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Title

Effectiveness, safety and costs of the FreeStyle Libre Glucose Monitoring System for children and adolescents with T1DM in Spain: A multicentre prospective observational study

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Abstract

Objectives

This study aims to evaluate the effectiveness, safety and costs of the FreeStyle Libre® (FSL) for Type 1 Diabetes Mellitus (T1DM) in childhood and adolescence.

Design

Prospective multicentre observational study.

Setting

Study carried out in 13 public hospitals throughout Spain. Patients were recruited between January 2019 and March 2020, with a 12-month follow-up.

Participants

165 patients with ages between 4 and 17 years and diagnosis of diabetes were included.

Primary and secondary outcome measures

The primary outcome was the change in HbA1c level from baseline to follow up. Mixed regression models with repeated measures were used. The cost intervention was estimated from the National Health System (NHS) perspective.

Results

There were 156 subjects included in the analysis. A statistically significant reduction of HbA1c was observed in the subgroup with baseline HbA1c≥7.5% (-0.46%, -0.49% and -0.35% at 3, 6 and 12 months, respectively), whereas well-controlled patients revealed a significant 12-month worsening (0.32%) (P<0.001 for the interaction). For the whole sample, there was a statistically significant reduction of severe hypoglycaemic events compared to the previous year (-0.37, P=0.004). Although the interaction with baseline HbA1c group did not attain statistical significance, descriptive results indicate that reduction could occur only in well-controlled patients. Adolescents showed a significantly lower sensor usage time and scans per day than children. Reduction of HbA1c was related to device adherence. No serious adverse effects were observed. The use of FSL could reduce total direct costs from the NHS perspective.

Conclusions
The results suggest that use of FSL in underage T1DM patients is related to a statistically significant reduction of severe hypoglycaemia. HbA1c was significantly improved only in patients with poor baseline control. Monitoring costs attributed to test strips and lancets, as well as costs attributable to caregivers´ productivity loss, are reduced among FSL users.

What is already known on this topic
Glucose monitoring devices may help people with diabetes monitor their glycaemia levels and the acute complications of the disease, thus improving their health-related quality of life.

What this study adds
This study provides nationally contextualised real-world scientific evidence on the effectiveness, safety and costs of the flash glucose monitoring systems (FreeStyle Libre® system [FSL]) indicated for DM1 in childhood and adolescence in Spain.

How this study might affect research, practice or policy
These findings support that the use of FSL reduces severe hypoglycaemia in underage T1DM patients. In addition, glucose levels are reduced in patients with HbA1c levels greater than 7.5%.
The use of FSL reduces the cost of disease monitoring in addition to costs attributable to lost productivity of parents/caregivers in underage patients with T1DM.

Keywords
Continuous glucose monitoring, HbA1c, Type 1 diabetes, costs, Spain.

Word count 4094

Introduction

Type 1 Diabetes Mellitus (T1DM) requires continuous medical monitoring, to reduce the development of vascular complications [1,2]. The early onset and chronic character of this condition increase the likelihood of reducing health-related quality of life (HRQoL) and health expectancy among young T1DM people [3]. A total of 586,000 children aged under 15 years suffer from T1DM globally [4]. In Spain, the incidence is 11.5-27.6/100,000[5], which represents a high cost to society [6].

To reduce the risk of short (metabolic) and long-term (vascular) diabetes complications, frequent determination of blood glucose levels is required. Continuous glucose monitoring systems, such as the flash glucose monitoring (FGM) systems contribute to glycaemia monitoring, as well as to reduce the daily number of fingersticks [7]; providing dynamic information to the user about their glucose level. FreeStyle Libre® (FSL), developed and marketed in Spain by Abbott Laboratories, has been indicated to measure glucose levels in the interstitial fluid in people aged over four years with T1DM. No serious adverse effects related to the use of these devices have been reported. Mild effects consist of skin problems in the area where the sensor is inserted, similar to other FGM [8,9].

FSL consists of: 1) an arm sensor that measures and stores interstitial glucose levels, wearable for 14 days [10]; 2) a reader that obtains glucose readings from the sensor when placed at a distance between 1-4 cm, storing up to 90 days of glucose measures and user-entered notes. The Libre View® software and the FreeStyle Libre Link®, and LibreLinkUp® Apps enables obtaining reports with the daily patterns of glucose levels.

Observational studies have revealed that the frequent use of FGM significantly reduced the frequency of hypoglycaemia and the level of HbA1c in patients with T1DM, compared to the conventional finger-pricking method [11]. In addition, the use of FGM can improve HRQoL and Diabetes Distress [12]. However, the existing literature is of limited scientific validity, so further studies are required to evaluate the effectiveness and safety of using FGM in young populations, as well as the use of resources in daily clinical practice.

The Spanish Network of Health Technology Assessment Agencies of the National Health System (RedETS) published a report in 2016 [13], later updated in 2017 [14], developed by the Canary Islands Health Service Evaluation Department (SESCS) [15], as part of RedETS [16], about the effectiveness, safety and cost-effectiveness of FSL in patients with T1DM and T2DM. From their conclusions and recommendations [17], the Spanish Ministry of Health assigned a post-launch evidence generation study to provide real world information on the effectiveness, safety, acceptability and potential use barriers, as well as on healthcare resources use and costs in the Spanish National Health Service. This publication aims to evaluate the effectiveness, safety and costs of the FSL for T1DM in childhood and adolescence to inform health policy decision-making at national level in regard to coverage and public funding in these population groups [18].

Material and methods

Study Design

Prospective multicentre observational study carried out in 13 public hospitals throughout Spain. Patients were recruited between January 2019 and March 2020, with a 12-month follow-up.

Participants

Patients were included if they were aged 4 to 17 years-old, diagnosed with T1DM at least one year before the start of the study, were on intensive insulin therapy, required more than six fingersticks per day and agreed to take part.

We excluded patients with hypoglycaemia unawareness (judged by the clinician); current systemic corticosteroid treatment for more than two weeks in the last three months; previous (within the last 12 months) or current use of a FGM device; pregnant adolescents; allergies to device adhesives; unwillingness to take part; absence of patient/caregiver skills to make appropriate use of the technology; and failure to sign informed consent.

Setting, logistics and recruitment

The study protocol was devised by SESCS researchers with the assistance of clinical experts from all participant hospitals, representatives of patient associations and the industry. A centralized information system (SIEM) was developed on the Spanish Ministry of Health's intranet, accessible both for the clinical researchers responsible for recruitment, clinical examination and data collection, as well as SESCS researchers.

Clinical researchers from participant hospitals were in charge of recruiting patients, informing and training both patients and caregivers and collecting self-reported and electronic health record stored (EHR) data. In addition, they had to get FSL stored information throughout the follow-up phase (3, 6, and 12 months). SESCS researchers were responsible for coordinating the project, and supervising data collection, monitoring quality assurance and data validation, analyses and reporting.

Spanish autonomous communities that were interested designated the hospitals they wished to take part in the study. Thirteen public hospitals were included between January 2019 and May 2020, distributed by eight Spanish autonomous communities.

Patient and public involvement

There was no patient or public involvement in the design of this study. Clinical researchers from participant hospitals were in charge of recruiting patients, informing and training both patients and caregivers and collecting self-reported and electronic health record stored (EHR) data. In addition, they had to get FSL stored information throughout the follow-up phase (3, 6, and 12 months). The results of the study will be disseminated among the clinical investigators of the participating hospitals.

Outcomes

Effectiveness

The primary outcome was the change in HbA1c level from baseline to follow up. Secondary outcomes included: 1) data extracted from the EHR at baseline and 3, 6 and 12 months: number of severe hypoglycaemia events (defined as those that require help from another person), ketoacidosis episodes, number of hospital admissions, and mortality; and 2) self-reported outcomes evaluated at baseline and at 12 months follow-up, by means of the EQ-5D-Y questionnaire [19]; with five categories, reporting the level of severity, ranging from 1 ("I have no problems") to 5 ("I have a lot of problems") in terms of mobility, self-care, activities of daily living, pain/discomfort and anxiety/depression. Furthermore, a visual analogue scale (VAS) measured self-perceived general health, ranging from "0" (worst health status) to "100" (best health status).

Knowledge about diabetes treatment was measured by means of a modified version of the questionnaire devised by Mitchell et al. [20]. It includes 14 items evaluating basic theoretical knowledge about the management of

T1DM and its treatment, as well as the patient/caregiver's self-perceived involvement in self-care. The final score is the sum of correct answers (range 0-14). To measure satisfaction with treatment, we used the six-item Diabetes Treatment Satisfaction Questionnaire (DTSQ) [21]. Response options range from 0 (very dissatisfied) to 6 (very satisfied) (range 0-36). Another two items measured the perceived frequency of hyperglycaemia and hypoglycaemia on a scale from 0 (never perceived) to 6 (most of the time).

Safety

Patients' self-reported device-related adverse events were collected at 3, 6 and 12-months of follow-up.

Adherence

To measure device adherence, the following variables were evaluated: 1) Number of daily scans; 2) Sensor usage time; and 3) Number of sensors used. These data were collected throughout the follow-up phase by means of the information stored in the device.

Use of healthcare resources

Data were extracted from EHR at baseline and at 12-months of follow-up on: 1) Number of hospitalizations; 2) Number of clinic visits (endocrinology, nursing, primary care/paediatrics, emergency); 3) Number of HbA1c assays; 4) Number of test strips and lancets used; and 5) Absenteeism from work (number of days the caregiver was absent from work due to problems related to the child's T1DM).

In addition to these measures, information on age, sex, body mass index (BMI), time since diagnosis, presence of comorbidities and pubertal stage according to the Tanner scale [22], which classifies patients into 5 stages ranging from stage 1 (childhood) to 5 (adult), was systematically collected.

Sample Size Calculation

We estimated a sample size requirement of 43 participants to detect a minimal clinically relevant change in HbA1c of 0.5% [23], assuming 95% confidence level, 80% power, a HbA1c standard deviation of 1, a pre-post correlation of 0.5 (conservative assumption), and a loss rate of 20%. In addition to the main effect in the whole sample, we were also interested in the effect of the intervention on subgroups defined by their baseline HbA1c level (greater or less than 7.5%), and age (<12 vs. ≥12 years-old). However, the analysis of interactions requires larger sample sizes to attain statistical power, which was not feasible within the study's time limits. Therefore, we aimed to multiply the sample at least by 4 (n=172) to increase the statistical power as much as possible.

Statistical analysis

Means and standard deviation (SD) were estimated for continuous variables, and count and percentage for qualitative variables. Baseline characteristics of patients were compared using student-*t*, Pearson chi-square, Fisher's exact test or Cochran Q, according to the type of variables.

Mixed regression models with repeated measures were used, adjusting for the interaction between time and baseline HbA1c (dichotomous variable) and age group, time, and its main effects. The duration of the disease and the presence of comorbidities were included as covariates. A linear link function was used for continuous dependent variables, a logistic function for dichotomous dependent variables and a Poisson function for count dependent variables. In the models with significant interaction, mixed regression models were performed for each interaction subgroup.

The relationship between adherence to the device and HbA1c reduction was analysed using two mixed linear regression models, whose independent variables were the percentage of time using sensor (12 months) and the number of monthly scans; basal HbA1c level was introduced as a covariable. Intercept was introduced as a random effect in all models.

For missing values during follow-up, multiple imputation by chained equations was performed using Stata version 15.0. The imputation model can be found in **online supplemental Appendix 1**.
A statistical significance level of 0.05 was considered. Analyses were performed with statistical software Stata V.15.0 [24] and SPSS V.20.0 [25].

Cost estimation

Intervention costs were estimated from the Spanish National Health System (NHS) perspective, including only direct health care costs during the 12 months of the study. The healthcare resources collected in this study, together with the corresponding unit costs and their information sources, can be found in **online supplemental Appendix 2 Table A1**. Costs were expressed as 2021 euros (€). When necessary, we adjusted for the consumer price index (CPI), using the Spanish Office for National Statistics (INE) - INE's income conversion tool [26]. The sensor's unit costs (€43.27) were not included in our analysis because it was donated by Abbot. In this way, only the difference in costs before and after use of the device was analysed without taking its cost into account, since this depends on the manufacturing company's economic offer.
Unit cost of test strips and lancets were estimated with the average costs of information provided by different regional health services of the Spanish NHS. Total costs were estimated multiplying the collected data on health resources used by their respective unit costs, and then added.
Descriptive statistics are presented for total costs aggregated and broken down into: primary care visits (nursing and physicians), emergency visits (hospital and non-hospitals), specialist physicians visits, laboratory tests (HbA1c assay) and monitoring instruments (test strips and lancets).
Given the nature of the costs and their non-normality nature, confidence intervals were estimated using a non-parametric bootstrapping method [27]. Analyses were performed using the statistical software SPSS V.20.0 [25] with the help of Microsoft Excel.
In addition, although the social perspective was not taken into account in this estimate, indirect costs of technology were reported using the human capital theory, i.e. considering the costs attributed to productivity losses of the parents or caregivers of the child with T1DM before and after one year of using the FSL.
To estimate the cost per day of absenteeism, the cost per hour worked in Spain published by the Statistical Office of the European Union (Eurostat) [28] was multiplied by the average number of daily working hours worked in Spain published in the INE's Labour Force Survey (LFS) [29].

Results

A total of 165 patients were registered. However, nine were excluded (flow-chart in **Figure 1**). For the analyses, a total of 156 patients were included.

Figure 1. Flow-chart

Patients' baseline characteristics, are shown in **Table 1,** according to subgroups by level of metabolic control and age. There was a higher percentage of participants in stage 1 and 5 in the subgroup with worse glycaemic control (*P*=0.02). In this subgroup the mean HbA1c value was 8.7%; with 6.8% (*P*<0.001) in the well-controlled group. Descriptive statistics obtained at each time point for the total sample and subgroups for each of the outcome measures can be found in **online supplemental Appendix 3**.

Table 1. Baseline characteristics of patients according to baseline HbA1c control and age groups

	Total (n=156)	HbA1c <7.5% (n=68)	HbA1c ≥7.5 % (n=88)	p	<12 years (n=53)	≥12 years (n=103)	p
Anthropometric characteristics							
Sex (male) n (%)	86 (55.1)	35 (51.5)	51 (58)	0.419	28 (52.8)	58 (56.3)	0.679
Age (years), mean (SD)	12.6 (3.2)	12.7 (2.84)	12.49 (3.39)	0.735	8.92 (2.09)	14.44 (1.58)	**<0.001**
Children < 12 years, n (%)	53 (34)	21 (30.9)	32 (36.4)	0.474	-	-	-
BMI (kg/m2), mean (SD)	20.3 (4.1)	20.18 (3.34)	20.39 (4.54)	0.754	17.81 (3.29)	21.57 (3.82)	**<0.001**
Pubertal status, n (%)				**0.022**			**<0.001**
I	51 (32.7)	19 (27.9)	32 (36.4)		44 (83)	7 (6.8)	
II	14 (9.0)	9 (13.2)	5 (5.7)		4 (7.5)	10 (9.7)	
III	20 (12.8)	7 (10.3)	13 (14.8)		4 (7.5)	16 (15.5)	
IV	23 (14.7)	16 (23.5)	7 (8)		0 (0)	23 (22.3)	
V	48 (30.8)	17 (25)	31 (35.2)		1 (1.9)	47 (45.6)	
Clinical characteristics							
Duration of diabetes (years), mean (SD)	5.65 (3.39)	5.52 (3.35)	5.75 (3.44)	0.671	4.06 (2.4)	6.47 (3.54)	**<0.001**
HbA1c, mean (SD)	7.86 (1.36)	6.82 (0.36)	8.65 (1.31)	**<0.001**	7.83 (1.17)	7.87 (1.45)	0.87
HbA1c <7.5%, n (%)	68 (43.6)	-	-		21 (39.6)	47 (45.6)	0.474
Presence of comorbidities, n (%)	50 (32.1)	27 (39.7)	23 (26.1)	0.072	17 (32.1)	33 (32)	0.996
Comorbidities, n (%)							
Asthma	6 (3.8)	5 (7.4)	1 (1.1)	0.199	1 (1.9)	5 (4.9)	0.65
Celiac Disease	8 (5.1)	6 (8.8)	2 (2.3)	0.261	5 (9.4)	3 (2.9)	0.102
Thyroiditis	18 (11.5)	12 (17.6)	6 (6.8)	0.178	6 (11.3)	12 (11.7)	0.941
ADHD	4 (2.6)	1 (1.5)	3 (3.4)	0.322	1 (1.9)	3 (2.9)	0.999
Others	19 (12.2)	7 (10.3)	12 (13.6)	0.057	5 (9.4)	14 (13.6)	0.369

SD = Standard deviation; HbA1c = Glycated haemoglobin; BMI = Body mass index; ADHD = Attention-Deficit/Hyperactivity Disorder. Other comorbidities: allergy, obesity, iron deficiency anemia, unilateral anorchia, immunoglobulin A (IgA) deficiency, intellectual disability, epilepsy, hypercholesterolemia, sensorineural hearing loss, migraines, idiopathic hypercalciuria, ovarian teratoma, nephrocalcinosis, psoriasis, allergic rhinitis, vasovagal syncope, syndrome Tourette's, eating disorder (ED) and obsessive-compulsive disorder (OCD).

Effectiveness

Glycated haemoglobin

The interaction between time and baseline HbA1c group was statistically significant at 3, 6 and 12 months (*P*<0.001) (**Table 2**). In the subgroup analysis, participants with baseline HbA1c<7.5% revealed an increase of 0.32% in HbA1c at 12 months (with respect to baseline) (*P*<0.001), without exceeding, on average, the threshold of poor control. Patients with poorly controlled baseline status had a statistically significant reduction in HbA1c at all follow-ups: B=-0.46% (*P*<0.001), B=-0.49% (*P*<0.001), and B=-0.43% (*P*=0.001), at 3, 6 and 12 months, respectively (**Table 2**). On average, this reduction did not attain the threshold of poor control.

Table 2. Multivariate mixed regression models for glycosylated haemoglobin

	Glycosylated haemoglobin					
Variable	**Total sample**		**HbA1c <7.5%**		**HbA1c ≥7.5%**	
	B (95%CI)	p	B (95%CI)	p	B (95%CI)	p
Time						
M3 (ref: M0)	0.03 (-0.18; 0.24)	0.765	0.03 (-0.09; 0.16)	0.611	-0.46 (-0.69; -0.23)	**<0.001**
M6 (ref: M0)	0.1 (-0.11; 0.32)	0.344	0.10 (-0.03; 0.23)	0.115	-0.49 (-0.73; -0.25)	**<0.001**
M12 (ref: M0)	0.32 (0.10; 0.55)	**0.005**	0.32 (0.18; 0.47)	**<0.001**	-0.43 (-0.68; -0.19)	**0.001**
Duration of T1DM	0.05 (0.007; 0.09)	**0.020**	-0.005 (-0.04; 0.03)	0.762	0.09 (0.02; 0.15)	**0.011**
Presence of comorbidities	-0.10 (-0.39; 0.18)	0.477	0.09 (-0.13; 0.30)	0.439	-0.22 (-0.70; 0.26)	0.372
Age group: ≥12 years (ref: <12 years)	0.17 (-0.12; 0.47)	0.253	0.09 (-0.15; 0.32)	0.473	0.26 (-0.21; 0.73)	0.274
Baseline HbA1c group: ≥7.5% (ref: HbA1c <7.5%)	1.81 (1.50; 2.13)	**<0.001**				
Time*Baseline HbA1c Group (ref: M0 & HbA1c <7.5%)						
M3 & HbA1c ≥7.5%	-0.49 (-0.78; -0.21)	**<0.001**				
M6 & HbA1c ≥7.5%	-0.59 (-0.88; -0.29)	**<0.001**				
M12 & HbA1c ≥7.5%	-0.76 (-1.05; -0.46)	**<0.001**				
Intercept	6.75 (6.41; 7.09)	**<0.001**	6.73 (6.50; 6.96)	**<0.001**	8.53 (8.12; 8.94)	**<0.001**

CI = Confidence Interval; HbA1c = Glycosylated Haemoglobin; M = Month; T1DM = Type 1 Diabetes Mellitus.

Severe hypoglycaemic (SH) events

The reduction in the number of self-reported events was significant at 12 months (β=-0.37; *P*=0.004) (**Table 3**). Although the interaction with the level of HbA1c at baseline was not statistically significant (*P*=0.117), the descriptive statistics (**online supplemental Appendix 3**) in patients with controlled HbA1c at baseline show a reduction in the mean number of events; with an increase in the poorly controlled subgroup.

SH events recorded in the EHR show significantly lower rates compared to self-reported events (**online supplemental Appendix 3**), without significant main or interaction effects (**Table 3**). The rate of SH events was significantly higher in the subgroup with poor HbA1c control (*P*=0.014) (**Table 3**).

Table 3. Multivariate mixed regression model for effectiveness measures

Variable	Self-reported severe hypoglycaemia events				Severe hypoglycemic events in the clinical history				Visual analogue scale (EQ-5D-Y)						Knowledge about DM1		Diabetes Treatment Satisfaction Questionnaire					
	Patients with hypoglycemia (Yes / No) Total sample		**Number of self-reported events** Total sample		**Patients with hypoglycemia (Yes / No)** Total sample		**Number of self-reported events** Total sample		Total sample		HbA1c <7.5%		HbA1c ≥7.5%		Total sample		**Perceived hyperglycemia** Total sample		**Perceived hypoglycemia** Total sample		**Satisfaction with treatment** Total sample	
	OR (95%CI)	p	β (95%CI)	p	OR (95%CI)	p	β (95%CI)	p	B (95%CI)	p	B (95%CI)	p	B (95%CI)	p	B (95%CI)	p	B (95%CI)	p	B (95%CI)	p	B (95%CI)	p
Time																						
M12 (ref: M0)	0.82 (0.35; 1.96)	.659	-0.37 (-0.62; -0.11)	**.004**	1.47 (0.32; 6.77)	.617	0.77 (-0.06; 1.60)	.069	-1.40 (-4.97; 2.16)	.440	-1.33 (-4.17; 1.51)	.359	-6.03 (-9.66; -2.41)	**.001**	0.45 (-0.17; 1.08)	.154	-0.08 (-0.50; 0.34)	.721	-0.23 (-0.70; 0.24)	.331	3.11 (0.99; 5.23)	**.004**
Duration of T1DM	1.01 (0.89; 1.15)	.850	-0.01 (-0.14; 0.12)	.922	0.97 (0.81; 1.18)	.806	-0.05 (-0.24; 0.14)	.587	-0.74 (-1.29; -0.19)	**.008**	-0.32 (-0.99; 0.35)	.348	-1.05 (-1.86; -0.24)	**.011**	0.01 (-0.08; 0.09)	.851	-0.003 (-0.06; 0.05)	.915	-0.005 (-0.07; 0.06)	.870	0.05 (-0.18; 0.29)	.650
Presence of comorbidities	0.81 (0.33; 1.98)	.641	0.26 (-0.60; 1.12)	.556	0.81 (0.26; 2.50)	.710	0.27 (-0.83; 1.38)	.624	0.87 (-2.91; 4.64)	.652	2.42 (-1.78; 6.63)	.259	-1.04 (-6.98; 4.89)	.731	0.02 (-0.52; 0.57)	.930	-0.005 (-0.43; 0.42)	.980	0.02 (-0.36; 0.41)	.91	-0.52 (-2.15; 1.11)	.534
Age group: ≥12 years (ref: <12 years)	0.56 (0.22; 1.42)	.221	-0.15 (-1.04; 0.75)	.745	1.32 (0.39; 4.44)	.651	0.32 (-0.87; 1.50)	.599	-3.11 (-6.99; 0.78)	.117	-3.84 (-8.61; 0.94)	.115	-2.82 (-8.49; 2.83)	.327	-0.09 (-0.67; 0.48)	.705	-0.05 (0.48; 0.38)	.819	-0.002 (-0.38; 0.37)	.99	-0.02 (-3.24; 0.76)	.980
Baseline HbA1c group: ≥7.5% (ref: HbA1c <7.5%)	0.41 (0.15; 1.17)	.097	-0.57 (-1.40; 0.26)	.176	2.17 (0.53; 8.88)	.280	1.54 (0.31; 2.77)	**.014**	-1.93 (-5.98; 2.11)	.349					-1.27 (-1.89; 0.65)	**<.001**	1.06 (0.60; 1.52)	**<.001**	-0.12 (-0.57; 0.33)	.593	-1.24 (-1.34; 4.22)	.225
Time*Baseline HbA1c Group (ref: M0 & HbA1c <7.5%)																						
M12 & HbA1c ≥7.5%	2.69 (0.81; 8.96)	.108	0.30 (-0.08; 0.68)	.117	2.01 (0.34; 11.68)	.437	-0.44 (-1.33; 0.45)	.333	-4.61 (-9.44; 0.21)	**.061**					-0.06 (-0.90; 0.78)	.892	-0.11 (-0.70; 0.48)	.703	0.16 (-0.46; 0.78)	.615	1.44 (-1.34; 4.22)	.310
Intercept	0.78 (0.27; 2.23)	.641	-0.78 (-1.74; 0.17)	.107	0.03 (0.004; 0.19)	**<.001**	-4.32 (-5.97; -2.67)	**<.001**	90.50 (86.13; 94.87)	<.001	90.44 (85.92; 94.96)	<.001	88.92 (83.96; 93.88)	<.001	12.43 (11.78; 13.07)	**<.001**	2.98 (2.49; 3.46)	**<.001**	2.29 (1.84; 2.74)	**<.001**	26.80 (24.80; 28.81)	**<.001**

CI = Confidence Interval; HbA1c = Glycosylated Haemoglobin; M = Months; OR = Odds Ratio; ref = reference.

Diabetic ketoacidosis and other serious adverse events

In the follow-up phase, six events of mild or moderate ketoacidosis were recorded at three (2), six (1), and 12 months (3), respectively; and four serious adverse events at three months (two admissions and one episode of ketosis without acidosis due to bubbles in the system); and at six months (one admission). No events were observed at 12-month follow-up. No patient died during follow-up.

Health-related quality of life

At 12 months of follow-up, the percentages of severe limitations for mobility, self-care, daily activities, anxiety and depression were similar to baseline values. However, a reduction was observed in the percentage of patients who self-reported pain (**online supplemental Appendix 3**).

VAS score (**Table 3**) in poorly controlled patients was significantly reduced at 12 months compared to the baseline score (B=-6.03; *P*=0.001). In the subgroup with good basal metabolic control, no statistically significant findings were observed.

Knowledge about T1DM

Patients with worse basal metabolic control showed a significantly lower score for disease-related knowledge (B=-1.27; *P*<0.001) (**Table 3**).

Satisfaction with treatment

General satisfaction with treatment significantly increased 3.1 points at 12 months of follow-up (*P*=0.004) (Table 5). There were no statistically significant differences in self-perceived hypo- and hyperglycaemia. For the latter, a higher score of 1.06 points (in a range of 0 to 6) was observed, in patients with HbA1c≥7.5%, compared to those with good control (*P*<0.001) (**Table 3**).

Safety

Mild adverse events related to the device during the follow-up phases had a 3.1% and 6.6% reduction for skin reactions and discomfort or pain, respectively, although these were not statistically significant (**Table 4**).

Table 4. Mild adverse effects caused by the sensor

	3 months (n=150)	**6 months (n=136)**	**12 months (n=128)**	**p**	**Differences 12–3 months,** % (95%CI)
Skin reactions, n (%)	21 (14.0)	16 (11.8)	14 (1.9)	.542	-3.1% (-25.2; 19.0)
Discomfort or pain, n (%)	17 (11.3)	13 (9.6)	6 (4.7)	.210	-6.6% (-29.3; 16.1)
Other minor events, n (%)	3 (2.0)	2 (1.5)	2 (1.6)	.999	-0.4% (-23.9; 23.1)

Among the other events, there were minor haemorrhages when the sensor was placed and wounds in the insertion area. In one case, the bleeding caused the patient to lose consciousness.
CI = Confidence Interval.

Adherence

Time of sensor use (**Table 5**) significantly increased at 6.4% at 12 months of follow-up (*P*=0.02), compared to three months. Longer duration of T1DM (*P*=0.008), and being older than 12 years (*P*=0.003), significantly reduced sensor use.

A reduction in the mean number of daily scans at three months occurred in poorly controlled patients (*P*=0.019). Those over 12 years of age underwent an average of four fewer scans than those under 12 years of age (*P*<0.001) (**Table 5**).

Controlled patients had an increase in the mean number of sensors use at 12 months of follow-up (B=7; *P*<0.001); also increasing in poorly controlled patients by 1.6 (*P*=0.005), and 9.4 (*P*<0.001) at 6 and 12 months, respectively (**Table 5**).

The percentage of time of use was statistically significantly related to a lower HbA1c level at 12 months (B=-0.01; p=0.013), as was the scans number (B=-0.21; *P*<0.001).

Table 5. Multivariate Mixed Regression Model for Adherence

	Sensor usage time, %		**Number of scans per day**		**Number of sensors used**					
Variable	Total sample		Total sample		Total sample		HbA1c basal < 7.5%		HbA1c basal ≥ 7.5%	
	B (95%CI)	p	B (95%CI)	p	B (95%CI)	p	B (95%CI)	p	B (95%CI)	p
Time										
M6 (ref: M3)	1.82 (-3.31; 6.98)	.487	-0.25 (-1.41;0.92)	.678	0.49 (-0.58; 1.56)	.367	0.51 (-0.37; 1.39)	.255	1.59 (0.48; 2.70)	**.005**
M12 (ref: M3)	6.42 (1.12; 11.72)	**.018**	0.30 (-0.91; 1.51)	.625	6.96 (5.85; 8.06)	**<.001**	6.97 (6.06; 7.87)	**<.001**	9.37 (8.25; 10.50)	**<.001**
Duration of T1DM	-1.02 (-1.77; -0.27)	**.008**	-0.08 (-0.29; 0.13)	.468	-0.06 (-0.20; 0.07)	.363	-0.11 (-0.25; 0.04)	.152	-0.03 (-0.24; 0.18)	.804
Presence of comorbidities	0.53 (-4.61; 5.66)	.840	-0.69 (-2.14; 0.75)	.348	-0.35 (-1.27; 0.56)	.453	-0.25 (-1.16; 0.66)	.585	-0.39 (-1.92; 1.14)	.617
Age group: ≥12 years (ref: <12 years)	-7.93 (-13.19; -2.66)	**.003**	-3.92 (-5.40; -2.43)	**<.001**	0.39 (-0.55; 1.33)	.417	0.03 (-0.98; 1.05)	.952	0.69 (-0.77; 2.14)	.354
Baseline HbA1c group: ≥7.5% (ref: HbA1c <7.5%)	-4.59 (-10.71; 1.53)	.142	-1.92 (-3.52; -0.31)	**.019**	0.12 (-1.04; 1.29)	.836				
Time*Baseline HbA1c Group (ref: M3 & HbA1c <7.5%)										
M6 & HbA1c ≥7.5%	0.38 (-6.58; 7.33)	.915	0.43 (-1.14; 2.01)	.590	1.09 (-0.36; 2.54)	.141				
M12 & HbA1c ≥7.5%	-1.35 (-8.48; 5.77)	.710	0.35 (-1.28; 1.97)	.676	2.41 (0.93; 3.90)	**.001**				
Intercept	89.10 (82.9; 95.3)	**<.001**	13.0 (11.32; 14.68)	**<.001**	6.19 (5.04; 7.33)	**<.001**	6.39 (5.34; 7.44)	**<.001**	6.13 (4.77; 7.49)	**<.001**

CI = Confidence Interval; HbA1c = Glycosylated Haemoglobin; M = Months; ref = reference.

Costs estimation

The estimated total annual costs per patient are shown in **Table A2 (online supplemental Appendix 2)**. Intervention short-term costs from an NHS perspective reveal that specialist visits and test strips and lancets costs represent a significant part of the total costs (38% and 41%, respectively), with an average annual cost per patient of €415.48 and €447.25 for specialist visits and strips and lancets, respectively.

The total annual costs before and after use of the FSL system can be found in **Figure A1 (online supplemental Appendix 2)**. All measured costs decreased after use of the device throughout 12 months follow-up, with the most striking difference in costs related to test strips and lancets use, an annual difference of €856.68 per patient. This information is outlined in **Table A3 (online supplemental Appendix 2)**. The annual average number of test strips per patient decreased from 2686.02 strips per year before the use of the FSL, to 883.98 strips per year after its use. The difference in the annual average use of lancets per patient also reduced from 1366.41, before FSL use, to 615.94, after its use.

Furthermore, a decrease in the total annual costs due to productivity losses of parents/caregivers of minor patients with T1DM was observed after the use of FSL (€545.67 versus €262.73) as shown in **Table A3 (online supplemental Appendix 2)**.

Discussion

Glucose monitoring devices may help people with T1DM control their glycaemia levels and reduce the frequency and/or severity of acute disease-complication rates, thus improving their HRQoL and life expectancy [30]. Two meta-analyses of case series on the effectiveness of the FSL yielded statistically significant HbA1c reductions in children/adolescents of -0.54% (n=447) [31] and -0.29% (n=959) [32], although with high statistical heterogeneity. Our study provides a statistically significant reduction of HbA1c only in the group with poor baseline control, (-0.46%, -0.49% and -0.35%), at 3, 6 and 12 months, respectively. Conspicuously, patients with basal controlled HbA1c levels revealed a significant 12-month worsening superior to 0.30%. Another case series in Spain (n=145) [33], with limited follow up to three months, also detected a reduction in patients with HbA1c≥7.5% (-0.41, *P*=0.004), and a statistically significant increase in well-controlled patients, i.e. a worsening in HbA1c levels (0.23, *P*=0.03). Other studies [31, 34], reported a moderating effect of baseline HbA1c levels on subsequent reduction, with greater improvements in poorly controlled patients of all ages. However, except the aforementioned Spanish study [33], there are no known studies whose results indicate a significant worsening in well-controlled patients.

Our study also revealed a significant reduction in the number of self-reported SH events for the whole sample (-0.37), but not in the number of patients with at least one event. The interaction effect with baseline HbA1c level was not statistically significant for these two variables (*P*=0.117 and *P*=0.108, respectively). However, these analyses were underpowered and the descriptive statistics suggest different subgroup effects, although none was statistically significant. The reduction of self-reported SH events occurred in patients with correct HbA1c control at baseline (0.39), whereas in the basally uncontrolled group, an increase was self-reported (0.37 more); together with an important increase in the rate of patients with at least one event (from 26% to 38%). These results could be reflecting the trade-off faced by patients with T1DM between the reduction of glucose levels and the associated risk of increasing the risk of hypoglycaemic events. Patients with higher HbA1c levels could have attained the reduction target, increasing the risk of SH; whereas some of those patients in need of reducing hypoglycaemic events, could increase their HbA1c levels. This interpretation is speculative since the commented results on self-reported SH were not statistically significant and underpowered, but it would help account for the unexpected significant worsening in self-perceived general health observed in the subgroup of poor baseline HbA1c control. Contrary to the HbA1c improvement achieved in our study, without observable effects on self-perceived HRQoL, suffering an SH event is a salient experience that may influence this self-perception.

Other studies [33] have also reported a significant and clinically meaningful improvement in the rate of SH events (from 4.2 to 0.2 events/100 patients-year), but their results are not reported separately according to basal levels of metabolic control. The largest case series published to date with children and adolescents [35], and with the longest follow-up (12 months), also detected a statistically significant reduction of SH events (53%, *P*=0.012) for the whole sample, with no changes in HbA1c.

The interaction of the intervention with the age group (<12 vs. ≥12 years-old) was not statistically significant in any case, but descriptive statistics show different non-significant trends among subgroups, with positive results only for younger participants: -0.26% vs. -0.05% (HbA1c), -1.06 vs. 0.68 (SH events) and -4.2% vs. 10.5% (people with one or more SH). Adolescents revealed significantly lower sensor usage time and scans per day than children, similar to the results observed in previous studies [36-38]. Regardless of these findings, their adherence was good, above 78% of the time at each successive evaluation. However, the only randomized controlled trial to date evaluating the effectiveness of FSL in adolescents (aged 13-20 years, with HbA1c≥9.0%)

[39], found no statistically significant differences in HbA1c reduction compared to traditional self-monitoring at six months. Therefore, an important uncertainty remains in regard to the effects of FSL in adolescents.

Despite the improvement in the degree of metabolic control that occurred in our study sample of patients with worse baseline HBA1c levels, no statistically significant improvement was observed in their knowledge of disease self-management. Device adherence was significantly related to the reduction of HbA1c, a result usually observed in the literature on glucose monitoring devices [36-38]. The same can be said about treatment satisfaction [40,41], which improved in the whole sample.

In regard to safety, no serious adverse effects were observed, a result consistent with the literature on glucose monitoring devices in general [9]. The rate of patients showing mild adverse events at three months was reduced at the end of follow-up to 18%, resulting in two losses at six months follow-up due to skin reaction to the sensor and another two at 12 months due to discomfort with the sensor.

With respect to costs analysis as observed in the international literature, our results showed that T1DM patients consume less healthcare resources using FSL [42]. Fundamentally, a striking decrease was observed in costs attributed to reactive strips and lancets, where an annual difference of €856.68 per patient is obtained. A decrease in the total indirect annual costs due to productivity losses of parents/carers of T1DM patients, was also observed (€545.67 versus €262.73).

The main limitation of this study lies in its uncontrolled design, which precludes comparison with an untreated group. Another relevant limitation is the limited sample size to analyse interaction effects. To minimize this limitation, the research team increased the recruited sample fourfold.

By the time of study execution, the FSL was already financed and introduced in some hospitals taking part and a large part of the target population was already using it. This scenario was an important recruitment obstacle to enlarge sample size. Our conclusions to be drawn are, therefore, limited by the low statistical power for interaction analyses and rare events such as severe hypoglycaemia. Moreover, the uncontrolled design of the study implies a low quality of evidence.

Our cost analysis has not taken into account the costs attributable to the possible adverse effects arising from the use of FSL and it has assumed that the possible failures of the device will be resolved at no additional cost to the NHS. Moreover, it was not possible to estimate the costs related to hospitalization of the patients since the number of days of each hospitalization was not recorded in this study. However, the extremely low number of total hospitalizations during the monitoring study indicates that including this cost in the estimate would not have produced substantial changes in the results.

