Patient Preferences and Health State Utilities Associated with Mealtime Insulin Concentrations Among Patients with Diabetes in Italy

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ABSTRACT

Introduction: Standard concentration (100 units/mL) mealtime insulin is frequently used to treat patients with type 1 (T1D) and type 2 diabetes (T2D). A more concentrated version of the medication (200 units/mL) has been available in Italy since 2016. This concentrated version is bioequivalent to the standard version and delivers the same amount of medication but in half the volume of liquid. The purpose of this study was to examine patient preferences and estimate health state utilities associated with standard and concentrated rapid-acting mealtime analog insulin.

Methods: Participants with T1D and T2D in Italy valued two health states in time trade-off interviews. The descriptions of diabetes and treatment in the two health states were identical, differing only in terms of insulin concentration (e.g., half as much liquid for the same dose, less effort needed to press the injection button, and fewer injection pens required with concentrated insulin). To ensure participants understood the health states, they were shown a short video illustrating the differences between concentrations.

Results: A total of 217 participants completed the interviews (49.8% male; mean age 56.1 years; 109 from Milan; 108 from Rome; 12.0% T1D; 88.0% T2D). When asked which health state they preferred, 98.2% responded the concentrated version, 0.9% said the standard version, and 0.9% had no preference. Mean [standard deviation (SD)] utilities rounded to three decimals were 0.892 (0.099) for the concentrated version and 0.884 (0.101) for the standard version. The mean (SD; *p* value) utility difference between the standard and

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concentrated rapid-acting insulin was 0.007 (0.019; $p < 0.0001$).

Conclusions: Findings from this study provide insight into patient preferences associated with concentration of rapid-acting insulin. Although the difference in utility is small, patients consistently preferred the concentrated formulation over the standard insulin, and for some patients this difference had an impact on utility valuations. These results suggest that the concentration of rapid-acting insulin should be considered because it could affect treatment preference and quality of life.

Key summary points

Why carry out this study?

• Guidelines from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) highlight the importance of considering patient preference when choosing treatments for patients with diabetes.

• Standard concentration rapid-acting analog insulin is frequently used to manage post-meal glucose levels in patients with diabetes, and a more concentrated formulation of this medication has been available for several years.

• The purpose of this study was to examine patient preference between the standard and concentrated formulations of mealtime insulin and explore whether this preference could be quantified with health state utilities.

What was learned from the study?

Results highlight patient preference for concentrated over standard rapid-acting insulin, while providing utility values that can represent patient preference in cost-effectiveness analyses comparing insulin formulations.

• The preference for concentrated rapid-acting insulin could be clinically meaningful because treatments that are preferred by patients may be associated with better treatment adherence, which contributes to positive health outcomes.

INTRODUCTION

A growing body of research suggests that treatment process and treatment convenience could have an impact on treatment preference and quality of life [1, 2]. In patients with diabetes, treatment process attributes, including features of injectable medication, have been shown to influence patient preference [3–7]. Treatment preference and satisfaction are important factors because they can contribute to treatment adherence, which could affect health outcomes [4, 7–13]. Furthermore, guidelines from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) highlight the importance of considering patient preference when choosing treatments for patients with diabetes [14]. Therefore, preferences for attributes of diabetes treatment should be considered as part of the treatment decision-making process to maximize adherence and improve outcomes.

Standard concentration (100 units/mL) rapid-acting analog insulin is frequently used to manage post-meal glucose levels in patients with type 1 and type 2 diabetes (T1D and T2D, respectively) [15, 16]. A more concentrated formulation of this medication (200 units/mL) has been available for several years in a range of countries, including Italy where it was introduced in 2016 [17, 18]. The concentrated insulin injection pen contains twice as many units

of insulin (600 vs. 300 units) as a standard insulin pen in a similar 3-mL cartridge. Since the new concentrated pen holds double the amount of mealtime insulin, patients will be able to use a single pen for twice as long compared to one containing the standard concentration, thereby requiring fewer pens each month [18]. It is possible that patients may perceive the concentrated formulation to be advantageous. For example, because each pen lasts twice as long, patients may travel with fewer pens on long trips, store fewer pens in the refrigerator, and dispose of fewer pens.

