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The SWITCH Study (Sensing With Insulin pump Therapy to Control HbA_{1c}): Design and Methods of a Randomized Controlled Crossover Trial on Sensor-Augmented Insulin Pump Efficacy in Type 1 Diabetes Suboptimally Controlled with Pump Therapy

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Abstract

Background: Studies investigating the effect of real-time continuous glucose monitoring (CGM) combined with pump therapy on glycemic outcomes in type 1 diabetes are increasing. Pump therapy is well established as a "gold standard" for insulin delivery, offering improvements over multiple daily insulin injections. However, there is still a proportion of subjects using continuous subcutaneous insulin infusion in whom goals for metabolic control are far from achieved or benefits of this type of insulin therapy are transient. The SWITCH (Sensing With Insulin pump Therapy to Control HbA_{1c} [hemoglobin A1c]) study is a multicenter, randomized, controlled, crossover study to evaluate if adding CGM to experienced pump patients with suboptimal metabolic control will provide additional insight enabling clinical and therapeutic benefit.

Methods: Subjects meeting the inclusion criteria were randomized to Sensor On or Sensor Off arms for 6 months, after a 1-month run-in period. Following a 4-month washout period, the subjects crossed over to the other study arm for 6 months. The primary end point was the between arm difference in HbA_{1c} levels. Among others, additional end points include time spent in different glycemic ranges, percentage of patients with HbA_{1c} <7%, number of hypoglycemic events, glucose variability parameters, safety outcomes, treatment satisfaction, and quality of life.

Results: Recruitment occurred between January 2008 and February 2009. A total of 153 patients were randomized. Study completion is anticipated in July 2010.

Conclusions: The results will establish if adding CGM to existing, capable, insulin pump users can enable better metabolic control.

Introduction

Real-time (RT) continuous glucose monitoring (CGM) allows people with diabetes to see their glucose levels continuously using a subcutaneous sensor, a transmitter, and a receiving device.[1] Accessibility of glucose values enables recognition of previously undetected glucose levels, direction and rate of change, and glucose trends. This possibility may offer benefits over using self-monitoring blood glucose (SMBG) alone guiding the patients in making lifestyle and treatment modifications to more effectively manage their diabetes. Indeed, the study by Deiss et al.[2] and the Juvenile Diabetes Research Foundation study[3] showed that RT-CGM can be associated with improved glycemic control regardless of the insulin delivery method in subjects with type 1 diabetes (T1D). Recently, Raccah et al.[4] also demonstrated that in patients previously naive to continuous subcutaneous insulin infusion (CSII), when switched to insulin pump, those with a

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sensor-augmented pump system had a better opportunity for hemoglobin A1c (HbA_{1c}) improvement. Likewise, in spite of a small sample size, O'Connell et al.[5] showed that well-controlled T1D patients can integrate RT-CGM into existing CSII treatment in order to improve glycemic control. Considering reported data, RT-CGM may possibly be viewed as a behavior-modification tool, and its success is directly dependent on the manner in which it is used.[6] In all the previously mentioned studies there was a positive association between overall sensor use and glycemic profile benefit.

Crossover studies of longer duration are not a conventionally applied methodology in diabetes. Benefits of this design include smaller sample size and greater efficiency than in parallel studies, as between-patient variation is removed as a subject acts as his or her own control. Challenges to this methodology include longer study duration and the risks to protocol compliance, dropouts, missing data, or the undesirable effects of carryover. Ludvigsson and Hanas,[7] DeVries et al.,[8] and the 5-Nations Trial[9] provided examples of crossover designs, but these studies compared pump therapy to multiple daily injection therapy. Only in the study by Ludvigsson and Hanas[7] was retrospective CGM incorporated in order to facilitate treatment and patient motivation. The authors emphasized that the study was conducted at the introduction of CGM into clinical practice, where device inexperience created challenges for patient education.[7] Similarly, STAR-1, a sensor-augmented pump versus conventional pump study, also attributed failure to show significant metabolic differences to the newness of the device, use of new device features by both treatment groups, and frequency of study visits.[10]

The aim of the SWITCH (Sensing With Insulin pump Therapy to Control HbA_{1c}) study is to determine whether patients with T1D with suboptimal glycemic control already using CSII can improve metabolic profile using sensor-augmented pump therapy (SAPT). In this present article the SWITCH study design and methods are described, in particular, the crossover design and a selection process, which includes a run-in period incorporating educational assessment, to augment subject compliance to the protocol. Hence, the methodological design described here intends to control for confounders and elucidate the value of RT-CGM.

