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The Role of Health Technology Assessment in the Adoption of New Technologies in Diabetes Care: A Review of HTA Reports on Freestyle Libre

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Abstract

Aims: This study aimed to identify all Health Technology Assessment (HTA) reports published by HTA bodies assessing FreeStyle Libre and consider how differences in methodologies contribute to variation in decision-making.

Methods: The literature search conducted in October 2018 targeted 158 HTA body websites in 45 countries. Data were extracted and results were analysed under four themes to assess clinical and economic evidence, engagement with stakeholders and conclusions and recommendations.

Results: This analysis included 17 HTA reports. Despite uncertainties in the evidence, a majority concluded FreeStyle Libre reduces the frequency and time in hypoglycaemia and improves patient satisfaction compared to self-monitoring blood glucose (SMBG). Across ten HTAs that considered patient and healthcare professional (HCP) feedback, there was strong support for the adoption of FreeStyle Libre. Of 3 HTA bodies that conducted cost-effectiveness, two concluded FreeStyle Libre is cost-effective and one that it was cost-effective amongst patients with high test frequencies. In 5 that conducted budget impact analysis, all concluded FreeStyle Libre is more expensive than SMBG and 3 noted FreeStyle Libre may be cost-saving amongst patients with a high-test frequency. Methodologies varied widely in respect to the approach to quality assessment, the assessment of early evidence and how stakeholder feedback is incorporated.

Conclusion: Different methodologies led to variation in conclusions. Despite this most concluded that compared to SMBG, FreeStyle Libre reduces the frequency and time in hypoglycaemia, and is likely cost-effective or cost saving in certain patient populations. The HTA reports that HCP and patient groups support adoption of FreeStyle Libre.

Keywords: Health Technology Assessment Review, FreeStyle Libre, Diabetes

Highlights

The challenges to conducting HTA in medical devices are widely acknowledged. HTA bodies apply different methodologies to conducting HTA in medical devices which leads to variation across HTA bodies conclusions and recommendations.

This review provides a comprehensive summary of all HTAs published on FreeStyle Libre by HTA bodies and considers how differences in HTA methodology contributed to variation in decision-making.

This analysis provides interesting insights into the methodological differences that appeared to contribute the most to variation in conclusions and recommendations across the HTA reports assessing FreeStyle Libre at different time points. These included: the approach to quality assessment, the consideration of early evidence, the type of evidence reviewed outside of RCTs, assessment of the economic case and consideration of stakeholder feedback. This raises some interesting questions for the future of HTA of medical devices which are considered in our discussion.

Introduction

Health Technology Assessment (HTA) is a process intended to inform decisions regarding the adoption of new innovations within healthcare systems. HTA typically involves the evaluation of clinical and economic evidence, but methodologies and the depth of the assessment will vary depending on the objectives [1]. Appraising randomised controlled trials (RCT) has traditionally been the focus of HTA, however a broader perspective of value is increasingly applied and different types of evidence are considered [2]. Many HTA processes now incorporate healthcare professional (HCP) and patients' feedback, recognising that experiential knowledge can contribute to a more comprehensive assessment [3]. Similarly, real world evidence (RWE) is increasingly used to fill evidence gaps where clinical trial data is limited or to consider local populations [4]. Best practice guidelines [5,6] have reduced variation in the way evidence is appraised; however, these do not specify the objectives of HTA and the type of evidence that should be considered. As HTA processes consider different types of evidence to varying degrees, conclusions and recommendations will inevitably differ.

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Differences in how HTA processes assess medical devices further contribute to this variability. Drummond et al., discuss medical device-specific challenges [7]. The medical device regulatory process is less rigorous than for pharmaceuticals; the evidence available when medical devices come to market may be less robust. Also, blinding patients or HCPs in clinical studies may be impossible. Furthermore, where a medical device is used to diagnose or monitor patients, it can be difficult to disaggregate the value of information provided from the clinical benefit of subsequent treatment.