The purpose of this study was to examine patient preferences between the standard and concentrated formulations of mealtime (i.e., rapid-acting) insulin and explore whether these preferences could be quantified in terms of health state utilities. Utility estimation is one way to examine and quantify patient preferences for attributes of the pharmaceutical treatment process [19]. Results yield utility scores that represent the strength of preference for various health states on a scale anchored to 0 (dead) and 1 (full health) [20]. This study was designed to provide utilities that could be used to represent patient preference in cost-effectiveness (cost-utility) models comparing insulin formulations.

METHODS

Overview of Study Design

This study was designed to estimate utilities associated with standard and concentrated mealtime insulin treatment for T1D and T2D in Italy. Vignette-based utility methodology was selected because generic preference-based measures are not designed to be sensitive to the impact of treatment process or treatment convenience on health state preference. In contrast, vignette-based methods are well-suited for isolating the utility impact of specific treatment-related attributes and are commonly used in studies of treatment process utilities [1]. Several previously published studies used this approach to estimate the utility impact of diabetes treatment attributes [21–24]. The utilities derived in

these previous studies have been used in a range of published cost-utility analyses (CUAs) of treatments for diabetes [25–30].

Two health state descriptions (often called vignettes or health states) were drafted and refined based on literature review, discussions with clinicians, and a pilot study. The descriptions of diabetes and treatment were identical in the two health states, except for the concentration of rapid-acting mealtime insulin. One health state described standard rapid-acting insulin based on the 100 units/mL formulation of insulin lispro [18], and the other described concentrated rapid-acting insulin based on the 200 units/mL formulation of insulin lispro [18]. Utilities for these two health states were elicited in a time trade-off (TTO) task with a 20-year time horizon. Because the health states differed only in insulin concentration, any difference in preference or the resulting utilities can be attributed to insulin concentration.

The TTO interviews were conducted with patients with T1D and T2D in April 2018 in two locations in Italy (Milan and Rome). Participants were required to provide written informed consent before completing study procedures, and all procedures and materials were approved by an independent institutional review board (Ethical & Independent Review Services; Study Number 18006). Thus, the study conformed with the Helsinki Declaration of 1964, as revised in 2013, concerning human and animal rights, and Springer's policy concerning informed consent has been followed.

Health State Development

A literature search was conducted to support health state content and guide subsequent discussions with clinicians. The literature search focused on standard (100 units/mL) and concentrated (200 units/mL) insulin lispro product information [18], glide force (i.e., the amount of effort required to press the pen's injection button) [31], and patient perceptions of standard and concentrated insulin [32–35].

Interviews were conducted with two Italian physicians, including one diabetes specialist

and one internal medicine physician. Both physicians had extensive experience treating patients with T1D and T2D, as well as experience prescribing standard and concentrated rapid-acting insulin. They provided insight into their patients' perceptions of the standard and concentrated formulations of rapid-acting insulin. Draft health states were revised based on suggestions from these physicians to ensure that health states clearly and accurately represented typical patient experiences.

A series of documents was developed for use in the valuation study. First, participants were shown a page of "introductory material" presenting the concept of an injection pen used to inject insulin shortly before each meal [see full text in Electronic Supplementary Material (ESM) Appendix A]. This page also introduced the concept of concentration as the amount of a substance in a given amount of liquid and explained that the two health states differed in insulin concentration. The participants were then shown a table that compared standard and concentrated insulin in terms of three key differences: (1) "amount of liquid each time you inject"; (2) "effort to inject"; and (3) "total amount of insulin in each injection pen" (see ESM Appendix B). The first and third of these differences are objective characteristics of the injection pens, as indicated in the Summary of Product Characteristics [18]. The second difference, "effort to inject" (i.e., glide force), has been examined in a previously published study, which found that the concentrated insulin pen required less effort (i.e., lower glide force) than the standard insulin pen [31].

After reviewing the introductory material and the table comparing the two types of insulin, participants were given the two health state vignettes, presented on individual cards (ESM Appendix C). The two vignettes began with the same description of diabetes and symptoms but differed in the description of rapid-acting mealtime insulin that followed. One of the vignettes described standard rapid-acting insulin, while the other described concentrated rapid-acting insulin. The statements distinguishing between standard and concentrated insulin corresponded to the three differentiating characteristics that participants had

previously seen in the comparison table (ESM Appendix B).

In addition to the introductory material, the table comparing standard versus concentrated insulin, and two health state cards, participants were shown a video illustrating the key differences between the two concentrations. There was no sound accompanying the animation. The images in the video were unbranded depictions of the injection pens.