To the best of our knowledge, this is the first comparative costs analysis study of FSL use in children and adolescents with T1DM in Spain using observational data in an actual use scenario. Therefore, although a cost-effectiveness analysis could not be performed in this study, due to the absence of a comparator, our results may contribute to inform future cost-effectiveness studies of FSL in Spain.

In conclusion, our results suggest that the use of FSL in young T1DM patients significantly reduces the rate of SH events, and improves HbA1c levels in patients with poor baseline control. However, futures studies should confirm whether these benefits could be at the cost of worsening severe hypoglycaemia in patients with lower HbA1c. No serious adverse events related to FSL were observed. The results also suggest that the use of FSL in young patients with T1DM leads to a decrease in monitoring costs. In addition, the use of FSL reduces costs attributable to lost productivity of parents/caregivers.

These outcomes correspond to low-quality evidence, mainly due to the study's uncontrolled design, in addition to the low statistical power in the case of rare complications such as SH.

Footnotes

Collaborators: The Health Professional Group included the following members (alphabetical order): Amparo González Vergaz (Hospital Severo Ochoa), Ana María Prado Carro (Complexo Hospitalario Universitario A Coruña), Anunciación Beisti Ortego (Fundación Hospital Calahorra), Ariadna Campos Martorell (Hospital Universitari Vall D'hebron), Atilano José Carcavilla Urqui (Hospital Universitario La Paz), Cristina Amparo Del Castillo Villaescusa (Hospital Universitario Dr. Peset Aleixandre), Estela Gil Poch (Hospital Universitario de Badajoz), Francisco Javier Arroyo Diez (Hospital Universitario de Badajoz), Gemma Novoa Gómez (Complexo Hospitalario Universitario de Ourense), Isabel González Casado (Hospital Universitario La Paz), Juncal Martínez Ibáñez (Fundación Hospital Calahorra), Laura Cuadrado Piqueras (Fundación Hospital Calahorra), Leticia Reis Iglesias (Complexo Hospitalario Universitario de Ourense), Lucia Garzón Lorenzo (Hospital Universitario 12 De Octubre), Luis Salamanca Fresno (Hospital Universitario La Paz), María Asunción Martínez Brocca (Hospital Universitario Virgen Macarena), María Aurea Rodríguez Blanco (Hospital Da Barbanza), María Del Mar Martínez López (Hospital Universitario 12 De Octubre), María Jesús Ferreiro Rodríguez (Complexo Hospitalario Universitario de Ourense), María Ruiz del Campo (Hospital San Pedro), Nerea Itza Martín (Hospital Universitario La Paz), Patricia García Navas (Hospital San Pedro), Rebeca García García (Hospital Universitario Central de Asturias).

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Patient consent for publication: Not applicable.

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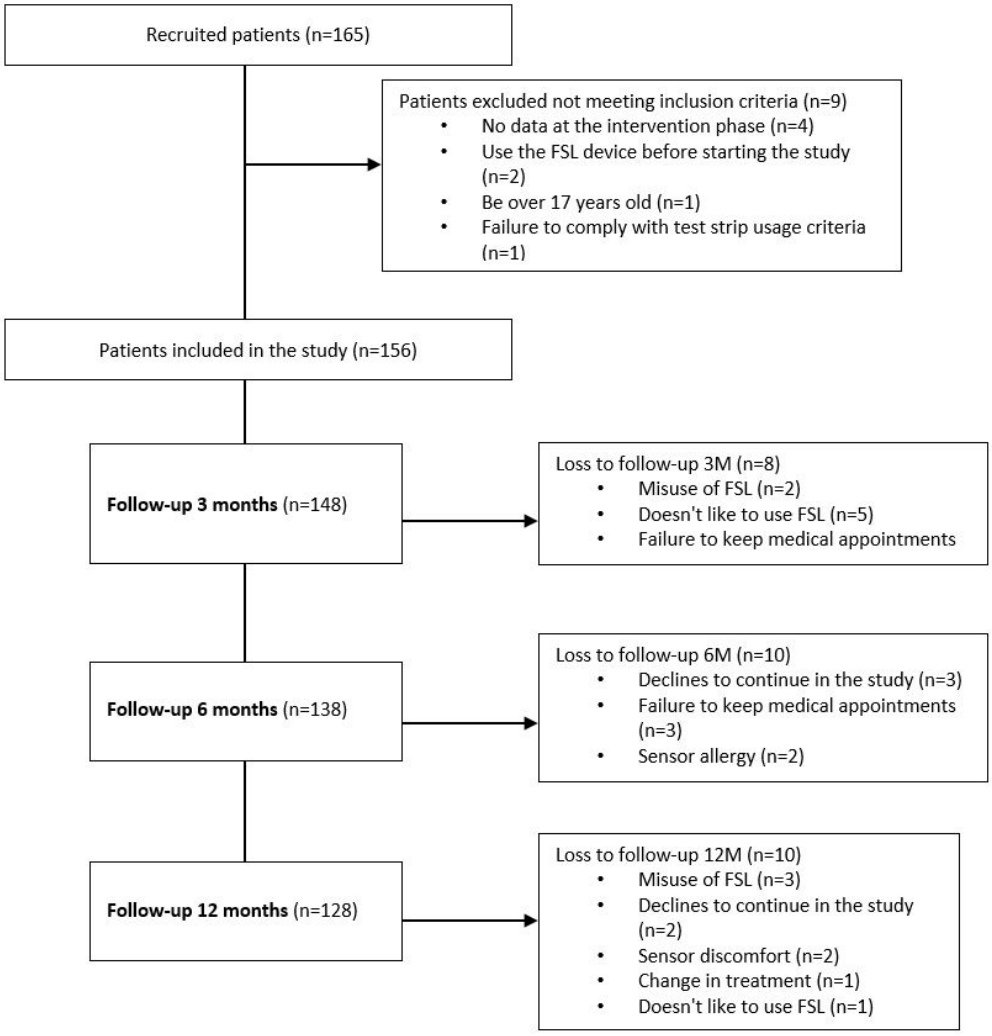

Figure 1. Flow-charts

214x223mm (96 x 96 DPI)

Appendix 1. Description of the missing data imputation model

Multiple imputation was performed by chained equations using Stata 15.0 software. The variables sex, age, pubertal stage, presence of comorbidities and duration of diabetes were considered regular and used as predictors for imputation. A total of 29 variables were imputed. Each variable was imputed in chronological order: 3, 6 and 12 months. As a general rule, the latest available information on the variable to be imputed was used. When information from other variables was used, the information from the same point in time was used. A total of 10 imputations were made for each missing data.

Order	Imputed variable	Variables used in imputation	Imputation model	n (%) missing
1	HbA1c 3M	Sex, Age, Pubertal stage, Presence of comorbidities, Time since diagnosis, HbA1c Baseline	pmm	7 (4,5)
2	HbA1c 6M	Sex, Age, Pubertal stage, Presence of comorbidities, Time since diagnosis, HbA1c 3M	pmm	20 (12,8)
3	HbA1c 12M	Sex, Age, Pubertal stage, Presence of comorbidities, Time since diagnosis, HbA1c 6M	pmm	28 (17,9)
4	BMI 6M	Sex, Age, Pubertal stage, Presence of comorbidities, Time since diagnosis, BMI Baseline	pmm	24 (15,4)
5	BMI 12M	Sex, Age, Pubertal stage, Presence of comorbidities, Time since diagnosis, BMI 6M	pmm	28 (17,9)
6	N.º severe hypoglycaemia events 3M	Sex, Age, Pubertal stage, Presence of comorbidities, Time since diagnosis, N.º severe hypoglycaemia events Baseline	poisson	7 (4,5)
7	N.º severe hypoglycaemia events 6M	Sex, Age, Pubertal stage, Presence of comorbidities, Time since diagnosis, N.º severe hypoglycaemia events 3M	poisson	7 (4,5)
8	N.º severe hypoglycaemia events 12M	Sex, Age, Pubertal stage, Presence of comorbidities, Time since diagnosis, N.º severe hypoglycaemia events 6M	poisson	7 (4,5)
9	N.º severe hypoglycaemia events on EHR 3M	Sex, Age, Pubertal stage, Presence of comorbidities, Time since diagnosis, N.º severe hypoglycaemia events 3M, N.º severe hypoglycaemia events on EHR Baseline	poisson	8 (5,1)
10	N.º severe hypoglycaemia events on EHR 6M	Sex, Age, Pubertal stage, Presence of comorbidities, Time since diagnosis, N.º severe hypoglycaemia events 6M, N.º severe hypoglycaemia events on EHR 3M	poisson	28 (17,9)
11	N.º severe hypoglycaemia events on EHR 12M	Sex, Age, Pubertal stage, Presence of comorbidities, Time since diagnosis, N.º severe hypoglycaemia events 12M, N.º severe hypoglycaemia events on EHR 6M	poisson	28 (17,9)
12	VAS 12M	Sex, Age, Pubertal stage, Presence of comorbidities, Time since diagnosis, Mobility EQ-5D-Y 12M, Self-care EQ-5D-Y 12M, Habitual activities EQ-5D-Y 12M, Pain/discomfort EQ-5D-Y 12M, Anxiety/depression EQ-5D-Y 12M, VAS Baseline	pmm	36 (23,1)
13	Knowledge about Baseline	Sex, Age, Pubertal stage, Presence of comorbidities, Time since diagnosis, HbA1c Baseline, BMI Baseline	pmm	14 (9,0)
14	Knowledge about 12M	Sex, Age, Pubertal stage, Presence of comorbidities, Time since diagnosis, HbA1c 12M, BMI 12M, Knowledge about Baseline	pmm	48 (30,8)
15	Hyperglycaemia DTSQ Baseline	Sex, Age, Pubertal stage, Presence of comorbidities, Time since diagnosis, HbA1c Baseline, Knowledge about Baseline	pmm	14 (9,0)
16	Hyperglycaemia DTSQ 12M	Sex, Age, Pubertal stage, Presence of comorbidities, Time since diagnosis, HbA1c 12M, Knowledge about 12M, Hyperglycaemia DTSQ Baseline	pmm	48 (30,8)
17	Hypoglycaemia DTSQ Baseline	Sex, Age, Pubertal stage, Presence of comorbidities, Time since diagnosis	pmm	14 (9,0)

18	Hypoglycaemia DTSQ 12M	Sex, Age, Pubertal stage, Presence of comorbidities, Time since diagnosis, Hypoglycaemia DTSQ Baseline	pmm	48 (30,8)
19	Satisfaction with treatment DTSQ Baseline	Sex, Age, Pubertal stage, Presence of comorbidities, Time since diagnosis, N.º severe hypoglycaemia events Baseline, N.º severe hypoglycaemia events on EHR Baseline, Knowledge about Baseline, Hyperglycaemia DTSQ Baseline,	pmm	14 (9,0)
20	Satisfaction with treatment DTSQ 12M	Sex, Age, Pubertal stage, Presence of comorbidities, Time since diagnosis, N.º severe hypoglycaemia events 12M, N.º severe hypoglycaemia events on EHR 12M, Knowledge about 12M, Hyperglycaemia DTSQ 12M, Satisfaction with treatment DTSQ Baseline	pmm	48 (30,8)
21	N.º of daily scans 3M	Sex, Age, Pubertal stage, Presence of comorbidities, Time since diagnosis, HbA1c 3M, BMI Baseline, N.º severe hypoglycaemia events 3M	pmm	8 (5,1)
22	N.º of daily scans 6M	Sex, Age, Pubertal stage, Presence of comorbidities, Time since diagnosis, HbA1c 6M, BMI 6M, N.º severe hypoglycaemia events 6M, N.º of daily scans 3M	pmm	19 (12,2)
23	N.º of daily scans 12M	Sex, Age, Pubertal stage, Presence of comorbidities, Time since diagnosis, HbA1c 12M, BMI 12M, N.º severe hypoglycaemia events 12M, N.º of daily scans 6M	pmm	28 (17,9)
24	Sensor usage time 3M	Sex, Age, Pubertal stage, Presence of comorbidities, Time since diagnosis, HbA1c 3M, N.º ketoacidosis 3M, N.º of daily scans 3M	pmm	8 (5,1)
25	Sensor usage time 6M	Sex, Age, Pubertal stage, Presence of comorbidities, Time since diagnosis, HbA1c 6M, N.º ketoacidosis 6M, N.º of daily scans 6M, Sensor usage time 3M	pmm	19 (12,2)
26	Sensor usage time 12M	Sex, Age, Pubertal stage, Presence of comorbidities, Time since diagnosis, HbA1c 12M, N.º ketoacidosis 12M, N.º of daily scans 12M, Sensor usage time 6M	pmm	28 (17,9)
27	N.º Sensors 3M	Sex, Age, Pubertal stage, Presence of comorbidities, Time since diagnosis, N.º ketoacidosis 3M, Sensor usage time 3M	pmm	7 (4,5)
28	N.º Sensors 6M	Sex, Age, Pubertal stage, Presence of comorbidities, Time since diagnosis, N.º ketoacidosis 6M, Sensor usage time 6M, N.º Sensors 3M	pmm	19 (12,2)
29	N.º Sensors 12M	Sex, Age, Pubertal stage, Presence of comorbidities, Time since diagnosis, N.º ketoacidosis 12M, Sensor usage time 12M, N.º Sensors 6M	pmm	28 (17,9)

DM = Diabetes Mellitus; T1DM = Type 1 Diabetes Mellitus; DTSQ = Diabetes Treatment Satisfaction Questionnaire; EQ-5D-Y = Health-related quality of life questionnaire; VAS = visual analogue scale; HbA1c = Glycated haemoglobin; EHR = Electronic Health Record; BMI = Body mass index; M = Months.

Appendix 2. Cost estimation

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Table A1. Use of resources and unit costs

	Unit cost €2021 (SD)	Source
Hospitalization /day	652.58 (188.86)	Public tariff*
Visit to specialist	95.65 (33.98)	Public tariff*
Visit to nurse at primary care	27.06 (7.52)	Public tariff*
Hospital emergency	207.54 (72.03)	Public tariff*
Visit to doctor at primary care	50.91 (17.63)	Public tariff*
Non-hospital emergency	99.41 (22.83)	Public tariff*
HbA1c determination	7.15 (5.16)	Public tariff*
Test strips	0.43 (0.15)	Consult*
Lancets	0.109 (0.11)	Consult*
Absenteeism day	166.896	Estimate based on Eurostat and INE

SD = Standard Deviation
* Spanish autonomous communities.
INE = Spanish Statistical Office.
Unit costs come from different sources, all national, and include official tariffs. Where possible, the average costs of those Spanish regions for which data were available were taken into account
To estimate the unit cost of test strips and lancets, the Spanish regions were consulted for their spending on these products. There was great heterogeneity between regions, not only in the unit cost (between €0.10 and €0.48), but also in the products financed, since lancets are only financed in some regions.

Table A2. Total annual cost per patient of the FSL flash glucose monitoring system (€2021)

	Primary care	Emergency	Specialist	Laboratory	Monitoring*	Total costs
Mean (SD)	136.78 (101.28)	50.70 (161.66)	415.48 (129.53)	29.05 (5.87)	447.25 (317.58)	1079.26 (425.73)
Min. – Max.	0 – 474.24	0 – 1245.24	0 – 956.5	14.30 – 71.50	0 – 1295.39	219.9 – 2501.19
CI95%	(119.88; 154.65)	(25.74; 80.73)	(393.81; 438.65)	(28.1; 30.16)	(392.57; 501.77)	(1007.41; 1152.15)

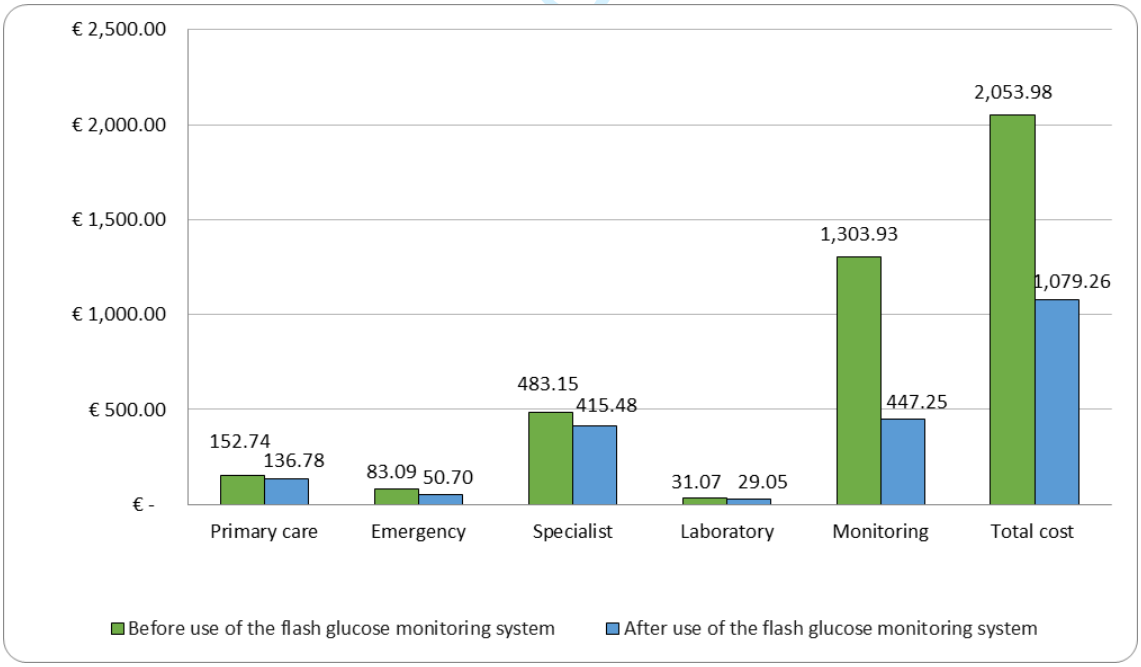
CI95% = Confidence interval at 95% by Bootstrap based on 10,000 samples; Max. = Maximum; Min. = Minimum; SD = Standard Deviation
*Test strips and lancets. Not include the cost of sensor

Table A3. Average number of test strips and lancets per patient and total annual costs due to lost parent/caregiver productivity before and after FSL use.

	Before use of the flash glucose monitoring system	After use of the flash glucose monitoring system
Average number of test strips and lancets per patient before and after use of the FSL device		
Yearly test strips, mean (SD)	2686,02 (527,63)	883.98 (669.45)
Yearly Lancets, mean (SD)	1366.41 (1063.44)	615.94 (482.03)
Total annual cost per patient due to productivity losses (€2021)		
Mean (SD)	545.67 (588.29)	262.73 (334.30)
Min. – Max.	0 – 3504.82	0 – 1668.96
CI95%	(448.55; 650.63)	(206.65; 322.71)

CI95% = Confidence interval at 95% by Bootstrap based on 10,000 samples; Max. = Maximum; Min. = Minimum; SD = Standard Deviation

Figure A1. Total annual costs per patient before and after use of the FSL (does not include cost of device)



Appendix 3. Evolution of outcome measures during follow-up (by age group and baseline HbA1c control)

	Baseline	3 months	6 months	12 months	Differences 12 months-Baseline
HbA1c, mean (SD)					
Total	7.86 (1.36)	7.58 (1.27)	7.59 (1.16)	7.73 (1.06)	-0.13 (-0.42; 0.16)
HbA1c <7.5%	6.82 (0.36)	6.86 (0.55)	6.96 (0.6)	7.14 (0.57)	0.32 (0.15; 0.49)
HbA1c ≥7.5%	8.65 (1.31)	8.18 (1.38)	8.14 (1.25)	8.2 (1.12)	-0.45 (-0.84; -0.06)
< 12 years	7.83 (1.17)	7.42 (0.93)	7.53 (0.96)	7.57 (0.8)	-0.26 (-0.59; 0.07)
≥ 12 years	7.87 (1.45)	7.66 (1.41)	7.63 (1.26)	7.82 (1.19)	-0.05 (-0.45; 0.35)
With self-reported severe hypoglycemia, n (%)					
Total	49 (31.4)	-	-	55 (36.9)	5.5% (-12.7; 23.7)
HbA1c <7.5%	26 (38.2)	-	-	24 (35.3)	-2.9% (-29.6; 23.8)
HbA1c ≥7.5%	23 (26.1)	-	-	31 (38.3)	12.2% (-12.6; 37.0)
< 12 years	22 (41.5)	-	-	19 (37.3)	-4.2% (-34.1; 25.7)
≥ 12 years	27 (26.2)	-	-	36 (36.7)	10.5% (-12.4; 33.4)
Nº. Self-reported severe hypoglycemia, mean (SD)					
Total	1.72 (3.65)	-	-	1.77 (5.08)	0.05 (-0.98; 1.1)
HbA1c <7.5%	2.34 (4.13)	-	-	1.95 (5.69)	-0.39 (-2.2; 1.4)
HbA1c ≥7.5%	1.26 (3.19)	-	-	1.63 (4.58)	0.37 (-0.86; 1.6)
< 12 years	2.12 (4.04)	-	-	1.06 (3.65)	-1.06 (-2.6; 0.48)
≥ 12 years	1.52 (3.43)	-	-	2.20 (5.76)	0.68 (-0.69; 2.1)
With severe hypoglycemia in the electronic clinical record, n (%)					
Total	19 (12.2)	-	-	23 (15.4)	3.2% (-17.6; 24.0)
HbA1c <7.5%	6 (8.8)	-	-	6 (8.8)	0% (-32.0; 32.0)
HbA1c ≥7.5%	13 (14.8)	-	-	17 (21.0)	6.2% (-21.1; 33.5)
< 12 years	9 (17.0)	-	-	6 (11.8)	-5.2% (-40.8; 30.4)
≥ 12 years	10 (9.7)	-	-	17 (17.4)	7.7% (-0.18; 0.33)
N.º Hypoglycemia in the electronic clinical record prior to the study, mean (SD)					
Total	0.39 (1.68)	-	-	0.54 (1.58)	0.15 (-0.23; 0.53)
HbA1c <7.5%	0.13 (0.45)	-	-	0.25 (1.06)	0.12 (-0.16; 0.40)
HbA1c ≥7.5%	0.59 (2.18)	-	-	0.78 (1.88)	0.19 (-0.43; 0.81)
< 12 years	0.34 (1.02)	-	-	0.61 (1.89)	0.27 (-0.32; 0.86)
≥ 12 years	0.42 (1.94)	-	-	0.5 (1.40)	0.08 (-0.39; 0.55)
Health-related quality of life (EQ-5D-Y), n (%)					
Mobility (no problems), n (%)					
Total	156 (100)	-	-	124 (100)	-
HbA1c <7.5%	68 (100)	-	-	54 (100)	-
HbA1c ≥7.5%	88 (100)	-	-	70 (100)	-
< 12 years	53 (100)	-	-	47 (100)	-
≥ 12 years	103 (100)	-	-	77 (100)	-
Self-Care (no problems), n (%)					
Total	154 (98.7)	-	-	123 (99.2)	-
HbA1c <7.5%	67 (98.5)	-	-	54 (100)	-
HbA1c ≥7.5%	87 (98.9)	-	-	69 (98.6)	-
< 12 years	51 (96.2)	-	-	47 (100)	-
≥ 12 years	103 (100)	-	-	76 (98.7)	-
Usual Activities (no problems), n (%)					
Total	154 (98.7)	-	-	122 (98.4)	-
HbA1c <7.5%	67 (98.5)	-	-	53 (98.1)	-
HbA1c ≥7.5%	87 (98.9)	-	-	69 (98.6)	-
< 12 years	53 (100)	-	-	47 (100)	-
≥ 12 years	101 (98.1)	-	-	75 (97.4)	-
Pain or Discomfort (no pain), n (%)					
Total	144 (92.3)	-	-	118 (95.2)	-
HbA1c <7.5%	62 (91.2)	-	-	53 (98.1)	-
HbA1c ≥7.5%	82 (93.2)	-	-	65 (92.9)	-
< 12 years	50 (94.3)	-	-	45 (95.7)	-
≥ 12 years	94 (91.3)	-	-	73 (94.8)	-

Pain or Discomfort (some pain), n (%)					
Total	12 (7.7)	-	-	6 (4.8)	-
HbA1c <7.5%	6 (8.8)	-	-	1 (1.9)	-
HbA1c ≥7.5%	6 (6.8)	-	-	5 (7.1)	-
< 12 years	3 (5.7)	-	-	2 (4.3)	-
≥ 12 years	9 (8.7)	-	-	4 (5.2)	-
Anxiety/Depression (no problems), n (%)					
Total	137 (87.8)	-	-	112 (90.3)	-
HbA1c <7.5%	62 (91.2)	-	-	50 (92.6)	-
HbA1c ≥7.5%	75 (85.2)	-	-	62 (88.6)	-
< 12 years	49 (92.5)	-	-	44 (93.6)	-
≥ 12 years	88 (85.4)	-	-	68 (88.3)	-
Anxiety/Depression (some problems), n (%)					
Total	16 (10.3)	-	-	10 (8.1)	-
HbA1c <7.5%	5 (7.4)	-	-	4 (7.4)	-
HbA1c ≥7.5%	11 (12.5)	-	-	6 (8.6)	-
< 12 years	3 (5.7)	-	-	2 (4.3)	-
≥ 12 years	13 (12.6)	-	-	8 (10.4)	-
VAS, mean (sd)					
Total	87.63 (12.46)	-	-	84.17 (12.28)	-3.5 (-6.4; -0.53)
HbA1c <7.5%	88.79 (10.05)	-	-	87.92 (10.08)	0.29 (-3.9; 4.5)
HbA1c ≥7.5%	86.74 (14.04)	-	-	81.29 (16.29)	-7.5 (-11.7; -3.3)
< 12 years	91.66 (9.72)	-	-	85.61 (14.97)	-6.1 (-11.0; -1.1)
≥ 12 years	85.56 (13.23)	-	-	83.27 (13.86)	-2.3 (-6.3; 1.7)
Knowledge about DM1 (modified version of Mitchell questionnaire), mean (SD)					
Total	11.68 (2.13)	-	-	12.09 (1.94)	0.41 (-0.11; 0.93)
HbA1c <7.5%	12.38 (1.98)	-	-	12.92 (1.35)	0.54 (-0.11; 1.2)
HbA1c ≥7.5%	11.12 (2.08)	-	-	11.38 (2.08)	0.26 (-0.45; 0.97)
< 12 years	11.87 (2.07)	-	-	11.9 (2.31)	0.03 (-0.90; 0.96)
≥ 12 years	11.59 (2.16)	-	-	12.21 (1.67)	0.62 (-0.001; 1.2)
Diabetes Treatment Satisfaction Questionnaire (DTSQ)					
Perceived hyperglycemia, mean (SD)					
Total	3.53 (1.51)	-	-	3.32 (1.44)	-0.21 (-0.58; 0.16)
HbA1c <7.5%	2.94 (1.28)	-	-	2.88 (1.44)	-0.06 (-0.57; 0.45)
HbA1c ≥7.5%	4.01 (1.51)	-	-	3.71 (1.34)	-0.3 (-0.79; 0.19)
< 12 years	3.62 (1.38)	-	-	3.44 (1.48)	-0.18 (-0.79; 0.43)
≥ 12 years	3.48 (1.57)	-	-	3.25 (1.42)	-0.23 (-0.71; 0.25)
Perceived hypoglycemia, mean (SD)					
Total	2.22 (1.35)	-	-	2.04 (1.32)	-0.18 (-0.52; 0.16)
HbA1c <7.5%	2.3 (1.36)	-	-	2 (1.31)	-0.3 (-0.80; 0.20)
HbA1c ≥7.5%	2.15 (1.35)	-	-	2.07 (1.34)	-0.08 (-0.54; 0.38)
< 12 years	2.19 (1.17)	-	-	2.05 (1.26)	-0.14 (-0.66; 0.38)
≥ 12 years	2.23 (1.44)	-	-	2.03 (1.36)	-0.2 (-0.64; 0.24)
Satisfaction with treatment, mean (SD)					
Total	25.89 (6.7)	-	-	29.82 (5.44)	3.93 (2.4; 5.5)
HbA1c <7.5%	26.58 (7.04)	-	-	29.78 (5.1)	3.2 (0.86; 5.5)
HbA1c ≥7.5%	25.33 (6.41)	-	-	29.86 (5.77)	4.53 (2.4; 6.6)
< 12 years	25.79 (6.71)	-	-	29.61 (5.87)	3.82 (1.1; 6.5)
≥ 12 years	25.95 (6.73)	-	-	29.96 (5.21)	4.01 (2.1; 5.9)
	Baseline	**3 months**	**6 months**	**12 months**	**Differences 12-3 months**
Sensor usage time (%), mean (SD)					
Total	-	81.60 (20.78)	84.42 (19.47)	88.55 (18.48)	6.95 (2.3; 11.6)
HbA1c <7.5%	-	83.99 (21.93)	86.60 (17.2)	91.70 (15.09)	7.71 (0.90; 14.5)
HbA1c ≥7.5%	-	79.63 (19.69)	82.57 (21.16)	86.01 (20.57)	6.38 (-0.8; 12.8)
< 12 years	-	87.59 (15.06)	90.60 (14.34)	94.51 (11.81)	6.92 (1.5; 12.3)
≥ 12 years	-	78.45 (22.67)	81.09 (21.07)	84.85 (20.84)	6.4 (-0.14; 12.9)
Number of scans per day, mean (SD)					

Total	-	9.16 (5.06)	9.33 (4.97)	9.84 (6.02)	0.68 (-0.64; 2.0)
HbA1c <7.5%	-	10.06 (5.11)	9.89 (5.07)	10.39 (5.45)	0.33 (-1.6; 2.2)
HbA1c ≥7.5%	-	8.41 (4.92)	8.85 (4.86)	9.39 (6.46)	0.98 (-0.87; 2.8)
< 12 years	-	11.67 (5.64)	11.27 (4.5)	12.96 (6.45)	1.29 (-1.1; 3.7)
≥ 12 years	-	7.83 (4.17)	8.27 (4.91)	7.90 (4.85)	0.07 (-1.3; 1.4)
Number of sensors used, mean (SD)					
Total	-	6.40 (1.36)	7.50 (2.86)	14.74 (5.81)	8.34 (7.4; 9.3)
HbA1c <7.5%	-	6.32 (1.37)	6.86 (1.76)	13.35 (4.47)	7.03 (5.9; 8.2)
HbA1c ≥7.5%	-	6.46 (1.36)	8.05 (3.46)	15.86 (6.51)	9.4 (7.9; 10.9)
< 12 years	-	6.63 (1.17)	6.90 (2.15)	14.73 (5.83)	8.1 (6.5; 7.8)
≥ 12 years	-	6.28 (1.44)	7.83 (3.15)	14.75 (5.83)	8.47 (7.3; 9.7)

SD = standard deviation; VAS = Visual Analogue Scale; HbA1c = Glycosylated Haemoglobin; CI = Confidence Interval; GT = glucose time.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5-6
		(*b*) Describe any methods used to examine subgroups and interactions	5-6
		(*c*) Explain how missing data were addressed	5-6
		(*d*) If applicable, explain how loss to follow-up was addressed	5-6
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	Apex1
		(c) Summarise follow-up time (eg, average and total amount)	7
Outcome data	15*	Report numbers of outcome events or summary measures over time	8

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	8 8 NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9
Discussion			
Key results	18	Summarise key results with reference to study objectives	10-11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10-11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Effectiveness, safety and costs of the FreeStyle Libre Glucose Monitoring System for children and adolescents with T1DM in Spain: a prospective uncontrolled pre-post study

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Effectiveness, safety and costs of the FreeStyle Libre Glucose Monitoring System for children and adolescents with T1DM in Spain: a prospective uncontrolled pre-post study

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Abstract

Objectives

Evaluate the effectiveness, safety and costs of the FreeStyle Libre® (FSL) for Type 1 Diabetes Mellitus (T1DM) in underage.

Design

Prospective multicentre pre-post study.

Setting

Patients were recruited from thirteen Spanish public hospitals with a 12-months follow-up.

Participants

A total of 156 patients were included.

Primary and secondary outcome measures

Primary outcome: HbA1c change. Secondary measures: severe hypoglycaemic events (self-reported and registered in clinical records), quality of life, disease knowledge, treatment satisfaction, adverse events, adherence, sensor usage time and scans. Healthcare resource utilization was assessed for cost analysis from the National Health System (NHS) perspective, incorporating direct healthcare costs. Data analysis utilized mixed regression models with repeated measures. Intervention's total cost estimated by multiplying health resource usage with unit costs.

Results

In the whole sample, HbA1c increased significantly (0.32%; 95%CI: 0.10, 0.55). In the subgroup with baseline HbA1c≥7.5% (n=88), there was a significant reduction at 3 (-0.46%; -0.69, -0.23), 6 (-0.49%; -0.73, -0.25), and 12 months (-0.43%; -0.68, -0.19). Well-controlled patients revealed a significant 12-month worsening (0.32%; 0.18, 0.47). Self-reported severe hypoglycaemia significantly decreased compared to the previous year for the whole sample (-0.37; -0.62, -0.11). Quality of life and knowledge showed no significant differences, but satisfaction significantly increased. Adolescents demonstrated lower sensor usage time and scans per day compared to

children. The reduction in HbA1c was significantly associated with device adherence. No serious adverse effects were observed. FSL use could reduce total direct costs from the NHS perspective.

Conclusions
The use of FSL in underage T1DM patients is associated with a significant reduction in severe hypoglycaemia and improved HbA1c levels in patients with poor baseline control. Findings suggest cost savings and productivity gains for caregivers. Causal evidence is limited due to the study design. Further research needed to confirm results and assess risks, especially for lower HbA1c patients.

Strengths and limitations of this study
- This study provides nationally contextualised real-world scientific evidence on the effectiveness, safety and costs of the flash glucose monitoring systems (FreeStyle Libre® system [FSL]) indicated for DM1 in childhood and adolescence in Spain.
- The study utilized a combination of self-reported outcomes, clinical data extracted from Electronic Health Records (EHR), and device-stored information from the FSL device, which provides a robust and multifaceted assessment of the outcomes.
- The uncontrolled design of the study precludes causal inferences and results from randomized trials are needed to draw definitive conclusions.
- The small sample size limit the generalizability and statistical power of the findings.
- The cost estimation analysis only considered direct healthcare costs from the Spanish National Health System perspective, and indirect costs were not fully taken into account, which may underestimate the overall economic impact of the intervention.

Keywords
Continuous glucose monitoring, HbA1c, Type 1 diabetes, costs, Spain.

Word count 4679

Introduction

Type 1 Diabetes Mellitus (T1DM) requires continuous medical monitoring, to reduce the development of vascular complications [1,2]. The early onset and chronic character of this condition increase the likelihood of reducing health-related quality of life (HRQoL) and health expectancy among young T1DM people [3]. A total of 586,000 children aged under 15 years suffer from T1DM globally [4]. In Spain, the incidence is 11.5-27.6/100,000[5], which represents a high cost to society [6].

To reduce the risk of short (metabolic) and long-term (vascular) diabetes complications, frequent determination of blood glucose levels is required. Continuous glucose monitoring systems, such as the flash glucose monitoring (FGM) systems, contribute to glycaemia monitoring, as well as to reduce the daily number of fingersticks [7], providing dynamic information to the users about their glucose level. FreeStyle Libre® (FSL), developed and marketed in Spain by Abbott Laboratories, has been indicated to measure glucose levels in the interstitial fluid in people aged over four years with T1DM. No serious adverse effects related to the use of these devices have been reported. Mild effects consist of skin problems in the area where the sensor is inserted, similar to other FGM [8,9].

In randomized trials, the FSL system has been shown to significantly reduce HbA1c levels and the frequency of hypoglycaemia in patients with T2DM, compared to the conventional finger-pricking method [10]. In T1DM, meta-analyses have revealed that the use of FSL is associated with significant HbA1c reductions from baseline to the last follow up, but in this case most studies had an uncontrolled design [11,12]. Approximately 30% of these studies included children and adolescents, which also led to obtaining significant pre-post HbA1c reductions. To the best of our knowledge, only one randomized trial has evaluated the FSL versus conventional glucose measurement in non-adults with T1DM [13]. This study included adolescents (13-20 years-old) and it found significantly higher satisfaction in the intervention group at 6 months, but no significant results on HbA1c or quality of life [13]. Therefore, the existing literature regarding the effectiveness of the FSL system in children and adolescents is of limited scientific validity.

Spain has a universal public health system, financed by taxes. The system is highly decentralized and the 17 Spanish administrative regions have their own health policy budget, which enables a tailored approach to meet the specific needs and demands of each region. The competences and portfolio of the Spanish Ministry of Health encompass a wide range of responsibilities aimed at ensuring the well-being and health of the population. These include policy development, regulation and oversight of healthcare services, public health initiatives, pharmaceutical regulation, health technology assessment and coordination of emergency responses, among others. The Spanish Network of Health Technology Assessment Agencies of the National Health System (RedETS) [14], published a report in 2016 [15], later updated in 2017 [16], devised by the Canary Islands Health Service Evaluation Department (SESCS) [17], about the effectiveness, safety and cost-effectiveness of FSL in patients with T1DM and T2DM. In 2019, the Spanish Ministry of Health decided to fund FSL for adult T1DM patients [18], and in 2020 the reimbursement was extended to any insulin-dependent patient not diagnosed with T1DM or T2DM [19].

Regarding children and adolescents with T1DM, the Spanish Ministry of Health decided to perform a post-launch evidence generation study to provide real world information on the effectiveness, safety, acceptability and potential use barriers, as well as on healthcare resources use and costs, to inform health policy decision-making on a national level in regard to coverage and public funding in these population groups [20,21]. This paper reports its results.

Material and methods

Study Design

Prospective multicentre pre-post study performed in 13 public hospitals throughout Spain (see **online supplemental Appendix 1**). Patients were recruited between January 2019 and March 2020, with a 12-month follow-up.

Interventions

FSL consists of: 1) an arm sensor that measures and stores interstitial glucose levels, wearable for 14 days [22]; 2) a reader that obtains glucose readings from the sensor when placed at a distance between 1-4 cm, storing up to 90 days of glucose measures and user-entered notes. The Libre View® software and the FreeStyle Libre Link®, and LibreLinkUp® Apps enables obtaining reports with the daily patterns of glucose levels.

