2.4$ U/24hrs in the placebo group ( $p < 0.001$ ) Metabolic control (glycosylated haemoglobin and fasting and 1hr post breakfast plasma glucose) was very similar in the two groups with no significant differences found up to 18 months The gliclazide group had a fasting and post breakfast test levels of C peptide as well as delta C peptide at 6, 12, and 18 months about double of those of the placebo group ( $p < 0.01$ to $P < 0.001$ )
Hierarchy of Evidence Grading	Ib
Comments	The trial was single blinded with only patients unaware of the allocation 'juvenile' population (range 12 to 25 yrs) Authors report no harm due to long term use of sulphonylureas has been documented The mechanisms by which the combination therapy may improve the residual B=-cell function has not been investigated Only C-peptide outcomes improved with the therapy

NCC CC ID	Ref ID: 1687
Reference / Citation	

Q 33 Can combination therapy (oral glucose lowering drugs and insulin) improve blood glucose control compared to insulin therapy alone in adults with Type 1 diabetes?

Author / Title / Reference / Yr	Burke, B. J., Hartog, M., & Waterfield, M. R. 1984, "Improved diabetic control in insulin-dependent diabetics treated with insulin and glibenclamide", <i>Acta Endocrinologica.</i> , vol. 107, no. 1, pp. 70-77.
N=	n=20, in cross over design, n=9 C-peptide secretors, n=11 C-peptide non secretors. UK One site only
Research Design	Randomised controlled trial
Aim	A study to determine the effect of adding glibenclamide to standard insulin therapy on indices of diabetic control
Operational Definition	Not stated
Population	Type 1 diabetics
Intervention	An intervention with 15mg glibenclamide daily (oral)
Comparison	Intervention compared to placebo for 3 months with a 1 month washout period
Outcome	Outcomes of mean daily blood glucose, index of glucose variation, HbA1, fasting blood glucose, C-peptide ratio, and responses to oral glucose test are reported as weekly mean scores for the 3 month duration of the therapy. Analysis is stratified according to fasting plasma C-peptide concentration above or below 0.07 nmol/l. Diabetic control was assessed by patients taking their own blood glucose samples using the capillary blood spot filter paper method on the same day of the week, but replicability not stated. An oral 50g glucose tolerance test was performed. Blood glucose was measured by a glucose oxidase method. Plasma C peptide was measured using the method of Heding (1975) The within assay coefficient of variation was 3.8%. Total glycosylated haemoglobin was assessed by the colorimetric method
Characteristics	Age =28yrs, Male =70%, Duration of diabetes =6yrs, HbA1 =8.5 %
Results	For C-peptide secretors mean blood glucose, HbA1, and variation in blood glucose were significantly lower on glibenclamide than on placebo (P=0.02, 0.05, and 0.05 respectively) For non C-peptide secretors none of the outcomes measured showed any significant differences between the two treatment periods A comparison of the C-peptide secretors to non secretors during placebo phase found no significant differences for mean blood glucose, HbA1 and index of variation of blood glucose. The plasma C-peptide response during the oral glucose test was increased and the plasma glucose to C-peptide ratio were reduced significantly in secretors compared to non secretors (p<0.001 for both comparisons).
Hierarchy of Evidence Grading	Ib
Comments	Of 20 patient only 1 (5%) failed to complete the protocol after hypoglycaemic reactions when on glibenclamide

	No analysis of the total study population as a whole with and without glibenclamide Evidence for separating the groups on the basis of their residual endogenous insulin secretion.
NCC CC ID	Ref ID: 1684
Reference / Citation	

## 7.4 Insulin regimen

Q 30 What method of insulin delivery aids optimal diabetic control in adults with stable Type 1 diabetes?

Author / Title / Reference / Yr	NICE. Guidance on the use of continuous subcutaneous insulin infusion for diabetes. 2003.
N=	20 studies identified from the search that compared CSII with MDI: 8 parallel RCTs, 9 randomised crossover studies, and three non-random crossover studies. 14 studies included adults with Type 1 diabetes, 4 studies pregnant women and two covered adolescents. Six further studies (1parallel RCT, 5 random crossover studies) compared analogue and soluble insulin in CSII. UK
Research Design	Systematic review
Aim	To assess efficacy of insulin pump devices
Population	People with insulin treated diabetes (Type 1 or Type 2). Excluding newly diagnosed patients
Intervention	CSII using insulin pumps
Comparison	Optimised MDI ( $\geq 3$ injections/day)
Outcome	Glycated Haemoglobin, insulin dose, weight change, cholesterol levels, patient preference, quality of life, adverse effects
Characteristics	Vary between studies
Results	14 studies compared CSII with MDI treatment of Type 1 diabetes in adults, of which 11 were RCTs and three were non-randomised studies. HbA1c levels were on average 0.6% points lower using CSII compared with MDI therapy. A meta-analysis was carried out on up to eight studies at various time points between 10 weeks and 1 year, demonstrated significant improvements at 4 months (when only RCTs were included) but not 6 months. A meta-analysis of five studies demonstrated that at 4 months patients receiving CSII therapy required on average 12 units/day less insulin compared with the MDI group, however this difference was not maintained in longer-term studies. Body weight showed no significant difference in the eight studies in which it was investigated. Three studies measured lipid levels but the data were insufficient for conclusions to be drawn Patient preference slightly favoured CSII therapy, however, the pumps used in many of the older studies are now obsolete and this may bias the results against pumps. These older studies may have also used obsolete basal insulin injections as a comparator, giving a bias in favour of CSII. A reduction of elimination of episodes of hypoglycaemia due to the use of CSII will tend to raise the average level of glycated

haemoglobin. However, the overall effect of CSII is to lower HbA1c below pre-pump levels. Some of the most recent studies favour CSII. Only one study reported a quality-of-life (QoL) measurement, which showed no significant differences between CSII and MDI.

The Assessment Group found little difference in the frequency of severe hypoglycaemia between the CSII and MDI treatments in most of the RCTs. A large body of observational studies, however, found significant reductions in the number of hypoglycaemic events with CSII treatment. The subset of patients enrolled into observational studies may have had greater difficulty with glycaemic control than patients enrolled in the CSII arm of RCTs

#### Evidence from patients and experts

The Committee considered evidence from CSII users, carers of people with diabetes, patient representative organisations and clinical experts.

The benefit to the person with diabetes as a result of reductions in glycated haemoglobin, insulin dose needed and episodes of hypoglycaemia with CSII therapy was unclear from the evidence available from the RCTs.

Advances in CSII and MDI may reduce the applicability of the earlier studies reviewed in the Assessment Report to the current situation. Also, patients enrolled into the clinical trials may not have been the patient group that would benefit most from CSII.

Patient representative groups and experts reported many examples of major improvements in quality of life with CSII therapy for people with diabetes who were previously unable to satisfactorily control blood glucose levels with MDI therapy, and had had their lives transformed by CSII therapy. Although MDI therapy may reduce glycated haemoglobin to an acceptable level in many people with diabetes, some people find the treatment suboptimal because it does not regulate glycaemia sufficiently to avoid the unpleasant symptoms of major swings in blood glucose levels and the occurrence of disabling hypoglycaemic attacks.

Once transferred to pump therapy, these patients saw a significant improvement in blood glucose levels, experienced less anxiety about hypoglycaemic episodes and found a great improvement in their quality of life because of the increased flexibility of their lifestyle.

#### Evidence from HTA

Mean improvement in glycated Haemoglobin = 0.6% with CSII c.f. MDI in short term (-0.64, 95%CI: -1.28, 0.01) and longer term (-0.61, 95%CI: -1.29, 0.07) studies.

Short term studies show a reduction in insulin dose of ~ 12 units (-11.60, 95%CI: -18.16, -5.63). This difference was less in long term studies.

Body weight did not differ significantly with CSII or MDI

Two studies reporting data on cholesterol levels found no significant difference between the treatments

Patient preference differed little between treatments. However, technological advances have significantly changed the ease of use of insulin pumps, therefore these findings are probably not relevant to the present day devices.

Hypoglycaemic findings did not differ significantly between treatments in most RCTs, but some found fewer with CSII.

Much greater reductions in the number of severe hypoglycaemic episodes were seen in some observational studies; however, these studies tend to select patients with particular problems, which may have influenced the results

	<p>Conclusions</p> <p>The Committee's view was that the proportion of people with Type 1 diabetes who would be appropriate for, and would take up, insulin pump therapy, would be of the order of 1% of the total. For this small group of people for whom CSII therapy could make a large difference, the following conditions would have to apply for the therapy to be considered cost effective. The diabetes would have to be poorly controlled, as measured by achievement of accepted levels of HbA1c, using MDI therapy (including a sufficiently long use of insulin glargine, where appropriate, to determine its effectiveness) CSII therapy should provide significantly better control than MDI therapy (with the use of insulin glargine, where appropriate) and prevent the occurrence of disabling hypoglycaemic events.</p>
Hierarchy of Evidence Grading	NICE
Comments	<ul style="list-style-type: none"> <li>• Titles and summaries assessed for inclusion were checked by two reviewers. Full texts of selected studies assessed for inclusion by one reviewer and checked by a second. Differences in opinion were resolved through discussion.</li> <li>• Quality of studies assessed in accordance with CRD Report 4.</li> <li>• Quality of reporting and methodology of the studies, many of which dated from many years ago was often poor by today's standards. Only 2 studies had adequate randomisation and none reported adequate allocation concealment.</li> <li>• Randomisation and allocation concealment were adequate in the parallel RCT comparing analogue and soluble insulin in CSII, but not reported in the crossover studies.</li> </ul> <p>Report assumes that people with Type 1 diabetes would normally try twice daily injections, then MDI, and finally progress to CSII. However, increasingly patients may start on MDI from diagnosis. CSII would not be used for newly diagnosed people.</p>
Trials included	
NCC CC ID	1979
Reference / Citation	

Q 30 What method of insulin delivery aids optimal diabetic control in adults with stable Type 1 diabetes?

Author / Title / Reference / Yr	Murray DP, Keenan P, Gayer E, Salmon P, Tomkin GH, Drury MI, O’Sullivan 1988 A randomised trial of the efficacy and acceptability of a pen injector. Diabetic Medicine 5:750—754															
N=	78: 41 allocated to multiple injections with pen injector, 37 allocated to conventional treatment Republic of Ireland															
Research Design	Randomised controlled Trial															
Aim	To test the utility of a pen injector for insulin delivery															
Population	Type 1 diabetes															
Intervention	Multiple injection regimen, using three times daily human soluble insulin (Actrapid) from a pen injector, injected 5–30 min before meals, and a single injection of human ultralente insulin (Ultratard) before bed;															
Comparison	Conventional treatment with twice daily syringe injection regimen.															
Outcome	Blood glucose control and hypoglycaemic episodes. Patient acceptability and satisfaction was measured in patients on the pen injector regimen.															
Characteristics	Age (years): pen regimen = 31.1±12.4; controls = 33.3±9.9; Sex (M/F): pen regimen = 17/24; controls = 17/20 Duration of diabetes (years): pen regimen = 9.7±5.7; controls = 10.4±6.9 Weight (kg): pen regimen = 75.9±8.0; controls = 65.6±9.6 (pless than0.05) Total dose (U/day): pen regimen = 52.0±20.0; controls = 48.9±20.9; GHb (%): pen regimen = 11.3±2.6; controls = 11.1±2.5															
Results	Adverse effects: One patient experienced burning sensation at the site of injection with ultralente. This was resolved by changing injection site to the abdomen. Blood glucose control: No significant difference was seen in blood glucose control between the two treatment groups. GHb and incidence of hypoglycaemic attacks per patient in the last 8 weeks of the study: <table border="1" data-bbox="524 1177 1572 1370"> <thead> <tr> <th></th> <th>Pen regimen</th> <th>Syringe regimen</th> </tr> </thead> <tbody> <tr> <td>GHb (%)</td> <td>11.2±2.0</td> <td>10.9±2.0</td> </tr> <tr> <td>Mild hypoglycaemia</td> <td>0.48 (0–11)</td> <td>0.47 (0–6)</td> </tr> <tr> <td>Moderate hypoglycaemia</td> <td>0.80 (0–6)</td> <td>0.80 (0–4)</td> </tr> <tr> <td>Severe hypoglycaemia</td> <td>0.00 (0–0)</td> <td>0.03 (0–1)</td> </tr> </tbody> </table>		Pen regimen	Syringe regimen	GHb (%)	11.2±2.0	10.9±2.0	Mild hypoglycaemia	0.48 (0–11)	0.47 (0–6)	Moderate hypoglycaemia	0.80 (0–6)	0.80 (0–4)	Severe hypoglycaemia	0.00 (0–0)	0.03 (0–1)
	Pen regimen	Syringe regimen														
GHb (%)	11.2±2.0	10.9±2.0														
Mild hypoglycaemia	0.48 (0–11)	0.47 (0–6)														
Moderate hypoglycaemia	0.80 (0–6)	0.80 (0–4)														
Severe hypoglycaemia	0.00 (0–0)	0.03 (0–1)														