Participants

All participants were required to be (1) at least 18 years of age; (2) diagnosed with diabetes by a recognized medical professional; (3) able to provide proof of treatment for or diagnosis of T1D or T2D; and (4) residing in Italy for the main valuation study or the UK for the pilot study. Participants were not eligible if they had a cognitive impairment, hearing difficulty, or severe pathology that could interfere with their ability to complete the interview. Participants who were currently receiving medication treatment for T1D or T2D were required to bring proof of medication, such as medication packaging, to the interview. Participants with T2D who were not receiving medication treatment were required to provide a knowledgeable description of diabetes diagnosis, symptoms, and treatment that clearly indicated they were honestly reporting their diagnosis. During patient recruitment, efforts were made to ensure that the ratio of T1D to T2D would be roughly similar to the ratio worldwide and in Italy (i.e., approximately 90% T2D) [36, 37].

All participant recruitment and screening procedures were conducted in compliance with Italian privacy law [Legislative Decree no 196 of 30 June 2003 (Codice in materia di protezione dei dati personali, the "Privacy Code")]. Patients were primarily recruited through a third-party database consisting of patients who had participated in previous studies and expressed interest in being contacted for future studies. Patients were also recruited through a network of professional interviewers who referred to their own contact lists to recruit. For this study, participants were contacted via telephone or e-mail,

depending on their preferred contact method listed in the database.

Pilot Study

A pilot study was conducted with 31 participants (seven with T1D and 24 with T2D; 58.1% male; mean age 51.2 years) to assess the clarity of the health states and utility assessment methodology. All seven participants with T1D reported receiving insulin treatment. Participants with T2D reported currently receiving oral medication (75.0%), insulin (4.2%), or no prescription medication (20.8%). Interviews were conducted in February 2018 in London to allow the study team to draft and revise study materials and finalize the interview procedures in English.

Participants completed health state valuation tasks and then provided feedback on interview materials and procedures. Very few participants reported difficulty understanding the health states or the TTO task. There were minimal suggestions for changes or edits. In general, participants said the video was a helpful depiction of the differences between standard and concentrated insulin. Minor edits were made to the health states and video based on feedback from pilot study participants, including revisions to formatting and wording to increase clarity.

Translations

After making edits based on the pilot study, all materials were translated into Italian for use in the main utility valuation study. The standardized interview guide, consent form, and demographic form were initially translated from English to Italian by a native Italian speaker. Then, trained translation project managers and a native Italian speaker who was not involved in the forward translation reviewed, proofread, and edited the translated materials. All Italian documents were reviewed by Italian members of the study team and the data collection staff. Additional edits were made to ensure that the materials would be clear and comprehensible to Italian-speaking study participants.

Translation of the health states followed the same translation process with an additional step of back-translation. A native English speaker who is fluent in Italian performed the back-translation, which was subsequently reviewed by a native Italian speaker and trained translation project managers.

Utility Interview Procedures and Scoring

After the study materials had been translated, health state utilities were elicited in a TTO valuation study. Participants were required to provide written informed consent before completing study procedures, and all procedures and materials were approved by an independent institutional review board (Ethical & Independent Review Services; Study Number 18006). Each one-on-one interview followed a semi-structured script to standardize assessment procedures. The principal investigator trained the five interviewers and observed each interviewer multiple times to ensure that procedures were followed in a consistent manner.

Participants were first introduced to the concepts in the health states via the introductory page (ESM Appendix A) and the health state comparison table (ESM Appendix B). They then reviewed the health states in detail (ESM Appendix C), followed by watching the video. Before the utility elicitation, respondents were asked which of the two health states was preferable.

Participants then valued the two health states in a TTO task with a 20-year time horizon and 1-year (i.e., 5%) trading increments. For each health state, participants were given a series of choices between spending a 20-year period in the health state being rated versus spending varying amounts of time in full health. Choices alternated between longer and shorter periods of time in full health [i.e., 20 years, 0 years (dead), 19, 1, 18, 2, 17, 3…]. Utility scores (u) were calculated as $u = x/y$ based on the point of indifference between y years in the health state being evaluated and x years in full health (followed by dead), yielding a utility score on a scale with the anchors of dead (0) and full health (1).

