Article title: Patients' Preferences for connected Insulin Pens: A Discrete Choice Experiment Among Patients with Type 1 and Type 2 Diabetes
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Online Resource 2: Supplemental Methods

Targeted Literature Review

To inform an initial set of attributes for inclusion in the discrete choice experiment (DCE), a literature search was conducted from 23 June 2020 to 29 June 2020. Two separate search strategies were executed in Ovid to identify relevant quantitative and qualitative studies. Retrieved studies were screened based on pre-specified eligibility criteria summarized in the table below.

Eligibility Criteria for Studies Included in the Targeted Literature Review

Category	Inclusion Criteria	Exclusion Criteria
Population	Adult patients with T1D/T2D	Non-adult patients Gestational diabetes
Study Design	Quantitative studies • Patient preference studies (e.g., DCE, BWS, SW, MCDA, thresholding, BRA, AHP) • Crossover studies Qualitative studies • PROs • Interviews • Focus groups	Publications of studies with the following designs: • Animal studies • In vitro/ex vivo studies • Gene expression/protein expression studies • Case studies/case series • Publications that are not of studies (e.g., reviews, editorials, conference abstracts)
Language	English	N/A
Timeframe	2015 – current	2014 – past

Abbreviations: AHP = analytic hierarchy process; BRA = benefit-risk analysis; BWS = best-worst scaling; DCE = discrete choice experiment; MCDA = multiple-criteria decision analysis; N/A = not applicable; PRO = patient reported outcomes; SW = swing weighting; T1D = type 1 diabetes mellitus: T2D = type 2 diabetes mellitus

A total of 144 studies were retrieved from the search, including 85 quantitative studies and 59 qualitative studies. These were reduced to 18 quantitative and 24 qualitative studies after title and abstract screening. The three most prevalent reasons for excluding studies were the following: the treatment area was not diabetes (42%), the study was not concerned with digital

technologies (25%), and the study type was not eligible for inclusion (22%). Full-text screening further excluded 23 studies, resulting in 19 studies for data extraction.

A total of 22 potentially patient-relevant attributes of digital technologies for diabetes insulin therapy were identified from the evidence review. These attributes were sorted into three groups:

- System attributes related to the capabilities and abilities of the connected system.
- Functionalities were the core features of a technology that provide key information for specific self-care decisions.
- Support related to wider information about the disease, technical information, and problem solving, as well as medical support where self-care may not be applicable.

Attribute selection

The findings from the evidence review were discussed during an attribute selection workshop, and candidate attributes were derived by identifying key technology aspects of potential devices with attributes identified as patient-relevant from the literature review.

Candidate attributes also informed the design of the vignettes discussed during the qualitative interviews. Results of the concepts identified during qualitative interviews are summarized in **Online Resource 3**.

Overall, five candidate attributes were selected. These included one device attribute that characterized the connected insulin pen:

- **Device type:** Two different technical solutions for connecting an insulin pen with a mobile phone were covered in the study. A SmartPen is a disposable insulin pen with an integrated Bluetooth® transmitter that can be paired to a mobile app. Once paired, the transmitter can transfer data to the phone. When all insulin in the pen is used or out of date, the pen is disposed of. Alternatively, a Smart Button is a Bluetooth®-enabled cap that can be attached to a disposable insulin pen. Once the Smart Button is paired to an app, the transmitter can transfer data to the phone. If multiple insulins are prescribed, the Smart Button can be used across both basal and bolus/mealtime insulins. When all insulin in the pen is used or out of date, the transmitter is removed, attached to a new pen, and the old pen is disposed of.

The remaining attributes related to the mobile app to which the device can transfer data:

- **Dosing support:** Dosing reminders (n = 10), dosing log (n = 9), and dose calculation (n = 3) were frequently reported as relevant functionalities in the literature. This also included aspects of the data presentation (n = 12) such as visualizations.
- **Glucose monitoring:** In the evidence review, glucose monitoring (n = 16) was the most frequently reported functionality relevant to digital technologies. An app that can be paired with a connected insulin pen may or may not offer the additional incorporation of blood glucose monitoring data. The integration of glucose data and dosing data in the app aims to provide patients with diabetes with a more complete picture of information

relevant to their insulin management. If blood glucose monitoring data is not available in the app, the patient can monitor their glucose levels either using standard paper diaries or additional applications that are not capable of receiving insulin dosing information from the connected insulin pens.