	<p>Severe hypoglycaemic episodes over the entire study period: pen regimen = 7; controls = 6  No episode of ketoacidosis occurred in the patients receiving the pen regimen.</p> <p>Insulin dose  Actual dose of insulin delivered in the pen injector regimen corresponded to that predicated by the Holman and Turner algorithm.</p> <p>Patient assessment  The majority of pen injector treated patients either omitted or altered the timing of snacks or meals.  Patients expressed a high degree of satisfaction with the pen injector, and the effect this regimen had on their diabetes.  95% (39/41) pen injector patients expressed a preference for the multiple injection regimen for future management of their diabetes</p>
Hierarchy of Evidence Grading	Ib
Comments	<p>All patients moderately well controlled, performed regular home blood glucose monitoring.  All patients were using a twice-daily regiment of fast and intermediate acting insulin, administered with disposable syringe.  Patients were randomised centrally in blocks of 6 to ensure an equal proportion of pen and syringe treated patients.  Following randomisation patients were followed for 20 weeks with regular blood glucose and GHb profiles performed at a central laboratory.  Doses of human ultralente and human soluble insulin were calculated according to the guidelines published by Holman and Turner.  After 6 months patients receiving the pen injector regimen completed a questionnaire designed to assess the acceptability of the multiple injection regimen.  The two groups were matched for age, sex duration of diabetes, total dose of insulin and GHb.  Patients randomised to MDI with a pen injector were heavier than those on conventional treatment.  Insulin dosage was usually adjusted by the attending physician, and patients with good understanding of diabetes were encouraged to adjust their own insulin dosage.  Hypoglycaemic episodes classified as: Grade 1 (mild): Mild symptoms before meals not requiring extra carbohydrate.  Grade 2 (moderate): sweating, dizziness or blurred vision responding rapidly to food.  Grade 3 (severe): reduction in conscious level requiring assistance from a 2<sup>nd</sup> person.  No details given of how this data was collected.  Patient satisfaction only measured post-hoc and only in the treatment group.  Patients underwent a 6-week run-in period on twice-daily conventional regimen to optimise control. Patients performed blood glucose control profiles at home every 2 weeks.  During the 20-week follow-up, patients on the pen injector regimen were advised to adjust the size and timing of their meals and snacks provided they made appropriate adjustments to insulin doses. It was also noted that on occasion it was possible for them to miss a meal altogether, provided the relevant pen injection was also admitted. This advice was only given to patients who were considered to have good control, and only in 2/3 participating sites.  Bias is evident in favour of pen injection because MDI is known to improve glycaemic control, even though it did not appear</p>

	<p>to in this study. Many factors were different between the treatment and control groups, leading to difficulties in proving clinical significance of the results. Authors state that they are investigating the efficacy and acceptability of a pen injector. However, it is not only the delivery method that is distinct in this study, the insulin regimens are significantly different. Groups were not treated equally throughout the study.</p> <p>No blinding of patients or investigators or concealment of allocation, some patients on pen injector regimen received additional education from physicians about dose adjustment not given to others in the same group or any members of the control group. This is also likely to impact on the outcome of the trial.</p> <p>No power analysis given, conclusions drawn do not match study executed.</p> <p>The results are difficult to interpret clinically, because of the differences between the treatments being compared.</p> <p>Questionnaire is not performed at study outset to gauge baseline satisfaction.</p> <p>Questionnaire is not performed in patients receiving the conventional regimen, therefore results are uncontrolled, and the validity of this exercise is therefore limited.</p> <p>Questionnaire is not validated and no description is given of the development process or any piloting.</p> <p>Two aims of this study are:</p> <p>To assess the effects of two different insulin regimens on metabolic control</p> <p>To assess the benefits and acceptability of one pen injector.</p> <p>Details not provided of the number of patients who were advised that they were allowed to alter their diet (and potentially miss some meals altogether) provided they altered their insulin regimen accordingly.</p> <p>Patient details not separated by site.</p> <p>Questionnaire is based on use of the pen injector, however, the authors conclude that the preference stated by patients for future management of their diabetes is for multiple injection regimen rather than specifically by pen injector. Insufficient distinction is made between these two factors.</p> <p>Authors conclude that the majority of patients on the pen injector were highly satisfied with the effect of this regimen on their diabetes, however, this regimen neither improved glycaemic control or hypoglycaemic episodes, so this cannot be clinically demonstrated in this study.</p>
NCC CC ID	1085
Reference / Citation	

Q 30 What method of insulin delivery aids optimal diabetic control in adults with stable Type 1 diabetes?

Author / Title / Reference / Yr	Canadian Coordinating Office for Health Technology Assessment (CCOHTA) 2001 Inhaled Insulin for the Treatment of Diabetes Mellitus. Issues In Emerging Health Technologies 18
N=	Eight recently published open label, randomised controlled trials (six in abstract form only), of three month duration. Four studies related to type 1 diabetes Canada
Research Design	Systematic review
Aim	A review of a novel form of insulin delivery
Population	People with type 1 and type 2 diabetes
Intervention	Insulin delivered through inhalation into the lungs
Comparison	Conventional treatment
Outcome	Glycaemic control through measures of HbA1c Lung function and occurrence of hypoglycaemia (severe, mild, moderate)
Characteristics	Vary between studies No reasons given for selection of studies, or quality of studies. Majority of studies considered are unpublished manufacturers abstracts and should be treated with caution until full papers and results are published. All studies included in this review excluded persons with diabetes who smoke, have asthma or have COPD
Results	Total combined sample of between 55 and 91 patients treated with inhaled insulin both the safety study (n=20) and the studies on efficacy (n=35 and 36) reported that inhaled insulin is comparable to sc. Insulin in terms of glycaemic control with no apparent affect on lung function The patient satisfaction study considered improvements in a quality of life instrument designed by the authors. Results showed greater improvements in quality of life in the inhaled insulin group. Adverse effects Of four studies that assessed lung function at baseline and at study end, non reported any change in pulmonary function after treatment with inhaled insulin. Lung function data were reported in one study and values did not differ between the inhaled and sc. groups. Reports of severe, moderate or mild hypoglycaemia did not differ between the patients taking insulin via sc. injection and those taking insulin via inhalation. Insulin delivery via inhalation, as an alternative to administration by injection, is under development.

	<p>The available evidence comparing subcutaneous (sc) insulin with inhaled insulin for persons with type 1 and type 2 diabetes , shows similar glycosylated haemoglobin HbA1c) levels after three months of treatment.</p> <p>Clinical trials suggest that insulin delivered by inhalation has a quicker onset of action relative to regular insulin. Insulin can thus be taken just prior to a meal rather than the 30 minutes prior to eating as required with s.c. injections of regular insulin.</p> <p>No changes in pulmonary function were noted in the studies, however data is limited to use for three months. Pulmonary thrombosis has subsequently been reported in one patient out of 1000, using Exubera and the Inhale Therapeutic Systems device.</p>
Hierarchy of Evidence Grading	Ia
Comments	<p>For delivery by inhalation the drug particle must be small enough to get into the lungs (1-3 mm)<sup>3</sup> but large enough not to be exhaled. Delivery must ensure that the drug reaches the lungs rather than being deposited in the mouth and throat.</p> <p>Two devices are currently being tested on patients with type 1 diabetes:</p> <p>A device has been developed that uses compressed air to create a cloud of drug for inhalation and uses the powered form of insulin, Exubera.</p> <p>A second, hand-held electronic, device is being developed to create an aerosol from liquid insulin.</p> <p>Of the four studies relating to type 1 diabetes, one reported on safety and reproducibility, one on patient satisfaction and the other two reported on efficacy</p> <p>Patients in the inhaled insulin group took insulin 3x daily pre-meal via inhalation, and once daily s.c. at bedtime</p> <p>Authors state that health economic data is not yet available for this technology</p> <p>It is unclear whether the eighth study included in this review is a complete report of one of the abstracts or a unique study.</p> <p>Authors state that: as most of these reports are published only in abstract form, there is very limited information on study methodology. Certain important details are not fully reported, such as specific dose, ease of use of the devices of any training required.</p> <p>Inhaled insulin delivery for patients with respiratory complications and diabetes has not been addressed by any studies to date.</p>
Trials included	See original article
NCC CC ID	1995
Reference / Citation	

Q 30 What method of insulin delivery aids optimal diabetic control in adults with stable Type 1 diabetes?

Author / Title / Reference / Yr	Skyler JS, Cefalu WT, Kourides IA, Landschulz WH, Balagtas CC, Cheng S-L, Gelfand R 2001 Efficacy of inhaled human insulin in type 1 diabetes mellitus: a randomised proof-of-concept study. <i>The Lancet</i> 357:331–335
N=	73 : 35 in inhaled group and 37 in s.c. group Multi-centre study at 10 centres in the USA
Research Design	Randomised Controlled Trial
Aim	To study the effect of inhaled insulin in people with diabetes
Population	IDDM patients, aged 18–55 years; on a stable insulin administration schedule (of $\geq 2$ months) of 2–3 injections/day. HbA1c 7.0–11.9%; fasting C-peptide concentrations $\leq 0.2$ nmol/L; weight 80–100% of ideal; non-smokers ( $\geq 6$ months); normal chest radiograph; normal pulmonary-function; normal electrocardiogram with normal sinus rhythm at 50–100 beat/min. Patients were willing to monitor blood glucose at home four times a day and comply with study protocol. Patients with peripheral neuropathy, mild nephropathy, or retinopathy were not excluded.
Intervention	preprandial inhaled insulin + bedtime s.c. ultralente insulin injection (s.c. human ultralente administered in the thigh or buttocks to maximise duration of action) inhaled insulin was taken immediately before meals using the dry-powder insulin formulation and aerosol delivery system—insulin is packaged in individual blisters containing 1 mg or 3 mg of recombinant human insulin in 5 mg of powder composed of mannitol, glycine, and sodium citrate. One inhalation of each strength delivers 3 and 9 units of s.c. injected insulin respectively
Comparison	usual insulin regimen (2/3 s.c. injections/day)
Outcome	Primary outcome: change in HbA1c Secondary outcomes: fasting and postprandial glucose response to a mixed meal, hypoglycaemia frequency and severity, pulmonary function and patient satisfaction. Adverse effects were recorded by the investigators. HbA1c was measured before randomisation (at weeks –1 and 0) and at weeks 4, 8, and 12, by HPLC. Glucose concentrations in plasma and insulin and C-peptide concentrations were measured in a central laboratory. Patients were instructed to check blood glucose in the event of hypoglycaemia. They recorded hypoglycaemic episodes on their weekly glucose-monitoring worksheets, from which the reported data were tabulated. Pulmonary-function tests were done by a pulmonary function laboratory with American Thoracic Society certified methods. At baseline and at the end of the study, patients completed a 15-item satisfaction questionnaire. Patients indicated their level of agreement with each statement using a 5-point Likert scale