Study Design and Methods

The study was conducted in four adult and four pediatric sites in Europe experienced in personal CGM and insulin pump therapy. The total study duration for the patient was 17 months, including a run-in period, two 6-month treatment periods, and a 4-month washout period (Fig. 1). Randomization was done electronically via case report form according to a predefined randomization sequence on a 1:1 ratio within age groups in each center. All HbA_{1c} measurements were sent to a centralized laboratory for analysis (Laboratorium für Klinische Forschung GmbH, Kiel, Germany). A total of 153 subjects were randomized to the study (Fig. 2). The study

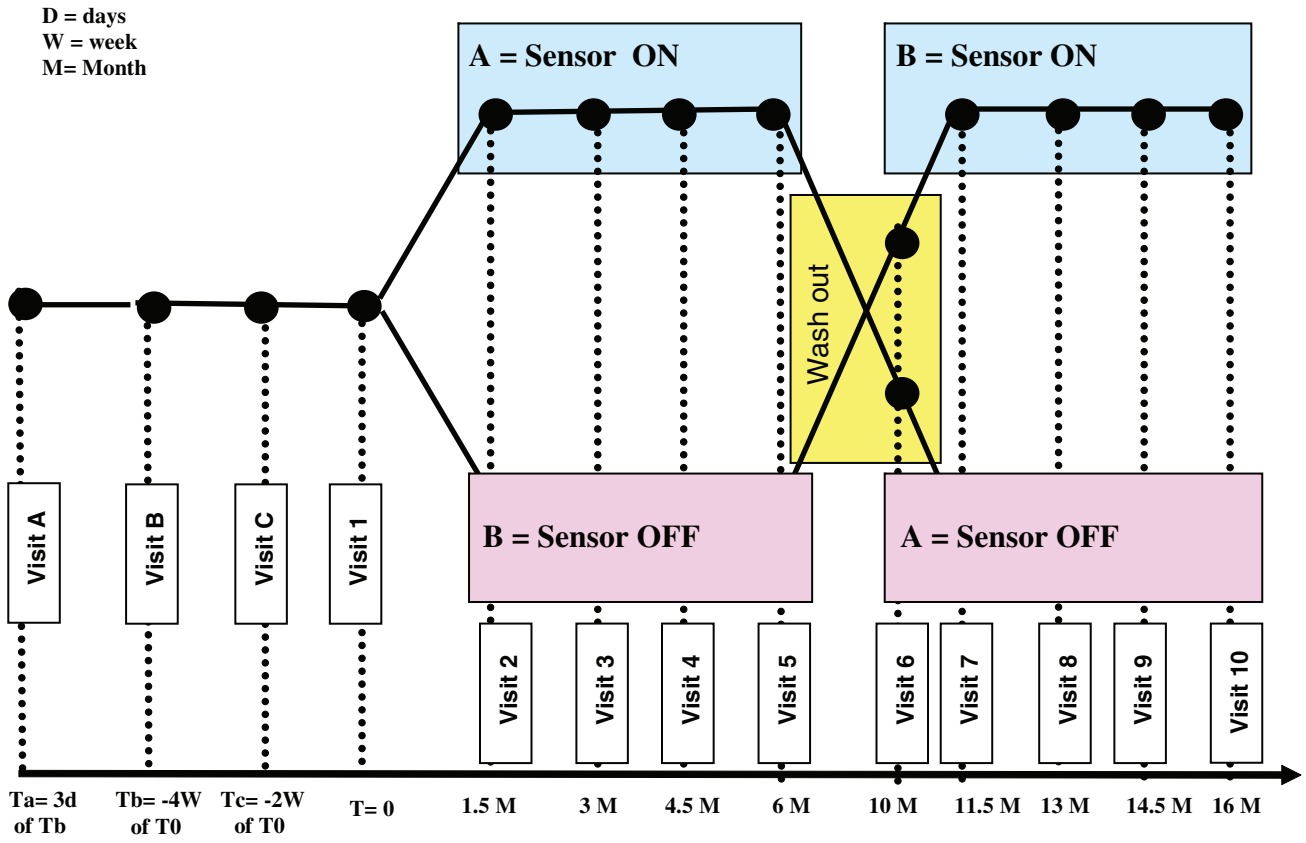

FIG. 1. The SWITCH (Sensing With Insulin pump Therapy to Control HbA_{1c} [hemoglobin A1c]) study design and visit plan. Color images available online at www.liebertonline.com/dia.

