Evidence Tables

INS 7: What methods of delivery of insulin therapy are effective at improving clinical outcomes in Type 2 diabetes?

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding
Asakura T, Seino H. Assessment of dose selection attributes with audible notification in insulin pen devices.[see comment]. Diabetes Technology & Therapeutics 2005; 7(4):620-626. Ref ID: 3217	Crossover RCT 1+	N=48 Single centre study performed in Japan	People with type 2 diabetes who had never previously used any type of insulin injection device; 30 men and 18 women; mean age 60.5 years; mean HbA1c 8.7%. All patients self-reported that they could “hear a voice over the telephone with no difficulty”.	Novopen 3 HumaPen Ergo Humalog Pen InnoLet Flexpen All patients tested every device. NB NO ACTUAL INSULIN INJECTIONS WERE PERFORMED IN THE TRIAL.	See intervention	All devices tested on the same day	Auditory confirmation of dose setting (patients described the clarity of the audible click as clear or poor). Tactile feedback (patients described the physical feeling of reassurance provided by the click as positive or poor), Confidence about dose setting (patients used a 1 to 5 rating scale to assess how	Significantly more patients detected an auditory confirmation of dose setting when using the Novopen 3 compared with the Humalog Pen (100% vs 63%, p<0.001) HumaPen Ergo (100% vs 75% p<0.001), and InnoLet 100% vs 90% p<0.01). The audible click for the FlexPen was also heard by more patients than the Humalog Pen (98% vs 63%, p<0.001) and HumaPen Ergo (98% vs 75% p<0.01). Thus in order of patients hearing the click sound the devices were NovoPen (100%), Flexpen (98%), InnoLet (90%), HumaPen Ergo (75%) and Humalog Pen (63%). Sound recordings confirmed that the NovoPen 3 produced the loudest clicks when setting a dose (p<0.001 for all comparisions). For tactile feedback the proportion of patients physically sensing they had dialled a correct dose was 100% for the Flexpen, 92% for the Novopen, 81% InnuLet, 67% HumaPen and 50% for the Humalog Pen. Significantly more patients reported that they had dialled the correct dose for the FlexPen	Not stated

							confident they were about setting the correct dose) Auditory volume test (sound level meter used).	compared with the Humalog Pen (p<0.001), HumaPen Ergo (p<0.001) and InnoLet (p<0.01). Significant differences were also noted between the NovoPen 3 and Humalog Pen (p<0.001) and the HumaPen Ergo (p<0.01). Patients reported most confidence in setting the correct dose with the NovoPen 3 (4.6 ± 0.5) and FlexPen (4.5 ± 0.9) when rating on a scale of 1 to 5. The scores for the NovoPen 3 were significanty higher than those for the InnoLet (3.9 ± 1.0, p<0.001) HumaPen Ergo (3.7 ± 1.1, p<0.001) and Humalog Pen (3.3 ± 1.2, p<0.001), whereas the FlexPen scored significantly higher than the Humalog Pen (p<0.01).	
Coscelli C. Safety, efficacy, acceptability of a pre-filled insulin pen in diabetic patients over 60 years old. Diabetes research and clinical practice 1995; 28(3):173-177. Ref ID: 480	Crossover RCT 1+	N=60. Performed in Italy.	Inclusion criteria: age 60 or over with diabetes onset and insulin treatment of more than one year; capable of performing home blood glucose monitoring and of recognizing hyopglycaemic episodes. Only one patient had type 1 diabetes. 29 men and 31 women were included with a mean age of 67.8 years. Mean duration of diabetes was 15 years and mean duration of insulin treatment was 7 years. Mean BMI 25.2kg/m2. Mean HbA1c 7.8%. Mean insulin dose 31.8 UI/day. 53 were treated with 2 injections a day and 7 with 3	Pre-filled insulin pen NovoLet. This is a disposable device containing an insulin reservoir of 150IU and can deliver up to 58 units in increments of 2 units.	Conventiona l syringe	2, 6 week treatment periods with a run in period of 2 weeks.	Hypoglycae mic episodes recorded every 2 weeks. Glycaemic control (6 point glucose profile and HbA1c) Acceptability of pen treatment. A questionnair e filled in after 2 and 6	There was no significant difference in the incidence of hypoglycaemic episodes between pen device and syringe treatments. Pre-lunch blood glucose values were lower during pen treatment (p<0.01) but no other significant differences were found between pen and syringes for blood glucose profiles. No significant difference was found in terms of HbA1c. Insulin requirement was 31.9 ± 8.9 and 32.3 ± 9 U/day during pen and syringe treatments respectively. Before using the pen participants found understanding how to use it: 33% very easy 57% easy 10% difficult	Novolet supplied to authors by Novo Nordisk