	(strongly disagree to strongly agree).																																						
Characteristics	Not recorded																																						
Results	<p>HbA1c concentrations</p> <p>Response to treatment during the course of the study did not differ between the two treatment groups.</p> <p>Mean baseline values (SD): inhaled insulin = 8.5% (1.1); s.c. insulin = 8.5 (1.1)</p> <p>HbA1c at 12 weeks (SD): inhaled insulin = 7.9% (1.0); s.c. insulin = 7.7 (0.9)</p> <p>No significant differences were seen between the 12-week change in HbA1c for the inhaled group and the s.c. group (adjusted difference = 0.2% (95% CI: -0.2 to 0.5))</p> <p>Meal glucose profiles</p> <p>These were not significantly different between the two groups baseline or throughout the study.</p> <p>Mean daily insulin dose (SD) after 12 weeks treatment</p> <p>Inhaled insulin = 12.2 mg (4.9) (equivalent to 36.6 (14.7)U of s.c. insulin) and 24.8 units (9.3) long-acting s.c. insulin</p> <p>s.c. insulin = 15.9 U (9.8) short acting insulin and 31.0 (13.2) long-acting insulin</p> <p>Hypoglycaemia</p> <p>No significant difference was seen in the occurrence or severity of hypoglycaemia between the two groups:</p> <p>No of people experiencing mild hypoglycaemia: Inhaled insulin = 33 (94.3%); s.c. insulin = 31 (83.8%)</p> <p>No of people experiencing severe hypoglycaemia: inhaled insulin = 5 (14.3%); s.c. insulin = 5 (13.5%)</p> <p>No of people episodes of mild hypoglycaemia: inhaled insulin = 550; s.c. insulin = 547</p> <p>No of people episodes of severe hypoglycaemia: inhaled insulin = 8; s.c. insulin = 10</p> <p>Body weight</p> <p>Body weight did not change significantly from baseline in overall satisfaction with inhaled insulin</p> <p>Pulmonary function:</p> <p>Pulmonary function was stable over the study period, results of the pulmonary function tests were not significantly different between the two treatment groups.</p> <table border="1"> <thead> <tr> <th></th> <th colspan="2">Inhaled insulin (n=35)</th> <th colspan="2">S.c. insulin (n=37)</th> </tr> <tr> <th></th> <th>Mean (SD) baseline value</th> <th>Change from baseline at week 12</th> <th>Mean (SD) baseline value</th> <th>Change from baseline at week 12</th> </tr> </thead> <tbody> <tr> <td colspan="5"><b>Spirometry</b></td> </tr> <tr> <td>FEV<sub>1</sub> (L)</td> <td>3.58 (0.79)</td> <td>-2.17 (5.23%)</td> <td>3.37 (0.73%)</td> <td>-1.02 (6.77%)</td> </tr> <tr> <td>FVC (L)</td> <td>4.43 (1.10)</td> <td>-1.68 (4.77%)</td> <td>4.27 (0.98%)</td> <td>-1.50 (8.04%)</td> </tr> <tr> <td>FEF<sub>25-75%</sub> (L/s)</td> <td>3.60 (0.89)</td> <td>-1.22 (18.11%)</td> <td>3.26 (0.97%)</td> <td>2.65 (15.91%)</td> </tr> <tr> <td>PEFR (L/s)</td> <td>8.08 (2.02)</td> <td>2.41 (18.00%)</td> <td>7.87 (2.20%)</td> <td>1.21 (16.32%)</td> </tr> </tbody> </table>					Inhaled insulin (n=35)		S.c. insulin (n=37)			Mean (SD) baseline value	Change from baseline at week 12	Mean (SD) baseline value	Change from baseline at week 12	<b>Spirometry</b>					FEV <sub>1</sub> (L)	3.58 (0.79)	-2.17 (5.23%)	3.37 (0.73%)	-1.02 (6.77%)	FVC (L)	4.43 (1.10)	-1.68 (4.77%)	4.27 (0.98%)	-1.50 (8.04%)	FEF <sub>25-75%</sub> (L/s)	3.60 (0.89)	-1.22 (18.11%)	3.26 (0.97%)	2.65 (15.91%)	PEFR (L/s)	8.08 (2.02)	2.41 (18.00%)	7.87 (2.20%)	1.21 (16.32%)
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	TLC	5.83 (1.55)	1.35 (8.36%)	5.87 (1.24%)	1.10 (9.49%)
	RV	1.46 (0.56)	8.65 (37.43%)	1.61 (0.52%)	8.70 (43.62%)
	VC	4.37 (1.13)	0.41 (8.26%)	4.24 (0.92%)	0.41 (8.26%)
	Diffusion capacity (mL/min per mm Hg)	26.50 (7.69)	-5.78 (11.43%)	27.17 (7.36%)	-7.71 (14.95%)
	Oxygen saturation (%)	97.85 (1.46)	-0.30 (1.44%)	97.76 (1.57%)	0.04 (1.46%)
FVC=forced vital capacity, FEV <sub>1</sub> =forced expiratory volume in 1 s, FEV <sub>25-75%</sub> =forced expiratory flow during middle half of FVC, PEF <sub>R</sub> =peak expiratory flow rate, TLC=total lung capacity, FRC=functional residual capacity, RV=residual volume, VC=vital capacity.					
<p>Satisfaction</p> <p>The estimated mean percentage change from baseline in overall satisfaction with inhaled insulin (35%) was greater than with s.c. insulin (11%; p = 0.01). In particular, six individual items showed significant evidence (p less than 0.05) that inhaled insulin resulted in more improvement from baseline than s.c. insulin therapy.</p> <p>Specifically, compared with s.c. insulin therapy, inhaled insulin was rated higher with regard to ease of administration, comfort, convenience, time with dosing, flexibility of eating schedule and ease of taking insulin many times a day. Patients on s.c. insulin therapy, however, were less self-conscious than those in inhaled insulin about taking insulin away from home. 82% of patients already on inhaled insulin elected to continue on a long-term extension with inhaled insulin. The most common reason for declining to do so involved the rigour of the testing protocol, particularly home glucose monitoring and frequency of clinic visits</p>					
Hierarchy of Evidence Grading	Ib				
Comments	<p>12 weeks trial</p> <p>Physical examinations and laboratory tests were done throughout the study.</p> <p>Patients were randomly assigned one of the two treatments using a computer-generated randomisation scheme.</p> <p>Randomisation was stratified on the basis of patients HbA<sub>1c</sub> (greater than 8.5% vs. ≤8.5%)</p> <p>Randomisation was stratified according to HbA<sub>1c</sub> to ensure that similarity at entry between the groups.</p> <p>61% of patients were taking insulin injections 3 times before entering the study (generally human soluble insulin before two or three meals, and human isophane insulin before breakfast and at bedtime).</p> <p>Patients on inhaled insulin were permitted to take additional insulin if home blood-glucose test results were high.</p> <p>Baseline characteristics of two groups were similar at the start of the trial</p>				

	<p>Participants monitored blood glucose 4 x daily (preceding insulin administration) adjusting insulin doses weekly to achieve preprandial glucose targets of 5.6 –8.9 mmol/L, however, the prescribed frequency of dosing was not changed during the course of the study.</p> <p>12 week parallel trial consisted of a screening visit, a 4-week baseline lead-in phase and a 12 week randomised treatment phase</p> <p>In the 4 weeks prior to randomisation, patients met with a dietitian and were asked to maintain a diet containing <math>\leq 30\%</math> fat for the duration of the study.</p> <p>Instruction was given in diet maintenance and blood glucose monitoring at the study outset.</p> <p>At the end of the baseline period, patients were admitted to the hospital or research unit for a 2 day period of instruction and dosing experience with preprandial inhaled insulin.</p> <p>This feasibility study shows no difference between the two forms of insulin.</p> <p>Patients are very rigorously selected and inclusion/exclusion criteria's very tight, therefore more studies are needed to validate these findings before this result can be deemed clinically important.</p> <p>Blinding not possible leading to possibility of bias.</p> <p>Authors state that analysis was performed on an intention to treat principle.</p> <p>Power analysis calculated that a sample size of 35 per group was required to provide 80% power to ensure that the upper limit of the two-sided 95% CI for the difference in change from baseline HbA1c between treatment groups would not exceed 1.0%.</p>
NCC CC ID	121
Reference / Citation	

Q 30 What method of insulin delivery aids optimal diabetic control in adults with stable Type 1 diabetes?

Author / Title / Reference / Yr	Gerber RA, Cappelleri JC, Kourides IA, Gelfand RA 2001 Treatment satisfaction with inhaled insulin in patients with type 1 diabetes. <i>Diabetes Care</i> 24:1556–1559
N=	73: 35 in inhaled group and 37 in s.c. group Multi-centre study at 10 centres in the USA
Research Design	Randomised Controlled Trial
Aim	To study the effect of inhaled insulin in people with diabetes
Population	IDDM patients, aged 18–55 years; on a stable insulin administration schedule (of $\geq 2$ months) of 2–3 injections/day. HbA1c 7.0–11.9%; fasting C-peptide concentrations $\leq 0.2$ nmol/L; weight 80–100% of ideal; non-smokers ( $\geq 6$ months); normal chest radiograph; normal pulmonary-function; normal electrocardiogram with normal sinus rhythm at 50–100 beat/min. Patients were willing to monitor blood glucose at home four times a day and comply with study protocol. Patients with peripheral neuropathy, mild nephropathy, or retinopathy were not excluded.
Intervention	preprandial inhaled insulin + bedtime s.c. ultralente insulin injection (s.c. human ultralente administered in the thigh or buttocks to maximise duration of action) inhaled insulin was taken immediately before meals using the dry-powder insulin formulation and aerosol delivery system—insulin is packaged in individual blisters containing 1 mg or 3 mg of recombinant human insulin in 5 mg of powder composed of mannitol, glycine, and sodium citrate. One inhalation of each strength delivers 3 and 9 units of s.c. injected insulin respectively
Comparison	usual insulin regimen (2/3 s.c. injections/day)
Outcome	Patient satisfaction measured with a 15-item self administered patient satisfaction with insulin therapy questionnaire Patients completed a 15-item self-administered satisfaction questionnaire, The Patient Satisfaction with Insulin Therapy (PSIT) Questionnaire, at baseline and week 12. The PSIT questionnaire underwent rigorous empirical development, and had an interpretable and rich factor structure. This questionnaire measures global (overall) satisfaction and two domains (subscales): convenience/ease of use and social comfort. Responses to each item consist of a five-point likert scale ranging from “strongly agree” to “strongly disagree”. Patient satisfaction scores for overall satisfaction, convenience/ease of use and social comfort were calculate. Responses to each item were analysed so that a higher item score indicated more satisfaction.