EQ-5D-3L Instrument

The EQ-5D-3L questionnaire was administered to characterize the sample in terms of overall health status. The EQ-5D is a generic, preference-weighted measure of health status [38–40]. The first section of this self-administered questionnaire includes five items assessing the dimensions of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Preference weightings are used to score responses on these five dimensions to obtain an "index score." The second section is a visual analog scale on which respondents rate their current health on a scale from 0 (worst imaginable health state) to 100 (best imaginable health state). The EQ-5D-3L index score was computed using tariffs derived from an Italian sample [41].

Statistical Analysis Procedures

Statistical analyses were completed using SAS version 9.4 (SAS Institute, Cary, NC, USA). Descriptive statistics were calculated for continuous variables (means and standard deviations) and categorical variables (frequencies and percentages). Demographic subgroups were compared with Chi-square analysis (for categorical variables) and independent t tests (for continuous variables). The pairwise comparisons between the two health state utilities were performed using a paired t test. The threshold for statistical significance was set at $p < 0.05$ for all comparisons.

RESULTS

Sample Description

Of the 310 potential participants who were screened, 51 did not meet inclusion criteria: 23 were unable to attend an interview session in Rome or Milan; five were outside the required age range; four did not have diabetes diagnosed by a physician; two did not remember their age at the time of diagnosis; five could not provide proof of diagnosis or treatment; and 12 said they did not want to sign a consent form. Of the

259 who were eligible, 236 were scheduled for interviews, of whom 220 actually attended their interview. Three of the 220 participants had difficulty understanding the utility interview procedures and health states and were therefore unable to provide valid data. Thus, a total of 217 interviews (108 in Rome, 109 in Milan) were successfully completed (see the demographic characteristics shown in Table 1). The sample was 50.2% female ($n = 109$), with a mean age of 56.1 years. The majority of participants reported ethnicity as White (98.6%). Most participants reported being employed (41.5% full-time and 14.3% part-time). Less than half of the sample reported having a "university degree" (24.0%) or higher. The most commonly reported comorbid health

Table 1 Demographic characteristics of participants who completed interviews ($N = 217$)

Characteristics	Statistics
Age (mean, SD)	56.1 (11.8)
Gender (n, %)	
Male	108 (49.8%)
Female	109 (50.2%)
Location (n, %)	
Rome	108 (49.8%)
Milan	109 (50.2%)
Ethnic/racial background (n, %)	
White	214 (98.6%)
Black	2 (0.9%)
Other	1 (0.5%)
Employment status (n, %)	
Full-time work	90 (41.5%)
Part-time work	31 (14.3%)
Other	96 (44.2%)
Education level (n, %)	
University degree	52 (24.0%)
No university degree	165 (76.0%)

SD Standard deviation

conditions were hypertension (50.7%), anxiety (24.4%), depression (9.7%), and diabetic retinopathy (9.2%).

The sample consisted of 26 participants (12.0%) with T1D and 191 participants (88.0%) with T2D (Table 2). Most participants (*n* = 214; 98.6%) reported that they were currently receiving medication treatment for diabetes, consisting of oral medication (84.3%), insulin (27.2%), non-insulin injectable medication (4.6%), and diet and exercise (6.5%). Of the 217 participants, 214 provided proof of current medication treatment. The other three participants provided a knowledgeable description of their diabetes symptoms and/or diagnosis which clearly indicated that they had been diagnosed with diabetes.

The mean EQ-5D-3L index score calculated using the Italian tariffs (0.91) [41] is the same as the mean score in a previous utility study conducted in a sample of patients with T2D in Italy [22]. The score range (0.36–1.00) and standard deviation (0.11) suggest that the sample was diverse in terms of health status.

Table 2 Clinical characteristics of study sample (*N* = 217)

Clinical characteristics	Statistics
Type of diabetes (*n*, %)	
Type 1 or juvenile diabetes	26 (12.0%)
Type 2, food diabetes, or adult diabetes	191 (88.0%)
Current treatment for diabetes (*n*, %)[a]	
Oral medication	183 (84.3%)
Insulin	59 (27.2%)
Injection	42 (19.4%)
Pump	17 (7.8%)
Both injection and pump	0
Non-insulin injectable medication	10 (4.6%)
Diet and exercise	14 (6.5%)
Dietary supplement	1 (0.5%)

[a] Not mutually exclusive

Preferences Between Standard and Concentrated Insulin

In the introductory task, participants were asked which health state they would prefer. Almost all participants (98.2%) preferred concentrated insulin. Two participants (0.9%) preferred standard insulin, and two participants (0.9%) said they had no preference. The pattern of preferences was similar in the T1D and T2D subgroups, with nearly all preferring concentrated insulin in both groups (T1D: *n* = 25, 96.2%; T2D: *n* = 188, 98.4%).