Participants

Patients were eligible for inclusion if they were aged between 4 and 17, had been diagnosed with T1DM for at least one year prior to the study, were receiving intensive insulin therapy, required more than six fingersticks per day, and provided their informed consent to participate.

We excluded patients who had hypoglycaemia unawareness (judged by the clinician), were currently undergoing systemic corticosteroid treatment for more than two weeks within the last three months, had previously used or were currently using a FGM device within the last 12 months, were pregnant adolescents, had allergies to device adhesives, were unwilling to participate, lacked the necessary skills to effectively use the technology (patient/caregiver) or failed to provide informed consent.

Setting, logistics and recruitment

The study protocol was devised by SESCS researchers with the assistance of clinical experts from all hospitals taking part, patient association and industry representatives. A centralized information system (SIEM) was developed on the Spanish Ministry of Health's intranet, accessible both for the clinical researchers responsible for recruitment, clinical examination and data collection, as well as SESCS researchers.

Clinical researchers from hospitals taking part were responsible for recruiting, informing and training both patients and caregivers. They collected self-reported data using various measurement scales and extracted clinical information from the electronic health record (EHR) at baseline, 3, 6, and 12 months. In addition, they retrieved the stored information from the FSL device during the follow-up phase (3, 6, and 12 months) on the SIEM platform. SESCS researchers were responsible for coordinating the project and supervising data collection, monitoring quality assurance and data validation, analyses and reporting.

Interested Spanish autonomous communities designated the hospitals they wished to take part in the study. Thirteen public hospitals were included between January 2019 and May 2020, distributed over eight Spanish autonomous communities.

Endpoints

Effectiveness

The primary endpoint was the change in HbA1c level from baseline to follow up. Secondary endpoints included: 1) data extracted from the EHR at baseline and 3, 6 and 12 months: number of severe hypoglycaemia events (defined as those that require help from another person), ketoacidosis episodes, number of hospital admissions and mortality; and 2) self-reported outcomes evaluated at baseline and at 12 months follow-up, by means of the EQ-5D-Y questionnaire [23]; with five categories, reporting the level of severity, ranging from 1 ("I have no problems") to 5 ("I have a lot of problems") in terms of mobility, self-care, activities of daily living, pain/discomfort and anxiety/depression. Furthermore, a visual analogue scale (VAS) measured self-perceived general health, ranging from "0" (worst health status) to "100" (best health status).

Knowledge about diabetes treatment was measured by means of a modified version of the questionnaire devised by Mitchell et al. [24]. This includes 14 items evaluating basic theoretical knowledge about the management of T1DM and its treatment, as well as the patient/caregiver's self-perceived involvement in self-care. The final score is the sum of correct answers (range 0-14). To measure satisfaction with treatment, we used the six-item Diabetes Treatment Satisfaction Questionnaire (DTSQ) [25]. Response options range from 0 (very dissatisfied) to 6 (very satisfied) (range 0-36). Another two items measured the perceived frequency of hyperglycaemia and hypoglycaemia on a scale from 0 (never perceived) to 6 (most of the time).

Safety

Patients' self-reported device-related adverse events were collected at 3, 6 and 12-months of follow-up.

Adherence

To measure device adherence, the following variables were evaluated: 1) Number of daily scans; 2) Sensor usage time (percentage); and 3) Number of sensors used. These data were collected throughout the follow-up phase by means of the information stored in the device.

Use of healthcare resources

Data were extracted from the EHR at baseline and at 12-months of follow-up on: 1) Number of hospitalizations; 2) Number of clinic visits (endocrinology, nursing, primary care/paediatrics, emergency); 3) Number of HbA1c assays; 4) Number of test strips and lancets used; and 5) Absenteeism from work (number of days the caregiver was absent from work due to problems related to the child's T1DM).

In addition to these measures, information on age, sex, body mass index (BMI), time since diagnosis, presence of comorbidities and pubertal stage according to the Tanner scale [26], which classifies patients into 5 stages ranging from stage 1 (childhood) to 5 (adult), was systematically collected.

Sample Size Calculation

We estimated a sample size requirement of 43 participants to detect a minimal clinically relevant change in HbA1c of 0.5% [27], assuming 95% confidence level, 80% power, a HbA1c standard deviation of 1, a pre-post correlation of 0.5 (conservative assumption), and a loss rate of 20%. In addition to the main effect in the whole sample, we were also interested in the effect of the intervention on subgroups defined by their baseline HbA1c level (greater or less than 7.5%), and age (<12 vs. ≥12 years-old). However, the analysis of interactions requires larger sample sizes to attain statistical power, which was not feasible within the study's time limits. Therefore, we aimed to multiply the sample at least by 4 (n=172) to increase the statistical power as much as possible.

Statistical analysis

Means and standard deviation (SD) were estimated for continuous variables, and count and percentage for qualitative variables. Baseline characteristics of patients were compared using student-*t*, Pearson chi-square, Fisher's exact test or Cochran Q, according to the type of variables.

Mixed regression models with repeated measures were used, adjusting for the interaction between time and baseline HbA1c (dichotomous variable) and age group, time and its main effects. The duration of the disease and the existence of comorbidities were included as covariates. A linear link function was used for continuous dependent variables, a logistic function for dichotomous dependent variables and a Poisson function for count dependent variables. In the models with significant interaction, mixed regression models were performed for each interaction subgroup.

The relationship between adherence to the device and HbA1c reduction was analysed using two mixed linear regression models, whose independent variables were the percentage of time using the sensor (12 months) and

the number of monthly scans; basal HbA1c level was introduced as a covariable. Intercept was introduced as a random effect in all models.

For missing values during follow-up, a comparability analysis was conducted between participants lost to follow-up and those who remained, prior to performing multiple imputation by chained equations using Stata version 15.0. The details of this comparability analysis and the imputation model can be found in **online supplemental Appendix 2**.

A level of 0.05 was considered statistically significant. Analyses were performed with the statistical software Stata V.15.0 [28] and SPSS V.20.0 [29].

Cost estimation

Intervention costs were estimated from the Spanish National Health System (NHS) perspective, including only direct healthcare costs during the 12 months of the study. The healthcare resources collected in this study, together with the corresponding unit costs and their information sources, can be found in **Table A1 in online supplemental Appendix 3**. Costs were expressed as 2021 euros (€). When necessary, we adjusted for the consumer price index (CPI), using the Spanish Office of National Statistics (INE) – the INE's income conversion tool [30]. The sensor's unit costs (€43.27) were not included in our analysis because it was donated by Abbot. Therefore, only the difference in costs before and after use of the device was analysed without taking its cost into account, since this depends on the manufacturing company's economic offer.

Unit cost of test strips and lancets were estimated with the average costs of information provided by different regional health services of the Spanish NHS. Total costs were estimated multiplying the collected data on health resources used by their respective unit costs, and then added.

Descriptive statistics are presented for total costs aggregated and broken down into: primary care visits (nursing and physicians), emergency visits (hospital and non-hospitals), specialist physicians visits, laboratory tests (HbA1c assay) and monitoring instruments (test strips and lancets).

Given the nature of the costs and their non-normal nature, confidence intervals were estimated using a non-parametric bootstrapping method [31]. Analyses were performed using the statistical software SPSS V.20.0 [29] with the help of Microsoft Excel.

In addition, although the social perspective was not taken into account in this estimate, indirect technology costs were reported using the human capital theory, i.e. considering the costs attributed to productivity losses of the parents or caregivers of the child with T1DM before and after one year of using the FSL.

To estimate the cost per day of absenteeism, the cost per hour worked in Spain published by the Statistical Office of the European Union (Eurostat) [32] was multiplied by the average number of daily working hours worked in Spain published in the INE's Labour Force Survey (LFS) [33].

Results

A total of 165 patients were initially registered for the study. However, nine patients were subsequently excluded as they did not meet the study's inclusion criteria (see flow-chart in **Figure 1**). Therefore, the final analysis included a total of 156 patients.

Figure 1. Flow-chart

Patients' baseline characteristics, are shown in **Table 1,** according to subgroups by level of metabolic control and age. There was a higher percentage of participants in stage 1 and 5 in the subgroup with worse glycaemic control (*P*=0.02). In this subgroup, the mean HbA1c value was 8.7%; with 6.8% (*P*<0.001) in the well-controlled group. Descriptive statistics obtained at each time point for the total sample and subgroups for each outcome measure can be found in **online supplemental Appendix 4**.

Table 1. Baseline characteristics of patients according to baseline HbA1c control and age groups

	Total (n=156)	**HbA1c <7.5% (n=68)**	**HbA1c ≥7.5 % (n=88)**	***P***	**<12 years (n=53)**	**≥12 years (n=103)**	***P***
Anthropometric characteristics							
Sex (male) n (%)	86 (55.1)	35 (51.5)	51 (58)	.419	28 (52.8)	58 (56.3)	.679
Age (years), mean (SD)	12.6 (3.2)	12.7 (2.84)	12.49 (3.39)	.735	NA	NA	**NA**
Children < 12 years, n (%)	53 (34)	21 (30.9)	32 (36.4)	.474	NA	NA	**NA**
BMI (kg/m^2), mean (SD)	20.3 (4.1)	20.18 (3.34)	20.39 (4.54)	.754	NA	NA	**NA**
Pubertal status, n (%)				**.022**			**<.001**
I	51 (32.7)	19 (27.9)	32 (36.4)		44 (83)	7 (6.8)	
II	14 (9.0)	9 (13.2)	5 (5.7)		4 (7.5)	10 (9.7)	
III	20 (12.8)	7 (10.3)	13 (14.8)		4 (7.5)	16 (15.5)	
IV	23 (14.7)	16 (23.5)	7 (8)		0 (0)	23 (22.3)	
V	48 (30.8)	17 (25)	31 (35.2)		1 (1.9)	47 (45.6)	
Clinical characteristics							
Duration of diabetes (years), mean (SD)	5.65 (3.39)	5.52 (3.35)	5.75 (3.44)	.671	4.06 (2.4)	6.47 (3.54)	**<.001**
HbA1c, mean (SD)	7.86 (1.36)	6.82 (0.36)	8.65 (1.31)	**NA**	7.83 (1.17)	7.87 (1.45)	.87
HbA1c <7.5%, n (%)	68 (43.6)	NA	NA		21 (39.6)	47 (45.6)	.474
Presence of comorbidities, n (%)	50 (32.1)	27 (39.7)	23 (26.1)	.072	17 (32.1)	33 (32)	.996
Comorbidities, n (%)							
Asthma	6 (3.8)	5 (7.4)	1 (1.1)	.199	1 (1.9)	5 (4.9)	.65
Coeliac Disease	8 (5.1)	6 (8.8)	2 (2.3)	.261	5 (9.4)	3 (2.9)	.102
Thyroiditis	18 (11.5)	12 (17.6)	6 (6.8)	.178	6 (11.3)	12 (11.7)	.941
ADHD	4 (2.6)	1 (1.5)	3 (3.4)	.322	1 (1.9)	3 (2.9)	.999
Others	19 (12.2)	7 (10.3)	12 (13.6)	.057	5 (9.4)	14 (13.6)	.369

ADHD = Attention-Deficit/Hyperactivity Disorder; BMI = Body mass index; HbA1c = Glycated haemoglobin; NA = Not Applicable; SD = Standard deviation.

Other comorbidities: allergy, obesity, iron deficiency anaemia, unilateral anorchia, immunoglobulin A (IgA) deficiency, intellectual disability, epilepsy, hypercholesterolaemia, sensorineural hearing loss, migraines, idiopathic hypercalciuria, ovarian teratoma, nephrocalcinosis, psoriasis, allergic rhinitis, vasovagal syncope, Tourette's syndrome, eating disorder (ED) and obsessive-compulsive disorder (OCD).

Effectiveness

Glycated haemoglobin

In the entire sample, there was a significant increase in HbA1c (0.32%, *P*<0.001). The interaction between time and the baseline HbA1c group was statistically significant at 3, 6 and 12 months (*P*<0.001) (**Table 2**). In the subgroup analysis, participants with baseline HbA1c<7.5% revealed an increase of 0.32% (0.18 to 0.47) in HbA1c at 12 months (with respect to baseline) (*P*<0.001), without exceeding, on average, the threshold of poor control. Patients with poorly controlled baseline status had a statistically significant reduction in HbA1c at all follow-ups: B=-0.46% (-0.69 to -0.23; *P*<0.001), B=-0.49% (-0.73 to -0.25; *P*<0.001), and B=-0.43% (-0.68 to -0.19; *P*=0.001), at 3, 6 and 12 months, respectively (**Table 2**). On average, this reduction did not attain the threshold of poor control.

Table 2. Multivariate mixed regression models for glycosylated haemoglobin

	Glycosylated haemoglobin					
Variable	**Total sample (n=156)**		**HbA1c <7.5% (n=68)**		**HbA1c ≥7.5% (n=88)**	
	B (95%CI)	*P*	B (95%CI)	*P*	B (95%CI)	*P*
Time						
M3 (ref: M0)	0.03 (-0.18; 0.24)	.765	0.03 (-0.09; 0.16)	.611	-0.46 (-0.69; -0.23)	**<.001**
M6 (ref: M0)	0.1 (-0.11; 0.32)	.344	0.10 (-0.03; 0.23)	.115	-0.49 (-0.73; -0.25)	**<.001**
M12 (ref: M0)	0.32 (0.10; 0.55)	**.005**	0.32 (0.18; 0.47)	**<.001**	-0.43 (-0.68; -0.19)	**.001**
Duration of T1DM	0.05 (0.007; 0.09)	**.020**	-0.005 (-0.04; 0.03)	.762	0.09 (0.02; 0.15)	**.011**
Presence of comorbidities	-0.10 (-0.39; 0.18)	.477	0.09 (-0.13; 0.30)	.439	-0.22 (-0.70; 0.26)	.372
Age group: ≥12 years (ref: <12 years)	0.17 (-0.12; 0.47)	.253	0.09 (-0.15; 0.32)	.473	0.26 (-0.21; 0.73)	.274
Baseline HbA1c group: ≥7.5% (ref: HbA1c <7.5%)	1.81 (1.50; 2.13)	**<.001**				
Time*Baseline HbA1c Group (ref: M0 & HbA1c <7.5%)						
M3 & HbA1c ≥7.5%	-0.49 (-0.78; -0.21)	**<.001**				
M6 & HbA1c ≥7.5%	-0.59 (-0.88; -0.29)	**<.001**				
M12 & HbA1c ≥7.5%	-0.76 (-1.05; -0.46)	**<.001**				
Intercept	6.75 (6.41; 7.09)	**<.001**	6.73 (6.50; 6.96)	**<.001**	8.53 (8.12; 8.94)	**<.001**

CI = Confidence Interval; HbA1c = Glycosylated Haemoglobin; M = Month; T1DM = Type 1 Diabetes Mellitus.

Severe hypoglycaemic (SH) events

The reduction in the number of self-reported events was significant at 12 months β=-0.37 (-0.62 to -0.11; *P*=0.004) (**Table 1 in online supplemental Appendix 5**). Although the interaction with the level of HbA1c at baseline was not statistically significant (*P*=0.117), the descriptive statistics (**online supplemental Appendix 4**) in patients with controlled HbA1c at baseline show a reduction in the mean number of events; with an increase in the poorly controlled subgroup.

SH events recorded in the EHR show significantly lower rates compared to self-reported events (**online supplemental Appendix 4**), without significant main or interaction effects (**Table 1 in online supplemental**

Appendix 5). The rate of SH events was significantly higher in the subgroup with poor HbA1c control (*P*=0.014) (**Table 1 in online supplemental Appendix 5**).

Diabetic ketoacidosis and other serious adverse events

In the follow-up phase, six mild or moderate ketoacidosis events were recorded at three (2), six (1), and 12 months (3), respectively; and four serious adverse events at three months (two admissions and one episode of ketosis without acidosis due to bubbles in the system); and at six months (one admission). No events were observed at 12-month follow-up. No patient died during follow-up.

Health-related quality of life

At 12 months follow-up, the percentages of severe limitations for mobility, self-care, daily activities, anxiety and depression were similar to baseline values. However, a reduction was observed in the percentage of patients who self-reported pain (**online supplemental Appendix 4**).

VAS score (**Table 1 in online supplemental Appendix 5**) did not show a significant change in the whole sample, and the interaction with baseline HbA1c values was slightly above the statistical significance level (*P*= 0.061). In poorly controlled patients, VAS scores were significantly reduced at 12 months compared to the baseline score B=-6.03 (-9.66 to -2.41; *P*=0.001). In the subgroup with good basal metabolic control, no statistically significant findings were observed.

Knowledge about T1DM

There was no significant change in patients' knowledge, nor a significant interaction with baseline HbA1c. Patients with worse basal metabolic control revealed a significantly lower score compared to well-controlled patients: B=-1.27 (-1.89 to 0.65; *P*<0.001) (**Table 1 in online supplemental Appendix 5**).

Satisfaction with treatment

General satisfaction with treatment significantly increased 3.1 points at 12 months of follow-up (0.99 to 5.23; *P*=0.004) (**Table 1 in online supplemental Appendix 5**). There were no statistically significant differences in self-perceived hypo- and hyperglycaemia. For the latter, a higher score of 1.06 points (in a range of 0 to 6) was observed, in patients with HbA1c≥7.5%, compared to those with good control (0.60 to 1.52; *P*<0.001) (**Table 1 in online supplemental Appendix 5**).

Safety

Mild adverse events related to the device during follow-up phases had a 3.1% and 6.6% reduction for skin reactions and discomfort or pain, respectively. However, these were not statistically significant (**Table 3**).

Table 3. Mild adverse effects caused by the sensor

	3 months (n=150)	**6 months (n=136)**	**12 months (n=128)**	***P***	**Differences 12–3 months,** % (95%CI)
Skin reactions, n (%)	21 (14.0)	16 (11.8)	14 (1.9)	.542	-3.1% (-25.2; 19.0)
Discomfort or pain, n (%)	17 (11.3)	13 (9.6)	6 (4.7)	.210	-6.6% (-29.3; 16.1)
Other minor events, n (%)	3 (2.0)	2 (1.5)	2 (1.6)	.999	-0.4% (-23.9; 23.1)

Among the other events, there were minor haemorrhages when the sensor was positioned and wounds in the insertion area. In one case, the patient lost consciousness because of the bleeding.
CI = Confidence Interval.

Adherence

Time of sensor use (**Table 2 in online supplemental Appendix 5**) significantly increased at 6.4% at 12 months of follow-up (1.12 to 11.72; *P*=0.02), compared to three months. Longer duration of T1DM (*P*=0.008), and age older than 12 years (*P*=0.003), significantly reduced sensor use.

A reduction in the mean number of daily scans at three months occurred in poorly controlled patients B=-1.92 (-3.52 to -0.31; *P*=0.019). Those aged over 12 underwent an average of four fewer scans than those aged under 12 years B=-3.92 (-5.4 to -2.43; *P*<0.001) (**Table 2 in online supplemental Appendix 5**).
Controlled patients revealed an increase in the mean number of sensors use at 12 months of follow-up B=7 (5.85 to 8.06; *P*<0.001); also increasing in poorly controlled patients by B=1.6 (0.48 to 2.7; *P*=0.005) at 6 months, and B=9.4 (8.25 to 10.5; *P*<0.001) at 12 months (**Table 2 in online supplemental Appendix 5**).
The percentage of time of use was statistically significantly related to a lower HbA1c level at 12 months (B=-0.01; *P*=0.013), as was the number of scans (B=-0.21; *P*<0.001).

Costs estimation

The estimated total annual costs per patient are shown in **Table A2 (online supplemental Appendix 3)**. Intervention short-term costs from an NHS perspective reveal that specialist visits and test strips and lancets costs account for a significant part of total costs (38% and 41%, respectively), with an average annual cost per patient of €415.48 and €447.25 for specialist visits and strips and lancets, respectively.
Total annual costs before and after use of the FSL system can be found in **Figure A1 (online supplemental Appendix 3)**. All measured costs decreased after use of the device throughout 12 months follow-up, with the most striking difference in costs related to test strips and lancets use, an annual difference of €856.68 per patient. This information is outlined in **Table A3 (online supplemental Appendix 3)**. The annual average number of test strips per patient decreased from 2686.02 strips per year before the use of the FSL, to 883.98 strips per year after its use. The difference in the annual average use of lancets per patient also reduced from 1366.41, before FSL use, to 615.94, after its use.
Furthermore, a decrease in total annual costs due to productivity losses of parents/caregivers of minor patients with T1DM was observed after the use of FSL (€545.67 versus €262.73) as shown in **Table A3 (online supplemental Appendix 3)**.

Patient and public involvement

There was no patient involvement in the design of this study. Clinical experts from all participant hospitals, representatives of patient associations and the industry took part in drawing up the protocol. We undertook with healthcare professionals to share the results with them in an easy-to-understand way.

Discussion

Glucose monitoring devices can help people with T1DM monitor their glycaemia levels and reduce the frequency and/or severity of acute disease-complication rates, thus improving their HRQoL and life expectancy [34]. Two meta-analyses of case series on the effectiveness of the FSL revealed statistically significant HbA1c reductions in children/adolescents with poor HbA1c monitoring (7.5%-9.6%, except two studies with 7.1% and 7.4%) of -0.54% (n=447) [35] and -0.29% (n=959) [36], although the effect was highly variable across studies. Our study only provides a statistically significant reduction of HbA1c in the group with poor baseline monitoring, (-0.46%, -0.49% and -0.35%), at 3, 6 and 12 months, respectively. Conspicuously, patients with basal controlled HbA1c levels revealed a significant 12-month worsening higher than 0.30%. Another case series in Spain (n=145) [37], with limited follow up to three months, also detected a reduction in patients with HbA1c≥7.5% (-0.41, *P*=0.004), and a statistically significant increase in well-monitored patients, i.e. a worsening in HbA1c levels (0.23, *P*=0.03). Other studies [35, 38], reported a moderating effect of baseline HbA1c levels on subsequent reduction, with greater improvements in poorly controlled patients of all ages. However, except the aforementioned Spanish study [37], there are no known studies whose results indicate a significant worsening in well-controlled patients.

Our study also revealed a significant reduction in the number of self-reported SH events for the whole sample (-0.37), but not in the number of patients with at least one event. The interaction effect with baseline HbA1c level was not statistically significant for these two variables (*P*=0.117 and *P*=0.108, respectively). However, these analyses were underpowered and the descriptive statistics suggest different subgroup effects, although none was statistically significant. The reduction of self-reported SH events occurred in patients with correct HbA1c monitoring at baseline (0.39), whereas in the basally uncontrolled group, an increase was self-reported (0.37 more); together with an important increase in the rate of patients with at least one event (from 26% to 38%). These results could be reflecting the trade-off faced by patients with T1DM between the reduction in glucose levels and the associated risk of increasing the risk of hypoglycaemic events. Patients with higher HbA1c levels could have attained the reduction target, increasing the risk of SH; whereas some of those patients in need of reducing hypoglycaemic events, could increase their HbA1c levels. This interpretation is speculative since the commented results on self-reported SH were not statistically significant and underpowered, but it would help account for the unexpected significant worsening in self-perceived general health observed in the subgroup of poor baseline HbA1c monitoring. Contrary to the HbA1c improvement attained in our study, without observable effects on self-perceived HRQoL, suffering an SH event is a salient experience that may impact this self-perception.

Other studies [37] have also reported a significant and clinically meaningful improvement in the rate of SH events (from 4.2 to 0.2 events/100 patients-year). However, their results are not reported separately according to basal levels of metabolic control. The largest case series published to date with children and adolescents [39], and with the longest follow-up (12 months), also revealed a statistically significant reduction of SH events (53%, *P*=0.012) for the whole sample, with no changes in HbA1c.

The interaction of the intervention with the age group (<12 vs. ≥12 years-old) was not statistically significant in any case. However, descriptive statistics reveal different non-significant trends among subgroups, with positive results only for younger participants: -0.26% vs. -0.05% (HbA1c), -1.06 vs. 0.68 (SH events) and -4.2% vs. 10.5% (people with one or more SH). Adolescents revealed significantly lower sensor usage time and scans per day than children, similar to the results observed in previous studies [40-42]. Regardless of these findings, their adherence was good, above 78% of the time at each successive evaluation. However, the only randomized controlled trial to date evaluating the effectiveness of FSL in adolescents (aged 13-20 years, with HbA1c≥9.0%) [13], did not reveal any statistically significant differences in HbA1c reduction compared to traditional self-monitoring at six months. Therefore, significant uncertainty remains in regard to the effects of FSL in adolescents.

Despite the improvement in the degree of metabolic control that occurred in our study sample of patients with worse baseline HBA1c levels, no statistically significant improvement was observed in their knowledge of disease self-management. Device adherence was significantly related to the reduction of HbA1c, a result usually

observed in the literature on glucose monitoring devices [40-42]. The same can be said about treatment satisfaction [43,44], which improved in the whole sample.

In regard to safety, no serious adverse effects were observed, a result consistent with the literature on glucose monitoring devices in general [9]. The number of patients showing mild adverse events at three months was reduced at the end of follow-up to 18%, resulting in two losses at six months follow-up due to skin reaction to the sensor and another two at 12 months due to discomfort with the sensor.

In terms of costs analysis as observed in the international literature, our results showed that T1DM patients consume less healthcare resources using FSL [45]. Fundamentally, a striking decrease was observed in costs attributed to reactive strips and lancets, where an annual difference of €856.68 per patient was obtained. A decrease in total indirect annual costs due to productivity losses of parents/carers of T1DM patients, was also observed (€545.67 versus €262.73).

The main limitation of this study lies in its uncontrolled design, which precludes comparison with an untreated group. Therefore, an inference of causality regarding the introduction of the FLS is not possible, because other factors such as child developmental growth, potential changes in target treatment or insulin administration methods could impact the observed changes. A “novelty effect”, related to the use of a technological device could also introduce a motivation bias that could affect self-management habits. Another relevant limitation is the limited sample size to analyse interaction effects, even when we increased the recruited sample fourfold. By the time of study execution, the FSL was already financed and introduced in some hospitals taking part and a large portion of the target population was already using it. This scenario was an important recruitment obstacle to enlarge sample size. Our conclusions to be drawn are, therefore, limited by the low statistical power for interaction analyses and rare events such as severe hypoglycaemia. All these limitations imply a low quality of the evidence.

The start-up of a monitoring study has been used to collect data on the use of resources and make initial estimates of the cost of the intervention. Therefore, our cost analysis was a secondary endpoint and complementary to this study’s primary endpoint and it has limitations. First, our analysis has not taken into account the costs attributable to the possible adverse effects arising from the use of FSL and it has assumed that possible failures of the device will be resolved at no additional cost to the Spanish NHS. Moreover, it was not possible to estimate the costs related to hospitalization of the patients since the number of days of each hospitalization was not recorded in this study. However, the extremely low number of total hospitalizations during the monitoring study indicates that including this cost in the estimate would not have produced substantial changes in the results. Finally, it must be taken into account that the unit cost of the FSL sensor has not been considered since it was delivered free of charge to the study participants.

To the best of our knowledge, this is the first comparative costs analysis study of FSL use in children and adolescents with T1DM in Spain using observational data in an actual use scenario. Therefore, although a cost-effectiveness analysis could not be performed in this study, due to the absence of a comparator, our results may contribute to inform future cost-effectiveness studies of FSL in Spain.

In conclusion, our results suggest that the use of FSL in young T1DM patients significantly reduces the rate of SH events, and improves HbA1c levels in patients with poor baseline monitoring. However, futures studies should confirm whether these benefits could be at the cost of worsening severe hypoglycaemia in patients with lower HbA1c. No serious adverse events related to FSL were observed. The results also suggest that the use of FSL in young patients with T1DM leads to a decrease in monitoring costs. In addition, the use of FSL reduces costs attributable to lost productivity of parents/caregivers. These outcomes correspond to low-quality evidence, mainly due to the study’s uncontrolled design, in addition to the low statistical power in the case of rare complications such as SH.

Based on these results and other information sources (i.e., international research and clinical expert advice), the Spanish Ministry of Health has decided to reimburse the FreeStyle Libre (FSL) for children and adolescents aged 4-17 years old with Type 1 diabetes who undergo intensive insulin therapy (multiple daily injections or insulin pump) and require at least six fingerstick blood glucose self-monitoring tests a day.

Footnotes

Collaborators: The Health Professional Group included the following members (in alphabetical order): Amparo González Vergaz (Hospital Severo Ochoa), Ana María Prado Carro (Complexo Hospitalario Universitario A Coruña), Anunciación Beisti Ortego (Fundación Hospital Calahorra), Ariadna Campos Martorell (Hospital Universitari Vall D'hebron), Atilano José Carcavilla Urqui (Hospital Universitario La Paz), Cristina Amparo Del Castillo Villaescusa (Hospital Universitario Dr. Peset Aleixandre), Estela Gil Poch (Hospital Universitario de Badajoz), Francisco Javier Arroyo Diez (Hospital Universitario de Badajoz), Gemma Novoa Gómez (Complexo Hospitalario Universitario de Ourense), Isabel González Casado (Hospital Universitario La Paz), Juncal Martínez Ibáñez (Fundación Hospital Calahorra), Laura Cuadrado Piqueras (Fundación Hospital Calahorra), Leticia Reis Iglesias (Complexo Hospitalario Universitario de Ourense), Lucia Garzón Lorenzo (Hospital Universitario 12 De Octubre), Luis Salamanca Fresno (Hospital Universitario La Paz), María Asunción Martínez Brocca (Hospital Universitario Virgen Macarena), María Aurea Rodríguez Blanco (Hospital Da Barbanza), María Del Mar Martínez López (Hospital Universitario 12 De Octubre), María Jesús Ferreiro Rodríguez (Complexo Hospitalario Universitario de Ourense), María Ruiz del Campo (Hospital San Pedro), Nerea Itza Martín (Hospital Universitario La Paz), Patricia García Navas (Hospital San Pedro), Rebeca García García (Hospital Universitario Central de Asturias).

Contributorship statement: YAP, ARS, LPP and PSA initiated the study. HGP did the acquisition of data. HGP, ARS, CVN and YRF contributed to the analysis and interpretation of data. HGP did the statistical analyses. HGP, ARS, CVN YAP and YRF wrote the first draft of the manuscript. HGP, ARS, YRF, CVN, YAP, LGP, MAGB, LPP AND PSA critically revised the manuscript and approved the final version. HGP is responsible for the overall content as the guarantor and accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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Ethics approval statement

Patient consent for publication: Not applicable.

Ethics approval: All participants provided written informed consent. The scientific and ethics committees approved the study protocol (Hospital Universitari Vall d'Hebron, ID-RTF065).

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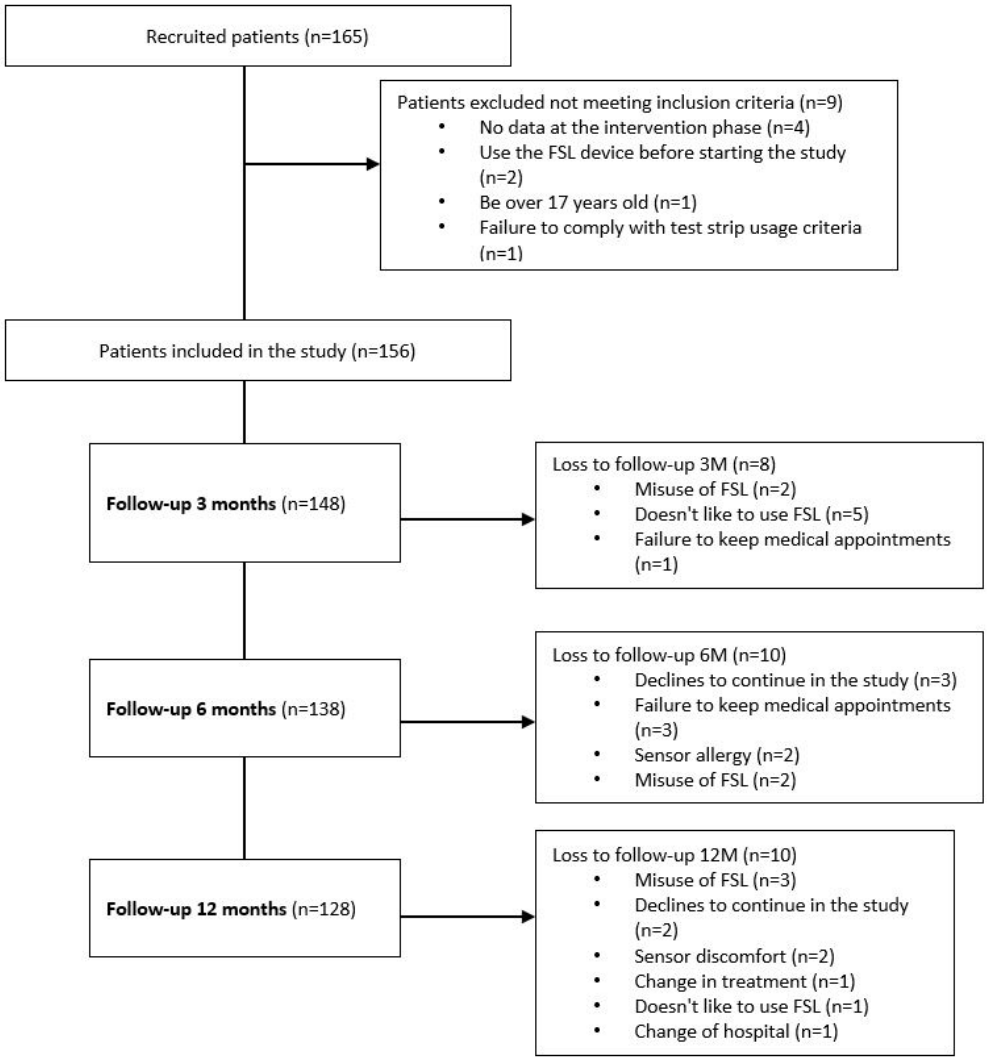

Figure1. Flow-charts

201x216mm (96 x 96 DPI)

Appendix 1. Participating hospitals and cases included in the study

Public hospitals	Regional Health Services	Number of patients
Hospital Universitario Virgen Macarena*	Andalucía	2
Hospital Universitario Central de Asturias*	Asturias	4
Hospital Universitario Vall D'hebron*	Cataluña	22
Hospital Universitario de Badajoz	Extremadura	30
Complejo Hospitalario Universitario A Coruña*	Galicia	23
Complejo Hospitalario Universitario de Ourense	Galicia	14
Hospital Da Barbanza	Galicia	5
Fundación Hospital Calahorra	La Rioja	1
Hospital San Pedro	La Rioja	13
Hospital Severo Ochoa	Madrid	21
Hospital Universitario 12 De Octubre*	Madrid	4
Hospital Universitario La Paz*	Madrid	16
Hospital Universitario Dr. Peset Aleixandre	Valencia	1
*Tertiary hospital		

Appendix 2. Comparability analysis and description of the missing data imputation model

Comparability analysis

For comparability analysis, the baseline characteristics of patients (gender, age, HbA1c, BMI, time since diagnosis, presence of comorbidities, and pubertal stage) were compared between participants who completed the different follow-up phases and those who had total or partial loss to follow-up at 3, 6, and 12 months. No significant differences were found for any of these variables at the 3-month follow-up. At 6 months, significant differences were observed between responders and non-responders in relation to pubertal stage V (25% vs. 75%) (p = 0.04). At the 12-month follow-up, differences were observed in pubertal stages IV (21.7% vs. 78.3%) and V (31.2% vs. 68.8%) (p = 0.007); significant differences were also observed in the mean age value (p = 0.04) between responders (12.3 years) and non-responders (13.7 years).

	3 months			**6 months**			**12 months**		
	Participants lost to follow-up (n=6)	**Participants who continued in the study (n=150)**	**p**	**Participants lost to follow-up (n=20)**	**Participants who continued in the study (n=136)**	**p**	**Participants lost to follow-up (n=28)**	**Participants who continued in the study (n=128)**	**p**
Sex (male), n (%)	4 (4.7)	82 (95.3)	0.562	8 (9.3)	78 (90.7)	0.145	16 (18.6)	70 (81.4)	0.813
Age (years), mean (SD)	13 (4.86)	12.55 (3.09)	0.829	13.3 (3.81)	12.46 (3.05)	0.266	13.68 (2.91)	12.32 (3.17)	**0.039**
HbA1c, mean (SD)	8.42 (0.62)	7.83 (1.38)	0.303	8.36 (2.01)	7.78 (1.23)	0.224	8.08 (1.81)	7.81 (1.24)	0.33
BMI, mean (SD)	20.73 (2.87)	20.28 (4.10)	0.789	21.33 (2.91)	20.14 (4.18)	0.224	21.33 (2.88)	20.07 (4.24)	0.135
Duración de la DM1, mean (SD)	7.19 (3.86)	5.59 (3.37)	0.257	6.42 (3.43)	5.54 (3.38)	0.275	6.74 (3.39)	5.41 (3.36)	0.061
Presence of comorbidities, n (%)	1 (2.0)	49 (98.0)	0.41	7 (14)	43 (86)	0.762	9 (18)	41 (82)	0.991
Pubertal status, n (%)			0.473			**0.043**			**0.007**
I	2 (3.9)	49 (96.1)		5 (9.8)	46 (90.2)		5 (9.8)	46 (90.2)	
II	0 (0)	14 (100)		1 (7.1)	13 (92.9)		3 (21.4)	11 (78.6)	
III	0 (0)	20 (100)		0 (0)	20 (100)		0 (0)	20 (100)	
IV	0 (0)	23 (100)		2 (8.7)	21 (91.3)		5 (21.7)	18 (78.3)	
V	4 (8.3)	44 (91.7)		12 (25)	36 (75)		15 (31.2)	33 (68.8)	

SD = Standard deviation; HbA1c = Glycated haemoglobin; BMI = Body mass index.

Description of the missing data imputation model

For multiple imputation was performed by chained equations using Stata 15.0 software. The variables sex. age. pubertal stage. presence of comorbidities and duration of diabetes were considered regular and used as predictors for imputation. A total of 29 variables were imputed. Each variable was imputed in chronological order: 3. 6 and 12 months. As a general rule. the latest available information on the variable to be imputed was used. When information from other variables was used. the information from the same point in time was used. A total of 10 imputations were made for each missing data.