			per day.				weeks of use by the patients at home.	At week 6 : The operations needed for insulin administration with the pen compared to the syringe were: 88% said faster 0% slower 12% no different Preselection of insulin dose with the pen compared with insulin withdrawal from the vial with the conventional syringe is: 0% said more difficult 86% easier 14% no different Insulin injections with the pen are: 2% said more painful 55% less painful 43% no different Which device is preferred? 90% disposable pen 2% conventional syringes 8% no difference. 6/60 patients found it difficult to learn how to use the pen and 3 of these left the study.	
Dreyer M. Comparison of metabolic control, safety, handling and patient acceptance of insulin delivery devices in patients with type 1 and type 2 diabetes. Journal of Drug Assessment 2005;	Crossover RCT 1+ 15 study centres in Germany	N=103	Male (59%) and female patients aged between 20 and 84 years (mean age 58) with both type 1 and 2 diabetes with a a BMI of <35 kg/m2 and an HbA1c of <11%. All patients had a minimum of 3 months experience with disposable	FlexPen A 3.0 pre-filled disposable insulin delivery system	NovoLet	6 weeks in each treatment group.	Acceptance and handling assessed by questionnaire. 4 point blood glucose profiles and	There were no differences between the devices in terms of HbA1c or glucose profiles. There were no major hypoglycaemic episodes. Handling and acceptance results: Results for all questions (excluding the question on pain) were significantly in favour of FlexPen.	Sponsered by Novo Nordisk

8(2):79-85. Ref ID: 741			or durable insulin pens.				HbA1c. Hypoglycaemic episodes recorded in study diary by patients and any adverse events.	When reading the insulin dose display, which device is easier? FlexPen:73% NovoLet:3% No difference:23% When setting the required dose of insulin for your injection, which device is easier? FlexPen:71% NovoLet:8% No difference:21% Which device makes you feel most confident than you have injected the correct amount of insulin? FlexPen:63% NovoLet:9% No difference:28% When injecting your insulin, which device is most discreet to use? FlexPen:39% NovoLet:9% No difference:52% When injecting your insulin which device is most stable? FlexPen:47% NovoLet:13% No difference:40% When injecting your insulin which device is least painful? FlexPen:16% NovoLet:10% No difference:74%	