Health State Utilities

In the TTO task, 36 (16.6%) of the 217 respondents rated the concentrated insulin health state higher than the standard insulin health state. None of the participants rated the standard insulin health state higher than the concentrated insulin health state. The remaining 181 (83.4%) participants had the same utility score for both health states. In the total sample, the mean utility scores were 0.884 for standard insulin and 0.892 for concentrated insulin, with a mean difference score of 0.007 (Table 3). A paired *t* test revealed that the difference between the two health state means was statistically significant ($p < 0.0001$). Results followed similar patterns in the T1D and T2D subgroups (Table 3). All participants perceived both health states to be better than dead, and therefore, there were no negative utility scores.

Subgroup Analysis

Utilities were calculated separately for subgroups of participants. There were no statistically significant differences in utility scores by age (younger vs. older, categorized based on median split), city of residency (Rome vs. Milan), employment status (employed vs. not employed), or type of diabetes (T1D vs. T2D).

Mean utility scores were significantly higher for female participants than male participants for both standard insulin (difference between female and male 0.031, *p* = 0.025) and concentrated insulin (difference between female and

Table 3 Health state utilities for the total sample and two subgroups

Health state utilities	N	Mean (SD) health state utility[a]	95% CI	Mean (SD) difference score[b]
Total sample[c]				
Standard insulin	217	0.884 (0.101)	0.871, 0.898	0.007 (0.019)
Concentrated insulin	217	0.892 (0.099)	0.879, 0.905	
Type 1 diabetes subgroup				
Standard insulin	26	0.903 (0.072)	0.874, 0.932	0.008 (0.015)
Concentrated insulin	26	0.911 (0.064)	0.885, 0.937	
Type 2 diabetes subgroup				
Standard insulin	191	0.882 (0.104)	0.867, 0.897	0.007 (0.020)
Concentrated insulin	191	0.889 (0.103)	0.875, 0.904	

CI Confidence interval, *SD* standard deviation

[a] Time trade-off utilities are on a scale anchored to 0 representing dead and 1 representing full health

[b] Difference between standard health state and concentrated health state is calculated as: concentrated − standard

[c] To five decimal places, the means are 0.88433 for the standard health state and 0.89182 for the concentrated health state, with a difference of 0.00749, which rounds to 0.007 at three decimal places

male 0.030, $p = 0.027$). However, the utility difference between standard and concentrated insulin was almost identical for female and male participants, suggesting that gender did not have an effect on preference between the two health states. The mean utility difference between standard and concentrated insulin was 0.007 for women and 0.008 for men.

Analyses were also run to compare preferences of insulin users ($n = 59$) to patients who were not using insulin ($n = 158$), and no significant differences emerged between these two groups. When asked "Which of these health states do you prefer?", 57 (96.6%) of the 59 insulin users and 156 (98.7%) of the 158 patients not using insulin said they preferred the concentrated insulin health state. The two groups were also similar with regard to rates of differentiation between the concentrated and standard insulin health states in the TTO valuation task. Of the 59 insulin users, nine (15.3%) had a higher utility for the concentrated insulin health state, while 50 (84.7%) had the same utility for the two health states. Of the 158 patients not using insulin, 27 (17.1%) had a higher utility for concentrated insulin, while 131 (82.9%) had the same utility for the two health states. t tests found no statistically

significant difference between the two groups in the utility of the concentrated insulin health state, the utility of the standard insulin health state, or the difference score between the two health states.

DISCUSSION

Findings from this Italian sample provide insight into patient preferences associated with rapid-acting insulin concentration. Results are consistent with those from previous studies showing a preference for concentrated over standard insulin [33, 35]. The findings of the current study add to previous research by demonstrating the strength of this preference, while providing utility values that can represent patient preference in cost-effectiveness analyses comparing insulin formulations. In the current study, this preference was almost unanimous, with 98.2% of patients preferring concentrated insulin. When asked to explain their preference for concentrated insulin, patients cited a variety of reasons, often mentioning overall convenience of the concentrated formulation (patient quotes translated into English: "convenience and comfort, it simplifies everything"). Patients

also frequently said they liked the concentrated insulin option because it enabled them to carry fewer pens when traveling ("You carry around half the amount during travels") and because less space was required in their refrigerators at home. Others mentioned the importance of generating less waste by using fewer injection pens with concentrated insulin ("thinking about the environment and the planet, less waste is better for everyone"; "I think it's more ecological").