Order	Imputed variable	Variables used in imputation	Imputation model	n (%) missing
1	HbA1c 3M	Sex. Age. Pubertal stage. Presence of comorbidities. Time since diagnosis. HbA1c Baseline	pmm	7 (4.5)
2	HbA1c 6M	Sex. Age. Pubertal stage. Presence of comorbidities. Time since diagnosis. HbA1c 3M	pmm	20 (12.8)
3	HbA1c 12M	Sex. Age. Pubertal stage. Presence of comorbidities. Time since diagnosis. HbA1c 6M	pmm	28 (17.9)
4	BMI 6M	Sex. Age. Pubertal stage. Presence of comorbidities. Time since diagnosis. BMI Baseline	pmm	24 (15.4)
5	BMI 12M	Sex. Age. Pubertal stage. Presence of comorbidities. Time since diagnosis. BMI 6M	pmm	28 (17.9)
6	N.º severe hypoglycaemia events 3M	Sex. Age. Pubertal stage. Presence of comorbidities. Time since diagnosis. N.º severe hypoglycaemia events Baseline	poisson	7 (4.5)
7	N.º severe hypoglycaemia events 6M	Sex. Age. Pubertal stage. Presence of comorbidities. Time since diagnosis. N.º severe hypoglycaemia events 3M	poisson	7 (4.5)
8	N.º severe hypoglycaemia events 12M	Sex. Age. Pubertal stage. Presence of comorbidities. Time since diagnosis. N.º severe hypoglycaemia events 6M	poisson	7 (4.5)
9	N.º severe hypoglycaemia events on EHR 3M	Sex. Age. Pubertal stage. Presence of comorbidities. Time since diagnosis. N.º severe hypoglycaemia events 3M. N.º severe hypoglycaemia events on EHR Baseline	poisson	8 (5.1)
10	N.º severe hypoglycaemia events on EHR 6M	Sex. Age. Pubertal stage. Presence of comorbidities. Time since diagnosis. N.º severe hypoglycaemia events 6M. N.º severe hypoglycaemia events on EHR 3M	poisson	28 (17.9)
11	N.º severe hypoglycaemia events on EHR 12M	Sex. Age. Pubertal stage. Presence of comorbidities. Time since diagnosis. N.º severe hypoglycaemia events 12M. N.º severe hypoglycaemia events on EHR 6M	poisson	28 (17.9)
12	VAS 12M	Sex. Age. Pubertal stage. Presence of comorbidities. Time since diagnosis. Mobility EQ-5D-Y 12M. Self-care EQ-5D-Y 12M. Habitual activities EQ-5D-Y 12M. Pain/discomfort EQ-5D-Y 12M. Anxiety/depression EQ-5D-Y 12M. VAS Baseline	pmm	36 (23.1)
13	Knowledge about Baseline	Sex. Age. Pubertal stage. Presence of comorbidities. Time since diagnosis. HbA1c Baseline. BMI Baseline	pmm	14 (9.0)
14	Knowledge about 12M	Sex. Age. Pubertal stage. Presence of comorbidities. Time since diagnosis. HbA1c 12M. BMI 12M. Knowledge about Baseline	pmm	48 (30.8)
15	Hyperglycaemia DTSQ Baseline	Sex. Age. Pubertal stage. Presence of comorbidities. Time since diagnosis. HbA1c Baseline. Knowledge about Baseline	pmm	14 (9.0)
16	Hyperglycaemia DTSQ 12M	Sex. Age. Pubertal stage. Presence of comorbidities. Time since diagnosis. HbA1c 12M. Knowledge about 12M. Hyperglycaemia DTSQ Baseline	pmm	48 (30.8)
17	Hypoglycaemia DTSQ Baseline	Sex. Age. Pubertal stage. Presence of comorbidities. Time since diagnosis	pmm	14 (9.0)
18	Hypoglycaemia DTSQ 12M	Sex. Age. Pubertal stage. Presence of comorbidities. Time since diagnosis. Hypoglycaemia DTSQ Baseline	pmm	48 (30.8)

19	Satisfaction with treatment DTSQ Baseline	Sex. Age. Pubertal stage. Presence of comorbidities. Time since diagnosis. N.º severe hypoglycaemia events Baseline. N.º severe hypoglycaemia events on EHR Baseline. Knowledge about Baseline. Hyperglycaemia DTSQ Baseline.	pmm	14 (9.0)
20	Satisfaction with treatment DTSQ 12M	Sex. Age. Pubertal stage. Presence of comorbidities. Time since diagnosis. N.º severe hypoglycaemia events 12M. N.º severe hypoglycaemia events on EHR 12M. Knowledge about 12M. Hyperglycaemia DTSQ 12M. Satisfaction with treatment DTSQ Baseline	pmm	48 (30.8)
21	N.º of daily scans 3M	Sex. Age. Pubertal stage. Presence of comorbidities. Time since diagnosis. HbA1c 3M. BMI Baseline. N.º severe hypoglycaemia events 3M	pmm	8 (5.1)
22	N.º of daily scans 6M	Sex. Age. Pubertal stage. Presence of comorbidities. Time since diagnosis. HbA1c 6M. BMI 6M. N.º severe hypoglycaemia events 6M. N.º of daily scans 3M	pmm	19 (12.2)
23	N.º of daily scans 12M	Sex. Age. Pubertal stage. Presence of comorbidities. Time since diagnosis. HbA1c 12M. BMI 12M. N.º severe hypoglycaemia events 12M. N.º of daily scans 6M	pmm	28 (17.9)
24	Sensor usage time 3M	Sex. Age. Pubertal stage. Presence of comorbidities. Time since diagnosis. HbA1c 3M. N.º ketoacidosis 3M. N.º of daily scans 3M	pmm	8 (5.1)
25	Sensor usage time 6M	Sex. Age. Pubertal stage. Presence of comorbidities. Time since diagnosis. HbA1c 6M. N.º ketoacidosis 6M. N.º of daily scans 6M. Sensor usage time 3M	pmm	19 (12.2)
26	Sensor usage time 12M	Sex. Age. Pubertal stage. Presence of comorbidities. Time since diagnosis. HbA1c 12M. N.º ketoacidosis 12M. N.º of daily scans 12M. Sensor usage time 6M	pmm	28 (17.9)
27	N.º Sensors 3M	Sex. Age. Pubertal stage. Presence of comorbidities. Time since diagnosis. N.º ketoacidosis 3M. Sensor usage time 3M	pmm	7 (4.5)
28	N.º Sensors 6M	Sex. Age. Pubertal stage. Presence of comorbidities. Time since diagnosis. N.º ketoacidosis 6M. Sensor usage time 6M. N.º Sensors 3M	pmm	19 (12.2)
29	N.º Sensors 12M	Sex. Age. Pubertal stage. Presence of comorbidities. Time since diagnosis. N.º ketoacidosis 12M. Sensor usage time 12M. N.º Sensors 6M	pmm	28 (17.9)

DM = Diabetes Mellitus; T1DM = Type 1 Diabetes Mellitus; DTSQ = Diabetes Treatment Satisfaction Questionnaire; EQ-5D-Y = Health-related quality of life questionnaire; VAS = visual analogue scale; HbA1c = Glycated haemoglobin; EHR = Electronic Health Record; BMI = Body mass index; M = Months.

Appendix 3. Cost estimation

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Table A1. Use of resources and unit costs

	Unit cost €2021 (SD)	Source
Hospitalization /day	652.58 (188.86)	Public tariff*
Visit to specialist	95.65 (33.98)	Public tariff*
Visit to nurse at primary care	27.06 (7.52)	Public tariff*
Hospital emergency	207.54 (72.03)	Public tariff*
Visit to doctor at primary care	50.91 (17.63)	Public tariff*
Non-hospital emergency	99.41 (22.83)	Public tariff*
HbA1c determination	7.15 (5.16)	Public tariff*
Test strips	0.43 (0.15)	Consult*
Lancets	0.109 (0.11)	Consult*
Absenteeism day	166.896	Estimate based on Eurostat and INE

SD = Standard Deviation
* Spanish autonomous communities.
INE = Spanish Statistical Office.
Unit costs come from different sources, all national, and include official tariffs. Where possible, the average costs of those Spanish regions for which data were available were taken into account
To estimate the unit cost of test strips and lancets, the Spanish regions were consulted for their spending on these products. There was great heterogeneity between regions, not only in the unit cost (between €0.10 and €0.48), but also in the products financed, since lancets are only financed in some regions.

Table A2. Total annual cost per patient of the FSL flash glucose monitoring system (€2021)

	Primary care	Emergency	Specialist	Laboratory	Monitoring*	Total costs
Mean (SD)	136.78 (101.28)	50.70 (161.66)	415.48 (129.53)	29.05 (5.87)	447.25 (317.58)	1079.26 (425.73)
Min. – Max.	0 – 474.24	0 – 1245.24	0 – 956.5	14.30 – 71.50	0 – 1295.39	219.9 – 2501.19
CI95%	(119.88; 154.65)	(25.74; 80.73)	(393.81; 438.65)	(28.1; 30.16)	(392.57; 501.77)	(1007.41; 1152.15)

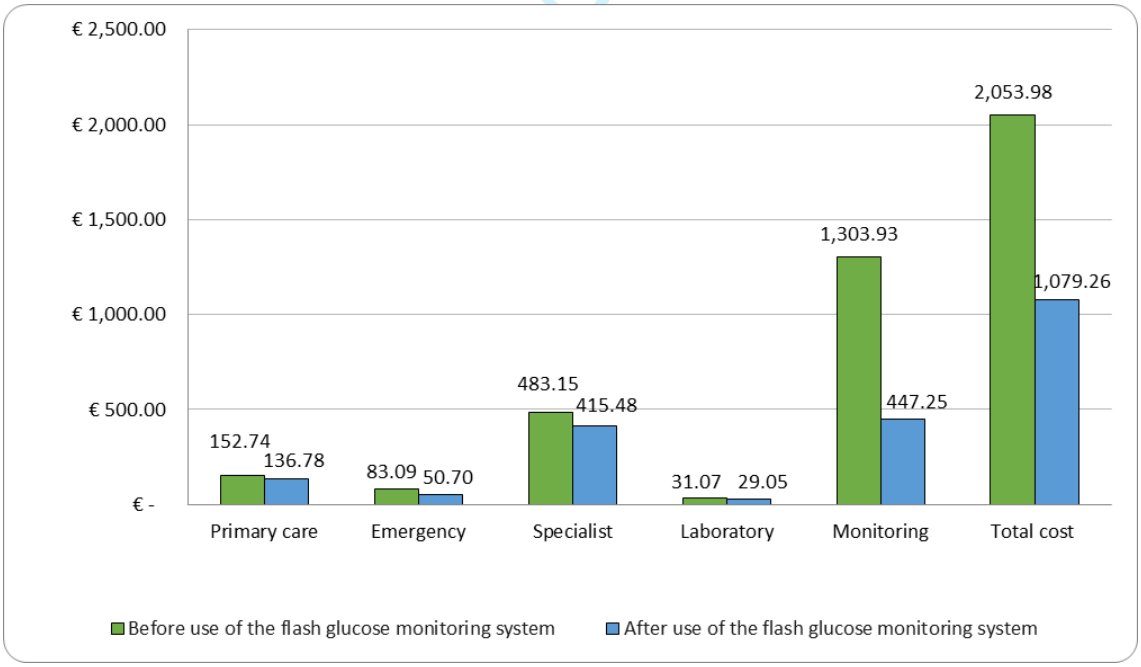
CI95% = Confidence interval at 95% by Bootstrap based on 10,000 samples; Max. = Maximum; Min. = Minimum; SD = Standard Deviation
*Test strips and lancets. Not include the cost of sensor

Table A3. Average number of test strips and lancets per patient and total annual costs due to lost parent/caregiver productivity before and after FSL use.

	Before use of the flash glucose monitoring system	After use of the flash glucose monitoring system
Average number of test strips and lancets per patient before and after use of the FSL device		
Yearly test strips, mean (SD)	2686,02 (527,63)	883.98 (669.45)
Yearly Lancets, mean (SD)	1366.41 (1063.44)	615.94 (482.03)
Total annual cost per patient due to productivity losses (€2021)		
Mean (SD)	545.67 (588.29)	262.73 (334.30)
Min. – Max.	0 – 3504.82	0 – 1668.96
CI95%	(448.55; 650.63)	(206.65; 322.71)

CI95% = Confidence interval at 95% by Bootstrap based on 10,000 samples; Max. = Maximum; Min. = Minimum; SD = Standard Deviation

Figure A1. Total annual costs per patient before and after use of the FSL (does not include cost of device)



Appendix 4. Evolution of outcome measures during follow-up (by age group and baseline HbA1c control)

	Baseline	3 months	6 months	12 months	Differences 12 months-Baseline
HbA1c, mean (SD)					
Total	7.86 (1.36)	7.58 (1.27)	7.59 (1.16)	7.73 (1.06)	-0.13 (-0.42; 0.16)
HbA1c <7.5%	6.82 (0.36)	6.86 (0.55)	6.96 (0.6)	7.14 (0.57)	0.32 (0.15; 0.49)
HbA1c ≥7.5%	8.65 (1.31)	8.18 (1.38)	8.14 (1.25)	8.2 (1.12)	-0.45 (-0.84; -0.06)
< 12 years	7.83 (1.17)	7.42 (0.93)	7.53 (0.96)	7.57 (0.8)	-0.26 (-0.59; 0.07)
≥ 12 years	7.87 (1.45)	7.66 (1.41)	7.63 (1.26)	7.82 (1.19)	-0.05 (-0.45; 0.35)
With self-reported severe hypoglycemia, n (%)					
Total	49 (31.4)	-	-	55 (36.9)	5.5% (-12.7; 23.7)
HbA1c <7.5%	26 (38.2)	-	-	24 (35.3)	-2.9% (-29.6; 23.8)
HbA1c ≥7.5%	23 (26.1)	-	-	31 (38.3)	12.2% (-12.6; 37.0)
< 12 years	22 (41.5)	-	-	19 (37.3)	-4.2% (-34.1; 25.7)
≥ 12 years	27 (26.2)	-	-	36 (36.7)	10.5% (-12.4; 33.4)
Nº. Self-reported severe hypoglycemia, mean (SD)					
Total	1.72 (3.65)	-	-	1.77 (5.08)	0.05 (-0.98; 1.1)
HbA1c <7.5%	2.34 (4.13)	-	-	1.95 (5.69)	-0.39 (-2.2; 1.4)
HbA1c ≥7.5%	1.26 (3.19)	-	-	1.63 (4.58)	0.37 (-0.86; 1.6)
< 12 years	2.12 (4.04)	-	-	1.06 (3.65)	-1.06 (-2.6; 0.48)
≥ 12 years	1.52 (3.43)	-	-	2.20 (5.76)	0.68 (-0.69; 2.1)
With severe hypoglycemia in the electronic clinical record, n (%)					
Total	19 (12.2)	-	-	23 (15.4)	3.2% (-17.6; 24.0)
HbA1c <7.5%	6 (8.8)	-	-	6 (8.8)	0% (-32.0; 32.0)
HbA1c ≥7.5%	13 (14.8)	-	-	17 (21.0)	6.2% (-21.1; 33.5)
< 12 years	9 (17.0)	-	-	6 (11.8)	-5.2% (-40.8; 30.4)
≥ 12 years	10 (9.7)	-	-	17 (17.4)	7.7% (-0.18; 0.33)
N.º Hypoglycemia in the electronic clinical record prior to the study, mean (SD)					
Total	0.39 (1.68)	-	-	0.54 (1.58)	0.15 (-0.23; 0.53)
HbA1c <7.5%	0.13 (0.45)	-	-	0.25 (1.06)	0.12 (-0.16; 0.40)
HbA1c ≥7.5%	0.59 (2.18)	-	-	0.78 (1.88)	0.19 (-0.43; 0.81)
< 12 years	0.34 (1.02)	-	-	0.61 (1.89)	0.27 (-0.32; 0.86)
≥ 12 years	0.42 (1.94)	-	-	0.5 (1.40)	0.08 (-0.39; 0.55)
Health-related quality of life (EQ-5D-Y), n (%)					
Mobility (no problems), n (%)					
Total	156 (100)	-	-	124 (100)	-
HbA1c <7.5%	68 (100)	-	-	54 (100)	-
HbA1c ≥7.5%	88 (100)	-	-	70 (100)	-
< 12 years	53 (100)	-	-	47 (100)	-
≥ 12 years	103 (100)	-	-	77 (100)	-
Self-Care (no problems), n (%)					
Total	154 (98.7)	-	-	123 (99.2)	-
HbA1c <7.5%	67 (98.5)	-	-	54 (100)	-
HbA1c ≥7.5%	87 (98.9)	-	-	69 (98.6)	-
< 12 years	51 (96.2)	-	-	47 (100)	-
≥ 12 years	103 (100)	-	-	76 (98.7)	-
Usual Activities (no problems), n (%)					
Total	154 (98.7)	-	-	122 (98.4)	-
HbA1c <7.5%	67 (98.5)	-	-	53 (98.1)	-
HbA1c ≥7.5%	87 (98.9)	-	-	69 (98.6)	-
< 12 years	53 (100)	-	-	47 (100)	-
≥ 12 years	101 (98.1)	-	-	75 (97.4)	-
Pain or Discomfort (no pain), n (%)					
Total	144 (92.3)	-	-	118 (95.2)	-
HbA1c <7.5%	62 (91.2)	-	-	53 (98.1)	-
HbA1c ≥7.5%	82 (93.2)	-	-	65 (92.9)	-

< 12 years	50 (94.3)	-	-	45 (95.7)	-
≥ 12 years	94 (91.3)	-	-	73 (94.8)	-
Pain or Discomfort (some pain), n (%)					
Total	12 (7.7)	-	-	6 (4.8)	-
HbA1c <7.5%	6 (8.8)	-	-	1 (1.9)	-
HbA1c ≥7.5%	6 (6.8)	-	-	5 (7.1)	-
< 12 years	3 (5.7)	-	-	2 (4.3)	-
≥ 12 years	9 (8.7)	-	-	4 (5.2)	-
Anxiety/Depression (no problems), n (%)					
Total	137 (87.8)	-	-	112 (90.3)	-
HbA1c <7.5%	62 (91.2)	-	-	50 (92.6)	-
HbA1c ≥7.5%	75 (85.2)	-	-	62 (88.6)	-
< 12 years	49 (92.5)	-	-	44 (93.6)	-
≥ 12 years	88 (85.4)	-	-	68 (88.3)	-
Anxiety/Depression (some problems), n (%)					
Total	16 (10.3)	-	-	10 (8.1)	-
HbA1c <7.5%	5 (7.4)	-	-	4 (7.4)	-
HbA1c ≥7.5%	11 (12.5)	-	-	6 (8.6)	-
< 12 years	3 (5.7)	-	-	2 (4.3)	-
≥ 12 years	13 (12.6)	-	-	8 (10.4)	-
VAS, mean (sd)					
Total	87.63 (12.46)	-	-	84.17 (12.28)	-3.5 (-6.4; -0.53)
HbA1c <7.5%	88.79 (10.05)	-	-	87.92 (10.08)	0.29 (-3.9; 4.5)
HbA1c ≥7.5%	86.74 (14.04)	-	-	81.29 (16.29)	-7.5 (-11.7; -3.3)
< 12 years	91.66 (9.72)	-	-	85.61 (14.97)	-6.1 (-11.0; -1.1)
≥ 12 years	85.56 (13.23)	-	-	83.27 (13.86)	-2.3 (-6.3; 1.7)
Knowledge about DM1 (modified version of Mitchell questionnaire), mean (SD)					
Total	11.68 (2.13)	-	-	12.09 (1.94)	0.41 (-0.11; 0.93)
HbA1c <7.5%	12.38 (1.98)	-	-	12.92 (1.35)	0.54 (-0.11; 1.2)
HbA1c ≥7.5%	11.12 (2.08)	-	-	11.38 (2.08)	0.26 (-0.45; 0.97)
< 12 years	11.87 (2.07)	-	-	11.9 (2.31)	0.03 (-0.90; 0.96)
≥ 12 years	11.59 (2.16)	-	-	12.21 (1.67)	0.62 (-0.001; 1.2)
Diabetes Treatment Satisfaction Questionnaire (DTSQ)					
Perceived hyperglycemia, mean (SD)					
Total	3.53 (1.51)	-	-	3.32 (1.44)	-0.21 (-0.58; 0.16)
HbA1c <7.5%	2.94 (1.28)	-	-	2.88 (1.44)	-0.06 (-0.57; 0.45)
HbA1c ≥7.5%	4.01 (1.51)	-	-	3.71 (1.34)	-0.3 (-0.79; 0.19)
< 12 years	3.62 (1.38)	-	-	3.44 (1.48)	-0.18 (-0.79; 0.43)
≥ 12 years	3.48 (1.57)	-	-	3.25 (1.42)	-0.23 (-0.71; 0.25)
Perceived hypoglycemia, mean (SD)					
Total	2.22 (1.35)	-	-	2.04 (1.32)	-0.18 (-0.52; 0.16)
HbA1c <7.5%	2.3 (1.36)	-	-	2 (1.31)	-0.3 (-0.80; 0.20)
HbA1c ≥7.5%	2.15 (1.35)	-	-	2.07 (1.34)	-0.08 (-0.54; 0.38)
< 12 years	2.19 (1.17)	-	-	2.05 (1.26)	-0.14 (-0.66; 0.38)
≥ 12 years	2.23 (1.44)	-	-	2.03 (1.36)	-0.2 (-0.64; 0.24)
Satisfaction with treatment, mean (SD)					
Total	25.89 (6.7)	-	-	29.82 (5.44)	3.93 (2.4; 5.5)
HbA1c <7.5%	26.58 (7.04)	-	-	29.78 (5.1)	3.2 (0.86; 5.5)
HbA1c ≥7.5%	25.33 (6.41)	-	-	29.86 (5.77)	4.53 (2.4; 6.6)
< 12 years	25.79 (6.71)	-	-	29.61 (5.87)	3.82 (1.1; 6.5)
≥ 12 years	25.95 (6.73)	-	-	29.96 (5.21)	4.01 (2.1; 5.9)
	Baseline	**3 months**	**6 months**	**12 months**	**Differences 12-3 months**
Sensor usage time (%), mean (SD)					
Total	-	81.60 (20.78)	84.42 (19.47)	88.55 (18.48)	6.95 (2.3; 11.6)
HbA1c <7.5%	-	83.99 (21.93)	86.60 (17.2)	91.70 (15.09)	7.71 (0.90; 14.5)
HbA1c ≥7.5%	-	79.63 (19.69)	82.57 (21.16)	86.01 (20.57)	6.38 (-0.8; 12.8)
< 12 years	-	87.59 (15.06)	90.60 (14.34)	94.51 (11.81)	6.92 (1.5; 12.3)

≥ 12 years	-	78.45 (22.67)	81.09 (21.07)	84.85 (20.84)	6.4 (-0.14; 12.9)
Number of scans per day, mean (SD)					
Total	-	9.16 (5.06)	9.33 (4.97)	9.84 (6.02)	0.68 (-0.64; 2.0)
HbA1c <7.5%	-	10.06 (5.11)	9.89 (5.07)	10.39 (5.45)	0.33 (-1.6; 2.2)
HbA1c ≥7.5%	-	8.41 (4.92)	8.85 (4.86)	9.39 (6.46)	0.98 (-0.87; 2.8)
< 12 years	-	11.67 (5.64)	11.27 (4.5)	12.96 (6.45)	1.29 (-1.1; 3.7)
≥ 12 years	-	7.83 (4.17)	8.27 (4.91)	7.90 (4.85)	0.07 (-1.3; 1.4)
Number of sensors used, mean (SD)					
Total	-	6.40 (1.36)	7.50 (2.86)	14.74 (5.81)	8.34 (7.4; 9.3)
HbA1c <7.5%	-	6.32 (1.37)	6.86 (1.76)	13.35 (4.47)	7.03 (5.9; 8.2)
HbA1c ≥7.5%	-	6.46 (1.36)	8.05 (3.46)	15.86 (6.51)	9.4 (7.9; 10.9)
< 12 years	-	6.63 (1.17)	6.90 (2.15)	14.73 (5.83)	8.1 (6.5; 7.8)
≥ 12 years	-	6.28 (1.44)	7.83 (3.15)	14.75 (5.83)	8.47 (7.3; 9.7)

SD = standard deviation; VAS = Visual Analogue Scale; HbA1c = Glycosylated Haemoglobin; CI = Confidence Interval; GT = glucose time.

Appendix 5. Multivariate Mixed Regression Model for Effectiveness Measures and Adherence

Table 1. Multivariate Mixed Regression Model for Effectiveness Measures

	Self-reported severe hypoglycaemia events				**Severe hypoglycaemic events in the clinical history**				**Visual analogue scale (EQ-5D-Y)**						**Knowledge about DM1**		**Diabetes Treatment Satisfaction Questionnaire**					
Variable	**Patients with hypoglycaemia (Yes/No)** Total sample (n=156)		**Number of self-reported events** Total sample (n=156)		**Patients with hypoglycaemia (Yes/No)** Total sample (n=156)		**Number of self-reported events** Total sample (n=156)		Total sample (n=156)		HbA1c <7.5% (n=68)		HbA1c ≥7.5% (n=88)		Total sample (n=156)		**Perceived hyperglycaemia** Total sample (n=156)		**Perceived hypoglycaemia** Total sample (n=156)		**Satisfaction with treatment** Total sample (n=156)	
	OR (95%CI)	*P*	β (95%CI)	*P*	OR (95%CI)	*P*	β (95%CI)	*P*	B (95%CI)	*P*	B (95%CI)	*P*	B (95%CI)	*P*	B (95%CI)	*P*	B (95%CI)	*P*	B (95%CI)	*P*	B (95%CI)	*P*
Time																						
M12 (ref: M0)	0.82 (0.35; 1.96)	.659	-0.37 (-0.62; -0.11)	**.004**	1.47 (0.32; 6.77)	.617	0.77 (-0.06; 1.60)	.069	-1.40 (-4.97; 2.16)	.440	-1.33 (-4.17; 1.51)	.359	-6.03 (-9.66; -2.41)	**.001**	0.45 (-0.17; 1.08)	.154	-0.08 (-0.50; 0.34)	.721	-0.23 (-0.70; 0.24)	.331	3.11 (0.99; 5.23)	**.004**
Duration of T1DM	1.01 (0.89; 1.15)	.850	-0.01 (-0.14; 0.12)	.922	0.97 (0.81; 1.18)	.806	-0.05 (-0.24; 0.14)	.587	-0.74 (-1.29; -0.19)	**.008**	-0.32 (-0.99; 0.35)	.348	-1.05 (-1.86; -0.24)	**.011**	0.01 (-0.08; 0.09)	.851	-0.003 (-0.06; 0.05)	.915	-0.005 (-0.07; 0.06)	.870	0.05 (-0.18; 0.29)	.650
Presence of comorbidities	0.81 (0.33; 1.98)	.641	0.26 (-0.60; 1.12)	.556	0.81 (0.26; 2.50)	.710	0.27 (-0.83; 1.38)	.624	0.87 (-2.91; 4.64)	.652	2.42 (-1.78; 6.63)	.259	-1.04 (-6.98; 4.89)	.731	0.02 (-0.52; 0.57)	.930	-0.005 (-0.43; 0.42)	.980	0.02 (-0.36; 0.41)	.91	-0.52 (-2.15; 1.11)	.534
Age group: ≥12 years (ref: <12 years)	0.56 (0.22; 1.42)	.221	-0.15 (-1.04; 0.75)	.745	1.32 (0.39; 4.44)	.651	0.32 (-0.87; 1.50)	.599	-3.11 (-6.99; 0.78)	.117	-3.84 (-8.61; 0.94)	.115	-2.82 (-8.49; 2.83)	.327	-0.09 (-0.67; 0.48)	.705	-0.05 (0.48; 0.38)	.819	-0.002 (-0.38; 0.37)	.99	-0.02 (-3.24; 0.76)	.980
Baseline HbA1c group: ≥7.5% (ref: HbA1c <7.5%)	0.41 (0.15; 1.17)	.097	-0.57 (-1.40; 0.26)	.176	2.17 (0.53; 8.88)	.280	1.54 (0.31; 2.77)	**.014**	-1.93 (-5.98; 2.11)	.349					-1.27 (-1.89; 0.65)	**<.001**	1.06 (0.60; 1.52)	**<.001**	-0.12 (-0.57; 0.33)	.593	-1.24 (-1.34; 4.22)	.225
Time*Baseline HbA1c Group (ref: M0 & HbA1c <7.5%)																						
M12 & HbA1c ≥7.5%	2.69 (0.81; 8.96)	.108	0.30 (-0.08; 0.68)	.117	2.01 (0.34; 11.68)	.437	-0.44 (-1.33; 0.45)	.333	-4.61 (-9.44; 0.21)	**.061**					-0.06 (-0.90; 0.78)	.892	-0.11 (-0.70; 0.48)	.703	0.16 (-0.46; 0.78)	.615	1.44 (-1.34; 4.22)	.310

Intercept	0.78 (0.27; 2.23)	.641	-0.78 (-1.74; 0.17)	.107	0.03 (0.004; 0.19)	**<.001**	-4.32 (-5.97; -2.67)	**<.001**	90.50 (86.13; 94.87)	<.001	90.44 (85.92; 94.96)	<.001	88.92 (83.96; 93.88)	<.001	12.43 (11.78; 13.07)	**<.001**	2.98 (2.49; 3.46)	**<.001**	2.29 (1.84; 2.74)	**<.001**	26.80 (24.80; 28.81)	**<.001**
CI = Confidence Interval; HbA1c = Glycosylated Haemoglobin; M = Months; OR = Odds Ratio; ref = reference.																						

Table 2. Multivariate Mixed Regression Model for Adherence

	Sensor usage time, %		**Number of scans per day**		**Number of sensors used**					
Variable	Total sample (n=156)		Total sample (n=156)		Total sample (n=156)		HbA1c basal < 7.5% (n=68)		HbA1c basal ≥ 7.5% (n=88)	
	B (95%CI)	*P*	B (95%CI)	*P*	B (95%CI)	*P*	B (95%CI)	*P*	B (95%CI)	*P*
Time										
M6 (ref: M3)	1.82 (-3.31; 6.98)	.487	-0.25 (-1.41;0.92)	.678	0.49 (-0.58; 1.56)	.367	0.51 (-0.37; 1.39)	.255	1.59 (0.48; 2.70)	**.005**
M12 (ref: M3)	6.42 (1.12; 11.72)	**.018**	0.30 (-0.91; 1.51)	.625	6.96 (5.85; 8.06)	**<.001**	6.97 (6.06; 7.87)	**<.001**	9.37 (8.25; 10.50)	**<.001**
Duration of T1DM	-1.02 (-1.77; -0.27)	**.008**	-0.08 (-0.29; 0.13)	.468	-0.06 (-0.20; 0.07)	.363	-0.11 (-0.25; 0.04)	.152	-0.03 (-0.24; 0.18)	.804
Presence of comorbidities	0.53 (-4.61; 5.66)	.840	-0.69 (-2.14; 0.75)	.348	-0.35 (-1.27; 0.56)	.453	-0.25 (-1.16; 0.66)	.585	-0.39 (-1.92; 1.14)	.617
Age group: ≥12 years (ref: <12 years)	-7.93 (-13.19; -2.66)	**.003**	-3.92 (-5.40; -2.43)	**<.001**	0.39 (-0.55; 1.33)	.417	0.03 (-0.98; 1.05)	.952	0.69 (-0.77; 2.14)	.354
Baseline HbA1c group: ≥7.5% (ref: HbA1c <7.5%)	-4.59 (-10.71; 1.53)	.142	-1.92 (-3.52; -0.31)	**.019**	0.12 (-1.04; 1.29)	.836				
Time*Baseline HbA1c Group (ref: M3 & HbA1c <7.5%)										
M6 & HbA1c ≥7.5%	0.38 (-6.58; 7.33)	.915	0.43 (-1.14; 2.01)	.590	1.09 (-0.36; 2.54)	.141				
M12 & HbA1c ≥7.5%	-1.35 (-8.48; 5.77)	.710	0.35 (-1.28; 1.97)	.676	2.41 (0.93; 3.90)	**.001**				
Intercept	89.10 (82.9; 95.3)	**<.001**	13.0 (11.32; 14.68)	**<.001**	6.19 (5.04; 7.33)	**<.001**	6.39 (5.34; 7.44)	**<.001**	6.13 (4.77; 7.49)	**<.001**
CI = Confidence Interval; HbA1c = Glycosylated Haemoglobin; M = Months; ref = reference.										

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5-6
		(*b*) Describe any methods used to examine subgroups and interactions	5-6
		(*c*) Explain how missing data were addressed	5-6
		(*d*) If applicable, explain how loss to follow-up was addressed	5-6
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	Apex1
		(c) Summarise follow-up time (eg, average and total amount)	7
Outcome data	15*	Report numbers of outcome events or summary measures over time	8

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	8 8 NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9
Discussion			
Key results	18	Summarise key results with reference to study objectives	10-11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10-11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Effectiveness, safety and costs of the FreeStyle Libre Glucose Monitoring System for children and adolescents with T1DM in Spain: a prospective uncontrolled pre-post study

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Effectiveness, safety and costs of the FreeStyle Libre Glucose Monitoring System for children and adolescents with T1DM in Spain: a prospective uncontrolled pre-post study

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Abstract

Objectives
Evaluate the effectiveness, safety and costs of FreeStyle Libre® (FSL) for Type 1 Diabetes Mellitus (T1DM) in underage.

Design
Prospective multicentre pre-post study.

Setting
Patients were recruited from thirteen Spanish public hospitals between January 2019 and March 2020 and followed up for 12 months.

Participants
156 patients were included.

Primary and secondary outcome measures
Primary outcome: HbA1c change. Secondary measures: severe hypoglycaemic events (self-reported and clinical records), quality of life, diabetes treatment knowledge, treatment satisfaction, adverse events, adherence, sensor usage time and scans. Healthcare resource utilization was assessed for cost analysis from the National Health System (NHS) perspective, incorporating direct healthcare costs. Data analysis utilized mixed regression models with repeated measures. Intervention's total cost estimated by multiplying health resource usage with unit costs.

Results
In the whole sample, HbA1c increased significantly (0.32%; 95%CI: 0.10, 0.55). In the subgroup with baseline HbA1c≥7.5% (n=88), there was a significant reduction at 3 (-0.46%; -0.69, -0.23), 6 (-0.49%; -0.73, -0.25), and 12 months (-0.43%; -0.68, -0.19). Well-controlled patients revealed a significant 12-month worsening (0.32%; 0.18, 0.47). Self-reported severe hypoglycaemia significantly decreased compared to the previous year for the whole sample (-0.37; -0.62, -0.11). Quality of life and diabetes treatment knowledge showed no significant differences, but satisfaction increased. Adolescents had lower sensor usage time and scans than children. The reduction in

HbA1c was significantly associated with device adherence. No serious adverse effects were observed. Using FSL could reduce healthcare and productivity losses related costs.

Conclusions
The use of FSL in underage T1DM patients is associated with a significant reduction in severe hypoglycaemia and improved HbA1c levels in patients with poor baseline control. Findings suggest cost savings and productivity gains for caregivers. Causal evidence is limited due to the study design. Further research needed to confirm results and assess risks, especially for lower HbA1c patients.

Strengths and limitations of this study
- This study provides nationally contextualised real-world scientific evidence on the effectiveness, safety and costs of the flash glucose monitoring systems (FreeStyle Libre® system [FSL]) indicated for DM1 in childhood and adolescence in Spain.
- The study utilized a combination of self-reported outcomes, clinical data extracted from Electronic Health Records (EHR), and device-stored information from the FSL device, which provides a robust and multifaceted assessment of the outcomes.
- The uncontrolled design of the study precludes causal inferences and results from randomized trials are needed to draw definitive conclusions.
- The small sample size limit the generalizability and statistical power of the findings.
- The cost estimation analysis only considered direct healthcare costs from the Spanish National Health System perspective, and indirect costs were not fully taken into account, which may underestimate the overall economic impact of the intervention.

Keywords
Continuous glucose monitoring, HbA1c, Type 1 diabetes, costs, Spain.

Word count 4866

Introduction

Type 1 Diabetes Mellitus (T1DM) requires continuous medical monitoring, to reduce the development of vascular complications [1,2]. The early onset and chronic character of this condition increase the likelihood of reducing health-related quality of life (HRQoL) and health expectancy among young T1DM people [3]. A total of 586,000 children aged under 15 years suffer from T1DM globally [4]. In Spain, the incidence is 11.5-27.6/100,000[5], which represents a high cost to society [6].

To reduce the risk of short (metabolic) and long-term (vascular) diabetes complications, frequent determination of blood glucose levels is required. Continuous glucose monitoring systems, such as the flash glucose monitoring (FGM) systems, contribute to glycaemia monitoring, as well as to reduce the daily number of fingersticks [7], providing dynamic information to the users about their glucose level. FreeStyle Libre® (FSL), developed and marketed in Spain by Abbott Laboratories, has been indicated to measure glucose levels in the interstitial fluid in people aged over four years with T1DM. No serious adverse effects related to the use of these devices have been reported. Mild effects consist of skin problems in the area where the sensor is inserted, similar to other FGM [8,9].

In randomized trials, the FSL system has been shown to significantly reduce HbA1c levels and the frequency of hypoglycaemia in patients with T2DM, compared to the conventional finger-pricking method [10]. In T1DM, most published studies had an uncontrolled design, and meta-analyses have revealed that the use of FSL is associated with significant HbA1c reductions from baseline to the last follow up [11,12]. Approximately 30% of these studies included children and adolescents, which also led to obtaining significant pre-post HbA1c reductions. To the best of our knowledge, only one randomized trial has evaluated the FSL versus conventional glucose measurement in non-adults (13-20 years-old) with T1DM [13], showing no significant results on HbA1c or quality of life [13].