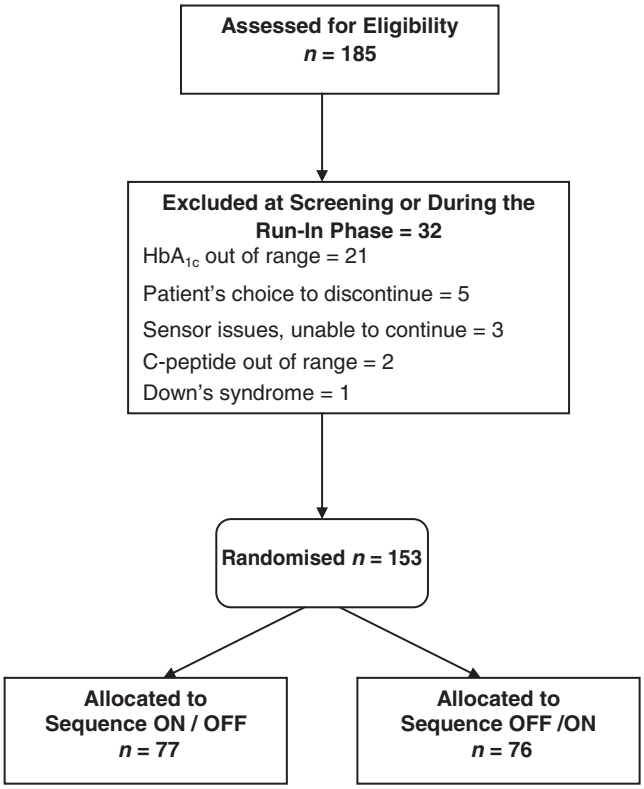

FIG. 2. The SWITCH (Sensing With Insulin pump Therapy to Control HbA_{1c} [hemoglobin A1c]) CONSORT flow chart to randomization.

protocol received institutional Ethics Committee approval at each of the study centers. A written consent was obtained from all participants, with additional parent consent for participants <18 years old.

Screening

Subjects between 6 years and 70 years of age with T1D for >1 year and CSII >6 months with suboptimal control (7.5% $\leq HbA_{1c} \leq 9.5\%$) who were naive to RT-CGM were invited to take a five-question multiple choice test concerning pump therapy and general diabetes understanding. If the exam was passed with 100% outcome, they were invited to join the study (Visit A). Other inclusion and exclusion criteria are listed in Table 1.

Run-in phase

Following inclusion, patients were switched to the Bayer Ascensia® Contour glucose meter (without radiofrequency communication capability) [Bayer Suisse (AG) Diabetes Care, Zurich, Switzerland] and the Medtronic MiniMed Paradigm® REAL-Time System (Medtronic Inc., Northridge, CA) and received retraining on the principles of diabetes therapy and practical aspects of the pump system (Visit B). The system was worn for 2 weeks, after which blinded CGM data were collected over the next 2 weeks using the Guardian® REAL-Time System Clinical (Medtronic Inc.) (Visit C). Centers provided training on sensor insertion and device use. Evaluation of the subject's understanding of this training and incorporation of training given at Visit B were assessed by getting nine correct answers in a 10-question test. Failure to pass this test resulted in a screening failure. (See Supplementary Appendix [Supplementary Data are available online at www.liebertonline.dia].)