The time at which HTA bodies assess evidence also contributes to variation [8]. Conducting HTA prematurely to improve patient care or drive efficiencies is associated with risk if the evidence is uncertain or has not yet been published. Delaying HTA may delay adoption, discourage innovation, postpone patients' benefits, and inhibit the opportunity to learn about medical devices in clinical practice.

Some HTA bodies assess medical devices under separate programs to accommodate these differences. Despite a growing consensus about their need, medical device-specific HTA programs are rare [9].

The FreeStyle Libre™ system (FreeStyle Libre) presents an interesting case study to consider different HTA processes and decision-making. FreeStyle Libre is a novel sensor-based, flash continuous glucose monitoring (CGM) system, which continuously measures glucose levels in a patient's interstitial fluid. In most countries FreeStyle Libre is indicated for use in adults and children (age 4 and older) with type 1 or type 2 diabetes mellitus (T1DM/T2DM) as well as pregnant women, for those who require insulin to control their blood glucose and are advised to monitor their glucose levels multiple times per day [Multiple daily insulin therapy, including pump users (MDI users)] to avoid the potentially serious consequences of hypo- or hyperglycaemia. The current standard method for monitoring is finger-prick testing (self-monitoring of blood glucose, SMBG), which is usually carried out several times per day. Clinical benefits have been demonstrated in two RCTs, IMPACT [10] in T1DM MDI and REPLACE [11] in T2DM MDI. Compared to SMBG, FreeStyle Libre offers a wide range of clinical and economic benefits [12] including the facilitation of better self-monitoring, reducing time in hypoglycaemia, increasing time in normal glucose range and improving quality of life and patient satisfaction and has been described by HAS as a rare "breakthrough technology".= [13].

The primary objective of the present study is to identify all HTA reports published by HTA bodies that have assessed FreeStyle Libre. The assessment methods, conclusions and recommendations will be summarised to enable comparisons and differences to be highlighted. This is intended to help decision-makers understand how the evidence for FreeStyle Libre has been assessed by different HTA bodies at different stages of evidence generation. A secondary objective of the analysis was to further understand how different medical device HTA methodologies contribute to variation in decision-making.

Materials and Methods

Grey literature search

The literature search aimed to identify all FreeStyle Libre HTA reports produced by HTA bodies, since CE approval in 2014. The review targeted HTA reports produced by HTA bodies in 45 countries where FreeStyle Libre had a market authorisation in October 2018. Inclusion criteria did not specify a date or language restriction. Further details on inclusion criteria are described in Supplementary Table 1.

A manual search of 158 HTA body websites was conducted in October 2018 (Supplementary Table 2), using pre-defined search-terms (Supplementary Figures 1 and 2). Searches were run using the Google search function on each website, executed in English and in local language where applicable. In addition to hand-searching, literature searches were run in the Centre for Reviews and Dissemination (CRD) [14] database using the same search terms. The results of the search strategy were reviewed by local market experts and cross-checked with a published literature review [15] to ensure no relevant HTA reports were omitted.

Data analysis

Data were extracted using a template capturing details of the HTA appraisal processes, the type of evidence reviewed, the outcomes reported, stakeholder feedback and the conclusions and recommendations from each report. Data was extracted by one reviewer and cross-checked by a second as well as a local market expert. The results were analysed under four themes: (1) assessment of clinical evidence; (2) assessment of economic evidence; (3) engagement with stakeholders; and (4) conclusions and recommendations. The results reported in our analysis reflect the data reported in each HTA report, supplemented by local knowledge. For example, where there were aspects of the HTA body's method that were not reported in the final HTA report but were known by our review team this was reported. The HTA reports were not assessed for risk of bias because all HTA reports produced by HTA bodies are assumed to be objective.