Spain has a universal public health system, financed by taxes. The system is highly decentralized and the 17 Spanish administrative regions have their own health policy budget, which enables a tailored approach to meet the specific needs and demands of each region. The competences and portfolio of the Spanish Ministry of Health encompass a wide range of responsibilities aimed at ensuring the well-being and health of the population. These include policy development, regulation and oversight of healthcare services, public health initiatives, pharmaceutical regulation, health technology assessment and coordination of emergency responses, among others. The Spanish Network of Health Technology Assessment Agencies of the National Health System (RedETS) [14], published a report in 2016 [15], later updated in 2017 [16], devised by the Canary Islands Health Service Evaluation Department (SESCS) [17], about the effectiveness, safety and cost-effectiveness of FSL in patients with T1DM and T2DM. In 2019, the Spanish Ministry of Health decided to fund FSL for adult T1DM patients [18], and in 2020 the reimbursement was extended to any insulin-dependent patient not diagnosed with T1DM or T2DM [19].

Regarding children and adolescents with T1DM, the Spanish Ministry of Health decided to perform a post-launch evidence generation study to provide real world information in the Spanish context on the effectiveness, safety, acceptability and potential use barriers, as well as on healthcare resources use and costs, to inform health policy decision-making on a national level in regard to coverage and public funding in these population groups [20,21]. This paper reports its results.

Methods

Study Design

Prospective multicentre pre-post study performed in 13 public hospitals throughout Spain (see **online supplemental Appendix 1**). Patients were recruited between January 2019 and March 2020, with a 12-month follow-up.

Interventions

FSL consists of: 1) an arm sensor that measures and stores interstitial glucose levels, wearable for 14 days [22]; 2) a reader that obtains glucose readings from the sensor when placed at a distance between 1-4 cm, storing up to 90 days of glucose measures and user-entered notes. The Libre View® software and the FreeStyle Libre Link®, and LibreLinkUp® Apps enables obtaining reports with the daily patterns of glucose levels.

Participants

Patients were eligible for inclusion if they were aged between 4 and 17, had been diagnosed with T1DM for at least one year prior to the study, were receiving intensive insulin therapy, required more than six fingersticks per day, and provided their informed consent to participate.

We excluded patients who had hypoglycaemia unawareness (judged by the clinician), were currently undergoing systemic corticosteroid treatment for more than two weeks within the last three months, had previously used or were currently using a FGM device within the last 12 months, were pregnant adolescents, had allergies to device adhesives, were unwilling to participate, lacked the necessary skills to effectively use the technology (patient/caregiver) or failed to provide informed consent.

Setting, logistics and recruitment

The study protocol was devised by SESCS researchers with the assistance of clinical experts from all hospitals taking part, patient association and industry representatives. A centralized information system (SIEM) was developed on the Spanish Ministry of Health's intranet, accessible both for the clinical researchers responsible for recruitment, clinical examination and data collection, as well as SESCS researchers.

Clinical researchers from hospitals taking part were responsible for recruiting, informing and training both patients and caregivers. They collected self-reported data using various measurement scales and extracted clinical information from the electronic health record (EHR) at baseline, 3, 6, and 12 months. In addition, they retrieved the stored information from the FSL device during the follow-up phase (3, 6, and 12 months) on the SIEM platform. SESCS researchers were responsible for coordinating the project and supervising data collection, monitoring quality assurance and data validation, analyses and reporting.

Interested Spanish autonomous communities designated the hospitals they wished to take part in the study. Thirteen public hospitals were included between January 2019 and May 2020, distributed over eight Spanish autonomous communities.

Endpoints

Effectiveness

The primary endpoint was the change in HbA1c level from baseline to follow up. Secondary endpoints included: 1) data extracted from the EHR at baseline and 3, 6 and 12 months: number of severe hypoglycaemia events (defined as those that require help from another person), ketoacidosis episodes, number of hospital admissions and mortality; and 2) self-reported outcomes evaluated at baseline and at 12 months follow-up, by means of the EQ-5D-Y questionnaire [23]; with five categories, reporting the level of severity, ranging from 1 ("I have no problems") to 5 ("I have a lot of problems") in terms of mobility, self-care, activities of daily living, pain/discomfort and anxiety/depression. Furthermore, a visual analogue scale (VAS) measured self-perceived general health, ranging from "0" (worst health status) to "100" (best health status).

Knowledge of diabetes treatment was measured by means of a modified version of the questionnaire devised by Mitchell et al. [24]. This includes 14 items evaluating basic theoretical knowledge about the management of T1DM and its treatment, as well as the patient/caregiver's self-perceived involvement in self-care. The final score is the sum of correct answers (range 0-14). To measure satisfaction with treatment, we used the six-item Diabetes Treatment Satisfaction Questionnaire (DTSQ) [25]. Response options range from 0 (very dissatisfied) to 6 (very satisfied) (range 0-36). Another two items measured the perceived frequency of hyperglycaemia and hypoglycaemia on a scale from 0 (never perceived) to 6 (most of the time).

Safety

Patients' self-reported device-related adverse events were collected at 3, 6 and 12-months of follow-up.

Adherence

To measure device adherence, the following variables were evaluated: 1) Number of daily scans; 2) Sensor usage time (percentage); and 3) Number of sensors used. These data were collected throughout the follow-up phase by means of the information stored in the device.

Use of healthcare resources

Data were extracted from the EHR at baseline and at 12-months of follow-up on: 1) Number of hospitalizations; 2) Number of clinic visits (endocrinology, nursing, primary care/paediatrics, emergency); 3) Number of HbA1c assays; 4) Number of test strips and lancets used; and 5) Absenteeism from work (number of days the caregiver was absent from work due to problems related to the child's T1DM).

In addition to these measures, information on age, sex, body mass index (BMI), time since diagnosis, presence of comorbidities and pubertal stage according to the Tanner scale [26], which classifies patients into 5 stages ranging from stage 1 (childhood) to 5 (adult), was systematically collected.

Sample Size Calculation

We estimated a sample size requirement of 43 participants to detect a minimal clinically relevant change in HbA1c of 0.5% [27], assuming 95% confidence level, 80% power, a HbA1c standard deviation of 1, a pre-post correlation of 0.5 (conservative assumption), and a loss rate of 20%. In addition to the main effect in the whole sample, we were also interested in the effect of the intervention on subgroups defined by their baseline HbA1c level (greater or less than 7.5%), and age (<12 vs. ≥12 years-old). However, the analysis of interactions requires larger sample sizes to attain statistical power, which was not feasible within the study's time limits. Therefore, we aimed to multiply the sample at least by 4 (n=172) to increase the statistical power as much as possible.

Statistical analysis

Means and standard deviation (SD) were estimated for continuous variables, and count and percentage for qualitative variables. Baseline characteristics of patients were compared using student-*t*, Pearson chi-square, Fisher's exact test or Cochran Q, according to the type of variables.

Mixed regression models with repeated measures were used, adjusting for the interaction between time and baseline HbA1c (dichotomous variable) and age group, time and its main effects. The duration of the disease and the existence of comorbidities were included as covariates. A linear link function was used for continuous dependent variables, a logistic function for dichotomous dependent variables and a Poisson function for count dependent variables. In the models with significant interaction, mixed regression models were performed for each interaction subgroup.

The relationship between adherence to the device and HbA1c reduction was analysed using two mixed linear regression models, whose independent variables were the percentage of time using the sensor (12 months) and

the number of monthly scans; basal HbA1c level was introduced as a covariable. Intercept was introduced as a random effect in all models.

For missing values during follow-up, a comparability analysis was conducted between participants lost to follow-up and those who remained, prior to performing multiple imputation by chained equations using Stata version 15.0. The details of this comparability analysis and the imputation model can be found in **online supplemental Appendix 2**.

A level of 0.05 was considered statistically significant. Analyses were performed with the statistical software Stata V.15.0 [28] and SPSS V.20.0 [29].

Cost estimation

Intervention costs were estimated from the Spanish National Health System (NHS) perspective, including only direct healthcare costs during the 12 months of the study. The healthcare resources collected in this study, together with the corresponding unit costs and their information sources, can be found in **Table A1 in online supplemental Appendix 3**. Costs were expressed as 2021 euros (€). When necessary, we adjusted for the consumer price index (CPI), using the Spanish Office of National Statistics (INE) – the INE's income conversion tool [30].

Unit cost of test strips and lancets were estimated with the average costs of information provided by different regional health services of the Spanish NHS. Total costs were estimated multiplying the collected data on health resources used by their respective unit costs, and then added.

Descriptive statistics are presented for total costs aggregated and broken down into: primary care visits (nursing and physicians), emergency visits (hospital and non-hospitals), specialist physicians visits, laboratory tests (HbA1c assay) and monitoring instruments (FSL sensor and test strips and lancets).

Given the nature of the costs and their non-normal nature, confidence intervals were estimated using a non-parametric bootstrapping method [31]. Analyses were performed using the statistical software SPSS V.20.0 [29] with the help of Microsoft Excel.

In addition, although the social perspective was not taken into account in this estimate, indirect technology costs were reported using the human capital theory, i.e. considering the costs attributed to productivity losses of the parents or caregivers of the child with T1DM before and after one year of using the FSL.

To estimate the cost per day of absenteeism, the cost per hour worked in Spain published by the Statistical Office of the European Union (Eurostat) [32] was multiplied by the average number of daily working hours worked in Spain published in the INE's Labour Force Survey (LFS) [33].

Patient and public involvement

There was no patient involvement in the design of this study. Clinical experts from all participant hospitals, representatives of patient associations and the industry took part in drawing up the protocol. We undertook with healthcare professionals to share the results with them in an easy-to-understand way.

Results

A total of 165 patients were initially registered for the study. However, nine patients were subsequently excluded as they did not meet the study's inclusion criteria (see flow-chart in **Figure 1**). Therefore, the final analysis included a total of 156 patients.

Figure 1. Flow-chart

Patients' baseline characteristics, are shown in **Table 1,** according to subgroups by level of metabolic control and age. There was a higher percentage of participants in stage 1 and 5 in the subgroup with worse glycaemic control (*P*=0.02). In this subgroup, the mean HbA1c value was 8.7%; with 6.8% (*P*<0.001) in the well-controlled group. Descriptive statistics obtained at each time point for the total sample and subgroups for each outcome measure can be found in **online supplemental Appendix 4**.

Table 1. Baseline characteristics of patients according to baseline HbA1c control and age groups

	Total (n=156)	**HbA1c <7.5% (n=68)**	**HbA1c ≥7.5 % (n=88)**	***P***	**<12 years (n=53)**	**≥12 years (n=103)**	***P***
Anthropometric characteristics							
Sex (male) n (%)	86 (55.1)	35 (51.5)	51 (58)	.419	28 (52.8)	58 (56.3)	.679
Age (years), mean (SD)	12.6 (3.2)	12.7 (2.84)	12.49 (3.39)	.735	NA	NA	**NA**
Children < 12 years, n (%)	53 (34)	21 (30.9)	32 (36.4)	.474	NA	NA	**NA**
BMI (kg/m^2), mean (SD)	20.3 (4.1)	20.18 (3.34)	20.39 (4.54)	.754	NA	NA	**NA**
Pubertal status, n (%)				**.022**			**<.001**
I	51 (32.7)	19 (27.9)	32 (36.4)		44 (83)	7 (6.8)	
II	14 (9.0)	9 (13.2)	5 (5.7)		4 (7.5)	10 (9.7)	
III	20 (12.8)	7 (10.3)	13 (14.8)		4 (7.5)	16 (15.5)	
IV	23 (14.7)	16 (23.5)	7 (8)		0 (0)	23 (22.3)	
V	48 (30.8)	17 (25)	31 (35.2)		1 (1.9)	47 (45.6)	
Clinical characteristics							
Duration of diabetes (years), mean (SD)	5.65 (3.39)	5.52 (3.35)	5.75 (3.44)	.671	4.06 (2.4)	6.47 (3.54)	**<.001**
HbA1c, mean (SD)	7.86 (1.36)	6.82 (0.36)	8.65 (1.31)	**NA**	7.83 (1.17)	7.87 (1.45)	.87
HbA1c <7.5%, n (%)	68 (43.6)	NA	NA		21 (39.6)	47 (45.6)	.474
Presence of comorbidities, n (%)	50 (32.1)	27 (39.7)	23 (26.1)	.072	17 (32.1)	33 (32)	.996
Comorbidities, n (%)							
Asthma	6 (3.8)	5 (7.4)	1 (1.1)	.199	1 (1.9)	5 (4.9)	.65
Coeliac Disease	8 (5.1)	6 (8.8)	2 (2.3)	.261	5 (9.4)	3 (2.9)	.102
Thyroiditis	18 (11.5)	12 (17.6)	6 (6.8)	.178	6 (11.3)	12 (11.7)	.941
ADHD	4 (2.6)	1 (1.5)	3 (3.4)	.322	1 (1.9)	3 (2.9)	.999
Others	19 (12.2)	7 (10.3)	12 (13.6)	.057	5 (9.4)	14 (13.6)	.369

ADHD = Attention-Deficit/Hyperactivity Disorder; BMI = Body mass index; HbA1c = Glycated haemoglobin; NA = Not Applicable; SD = Standard deviation.

Other comorbidities: allergy, obesity, iron deficiency anaemia, unilateral anorchia, immunoglobulin A (IgA) deficiency, intellectual disability, epilepsy, hypercholesterolaemia, sensorineural hearing loss, migraines, idiopathic hypercalciuria, ovarian teratoma, nephrocalcinosis, psoriasis, allergic rhinitis, vasovagal syncope, Tourette's syndrome, eating disorder (ED) and obsessive-compulsive disorder (OCD).

Effectiveness

Glycated haemoglobin

In the entire sample, there was a significant increase in HbA1c (0.32%, *P*<0.001). The interaction between time and the baseline HbA1c group was statistically significant at 3, 6 and 12 months (*P*<0.001) (**Table 2**). In the subgroup analysis, participants with baseline HbA1c<7.5% revealed an increase of 0.32% (0.18 to 0.47) in HbA1c at 12 months (with respect to baseline) (*P*<0.001), without exceeding, on average, the threshold of poor control. Patients with poorly controlled baseline status had a statistically significant reduction in HbA1c at all follow-ups: B=-0.46% (-0.69 to -0.23; *P*<0.001), B=-0.49% (-0.73 to -0.25; *P*<0.001), and B=-0.43% (-0.68 to -0.19; *P*=0.001), at 3, 6 and 12 months, respectively (**Table 2**). On average, this reduction did not attain the threshold of poor control.

Table 2. Multivariate Mixed Regression Models for Glycosylated Haemoglobin

	Glycosylated Haemoglobin					
Variable	**Total sample (n=156)**		**HbA1c <7.5% (n=68)**		**HbA1c ≥7.5% (n=88)**	
	B (95%CI)	*P*	B (95%CI)	*P*	B (95%CI)	*P*
Time						
M3 (ref: M0)	0.03 (-0.18; 0.24)	.765	0.03 (-0.09; 0.16)	.611	-0.46 (-0.69; -0.23)	**<.001**
M6 (ref: M0)	0.1 (-0.11; 0.32)	.344	0.10 (-0.03; 0.23)	.115	-0.49 (-0.73; -0.25)	**<.001**
M12 (ref: M0)	0.32 (0.10; 0.55)	**.005**	0.32 (0.18; 0.47)	**<.001**	-0.43 (-0.68; -0.19)	**.001**
Duration of T1DM	0.05 (0.007; 0.09)	**.020**	-0.005 (-0.04; 0.03)	.762	0.09 (0.02; 0.15)	**.011**
Presence of comorbidities	-0.10 (-0.39; 0.18)	.477	0.09 (-0.13; 0.30)	.439	-0.22 (-0.70; 0.26)	.372
Age group: ≥12 years (ref: <12 years)	0.17 (-0.12; 0.47)	.253	0.09 (-0.15; 0.32)	.473	0.26 (-0.21; 0.73)	.274
Baseline HbA1c group: ≥7.5% (ref: HbA1c <7.5%)	1.81 (1.50; 2.13)	**<.001**				
Time*Baseline HbA1c Group (ref: M0 & HbA1c <7.5%)						
M3 & HbA1c ≥7.5%	-0.49 (-0.78; -0.21)	**<.001**				
M6 & HbA1c ≥7.5%	-0.59 (-0.88; -0.29)	**<.001**				
M12 & HbA1c ≥7.5%	-0.76 (-1.05; -0.46)	**<.001**				
Intercept	6.75 (6.41; 7.09)	**<.001**	6.73 (6.50; 6.96)	**<.001**	8.53 (8.12; 8.94)	**<.001**

CI = Confidence Interval; HbA1c = Glycosylated Haemoglobin; M = Month; T1DM = Type 1 Diabetes Mellitus.

Severe hypoglycaemic (SH) events

The reduction in the number of self-reported events was significant at 12 months β=-0.37 (-0.62 to -0.11; *P*=0.004) (**Table 1 in online supplemental Appendix 5**). Although the interaction with the level of HbA1c at baseline was not statistically significant (*P*=0.117), the descriptive statistics (**online supplemental Appendix 4**) in patients with controlled HbA1c at baseline show a reduction in the mean number of events; with an increase in the poorly controlled subgroup.

SH events recorded in the EHR show significantly lower rates compared to self-reported events (**online supplemental Appendix 4**), without significant main or interaction effects (**Table 1 in online supplemental**

Appendix 5). The rate of SH events was significantly higher in the subgroup with poor HbA1c control (*P*=0.014) (**Table 1 in online supplemental Appendix 5**).

Diabetic ketoacidosis and other serious adverse events

In the follow-up phase, six mild or moderate ketoacidosis events were recorded at three (2), six (1), and 12 months (3), respectively; and four serious adverse events at three months (two admissions and one episode of ketosis without acidosis due to bubbles in the system); and at six months (one admission). No events were observed at 12-month follow-up. No patient died during follow-up.

Health-related quality of life

At 12 months follow-up, the percentages of severe limitations for mobility, self-care, daily activities, anxiety and depression were similar to baseline values. However, a reduction was observed in the percentage of patients who self-reported pain (**online supplemental Appendix 4**).

VAS score (**Table 1 in online supplemental Appendix 5**) did not show a significant change in the whole sample, and the interaction with baseline HbA1c values was slightly above the statistical significance level (*P*= 0.061). In poorly controlled patients, VAS scores were significantly reduced at 12 months compared to the baseline score B=-6.03 (-9.66 to -2.41; *P*=0.001). In the subgroup with good basal metabolic control, no statistically significant findings were observed.

Knowledge of diabetes treatment

There was no significant change in patients' Knowledge of diabetes treatment, nor a significant interaction with baseline HbA1c. Patients with worse basal metabolic control revealed a significantly lower score compared to well-controlled patients: B=-1.27 (-1.89 to -0.65; *P*<0.001) (**Table 1 in online supplemental Appendix 5**).

Satisfaction with treatment

General satisfaction with treatment significantly increased 3.1 points at 12 months of follow-up (0.99 to 5.23; *P*=0.004) (**Table 1 in online supplemental Appendix 5**). There were no statistically significant differences in self-perceived hypo- and hyperglycaemia. For the latter, a higher score of 1.06 points (in a range of 0 to 6) was observed, in patients with HbA1c≥7.5%, compared to those with good control (0.60 to 1.52; *P*<0.001) (**Table 1 in online supplemental Appendix 5**).

Safety

Mild adverse events related to the device during follow-up phases had a 3.1% and 6.6% reduction for skin reactions and discomfort or pain, respectively. However, these were not statistically significant (**Table 3**).

Table 3. Mild Adverse Effects caused by the sensor

	3 months (n=150)	**6 months (n=136)**	**12 months (n=128)**	***P***	**Differences 12–3 months,** % (95%CI)
Skin reactions, n (%)	21 (14.0)	16 (11.8)	14 (1.9)	.542	-3.1% (-25.2; 19.0)
Discomfort or pain, n (%)	17 (11.3)	13 (9.6)	6 (4.7)	.210	-6.6% (-29.3; 16.1)
Other minor events, n (%)	3 (2.0)	2 (1.5)	2 (1.6)	.999	-0.4% (-23.9; 23.1)

Among the other events, there were minor haemorrhages when the sensor was positioned and wounds in the insertion area. In one case, the patient lost consciousness because of the bleeding.
CI = Confidence Interval.

Adherence

Time of sensor use (**Table 2 in online supplemental Appendix 5**) significantly increased at 6.4% at 12 months of follow-up (1.12 to 11.72; *P*=0.02), compared to three months. Longer duration of T1DM (*P*=0.008), and age older than 12 years (*P*=0.003), significantly reduced sensor use.

A reduction in the mean number of daily scans at three months occurred in poorly controlled patients B=-1.92 (-3.52 to -0.31; *P*=0.019). Those aged over 12 underwent an average of four fewer scans than those aged under 12 years B=-3.92 (-5.4 to -2.43; *P*<0.001) (**Table 2 in online supplemental Appendix 5**).
Controlled patients revealed an increase in the mean number of sensors use at 12 months of follow-up B=7 (5.85 to 8.06; *P*<0.001); also increasing in poorly controlled patients by B=1.6 (0.48 to 2.7; *P*=0.005) at 6 months, and B=9.4 (8.25 to 10.5; *P*<0.001) at 12 months (**Table 2 in online supplemental Appendix 5**).
The percentage of time of use was statistically significantly related to a lower HbA1c level at 12 months (B=-0.01; *P*=0.013), as was the number of scans (B=-0.21; *P*<0.001).

Cost estimation

The estimated total annual costs per patient are shown in **Table A2 (online supplemental Appendix 3)**. Intervention short-term costs from an NHS perspective reveal that specialist visits and test strips and lancets costs account for a significant part of total costs (38% and 41%, respectively), with an average annual cost per patient of €415.48 and €447.25 for specialist visits and strips and lancets, respectively. Regarding the cost of the FSL sensor, it amounts to €43.27 according to information provided by the manufacturer. Taking into account an average number of sensors per patient per year of 26 (considering a sensor half-life of 14 days), the total annual cost of the sensor amounts to €1,125 per patient/year. This means that the average total annual costs per patient with the use of FSL amounts to €2204.26 (**Table A2 (online supplemental Appendix 3)**).
Total annual costs before and after use of the FSL system can be found in **Figure A1 (online supplemental Appendix 3)**. All measured costs decreased after use of the device throughout 12 months follow-up, with the most striking difference in costs related to test strips and lancets use, an annual difference of €856.68 per patient. This information is outlined in **Table A3 (online supplemental Appendix 3)**. The annual average number of test strips per patient decreased from 2686.02 strips per year before the use of the FSL, to 883.98 strips per year after its use. The difference in the annual average use of lancets per patient also reduced from 1366.41, before FSL use, to 615.94, after its use.
Furthermore, a decrease in total annual costs due to productivity losses of parents/caregivers of minor patients with T1DM was observed after the use of FSL (€545.67 versus €262.73) as shown in **Table A3 (online supplemental Appendix 3)**.

Discussion

Glucose monitoring devices can help people with T1DM monitor their glycaemia levels and reduce the frequency and/or severity of acute disease-complication rates, thus improving their HRQoL and life expectancy [34]. Two meta-analyses of case series on the effectiveness of the FSL revealed statistically significant HbA1c reductions in children/adolescents with poor HbA1c control (7.5%-9.6%, except two studies with 7.1% and 7.4%) of -0.54% (n=447) [35] and -0.29% (n=959) [11], although the effect was highly variable across studies. Our study only provides a statistically significant reduction of HbA1c in the group with poor baseline monitoring, (-0.46%, -0.49% and -0.35%), at 3, 6 and 12 months, respectively. On the contrary, patients with basal controlled HbA1c levels revealed a significant 12-month worsening higher than 0.30%. Another case series in Spain (n=145) [36], with limited follow up to three months, also detected a reduction in patients with HbA1c≥7.5% (-0.41, *P*=0.004), and a statistically significant increase in well-monitored patients, i.e. a worsening in HbA1c levels (0.23, *P*=0.03). The uncontrolled design of the study precludes ruling out that this result just reflects a regression to the mean. A recent meta-analysis of randomized controlled trials on the effectiveness of continuous glucose monitoring in people with T1DM showed a significant effect only in studies with mean HbA1c values at baseline >8% (-0.49%) [37]. However, apart from not being based exclusively on non-adult population, this result is based on meta-analysis and not on the analysis of interactions in the individual studies, and therefore it is subjected to potential risk of ecological fallacy.

The results also revealed a significant reduction in the number of self-reported SH events for the whole sample (-0.37), but not in the number of patients with at least one event. The interaction effect with baseline HbA1c level was not statistically significant for these two variables (*P*=0.117 and *P*=0.108, respectively). The descriptive statistics suggest different subgroup effects, although none was statistically significant. The reduction of self-reported SH events occurred in patients with controlled HbA1c levels at baseline (0.39), whereas in the basally uncontrolled group, an increase was self-reported (0.37 more); together with an important increase in the rate of patients with at least one event (from 26% to 38%). Again, an effect of regression to the mean could be the explanation for this result since, as expected, patients with controlled HbA1c at baseline showed higher SH rates and means. Alternatively, the results on both HbA1c and SH could be reflecting the trade-off faced by patients with T1DM between the reduction in glucose levels and the associated risk of increasing hypoglycaemic events. This interpretation is speculative given the commented methodological limitations of the study, but it would help account for the unexpected significant worsening in self-perceived general health observed in the subgroup of poor baseline HbA1c monitoring. That is, contrary to the HbA1c improvement attained, that has no observable effects on self-perceived HRQoL, suffering an SH event is a salient experience that may impact this self-perception.

Other studies [36] have also reported a significant and clinically meaningful improvement in the rate of SH events (from 4.2 to 0.2 events/100 patients-year). However, their results are not reported separately according to basal levels of metabolic control. The largest case series published to date with children and adolescents [38], and with the longest follow-up (12 months), also revealed a statistically significant reduction of SH events (53%, *P*=0.012) for the whole sample, with no changes in HbA1c.

The interaction of the intervention with the age group (<12 vs. ≥12 years-old) was not statistically significant in any case. However, descriptive statistics reveal different non-significant trends among subgroups, with positive results only for younger participants: -0.26% vs. -0.05% (HbA1c), -1.06 vs. 0.68 (SH events) and -4.2% vs. 10.5% (people with one or more SH). Adolescents revealed significantly lower sensor usage time and scans per day than children, similar to the results observed in previous studies [39-41]. Adolescents and young adults face specific challenges and barriers regarding the use of glucose monitoring sensors, such as concerns about self-image and how people perceive them [42,43], differential emotional reactions to diabetes burden [44] or a lesser interest in glucose data analysis [45], and therefore specific strategies might be necessary to increase sensor use in this population [46]. Nonetheless, adolescents in our sample showed adequate adherence throughout the study, above 78% of the time at each successive evaluation. Regarding the effectiveness of the FLS in adolescents,

the only randomized controlled trial to date included participants aged 13-20 years, with HbA1c≥9.0%) [13], and although it found significantly higher satisfaction in the intervention group at 6 months, it did not reveal any statistically significant differences in HbA1c reduction compared to traditional self-monitoring. Therefore, significant uncertainty remains in regard to the effects of FSL in adolescents.

Despite the improvement in the degree of metabolic control that occurred in our study sample of patients with worse baseline HBA1c levels, no statistically significant improvement was observed in their knowledge of diabetes treatment. Device adherence was significantly related to the reduction of HbA1c, a result usually observed in the literature on glucose monitoring devices [39-41]. The same can be said about treatment satisfaction [47,48], which improved in the whole sample.

In regard to safety, no serious adverse effects were observed, a result consistent with the literature on glucose monitoring devices in general [9]. The number of patients showing mild adverse events at three months was reduced at the end of follow-up to 18%, resulting in two losses at six months follow-up due to skin reaction to the sensor and another two at 12 months due to discomfort with the sensor.

In terms of costs analysis as observed in the international literature, our results showed that T1DM patients consume less healthcare resources using FSL [49]. Fundamentally, a striking decrease was observed in costs attributed to reactive strips and lancets, where an annual difference of €856.68 per patient was obtained (not including cost of sensor). A decrease in total indirect annual costs due to productivity losses of parents/carers of T1DM patients, was also observed (€545.67 versus €262.73). Despite the savings observed in all cost categories, when the cost of the device is taken into account, there is no potential savings with the use of the FSL. However, this information can be useful for decision-making and negotiating the price of the device.

The main limitation of this study lies in its uncontrolled design, which precludes comparison with an untreated group. Therefore, an inference of causality regarding the introduction of the FLS is not possible, because other factors such as child developmental growth, potential changes in target treatment or insulin administration methods or a regression to the mean could affect the observed changes. A “novelty effect”, related to the use of a technological device could also introduce a motivation bias that could affect self-management habits. Another relevant limitation is the limited sample size to analyse interaction effects, even when we increased the recruited sample fourfold. By the time of study execution, the FSL was already financed and introduced in some hospitals taking part and a large portion of the target population was already using it. This scenario was an important recruitment obstacle to enlarge sample size. Our conclusions to be drawn are, therefore, limited by the low statistical power for interaction analyses and rare events such as severe hypoglycaemia. All these limitations imply a low quality of the evidence.

The start-up of a monitoring study has been used to collect data on the use of resources and make initial estimates of the cost of the intervention. Therefore, our cost analysis was a secondary endpoint and complementary to this study’s primary endpoint and it has limitations. First, our analysis has not taken into account the costs attributable to the possible adverse effects arising from the use of FSL and it has assumed that possible failures of the device will be resolved at no additional cost to the Spanish NHS. Moreover, it was not possible to estimate the costs related to hospitalization of the patients since the number of days of each hospitalization was not recorded in this study. However, the extremely low number of total hospitalizations during the monitoring study indicates that including this cost in the estimate would not have produced substantial changes in the results.

To the best of our knowledge, this is the first comparative costs analysis study of FSL use in children and adolescents with T1DM in Spain using observational data in an actual use scenario. Therefore, although a cost-effectiveness analysis could not be performed in this study, due to the absence of a comparator, our results may contribute to inform future cost-effectiveness studies of FSL in Spain.

Conclusion

Our results showed that the use of FSL in young T1DM patients significantly reduced the rate of SH events, and improved HbA1c levels in patients with poor baseline monitoring. However, futures studies should confirm whether these benefits could be at the cost of worsening severe hypoglycaemia in patients with lower HbA1c. No serious adverse events related to FSL were observed. The results also suggest that the use of FSL in young patients with T1DM leads to a decrease in monitoring costs. In addition, the use of FSL reduces costs attributable to lost productivity of parents/caregivers. These outcomes correspond to low-quality evidence, mainly due to the study's uncontrolled design, in addition to the low statistical power in the case of rare complications such as SH.

Based on these results and other information sources (i.e., international research and clinical expert advice), the Spanish Ministry of Health has decided to reimburse the FreeStyle Libre (FSL) for children and adolescents aged 4-17 years old with Type 1 diabetes who undergo intensive insulin therapy (multiple daily injections or insulin pump) and require at least six fingerstick blood glucose self-monitoring tests a day.

Footnotes

Collaborators: The Health Professional Group included the following members (in alphabetical order): Amparo González Vergaz (Hospital Severo Ochoa), Ana María Prado Carro (Complexo Hospitalario Universitario A Coruña), Anunciación Beisti Ortego (Fundación Hospital Calahorra), Ariadna Campos Martorell (Hospital Universitari Vall D'hebron), Atilano José Carcavilla Urqui (Hospital Universitario La Paz), Cristina Amparo Del Castillo Villaescusa (Hospital Universitario Dr. Peset Aleixandre), Estela Gil Poch (Hospital Universitario de Badajoz), Francisco Javier Arroyo Diez (Hospital Universitario de Badajoz), Gemma Novoa Gómez (Complexo Hospitalario Universitario de Ourense), Isabel González Casado (Hospital Universitario La Paz), Juncal Martínez Ibáñez (Fundación Hospital Calahorra), Laura Cuadrado Piqueras (Fundación Hospital Calahorra), Leticia Reis Iglesias (Complexo Hospitalario Universitario de Ourense), Lucia Garzón Lorenzo (Hospital Universitario 12 De Octubre), Luis Salamanca Fresno (Hospital Universitario La Paz), María Asunción Martínez Brocca (Hospital Universitario Virgen Macarena), María Aurea Rodríguez Blanco (Hospital Da Barbanza), María Del Mar Martínez López (Hospital Universitario 12 De Octubre), María Jesús Ferreiro Rodríguez (Complexo Hospitalario Universitario de Ourense), María Ruiz del Campo (Hospital San Pedro), Nerea Itza Martín (Hospital Universitario La Paz), Patricia García Navas (Hospital San Pedro), Rebeca García García (Hospital Universitario Central de Asturias).

Contributors: YAP, ARS, LPP and PSA initiated the study. HGP did the acquisition of data. HGP, ARS, CVN and YRF contributed to the analysis and interpretation of data. HGP did the statistical analyses. HGP, ARS, CVN YAP and YRF wrote the first draft of the manuscript. HGP, ARS, YRF, CVN, YAP, LGP, MAGB, LPP AND PSA critically revised the manuscript and approved the final version. HGP is responsible for the overall content as the guarantor and accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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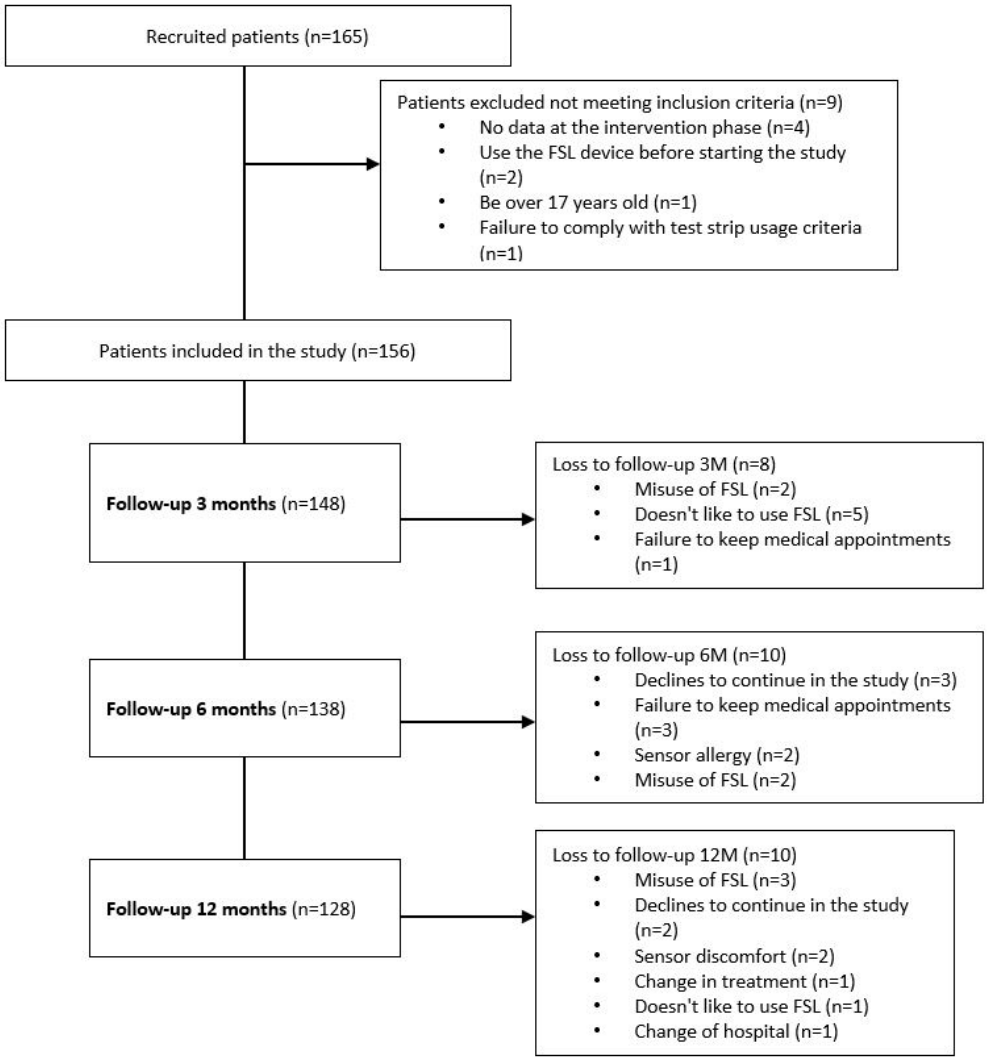

Figure1. Flow-charts

201x216mm (96 x 96 DPI)

Appendix 1. Participating hospitals and cases included in the study

Public hospitals	Regional Health Services	Number of patients
Hospital Universitario Virgen Macarena*	Andalucía	2
Hospital Universitario Central de Asturias*	Asturias	4
Hospital Universitario Vall D'hebron*	Cataluña	22
Hospital Universitario de Badajoz	Extremadura	30
Complejo Hospitalario Universitario A Coruña*	Galicia	23
Complejo Hospitalario Universitario de Ourense	Galicia	14
Hospital Da Barbanza	Galicia	5
Fundación Hospital Calahorra	La Rioja	1
Hospital San Pedro	La Rioja	13
Hospital Severo Ochoa	Madrid	21
Hospital Universitario 12 De Octubre*	Madrid	4
Hospital Universitario La Paz*	Madrid	16
Hospital Universitario Dr. Peset Aleixandre	Valencia	1
*Tertiary hospital		

Appendix 2. Comparability analysis and description of the missing data imputation model

Comparability analysis

For comparability analysis, the baseline characteristics of patients (gender, age, HbA1c, BMI, time since diagnosis, presence of comorbidities, and pubertal stage) were compared between participants who completed the different follow-up phases and those who had total or partial loss to follow-up at 3, 6, and 12 months. No significant differences were found for any of these variables at the 3-month follow-up. At 6 months, significant differences were observed between responders and non-responders in relation to pubertal stage V (25% vs. 75%) (p = 0.04). At the 12-month follow-up, differences were observed in pubertal stages IV (21.7% vs. 78.3%) and V (31.2% vs. 68.8%) (p = 0.007); significant differences were also observed in the mean age value (p = 0.04) between responders (12.3 years) and non-responders (13.7 years).