	All 15-item scores were summed equally to arrive at the overall satisfaction score (range 15–75)
Characteristics	Not recorded
Results	<p>Overall satisfaction</p> <p>Mean percentage improvement (as reported in Skyler et al): mean percentage improvement from baseline in global (overall) satisfaction with inhaled insulin (35.1%, 95% CI 18.0–52.2) was considerably greater (<i>P</i> less than 0.01) than with subcutaneous insulin (10.6%, 4.7–16.5). Therefore, inhaled insulin resulted in 24.5% (6.6–42.5) more improvement in overall satisfaction than subcutaneous insulin. The mean percentage improvement within each treatment group was statistically significant from zero (<i>P</i> less than 0.01).</p> <p>Convenience/ease of use</p> <p>The mean percentage improvement in convenience/ease of use was substantially greater with inhaled insulin (41.3%, 22.9–59.6) than with subcutaneous insulin (11.2%, 4.1–18.3; <i>P</i> less than 0.01). Therefore, inhaled insulin resulted in 30.1% (10.7–49.5) more improvement in convenience/ease of use than subcutaneous insulin. The mean percentage improvement within each treatment group was statistically significant from zero (<i>P</i> less than 0.01).</p> <p>Social comfort</p> <p>The mean percentage improvement in social comfort with inhaled insulin (28.0%, 8.0–47.9) was higher than subcutaneous insulin (18.0%, 2.9–33.0) but not statistically significant from it (95% CI -14.6 to 34.6%; <i>P</i> = 0.42). The mean percentage improvement within each treatment group was statistically significant from zero (inhaled insulin, <i>P</i> less than 0.01; subcutaneous insulin, <i>P</i> = 0.02).</p> <p>Preference</p> <p>Subjects in the inhaled insulin group gave significantly more agreement than those in the subcutaneous group (Wilcoxon's rank-sum test; <i>P</i> less than 0.01) on the 5-point Likert scale item "I would like to continue to take insulin the way I took it during the study" asked at the end of the study.</p>
Hierarchy of Evidence Grading	Ib
Comments	<p>Questionnaire is self administered</p> <p>No details given of patient instruction on completing questionnaire.</p> <p>Although development of questionnaire is described as rigorous, and the development process has been published elsewhere, it has not been previously validated and therefore may be biased to answering the specific question set here.</p> <p>Also bias due to no mention of blinding of participants and investigators.</p> <p>Pearson correlations (<i>r</i>) and analysis of covariance were used to assess the association between overall satisfaction and 12-week change in HbA1c after controlling for treatment regimen.</p> <p>Scores on convenience/ease of use (10 items, range 10–50) and social comfort (5 items, range 5–25) were each used to calculate a percentage change with satisfaction from baseline for each subject. Within group percent change was evaluated with a student t test.</p> <p>No improvement is seen in social comfort, authors conclude that this does not necessarily imply that there is no effect on social comfort. A type II error is a possibility. More likely, a larger sample size would have increased the sensitivity to detect an effect on social comfort.</p>

	<p>Some improvements in patient satisfaction were also observed in subjects in the s.c. insulin group, even though they continued their usual insulin regimen. This could be due to the involvement in a controlled trial and the benefits of monitoring care (for example, clinicians and coordinators attending to subjects at least on a weekly basis.).</p> <p>There is also a link between satisfaction and improved glycaemic control. This relationship is expected to be bi-directional, and this study was not designed to measure this causal relationship.</p> <p>The results of this trial suggest that inhaled insulin regimen is preferred and provides substantially more improvement in patient satisfaction than a conventional s.c. insulin regimen. In patients with Type 1 diabetes, administration of rapid-onset inhaled insulin may offer the first practical non-invasive alternative to regular insulin injections. Improved satisfaction may increase willingness of patients to initiate and comply with insulin therapy and therefore achieve better glycaemic control.</p>
NCC CC ID	1086
Reference / Citation	

Q 30 What method of insulin delivery aids optimal diabetic control in adults with stable Type 1 diabetes?

Author / Title / Reference / Yr	Bantle JP, Neal L, Frankamp LM 1993 Effects of the anatomical region used for insulin injections on glycaemic in type 1 diabetes subjects. Diabetes care 16:1592–1597
N=	22
Research Design	Randomised Controlled Trial
Aim	Hypothesis: s.c. injection of insulin in the abdomen would produce a greater reduction in plasma glucose than injection of the same amount of insulin in the thigh
Population	Type 1 diabetic subjects
Intervention	Regular insulin injected s.c. in the abdomen on one morning
Comparison	Injection in an anterior thigh on another morning
Outcome	Glycaemic control measured by plasma glucose and serum free insulin Patients studied for 2 days on two occasions. Test doses of insulin regular insulin: 0.11–0.29 U/kg of body weight (mean: 0.19 U/kg) Blood samples for measurement of plasma glucose and serum free insulin were obtained immediately before insulin injections and after the injections at 1 hour, and then seven subsequent half hourly intervals. All subjects ate breakfast ½ hour following injection. NPH and regular insulins were given as a single injection. Two day testing was repeated on the following two days (3 and 4) and blood samples were taken immediately before and at 1 hour and ten subsequent half hourly intervals following injection
Characteristics	Sex (M/F): 9/13; Age: 29 years (range: 20–44); Duration of diabetes: 16 years (range: 2–28); Mean HbA1c: 8.5% (range 6.3–12.7)
Results	Preinjection, fasting plasma glucose values were comparable between the different groups. Injections with regular insulin Plasma glucose levels After injections of regular insulin in the abdomen, postprandial plasma glucose values were significantly lower at multiple time points after injections of regular insulin in the thigh. The plasma glucose area after an injection of regular insulin in the abdomen was 20% lower than the plasma glucose area after injections of regular insulin in the thigh (p=0.003) Following injections of regular insulin in the abdomen, peak plasma glucose was 18% (3.3 mM) lower (p=0.001) and peak

	<p>increment in plasma glucose was 29% (3.1 mM) lower (pless than0.0010) than following thigh injections</p> <p>Serum free insulin</p> <p>Mean fasting serum free insulin values were similar at baseline in the two groups</p> <p>Postprandial serum free insulin values were significantly higher at the first four time points following injections in the abdomen compared to injections administered in the thigh.</p> <p>Serum free insulin area was 30% higher after injections in the abdomen compared to those administered in the thigh (P=0.005).</p> <p>Peak serum free insulin was 28% (58 pM) higher and peak increment in serum free insulin was 38% (54 pM) higher after injections in the abdomen compared to those administered in the thigh (P=0.005 and P=0.017, respectively).</p> <p>Injections with NPH and regular insulin</p> <p>Plasma glucose levels</p> <p>Plasma glucose values lower between the 1 hour and 7 hours following abdominal injections, compared with injections in the thigh, however, only the difference at 1 hour was statistically significant</p> <p>Morning plasma glucose area was 11% lower, morning peak plasma glucose was 12% lower (2.5 pM) and morning peak increment in plasma glucose was 18% (2.5 pM) lower after abdomen injections compared to injections administered in the thigh (p=0.068, p=0.030 and p=0.008, respectively)</p> <p>Afternoon values were not significantly different.</p> <p>Serum free insulin</p> <p>No significant differences were seen in serum free insulin values at any of the time points after abdominal and thigh injections of NPH and regular insulins</p>
Hierarchy of Evidence Grading	Ib
Comments	<p>21 patients were treated with NPH and regular insulins in combination; 1 treated with NPH insulin alone. 15 patients were receiving animal insulin and 7 subjects animal insulins. Number of daily injections: one injection, n=1; two injections, n=13; three injections, n=7; four injections, n=1; 17 subjects showed evidence of <math>\geq 1</math> microvascular complications</p> <p>All injections of insulin were given by clinical research centre nurses. Subjects were given an individualised meal plan.</p> <p>Subjects experiencing symptomatic hypoglycaemia were treated with 20 g oral glucose.</p> <p>No details given of selection of patients</p> <p>Length of study only short.</p> <p>No power analysis included in study. Authors conclude that the subject sample size of 22 did not provide sufficient power to demonstrate difference at the specific time points, with particular reference to the inconclusive results following injections with NPH and regular insulin.</p> <p>Conclusion: An s.c. injection of regular insulin in the abdomen before a meal produced a more rapid rise in serum free insulin, a greater peak serum free insulin value, and a greater attenuation of the postprandial rise in plasma glucose than injection of the same dose of insulin in the thigh. Data suggest that premeal doses of regular insulin should be given in the abdomen to maximise effectiveness. Also s.c. injection of NPH and regular insulins in the abdomen before breakfast, when compared with injection of the same doses of insulins in the thigh, attenuates the postprandial rise in plasma glucose after breakfast but not</p>

	after lunch.
NCC CC ID	1096
Reference / Citation	

Q 30 What method of insulin delivery aids optimal diabetic control in adults with stable Type 1 diabetes?

Author / Title / Reference / Yr	De Meijer PHEM, Lutterman JA, van Leir HJJ, van't Laar A 1990 The variability of the absorption of s.c. injected insulin: effect of injection technique and relation with brittleness. Diabetic Medicine 7:499–505
N=	26 The Netherlands
Research Design	Cohort study
Aim	To evaluate the effect of depth of injection
Population	'stable' type 1 diabetes
Intervention	125I-soluble insulin injected deep subcutaneously at the fat-muscle boundary Patients were treated with $\geq 2$ insulin injections/day in the upper leg. They were free of lipohypertrophy, retinopathy, neuropathy or nephropathy except two patients with proteinuria. Injection of insulin was with a 1 ml syringe and a 0.5 x 24 mm needle. All injections were given by the same investigator, alternately in left and right leg.
Comparison	125I-soluble insulin injected superficially at a depth of 3 mm beneath the skin surface
Outcome	Absorption rate of insulin measured by the disappearance of radioactivity from the injection site of 125I-labelled human neutral soluble insulin Radioactivity at the injection site was measured immediately after injection of 8U of insulin at every 30 min for 8 hours. In 10 subjects plasma concentrations of free insulin and glucose were measured before and every 30 min after the injection. These subjects fasted throughout the study. Plasma glucose concentrations $\leq 2.5$ mmol/L were corrected with good, after which glucose and insulin concentrations were not used for calculations. Subjects only used soluble insulin the day before the study instead of their usual regimen.
Characteristics	Sex (M/F): 12/14; Age: 31 $\pm$ 10 years; duration of diabetes: 10 $\pm$ 4 years; insulin dose: 53 $\pm$ 17 U/24h; HbA1c: 10 $\pm$ 1%
Results	Insulin absorption rate Residual radioactivity after deep injection was significantly lower at 7 and 8 h after injection (pless than0.05), however, curves tested over all time-points did not differ significantly. No correlation was found between thickness of s.c. fat and the coefficient variation T50 (time to 50% disappearance from the injection site) for either deep or superficial injection. Serum free insulin Mean values of free insulin were significantly (p=0.02) lower before deep injection than before superficial injection, each value was corrected for its basal value. After deep injection a significantly higher (pless than0.05) increase was found at 0.25, 2, 2.5, 4, 4.5 and 5 hours after injection. When tested over all time points there was no significant difference for free insulin curves between the two

	<p>techniques (p=0.02).  Plasma glucose concentrations  Mean plasma concentrations were not significantly different following injection at any time point throughout the study.</p>
Hierarchy of Evidence Grading	
Comments	<p>All subjects were seated throughout the study (prolonging time of absorption compared to the supine position)  No details given of selection of subjects  No explanation given for reason for selection of 10 patients for free insulin and plasma glucose concentrations, or why the remaining patients were not selected for this part of the study  Authors conclude that the difference between deep and superficial s.c. injection is of little clinical significance</p>
NCC CC ID	1005
Reference / Citation	

Q 30 What method of insulin delivery aids optimal diabetic control in adults with stable Type 1 diabetes?