Results

Study overview

In total 17 HTA reports were included in this analysis. Further details of the search results are reported in Supplement 1. Three HTA reports were published by North American bodies and the remainder were published by European bodies, as detailed in Table 1. Most HTAs reviewed only FreeStyle Libre; however, the European network for health technology assessment (EUnetHTA) [16] and Washington State [17] reviewed FreeStyle Libre alongside other CGM devices. All HTAs considered FreeStyle Libre in both T1DM and T2DM MDI populations and most included both adults and children. SMBG was the primary comparator in all evaluations, with the exception of a HTA by the Zorginstituut Nederlands (ZiN) [18]. The primary objective of ZiN HTA was to consider if the technical accuracy of FreeStyle Libre was similar to real-time CGMs (rt-CGM). All HTA reports included an assessment of the clinical evidence and all except the reports by HAS [19], NICE [20], EUnetHTA [16] and Regione Lombardia [21] considered economic evidence.

Assessment of clinical evidence

In all HTA reports, the assessment of the clinical evidence focused mainly on RCTs, as detailed in Table 2. Figure 1, illustrates the timelines for when the FreeStyle Libre HTA reports and key clinical and economic FreeStyle Libre manuscripts were published. This highlights differences between HTA bodies in terms of how they considered unpublished data. Four HTAs were completed prematurely, before the results of IMPACT and REPLACE had been published. HAS [19] appraised the results of IMPACT [10] and REPLACE [11] prior to manuscript publication. In contrast Agència del Qualitat I Avaluació Sanitàries de Catalunya (AQuAS) [22], SESCS [23] and CADTH [24] did not appraise the results of REPLACE [11], however SESCS [25] updated their HTA report after the results of REPLACE had been published. Figure 1 also highlights the timeline at which further key evidence on FreeStyle Libre was published, including 12 month data from IMPACT

Agency	Country	Region	Year	FreeStyle Libre only?	Population	Comparator	Clinical Evidence	Economic Evidence	Recommendation on Reimbursement
AQuAS [22]	Spain	Regional	2016	Yes	T1/T2 Adult & children	SMBG	Yes	Yes	No - out of scope**
HAS [19]	France	National	2016	Yes	T1/T2 Adult & children	SMBG	Yes	No	Yes
SESCSa [23]	Spain	Regional	2016	Yes	T1/T2 Adult & children	SMBG	Yes	Yes	Yes
SESCSb* [25]	Spain	Regional	2017	Yes	T1/T2 Adult & children	SMBG	Yes	Yes	Yes
CADTH [24]	Canada	Regional	2017	Yes	T1/T2 Adult & children	SMBG	Yes	Yes	No - out of scope**
HTAG [36]	Ireland	National	2017	Yes	T1/T2 Adult & children	SMBG	Yes	Yes	Yes
NICE [20]	England	National	2017	Yes	T1/T2 Adult & children	SMBG	Yes	No	No - out of scope**
NIPH [29]	Norway	National	2017	Yes	T1/T2 Adult & children	SMBG	Yes	Yes	No - out of scope**
Regione Lombadia [21]	Italy	Regional	2017	Yes	T1/T2	SMBG	Yes	No*	Yes
TLV [34]	Sweden	National	2017	Yes	T1/T2 Adult & children	SMBG	Yes	Yes	No - out of scope**
Washington State [17]	USA	Regional	2017	No	T1/T2 Adult & children	SMBG	Yes	Yes	No - out of scope**
EUnetHTA [16]	NA	Pan-European	2018	No	T1/T2 Adult & children	SMBG	Yes	No	No - out of scope**
HIS [35]	Scotland	National	2018	Yes	T1/T2 Adult & children	SMBG	Yes	Yes	Yes
INESSS [30]	Canada	Regional	2018	Yes	T1/T2 Adult	SMBG	Yes	Yes	Yes
INFARMED [39]	Portugal	National	2018	No	T1/T2 Adult & children	SMBG	Yes	Yes	Yes
HTW [31]	Wales	National	2018	Yes	T1/T2 Adult & children	SMBG	Yes	Yes	Yes
ZIN [18]	Netherlands	National	2018	Yes	T1/T2 Adult & children	rt-CGM & SMBG	Yes	No	Yes

Table 1: Overview of Included Health Technology Assessment Reports.