								In terms of handling, which device do you prefer? FlexPen:54% NovoLet:12% No difference:34% Overall which device do you find easier to use? FlexPen:73% NovoLet:8% No difference:19% Overall, which device would you prefer to continue using? FlexPen:77% NovoLet:12% No difference:10%	
Kadiri A, Chraibi A, Marouan F, Ababou MR, el GN, Wadjinny A et al. Comparison of NovoPen 3 and syringes/vials in the acceptance of insulin therapy in NIDDM patients with secondary failure to oral hypoglycaemic agents. Diabetes Research & Clinical Practice 1998; 41(1):15-23. Ref ID: 315	Crossover RCT 1+ performed at 8 study centres in Morocco	N=96 N=78 finished the study	Patients with NIDDM and secondary failure were recruited. Secondary failure was non-acceptable metabolic control with fasting blood glucose greater than 7.8mmol/l and HbA1c levels more than 25% above the upper limit of the normal reference range for the lab in question. All patients had been treated with OHAs and diet for at least one year (mean 5.7 years).	NovoPen 3 Tablet treatment was stopped when initiating insulin therapy in the study.	Conventional syringes and vials	12 weeks using each delivery system before crossover	The acceptance of insulin injections was evaluated by questionnaire at the end of each treatment period. Blood glucose profiles and HbA1c. Insulin dose Hypoglycae	Practical aspects of insulin administration: Most patients starting insulin using the NovoPen 3 found the insulin injections easy (58%) or very easy (19%) with these proportions increasing slightly at the end of 12 weeks to 63% and 33% respectively. Those who commenced insulin with conventional syringes found it more difficult with only 24% finding it very easy by the end of 12 weeks and 51% finding it easy. The difference between groups in the ease of administration was significant both at the start (p=0.0039) and end of treatment (p=0.0005). Injection pain Injection pain was significantly lower with NovoPen 3 than with syringes and	Novo Nordisk

							mic episodes and adverse events.	vials (p=0.0018). Patients commencing on syringes reported a significantly lower level of injection pain after the switch to using NovoPen 3 (p=0.0003). Acceptance of insulin injections Acceptance of insulin injections was significantly higher by patients using Novopen 3 than by those using syringes and vial (p=0.059). When those initially using NovoPen 3 switched to syringes and vials there was a significant decrease in the acceptance of injections as part of daily life (p=0.0052). Insulin dosing Setting and drawing up the dose of insulin was easier for patients using NovoPen 3 (p=0.0490). Preference of injection system At the end of the study most patients (89.5%) said that they preferred NovoPen 3 to syringes and vials. Metabolic control Glycaemic control improved compared with baseline after starting insulin therapy with no differences between delivery systems. Safety The number of reported hypoglycaemic episodes was low and not significantly different between groups.	
Shelmet J. Preference and resource utilization in elderly patients: InnoLet versus	Multicentre Crossover RCT	N=79 N=73 completed the study	Type 1 or 2 patients currently injecting their own insulin but had difficulties (requiring some assistance	InnoLet with 30G x 8mm needles	Conventional disposable 0.5cc insulin syringe with	6 weeks using each device.	Resource utilisation (not reported here)	Patient preference, handling and acceptance of InnoLet: If you were given the choice of using	Novo Nordisk

vial/syringe. Diabetes research and clinical practice 2004; 63(1):27-35. Ref ID: 689	performed at 11 sites in the US		from a nurse or caregiver) due to motor dysfunction and / or visual problems. Patients were familiar with either a pen and or vial and syringe method of injecting. Mean age 68.2 years, 42% male, 82% white, 8% black, 10% Hispanic, mean BMI 33kg/m2, mean HbA1c 7.5%, mean 16.5 years since diagnosis, 97% were type 2.		30G permanently attached needle		Patient preference and acceptance questionnaire Serum fructosamine levels. Hypoglycaemia and adverse events	one of the two systems which would your prefer? InnoLet:82% Vial and syringe: 10% No preference: 8% (p<0.001) Given your disability, how would you rate the InnoLet compared to the vial and syringe: Easier to use:82% The same:12% Harder to use:4% Just after changing to InnoLet, how did you find managing the practical aspects (dosing and injecting) of the new insulin system? Very easy or easy:86% Little difficult: 13% Difficult or very difficult:1% How do you now find the practical aspects of insulin administration after switching to InnoLet? Easy or very easy: 97% Difficult or a little difficult: 3% In terms of reliability of injecting your insulin, rate the InnoLet More reliable:62% About the same:34% Less reliable:3% Were you able to inject yourself with less nursing assistance when using InnoLet? Less assistance:84% More assistance:3%	