Treatment periods

Subjects were randomized at Visit 1 to either Sensor ON or Sensor OFF arms for 6 months. The Sensor ON arm received additional training and passed the Paradigm REAL-Time Comprehension exam (90% result on a 12-question test). Failure to pass this test resulted in re-education in the challenging areas. Subjects were advised to wear the sensor 85% of the time in the first 3 weeks to go through the "learning curve" and any potential challenges with the technology at this early stage. Subsequently, the subjects were advised to wear the sensor "continuously" or at minimum 80% for the duration of the treatment period. The Sensor OFF arm received this training and testing at Visit 6, after crossover following the washout period. Investigators were given a technical training checklist, and patients were provided optional diaries. For all subjects, study visits occurred every 6 weeks, when devices were uploaded by the medical team using the Medtronic CareLink® Therapy Management System and results were reviewed for treatment optimization. Visit frequency was determined by the memory capacity of the device, for example, if all features of the pump were used at maximum for the Sensor ON arm it would ensure no loss of data from memory overload. The RT-CGM and pump profiles for the Sensor ON arm were reviewed to make therapy adjustments, whereas SMBG data and pump profiles were used in the Sensor OFF arm. Patients were requested to perform more than four SMBG tests per day. Additionally, blinded CGM was collected from the Guardian REAL-Time Clinical device for 2 weeks prior to each visit in Sensor OFF arm. No treatment protocols or fixed algorithms were provided to the centers, and therapy adjustments were made in partnership with subjects at clinic visits. It remained the medical responsibility of the treating physician to guide the subject in reaction to RT-CGM values and hyper- and hypoglycemic alerts. Subjects were encouraged to make self-adjustments to their treatment, and examples of therapy changes were provided in the optional patient diary. Treatment satisfaction questionnaires[11] (Diabetes Treatment Satisfaction Questionnaires, subjects >18 years) and quality of life questionnaires[12] (PedsQL subjects ≤18 years old) are given to the subject at the start and end of each treatment period (Visit B, Visit 5, Visit 6, and Visit 10).

Washout

During this 4-month period, subjects continued with the provided study devices and wore the blinded device to collect CGM data 2 weeks before the end of the washout period. No RT-CGM was used by the subjects during this period. No other protocol was given to the subject in order to affect similar conditions between Visit 1 and Visit 6. As we found no published data on carryover in RT-CGM, the SWITCH study controlled for a possible carryover effect with a 4-month washout period, which we defined from unpublished data from previous studies and the half-life of the HbA_{1c} measurement. Device uploads following the washout period (Visit 6) were reviewed for evidence of RT-CGM use, and if

Table 1. The SWITCH Study Inclusion and Exclusion Criteria

Inclusion criteria
Diagnosed with type 1 diabetes mellitus at least 12 months prior to signature of PIC
Documented suppressed C-peptide (<0.2 nmol) in the patient file measured within the last 3 months, or as evidenced by central lab value taken at screening
Aged between 6 and 70 years old (inclusive) at signature of PIC (children, 6 years inclusive to 18 years inclusive; adults, 19 years inclusive to 71 years exclusive)
HbA_{1c} (DCCT standard) must be ≥7.5% and ≤9.5% as evidenced by central lab value taken at screening
Treated by CSII at least 6 months prior to signature of PIC
Performance of an average of four SMBG tests per day, as evidenced from patient files or SMBG memory recall or meter downloads
Treated by the investigator's center for at least 6 months prior to signature of PIC
Female patients of child-bearing potential are using adequate contraception means, as assessed by the investigator.
Exclusion criteria
Patient has previous experience with PRT System or Guardian REAL-Time within 4 months prior to signature of PIC.
Existing pregnancy or intention to conceive (as assessed by investigator)
Hypoglycemic unawareness as assessed by the investigator or evidence of three or more incidents in the last 12 months of severe hypoglycemia with documented blood glucose below 50 mg/dL, resulting in unconsciousness, hospitalization, or third-party assistance, where recovery follows treatment with glucose or glucagon or similar
Hearing or vision impairment so that glucose display and alarms cannot be recognized
Documented cutaneous allergy or disease (allergy to sensor or components of the sensor, psoriasis, *Staphylococcus*, exanthema, etc.)
Any documented concomitant chronic disease known to affect diabetes control (e.g., altered renal function, active cancer undergoing treatment, Crohn's disease, ulcerative colitis, Addison disease) or any concomitant pharmacological treatment that might modify glycemic values (e.g., chronic corticosteroid therapy), eating disorders, and morbid obesity (defined as adults with BMI >35 kg/m^2 and children with BMI >2 SD for age) as assessed by the investigator
Any other medical, social, or psychological condition that, in the investigator's opinion, makes the patient unable to comply with the study protocol and all study procedures
Plans to travel for extended periods (3+ weeks) where the devices cannot be supplied or replaced and/or medical support is limited (e.g., exotic countries, remote places)
Participation in another clinical study, ongoing or completed less than 3 months prior to signature of PIC
Alcohol or drug abuse, other than nicotine
For pediatric subjects: does not have a reliable support person

BMI, body mass index; CSII, continuous subcutaneous insulin infusion; DCCT, Diabetes Control and Complications Trial; HBA_{1c}, hemoglobin A1c; PRT, Paradigm REAL-Time; PIC, patient informed consent; SMBG, self-monitoring blood glucose; SWITCH, Sensing With Insulin pump Therapy to Control HbA_{1c}.

necessary the washout period could be extended to ensure compliance.