*Narrative discussion on the economic and financial impact but does not report any costs or asess economic data

**Out of scope of the HTA process to make a recommendation on reimbursement

Abbreviations : AQuAS: Agència del Qualitat I Avaluació Sanitàries de Catalunya; CADTH: Canadian Agency for Drug and Technologies in Health; EUnetHTA: European Network of Health Technology Appraisal; HAS: Haute Autorité de Santé; HIS: Health Improvement Scotland; HTAG: Health Technology Assessment Group; HTW: Health Technology Wales; INESSS: Institut national d'excellence en santé et en services; NA: not applicable; NICE: National Institute of Health and Care Excellence; NIPH: Norwegian Institute of Public Health; r-t CGMs: real-time continuous glucose monitoring; SESCS: Servicio de Evaluación y Planificación, Canarias; SMBG: self monitoring blood glucose; TLV: Tandvårds-och läkemedelsförmånsverket; Wasington State : Washington State Health Care Authority. ZIN: Zorginstituut Nederland.

[26], outcome data in paediatric patients [27], results from real world studies [28] and the findings of an economic analysis [12].

All HTA reports present similar clinical outcomes from the RCTs. Evidence synthesis was rarely applied due to population heterogeneity. EUnetHTA [16] converted means to medians and presented the results of both RCTs [10,11] on a forest plot. The Norwegian Institute of Public Health (NIPH) [29] report was the only HTA to pool the results of the RCTs in a meta-analysis. This was against the advice of clinical experts and population heterogeneity was acknowledged as a limitation. Most of the HTAs also reported patient and safety outcomes from the RCTs as detailed in Table 2.

Five HTA reports [Servicio de Evaluación y Planificación, Canarias (SESCS) [23,25], NIPH [29], Washington State [17], EUnetHTA [16] and (Institut national d'excellence en santé et en services) INESSS [30]] used a quality assessment tool, as detailed in Table 2. The Health Technology Wales (HTW) report [31] did not directly use an assessment tool but references the EUnetHTA [16] report which did. Where a grading tool was applied, the RCTs were assessed using the Cochrane risk of bias [32] or GRADE [33] and rated as moderate or low quality or as having a high risk of bias.

Where an assessment tool was not used, most of the HTA reports commented on study quality. Here the conclusions were mixed, ranging from NICE [20] describing the RCTs as "good quality" [20], the Tandvårds-och läkemedelsförmånsverket (TLV) noting a moderate to high degree of uncertainty [34] and Regione Lombardia assessing the evidence as poor [21].

All HTA reports described areas of uncertainty. The limitations discussed included lack of efficacy in HbA1c, the clinical utility of reduced time or frequency of glycaemia, lack of blinding, issues with the study protocol or limitations in the way data was analysed or reported. These are detailed in Supplementary Table 3.

Where a formal assessment tool was applied, the lack of blinding appeared to be the primary reason for an unfavourable rating. Risk of bias due to lack of blinding was also highlighted by HTA bodies that did not use an assessment tool including (NICE) [20], HIS [35] and TLV [34] but these HTA bodies acknowledged that this was an unavoidable challenge to conducting trials with this type of medical device.

Five HTA reports [HAS [19], NICE [20], CADTH [24], ZiN [18] and the TLV [34]] reviewed accuracy studies, as detailed in Table 2. The outcomes reported included concordance with Parkes and Clarke error