The current study builds on previous findings by showing that the preference for concentrated over standard insulin can be quantified in health state utilities. There was a mean utility difference of 0.007 between the two types of insulin, with concentrated insulin having the higher mean score. These findings add to the growing body of literature on utilities representing treatment process attributes [1, 2]. Treatment process utilities are increasingly being published and used to represent treatment preference in economic modeling.

The utility difference between standard and concentrated insulin may be incorporated into cost-utility models to inform resource allocation decision-making about these insulin formulations. However, in some countries, such as Italy, it may not be necessary to consider cost–benefit trade-offs when making these decisions because standard and concentrated formulations are the same price per unit of insulin [17, 42]. The concentrated formulation should be used to maximize preference, which could have a positive impact on treatment adherence and possibly treatment outcomes with no added cost.

When considering whether to use the current results in a cost-utility model, researchers should consider the magnitude of the utility difference between health states. For a preference between health states to result in different utility scores, the preference must be strong enough to cause a respondent to trade different amounts of time from a hypothetical life span. Despite the consistent preference for concentrated insulin in this study, the majority of patients (83.4%) did not trade different amounts of time when valuing the two health states. This resulted in a relatively small utility difference between the health states. It is not

known whether this utility difference can be considered clinically meaningful. Therefore, the difference score of 0.007 should be used in CUAs with appropriate caution. One approach would be to conduct a base case analysis without this utility adjustment, followed by a sensitivity analysis adjusting for the preference of concentrated over standard insulin. Reviewers could then consider results both with and without the small difference in utility.

Other limitations should also be considered. As with all vignette-based utility assessments, the resulting utility scores represent the specific health states, which are based on descriptions of a disease and its treatment rather than actual patient experience. The extent to which the current results might differ from utilities derived from patients who have actually used both insulin concentrations is not known. There are other limitations associated with characteristics of the sample. Patients were recruited and interviewed in two cities in Italy, and generalizability of these preferences to other countries is unknown. Furthermore, the subgroup of patients with T1D was small. Therefore, results for this subgroup should be interpreted with caution.

Another limitation is that the health states described only rapid-acting mealtime insulin, and the resulting preferences for concentrated insulin are not necessarily applicable to other treatments. For example, the utility difference between standard and concentrated formulations may not be the same for a basal insulin administered only once per day. Future research may examine whether preferences between the different formulations can be generalized to treatments other than rapid-acting mealtime insulin.

CONCLUSIONS

This study adds to literature suggesting that concentration of rapid-acting insulin should be considered because it could have an impact on patient preference. Patients consistently preferred concentrated over standard insulin, and for some patients this difference had an impact on utility valuations. This preference could be clinically meaningful because treatments that are preferred by patients may be associated with

better treatment adherence, which can influence health outcomes.

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Compliance with Ethics Guidelines. Participants were required to provide written informed consent before completing study procedures, and all procedures and materials were approved by an independent institutional review board (Ethical & Independent Review Services; Study Number 18006). Thus, the study conformed with the Helsinki Declaration of 1964, as revised in 2013, concerning human and animal rights, and Springer's policy concerning informed consent has been followed.

Data Availability. The dataset is available from the corresponding author on reasonable request.

REFERENCES

1. Brennan VK, Dixon S. Incorporating process utility into quality adjusted life years: a systematic review of empirical studies. Pharmacoeconomics. 2013;31(8):677–91.

2. Higgins A, Barnett J, Meads C, Singh J, Longworth L. Does convenience matter in health care delivery? A systematic review of convenience-based aspects of process utility. Val Health. 2014;17(8):877–87.

3. Gelhorn HL, Poon JL, Davies EW, Paczkowski R, Curtis SE, Boye KS. Evaluating preferences for profiles of GLP-1 receptor agonists among injection-naive type 2 diabetes patients in the UK. Patient Prefer Adherence. 2015;9:1611–22.