								About the same:8% How do you find setting of the insulin dose with InnoLet? Easy: 96% Did you ever drawer up an incorrect insulin dose? Never drawn an incorrect dose: 86% Sometimes drew an incorrect dose: 10% How did you find the injections? No pain at all using InnoLet:73% InnoLet was slightly painful:26% Injecting myself: Has become a part of my daily life:80% Dislike it but have no problem with the delivery system: 20% Glycaemic control No change in glycaemic control was observed during the entire study period. Safety evaluation No events were considered by the investigator to be related to study treatment. Adverse device events: Two adverse device effects were reported during the study (malfunctioning of the InnoLet device). There was drippage from the needle following the injection.	

Korytkowski M, Bell D, Jacobsen C, Suwannasari R, FlexPen Study Team. A multicenter, randomized, open-label, comparative, two-period crossover trial of preference, efficacy, and safety profiles of a prefilled, disposable pen and conventional vial/syringe for insulin injection in patients with type 1 or 2 diabetes mellitus. Clinical Therapeutics 2003; 25(11):2836-2848. Ref ID: 145	RCT multicentre, crossover open-label study. 1+	108 from nine sites in the US	Patients with type 1 and 2 DM. All patients were syringe/vial users and were naive to the use of other insulin delivery devices. All patients continued to use the biphasic insulin aspart 70/30 mixture and their usual QD or BID schedule throughout the trial. 121 patients entered the 4-week run-in period. Mean age (SD) was 57.0 (12.4) years (age range 28-81). Sixty-two (51%) were men and 59 (49%) were women. Mean (SD) BMI was 31 (5.5.) kg/m2. thirteen of these patients (11%) dropped out by the end of the run-in period because of AEs, noncompliance with the protocol, or withdrawal of consent. At week 4, the remaining 108 patients were randomized.	Vial/syringe[1] To inject insulin aspart 70/30	Flexpen Prefilled, disposable pen To inject insulin aspart 70/30	8 weeks (2 x 4 weeks) precedeed of a 4-week run in perio d[2]	Patient acceptance Insulin regimen HbA1c FPG Adverse events	**Patient acceptance** Primary efficacy end point question "Overall, which device would you prefer to continue using?" Overall patient preference among the 105 patients who completed the treatment sequence with both delivery systems. 74% (78/105) indicated a preference for the pen (95% CI, 71%to 87%), 20% (21/05) indicated a preference for the vial/syringe, and only 6% (6/105) responded that they had no preference. The sequence of injection device use (syringe before pen or pen before syringe) had no impact on treatment preference. It was observed that patients who preferred the pen were younger (mean [SD] age, 56 [11.2] years, mean [SD] time since diagnosis, 13 {8.2] years than those who preferred the vial/syringe (mean [SD] age, 64 [13.8] years, mean [SD] time since diagnosis, 15 {8.1] years 85% of patients (89/105) reported that they found it easier to read the insulin dose scale with the pen than the vial/syringe. In contrast, 10% of patients (10/105) found reading the insulin dose scale easier using the vial/syringe. In response to the question regarding	Novo Nordisk

[1] The two insulin delivery systems had comparable needle sizes (30G x 8mm needle with the disposable pen and 30G x 7.9mm needle with the syringe)

[2] During the 4-week run-in period, patients used their previous mode of delivery (i.e. their own syringes) to administer a mixture of 70% insulin aspart protamime suspension and 30% insulin aspart.