Author / Title / Reference / Yr	Fleming DR, Jacober Sj, Vandenberg MA, Fitzgerald JT, Grunberger G 1997 The safety of injecting insulin through clothing. Diabetes Care 20:244–247
N=	50 USA
Research Design	Randomised Controlled Trial
Aim	To assess the safety
Population	Mixed diabetes population
Intervention	Experimental s.c insulin syringe-injection practice through clothing (subjects to inject insulin into either thigh through only one layer of fabric).
Comparison	Conventional s.c. insulin syringe-injection practice with skin preparation (subjects instructed to wipe their skin on either thigh with alcohol, allow it to dry, and then inject the insulin)
Outcome	Blood glucose control and hypoglycaemic episodes. Patient satisfaction was measured in patients on the pen injector regimen. All participants received weekly log sheets with both verbal and written instructions to record behaviour and evaluation of technique (benefit codes for: <i>saves time, convenient, less noticeable</i> and <i>less awareness</i> and problem codes for: <i>blood, bruising, pain</i> and <i>infection</i> ) and open-ended comments. Skin assessment and complete blood count with differential and glycosylated haemoglobin measurement performed at 10 and 20 weeks. Weekly injection logs collected at end of study, and only reviewed by investigators at this time
Characteristics	Sex M/F: 21/21; Age (range): 41±11 (23–63) years; Caucasian = 86%; African-American = 12%; Educational history: School ≥16 years = 50%; ≤12 years 21%; Duration of diabetes (range)= 14±8 (1–33) years Type 1 diabetes = 78%; 1 injection/day = 12%; 2 injections/day = 57%; 3 injections/day = 19%; 4 injections/day = 12%
Results	84% (42/50) of patients completed the study. Demographic characteristics of those who completed the study did not differ from drop-outs. Total number of injections through clothing = 7275; number of patient-days = 3339  Log entries Logs were not completed according to instructions by all participants. To avoid over-representation of entries from a specific

phase of the study, logbook entries were analysed for only week 1, 10, 11 and 12 ( the first and last week of each phase) If a benefit or problem was recorded on any given day over this time it received a score of 1 for that day (max benefits/problems per day per patient = 4). Average number of benefits per day was determined by dividing the total number of benefits recorded by the number of days entries were made.

Insulin injections	N=29	Number of entries/day	P
Problems:	Injection with skin preparation	0.32±0.33	0.19
	Injection through clothing	0.40±0.37	
Benefits:	Injection with skin preparation	0	less than 0.01
	Injection through clothing	1.34±1.11	

The average number of recorded problems per technique per day did not differ between the two methods. However, the average number of recorded benefits during the experimental method was significantly greater than that during the conventional method.

Patients open-ended comments suggested that they found the injection-through-clothing technique convenient when they were away from home, and noted less constraint in rotating injection sites because all sites could be readily accessed through clothing as opposed to partial disrobing. Some patients reported difficulty injecting through thick cloth such as denim, while others noted small blood stains on clothing, but no difference in either bleeding or bruising was noted between methods.

#### Blood measurements

No significant differences were found between the results of patients in the two groups, or within each group at each phase of the trial.

	n	Baseline	10 weeks	20 weeks	P value
WBC					
A	24	6.30±1.91	6.40±2.09	6.07±1.82	0.30
B	14	6.81±2.90	6.74±3.20	7.09±2.98	
GHb					
A	24	10.73±2.04	10.94±2.45	10.61±2.43	0.63
B	15	10.79±2.54	11.39±2.86	10.73±2.87	

#### Skin assessment:

No reports were made of adverse skin reactions throughout the study period and no enrolled subject experience or demonstrated on physical examination any erythema, induration, abscess or rash of the thighs.

Hierarchy of Evidence Grading

Ib

Comments

Patients were enrolled over a 12 month period (1994–1995)  
Participants randomised into one of two treatment groups:

	<p>Group A: injected insulin through clothing for 10 weeks followed by the 10 weeks of the conventional technique.  Group B: injected insulin by the conventional technique for first 10 weeks followed by the experimental technique for 10 weeks.</p> <p>Patients were instructed only to inject into the thigh.  Individuals on MDI were instructed to administer <math>\geq 1</math> injection per day through clothing during the experimental phase and had the option of injecting more or all of their injections through their clothing.  Participants were not given any specific instructions regarding rotation of injection sites, other than limiting the sites to the thighs.  All subjects were educated regarding the signs and symptoms of infection and were told to inspect thighs daily and notify investigators immediately if infection was suspected.  All participants were re-instructed on injection techniques and reminded to record injections in the daily logs at time of cross-over of technique (10 weeks).  No details of randomisation procedure or concealment of allocation provided.  Blinding procedures are not discussed.  Patients are unaccounted for. Authors report 42 patients completing the study, however, lab results are only available for 39 patients and log results for 29 subjects.  Conclusion: insulin injection through clothing is safe and convenient.  Authors also state: <i>The technique of injecting through clothing probably adds little risk beyond omitting alcohol-swabbed skin preparation.</i> Suggesting that they do not know what question they are trying to answer, because this is the factor they have used as their control</p>
NCC CC ID	1094
Reference / Citation	

Q31 In adults with Type 1 diabetes and poorly controlled blood glucose what methods of insulin delivery can improve diabetic control?

Author / Title / Reference / Yr	DeVries, J. H., Snoek, F. J., Kostense, P. J., Masurel, N., Heine, R. J., & Dutch Insulin Pump Study Group 2002, "A randomized trial of continuous subcutaneous insulin infusion and intensive injection therapy in type 1 diabetes for patients with long-standing poor glycaemic control.[comment]", <i>Diabetes Care.</i> , vol. 25, no. 11, pp. 2074-2080.
N=	n=79, insulin pump =39, injections =40 The Netherlands 11 sites
Research Design	Randomised controlled trial
Aim	To assess the efficacy of continuous subcutaneous insulin infusion in improving glycaemic control and health-related quality of life in type 1 diabetic patients with long-standing poor glycaemic control
Operational Definition	Persistent poor control while on three or more insulin injections a day (defined as a mean of all HbA1c values measured greater than 8.5% in the last 6 months before the trial).
Population	Type 1 diabetes
Intervention	All patients were advised to note at least two blood glucose self- measurements per day in a dosage adjustment recommendations were derived from an algorithm based on nine-point home blood glucose profiles in the treatment period. In those randomised to continuous subcutaneous insulin infusion, education was given on pump usage. The starting dose was 90% of the previously used total insulin dose per day
Comparison	Compared with injection therapy, where 80% of the previously given pre- meal human insulin dose was given as insulin aspart as a continuous therapy.
Outcome	Subjects were seen at 2, 4, 8, 12, and 16 weeks after randomisation. Change in HbA1c in both from baseline to 12 and 16 weeks was evaluated and the effects of these modes of treatment on health-related quality of life was assessed Change in HbA1c from baseline to 12 and 16 weeks was assessed by blood was samples at these three time points. HbA1c values were assessed using an ion-exchange high-performance liquid chromatography. Number of hypoglycaemias were recorded classified as mild hypoglycaemia defined as a value less than 3.9 mmol/l at SMBG in the last 3 weeks of the study confirmed in the meter read outs. Severe hypoglycaemia was defined by a requirement of third-party help. Changes in dimensions of the quality of life measures were tested by the 36-Item Short-Form survey (SF-36) which has been previously validated, and by the Diabetes Treatment Satisfaction Questionnaire
Characteristics	Age =37yrs, Male =54%, Duration of diabetes =18yrs, HbA1c =9.26%, Type 1 diabetes =100%
Results	Change in HbA1c in the insulin pump group was significantly greater than in the insulin injection group: $-0.91 \pm 1.28$ vs. $-0.07 \pm 0.70\%$ , ( $p = 0.002$ ) difference 0.84% (95% CI -1.31 to -0.36).

	<p>The mean glucose value in 34 hour glucose profiles showed no significant differences between the groups</p> <p>Mild hypoglycaemic episodes increased in the insulin pump group as compared with the injection group: <math>0.98 \pm 2.02</math> vs. <math>-0.02 \pm 1.18</math> episodes per patient week (<math>p= 0.028</math>) difference <math>0.99</math> (95% CI <math>0.11</math> to <math>1.87</math>) episodes per patient week.</p> <p>The number of patients suffering severe hypo- glycaemic episodes was similar in both groups</p> <p>Change in weight was similar in both groups</p> <p>Insulin requirements decreased in the insulin pump group and remained stable in the injection group: <math>-15.8 \pm 15.06</math> vs. <math>2.9 \pm 17.01</math> units/day, (<math>p</math> less than <math>0.001</math>)</p> <p>The scores on the general health and mental health subscales of the SF-36 improved more in the insulin pump treatment group, as compared with the injection therapy group; <math>+5.9</math> versus <math>-1.2</math> (<math>p= 0.048</math>) and <math>+5.2</math> vs. <math>-0.6</math> (<math>p= 0.050</math>), respectively.</p> <p>The overall score was not stated and may not be significantly changed by treatment type</p> <p>There were no significant differences in treatment satisfaction scores between the two groups</p>
Hierarchy of Evidence Grading	Ib
Comments	<p>High and uneven drop out for a short term outcome assessment, if those who withdrew from the pump arm were gaining less benefits then an overestimation of effect would be found without intention to treat analysis</p> <p>No additional therapy was provided to either group however the infusion pump group were provided with protocolled education on usage of equipment. However the general education given to both groups in the 14 week run in period produced stable HbA1c before randomisation.</p> <p>Initially trial was designed as a crossover trial but attrition in the second phase necessitated an analysis of first phase as a parallel group trial</p> <p>14 week run-in phase to exclude patients not able to comply with the demands of a good clinical practice trial, especially in terms of a minimum frequency of self-monitoring of blood glucose</p> <p>Insulin pump therapy is not a panacea for all patients in poor glycaemic control. Only those with a readiness to change can be expected to benefit.</p> <p>The discomfort of always having to wear the pump and the increased rate of mild hypoglycaemia apparently were counterbalanced by the achieved improvement in glycaemic control in these patients with long-standing poor control</p>
NCC CC ID	Ref ID: 1918
Reference / Citation	

## 7.5 Hypoglycaemia

Question 71: What is the most appropriate medical intervention for adults with type 1 diabetes with severe hypoglycaemia?	
Author / Title / Reference / Yr	Patrick AW, Collier A, Hepburn DA, Steedman DJ, Clarke BF, Robertson C 1990 Comparison of intramuscular glucagon and intravenous dextrose in the treatment of hypoglycaemic coma in accident and emergency department. Archives of Emergency Medicine 7:73-77
N=	29 insulin treated diabetic people presenting consecutively to the Accident and Emergency department Scotland
Research Design	Randomised Controlled Trial
Aim	To compare intramuscular glucagon and intravenous dextrose in the treatment of hypoglycaemic coma in an accident and emergency department
Population	People had hypoglycaemia diagnosed on a capillary blood specimen with a Reflolux II Meter
Intervention	N=15 Intramuscular glucagon (1 mg i.m.)
Comparison	N=14 Intravenous dextrose (50 ml 50% i.v.)
Outcome	Restoration of normal conscious level and average duration of hypoglycaemic coma
Characteristics	Mean age: 47/48 years in glucagon/dextrose treated group respectively
Results	Initial plasma glucose, glycated haemoglobin and estimated duration of coma were not significantly different prior to treatment. Average duration of coma: 120 min (range 60-240 min) in glucagon treated people, and 120 min (range 20-480 min) in dextrose treated people Significantly slower recovery to normal conscious levels was seen in the glucagon-treated group compared to the dextrose treated group: 9 min (range 5-30 min) vs. 3 min (range 2-15 min) respectively; pless than0.01 Two glucagons treated people required administration of additional i.v. dextrose after failure to show signs of clinical recovery within 15 min of treatment. No correlation was seen between time taken to recovery of consciousness and either initial plasma glucose concentration or duration of hypoglycaemia

	All but one patient in each group reported either partial or total loss of awareness of the onset of hypoglycaemia.
Hierarchy of Evidence Grading	1b
Comments	<p>People randomly allocated to treatment  Drugs administered to right thigh  Venous blood withdrawn prior to treatment. Measurements taken for plasma glucose, alcohol and glycated haemoglobin.  Additional samples taken at 5, 10, 15 and 30 min after initiation of treatment for plasma glucose estimation  Time taken to recovery of normal conscious level noted, additional 12.5 g of dextrose i.v. administered in absence of recovery after 15 mins  Duration of hypoglycaemia prior to treatment established by retrospective questioning of relatives or family.  Precipitating causes and details of insulin and other drug therapy, as well as possible precipitating causes or preceding loss of awareness of the onset of hypoglycaemia were also obtained from families and friends  No participants were receiving treatment with beta blockers or other drugs which might alter hypoglycaemic awareness of affect the counterregulatory response.  Precipitating factors of hypoglycaemia unknown, three people had detectable levels of alcohol in their plasma, maximum level recorded = 3 mmol/L  Regular treatment of participants: twice daily mixture of soluble, and isophane or lente insulins (n=19), or once daily lente or protamine zinc insulins, either with or without additional soluble insulin before breakfast (n=10)  Experimental protocol not described in detail, leading to possible bias, no details of blinding outlined  No clinical definition of outcome: 'normal conscious levels' not defined  No details of statistical methods  Duration of coma, precipitating factors, and other therapy collected retrospectively, possible recollection bias. Only rough estimation of coma duration was possible in several cases.</p>
NCC CC ID	665
Reference / Citation	

Question 71: What is the most appropriate medical intervention for adults with type 1 diabetes with severe hypoglycaemia?