4. Hixson-Wallace JA, Dotson JB, Blakey SA. Effect of regimen complexity on patient satisfaction and compliance with warfarin therapy. Clin Appl Thromb Hemost. 2001;7(1):33–7.

5. Matza LS, Boye KS, Currie BM, et al. Patient perceptions of injection devices used with dulaglutide and liraglutide for treatment of type 2 diabetes. Curr Med Res Opin. 2018;34(8):1457–64.

6. Matza LS, Boye KS, Stewart KD, Davies EW, Paczkowski R. Health state utilities associated with attributes of weekly injection devices for treatment of type 2 diabetes. BMC Health Serv Res. 2017;17(1):774.

7. Shikiar R, Rentz AM. Satisfaction with medication: an overview of conceptual, methodologic, and regulatory issues. Val Health. 2004;7(2):204–15.

8. Freemantle N, Satram-Hoang S, Tang ET, et al. Final results of the DAPS (Denosumab Adherence Preference Satisfaction) study: a 24-month, randomized, crossover comparison with alendronate in postmenopausal women. Osteoporos Int. 2012;23(1):317–26.

9. Morris LS, Schulz RM. Medication compliance: the patient's perspective. Clin Ther. 1993;15(3):593–606.

10. Raue PJ, Schulberg HC, Heo M, Klimstra S, Bruce ML. Patients' depression treatment preferences and initiation, adherence, and outcome: a randomized primary care study. Psychiatr Serv. 2009;60(3):337–43.

11. Schaller M, Sigurgeirsson B, Sarkany M. Patient-reported outcomes from two randomised studies comparing once-weekly application of amorolfine 5% nail lacquer to other methods of topical treatment in distal and lateral subungual onychomycosis. Mycoses. 2017;60(12):800–7.

12. Shikiar R, Rentz AM, Barone J, Duncanson F, Katz E. Patient satisfaction with ofloxacin (F) and polymyxin B/Neomycin/Hydrocortisone© in the treatment of otitis externa: results from two randomized clinical trials. J Manag Care Med. 2002;6(3):24–7.

13. Shingler SL, Bennett BM, Cramer JA, Towse A, Twelves C, Lloyd AJ. Treatment preference, adherence and outcomes in patients with cancer: literature review and development of a theoretical model. Curr Med Res Opin. 2014;30(11):2329–41.

14. Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2018;41(12):2669–701.

15. Anderson JH Jr, Brunelle RL, Keohane P, et al. Mealtime treatment with insulin analog improves postprandial hyperglycemia and hypoglycemia in patients with non-insulin-dependent diabetes mellitus. Multicenter Insulin Lispro Study Group. Arch Internal Med. 1997;157(11):1249–55.

16. Anderson JH Jr, Brunelle RL, Koivisto VA, et al. Reduction of postprandial hyperglycemia and frequency of hypoglycemia in IDDM patients on insulin-analog treatment. Multicenter Insulin Lispro Study Group. Diabetes. 1997;46(2):265–70.

17. Agenzia Italiana Del Farmaco (AIFA). Humalog 200UI (€110,21/pack). Gazzetta Ufficiale della Repubblica Italiana del 28/07/2016. Serie generale 175. Rome: Gazzetta Ufficiale della Repubblica Italiana, Istituto Poligrafico e Zecca dello Stato; p 32 2016.

18. Eli Lilly and Company. Summary of Product Characteristics—Humalog 100 units/ml. Eli Lilly Nederland B.V., Utrecht, The Netherlands; 2017.

19. Stewart KD, Johnston JA, Matza LS, et al. Preference for pharmaceutical formulation and treatment process attributes. Patient Prefer Adherence. 2016;10:1385–99.

20. Brazier J, Ratcliffe J, Salomon JA, Tsuchiya A. Measuring and valuing health benefits for economic evaluation. 2nd ed. Oxford: Oxford University Press; 2017.

21. Boye KS, Matza LS, Walter KN, Van Brunt K, Palsgrove AC, Tynan A. Utilities and disutilities for attributes of injectable treatments for type 2 diabetes. Eur J Health Econ. 2011;12(3):219–30.

22. Matza LS, Boye KS, Jordan JB, et al. Patient preferences in Italy: health state utilities associated with attributes of weekly injection devices for treatment of type 2 diabetes. Patient Prefer Adherence. 2018;12:971–9.