								patient confidence with setting the required dose, 82% of patients (86/105) indicated more confidence with the pen device, whereas 11% (12/105) were more confident with the vial/syringe. 73% of patients (77/105) felt more confident in the accuracy of the insulin dose delivered with the pen, compared with 19% (20/105) for the vial/syringe. 85% of responders (88/104) indicated that the pen was more discreet to use in a public place, compared with 9% (9/104) for the vial/syringe. 61% of patients (63/103) felt that with the pen, they were more confident in their own ability to maintain glycemic control, compared with 16% (16/103) for the vial/syringe. Finally, 74% of patients (77/104) found the pen device to be easier overall to use, compared with 21% (22/104) for the vial/syringe. <u>The preference/ease of use questions were not assessed for significance.</u> **Glycemic control** A statistically significant improvement in glycaemic control occurred during the entire study, with average reduction of HbA1c values of 0.3% in the total population treated. Mean FPG and 4-point blood glucose profiles for use of both devices were	

								generally comparable, showing no statistically significant differences. **Insulin Regimen** For the patients who completed the study, the mean (SEM) total daily insulin dose of biphasic insulin aspart 70/30 mixture with the pen was 55 (2.66) U/d (range, 5-120 U/d); with the vial/syringe, it was 54 (2.65) U/d (range, 5-120 U/d) **Safety profile** Overall, the safety profiles for pen and the vial/syringe appeared similar. **Drop-out** Of the 108 patients randomized, 103 patients (95%) completed the study. Five patients (5%) discontinued study treatment because of AEs, noncompliance with the protocol, or withdrawal of consent.	
Fox C, McKinnon C, Wall A, Lawton SA. Ability to handle, and patient preference for, insulin delivery devices in visually impaired patients with type 2 diabetes. Practical Diabetes International 2002; 19(4):104-107. Ref ID: 742	RCT multicentre, crossover open-label study performed at 3 centres in the UK, 1+	N=86	Insulin-naïve patients with type 2 diabetes were included if they were 55 years or more with diet and or oral hypoglycaemic agent treated diabetes. Visual acuity (corrected near vision) in the best eye was between 0.5 (20/40) and 0.1 (20/200) as assessed with a Rosenbaum card. There were 51 males and 35 females with mean age 69 years and mean disease duration 6 years. Visual acuity ranged between 0.29	InnoLet Pen Humulin Pen (both used 30G 8mm needles)	Vial and 0.5ml syringe (with a pre-attached Micro-Fine + 8mm needle).	All devices tested on the same day	Accuracy when viewing dose scale (patients were asked to read 4 randomly selected whole numeral dose settings on each insulin delivery system).	**Visual Accuracy when reading dose scale:** **All 4 doses read correctly:** **InnoLet 92% a,b** **Humulin pen 45%** **Syringe 61%** **There was a significant difference (p<0.001) between InnoLet and the other two systems.** **% of patients able to intuitively set and dispense 20U insulin dose** **InnoLet 84% a,c** **Humulin pen 41%** **Syringe 31%**	Novo Nordisk

			and 0.5 in 54% of patients, 0.2 and 0.29 in 20% of patients and 0.1 and 0.2% in 26% patients. 6% reported a subjective hand disability.				Handling test Part 1: Intuitive test: Patients were asked to set and discharge a 20 unit insulin dose with a minimum of standardised instruction and no specific training in a set time. Part II: written instruction: Patients were provided with the manufacturers instruction leaflets on how to operate the device and then had to dispense 3 random doses of insulin	**% of patients able to set and dispense three insulin doses after written instruction** **InnoLet 80% a,b** **Humulin pen 61%** **Syringe 27%** **% of patients able to set and dispense three insulin doses after both written instruction and brief verbal instruction/demonstration** **InnoLet 99%** **Humulin pen 85%** **Syringe 64%** **a p<0.001 versus syringe** **b p<0.001 versus Humulin Pen** **c p<0.01 versus Humulin Pen** **Preferred delivery system:** **InnoLet 87%** **Humulin Pen 13%** Syringe 0% InnoLet was significantly preferred to the Humulin pen (p<0.001).	