Author / Title / Reference / Yr	Collier A, Steedman DJ, Patrick AW, Nimmo GR, Matthews SM, Macintyre CA, Little K, Clarke B 1987 Comparison of intravenous glucagon and dextrose in treatment of severe hypoglycaemia in an accident and emergency department. Diabetes Care 712-715
N=	49 consecutive insulin treated diabetic subjects with hypoglycaemic coma referred to the accident and emergency department Scotland
Research Design	Randomised Controlled Trial
Aim	To compare intravenous glucagon and dextrose in treatment of severe hypoglycaemia in an accident and emergency department
Population	People referred to the accident emergency department for hypoglycaemic coma
Intervention	n=25 i.v. glucagon (1 mg)
Comparison	n=24 50 ml 50% dextrose (25g)
Outcome	Time taken to return to a normal level of consciousness, adverse effects during treatment.
Characteristics	Mean age: glucagon group = 39.4±17.1; dextrose group = 40.2±14.2 years Duration of diabetes: glucagon group = 14.0 (4-47.2); dextrose group = 13.0 (2-32.0)
Results	<p>People in the two groups were comparable in terms of initial blood glucose, prevailing glycaemic control, age, duration of diabetes and duration of hypoglycaemia (1.3 (range 0.3-4.0) vs. 1.5 (0.3-9.0) h)</p> <p>A significant difference was seen in the subsequent glycaemic profiles between the two treatment groups (no raw data provided)</p> <p>Time to regain normal consciousness</p> <p>The glucagon treated group was slower to achieve normal conscious level compared to the dextrose treated people. Median time: 6.5 min (range 2–16 min) vs. 4 min (range 1-15 min), respectively (p less than 0.001)</p> <p>All people returned to a normal level of consciousness within 30 min of admission.</p> <p>Plasma glucose levels at admission or duration of hypoglycaemia did not correlate with the time to recovery of normal consciousness in either groups of people.</p> <p>Side effects</p> <p>Eight people in the glucagon group vomited compared with 9 in the dextrose group</p> <p>Thirteen people in the glucagon group reported headaches on return to normal consciousness compared with 12 in the dextrose group.</p> <p>Other factors</p>

	<p>Two people in both groups required additional administration of (12.5 g i.v.) dextrose</p> <p>Precipitating factors for hypoglycaemia were difficult to elicit: no obvious cause was found in 30% of people, 12 people reported missing a meal, 10 were considered to have an irresponsible attitude toward diabetes control, three people had blood alcohol levels greater than 100 mg/dL and 1 patient became hypoglycaemic due to marked fluctuations in insulin requirements due to pregnancy.</p> <p>One patient received s.c. glucagon administration prior to admission (plasma glucose on arrival was 56 mg/dL compared to mean 18 mg/dL across the groups and consciousness level was a borderline grade 3)</p>
Hierarchy of Evidence Grading	1b
Comments	<p>Consciousness assessed and graded as: 0: normal orientation in time and place; 1: drowsy; 2: maximal response to minimal stimuli; 3: minimal response to maximal stimuli; and 4: unresponsive to painful stimuli</p> <p>People randomly allocated to emergency treatment</p> <p>Blood was taken for plasma glucose estimation at 5, 10, 15 and 30 min</p> <p>Return to consciousness was evaluated by the same observer in all participants</p> <p>Additional i.v. dextrose (12.5 g) was administered to people failing to achieve grade 3 consciousness at 15 and 30 min</p> <p>Following recovery from hypoglycaemia, all people were questioned about headache symptoms and it was noted whether they had vomited after administration of treatment.</p> <p>Details of age, duration of diabetes, insulin dosage, most likely precipitating cause of hypoglycaemia and estimation of duration of the hypoglycaemic episode were established through questionnaires completed by participants or family and friends</p> <p>Patients reported the usual cause of hypoglycaemia, and any steps taken to try to abort the episode</p> <p>One patient with Addison's disease was excluded from the statistical analysis</p> <p>No power analysis given at outset, no details given of why the participants were selected to take part in this study</p> <p>No details are provided of any blinding of this study</p> <p>Authors state that significant differences were seen in glycaemic profiles between the two groups following treatment, although no raw data are provided for this.</p> <p>Length of hypoglycaemic episode and precipitating factors are retrospectively collected from participants and present friends and relatives following return to consciousness, leading to possible recall bias.</p> <p>Exclusion criteria prior to inclusion in the study are not explicit. One patient who entered the study was pregnant one had received prior s.c. glucagon administration leading to exceptionally high plasma glucose levels at admission compared to the mean. No details are given of the treatment regimen received by these people. Due to the small sample size the results of these people may affect the outcome of the study.</p> <p>One patient with Addison's disease was excluded from the statistical analysis of this study</p>
NCC CC ID	668
Reference / Citation	

Q 28 what specific advice can be given to adults with Type 1 diabetes for the management and prevention of hypoglycaemia?

Author / Title / Reference / Yr	Yale JF, Begg I, Gerstein H, Houlden R, Jones H, Maheux P, Pacaud D 2001 Canadian diabetes association clinical practice guidelines for the prevention and management of hypoglycaemia in diabetes. Canadian Journal of Diabetes 26:22–35
N=	47 studies of various design in people with type 1 diabetes
Research Design	Systematic review - Guidelines
Aim	To determine practical management options to reduce the effect of hypoglycaemia
Population	Type 1 diabetes
Intervention	Management and prevention of hypoglycaemia by various interventions
Comparison	Varied between studies
Outcome	Correction or reduction in frequency of hypoglycaemia
Characteristics	Varied between studies
Results	<p>Hypoglycaemia occurs on average in people with type 1 diabetes at a frequency of approximately 2 episodes per week.</p> <p>Hypoglycaemia and insulin therapy</p> <p>Intensive vs. conventional insulin therapy</p> <p>Hypoglycaemia is the most common effect of intensive insulin therapy in type 1 diabetes. Some studies have reported an increase in severe hypoglycaemia, although this is not universal</p> <p>Rapid-acting insulin analogues vs. human regular insulin</p> <p>Studies have found no differences in onset, magnitude and temporal pattern of the physiological, symptomatic and counter-regulatory hormonal responses to acute hypoglycaemia induced by regular human insulin compared with the rapid acting insulin analogues</p> <p>Animal vs. human insulin</p> <p>A number of studies have suggested no significant clinical difference in the symptomatic response to or in the frequency of hypoglycaemia between animal and human insulin.</p> <p>Lifestyle factors</p> <p>Studies suggest self-management behaviours, less food, more insulin and more activity are associated with 85% of hypoglycaemic episodes.</p> <p>Food and snacks</p> <p>Patients on fixed-dose insulin regimens should have an individualised meal and activity plan developed, that the person can and will follow.</p> <p>Patients should be taught how to make adjustments to insulin dosage, diet and physical activity in response to blood glucose</p>

levels

Bedtime snack may be needed to avoid nocturnal hypoglycaemia. One study showed that the addition of protein to carbohydrate at bedtime has not demonstrated a reduction in hypoglycaemia.

Prepared snack bars with cornstarch have demonstrated some effectiveness in reducing overnight hypoglycaemia

High protein content (vs. high fat content) of an evening meal has also demonstrated some protection against nocturnal hypoglycaemia

Exercise

Low-to moderate-intensity exercise lowers glucose levels during and after activity, increasing the risk of a hypoglycaemic episode. This effect can be altered by modifying diet, insulin and type and timing of the exercise.

Self monitoring of glucose level before during and after exercise is important for establishing the patient's response to exercise and guideline the appropriate management of exercise.

Hypoglycaemia unawareness and glucose counterregulation

Major risk factors for severe hypoglycaemia are: prior episode of severe hypoglycaemia, HbA1c less than 6%, hypoglycaemia unawareness, long duration of diabetes and autonomic neuropathy

Severe hypoglycaemic episodes occur mainly at night, or in the absence of awareness that makes patients alert to correct their glucose levels

Following the first few years of diagnosis when glucagon responses to hypoglycaemia are lost, patients depend on sympathoadrenal responses for glucose counterregulation and hypoglycaemia awareness.

Autonomic neuropathy has been shown to be an independent risk factor for severe hypoglycaemia, and further reduces epinephrine and norepinephrine responses to hypoglycaemia.

The incidence of prior hypoglycaemic episodes is a crucial factor leading to hypoglycaemia unawareness due to a worsening in the defect of the hormonal responses to hypoglycaemia, leading to a reduction in the self-detection of hypoglycaemia.

Strict avoidance of hypoglycaemia from 2 days to 3 months has been associated with an improvement in the recognition of severe hypoglycaemia in the counterregulatory hormone responses, or both

Blood glucose awareness training (BGAT) may have a positive effect on increasing accurate detection and treatment of hypoglycaemia. The BGAT programme involves instruction in interpretation of physical symptoms, performance cues and moods and feelings as internal cues to blood glucose awareness; it also involves instruction on food, exercise, insulin dosage and action, time of day, and last blood glucose reading as external cues to estimate blood glucose level. BGAT allowed reduced-awareness subjects (with some, but not many, hypoglycaemic symptoms) to detect a greater percentage of blood glucose levels less than 3.9 mmol/l (35–45%,  $p=0.006$ )

Ingestion of caffeine increases the sympathoadrenal and symptomatic responses during moderate hypoglycaemia. However, there is no data on the impact of caffeine consumption on the frequency of severe hypoglycaemic episodes.

Long-term complications of severe hypoglycaemia

The potential long-term complications of severe hypoglycaemia are mild intellectual impairment and permanent neurologic sequelae such as haemiparesis and pontine dysfunction. The latter are rare and reported only in case studies.

available prospective studies did not find an association between intensive diabetes management and cognitive function. Since intensive management is linked with more frequent severe hypoglycaemia, it is extrapolated that, similarly, severe hypoglycaemia is not linked with a decrease in cognitive function. However, the time interval studied was relatively short (5

years)

However, retrospective studies suggested a link with frequent severe hypoglycaemia (5 or more episodes) and a decrease in intellectual performance. People with diabetes with a history of severe hypoglycaemia, when compared to matched subjects with diabetes without severe hypoglycaemia and patients without diabetes, were found to perform more poorly in a number of intellectual tests: immediate memory and finger tapping , word recall test and verbal fluency , performance IQ , Weschler Performance test and Trail Making Test. In some studies, a correlation was found between the frequency of severe hypoglycaemic reactions and the performance IQ.

#### Treatment for hypoglycaemia

Little evidence is available to support the widely recommended treatment for acute hypoglycaemia as 10g of a variety of carbohydrates.

More recent evidence suggests that 15g of glucose (monosaccharide) is required to produce a rise in blood glucose of approximately 2.1 mmol/l within 20 minutes, with adequate symptom relief for most people.

A 20g oral glucose dose will produce a blood glucose increment of approximately 3.6 mmol/L at 45 minutes.