	3 months			**6 months**			**12 months**		
	Participants lost to follow-up (n=6)	**Participants who continued in the study (n=150)**	**p**	**Participants lost to follow-up (n=20)**	**Participants who continued in the study (n=136)**	**p**	**Participants lost to follow-up (n=28)**	**Participants who continued in the study (n=128)**	**p**
Sex (male), n (%)	4 (4.7)	82 (95.3)	0.562	8 (9.3)	78 (90.7)	0.145	16 (18.6)	70 (81.4)	0.813
Age (years), mean (SD)	13 (4.86)	12.55 (3.09)	0.829	13.3 (3.81)	12.46 (3.05)	0.266	13.68 (2.91)	12.32 (3.17)	**0.039**
HbA1c, mean (SD)	8.42 (0.62)	7.83 (1.38)	0.303	8.36 (2.01)	7.78 (1.23)	0.224	8.08 (1.81)	7.81 (1.24)	0.33
BMI, mean (SD)	20.73 (2.87)	20.28 (4.10)	0.789	21.33 (2.91)	20.14 (4.18)	0.224	21.33 (2.88)	20.07 (4.24)	0.135
Duración de la DM1, mean (SD)	7.19 (3.86)	5.59 (3.37)	0.257	6.42 (3.43)	5.54 (3.38)	0.275	6.74 (3.39)	5.41 (3.36)	0.061
Presence of comorbidities, n (%)	1 (2.0)	49 (98.0)	0.41	7 (14)	43 (86)	0.762	9 (18)	41 (82)	0.991
Pubertal status, n (%)			0.473			**0.043**			**0.007**
I	2 (3.9)	49 (96.1)		5 (9.8)	46 (90.2)		5 (9.8)	46 (90.2)	
II	0 (0)	14 (100)		1 (7.1)	13 (92.9)		3 (21.4)	11 (78.6)	
III	0 (0)	20 (100)		0 (0)	20 (100)		0 (0)	20 (100)	
IV	0 (0)	23 (100)		2 (8.7)	21 (91.3)		5 (21.7)	18 (78.3)	
V	4 (8.3)	44 (91.7)		12 (25)	36 (75)		15 (31.2)	33 (68.8)	

SD = Standard deviation; HbA1c = Glycated haemoglobin; BMI = Body mass index.

Description of the missing data imputation model

For multiple imputation was performed by chained equations using Stata 15.0 software. The variables sex. age. pubertal stage. presence of comorbidities and duration of diabetes were considered regular and used as predictors for imputation. A total of 29 variables were imputed. Each variable was imputed in chronological order: 3. 6 and 12 months. As a general rule. the latest available information on the variable to be imputed was used. When information from other variables was used. the information from the same point in time was used. A total of 10 imputations were made for each missing data.

Order	Imputed variable	Variables used in imputation	Imputation model	n (%) missing
1	HbA1c 3M	Sex. Age. Pubertal stage. Presence of comorbidities. Time since diagnosis. HbA1c Baseline	pmm	7 (4.5)
2	HbA1c 6M	Sex. Age. Pubertal stage. Presence of comorbidities. Time since diagnosis. HbA1c 3M	pmm	20 (12.8)
3	HbA1c 12M	Sex. Age. Pubertal stage. Presence of comorbidities. Time since diagnosis. HbA1c 6M	pmm	28 (17.9)
4	BMI 6M	Sex. Age. Pubertal stage. Presence of comorbidities. Time since diagnosis. BMI Baseline	pmm	24 (15.4)
5	BMI 12M	Sex. Age. Pubertal stage. Presence of comorbidities. Time since diagnosis. BMI 6M	pmm	28 (17.9)
6	N.º severe hypoglycaemia events 3M	Sex. Age. Pubertal stage. Presence of comorbidities. Time since diagnosis. N.º severe hypoglycaemia events Baseline	poisson	7 (4.5)
7	N.º severe hypoglycaemia events 6M	Sex. Age. Pubertal stage. Presence of comorbidities. Time since diagnosis. N.º severe hypoglycaemia events 3M	poisson	7 (4.5)
8	N.º severe hypoglycaemia events 12M	Sex. Age. Pubertal stage. Presence of comorbidities. Time since diagnosis. N.º severe hypoglycaemia events 6M	poisson	7 (4.5)
9	N.º severe hypoglycaemia events on EHR 3M	Sex. Age. Pubertal stage. Presence of comorbidities. Time since diagnosis. N.º severe hypoglycaemia events 3M. N.º severe hypoglycaemia events on EHR Baseline	poisson	8 (5.1)
10	N.º severe hypoglycaemia events on EHR 6M	Sex. Age. Pubertal stage. Presence of comorbidities. Time since diagnosis. N.º severe hypoglycaemia events 6M. N.º severe hypoglycaemia events on EHR 3M	poisson	28 (17.9)
11	N.º severe hypoglycaemia events on EHR 12M	Sex. Age. Pubertal stage. Presence of comorbidities. Time since diagnosis. N.º severe hypoglycaemia events 12M. N.º severe hypoglycaemia events on EHR 6M	poisson	28 (17.9)
12	VAS 12M	Sex. Age. Pubertal stage. Presence of comorbidities. Time since diagnosis. Mobility EQ-5D-Y 12M. Self-care EQ-5D-Y 12M. Habitual activities EQ-5D-Y 12M. Pain/discomfort EQ-5D-Y 12M. Anxiety/depression EQ-5D-Y 12M. VAS Baseline	pmm	36 (23.1)
13	Knowledge about Baseline	Sex. Age. Pubertal stage. Presence of comorbidities. Time since diagnosis. HbA1c Baseline. BMI Baseline	pmm	14 (9.0)
14	Knowledge about 12M	Sex. Age. Pubertal stage. Presence of comorbidities. Time since diagnosis. HbA1c 12M. BMI 12M. Knowledge about Baseline	pmm	48 (30.8)
15	Hyperglycaemia DTSQ Baseline	Sex. Age. Pubertal stage. Presence of comorbidities. Time since diagnosis. HbA1c Baseline. Knowledge about Baseline	pmm	14 (9.0)
16	Hyperglycaemia DTSQ 12M	Sex. Age. Pubertal stage. Presence of comorbidities. Time since diagnosis. HbA1c 12M. Knowledge about 12M. Hyperglycaemia DTSQ Baseline	pmm	48 (30.8)
17	Hypoglycaemia DTSQ Baseline	Sex. Age. Pubertal stage. Presence of comorbidities. Time since diagnosis	pmm	14 (9.0)
18	Hypoglycaemia DTSQ 12M	Sex. Age. Pubertal stage. Presence of comorbidities. Time since diagnosis. Hypoglycaemia DTSQ Baseline	pmm	48 (30.8)

19	Satisfaction with treatment DTSQ Baseline	Sex. Age. Pubertal stage. Presence of comorbidities. Time since diagnosis. N.º severe hypoglycaemia events Baseline. N.º severe hypoglycaemia events on EHR Baseline. Knowledge about Baseline. Hyperglycaemia DTSQ Baseline.	pmm	14 (9.0)
20	Satisfaction with treatment DTSQ 12M	Sex. Age. Pubertal stage. Presence of comorbidities. Time since diagnosis. N.º severe hypoglycaemia events 12M. N.º severe hypoglycaemia events on EHR 12M. Knowledge about 12M. Hyperglycaemia DTSQ 12M. Satisfaction with treatment DTSQ Baseline	pmm	48 (30.8)
21	N.º of daily scans 3M	Sex. Age. Pubertal stage. Presence of comorbidities. Time since diagnosis. HbA1c 3M. BMI Baseline. N.º severe hypoglycaemia events 3M	pmm	8 (5.1)
22	N.º of daily scans 6M	Sex. Age. Pubertal stage. Presence of comorbidities. Time since diagnosis. HbA1c 6M. BMI 6M. N.º severe hypoglycaemia events 6M. N.º of daily scans 3M	pmm	19 (12.2)
23	N.º of daily scans 12M	Sex. Age. Pubertal stage. Presence of comorbidities. Time since diagnosis. HbA1c 12M. BMI 12M. N.º severe hypoglycaemia events 12M. N.º of daily scans 6M	pmm	28 (17.9)
24	Sensor usage time 3M	Sex. Age. Pubertal stage. Presence of comorbidities. Time since diagnosis. HbA1c 3M. N.º ketoacidosis 3M. N.º of daily scans 3M	pmm	8 (5.1)
25	Sensor usage time 6M	Sex. Age. Pubertal stage. Presence of comorbidities. Time since diagnosis. HbA1c 6M. N.º ketoacidosis 6M. N.º of daily scans 6M. Sensor usage time 3M	pmm	19 (12.2)
26	Sensor usage time 12M	Sex. Age. Pubertal stage. Presence of comorbidities. Time since diagnosis. HbA1c 12M. N.º ketoacidosis 12M. N.º of daily scans 12M. Sensor usage time 6M	pmm	28 (17.9)
27	N.º Sensors 3M	Sex. Age. Pubertal stage. Presence of comorbidities. Time since diagnosis. N.º ketoacidosis 3M. Sensor usage time 3M	pmm	7 (4.5)
28	N.º Sensors 6M	Sex. Age. Pubertal stage. Presence of comorbidities. Time since diagnosis. N.º ketoacidosis 6M. Sensor usage time 6M. N.º Sensors 3M	pmm	19 (12.2)
29	N.º Sensors 12M	Sex. Age. Pubertal stage. Presence of comorbidities. Time since diagnosis. N.º ketoacidosis 12M. Sensor usage time 12M. N.º Sensors 6M	pmm	28 (17.9)

DM = Diabetes Mellitus; T1DM = Type 1 Diabetes Mellitus; DTSQ = Diabetes Treatment Satisfaction Questionnaire; EQ-5D-Y = Health-related quality of life questionnaire; VAS = visual analogue scale; HbA1c = Glycated haemoglobin; EHR = Electronic Health Record; BMI = Body mass index; M = Months.

Appendix 3. Cost estimation

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Table A1. Use of resources and unit costs

	Unit cost €2021 (SD)	Source
Hospitalization /day	652.58 (188.86)	Public tariff*
Visit to specialist	95.65 (33.98)	Public tariff*
Visit to nurse at primary care	27.06 (7.52)	Public tariff*
Hospital emergency	207.54 (72.03)	Public tariff*
Visit to doctor at primary care	50.91 (17.63)	Public tariff*
Non-hospital emergency	99.41 (22.83)	Public tariff*
HbA1c determination	7.15 (5.16)	Public tariff*
Test strips	0.43 (0.15)	Consult*
Lancets	0.109 (0.11)	Consult*
FSL sensor device	43.27	Information provided by the manufacturer
Absenteeism day	166.896	Estimate based on Eurostat and INE

FSL = FreeStyle Libre®; SD = Standard Deviation
* Spanish autonomous communities.
INE = Spanish Statistical Office.
Unit costs come from different sources, all national, and include official tariffs. Where possible, the average costs of those Spanish regions for which data were available were taken into account
To estimate the unit cost of test strips and lancets, the Spanish regions were consulted for their spending on these products. There was great heterogeneity between regions, not only in the unit cost (between €0.10 and €0.48), but also in the products financed, since lancets are only financed in some regions.

Table A2. Total annual cost per patient of the FSL flash glucose monitoring system (€2021)

	Primary care	Emergency	Specialist	Laboratory	Monitoring*	Total costs
Mean (SD)	136.78 (101.28)	50.70 (161.66)	415.48 (129.53)	29.05 (5.87)	1572.25 (317.58)	2204.26 (425.73)
Min. – Max.	0 – 474.24	0 – 1245.24	0 – 956.5	14.30 – 71.50	1125 – 2420.39	1344.90 – 3626.20
CI95%	(119.88; 154.65)	(25.74; 80.73)	(393.81; 438.65)	(28.1; 30.16)	(1519.13; 1627.46)	(2131.33; 2278.01)

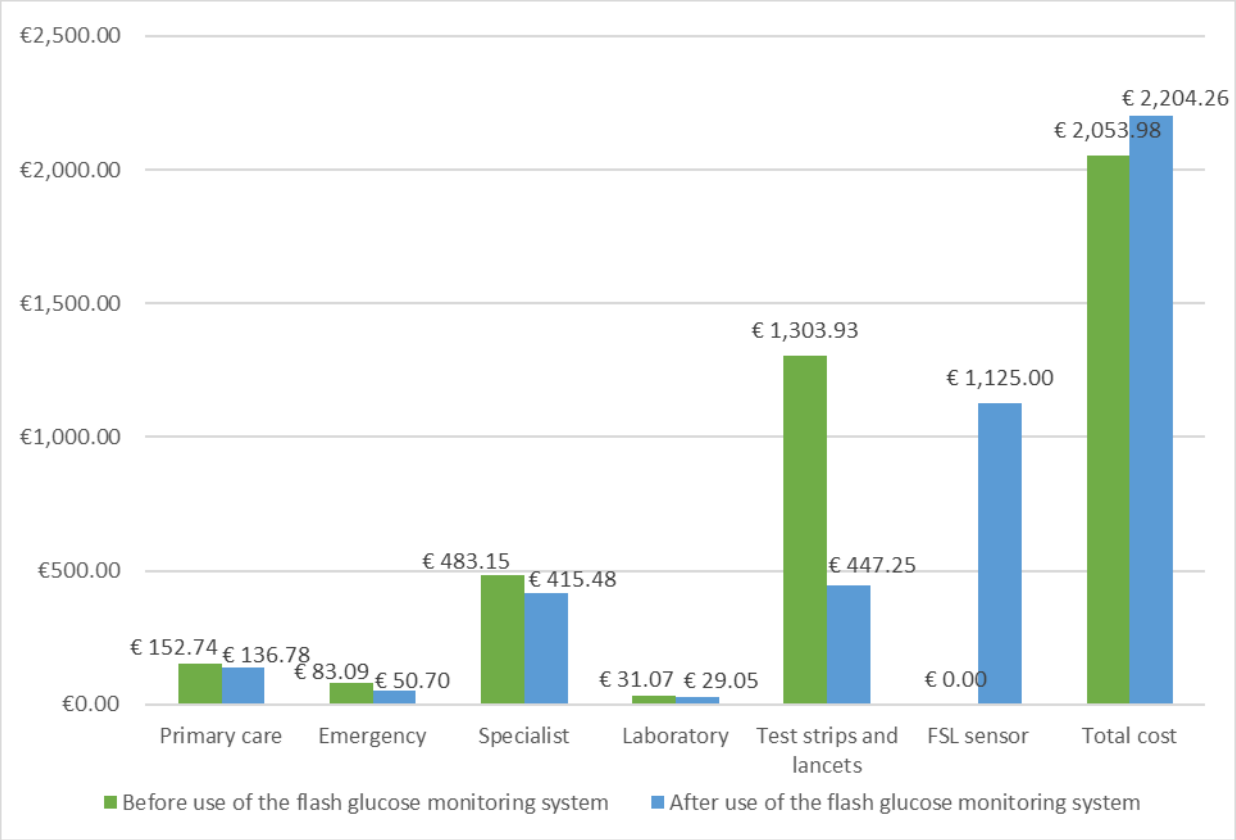
CI95% = Confidence interval at 95% by Bootstrap based on 10,000 samples; Max. = Maximum; Min. = Minimum; SD = Standard Deviation
*Including cost of test strips and lancets, and cost of sensor

Table A3. Average number of test strips and lancets per patient and total annual costs due to lost parent/caregiver productivity before and after FSL use.

	Before use of the flash glucose monitoring system	After use of the flash glucose monitoring system
Average number of test strips and lancets per patient before and after use of the FSL device		
Yearly test strips, mean (SD)	2686,02 (527,63)	883.98 (669.45)
Yearly Lancets, mean (SD)	1366.41 (1063.44)	615.94 (482.03)
Total annual cost per patient due to productivity losses (€2021)		
Mean (SD)	545.67 (588.29)	262.73 (334.30)
Min. – Max.	0 – 3504.82	0 – 1668.96
CI95%	(448.55; 650.63)	(206.65; 322.71)

CI95% = Confidence interval at 95% by Bootstrap based on 10,000 samples; Max. = Maximum; Min. = Minimum; SD = Standard Deviation

Figure A1. Total annual costs per patient before and after use of the FSL



Appendix 4. Evolution of outcome measures during follow-up (by age group and baseline HbA1c control)

	Baseline	3 months	6 months	12 months	Differences 12 months-Baseline
HbA1c, mean (SD)					
Total	7.86 (1.36)	7.58 (1.27)	7.59 (1.16)	7.73 (1.06)	-0.13 (-0.42; 0.16)
HbA1c <7.5%	6.82 (0.36)	6.86 (0.55)	6.96 (0.6)	7.14 (0.57)	0.32 (0.15; 0.49)
HbA1c ≥7.5%	8.65 (1.31)	8.18 (1.38)	8.14 (1.25)	8.2 (1.12)	-0.45 (-0.84; -0.06)
< 12 years	7.83 (1.17)	7.42 (0.93)	7.53 (0.96)	7.57 (0.8)	-0.26 (-0.59; 0.07)
≥ 12 years	7.87 (1.45)	7.66 (1.41)	7.63 (1.26)	7.82 (1.19)	-0.05 (-0.45; 0.35)
With self-reported severe hypoglycemia, n (%)					
Total	49 (31.4)	-	-	55 (36.9)	5.5% (-12.7; 23.7)
HbA1c <7.5%	26 (38.2)	-	-	24 (35.3)	-2.9% (-29.6; 23.8)
HbA1c ≥7.5%	23 (26.1)	-	-	31 (38.3)	12.2% (-12.6; 37.0)
< 12 years	22 (41.5)	-	-	19 (37.3)	-4.2% (-34.1; 25.7)
≥ 12 years	27 (26.2)	-	-	36 (36.7)	10.5% (-12.4; 33.4)
Nº. Self-reported severe hypoglycemia, mean (SD)					
Total	1.72 (3.65)	-	-	1.77 (5.08)	0.05 (-0.98; 1.1)
HbA1c <7.5%	2.34 (4.13)	-	-	1.95 (5.69)	-0.39 (-2.2; 1.4)
HbA1c ≥7.5%	1.26 (3.19)	-	-	1.63 (4.58)	0.37 (-0.86; 1.6)
< 12 years	2.12 (4.04)	-	-	1.06 (3.65)	-1.06 (-2.6; 0.48)
≥ 12 years	1.52 (3.43)	-	-	2.20 (5.76)	0.68 (-0.69; 2.1)
With severe hypoglycemia in the electronic clinical record, n (%)					
Total	19 (12.2)	-	-	23 (15.4)	3.2% (-17.6; 24.0)
HbA1c <7.5%	6 (8.8)	-	-	6 (8.8)	0% (-32.0; 32.0)
HbA1c ≥7.5%	13 (14.8)	-	-	17 (21.0)	6.2% (-21.1; 33.5)
< 12 years	9 (17.0)	-	-	6 (11.8)	-5.2% (-40.8; 30.4)
≥ 12 years	10 (9.7)	-	-	17 (17.4)	7.7% (-0.18; 0.33)
N.º Hypoglycemia in the electronic clinical record prior to the study, mean (SD)					
Total	0.39 (1.68)	-	-	0.54 (1.58)	0.15 (-0.23; 0.53)
HbA1c <7.5%	0.13 (0.45)	-	-	0.25 (1.06)	0.12 (-0.16; 0.40)
HbA1c ≥7.5%	0.59 (2.18)	-	-	0.78 (1.88)	0.19 (-0.43; 0.81)
< 12 years	0.34 (1.02)	-	-	0.61 (1.89)	0.27 (-0.32; 0.86)
≥ 12 years	0.42 (1.94)	-	-	0.5 (1.40)	0.08 (-0.39; 0.55)
Health-related quality of life (EQ-5D-Y), n (%)					
Mobility (no problems), n (%)					
Total	156 (100)	-	-	124 (100)	-
HbA1c <7.5%	68 (100)	-	-	54 (100)	-
HbA1c ≥7.5%	88 (100)	-	-	70 (100)	-
< 12 years	53 (100)	-	-	47 (100)	-
≥ 12 years	103 (100)	-	-	77 (100)	-
Self-Care (no problems), n (%)					
Total	154 (98.7)	-	-	123 (99.2)	-
HbA1c <7.5%	67 (98.5)	-	-	54 (100)	-
HbA1c ≥7.5%	87 (98.9)	-	-	69 (98.6)	-
< 12 years	51 (96.2)	-	-	47 (100)	-
≥ 12 years	103 (100)	-	-	76 (98.7)	-
Usual Activities (no problems), n (%)					
Total	154 (98.7)	-	-	122 (98.4)	-
HbA1c <7.5%	67 (98.5)	-	-	53 (98.1)	-
HbA1c ≥7.5%	87 (98.9)	-	-	69 (98.6)	-
< 12 years	53 (100)	-	-	47 (100)	-
≥ 12 years	101 (98.1)	-	-	75 (97.4)	-
Pain or Discomfort (no pain), n (%)					
Total	144 (92.3)	-	-	118 (95.2)	-
HbA1c <7.5%	62 (91.2)	-	-	53 (98.1)	-
HbA1c ≥7.5%	82 (93.2)	-	-	65 (92.9)	-

< 12 years	50 (94.3)	-	-	45 (95.7)	-
≥ 12 years	94 (91.3)	-	-	73 (94.8)	-
Pain or Discomfort (some pain), n (%)					
Total	12 (7.7)	-	-	6 (4.8)	-
HbA1c <7.5%	6 (8.8)	-	-	1 (1.9)	-
HbA1c ≥7.5%	6 (6.8)	-	-	5 (7.1)	-
< 12 years	3 (5.7)	-	-	2 (4.3)	-
≥ 12 years	9 (8.7)	-	-	4 (5.2)	-
Anxiety/Depression (no problems), n (%)					
Total	137 (87.8)	-	-	112 (90.3)	-
HbA1c <7.5%	62 (91.2)	-	-	50 (92.6)	-
HbA1c ≥7.5%	75 (85.2)	-	-	62 (88.6)	-
< 12 years	49 (92.5)	-	-	44 (93.6)	-
≥ 12 years	88 (85.4)	-	-	68 (88.3)	-
Anxiety/Depression (some problems), n (%)					
Total	16 (10.3)	-	-	10 (8.1)	-
HbA1c <7.5%	5 (7.4)	-	-	4 (7.4)	-
HbA1c ≥7.5%	11 (12.5)	-	-	6 (8.6)	-
< 12 years	3 (5.7)	-	-	2 (4.3)	-
≥ 12 years	13 (12.6)	-	-	8 (10.4)	-
VAS, mean (sd)					
Total	87.63 (12.46)	-	-	84.17 (12.28)	-3.5 (-6.4; -0.53)
HbA1c <7.5%	88.79 (10.05)	-	-	87.92 (10.08)	0.29 (-3.9; 4.5)
HbA1c ≥7.5%	86.74 (14.04)	-	-	81.29 (16.29)	-7.5 (-11.7; -3.3)
< 12 years	91.66 (9.72)	-	-	85.61 (14.97)	-6.1 (-11.0; -1.1)
≥ 12 years	85.56 (13.23)	-	-	83.27 (13.86)	-2.3 (-6.3; 1.7)
Knowledge of diabetes treatment (modified version of Mitchell questionnaire), mean (SD)					
Total	11.68 (2.13)	-	-	12.09 (1.94)	0.41 (-0.11; 0.93)
HbA1c <7.5%	12.38 (1.98)	-	-	12.92 (1.35)	0.54 (-0.11; 1.2)
HbA1c ≥7.5%	11.12 (2.08)	-	-	11.38 (2.08)	0.26 (-0.45; 0.97)
< 12 years	11.87 (2.07)	-	-	11.9 (2.31)	0.03 (-0.90; 0.96)
≥ 12 years	11.59 (2.16)	-	-	12.21 (1.67)	0.62 (-0.001; 1.2)
Diabetes Treatment Satisfaction Questionnaire (DTSQ)					
Perceived hyperglycemia, mean (SD)					
Total	3.53 (1.51)	-	-	3.32 (1.44)	-0.21 (-0.58; 0.16)
HbA1c <7.5%	2.94 (1.28)	-	-	2.88 (1.44)	-0.06 (-0.57; 0.45)
HbA1c ≥7.5%	4.01 (1.51)	-	-	3.71 (1.34)	-0.3 (-0.79; 0.19)
< 12 years	3.62 (1.38)	-	-	3.44 (1.48)	-0.18 (-0.79; 0.43)
≥ 12 years	3.48 (1.57)	-	-	3.25 (1.42)	-0.23 (-0.71; 0.25)
Perceived hypoglycemia, mean (SD)					
Total	2.22 (1.35)	-	-	2.04 (1.32)	-0.18 (-0.52; 0.16)
HbA1c <7.5%	2.3 (1.36)	-	-	2 (1.31)	-0.3 (-0.80; 0.20)
HbA1c ≥7.5%	2.15 (1.35)	-	-	2.07 (1.34)	-0.08 (-0.54; 0.38)
< 12 years	2.19 (1.17)	-	-	2.05 (1.26)	-0.14 (-0.66; 0.38)
≥ 12 years	2.23 (1.44)	-	-	2.03 (1.36)	-0.2 (-0.64; 0.24)
Satisfaction with treatment, mean (SD)					
Total	25.89 (6.7)	-	-	29.82 (5.44)	3.93 (2.4; 5.5)
HbA1c <7.5%	26.58 (7.04)	-	-	29.78 (5.1)	3.2 (0.86; 5.5)
HbA1c ≥7.5%	25.33 (6.41)	-	-	29.86 (5.77)	4.53 (2.4; 6.6)
< 12 years	25.79 (6.71)	-	-	29.61 (5.87)	3.82 (1.1; 6.5)
≥ 12 years	25.95 (6.73)	-	-	29.96 (5.21)	4.01 (2.1; 5.9)
	Baseline	**3 months**	**6 months**	**12 months**	**Differences 12-3 months**
Sensor usage time (%), mean (SD)					
Total	-	81.60 (20.78)	84.42 (19.47)	88.55 (18.48)	6.95 (2.3; 11.6)
HbA1c <7.5%	-	83.99 (21.93)	86.60 (17.2)	91.70 (15.09)	7.71 (0.90; 14.5)
HbA1c ≥7.5%	-	79.63 (19.69)	82.57 (21.16)	86.01 (20.57)	6.38 (-0.8; 12.8)
< 12 years	-	87.59 (15.06)	90.60 (14.34)	94.51 (11.81)	6.92 (1.5; 12.3)

≥ 12 years	-	78.45 (22.67)	81.09 (21.07)	84.85 (20.84)	6.4 (-0.14; 12.9)
Number of scans per day, mean (SD)					
Total	-	9.16 (5.06)	9.33 (4.97)	9.84 (6.02)	0.68 (-0.64; 2.0)
HbA1c <7.5%	-	10.06 (5.11)	9.89 (5.07)	10.39 (5.45)	0.33 (-1.6; 2.2)
HbA1c ≥7.5%	-	8.41 (4.92)	8.85 (4.86)	9.39 (6.46)	0.98 (-0.87; 2.8)
< 12 years	-	11.67 (5.64)	11.27 (4.5)	12.96 (6.45)	1.29 (-1.1; 3.7)
≥ 12 years	-	7.83 (4.17)	8.27 (4.91)	7.90 (4.85)	0.07 (-1.3; 1.4)
Number of sensors used, mean (SD)					
Total	-	6.40 (1.36)	7.50 (2.86)	14.74 (5.81)	8.34 (7.4; 9.3)
HbA1c <7.5%	-	6.32 (1.37)	6.86 (1.76)	13.35 (4.47)	7.03 (5.9; 8.2)
HbA1c ≥7.5%	-	6.46 (1.36)	8.05 (3.46)	15.86 (6.51)	9.4 (7.9; 10.9)
< 12 years	-	6.63 (1.17)	6.90 (2.15)	14.73 (5.83)	8.1 (6.5; 7.8)
≥ 12 years	-	6.28 (1.44)	7.83 (3.15)	14.75 (5.83)	8.47 (7.3; 9.7)

SD = standard deviation; VAS = Visual Analogue Scale; HbA1c = Glycosylated Haemoglobin; CI = Confidence Interval; GT = glucose time.

Appendix 5. Multivariate Mixed Regression Model for Effectiveness Measures and Adherence

Table 1. Multivariate Mixed Regression Model for Effectiveness Measures

Variable	Self-reported severe hypoglycaemia events				Severe hypoglycaemic events in the clinical history				Visual analogue scale (EQ-5D-Y)						Knowledge of diabetes treatment		Diabetes Treatment Satisfaction Questionnaire					
	Patients with hypoglycaemia (Yes/No) Total sample (n=156)		**Number of self-reported events** Total sample (n=156)		**Patients with hypoglycaemia (Yes/No)** Total sample (n=156)		**Number of self-reported events** Total sample (n=156)		Total sample (n=156)		HbA1c <7.5% (n=68)		HbA1c ≥7.5% (n=88)		Total sample (n=156)		**Perceived hyperglycaemia** Total sample (n=156)		**Perceived hypoglycaemia** Total sample (n=156)		**Satisfaction with treatment** Total sample (n=156)	
	OR (95%CI)	*P*	β (95%CI)	*P*	OR (95%CI)	*P*	β (95%CI)	*P*	B (95%CI)	*P*	B (95%CI)	*P*	B (95%CI)	*P*	B (95%CI)	*P*	B (95%CI)	*P*	B (95%CI)	*P*	B (95%CI)	*P*
Time																						
M12 (ref: M0)	0.82 (0.35; 1.96)	.659	-0.37 (-0.62; -0.11)	**.004**	1.47 (0.32; 6.77)	.617	0.77 (-0.06; 1.60)	.069	-1.40 (-4.97; 2.16)	.440	-1.33 (-4.17; 1.51)	.359	-6.03 (-9.66; -2.41)	**.001**	0.45 (-0.17; 1.08)	.154	-0.08 (-0.50; 0.34)	.721	-0.23 (-0.70; 0.24)	.331	3.11 (0.99; 5.23)	**.004**
Duration of T1DM	1.01 (0.89; 1.15)	.850	-0.01 (-0.14; 0.12)	.922	0.97 (0.81; 1.18)	.806	-0.05 (-0.24; 0.14)	.587	-0.74 (-1.29; -0.19)	**.008**	-0.32 (-0.99; 0.35)	.348	-1.05 (-1.86; -0.24)	**.011**	0.01 (-0.08; 0.09)	.851	-0.003 (-0.06; 0.05)	.915	-0.005 (-0.07; 0.06)	.870	0.05 (-0.18; 0.29)	.650
Presence of comorbidities	0.81 (0.33; 1.98)	.641	0.26 (-0.60; 1.12)	.556	0.81 (0.26; 2.50)	.710	0.27 (-0.83; 1.38)	.624	0.87 (-2.91; 4.64)	.652	2.42 (-1.78; 6.63)	.259	-1.04 (-6.98; 4.89)	.731	0.02 (-0.52; 0.57)	.930	-0.005 (-0.43; 0.42)	.980	0.02 (-0.36; 0.41)	.91	-0.52 (-2.15; 1.11)	.534
Age group: ≥12 years (ref: <12 years)	0.56 (0.22; 1.42)	.221	-0.15 (-1.04; 0.75)	.745	1.32 (0.39; 4.44)	.651	0.32 (-0.87; 1.50)	.599	-3.11 (-6.99; 0.78)	.117	-3.84 (-8.61; 0.94)	.115	-2.82 (-8.49; 2.83)	.327	-0.09 (-0.67; 0.48)	.705	-0.05 (0.48; 0.38)	.819	-0.002 (-0.38; 0.37)	.99	-0.02 (-3.24; 0.76)	.980
Baseline HbA1c group: ≥7.5% (ref: HbA1c <7.5%)	0.41 (0.15; 1.17)	.097	-0.57 (-1.40; 0.26)	.176	2.17 (0.53; 8.88)	.280	1.54 (0.31; 2.77)	**.014**	-1.93 (-5.98; 2.11)	.349					-1.27 (-1.89; -0.65)	**<.001**	1.06 (0.60; 1.52)	**<.001**	-0.12 (-0.57; 0.33)	.593	-1.24 (-1.34; 4.22)	.225
Time*Baseline HbA1c Group (ref: M0 & HbA1c <7.5%)																						
M12 & HbA1c ≥7.5%	2.69	.108	0.30	.117	2.01	.437	-0.44	.333	-4.61	**.061**					-0.06	.892	-0.11	.703	0.16	.615	1.44	.310

	(0.81; 8.96)		(-0.08; 0.68)		(0.34; 11.68)		(-1.33; 0.45)		(-9.44; 0.21)						(-0.90; 0.78)		(-0.70; 0.48)		(-0.46; 0.78)		(-1.34; 4.22)	
Intercept	0.78 (0.27; 2.23)	.641	-0.78 (-1.74; 0.17)	.107	0.03 (0.004; 0.19)	**<.001**	-4.32 (-5.97; -2.67)	**<.001**	90.50 (86.13; 94.87)	<.001	90.44 (85.92; 94.96)	<.001	88.92 (83.96; 93.88)	<.001	12.43 (11.78; 13.07)	**<.001**	2.98 (2.49; 3.46)	**<.001**	2.29 (1.84; 2.74)	**<.001**	26.80 (24.80; 28.81)	**<.001**
CI = Confidence Interval; HbA1c = Glycosylated Haemoglobin; M = Months; OR = Odds Ratio; ref = reference.																						

Table 2. Multivariate Mixed Regression Model for Adherence

	Sensor usage time, %		**Number of scans per day**		**Number of sensors used**					
Variable	Total sample (n=156)		Total sample (n=156)		Total sample (n=156)		HbA1c basal < 7.5% (n=68)		HbA1c basal ≥ 7.5% (n=88)	
	B (95%CI)	*P*	B (95%CI)	*P*	B (95%CI)	*P*	B (95%CI)	*P*	B (95%CI)	*P*
Time										
M6 (ref: M3)	1.82 (-3.31; 6.98)	.487	-0.25 (-1.41;0.92)	.678	0.49 (-0.58; 1.56)	.367	0.51 (-0.37; 1.39)	.255	1.59 (0.48; 2.70)	**.005**
M12 (ref: M3)	6.42 (1.12; 11.72)	**.018**	0.30 (-0.91; 1.51)	.625	6.96 (5.85; 8.06)	**<.001**	6.97 (6.06; 7.87)	**<.001**	9.37 (8.25; 10.50)	**<.001**
Duration of T1DM	-1.02 (-1.77; -0.27)	**.008**	-0.08 (-0.29; 0.13)	.468	-0.06 (-0.20; 0.07)	.363	-0.11 (-0.25; 0.04)	.152	-0.03 (-0.24; 0.18)	.804
Presence of comorbidities	0.53 (-4.61; 5.66)	.840	-0.69 (-2.14; 0.75)	.348	-0.35 (-1.27; 0.56)	.453	-0.25 (-1.16; 0.66)	.585	-0.39 (-1.92; 1.14)	.617
Age group: ≥12 years (ref: <12 years)	-7.93 (-13.19; -2.66)	**.003**	-3.92 (-5.40; -2.43)	**<.001**	0.39 (-0.55; 1.33)	.417	0.03 (-0.98; 1.05)	.952	0.69 (-0.77; 2.14)	.354
Baseline HbA1c group: ≥7.5% (ref: HbA1c <7.5%)	-4.59 (-10.71; 1.53)	.142	-1.92 (-3.52; -0.31)	**.019**	0.12 (-1.04; 1.29)	.836				
Time*Baseline HbA1c Group (ref: M3 & HbA1c <7.5%)										
M6 & HbA1c ≥7.5%	0.38 (-6.58; 7.33)	.915	0.43 (-1.14; 2.01)	.590	1.09 (-0.36; 2.54)	.141				
M12 & HbA1c ≥7.5%	-1.35 (-8.48; 5.77)	.710	0.35 (-1.28; 1.97)	.676	2.41 (0.93; 3.90)	**.001**				

Intercept	89.10 (82.9; 95.3)	**<.001**	13.0 (11.32; 14.68)	**<.001**	6.19 (5.04; 7.33)	**<.001**	6.39 (5.34; 7.44)	**<.001**	6.13 (4.77; 7.49)	**<.001**
CI = Confidence Interval; HbA1c = Glycosylated Haemoglobin; M = Months; ref = reference.										

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5-6
		(*b*) Describe any methods used to examine subgroups and interactions	5-6
		(*c*) Explain how missing data were addressed	5-6
		(*d*) If applicable, explain how loss to follow-up was addressed	5-6
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	Apex1
		(c) Summarise follow-up time (eg, average and total amount)	7
Outcome data	15*	Report numbers of outcome events or summary measures over time	8

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	8 8 NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9
Discussion			
Key results	18	Summarise key results with reference to study objectives	10-11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10-11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Effectiveness, safety and costs of the FreeStyle Libre glucose monitoring system for children and adolescents with type 1 diabetes in Spain: a prospective, uncontrolled, pre-post study

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Effectiveness, safety and costs of the FreeStyle Libre glucose monitoring system for children and adolescents with type 1 diabetes in Spain: a prospective, uncontrolled, pre-post study

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Abstract

Objectives
To evaluate the effectiveness, safety and costs of FreeStyle Libre (FSL) glucose monitoring system for children and adolescents with type 1 diabetes mellitus (T1DM) in Spain.

Design
Prospective, multicentre pre-post study.

Setting
Thirteen Spanish public hospitals recruited patients from January 2019 to March 2020, with a 12-month follow-up.

Participants
156 patients were included.

Primary and secondary outcome measures
Primary: HbA1c change. Secondary: severe hypoglycaemic events (self-reported and clinical records), quality of life, diabetes treatment knowledge, treatment satisfaction, adverse events, adherence, sensor usage time and scans. Healthcare resource utilization was assessed for cost analysis from the National Health System (NHS) perspective, incorporating direct healthcare costs. Data analysis utilized mixed regression models with repeated measures. The intervention's total cost was estimated by multiplying health resource usage with unit costs.

Results
In the whole sample, HbA1c increased significantly (0.32%; 95%CI: 0.10, 0.55). In the subgroup with baseline HbA1c ≥7.5% (n=88), there was a significant reduction at 3 (-0.46%; -0.69, -0.23), 6 (-0.49%; -0.73, -0.25), and 12 months (-0.43%; -0.68, -0.19). Well-controlled patients had a significant 12-month worsening (0.32%; 0.18, 0.47). Self-reported severe hypoglycaemia significantly decreased compared to the previous year for the whole sample (-0.37; -0.62, -0.11). Quality of life and diabetes treatment knowledge showed no significant differences, but satisfaction increased. Adolescents had lower sensor usage time and scans than children. Reduction in HbA1c was significantly associated with device adherence. No serious adverse effects were observed. Data suggest that use of FSL could reduce healthcare resource use (strips and lancets) and costs related to productivity loss.