23. Matza LS, Boye KS, Yurgin N, et al. Utilities and disutilities for type 2 diabetes treatment-related attributes. Qual Life Res. 2007;16(7):1251–65.

24. Matza LS, Stewart KD, Davies EW, Hellmund R, Polonsky WH, Kerr D. Health state utilities associated with glucose monitoring devices. Val Health. 2017;20(3):507–11.

25. Beaudet A, Palmer JL, Timlin L, et al. Cost-utility of exenatide once weekly compared with insulin glargine in patients with type 2 diabetes in the UK. J Med Econ. 2011;14(3):357–66.

26. Bilir SP, Li H, Wehler EA, Hellmund R, Munakata J. Cost effectiveness analysis of a flash glucose monitoring system for type 1 diabetes (T1DM) patients receiving intensive insulin treatment in Europe and Australia. Val Health. 2016;19(7):A697–8.

27. Nauck MA, Petrie JR, Sesti G, et al. A phase 2, randomized, dose-finding study of the novel once-weekly human GLP-1 analog, semaglutide, compared with placebo and open-label liraglutide in patients with type 2 diabetes. Diabetes Care. 2016;39(2):231–41.

28. Mittendorf T, Smith-Palmer J, Timlin L, Happich M, Goodall G. Evaluation of exenatide vs. insulin glargine in type 2 diabetes: cost-effectiveness analysis in the German setting. Diabetes Obes Metab. 2009;11(11):1068–79.

29. Samyshkin Y, Guillermin AL, Best JH, Brunell SC, Lloyd A. Long-term cost-utility analysis of exenatide once weekly versus insulin glargine for the treatment of type 2 diabetes patients in the US. J Med Econ. 2012;15(Suppl 2):6–13.

30. Sinha A, Rajan M, Hoerger T, Pogach L. Costs and consequences associated with newer medications for glycemic control in type 2 diabetes. Diabetes Care. 2010;33(4):695–700.

31. Rees TM, Lennartz AH, Ignaut DA. A comparison of glide force characteristics between 2 prefilled insulin lispro pens. J Diabetes Sci Technol. 2015;9(2):316–9.

32. Fusco A, Colarusso S, Piscopo M, et al. Despite being apparently equal, concentrated lispro-200 performs metabolically and subjectively better than lispro-100. Divers Equal Health Care. 2018;15(2):57–65.

33. Gentile S, Fusco A, Colarusso S, et al. A randomized, open-label, comparative, crossover trial on preference, efficacy, and safety profiles of lispro insulin u-100 versus concentrated lispro insulin u-200 in patients with type 2 diabetes mellitus: a possible contribution to greater treatment adherence. Expert Opin Drug Saf. 2018;17(5):445–50.

34. Van Brunt K, Pedersini R, Rooney J, Corrigan SM. Behaviours, thoughts and perceptions around mealtime insulin usage and wastage among people with type 1 and type 2 diabetes mellitus: a cross-sectional survey study. Diabetes Res Clin Pract. 2017;126:30–42.

35. Wang T, Conrad KA, van Brunt K, Rees TM. Attributes influencing insulin pen preference among caregivers and patients with diabetes who require greater than 20 units of mealtime insulin. J Diabetes Sci Technol. 2016;10(4):923–31.

36. Disoteo O, Grimaldi F, Papini E, et al. State-of-the-art review on diabetes care in Italy. Ann Global Health. 2015;81(6):803–13.

37. Italian National Institute of Statistics (ISTAT). Diabetes in Italy years 2000–2016. Gargiulo L, Burgio A, Grippo F, editors. January 20, 2017 https://www.istat.it/it/files//2017/07/Report_Diabetes_En_def.pdf. Accessed 20 Jan 2019.

38. Brooks R. EuroQol: the current state of play. Health Policy. 1996;37(1):53–72.

39. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011;20(10):1727–36.

40. The EuroQol Group. EuroQol—a new facility for the measurement of health-related quality of life. Health Policy. 1990;16(3):199–208.

41. Scalone L, Cortesi PA, Ciampichini R, et al. Italian population-based values of EQ-5D health states. Val Health. 2013;16(5):814–22.

42. Agenzia Italiana Del Farmaco (AIFA). Humalog 100 UI (€55,12/pack). Supplemento ordinario n. 23. Serie generale 35. Rome: Gazzetta Ufficiale della Repubblica Italiana, Istituto Poligrafico e Zecca dello Stato; 2009.