Other treatments such as milk and orange juice are slower to raise blood glucose levels and provide symptom relief

Glucose gel is a slower treatment (less than 1mmol/l rise at 20 mins) and therefore needs swallowing to have a significant effect

No evidence is available for the buccal administration of glucose gel as absorption through the mucosa is minimal, if any. Patients taking alpha-glucosidase inhibitors should use glucose (dextrose) tablets, or if unavailable, milk or honey to treat hypoglycaemia.

#### Physical Training and Exercise

In anyone treated with insulin, recommendations regarding alterations of diet, insulin regimen, injection sites and self-monitoring should be appropriate for the general level of physical activity or specific types of exercise undertaken. Oral agent doses may need to be decreased. *[Grade D, consensus]*

Self-monitoring of glucose level before, during and especially for many hours after exercise, is important for establishing the patient's response to exercise and guiding the appropriate management of exercise. *[Grade D, consensus]*

General advice regarding physical activity include:

For those on insulin or insulin secretagogues, ingest rapidly absorbed carbohydrate if pre-exercise glucose level is under 5 mmol/L.

For those on insulin injections, administer insulin into a site away from the most actively exercising extremities. *[Grade D, consensus]*

#### Insulin Use in Type 1 Diabetes

All patients currently on or starting intensive insulin programs should be counselled about the risk and prevention of hypoglycaemia. They should be advised to perform frequent blood glucose monitoring and receive appropriate instruction on how to make adjustments in insulin dosage, diet and physical activity in response to blood glucose levels. The diabetes health care team

should review the patient's experience with hypoglycaemia at each visit. This should include an estimate of cause, frequency,

symptoms, and recognition, severity and treatment. *[Grade D, consensus]*

To reduce the risk of symptomatic nocturnal hypoglycaemia, patients should periodically monitor overnight blood glucose levels at a time that corresponds with the peak action time of their overnight insulin and consume a bedtime snack with at least 15 g carbohydrate and protein if the bedtime blood glucose level is under 7 mmol/L. *[Grade D, consensus]*

Regular or a rapid-acting insulin analogue, or both, can be used before meals in intensified therapy (multiple daily injections and CSII). Lispro has been associated with lower post-prandial glucose levels and lower rates of hypoglycaemia than regular insulin. *[Grade A, Level 1]*

Aspart insulin has been associated with lower rates of hypoglycaemia compared to human regular insulin. *[Grade B, Level 2]*

Patients experiencing frequent hypoglycaemic episodes on regular insulin should be tried on a fast-acting insulin analogue. *[Grade D, consensus]*

Lispro is the preferred insulin for use in CSII. *[Grade B, Level 2]*

Substituting a rapid-acting insulin analogue for human regular insulin at supertime may prevent the delayed nighttime effect of regular insulin and reduce the risk of nocturnal hypoglycaemia (45-48). Administering basal insulin at bedtime rather than at supertime, or instituting CSII, may also reduce the risk of nocturnal hypoglycaemia. *[Grade D, consensus]*

Risk factors for severe hypoglycaemia should be identified in people with type 1 diabetes so that appropriate strategies can be used to prevent hypoglycaemia. *(Grade A)*. Established risk factors include a history of previous severe hypoglycaemic event *[Level 1]*, a greater reduction in HbA1c *[Level 1]* and recurrent previous hypoglycaemic reactions *[Level 1]*

The patients at high risk should be informed of their risk, counselled along with their significant others on avoidance and treatment (including glucagon), and if necessary have their insulin regimen adjusted appropriately to avoid these events. *[Grade D, consensus]*

During insulin therapy of type 1 diabetes, the frequency of mild hypoglycaemic episodes should be minimized, particularly in those at high risk, in an attempt to reduce the development of hypoglycaemia unawareness. *[Grade D, consensus]*

In individuals with hypoglycaemia unawareness, the following strategies should be implemented to reduce the risk of hypoglycaemia, the risk of hypoglycaemia unawareness, and to increase physiologic counter-regulatory responses to hypoglycaemia:

- increased frequency of glucose monitoring, increase in the glucose targets, and multiple insulin injections with increased glucose targets *[Grade D, level 4]*

Patients switching from animal to human insulin do not require counselling about any change in frequency or perception of hypoglycaemia. *[Grade A, Level 1]*

In hospitalised patients, efforts must be made to ensure that patients on insulin have ready access to an appropriate form of glucose at all times, particularly when NPO or during diagnostic procedures. *[Grade D]*

**Treatment of hypoglycaemia**

Mild to moderate hypoglycaemia should be treated by the oral ingestion of 15 g of carbohydrate, preferably as glucose or sucrose tablets or solution or hydrolysed polysaccharide. These are preferable to orange juice and glucose gels *[Grade B, level 2]*. Patients should be encouraged to wait 15 minutes, retest blood glucose and retreat with another 15 g of glucose if the blood glucose remains less than 4.0 mmol/L. *[Grade D, consensus]*

	<p>Severe hypoglycaemia in a conscious person should be treated by the oral ingestion of 20 g of carbohydrate, preferably as glucose tablets or equivalent. Patients should be encouraged to wait 15 minutes, retest blood glucose and retreat with another 15 g glucose if it remains less than 4.0 mmol/L. <i>[Grade D, consensus]</i></p> <p>To prevent repeated hypoglycaemia, the person should have in addition to the fast-acting treatment above, once the hypoglycaemia has been reversed, their usual meal or snack. A snack (including 15 g of carbohydrate and a protein source) is recommended if a meal is more than 1 hour away and in the absence of complicating factors. <i>[Grade D, consensus]</i></p> <p>All patients currently on or starting therapy with insulin or insulin secretagogues should be counselled about the recognition and prevention of drug-induced hypoglycaemia. <i>[Grade D, consensus]</i></p>																				
Hierarchy of Evidence Grading	Ia (various)																				
Comments	<p>An Expert committee was established including healthcare professionals from diabetologists to dietitians, and methodologists from Canada.</p> <p>The methodologists then evaluated the literature and developed recommendations on the key areas, assigning levels of evidence to the relevant citations and making grading recommendations based on the validated methods. This evidence was then summarised in a series of documents for the Expert committee.</p> <p>All recommendations reviewed by 3 methodologists not directly involved in initial assessment of evidence and grading of recommendations.</p> <p>Recommendations are an update of the Canadian medical association 1998 clinical guidelines for the management of diabetes.</p> <p>Hypoglycaemic symptoms (% frequency):</p> <table border="1"> <thead> <tr> <th>Neurogenic (Autonomic)</th> <th>Neuroglycopenic</th> </tr> </thead> <tbody> <tr> <td>Trembling (32–78%)</td> <td>Difficulty concentrating (31–75%)</td> </tr> <tr> <td>Palpitations (8–62%)</td> <td>Confusion (13–53%)</td> </tr> <tr> <td>Sweating (47–84%)</td> <td>Weakness (28–71%)</td> </tr> <tr> <td>Anxiety (10–44%)</td> <td>Drowsiness (16–33%)</td> </tr> <tr> <td>Hunger (39–49%)</td> <td>Vision changes (24–60%)</td> </tr> <tr> <td>Nausea (5–20%)</td> <td>Difficulty speaking (7–41%)</td> </tr> <tr> <td>Tingling (10–39%)</td> <td>Headache (24–36%)</td> </tr> <tr> <td></td> <td>Dizziness (11–41%)</td> </tr> <tr> <td></td> <td>Tiredness (38–46%)</td> </tr> </tbody> </table> <p>No details given of search strategy employed by stakeholders, or even if a systematic search was employed.</p> <p>No indication given as to whether papers were rejected due to poor quality</p> <p>Details not provided for magnitude of effect in each study, or population size.</p>	Neurogenic (Autonomic)	Neuroglycopenic	Trembling (32–78%)	Difficulty concentrating (31–75%)	Palpitations (8–62%)	Confusion (13–53%)	Sweating (47–84%)	Weakness (28–71%)	Anxiety (10–44%)	Drowsiness (16–33%)	Hunger (39–49%)	Vision changes (24–60%)	Nausea (5–20%)	Difficulty speaking (7–41%)	Tingling (10–39%)	Headache (24–36%)		Dizziness (11–41%)		Tiredness (38–46%)
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Trials included	See original study																				
NCC CC ID	1996																				
Reference / Citation																					



Q28 What specific advice can be given to adults with Type 1 diabetes for the management and prevention of hypoglycaemia?

Author / Title / Reference / Yr	Broers, S., Van Vliet, K. P., Everaerd, W., Le Cessie, S., & Radder, J. K. 2002, "Modest contribution of psychosocial variables to hypoglycaemic awareness in Type 1 diabetes", <i>Journal of Psychosomatic Research</i> , vol. 52, no. 2, pp. 97-106.
N=	n=123 Holland
Research Design	Case control study
Aim	A study to assess relationships between hypoglycaemic awareness and diabetes-related, psychosocial and demographic characteristics
Population	Type 1 diabetes
Intervention	The study assesses the contribution of a range of demographic, diabetes related, and psychological characteristics to hypoglycaemic awareness. Over a 4 to 6 week period. The parameters include Negative affectivity, Somatic awareness, Bustle and variety of the daily life, and degree each of 20 symptoms; as assessed by questionnaire. Sensitivity and specificity of the symptom beliefs in terms of the degree of agreement between 'actual' and 'believed' hypoglycaemic symptoms were made for every patient by the use of measured blood glucose values from the handheld computer with data dichotomised to Hypoglycaemia (less than 3.9 mmol/l) versus no hypoglycaemia (greater than 3.9 mmol/l),
Comparison	Comparison of different scores in the same parameters
Outcome	Hypoglycaemic awareness. The percentage of recognised hypoglycaemic episodes (% RH) was defined as the percentage of measured blood glucose values less than 3.9 mmol/l that was accompanied by an estimation less than 3.9 mmol/l, or by an estimation within 20% of the measured value, for each of the test occurrences
Characteristics	Age =42yrs, Male =55%, Duration of diabetes =21.4 yrs, HbA1c= 7.5%
Results	<p>Univariate analysis</p> <p>A moderate but significant positive correlation (<math>r=.52</math>, <math>p=.000</math>) between hypoglycaemic awareness and the number of actual hypoglycaemic symptoms (see was observed).</p> <p>The four symptoms that were actually related to hypoglycaemia for the most patients were: trembling (41.1%), problems with coordination (34.7%), difficulty concentrating (33.7%) and dizziness (32.6%). The four symptoms that were believed to be hypoglycaemic symptoms by the most patients were: difficulty concentrating (69.5%), sweating (54.7%), confusion (51.6%) and irritability (43.2%).</p> <p>Of the diabetes-related variables, disease duration (<math>r= -.25</math>, <math>p=0.01</math>) and antecedent hypoglycaemia (<math>r=-.20</math>, <math>p=0.05</math>) were both negatively associated to the % RH.</p> <p>Multivariate regression</p> <p>Hypoglycaemic awareness was predicted by the duration of the diabetes <math>B=-0.79</math> (<math>SE= 0.37</math>) (<math>p=0.04</math>), the use of CSII versus insulin injections <math>B= 24.7</math> (<math>SE= 11.9</math>) (<math>p=0.04</math>), and the sensitivity of the symptom beliefs (<math>B=0.21</math> (<math>SE =0.11</math>) (<math>p=0.07</math>)).</p> <p>Only 17% of the variance in hypoglycaemic awareness was explained by the model</p>

Hierarchy of Evidence Grading	IIa
Comments	<p>The indication that those who withdrew from the study had a higher HbA1c level than those participating suggests that people in the study already had good glycaemic control and may be less prone to hypoglycaemia with the outcomes thus being diminished.</p> <p>The measure of assessment of psychological characteristics was not validated and could have had unknown effects on the results.</p> <p>Only 65 people were included in final multivariate model with data available for all parameters</p> <p>People who used an insulin pump recognised hypoglycaemia more often than those who used insulin injections.</p> <p>Possibly, the single questions used were too crude to assess the underlying concepts, and a validated questionnaire would have led to other results.</p> <p>People may become more sensitive to physical sensations when they regularly take time to ‘listen’ to their body, and may learn which symptoms represent hypoglycaemia by the keeping of a ‘symptom diary.’</p> <p>Only a small proportion of the variance in hypoglycaemic awareness was explained in the present study. It seems likely that other variables, which have not been measured, play a role in hypoglycaemic awareness.</p>
NCC CC ID	1937
Reference / Citation	

Q 28 What specific advice can be given to adults with Type 1 diabetes for the management and prevention of hypoglycaemia?