Conclusions
The use of FSL in young patients with T1DM was associated with a significant reduction in severe hypoglycaemia, and improved HbA1c levels were seen in patients with poor baseline control. Findings suggest cost savings and productivity gains for caregivers. Causal evidence is limited due to the study design. Further research is needed to confirm results and assess risks, especially for patients with lower baseline HbA1c.

Strengths and limitations of this study
- This study provides nationally contextualised real-world scientific evidence on the effectiveness, safety and costs of the flash glucose monitoring systems (FreeStyle Libre [FSL]) indicated for type 1 diabetes in childhood and adolescence in Spain.
- The study utilized a combination of self-reported outcomes, clinical data extracted from electronic health records, and device-stored information from the FSL devices, which provides a robust and multifaceted assessment of the outcomes.
- The uncontrolled design of the study precludes causal inferences and results from randomized trials are needed to draw definitive conclusions.
- The small sample size limits the generalizability and statistical power of the findings.
- The cost estimation analysis only considered direct healthcare costs from the Spanish National Health System perspective, and indirect costs were not fully taken into account, which may underestimate the overall economic impact of the intervention.

Keywords
Continuous glucose monitoring, HbA1c, Type 1 diabetes, costs, Spain.

Word count 4866

INTRODUCTION

Type 1 diabetes mellitus (T1DM) requires continuous medical monitoring, to reduce the development of vascular complications [1,2]. The early onset and chronic character of this condition increase the likelihood of reducing health-related quality of life (HRQoL) and health expectancy among young T1DM people [3]. A total of 586,000 children aged under 15 years suffer from T1DM globally [4]. In Spain, the incidence is 11.5-27.6/100,000[5], which represents a high cost to society [6].

To reduce the risk of short (metabolic) and long-term (vascular) diabetes complications, frequent determination of blood glucose levels is required. Continuous glucose monitoring systems, such as the flash glucose monitoring (FGM) systems, contribute to glycaemia monitoring, as well as to reduce the daily number of fingersticks [7], providing dynamic information to the users about their glucose level. FreeStyle Libre (FSL), developed and marketed in Spain by Abbott Laboratories, has been indicated to measure glucose levels in the interstitial fluid in people aged over four years with T1DM. No serious adverse effects related to the use of these devices have been reported. Mild effects consist of skin problems in the area where the sensor is inserted, similar to other FGM [8,9].

In randomized trials, the FSL system has been shown to significantly reduce HbA1c levels and the frequency of hypoglycaemia in patients with T2DM, compared to the conventional finger-pricking method [10]. In T1DM, most published studies had an uncontrolled design, and meta-analyses have revealed that the use of FSL is associated with significant HbA1c reductions from baseline to the last follow up [11,12]. Approximately 30% of these studies included children and adolescents, which also led to obtaining significant pre-post HbA1c reductions. To the best of our knowledge, only one randomized trial has evaluated the FSL versus conventional glucose measurement in non-adults (13-20 years-old) with T1DM [13], showing no significant results on HbA1c or quality of life [13].

Spain has a universal public health system, financed by taxes. The system is highly decentralized and the 17 Spanish administrative regions have their own health policy budget, which enables a tailored approach to meet the specific needs and demands of each region. The competences and portfolio of the Spanish Ministry of Health encompass a wide range of responsibilities aimed at ensuring the well-being and health of the population. These include policy development, regulation and oversight of healthcare services, public health initiatives, pharmaceutical regulation, health technology assessment and coordination of emergency responses, among others. The Spanish Network of Health Technology Assessment Agencies of the National Health System (RedETS) [14], published a report in 2016 [15], later updated in 2017 [16], devised by the Canary Islands Health Service Evaluation Department (SESCS) [17], about the effectiveness, safety and cost-effectiveness of FSL in patients with T1DM and T2DM. In 2019, the Spanish Ministry of Health decided to fund FSL for adult T1DM patients [18], and in 2020 the reimbursement was extended to any insulin-dependent patient not diagnosed with T1DM or T2DM [19].

Regarding children and adolescents with T1DM, the Spanish Ministry of Health decided to perform a post-launch evidence generation study to provide real world information in the Spanish context on the effectiveness, safety, acceptability and potential use barriers, as well as on healthcare resources use and costs, to inform health policy decision-making on a national level in regard to coverage and public funding in these population groups [20,21]. This paper reports its results.

METHODS

Study design

Prospective, multicentre, pre-post study performed in 13 public hospitals throughout Spain (see **online supplemental Appendix 1**). Patients were recruited between January 2019 and March 2020, with a 12-month follow-up.

Interventions

FSL consists of: 1) an arm sensor that measures and stores interstitial glucose levels, wearable for 14 days [22]; 2) a reader that obtains glucose readings from the sensor when placed at a distance between 1-4 cm, storing up to 90 days of glucose measures and user-entered notes. The Libre View® software and the FreeStyle Libre Link®, and LibreLinkUp® Apps enables obtaining reports with the daily patterns of glucose levels.

Participants

Patients were eligible for inclusion if they were aged between 4 and 17, had been diagnosed with T1DM for at least one year prior to the study, were receiving intensive insulin therapy, required more than six fingersticks per day, and provided their informed consent to participate.

We excluded patients who had hypoglycaemia unawareness (judged by the clinician), were currently undergoing systemic corticosteroid treatment for more than two weeks within the last three months, had previously used or were currently using a FGM device within the last 12 months, were pregnant adolescents, had allergies to device adhesives, were unwilling to participate, lacked the necessary skills to effectively use the technology (patient/caregiver) or failed to provide informed consent.

Setting, logistics and recruitment

The study protocol was devised by SESCS researchers with the assistance of clinical experts from all hospitals taking part, patient association and industry representatives. A centralized information system (SIEM) was developed on the Spanish Ministry of Health's intranet, accessible both for the clinical researchers responsible for recruitment, clinical examination and data collection, as well as SESCS researchers.

Clinical researchers from hospitals taking part were responsible for recruiting, informing and training both patients and caregivers. They collected self-reported data using various measurement scales and extracted clinical information from the electronic health record (EHR) at baseline, 3, 6, and 12 months. In addition, they retrieved the stored information from the FSL device during the follow-up phase (3, 6, and 12 months) on the SIEM platform. SESCS researchers were responsible for coordinating the project and supervising data collection, monitoring quality assurance and data validation, analyses and reporting.

Interested Spanish autonomous communities designated the hospitals they wished to take part in the study. Thirteen public hospitals were included between January 2019 and May 2020, distributed over eight Spanish autonomous communities.

Endpoints

Effectiveness

The primary endpoint was the change in HbA1c level from baseline to follow up. Secondary endpoints included: 1) data extracted from the EHR at baseline and 3, 6 and 12 months: number of severe hypoglycaemia events (defined as those that require help from another person), ketoacidosis episodes, number of hospital admissions and mortality; and 2) self-reported outcomes evaluated at baseline and at 12 months follow-up, by means of the EQ-5D-Y questionnaire [23]; with five categories, reporting the level of severity, ranging from 1 ("I have no problems") to 5 ("I have a lot of problems") in terms of mobility, self-care, activities of daily living, pain/discomfort and anxiety/depression. Furthermore, a visual analogue scale (VAS) measured self-perceived general health, ranging from "0" (worst health status) to "100" (best health status).

Knowledge of diabetes treatment was measured by means of a modified version of the questionnaire devised by Mitchell et al. [24]. This includes 14 items evaluating basic theoretical knowledge about the management of T1DM and its treatment, as well as the patient/caregiver's self-perceived involvement in self-care. The final score is the sum of correct answers (range 0-14). To measure satisfaction with treatment, we used the six-item Diabetes Treatment Satisfaction Questionnaire (DTSQ) [25]. Response options range from 0 (very dissatisfied) to 6 (very satisfied) (range 0-36). Another two items measured the perceived frequency of hyperglycaemia and hypoglycaemia on a scale from 0 (never perceived) to 6 (most of the time).

Safety

Patients' self-reported device-related adverse events were collected at 3, 6 and 12-months of follow-up.

Adherence

To measure device adherence, the following variables were evaluated: 1) Number of daily scans; 2) Sensor usage time (percentage); and 3) Number of sensors used. These data were collected throughout the follow-up phase by means of the information stored in the device.

Use of healthcare resources

Data were extracted from the EHR at baseline and at 12-months of follow-up on: 1) Number of hospitalizations; 2) Number of clinic visits (endocrinology, nursing, primary care/paediatrics, emergency); 3) Number of HbA1c assays; 4) Number of test strips and lancets used; and 5) Absenteeism from work (number of days the caregiver was absent from work due to problems related to the child's T1DM).

In addition to these measures, information on age, sex, body mass index (BMI), time since diagnosis, presence of comorbidities and pubertal stage according to the Tanner scale [26], which classifies patients into 5 stages ranging from stage 1 (childhood) to 5 (adult), was systematically collected.

Sample size calculation

We estimated a sample size requirement of 43 participants to detect a minimal clinically relevant change in HbA1c of 0.5% [27], assuming 95% confidence level, 80% power, a HbA1c standard deviation of 1, a pre-post correlation of 0.5 (conservative assumption), and a loss rate of 20%. In addition to the main effect in the whole sample, we were also interested in the effect of the intervention on subgroups defined by their baseline HbA1c level (greater or less than 7.5%), and age (<12 vs. ≥12 years-old). However, the analysis of interactions requires larger sample sizes to attain statistical power, which was not feasible within the study's time limits. Therefore, we aimed to multiply the sample at least by 4 (n=172) to increase the statistical power as much as possible.

Statistical analysis

Means and standard deviation (SD) were estimated for continuous variables, and count and percentage for qualitative variables. Baseline characteristics of patients were compared using student-*t*, Pearson chi-square, Fisher's exact test or Cochran Q, according to the type of variables.

Mixed regression models with repeated measures were used, adjusting for the interaction between time and baseline HbA1c (dichotomous variable) and age group, time and its main effects. The duration of the disease and the existence of comorbidities were included as covariates. A linear link function was used for continuous dependent variables, a logistic function for dichotomous dependent variables and a Poisson function for count dependent variables. In the models with significant interaction, mixed regression models were performed for each interaction subgroup.

The relationship between adherence to the device and HbA1c reduction was analysed using two mixed linear regression models, whose independent variables were the percentage of time using the sensor (12 months) and

the number of monthly scans; basal HbA1c level was introduced as a covariable. Intercept was introduced as a random effect in all models.

For missing values during follow-up, a comparability analysis was conducted between participants lost to follow-up and those who remained, prior to performing multiple imputation by chained equations using Stata version 15.0. The details of this comparability analysis and the imputation model can be found in **online supplemental Appendix 2**.

A level of 0.05 was considered statistically significant. Analyses were performed with the statistical software Stata V.15.0 [28] and SPSS V.20.0 [29].

Cost estimation

Intervention costs were estimated from the Spanish National Health System (NHS) perspective, including only direct healthcare costs during the 12 months of the study. The healthcare resources collected in this study, together with the corresponding unit costs and their information sources, can be found in **Table A1 in online supplemental Appendix 3**. Costs were expressed as 2021 euros (€). When necessary, we adjusted for the consumer price index (CPI), using the Spanish Office of National Statistics (INE) – the INE's income conversion tool [30].

Unit cost of test strips and lancets were estimated with the average costs of information provided by different regional health services of the Spanish NHS. Total costs were estimated multiplying the collected data on health resources used by their respective unit costs, and then added.

Descriptive statistics are presented for total costs aggregated and broken down into: primary care visits (nursing and physicians), emergency visits (hospital and non-hospitals), specialist physicians visits, laboratory tests (HbA1c assay) and monitoring instruments (FSL sensor and test strips and lancets).

Given the nature of the costs and their non-normal nature, confidence intervals were estimated using a non-parametric bootstrapping method [31]. Analyses were performed using the statistical software SPSS V.20.0 [29] with the help of Microsoft Excel.

In addition, although the social perspective was not taken into account in this estimate, indirect technology costs were reported using the human capital theory, i.e. considering the costs attributed to productivity losses of the parents or caregivers of the child with T1DM before and after one year of using the FSL.

To estimate the cost per day of absenteeism, the cost per hour worked in Spain published by the Statistical Office of the European Union (Eurostat) [32] was multiplied by the average number of daily working hours worked in Spain published in the INE's Labour Force Survey (LFS) [33].

Patient and public involvement

There was no patient involvement in the design of this study. Clinical experts from all participant hospitals, representatives of patient associations and the industry took part in drawing up the protocol. We undertook with healthcare professionals to share the results with them in an easy-to-understand way.

RESULTS

A total of 165 patients were initially registered for the study. However, nine patients were subsequently excluded as they did not meet the study's inclusion criteria (**Figure 1**). Therefore, the final analysis included a total of 156 patients.

Patient baseline characteristics are shown in **Table 1** according to subgroups by level of metabolic control and age. There was a higher percentage of participants in stage 1 and 5 in the subgroup with worse glycaemic control (*P*=0.02). In this subgroup, the mean HbA1c value was 8.7%; with 6.8% (*P*<0.001) in the well-controlled group. Descriptive statistics obtained at each time point for the total sample and subgroups for each outcome measure can be found in **online supplemental Appendix 4**.

Table 1. Baseline characteristics of patients according to baseline HbA1c and age groups

	Total (n=156)	**HbA1c <7.5% (n=68)**	**HbA1c ≥7.5 % (n=88)**	***P***	**<12 years (n=53)**	**≥12 years (n=103)**	***P***
Anthropometric characteristics							
Sex (male) n (%)	86 (55.1)	35 (51.5)	51 (58)	.419	28 (52.8)	58 (56.3)	.679
Age (years), mean (SD)	12.6 (3.2)	12.7 (2.84)	12.49 (3.39)	.735	NA	NA	**NA**
Children <12 years, n (%)	53 (34)	21 (30.9)	32 (36.4)	.474	NA	NA	**NA**
BMI (kg/m^2), mean (SD)	20.3 (4.1)	20.18 (3.34)	20.39 (4.54)	.754	NA	NA	**NA**
Pubertal status, n (%)				**.022**			**<.001**
I	51 (32.7)	19 (27.9)	32 (36.4)		44 (83)	7 (6.8)	
II	14 (9.0)	9 (13.2)	5 (5.7)		4 (7.5)	10 (9.7)	
III	20 (12.8)	7 (10.3)	13 (14.8)		4 (7.5)	16 (15.5)	
IV	23 (14.7)	16 (23.5)	7 (8)		0 (0)	23 (22.3)	
V	48 (30.8)	17 (25)	31 (35.2)		1 (1.9)	47 (45.6)	
Clinical characteristics							
Duration of diabetes (years), mean (SD)	5.65 (3.39)	5.52 (3.35)	5.75 (3.44)	.671	4.06 (2.4)	6.47 (3.54)	**<.001**
HbA1c, mean (SD)	7.86 (1.36)	6.82 (0.36)	8.65 (1.31)	**NA**	7.83 (1.17)	7.87 (1.45)	.87
HbA1c <7.5%, n (%)	68 (43.6)	NA	NA		21 (39.6)	47 (45.6)	.474
Presence of comorbidities, n (%)	50 (32.1)	27 (39.7)	23 (26.1)	.072	17 (32.1)	33 (32)	.996
Comorbidities, n (%)							
Asthma	6 (3.8)	5 (7.4)	1 (1.1)	.199	1 (1.9)	5 (4.9)	.65
Coeliac Disease	8 (5.1)	6 (8.8)	2 (2.3)	.261	5 (9.4)	3 (2.9)	.102
Thyroiditis	18 (11.5)	12 (17.6)	6 (6.8)	.178	6 (11.3)	12 (11.7)	.941
ADHD	4 (2.6)	1 (1.5)	3 (3.4)	.322	1 (1.9)	3 (2.9)	.999
Others	19 (12.2)	7 (10.3)	12 (13.6)	.057	5 (9.4)	14 (13.6)	.369

ADHD = Attention-Deficit/Hyperactivity Disorder; BMI = body mass index; HbA1c = glycated haemoglobin; NA = Not Applicable; SD = standard deviation.
Other comorbidities: allergy, obesity, iron deficiency anaemia, unilateral anorchia, immunoglobulin A (IgA) deficiency, intellectual disability, epilepsy, hypercholesterolaemia, sensorineural hearing loss, migraines, idiopathic hypercalciuria, ovarian teratoma, nephrocalcinosis, psoriasis, allergic rhinitis, vasovagal syncope, Tourette's syndrome, eating disorder (ED) and obsessive-compulsive disorder (OCD).

Effectiveness

Glycated haemoglobin

In the entire sample, there was a significant increase in HbA1c (0.32%, *P*<0.001). The interaction between time and the baseline HbA1c group was statistically significant at 3, 6 and 12 months (*P*<0.001) (**Table 2**). In the subgroup analysis, participants with baseline HbA1c<7.5% revealed an increase of 0.32% (0.18 to 0.47) in HbA1c at 12 months (with respect to baseline) (*P*<0.001), without exceeding, on average, the threshold of poor control. Patients with poorly controlled baseline status had a statistically significant reduction in HbA1c at all follow-ups: B=-0.46% (-0.69 to -0.23; *P*<0.001), B=-0.49% (-0.73 to -0.25; *P*<0.001), and B=-0.43% (-0.68 to -0.19; *P*=0.001), at 3, 6 and 12 months, respectively (**Table 2**). On average, this reduction did not attain the threshold of poor control.

Table 2. Multivariate mixed regression models for HbA1c

Variable	Total sample (n=156)		HbA1c <7.5% (n=68)		HbA1c ≥7.5% (n=88)	
	B (95%CI)	*P*	B (95%CI)	*P*	B (95%CI)	*P*
Time						
M3 (ref: M0)	0.03 (-0.18; 0.24)	.765	0.03 (-0.09; 0.16)	.611	-0.46 (-0.69; -0.23)	**<.001**
M6 (ref: M0)	0.1 (-0.11; 0.32)	.344	0.10 (-0.03; 0.23)	.115	-0.49 (-0.73; -0.25)	**<.001**
M12 (ref: M0)	0.32 (0.10; 0.55)	**.005**	0.32 (0.18; 0.47)	**<.001**	-0.43 (-0.68; -0.19)	**.001**
Duration of T1DM	0.05 (0.007; 0.09)	**.020**	-0.005 (-0.04; 0.03)	.762	0.09 (0.02; 0.15)	**.011**
Presence of comorbidities	-0.10 (-0.39; 0.18)	.477	0.09 (-0.13; 0.30)	.439	-0.22 (-0.70; 0.26)	.372
Age group: ≥12 years (ref: <12 years)	0.17 (-0.12; 0.47)	.253	0.09 (-0.15; 0.32)	.473	0.26 (-0.21; 0.73)	.274
Baseline HbA1c group: ≥7.5% (ref: HbA1c <7.5%)	1.81 (1.50; 2.13)	**<.001**				
Time*Baseline HbA1c Group (ref: M0 & HbA1c <7.5%)						
M3 & HbA1c ≥7.5%	-0.49 (-0.78; -0.21)	**<.001**				
M6 & HbA1c ≥7.5%	-0.59 (-0.88; -0.29)	**<.001**				
M12 & HbA1c ≥7.5%	-0.76 (-1.05; -0.46)	**<.001**				
Intercept	6.75 (6.41; 7.09)	**<.001**	6.73 (6.50; 6.96)	**<.001**	8.53 (8.12; 8.94)	**<.001**

CI = confidence interval; HbA1c = glycated haemoglobin; M = month; T1DM = type 1 diabetes mellitus.

Severe hypoglycaemic (SH) events

The reduction in the number of self-reported events was significant at 12 months β=-0.37 (-0.62 to -0.11; *P*=0.004) (**Table 1 in online supplemental Appendix 5**). Although the interaction with the level of HbA1c at baseline was not statistically significant (*P*=0.117), the descriptive statistics (**online supplemental Appendix 4**) in patients with controlled HbA1c at baseline show a reduction in the mean number of events; with an increase in the poorly controlled subgroup.

SH events recorded in the EHR show significantly lower rates compared to self-reported events (**online supplemental Appendix 4**), without significant main or interaction effects (**Table 1 in online supplemental Appendix 5**). The rate of SH events was significantly higher in the subgroup with poor HbA1c control (*P*=0.014) (**Table 1 in online supplemental Appendix 5**).

Diabetic ketoacidosis and other serious adverse events

In the follow-up phase, six mild or moderate ketoacidosis events were recorded at three (2), six (1), and 12 months (3), respectively; and four serious adverse events at three months (two admissions and one episode of ketosis without acidosis due to bubbles in the system); and at six months (one admission). No events were observed at 12-month follow-up. No patient died during follow-up.

Health-related quality of life

At 12 months follow-up, the percentages of severe limitations for mobility, self-care, daily activities, anxiety and depression were similar to baseline values. However, a reduction was observed in the percentage of patients who self-reported pain (**online supplemental Appendix 4**).

VAS score (**Table 1 in online supplemental Appendix 5**) did not show a significant change in the whole sample, and the interaction with baseline HbA1c values was slightly above the statistical significance level (*P*= 0.061). In poorly controlled patients, VAS scores were significantly reduced at 12 months compared to the baseline score B=-6.03 (-9.66 to -2.41; *P*=0.001). In the subgroup with good basal metabolic control, no statistically significant findings were observed.

Knowledge of diabetes treatment

There was no significant change in patients' Knowledge of diabetes treatment, nor a significant interaction with baseline HbA1c. Patients with worse basal metabolic control revealed a significantly lower score compared to well-controlled patients: B=-1.27 (-1.89 to -0.65; *P*<0.001) (**Table 1 in online supplemental Appendix 5**).

Satisfaction with treatment

General satisfaction with treatment significantly increased 3.1 points at 12 months of follow-up (0.99 to 5.23; *P*=0.004) (**Table 1 in online supplemental Appendix 5**). There were no statistically significant differences in self-perceived hypo- and hyperglycaemia. For the latter, a higher score of 1.06 points (in a range of 0 to 6) was observed, in patients with HbA1c≥7.5%, compared to those with good control (0.60 to 1.52; *P*<0.001) (**Table 1 in online supplemental Appendix 5**).

Safety

Mild adverse events related to the device during follow-up phases had a 3.1% and 6.6% reduction for skin reactions and discomfort or pain, respectively. However, these were not statistically significant (**Table 3**).

Table 3. Mild adverse effects caused by the sensor

	3 months (n=150)	6 months (n=136)	12 months (n=128)	*P*	Differences 12–3 months, % (95%CI)
Skin reactions, n (%)	21 (14.0)	16 (11.8)	14 (10.9)	.542	-3.1% (-25.2; 19.0)
Discomfort or pain, n (%)	17 (11.3)	13 (9.6)	6 (4.7)	.210	-6.6% (-29.3; 16.1)
Other minor events, n (%)	3 (2.0)	2 (1.5)	2 (1.6)	.999	-0.4% (-23.9; 23.1)

Among the other events, there were minor haemorrhages when the sensor was positioned and wounds in the insertion area. In one case, the patient lost consciousness because of the bleeding.
CI = confidence interval.

Adherence

Time of sensor use (**Table 2 in online supplemental Appendix 5**) significantly increased at 6.4% at 12 months of follow-up (1.12 to 11.72; *P*=0.02), compared to three months. Longer duration of T1DM (*P*=0.008), and age older than 12 years (*P*=0.003), significantly reduced sensor use.

A reduction in the mean number of daily scans at three months occurred in poorly controlled patients B=-1.92 (-3.52 to -0.31; *P*=0.019). Those aged over 12 underwent an average of four fewer scans than those aged under 12 years B=-3.92 (-5.4 to -2.43; *P*<0.001) (**Table 2 in online supplemental Appendix 5**).

Controlled patients revealed an increase in the mean number of sensors use at 12 months of follow-up B=7 (5.85 to 8.06; *P*<0.001); also increasing in poorly controlled patients by B=1.6 (0.48 to 2.7; *P*=0.005) at 6 months, and B=9.4 (8.25 to 10.5; *P*<0.001) at 12 months (**Table 2 in online supplemental Appendix 5**).
The percentage of time of use was statistically significantly related to a lower HbA1c level at 12 months (B=-0.01; *P*=0.013), as was the number of scans (B=-0.21; *P*<0.001).

Cost estimation

The estimated total annual costs per patient are shown in **Table A2 (online supplemental Appendix 3)**. Intervention short-term costs from an NHS perspective reveal that specialist visits and test strips and lancets costs account for a significant part of total costs (38% and 41%, respectively), with an average annual cost per patient of €415.48 and €447.25 for specialist visits and strips and lancets, respectively. Regarding the cost of the FSL sensor, it amounts to €43.27 according to information provided by the manufacturer. Taking into account an average number of sensors per patient per year of 26 (considering a sensor half-life of 14 days), the total annual cost of the sensor amounts to €1,125 per patient/year. This means that the average total annual costs per patient with the use of FSL amounts to €2204.26 (**Table A2 (online supplemental Appendix 3)**).
Total annual costs before and after use of the FSL system can be found in **Figure 2**. All measured costs decreased after use of the device throughout 12 months follow-up, with the most striking difference in costs related to test strips and lancets use, an annual difference of €856.68 per patient.

This information is outlined in **Table A3 (online supplemental Appendix 3)**. The annual average number of test strips per patient decreased from 2686.02 strips per year before the use of the FSL, to 883.98 strips per year after its use. The difference in the annual average use of lancets per patient also reduced from 1366.41 before FSL use to 615.94 after its use.
Furthermore, a decrease in total annual costs due to productivity losses of parents/caregivers of minor patients with T1DM was observed after the use of FSL (€545.67 versus €262.73) as shown in **Table A3 (online supplemental Appendix 3)**.

DISCUSSION

Glucose monitoring devices can help people with T1DM monitor their glycaemia levels and reduce the frequency and/or severity of acute disease-complication rates, thus improving their HRQoL and life expectancy [34]. Two meta-analyses of case series on the effectiveness of the FSL revealed statistically significant HbA1c reductions in children/adolescents with poor HbA1c control (7.5%-9.6%, except two studies with 7.1% and 7.4%) of -0.54% (n=447) [35] and -0.29% (n=959) [11], although the effect was highly variable across studies. Our study only provides a statistically significant reduction of HbA1c in the group with poor baseline monitoring, (-0.46%, -0.49% and -0.35%), at 3, 6 and 12 months, respectively. On the contrary, patients with basal controlled HbA1c levels revealed a significant 12-month worsening higher than 0.30%. Another case series in Spain (n=145) [36], with limited follow up to three months, also detected a reduction in patients with HbA1c≥7.5% (-0.41, *P*=0.004), and a statistically significant increase in well-monitored patients, i.e. a worsening in HbA1c levels (0.23, *P*=0.03). The uncontrolled design of the study precludes ruling out that this result just reflects a regression to the mean. A recent meta-analysis of randomized controlled trials on the effectiveness of continuous glucose monitoring in people with T1DM showed a significant effect only in studies with mean HbA1c values at baseline >8% (-0.49%) [37]. However, apart from not being based exclusively on non-adult population, this result is based on meta-analysis and not on the analysis of interactions in the individual studies, and therefore it is subjected to potential risk of ecological fallacy.

The results also revealed a significant reduction in the number of self-reported SH events for the whole sample (-0.37), but not in the number of patients with at least one event. The interaction effect with baseline HbA1c level was not statistically significant for these two variables (*P*=0.117 and *P*=0.108, respectively). The descriptive statistics suggest different subgroup effects, although none was statistically significant. The reduction of self-reported SH events occurred in patients with controlled HbA1c levels at baseline (0.39), whereas in the basally uncontrolled group, an increase was self-reported (0.37 more); together with an important increase in the rate of patients with at least one event (from 26% to 38%). Again, an effect of regression to the mean could be the explanation for this result since, as expected, patients with controlled HbA1c at baseline showed higher SH rates and means. Alternatively, the results on both HbA1c and SH could be reflecting the trade-off faced by patients with T1DM between the reduction in glucose levels and the associated risk of increasing hypoglycaemic events. This interpretation is speculative given the commented methodological limitations of the study, but it would help account for the unexpected significant worsening in self-perceived general health observed in the subgroup of poor baseline HbA1c monitoring. That is, contrary to the HbA1c improvement attained, that has no observable effects on self-perceived HRQoL, suffering an SH event is a salient experience that may impact this self-perception.

Other studies [36] have also reported a significant and clinically meaningful improvement in the rate of SH events (from 4.2 to 0.2 events/100 patients-year). However, their results are not reported separately according to basal levels of metabolic control. The largest case series published to date with children and adolescents [38], and with the longest follow-up (12 months), also revealed a statistically significant reduction of SH events (53%, *P*=0.012) for the whole sample, with no changes in HbA1c.

The interaction of the intervention with the age group (<12 vs. ≥12 years-old) was not statistically significant in any case. However, descriptive statistics reveal different non-significant trends among subgroups, with positive results only for younger participants: -0.26% vs. -0.05% (HbA1c), -1.06 vs. 0.68 (SH events) and -4.2% vs. 10.5% (people with one or more SH). Adolescents revealed significantly lower sensor usage time and scans per day than children, similar to the results observed in previous studies [39-41]. Adolescents and young adults face specific challenges and barriers regarding the use of glucose monitoring sensors, such as concerns about self-image and how people perceive them [42,43], differential emotional reactions to diabetes burden [44] or a lesser interest in glucose data analysis [45], and therefore specific strategies might be necessary to increase sensor use in this population [46]. Nonetheless, adolescents in our sample showed adequate adherence throughout the study, above 78% of the time at each successive evaluation. Regarding the effectiveness of the FLS in adolescents,

the only randomized controlled trial to date included participants aged 13-20 years, with HbA1c≥9.0%) [13], and although it found significantly higher satisfaction in the intervention group at 6 months, it did not reveal any statistically significant differences in HbA1c reduction compared to traditional self-monitoring. Therefore, significant uncertainty remains in regard to the effects of FSL in adolescents.

Despite the improvement in the degree of metabolic control that occurred in our study sample of patients with worse baseline HBA1c levels, no statistically significant improvement was observed in their knowledge of diabetes treatment. Device adherence was significantly related to the reduction of HbA1c, a result usually observed in the literature on glucose monitoring devices [39-41]. The same can be said about treatment satisfaction [47,48], which improved in the whole sample.

In regard to safety, no serious adverse effects were observed, a result consistent with the literature on glucose monitoring devices in general [9]. The number of patients showing mild adverse events at three months was reduced at the end of follow-up to 18%, resulting in two losses at six months follow-up due to skin reaction to the sensor and another two at 12 months due to discomfort with the sensor.

In terms of costs analysis as observed in the international literature, our results showed that T1DM patients consume less healthcare resources using FSL [49]. Fundamentally, a striking decrease was observed in costs attributed to reactive strips and lancets, where an annual difference of €856.68 per patient was obtained (not including cost of sensor). A decrease in total indirect annual costs due to productivity losses of parents/carers of T1DM patients, was also observed (€545.67 versus €262.73). Despite the savings observed in all cost categories, when the cost of the device is taken into account, there is no potential savings with the use of the FSL. However, this information can be useful for decision-making and negotiating the price of the device.

The main limitation of this study lies in its uncontrolled design, which precludes comparison with an untreated group. Therefore, an inference of causality regarding the introduction of the FLS is not possible, because other factors such as child developmental growth, potential changes in target treatment or insulin administration methods or a regression to the mean could affect the observed changes. A “novelty effect”, related to the use of a technological device could also introduce a motivation bias that could affect self-management habits. Another relevant limitation is the limited sample size to analyse interaction effects, even when we increased the recruited sample fourfold. By the time of study execution, the FSL was already financed and introduced in some hospitals taking part and a large portion of the target population was already using it. This scenario was an important recruitment obstacle to enlarge sample size. Our conclusions to be drawn are, therefore, limited by the low statistical power for interaction analyses and rare events such as severe hypoglycaemia. All these limitations imply a low quality of the evidence.

The start-up of a monitoring study has been used to collect data on the use of resources and make initial estimates of the cost of the intervention. Therefore, our cost analysis was a secondary endpoint and complementary to this study’s primary endpoint and it has limitations. First, our analysis has not taken into account the costs attributable to the possible adverse effects arising from the use of FSL and it has assumed that possible failures of the device will be resolved at no additional cost to the Spanish NHS. Moreover, it was not possible to estimate the costs related to hospitalization of the patients since the number of days of each hospitalization was not recorded in this study. However, the extremely low number of total hospitalizations during the monitoring study indicates that including this cost in the estimate would not have produced substantial changes in the results.

To the best of our knowledge, this is the first comparative costs analysis study of FSL use in children and adolescents with T1DM in Spain using observational data in an actual use scenario. Therefore, although a cost-effectiveness analysis could not be performed in this study, due to the absence of a comparator, our results may contribute to inform future cost-effectiveness studies of FSL in Spain.

CONCLUSION

Our results showed that the use of FSL in young T1DM patients significantly reduced the rate of SH events, and improved HbA1c levels in patients with poor baseline control. However, futures studies should confirm whether these benefits could be at the cost of worsening outcomes in patients with lower HbA1c. No serious adverse events related to FSL were observed. The results also suggest that the use of FSL in young patients with T1DM leads to a decrease in monitoring costs. In addition, the use of FSL reduces costs attributable to lost productivity of parents/caregivers. However, these outcomes correspond to low-quality evidence, mainly due to the study's uncontrolled design, in addition to the low statistical power in the case of rare complications such as SH.

Based on these results and other information sources (i.e., international research and clinical expert advice), the Spanish Ministry of Health has decided to reimburse the FreeStyle Libre (FSL) for children and adolescents aged 4-17 years with type 1 diabetes who are treated with intensive insulin therapy (multiple daily injections or insulin pump) and require at least six fingerstick blood glucose self-monitoring tests a day.

Footnotes

Collaborators: The Health Professional Group included the following members (in alphabetical order): Amparo González Vergaz (Hospital Severo Ochoa), Ana María Prado Carro (Complexo Hospitalario Universitario A Coruña), Anunciación Beisti Ortego (Fundación Hospital Calahorra), Ariadna Campos Martorell (Hospital Universitari Vall D'hebron), Atilano José Carcavilla Urqui (Hospital Universitario La Paz), Cristina Amparo Del Castillo Villaescusa (Hospital Universitario Dr. Peset Aleixandre), Estela Gil Poch (Hospital Universitario de Badajoz), Francisco Javier Arroyo Diez (Hospital Universitario de Badajoz), Gemma Novoa Gómez (Complexo Hospitalario Universitario de Ourense), Isabel González Casado (Hospital Universitario La Paz), Juncal Martínez Ibáñez (Fundación Hospital Calahorra), Laura Cuadrado Piqueras (Fundación Hospital Calahorra), Leticia Reis Iglesias (Complexo Hospitalario Universitario de Ourense), Lucia Garzón Lorenzo (Hospital Universitario 12 De Octubre), Luis Salamanca Fresno (Hospital Universitario La Paz), María Asunción Martínez Brocca (Hospital Universitario Virgen Macarena), María Aurea Rodríguez Blanco (Hospital Da Barbanza), María Del Mar Martínez López (Hospital Universitario 12 De Octubre), María Jesús Ferreiro Rodríguez (Complexo Hospitalario Universitario de Ourense), María Ruiz del Campo (Hospital San Pedro), Nerea Itza Martín (Hospital Universitario La Paz), Patricia García Navas (Hospital San Pedro), Rebeca García García (Hospital Universitario Central de Asturias).

Contributors: YAP, ARS, LPP and PSA initiated the study. HGP did the acquisition of data. HGP, ARS, CVN and YRF contributed to the analysis and interpretation of data. HGP did the statistical analyses. HGP, ARS, CVN YAP and YRF wrote the first draft of the manuscript. HGP, ARS, YRF, CVN, YAP, LGP, MAGB, LPP AND PSA critically revised the manuscript and approved the final version. HGP is responsible for the overall content as the guarantor and accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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Patient consent for publication: Not applicable.

Ethics approval: The scientific and ethics committees approved the study protocol (Hospital Universitari Vall d'Hebron, ID-RTF065). All participants provided written informed consent.