							Part III: Verbal Instruction and demonstration: Patients only did this if they did not complete the previous section successfully. Verbal instruction and demonstration given and then patients given 3 further randomly selected doses to set and dispense. Patient preference measured by questionnaire		
Stockl K, Ory C, Vanderplas A, Nicklasson L, Lyness W, Cobden D, Chang E. An evaluation of	RCT 1- Multicentre, open-label,	N=260 N=162 used for primary	Inclusion criteria: ≥18 years at enrolment, diagnosed with T1 or T2D, HbA1c ≤10%, using at least one daily injection of NPH, regular or	Disposable doser, a pre-filled disposable insulin	Standard insulin vial and syringe	24 weeks 12 weeks in each arm	Primary endpoint: patient preference of insulin	**Delivery system preference (N=162)** 71.5% reported an overall preference for the disposable doser (p<0.0001) The disposable doser was also	Novo-Nordisk

patient preference for an alternative insulin delivery system compared to standard vial and syringe. Current Medical Research and Opinion 2007; 23 (1): 133-145 Ref ID: 4979	randomised cross-over trial	endpoint analysis All recruited from centres in the USA 88.9% T2D 20.4% loss to follow up 12.3% exposed to either delivery system for < 9 weeks or >15 week gap between visit dates	70/30 insulin; and to have been using insulin for at least 6 months. Exclusion criteria: inability to read or write English, unable to administer their own injections, had used an alternative insulin delivery system in the 6 months prior to enrolment, pregnant or lactating or had the intention of becoming pregnant, use of anti-psychotics, cognitive impairment, or a history of alcohol abuse. Baseline characteristics: there was a significant difference in HbA1c between groups at randomisation. The participants randomised to disposable doser had a lower HbA1c than those first randomised to the vial/syringe arm (mean ± SD: 7.2 ± 1.3 vs. 7.8 ± 1.3; p<0.05) There were no other significant differences between the groups. Assessment of bias: excluded patients who did	delivery system			delivery system, as measured by the Insulin Device Preference Questionnaire[3] Secondary measures: Diabetes Fear of Self Injection, Thoughts about Taking Insulin[4], Insulin Treatment Satisfaction Questionnaire (ITSQ), Problem areas in Diabetes (PAID). HbA1c	preferred for the following: Convenient method of insulin administration (74.1%, p<0.0001) Easier method of insulin administration (75.2%, p<0.0001) More comfortable to use in public (72.3%, p<0.0001) Least unpleasant method to use (67.9%, p<0.0001) Made it easier to take all insulin doses (62.3%, p=0.0006) Made life with diabetes easier (62.2%, p=0.0007) **Fear of Self Injection** Summary score for overall fear of self-injection was lower after using the disposable doser (mean score ± SEM: 9.5 ± 0.2 vs. 11.2 ± 0.4; p<0.05) **Thoughts about taking insulin questionnaire** Summary score for overall degree of non-compliance was lower after using disposable doser than vial/syringe (mean score ± SEM: 10.3 ± 0.3 vs. 12.0 ± 0.5; p<0.05) I**TSQ** Higher insulin treatment satisfaction was reported after using the disposable doser in the areas of: convenience of regimen (p<0.0001) lifestyle flexibility (p=0.0006) glycaemic control (p<0.0001)	

[3] This questionnaire was developed for this study.
[4] This questionnaire was developed for this study.

			not complete the entire study according to protocol from this analysis, open-label study, of those who discontinued, do not say in which arm they discontinued, overall 33% did not complete the study.					insulin delivery satisfaction (p<0.0001) overall satisfaction (p<0.0001) Transformed summary score for overall treatment satisfaction was higher after using the disposable doser (mean score ± SEM: 79.0 ± 1.3 vs. 70.4 ± 1.7; p<0.0001) **PAID** On 17/20 items patients reported lower amount of problem areas in diabetes after using disposable doser (p<0.05) Summary score was lower after using disposable doser (mean score ± SEM: 20.8 ± 1.5 vs. 26.1 ± 1.9; p<0.05) **Adverse events** 7/260 (2.7%) had a serious adverse event, all were deemed unrelated to study treatment.	