- **Additional app features:** Digital technologies for diabetes are becoming increasingly complex, with the aim of capturing wider lifestyle factors relevant to self-management of diabetes. For example, diet and physical activity are critical elements of diabetes self-management, with current guidelines recommending long-term weight loss of 5% to 7% of body weight and 150 minutes of at least moderate-intensity physical activity per week. Consistently, nutrition and diet trackers (n = 15) as well as physical activity trackers (n = 12) were commonly reported functions of digital technologies in the evidence review.
- **Data sharing:** Numerous apps have features that enable users to email and export data into a file to share with healthcare professionals, caregivers, and family members. Data sharing can facilitate close communication with healthcare professionals, caregivers, support groups, and family members. Data can be shared in multiple ways, ranging from targeted forwarding via email or text to grant selected individuals direct access to the data. Data sharing was also identified as relevant from the evidence review.

Statistical Analysis

The collected DCE data were analysed within the random utility maximisation framework,[1-4] which assumes that a person n chooses the alternative j in the DCE task t that results in the highest utility $u(\boldsymbol{x}_{jnt})$. The treatment utility was defined as:

$$u(\boldsymbol{x}_{jnt}) = v(\boldsymbol{x}_{jnt}) + \varepsilon_{jnt} \quad (1)$$

where $v(\boldsymbol{x}_{jnt})$ was the observed (systematic) utility component, and ε_{jnt} is the unobserved (random) utility error component, which is assumed to be identically and independently distributed according to an extreme value type I distribution. Three models were estimated based on this framework: 1) a random-constant logit (RCL) model; 2) a random-constant mixed logit (RCMXL) model; and 3) an interacted random-constant logit (IRCL) model. Four outputs were generated: 1) marginal utilities (model estimates); 2) RAI scores; 3) average marginal effects (AME); and 4) predicted choice probabilities (PCP).

Random-Constant Logit Model (Main Model)

The RCL model defined the systematic utility as a linear and additive function:

$$\begin{aligned} v(\boldsymbol{x}_{jnt}) = {} & \alpha_{standardpen|c} + \beta_1 \text{device.smartbuttom}_{jnt} + \beta_2 \text{dosing.visualisation}_{jnt} \\ & + \beta_3 \text{dosing.suggestion}_{jnt} + \beta_4 \text{monitor.manual}_{jnt} + \beta_5 \text{monitor.automatic}_{jnt} \\ & + \beta_6 \text{tracker.dietry}_{jnt} + \beta_7 \text{tracker.physical}_{jnt} + \beta_8 \text{tracker.both}_{jnt} \\ & + \beta_9 \text{sharing.email}_{jnt} + \beta_{10} \text{sharing.access}_{jnt} \end{aligned} \quad (2)$$

where $\alpha_{standardpen|c}$ and $\beta_{k\in[1;10]}$ were model parameters to be estimated as summarized below.

Model Parameters

Attribute	Levels	Parameters
Constant	Connected pen	Reference level
	Non-connected pen	$\alpha_{standardpen\|c}$
Device	SmartPen	Reference level
	Smart button	β_1
Insulin Dosing Support	Automated dose recording	Reference level
	Automated dose recording + visualization	β_2
	Automated dose recording + visualization + dosing suggestion	β_3
Glucose Monitoring	Not available	Reference level
	Manual entry of glucose level	β_4
	Automatic transfer of glucose level	β_5
Additional Features	Not available	Reference level
	Dietary tracker	β_6
	Physical activity tracker	β_7
	Dietary tracker + physical activity trackers	β_8
Data Sharing	Not available	Reference level
	Send summary report by email	β_9
	Grant access to app data	β_{10}

The $\beta_{k\in[1;10]}$ parameters measured the utility effects of deviating from a reference level within an attribute (e.g., β_2 is the effect of adding visualisation to automated dose logging). The $\alpha_{standardpen|c}$ parameter was an alternative-specific constant that captured participants' overall tendency to choose a non-connected pen over a connected pen (i.e., status-quo). To account for heterogeneity in opt-in behaviour (e.g., driven by attitudes towards using a connected pen), the model allowed for a finite mixture of constants. This mixture assumed that there were C groups of patients with distinct constants that resulted in different tendencies to remain at the status-quo. The number of groups was selected based on the lowest Bayesian information criterion.