Author / Title / Reference / Yr	Kingsley BT, Weinger K, Bajaj M, Levy CJ, Simonson DC, Quigley M, Cox DJ, Jacobson AM 1999 Blood glucose awareness training and epinephrine responses to hypoglycaemia during intensive treatment in Type 1 diabetes. Diabetes Care 7:1022–1028
N=	N=47 USA
Research Design	Randomised controlled trial
Aim	A study to assess the effectiveness of blood glucose awareness training to reduce incidence of Hypoglycaemia
Population	Type 1 diabetes
Intervention	8 session group education programme in Blood glucose awareness training (BGAT) (using the revised BGAT-3 version involving instruction in interpretation of physical symptoms, performance cues and moods, and feelings as internal cues to blood glucose awareness, also including instruction on food, exercise, insulin dosage and action, time of day and last blood glucose reading as external cues to estimate blood glucose level.)
Comparison	An equivalent number and duration of sessions in cholesterol education (control)
Outcome	Glycaemic control measured by HbA1c and hypoglycaemia frequency
Characteristics	Sex (M/F): 23/24; Age: 34±8 years; Duration of diabetes: 9.0±3 (range 3–15) years; HbA1c 9.0±1.2%
Results	<p>Glycaemic control and hypoglycaemia frequency</p> <p>During 4 months IDT, glycaemic control measured by HbA1c improved in BGAT and control groups. HbA1c fell from 9.1±1.4 to 7.9±1.1% (pless than0.001) in the BGAT group 9.0±1.1 to 7.8±8.0% (pless than0.001) in the controls. No significant difference was seen between the two groups</p> <p>Hypoglycaemia frequency measured by the daily number of readings less than3.9 mmol/L increased in both groups from 0.45±0.06 to 0.69±0.07 episodes per day in the BGAT group (pless than0.001) and 0.05±0.08 to 0.68±0.06 episodes in controls (pless than0.05). Differences between the groups were not significant.</p> <p>No differences were recorded in the severity of hypoglycaemia between the two intervention groups.</p> <p>Counter-regulatory hormones</p> <p>Epinephrine levels increased from baseline following IDT in both groups. Following IDT epinephrine levels were significantly lower in the control group compared with the BGAT group at blood glucose levels of 2.8 mmol/L (1,162±165 vs. 1,850±255 pmol/l) and 2.2 mmol/l (2,217±263 vs. 3,220±382 pmol/l) pless than0.05 between groups.</p> <p>Levels of norepinephrine, ACTH, cortisol, and hGH did not differ between control and BGAT groups before or after IDT and</p>

	<p>education.</p> <p>Symptom scores Neurogenic and neuroglycopenic symptom scores did not differ between control and BGAT groups before or after IDT. Self-reported neurogenic symptoms were significantly reduced in subjects undergoing BGAT during IDT compared to the control group (pless than0.004), whereas neuroglycopenic symptoms did not differ in BGAT and control groups. Blood glucose estimation accuracy was similar in control and BGAT groups before IDT. Following IDT blood glucose estimations errors did not differ significantly between groups. BGAT subjects had a greater improvement in detection of low blood glucose levels and fewer undetected low blood glucose readings.</p> <p>Subgroup analysis of patients at high risk of hypoglycaemia (n=26) HbA1c improved from 9.0±0.4 to 7.4±0.2% in the control group (pless than0.01) and from 8.8±0.5 to 7.5±0.2% in the BGAT group (pless than0.01), but no significance difference was seen between the two groups. No difference was seen between the groups in hypoglycaemia frequency following BGAT compared to controls. An increase in the proportion of hypoglycaemic episodes <math>\leq 2.8</math> mmol/l was seen in the control but not BGAT group; however, the difference between the two groups was not significant.</p> <p>Counterregulatory hormones Epinephrine levels did not differ between control and BGAT groups prior to IDT. After 4 months of IDT the change in ephinephrine response to hypoglycaemia with IDT differed in the control and BGAT groups (repeated measure ANOVA, F=4.4, pless than0.05). Levels of norepinephrine, ACTH, cortisol and hGH did not differ in control and BGAT groups before or after BGAT.</p> <p>Symptom scores These did not differ between the two groups; no significant decrease in neurogenic or neuoglycopenic symptoms was seen in the BGAT group compared to the controls (p=0.11 and 0.93 respectively)</p> <p>Blood glucose estimation Accuracy did not differ in control and BGAT groups before or after 4 months intensive diabetes treatment. Subjects undergoing BGAT had fewer undetected low blood glucose readings than those in the control group (pless than0.04)</p>
Hierarchy of Evidence Grading	Ib
Comments	<p>60 subjects enrolled in the study. 8 patients dropped out because of moving from the area (n=3), or having a change in job and time involvement (n=4) or non-study-related injury (n=1). 5 subjects experienced technical difficulties either during one of the clamp procedures (n=3) or with laboratory assays (n=2). Final study sample therefore consisted of 47 subjects. None of the remaining patients had any evidence of complications.</p> <p>Subjects were followed in an outpatient clinic over a 4 to 5 month period.</p> <p>Subjects were seen monthly by study physicians, nurse educators and a nutritionist, and had weekly telephone contact with their nurse educator to optimise glycaemic control. Patients took 3–5 insulin injections/day and performed ~ 5 home blood glucose measurements/day.</p>

	<p>Before and after 4 months of intensive diabetes treatment, subjects underwent paired identical hypoglycaemic insulin clamp procedures.</p> <p>At baseline at each glucose level, subjects completed a 35-item self-administered mood and symptom questionnaire (MSQ), rating each item on a 7 point likert scale, with 0 standing for feeling the symptom “not at all” and 6 “a lot”. Mean score of trembling, sweating, pounding heart and fast pulse was used to represent neurogenic symptoms, and the mean of being light headed, difficulty concentrating, uncoordinated, confused and feeling weak to represent neuroglycopenic symptoms.</p> <p>On completion of questionnaire, patients estimated and recorded their blood glucose level.</p> <p>HbA1c was measured at baseline and at each monthly visit. Home blood glucose meter readings were downloaded to a p.c., providing data on glucose levels for 4 weeks, and were used to analyse frequency of hypoglycaemia.</p> <p>An estimate of blood glucose within 20% of the actual meter reading was taken as correct</p> <p>Validated BGAT protocol applied.</p> <p>Validated symptom and mood questionnaire used.</p> <p>No details of randomisation procedure or concealment of allocation</p> <p>Blinding of patients and investigators not discussed.</p> <p>Findings on hypoglycaemia frequency based on home blood glucose testing, leaving potential for subjects to not have treated or recorded all of their low blood glucose readings and no data is available on nocturnal hypoglycaemic episodes.</p>
NCC CC ID	1133
Reference / Citation	

Q 28 What specific advice can be given to adults with Type 1 diabetes for the management and prevention of hypoglycaemia?

Author / Title / Reference / Yr	Fritsche S, Stumvoll M, Renn W, Schumling RM 1998 Diabetes teaching program improves glycemic control and preserves perception of hypoglycemia. Diabetes Research and Clinical Practice 40:129–135
N=	N=54 Germany
Research Design	Case series
Aim	To track the progression of hypoglycaemia in people undergoing a teaching programme
Population	Type 1 diabetes
Intervention	Structured inpatient diabetes education programme
Comparison	Not applicable
Outcome	HbA1c, blood glucose accuracy index, sensitivity and prevalence of low blood glucose
Characteristics	Age: 33.7±11.7 years; Sex (M/F): 26/28; duration of diabetes: 11.7±9.3 years
Results	<p>33 patients (61%) kept a constant diary and estimated blood glucose regularly during the study. The remaining 21 patients were excluded from the study.</p> <p>Of the excluded patients 38% had a history of severe hypoglycaemia. These patients did not differ from the patients included in the study.</p> <p>Of the remaining patients, those with repeated severe hypoglycaemia were older and had longer duration of diabetes, compared to patents without repeated severe hypoglycaemia, although levels of HbA1c did not differ at baseline.</p> <p>Blood glucose levels</p> <p>Perception</p> <p>Accuracy of blood glucose perception in all the patients did not change following introduction of DTTP and IT (p=0.25). Taken according to history of hypoglycaemia, patients with a history of repeated hypoglycaemia were able to improve the accuracy of blood glucose perception following DTTP, unlike those with no history.</p> <p>Sensitivity</p> <p>No significant improvement was seen in blood glucose sensitivity following a teaching programme either when considering the entire cohort, or when patients were divided up according to hypoglycaemia history.</p>

	<p>Prevalence of low blood glucose  Prevalence of blood glucose levels less than 3.9 mmol/l did not change following the teaching programme, however there was a tendency towards a lower frequency of low blood glucose readings in group H.  Correlation of sensitivity for blood glucose levels and glycaemic control  There was no linear correlation between the change of sensitivity for low blood glucose levels and HbA1c (<math>r=0.1</math>; <math>p=0.4</math>).  No linear correlation was seen between sensitivity for and prevalence of low blood glucose levels (<math>r=0.3</math>; <math>p=0.1</math>)</p>
Hierarchy of Evidence Grading	III
Comments	<p>54 Patients consecutively referred to teaching and treatment programme for intensification of insulin regimen. 33 completed the study. These patients were grouped according to presence (<math>n=11</math>) or absence (<math>n=22</math>) of history of repeated hypoglycaemia. No participants had clinical evidence of autonomic neuropathy or advanced secondary complications e.g. advanced retinopathy, macroproteinuria or symptomatic macrovascular disease  Patient's blood glucose diaries examined at end of study.  Patients underwent a structured interview about the frequency and severity of severe hypoglycaemia (requiring i.v. glucose or s.c. glucagon), results were double checked with relatives and GPs.  The 5 day inpatient program consisted of 25 60-min lessons emphasising insulin dose adaptation for food intake and exercise as well as correction or prevention of hypoglycaemia and hyperglycaemia. Patients learned to estimate carbohydrate content of foods and how to treat and recognise hypoglycaemia.  Patients also specifically learned how to prevent unrecognised night-time hypoglycaemia. When blood glucose readings were below 8 mmol/l at bedtime patients were instructed to eat a snack with a variable carbohydrate content aiming for a blood glucose level of 8–10 mmol/l before going to bed.  Patients were tested and trained by nurses in their ability to accurately measure blood glucose.  Patients also estimated blood glucose before each measurement <math>\geq 4</math> times/day. No specific training was given in blood glucose perception, but received written instructions detailing mechanisms of blood glucose perception.  Instructions also listed actions influencing blood glucose such as amount, type and timing of insulin, food, exercise, alcohol and illness.  Study looking at the ability to alleviate the increase in hypoglycaemia and reduction in blood glucose awareness following improved metabolic control, through the use of structured inpatient diabetes treatment and teaching programme.  Small sample size (<math>n=11</math> in severe hypoglycaemia group)  Study has high drop out rate, and only compliant patients were included in the final results, therefore there was a positive selection of estimating patients in this study.  Some patients may have already been familiar with estimating blood glucose since two thirds reported to occasionally have relied on blood glucose estimates before the study when adjusting their insulin dose.  Patients with and without a history of repeated severe hypoglycaemia differed in age and diabetes duration, and also in certain aspect of blood glucose awareness.</p>

NCC CC ID	1137
Reference / Citation	