Sample size estimation and statistical analysis

Sample size of 124 subjects (62 randomized to sequence ON/OFF and 62 randomized to sequence OFF/ON) was calculated assuming a two-tailed matched-pairs *t* test and a type I error of 5%. With this sample size the study is powered at 90% to detect a mean difference of 0.3% in HbA_{1c}. An SD of 1.0% has been assumed. In order to account for the duration of the study and possible dropouts or nonevaluable subjects, the sample size is increase by approximately 20%, giving a sample size of 160.

The primary end point is the difference in HbA_{1c} level between the Sensor ON and the Sensor OFF after 6 months of follow-up. Mean, SD, and 95% confidence intervals for the 6-month HbA_{1c} level will be reported.

The two groups will be compared using an analysis of variance adjusting for period effect and declaring subject as random effect. Period will be included in the model regardless of statistical significance. A 95% confidence interval and a *P* value will be given for the difference of the study arms based on the analysis of variance model. It is known that preliminary testing for carryover has harmful effects and should be avoided;[13,14] therefore this has been already addressed in the design phase of the study by using a 4-month washout period. Data will be analyzed using Per Protocol as well as Intent to Treat principles. The Intent to Treat population consists of all randomized patients irrespective of their compliance to the planned course of treatment or deviations from the protocol. In case of missing data in the Intent to Treat analysis, measurements from the same study period will be carried forward to substitute for missing end-of-period values, if they originate from at least 3 months from start of the period (Visit 3 in the first period and Visit 8 in the second period). If no measurements can be carried forward, as a conservative approach the end-of-period data that are available only for one period will be used to impute missing data in the other period. The Per Protocol population for the primary analysis of HbA_{1c} level is defined as the set of successfully randomized subjects (regardless of number of SMBG) with minimum sensor use (Sensor ON arm), with no violation of entry criteria and who are compliant with the protocol. HbA_{1c} data will be included in the analysis also in case the associated blinded sensor data for patients in the Sensor OFF arm are missing.

Secondary end points will be compared using an analysis of variance model similar to the one defined for the analysis of the primary end point. Sensor data for the secondary end points will be extracted from CareLink Clinical during the 15-day period prior the end-of-period visit day (Visit 5 and Visit

10 in Fig. 1). Included subjects will have at least 7 days of data. Summary statistics such as mean, SD, median, range, and percentiles will be given for additional end points. The statistical analysis plan for the SWITCH study was externally reviewed by the Jaeb Center for Health Research, Tampa, FL.

Discussion

The SWITCH study will be the first randomized crossover trial evaluating the inherent impact of sensor therapy in children and adults with T1D with suboptimal glycemic control despite using CSII. The study subjects are established patients using CSII, yet despite good knowledge of the condition and pump therapy and that they attend a highly experienced CSII-specialized center, good metabolic control has still not manifested. The SWITCH study population comprised adults and children with almost equal representation and dictates the same level of sensor usage compliance. SWITCH intends to elucidate whether the possible glycemic benefits seen in participants with suboptimal metabolic control despite previous intensive management with pump therapy are related to the introduction of RT-CGM, rather than reflecting the improvement associated to a better use of CSII technology. Knowledge gained from other studies has been applied by including assessments of the patient's level of knowledge regarding the disease and the therapy via mandatory tests and, by implementing a training checklist, to ensure appropriate therapy coverage by the participating centers teaching RT-CGM.

The last subject visit in SWITCH study is expected in July 2010 and will be followed by comprehensive data analyses.

Appendix

Steering Committee

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Author Disclosure Statement

I.C. reports receiving lectures and consulting fees from Medtronic Inc., Bayer AG, GSK, Eli Lilly & Co., NovoNordisk A/S, Sanofi-Aventis, Novartis, and MSD. T.B. reports receiving consulting fees from Medtronic Inc. and Bayer AG, speaking fees from Bayer AG, Eli Lilly & Co., Medtronic Inc., and Novo Nordisk A/S, and research grants from Abbott Diabetes Care. M.G. reports receiving lectures fees from Medtronic Inc, GSK, NovoNordisk A/S, Sanofi-Aventis, Novartis, and MSD. H.G. and J.C. are fulltime employees of Medtronic Inc. J.B. reports receiving lectures fees from Medtronic Inc., Abbot Diabetes Care, Sanofi-Aventis, and MSD and consulting fees from Abbot Diabetes Care, Sanofi-Aventis, MSD, and Astra-Zeneca.