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FIGURE TITLES

Figure 1. Study flowchart

Figure 2. Total annual costs per patient before and after use of the FSL

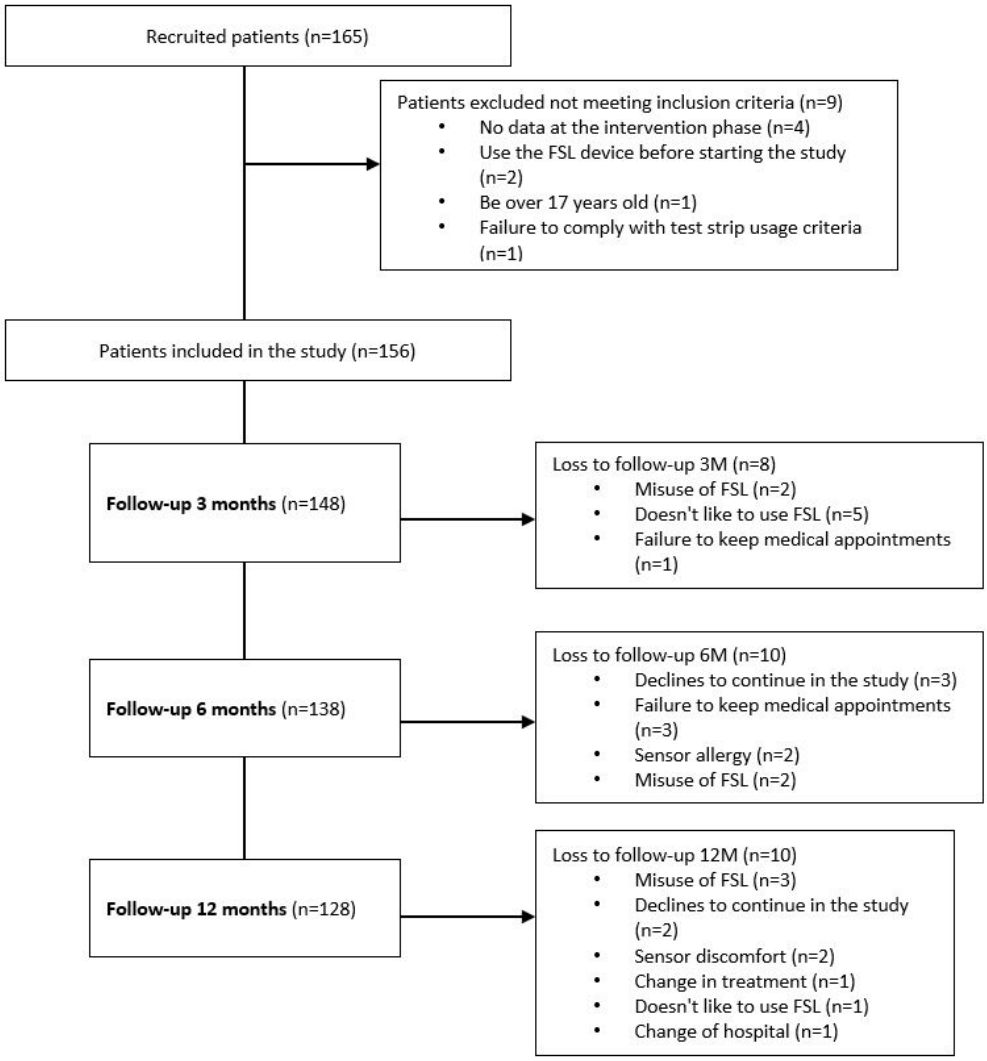

Figure1. Flow-charts

201x216mm (96 x 96 DPI)

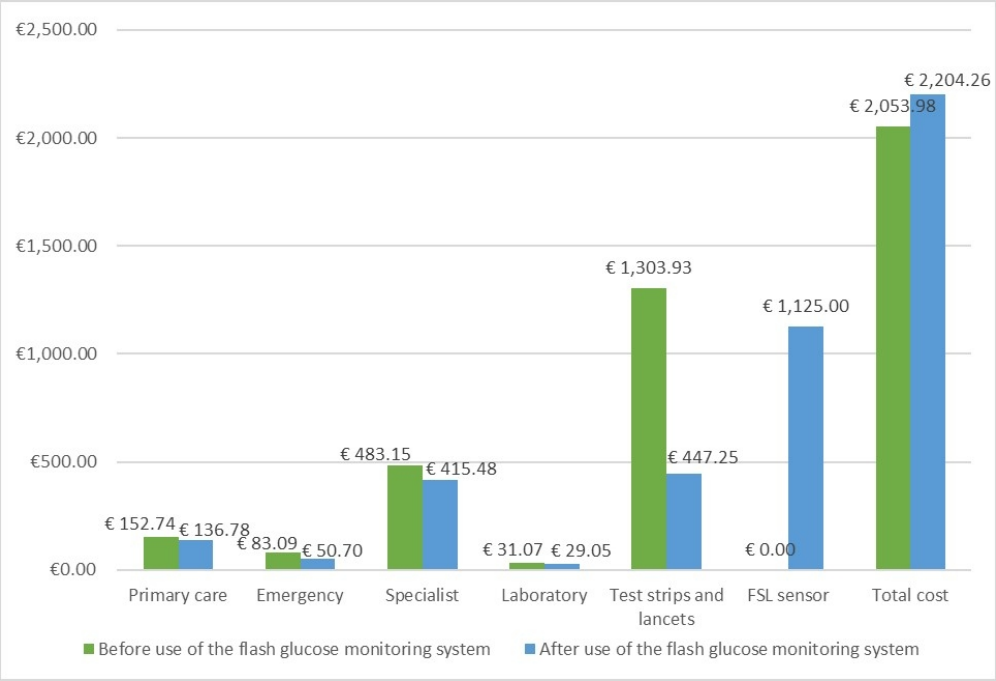

Figure 2. Total annual costs per patient before and after use of the FSL

163x111mm (150 x 150 DPI)

Appendix 1. Participating hospitals and cases included in the study

Public hospitals	Regional Health Services	Number of patients
Virgen Macarena University Hospital*	Andalucía	2
Central de Asturias University Hospital*	Asturias	4
Vall D'hebron University Hospital*	Cataluña	22
Badajoz University Hospital	Extremadura	30
A Coruña University Hospital Complex*	Galicia	23
Ourense University Hospital Complex	Galicia	14
Barbanza Hospital	Galicia	5
Calahorra Hospital Foundation	La Rioja	1
San Pedro Hospital	La Rioja	13
Severo Ochoa Hospital	Madrid	21
12 De Octubre University Hospital*	Madrid	4
La Paz University Hospital*	Madrid	16
Dr. Peset Aleixandre University Hospital	Valencia	1
*Tertiary hospital		

Appendix 2. Comparability analysis and description of the missing data imputation model

Comparability analysis

For comparability analysis, the baseline characteristics of patients (gender, age, HbA1c, BMI, time since diagnosis, presence of comorbidities, and pubertal stage) were compared between participants who completed the different follow-up phases and those who had total or partial loss to follow-up at 3, 6, and 12 months. No significant differences were found for any of these variables at the 3-month follow-up. At 6 months, significant differences were observed between responders and non-responders in relation to pubertal stage V (25% vs. 75%) (p = 0.04). At the 12-month follow-up, differences were observed in pubertal stages IV (21.7% vs. 78.3%) and V (31.2% vs. 68.8%) (p = 0.007); significant differences were also observed in the mean age value (p = 0.04) between responders (12.3 years) and non-responders (13.7 years).

	3 months			**6 months**			**12 months**		
	Participants lost to follow-up (n=6)	**Participants who continued in the study (n=150)**	**p**	**Participants lost to follow-up (n=20)**	**Participants who continued in the study (n=136)**	**p**	**Participants lost to follow-up (n=28)**	**Participants who continued in the study (n=128)**	**p**
Sex (male), n (%)	4 (4.7)	82 (95.3)	0.562	8 (9.3)	78 (90.7)	0.145	16 (18.6)	70 (81.4)	0.813
Age (years), mean (SD)	13 (4.86)	12.55 (3.09)	0.829	13.3 (3.81)	12.46 (3.05)	0.266	13.68 (2.91)	12.32 (3.17)	**0.039**
HbA1c, mean (SD)	8.42 (0.62)	7.83 (1.38)	0.303	8.36 (2.01)	7.78 (1.23)	0.224	8.08 (1.81)	7.81 (1.24)	0.33
BMI, mean (SD)	20.73 (2.87)	20.28 (4.10)	0.789	21.33 (2.91)	20.14 (4.18)	0.224	21.33 (2.88)	20.07 (4.24)	0.135
Duration of DM1, mean (SD)	7.19 (3.86)	5.59 (3.37)	0.257	6.42 (3.43)	5.54 (3.38)	0.275	6.74 (3.39)	5.41 (3.36)	0.061
Presence of comorbidities, n (%)	1 (2.0)	49 (98.0)	0.41	7 (14)	43 (86)	0.762	9 (18)	41 (82)	0.991
Pubertal status, n (%)			0.473			**0.043**			**0.007**
I	2 (3.9)	49 (96.1)		5 (9.8)	46 (90.2)		5 (9.8)	46 (90.2)	
II	0 (0)	14 (100)		1 (7.1)	13 (92.9)		3 (21.4)	11 (78.6)	
III	0 (0)	20 (100)		0 (0)	20 (100)		0 (0)	20 (100)	
IV	0 (0)	23 (100)		2 (8.7)	21 (91.3)		5 (21.7)	18 (78.3)	
V	4 (8.3)	44 (91.7)		12 (25)	36 (75)		15 (31.2)	33 (68.8)	

SD = Standard deviation; HbA1c = Glycated haemoglobin; BMI = Body mass index.

Description of the missing data imputation model

For multiple imputation was performed by chained equations using Stata 15.0 software. The variables sex, age, pubertal stage, presence of comorbidities and duration of diabetes were considered regular and used as predictors for imputation. A total of 29 variables were imputed. Each variable was imputed in chronological order: 3, 6 and 12 months. As a general rule, the latest available information on the variable to be imputed was used. When information from other variables was used, the information from the same point in time was used. A total of 10 imputations were made for each missing data.

Order	Imputed variable	Variables used in imputation	Imputation model	n (%) missing
1	HbA1c 3M	Sex, Age, Pubertal stage, Presence of comorbidities, Time since diagnosis, HbA1c Baseline	pmm	7 (4.5)
2	HbA1c 6M	Sex, Age, Pubertal stage, Presence of comorbidities, Time since diagnosis, HbA1c 3M	pmm	20 (12.8)
3	HbA1c 12M	Sex, Age, Pubertal stage, Presence of comorbidities, Time since diagnosis, HbA1c 6M	pmm	28 (17.9)
4	BMI 6M	Sex, Age, Pubertal stage, Presence of comorbidities, Time since diagnosis, BMI Baseline	pmm	24 (15.4)
5	BMI 12M	Sex, Age, Pubertal stage, Presence of comorbidities, Time since diagnosis, BMI 6M	pmm	28 (17.9)
6	N. º severe hypoglycaemia events 3M	Sex, Age, Pubertal stage, Presence of comorbidities, Time since diagnosis, N. º severe hypoglycaemia events Baseline	poisson	7 (4.5)
7	N. º severe hypoglycaemia events 6M	Sex, Age, Pubertal stage, Presence of comorbidities, Time since diagnosis, N. º severe hypoglycaemia events 3M	poisson	7 (4.5)
8	N. º severe hypoglycaemia events 12M	Sex, Age, Pubertal stage, Presence of comorbidities, Time since diagnosis, N. º severe hypoglycaemia events 6M	poisson	7 (4.5)
9	N. º severe hypoglycaemia events on EHR 3M	Sex, Age, Pubertal stage, Presence of comorbidities, Time since diagnosis, N. º severe hypoglycaemia events 3M, N. º severe hypoglycaemia events on EHR Baseline	poisson	8 (5.1)
10	N. º severe hypoglycaemia events on EHR 6M	Sex, Age, Pubertal stage, Presence of comorbidities, Time since diagnosis, N. º severe hypoglycaemia events 6M, N. º severe hypoglycaemia events on EHR 3M	poisson	28 (17.9)
11	N. º severe hypoglycaemia events on EHR 12M	Sex, Age, Pubertal stage, Presence of comorbidities, Time since diagnosis, N. º severe hypoglycaemia events 12M, N. º severe hypoglycaemia events on EHR 6M	poisson	28 (17.9)
12	VAS 12M	Sex, Age, Pubertal stage, Presence of comorbidities, Time since diagnosis, Mobility EQ-5D-Y 12M, Self-care EQ-5D-Y 12M, Habitual activities EQ-5D-Y 12M, Pain/discomfort EQ-5D-Y 12M, Anxiety/depression EQ-5D-Y 12M, VAS Baseline	pmm	36 (23.1)
13	Knowledge about Baseline	Sex, Age, Pubertal stage, Presence of comorbidities, Time since diagnosis, HbA1c Baseline, BMI Baseline	pmm	14 (9.0)
14	Knowledge about 12M	Sex, Age, Pubertal stage, Presence of comorbidities, Time since diagnosis, HbA1c 12M, BMI 12M, Knowledge about Baseline	pmm	48 (30.8)
15	Hyperglycaemia DTSQ Baseline	Sex, Age, Pubertal stage, Presence of comorbidities, Time since diagnosis, HbA1c Baseline, Knowledge about Baseline	pmm	14 (9.0)
16	Hyperglycaemia DTSQ 12M	Sex, Age, Pubertal stage, Presence of comorbidities, Time since diagnosis, HbA1c 12M, Knowledge about 12M, Hyperglycaemia DTSQ Baseline	pmm	48 (30.8)
17	Hypoglycaemia DTSQ Baseline	Sex, Age, Pubertal stage, Presence of comorbidities, Time since diagnosis	pmm	14 (9.0)
18	Hypoglycaemia DTSQ 12M	Sex, Age, Pubertal stage, Presence of comorbidities, Time since diagnosis, Hypoglycaemia DTSQ Baseline	pmm	48 (30.8)

19	Satisfaction with treatment DTSQ Baseline	Sex, Age, Pubertal stage, Presence of comorbidities, Time since diagnosis, N. º severe hypoglycaemia events Baseline, N. º severe hypoglycaemia events on EHR Baseline, Knowledge about Baseline, Hyperglycaemia DTSQ Baseline,	pmm	14 (9.0)
20	Satisfaction with treatment DTSQ 12M	Sex, Age, Pubertal stage, Presence of comorbidities, Time since diagnosis, N. º severe hypoglycaemia events 12M, N. º severe hypoglycaemia events on EHR 12M, Knowledge about 12M, Hyperglycaemia DTSQ 12M, Satisfaction with treatment DTSQ Baseline	pmm	48 (30.8)
21	N. º of daily scans 3M	Sex, Age, Pubertal stage, Presence of comorbidities, Time since diagnosis, HbA1c 3M, BMI Baseline, N. º severe hypoglycaemia events 3M	pmm	8 (5.1)
22	N. º of daily scans 6M	Sex, Age, Pubertal stage, Presence of comorbidities, Time since diagnosis, HbA1c 6M, BMI 6M, N. º severe hypoglycaemia events 6M, N. º of daily scans 3M	pmm	19 (12.2)
23	N. º of daily scans 12M	Sex, Age, Pubertal stage, Presence of comorbidities, Time since diagnosis, HbA1c 12M, BMI 12M, N. º severe hypoglycaemia events 12M, N. º of daily scans 6M	pmm	28 (17.9)
24	Sensor usage time 3M	Sex, Age, Pubertal stage, Presence of comorbidities, Time since diagnosis, HbA1c 3M, N. º ketoacidosis 3M, N. º of daily scans 3M	pmm	8 (5.1)
25	Sensor usage time 6M	Sex, Age, Pubertal stage, Presence of comorbidities, Time since diagnosis, HbA1c 6M, N. º ketoacidosis 6M, N. º of daily scans 6M, Sensor usage time 3M	pmm	19 (12.2)
26	Sensor usage time 12M	Sex, Age, Pubertal stage, Presence of comorbidities, Time since diagnosis, HbA1c 12M, N. º ketoacidosis 12M, N. º of daily scans 12M, Sensor usage time 6M	pmm	28 (17.9)
27	N. º Sensors 3M	Sex, Age, Pubertal stage, Presence of comorbidities, Time since diagnosis, N. º ketoacidosis 3M, Sensor usage time 3M	pmm	7 (4.5)
28	N. º Sensors 6M	Sex, Age, Pubertal stage, Presence of comorbidities, Time since diagnosis, N. º ketoacidosis 6M, Sensor usage time 6M, N. º Sensors 3M	pmm	19 (12.2)
29	N. º Sensors 12M	Sex, Age, Pubertal stage, Presence of comorbidities, Time since diagnosis, N. º ketoacidosis 12M, Sensor usage time 12M, N. º Sensors 6M	pmm	28 (17.9)

DM = Diabetes Mellitus; T1DM = Type 1 Diabetes Mellitus; DTSQ = Diabetes Treatment Satisfaction Questionnaire; EQ-5D-Y = Health-related quality of life questionnaire; VAS = visual analogue scale; HbA1c = Glycated haemoglobin; EHR = Electronic Health Record; BMI = Body mass index; M = Months.

Appendix 3. Cost estimation

List of tables:

Table A1. Use of resources and unit costs		
	Unit cost €2021 (SD)	**Source**
Hospitalization /day	652.58 (188.86)	Public tariff*
Visit to specialist	95.65 (33.98)	Public tariff*
Visit to nurse at primary care	27.06 (7.52)	Public tariff*
Hospital emergency	207.54 (72.03)	Public tariff*
Visit to doctor at primary care	50.91 (17.63)	Public tariff*
Non-hospital emergency	99.41 (22.83)	Public tariff*
HbA1c determination	7.15 (5.16)	Public tariff*
Test strips	0.43 (0.15)	Consult*
Lancets	0.109 (0.11)	Consult*
FSL sensor device	43.27	Information provided by the manufacturer
Absenteeism day	166.896	Estimate based on Eurostat and INE

FSL = FreeStyle Libre®; SD = Standard deviation.
* Spanish autonomous communities.
INE = Spanish Statistical Office.
Unit costs come from different sources, all national, and include official tariffs. Where possible, the average costs of those Spanish regions for which data were available were taken into account
To estimate the unit cost of test strips and lancets, the Spanish regions were consulted for their spending on these products. There was great heterogeneity between regions, not only in the unit cost (between €0.10 and €0.48), but also in the products financed, since lancets are only financed in some regions.

Table A2. Total annual cost per patient of the FSL flash glucose monitoring system (€2021)

	Primary care	**Emergency**	**Specialist**	**Laboratory**	**Monitoring***	**Total costs**
Mean (SD)	136.78 (101.28)	50.70 (161.66)	415.48 (129.53)	29.05 (5.87)	1572.25 (317.58)	2204.26 (425.73)
Min. – Max.	0 – 474.24	0 – 1245.24	0 – 956.5	14.30 – 71.50	1125 – 2420.39	1344.90 – 3626.20
95%CI	(119.88; 154.65)	(25.74; 80.73)	(393.81; 438.65)	(28.1; 30.16)	(1519.13; 1627.46)	(2131.33; 2278.01)

95%CI = Confidence interval at 95% by Bootstrap based on 10,000 samples; Max. = Maximum; Min. = Minimum; SD = Standard Deviation
*Including cost of test strips and lancets, and cost of sensor

Table A3. Average number of test strips and lancets per patient and total annual costs due to lost parent/caregiver productivity before and after FSL use.

	Before use of the flash glucose monitoring system	After use of the flash glucose monitoring system
Average number of test strips and lancets per patient before and after use of the FSL device		
Yearly test strips, mean (SD)	2686,02 (527,63)	883.98 (669.45)
Yearly Lancets, mean (SD)	1366.41 (1063.44)	615.94 (482.03)
Total annual cost per patient due to productivity losses (€2021)		
Mean (SD)	545.67 (588.29)	262.73 (334.30)
Min. – Max.	0 – 3504.82	0 – 1668.96
95%CI	(448.55; 650.63)	(206.65; 322.71)
95%CI = Confidence interval at 95% by Bootstrap based on 10,000 samples; Max. = Maximum; Min. = Minimum; SD = Standard deviation.		

Appendix 4. Evolution of outcome measures during follow-up (by age group and baseline HbA1c control)

	Baseline	3 months	6 months	12 months	Differences 12 months-Baseline (95%CI)
HbA1c, mean (SD)					
Total	7.86 (1.36)	7.58 (1.27)	7.59 (1.16)	7.73 (1.06)	-0.13 (-0.42; 0.16)
HbA1c <7.5%	6.82 (0.36)	6.86 (0.55)	6.96 (0.6)	7.14 (0.57)	0.32 (0.15; 0.49)
HbA1c ≥7.5%	8.65 (1.31)	8.18 (1.38)	8.14 (1.25)	8.2 (1.12)	-0.45 (-0.84; -0.06)
<12 years	7.83 (1.17)	7.42 (0.93)	7.53 (0.96)	7.57 (0.8)	-0.26 (-0.59; 0.07)
≥12 years	7.87 (1.45)	7.66 (1.41)	7.63 (1.26)	7.82 (1.19)	-0.05 (-0.45; 0.35)
With self-reported severe hypoglycaemia, n (%)					
Total	49 (31.4)	-	-	55 (36.9)	5.5% (-12.7; 23.7)
HbA1c <7.5%	26 (38.2)	-	-	24 (35.3)	-2.9% (-29.6; 23.8)
HbA1c ≥7.5%	23 (26.1)	-	-	31 (38.3)	12.2% (-12.6; 37.0)
<12 years	22 (41.5)	-	-	19 (37.3)	-4.2% (-34.1; 25.7)
≥12 years	27 (26.2)	-	-	36 (36.7)	10.5% (-12.4; 33.4)
Nº. Self-reported severe hypoglycaemia, mean (SD)					
Total	1.72 (3.65)	-	-	1.77 (5.08)	0.05 (-0.98; 1.1)
HbA1c <7.5%	2.34 (4.13)	-	-	1.95 (5.69)	-0.39 (-2.2; 1.4)
HbA1c ≥7.5%	1.26 (3.19)	-	-	1.63 (4.58)	0.37 (-0.86; 1.6)
<12 years	2.12 (4.04)	-	-	1.06 (3.65)	-1.06 (-2.6; 0.48)
≥12 years	1.52 (3.43)	-	-	2.20 (5.76)	0.68 (-0.69; 2.1)
With severe hypoglycaemia in the electronic clinical record, n (%)					
Total	19 (12.2)	-	-	23 (15.4)	3.2% (-17.6; 24.0)
HbA1c <7.5%	6 (8.8)	-	-	6 (8.8)	0% (-32.0; 32.0)
HbA1c ≥7.5%	13 (14.8)	-	-	17 (21.0)	6.2% (-21.1; 33.5)
<12 years	9 (17.0)	-	-	6 (11.8)	-5.2% (-40.8; 30.4)
≥12 years	10 (9.7)	-	-	17 (17.4)	7.7% (-0.18; 0.33)
N. º Hypoglycaemia in the electronic clinical record prior to the study, mean (SD)					
Total	0.39 (1.68)	-	-	0.54 (1.58)	0.15 (-0.23; 0.53)
HbA1c <7.5%	0.13 (0.45)	-	-	0.25 (1.06)	0.12 (-0.16; 0.40)
HbA1c ≥7.5%	0.59 (2.18)	-	-	0.78 (1.88)	0.19 (-0.43; 0.81)
<12 years	0.34 (1.02)	-	-	0.61 (1.89)	0.27 (-0.32; 0.86)
≥12 years	0.42 (1.94)	-	-	0.5 (1.40)	0.08 (-0.39; 0.55)
Health-related quality of life (EQ-5D-Y)					
Mobility (no problems), n (%)					
Total	156 (100)	-	-	124 (100)	-
HbA1c <7.5%	68 (100)	-	-	54 (100)	-
HbA1c ≥7.5%	88 (100)	-	-	70 (100)	-
<12 years	53 (100)	-	-	47 (100)	-
≥12 years	103 (100)	-	-	77 (100)	-
Self-Care (no problems), n (%)					
Total	154 (98.7)	-	-	123 (99.2)	-
HbA1c <7.5%	67 (98.5)	-	-	54 (100)	-
HbA1c ≥7.5%	87 (98.9)	-	-	69 (98.6)	-
<12 years	51 (96.2)	-	-	47 (100)	-
≥12 years	103 (100)	-	-	76 (98.7)	-
Usual Activities (no problems), n (%)					
Total	154 (98.7)	-	-	122 (98.4)	-
HbA1c <7.5%	67 (98.5)	-	-	53 (98.1)	-
HbA1c ≥7.5%	87 (98.9)	-	-	69 (98.6)	-
<12 years	53 (100)	-	-	47 (100)	-
≥12 years	101 (98.1)	-	-	75 (97.4)	-
Pain or Discomfort (no pain), n (%)					

Total	144 (92.3)	-	-	118 (95.2)	-
HbA1c <7.5%	62 (91.2)	-	-	53 (98.1)	-
HbA1c ≥7.5%	82 (93.2)	-	-	65 (92.9)	-
<12 years	50 (94.3)	-	-	45 (95.7)	-
≥12 years	94 (91.3)	-	-	73 (94.8)	-
Pain or Discomfort (some pain), n (%)					
Total	12 (7.7)	-	-	6 (4.8)	-
HbA1c <7.5%	6 (8.8)	-	-	1 (1.9)	-
HbA1c ≥7.5%	6 (6.8)	-	-	5 (7.1)	-
<12 years	3 (5.7)	-	-	2 (4.3)	-
≥12 years	9 (8.7)	-	-	4 (5.2)	-
Anxiety/Depression (no problems), n (%)					
Total	137 (87.8)	-	-	112 (90.3)	-
HbA1c <7.5%	62 (91.2)	-	-	50 (92.6)	-
HbA1c ≥7.5%	75 (85.2)	-	-	62 (88.6)	-
<12 years	49 (92.5)	-	-	44 (93.6)	-
≥12 years	88 (85.4)	-	-	68 (88.3)	-
Anxiety/Depression (some problems), n (%)					
Total	16 (10.3)	-	-	10 (8.1)	-
HbA1c <7.5%	5 (7.4)	-	-	4 (7.4)	-
HbA1c ≥7.5%	11 (12.5)	-	-	6 (8.6)	-
<12 years	3 (5.7)	-	-	2 (4.3)	-
≥12 years	13 (12.6)	-	-	8 (10.4)	-
VAS, mean (SD)					
Total	87.63 (12.46)	-	-	84.17 (12.28)	-3.5 (-6.4; -0.53)
HbA1c <7.5%	88.79 (10.05)	-	-	87.92 (10.08)	0.29 (-3.9; 4.5)
HbA1c ≥7.5%	86.74 (14.04)	-	-	81.29 (16.29)	-7.5 (-11.7; -3.3)
<12 years	91.66 (9.72)	-	-	85.61 (14.97)	-6.1 (-11.0; -1.1)
≥12 years	85.56 (13.23)	-	-	83.27 (13.86)	-2.3 (-6.3; 1.7)
Knowledge of diabetes treatment (*modified version of Mitchell questionnaire*), mean (SD)					
Total	11.68 (2.13)	-	-	12.09 (1.94)	0.41 (-0.11; 0.93)
HbA1c <7.5%	12.38 (1.98)	-	-	12.92 (1.35)	0.54 (-0.11; 1.2)
HbA1c ≥7.5%	11.12 (2.08)	-	-	11.38 (2.08)	0.26 (-0.45; 0.97)
<12 years	11.87 (2.07)	-	-	11.9 (2.31)	0.03 (-0.90; 0.96)
≥12 years	11.59 (2.16)	-	-	12.21 (1.67)	0.62 (-0.001; 1.2)
Diabetes Treatment Satisfaction Questionnaire (DTSQ)					
Perceived hyperglycaemia, mean (SD)					
Total	3.53 (1.51)	-	-	3.32 (1.44)	-0.21 (-0.58; 0.16)
HbA1c <7.5%	2.94 (1.28)	-	-	2.88 (1.44)	-0.06 (-0.57; 0.45)
HbA1c ≥7.5%	4.01 (1.51)	-	-	3.71 (1.34)	-0.3 (-0.79; 0.19)
<12 years	3.62 (1.38)	-	-	3.44 (1.48)	-0.18 (-0.79; 0.43)
≥12 years	3.48 (1.57)	-	-	3.25 (1.42)	-0.23 (-0.71; 0.25)
Perceived hypoglycaemia, mean (SD)					
Total	2.22 (1.35)	-	-	2.04 (1.32)	-0.18 (-0.52; 0.16)
HbA1c <7.5%	2.3 (1.36)	-	-	2 (1.31)	-0.3 (-0.80; 0.20)
HbA1c ≥7.5%	2.15 (1.35)	-	-	2.07 (1.34)	-0.08 (-0.54; 0.38)
<12 years	2.19 (1.17)	-	-	2.05 (1.26)	-0.14 (-0.66; 0.38)
≥12 years	2.23 (1.44)	-	-	2.03 (1.36)	-0.2 (-0.64; 0.24)
Satisfaction with treatment, mean (SD)					
Total	25.89 (6.7)	-	-	29.82 (5.44)	3.93 (2.4; 5.5)
HbA1c <7.5%	26.58 (7.04)	-	-	29.78 (5.1)	3.2 (0.86; 5.5)
HbA1c ≥7.5%	25.33 (6.41)	-	-	29.86 (5.77)	4.53 (2.4; 6.6)
<12 years	25.79 (6.71)	-	-	29.61 (5.87)	3.82 (1.1; 6.5)
≥12 years	25.95 (6.73)	-	-	29.96 (5.21)	4.01 (2.1; 5.9)

	Baseline	3 months	6 months	12 months	Differences 12-3 months (95%CI)
Sensor usage time (%), mean (SD)					
Total	-	81.60 (20.78)	84.42 (19.47)	88.55 (18.48)	6.95 (2.3; 11.6)
HbA1c <7.5%	-	83.99 (21.93)	86.60 (17.2)	91.70 (15.09)	7.71 (0.90; 14.5)
HbA1c ≥7.5%	-	79.63 (19.69)	82.57 (21.16)	86.01 (20.57)	6.38 (-0.8; 12.8)
<12 years	-	87.59 (15.06)	90.60 (14.34)	94.51 (11.81)	6.92 (1.5; 12.3)
≥12 years	-	78.45 (22.67)	81.09 (21.07)	84.85 (20.84)	6.4 (-0.14; 12.9)
Number of scans per day, mean (SD)					
Total	-	9.16 (5.06)	9.33 (4.97)	9.84 (6.02)	0.68 (-0.64; 2.0)
HbA1c <7.5%	-	10.06 (5.11)	9.89 (5.07)	10.39 (5.45)	0.33 (-1.6; 2.2)
HbA1c ≥7.5%	-	8.41 (4.92)	8.85 (4.86)	9.39 (6.46)	0.98 (-0.87; 2.8)
<12 years	-	11.67 (5.64)	11.27 (4.5)	12.96 (6.45)	1.29 (-1.1; 3.7)
≥12 years	-	7.83 (4.17)	8.27 (4.91)	7.90 (4.85)	0.07 (-1.3; 1.4)
Number of sensors used, mean (SD)					
Total	-	6.40 (1.36)	7.50 (2.86)	14.74 (5.81)	8.34 (7.4; 9.3)
HbA1c <7.5%	-	6.32 (1.37)	6.86 (1.76)	13.35 (4.47)	7.03 (5.9; 8.2)
HbA1c ≥7.5%	-	6.46 (1.36)	8.05 (3.46)	15.86 (6.51)	9.4 (7.9; 10.9)
<12 years	-	6.63 (1.17)	6.90 (2.15)	14.73 (5.83)	8.1 (6.5; 7.8)
≥12 years	-	6.28 (1.44)	7.83 (3.15)	14.75 (5.83)	8.47 (7.3; 9.7)

SD = standard deviation; VAS = Visual Analogue Scale; HbA1c = Glycosylated Haemoglobin; CI = Confidence Interval.

Appendix 5. Multivariate Mixed Regression Model for Effectiveness Measures and Adherence

Table 1. Multivariate Mixed Regression Model for Effectiveness Measures

	Self-reported severe hypoglycaemia events				Severe hypoglycaemic events in the clinical history				Visual analogue scale (EQ-5D-Y)						Knowledge of diabetes treatment		Diabetes Treatment Satisfaction Questionnaire					
Variable	**Patients with hypoglycaemia (Yes/No)** Total sample (n=156)		**Number of self-reported events** Total sample (n=156)		**Patients with hypoglycaemia (Yes/No)** Total sample (n=156)		**Number of self-reported events** Total sample (n=156)		Total sample (n=156)		HbA1c <7.5% (n=68)		HbA1c ≥7.5% (n=88)		Total sample (n=156)		**Perceived hyperglycaemia** Total sample (n=156)		**Perceived hypoglycaemia** Total sample (n=156)		**Satisfaction with treatment** Total sample (n=156)	
	OR (95%CI)	*P*	β (95%CI)	*P*	OR (95%CI)	*P*	β (95%CI)	*P*	B (95%CI)	*P*	B (95%CI)	*P*	B (95%CI)	*P*	B (95%CI)	*P*	B (95%CI)	*P*	B (95%CI)	*P*	B (95%CI)	*P*
Time																						
M12 (ref: M0)	0.82 (0.35; 1.96)	.659	-0.37 (-0.62; -0.11)	**.004**	1.47 (0.32; 6.77)	.617	0.77 (-0.06; 1.60)	.069	-1.40 (-4.97; 2.16)	.440	-1.33 (-4.17; 1.51)	.359	-6.03 (-9.66; -2.41)	**.001**	0.45 (-0.17; 1.08)	.154	-0.08 (-0.50; 0.34)	.721	-0.23 (-0.70; 0.24)	.331	3.11 (0.99; 5.23)	**.004**
Duration of T1DM	1.01 (0.89; 1.15)	.850	-0.01 (-0.14; 0.12)	.922	0.97 (0.81; 1.18)	.806	-0.05 (-0.24; 0.14)	.587	-0.74 (-1.29; -0.19)	**.008**	-0.32 (-0.99; 0.35)	.348	-1.05 (-1.86; -0.24)	**.011**	0.01 (-0.08; 0.09)	.851	-0.003 (-0.06; 0.05)	.915	-0.005 (-0.07; 0.06)	.870	0.05 (-0.18; 0.29)	.650
Presence of comorbidities	0.81 (0.33; 1.98)	.641	0.26 (-0.60; 1.12)	.556	0.81 (0.26; 2.50)	.710	0.27 (-0.83; 1.38)	.624	0.87 (-2.91; 4.64)	.652	2.42 (-1.78; 6.63)	.259	-1.04 (-6.98; 4.89)	.731	0.02 (-0.52; 0.57)	.930	-0.005 (-0.43; 0.42)	.980	0.02 (-0.36; 0.41)	.91	-0.52 (-2.15; 1.11)	.534
Age group: ≥12 years (ref: <12 years)	0.56 (0.22; 1.42)	.221	-0.15 (-1.04; 0.75)	.745	1.32 (0.39; 4.44)	.651	0.32 (-0.87; 1.50)	.599	-3.11 (-6.99; 0.78)	.117	-3.84 (-8.61; 0.94)	.115	-2.82 (-8.49; 2.83)	.327	-0.09 (-0.67; 0.48)	.705	-0.05 (0.48; 0.38)	.819	-0.002 (-0.38; 0.37)	.99	-0.02 (-3.24; 0.76)	.980
Baseline HbA1c group: ≥7.5% (ref: HbA1c <7.5%)	0.41 (0.15; 1.17)	.097	-0.57 (-1.40; 0.26)	.176	2.17 (0.53; 8.88)	.280	1.54 (0.31; 2.77)	**.014**	-1.93 (-5.98; 2.11)	.349					-1.27 (-1.89; -0.65)	**<.001**	1.06 (0.60; 1.52)	**<.001**	-0.12 (-0.57; 0.33)	.593	-1.24 (-1.34; 4.22)	.225
Time*Baseline HbA1c Group (ref: M0 & HbA1c <7.5%)																						
M12 & HbA1c ≥7.5%	2.69 (0.81; 8.96)	.108	0.30 (-0.08; 0.68)	.117	2.01 (0.34; 11.68)	.437	-0.44 (-1.33; 0.45)	.333	-4.61 (-9.44; 0.21)	**.061**					-0.06 (-0.90; 0.78)	.892	-0.11 (-0.70; 0.48)	.703	0.16 (-0.46; 0.78)	.615	1.44 (-1.34; 4.22)	.310
Intercept	0.78 (0.27; 2.23)	.641	-0.78 (-1.74; 0.17)	.107	0.03 (0.004; 0.19)	**<.001**	-4.32 (-5.97; -2.67)	**<.001**	90.50 (86.13; 94.87)	<.001	90.44 (85.92; 94.96)	<.001	88.92 (83.96; 93.88)	<.001	12.43 (11.78; 13.07)	**<.001**	2.98 (2.49; 3.46)	**<.001**	2.29 (1.84; 2.74)	**<.001**	26.80 (24.80; 28.81)	**<.001**

CI = Confidence Interval; HbA1c = Glycosylated Haemoglobin; M = Months; OR = Odds Ratio; ref = reference.

Table 2. Multivariate Mixed Regression Model for Adherence

Variable	Sensor usage time, %		Number of scans per day		Number of sensors used					
	Total sample (n=156)		Total sample (n=156)		Total sample (n=156)		HbA1c basal <7.5% (n=68)		HbA1c basal ≥7.5% (n=88)	
	B (95%CI)	*P*	B (95%CI)	*P*	B (95%CI)	*P*	B (95%CI)	*P*	B (95%CI)	*P*
Time										
M6 (ref: M3)	1.82 (-3.31; 6.98)	.487	-0.25 (-1.41;0.92)	.678	0.49 (-0.58; 1.56)	.367	0.51 (-0.37; 1.39)	.255	1.59 (0.48; 2.70)	**.005**
M12 (ref: M3)	6.42 (1.12; 11.72)	**.018**	0.30 (-0.91; 1.51)	.625	6.96 (5.85; 8.06)	**<.001**	6.97 (6.06; 7.87)	**<.001**	9.37 (8.25; 10.50)	**<.001**
Duration of T1DM	-1.02 (-1.77; -0.27)	**.008**	-0.08 (-0.29; 0.13)	.468	-0.06 (-0.20; 0.07)	.363	-0.11 (-0.25; 0.04)	.152	-0.03 (-0.24; 0.18)	.804
Presence of comorbidities	0.53 (-4.61; 5.66)	.840	-0.69 (-2.14; 0.75)	.348	-0.35 (-1.27; 0.56)	.453	-0.25 (-1.16; 0.66)	.585	-0.39 (-1.92; 1.14)	.617
Age group: ≥12 years (ref: <12 years)	-7.93 (-13.19; -2.66)	**.003**	-3.92 (-5.40; -2.43)	**<.001**	0.39 (-0.55; 1.33)	.417	0.03 (-0.98; 1.05)	.952	0.69 (-0.77; 2.14)	.354
Baseline HbA1c group: ≥7.5% (ref: HbA1c <7.5%)	-4.59 (-10.71; 1.53)	.142	-1.92 (-3.52; -0.31)	**.019**	0.12 (-1.04; 1.29)	.836				
Time*Baseline HbA1c Group (ref: M3 & HbA1c <7.5%)										
M6 & HbA1c ≥7.5%	0.38 (-6.58; 7.33)	.915	0.43 (-1.14; 2.01)	.590	1.09 (-0.36; 2.54)	.141				
M12 & HbA1c ≥7.5%	-1.35 (-8.48; 5.77)	.710	0.35 (-1.28; 1.97)	.676	2.41 (0.93; 3.90)	**.001**				
Intercept	89.10 (82.9; 95.3)	**<.001**	13.0 (11.32; 14.68)	**<.001**	6.19 (5.04; 7.33)	**<.001**	6.39 (5.34; 7.44)	**<.001**	6.13 (4.77; 7.49)	**<.001**

CI = Confidence Interval; HbA1c = Glycosylated Haemoglobin; M = Months; ref = reference.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5-6
		(*b*) Describe any methods used to examine subgroups and interactions	5-6
		(*c*) Explain how missing data were addressed	5-6
		(*d*) If applicable, explain how loss to follow-up was addressed	5-6
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	Apex1
		(c) Summarise follow-up time (eg, average and total amount)	7
Outcome data	15*	Report numbers of outcome events or summary measures over time	8

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	8 8 NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9
Discussion			
Key results	18	Summarise key results with reference to study objectives	10-11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10-11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.