Interacted Random-Constant Logit Model

The IRCL model was used to investigate the systematic effect of personal characteristics on preferences. Instead of splitting the full sample into different subgroups and running separate RCL models for each subgroup, the IRCL captured the effect of changes in the personal characteristics using interaction effects. The interaction terms were obtained by multiplying the mean-centred personal characteristics with the attribute levels, such that each term effect captured the deviation from the subgroup relative to the overall sample. Delta method was used to obtain the standard errors (SEs).[5] A separate IRCL model was estimated for each of the following characteristics:

- Age (3 subgroups: 18–44; 45–64; 65+ years old)
- Type of diabetes (2 subgroups: T1D; T2D)

- Country of residence (2 subgroups: UK; US)
- Insulin regimen (2 subgroups: basal only; basal and bolus)

Random-Constant Mixed Logit Model

While the IRCL allowed for capturing variability in preferences based on personal characteristics, preference heterogeneity may exist over and above these observable differences. The objective of the RCMXL model was to account for such unobserved heterogeneity.[6] This was implemented by assuming that $\beta_{k\in[1;10]}$ parameters were individual specific and, as a result, normal distributed in the population. The RCMXL model estimated the means ($\bar{\beta}_{k\in[1;10]}$) and standard deviations ($\sigma_{k\in[1;10]}$) of these normal distributions. A significant standard deviation denoted the presence of preference heterogeneity. The model was estimated with 3,000 Halton draws.

Relative Attribute Importance Scores

RAI scores were calculated to capture the importance of an attribute relative to all other attributes. RAI scores reflected the variation in utility that could be attributed to the largest possible change in a particular attribute, relative to all other attributes:

$$\mathrm{RAI}_k = 100 \times \frac{\hat{\beta}_k^{\max} - \hat{\beta}_k^{\min}}{\sum_{k\in[1;K]}\left(\hat{\beta}_k^{\max} - \hat{\beta}_k^{\min}\right)} \tag{3}$$

The difference ($\hat{\beta}_k^{\max} - \hat{\beta}_k^{\min}$) corresponded to the largest change in utility obtained by moving from the worst (least desirable) to best (most desirable) level of the kth attribute. The Krinsky-Robb procedure in 10,000 iterations will be implemented to compute the 95% confidence intervals around the RAI scores.[7]

The utility change for the "dosing support" attribute was obtained by combining β_3 with the negative of the average $\alpha_{standardpen}$ as estimated by a modified model that used effects coding for the device attribute. This negative constant captured the value of a connected insulin pen with automated dosing log as its only function. This approach was taken, because a conventional RAI score would not capture the value of an automated dosing log but the value of providing visualisation and dose recommendations in addition to an automated dosing log. This would underestimate the value of dosing support provided by a connected insulin pen.

Average Marginal Effects

AME indicated the effect of discrete changes in attributes on the probability of preferring a connected insulin pen over a non-connected pen. AMEs were obtained as

$$AME_{[k_r\rightarrow k_l]} = \frac{1}{NT}\sum_{n\in[1;N]}\sum_{t\in[1;T]}\left(PCP'_{nt[k_l]} - PCP_{nt[k_r]}\right) \tag{4}$$

where $PCP'_{nt[k_l]}$ corresponded to the probability that person n chose a connected-enabled pen in task t after the attribute k was changed from its reference level r to its new level l. Similarly, $PCP_{nt[k_r]}$ corresponded to the PCP before the change.

Predicted Choice Probabilities

PCPs were used to compare the relative desirability of different pen profiles **(Supplemental Table 3)**:

$$PCP_j = \frac{\exp[v(\boldsymbol{x}_{jnt})]}{\sum_{j\in[1;J]} \exp[v(\boldsymbol{x}_{jnt})]} \quad (5)$$

where $v(\boldsymbol{x}_{jnt})$ corresponded to the indirect utility of the pen profiles. The delta method was used to obtain the SEs and compute the 95% CIs around the PCP.

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