References

1. Gilliam LK, Hirsch IB: Practical aspects of real-time continuous glucose monitoring. Diabetes Technol Ther 2009; 11(Suppl 1):S75–S82.
2. Deiss D, Bolinder J, Riveline JP, Battelino T, Bosi E, Tubiana-Rufi N, Kerr D, Phillip M: Improved glycemic control in poorly controlled patients with type 1 diabetes using real-time continuous glucose monitoring. Diabetes Care 2006;29:2730–2732.
3. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group, Tamborlane WV, Beck RW, Bode BW, Buckingham B, Chase HP, Clemons R, Fiallo-Scharer R, Fox LA, Gilliam LK, Hirsch IB, Huang ES, Kollman C, Kowalski AJ, Laffel L, Lawrence JM, Lee J, Mauras N, O'Grady M, Ruedy KJ, Tansey M, Tsalikian E, Weinzimer S, Wilson DM, Wolpert H, Wysocki T, Xing D: Continuous glucose monitoring and intensive treatment of type 1 diabetes. N Engl J Med 2008;359:1464–1476.
4. Raccah D, Sulmont V, Reznik Y, Guerci B, Renard E, Hanaire H, Jeandidier N, Nicolino M: Incremental value of continuous glucose monitoring when starting pump therapy in patients with poorly controlled type 1 diabetes: the Real-Trend study. Diabetes Care 2009;32:2245–2250.
5. O'Connell MA, Donath S, O'Neal DN, Colman PG, Ambler GR, Jones TW, Davis EA, Cameron FJ: Glycaemic impact of patient-led use of sensor-guided pump therapy in type 1 diabetes: a randomised controlled trial. Diabetologia 2009; 52:1250–1257.
6. Cohen O, Körner A, Chlup R, Zoupas CS, Ragozin AK, Wudi K, Bartaskova D, Pappas A, Niederland T, Taybani Z, Barák L, Vazeou A; Central and Eastern Europe, Greece, and Israel Continuous Glucose Sensing Collaborative Study Group: Improved glycemic control through continuous glucose sensor-augmented insulin pump therapy: prospective results from a community and academic practice patient registry. J Diabetes Sci Technol 2009;3:804–811.
7. Ludvigsson J, Hanas R: Continuous subcutaneous glucose monitoring improved metabolic control in pediatric patients with type 1 diabetes: a controlled crossover study. Pediatrics 2003;111:933–938.

8. DeVries JH, Snoek FJ, Kostense PJ, Masurel N, Heine RJ: A randomized trial of continuous subcutaneous insulin infusion and intensive injection therapy in type 1 diabetes for patients with long-standing poor glycemic control. Diabetes Care 2002;25:2074–2080.
9. Hoogma RP, Hammond PJ, Gomis R, Kerr D, Bruttomesso D, Bouter KP, Wiefels KJ, de la Calle H, Schweitzer DH, Pfohl M, Torlone E, Krinelke LG, Bolli GB; 5-Nations Study Group: Comparison of the effects of continuous subcutaneous insulin infusion (CSII) and NPH-based multiple daily insulin injections (MDI) on glycaemic control and quality of life: results of the 5-nations trial. Diabet Med 2006;23:141–147.
10. Hirsch IB, Abelseth J, Bode BW, Fischer JS, Kaufman FR, Mastrototaro J, Parkin CG, Wolpert HA, Buckingham BA: Sensor-augmented insulin pump therapy: results of the first randomized treat-to-target study. Diabetes Technol Ther 2008;10:377–383.
11. Bradley C, Lewis KS: Measures of psychological well-being and treatment satisfaction developed from the responses of people with tablet-treated diabetes. Diabet Med 1990;7:445–451.
12. Varni JW, Seid M, Rode CA: The PedsQL: measurement model for the pediatric quality of life inventory. Med Care 1999;37:126–139.
13. Senn S: Cross-Over Trials in Clinical Research. Chichester, UK: John Wiley & Sons, 2002.
14. Jones B, Kenward M: Design and Analysis of Cross-Over Trials, 2nd ed. Boca Raton, FL: Chapman & Hall/CRC, 2003.

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