Agency	Man.'s Submission*	Cond-ucted LR?	RCTs Reviewed		RCT Outcomes reported by Health Technology Assessment body			Assessment			
			IMPACT	REPLACE	Clinical	QoL/PRO	Safety	Used assessment tool?	Conducted meta -analysis?	Reviewed other publications?	Reviewed RWE?
AQuAS [22]	Not reported*	Unclear, search strategy not described in HTA report*	Yes	Yes	Time in hypoglycaemia/ day; Nocturnal hypoglycaemia; Time in hyperglycaemia; Glycaemic variability; HbA1c; Monitoring frequency	DTSQ and DQoL	AEs, SAEs, withdrawal due to AE	Not reported*	No	Comparison study with CGM	No
HAS [19]	Yes	Yes, but search strategy not described in HTA report	Yes	Yes	Time in hypoglycaemia/day; HbA1c reduction; Tolerability; Monitoring frequency	DTSQ, DQoL	AEs, SAEs, withdrawal due to AE	Not reported*	No	2 accuracy studies (Bailey et al, BEAGLE)	No
SESCSa [23]	No	Yes	Yes	No	Time in hypoglycaemia/day; Time in hyperglycaemia, Glycaemic variability; Level of HbA1c; Metabolic variables	DTSQ, DQoL, HFS, DDS,	AEs, SAEs, device related AEs	Cochrane risk of bias	No	No / Not reported	No
SESCSb [25]	Yes	Yes, updated prior SLR	Yes	Yes	Time in hypoglycaemia/day; Time in hyperglycaemia, Glycaemic variability; Level of HbA1c; Metabolic variables	DTSQ, DQoL, HFS, DDS,	AEs, SAEs, device related AEs	Cochrane risk of bias	No	No / Not reported	No
CADTH [24]	No	Yes, non-systematic	Yes	No	Change in hypoglycaemia; Time in hypoglycaemia/day; Monitoring frequency	Patient satisfaction and overall treatment satisfaction	Serious device related AEs	Not reported*	No	3 non-randomised studies & 5 accuracy studies	No
HTAG [36]	Yes	Unclear, search strategy not described in HTA report*	Yes	Yes	Various measures of hypoglycaemia and time in range; Monitoring frequency	Not reported	Not reported but comments on safety profile	Not reported*	No	No / Not reported	No
NICE [20]	Yes	Yes	Yes	Yes	Hypoglycaemia; Hypoglycaemic events per day; HbA1c; Monitoring frequency. Sub-group analysis considered: Time in euglycemic range; Length of time the sensor; Time in hypoglycaemia	Satisfaction: significant compared to SMBG	AEs, SAEs, device related AEs	Not reported*	No	3 studies	No
NIPH [29]	Yes	Yes	Yes	Yes	HbA1c; Time in range: glucose 3.9-10 mmol/L; Time in range: < 3.9 mmol/L; Events: <3.9 mmol/L; time in Glucose <3.1 mmol/L at night; Events: hypoglycaemic events at night; time in Glucose < 3.1 mmol/L within 24 h; Events Glucose < 3.1 mmol/L within 24 h; time with Glucose > 10.0	QoL discussed but does not report results by RCT	AEs, SAEs, device related AEs	Cochrane risk of bias & GRADE	Yes, against advice of clinical experts	Not reported*	Not reported*

Regione Lombadia [21]	Yes, but not reported	Unclear, search strategy not described in HTA report*	Yes	Yes	Time spent by the patient with a blood sugar lower than 70 mg/dL; Number and duration of hypoglycaemia events; HbA1c	QoL discussed but does not report results by RCT	AEs, SAEs, withdrawal due to AE	Not reported*	No	Not reported*	Not reported*
TLV [34]	Yes	Unclear	Yes	Yes	Time in hypoglycaemia/ day; Number of hypoglycaemias/day; Number of nightly hypoglycaemias; Number of serious hypoglycaemias during the study period	DQoL & Patient satisfaction	Not reported*	Not reported*	No	8 non-randomised studies reviewed	Yes
Washington State [17]	Yes, but not reported	Yes	Yes	Yes	Change from baseline in HbA1c; Hypoglycaemia hours per day Number of events;	DTSQ, DQoL, DDS,	AEs, SAEs, device-related AEs and withdrawal due to AE	GRADE	No	Not reported*	Not reported*
EUnetHTA [16]	Yes	Yes	Yes	Yes	Outcomes converted from median to mean and presented on forest plots HbA1c Time spent in target glycaemic range; Time spent in hyperglycaemia; Time spent in hypoglycaemia; Number of Hypoglycaemia events; Monitoring frequency	DTSQ and DQoL	AEs, SAEs, device-related AEs	Cochrane risk of bias & GRADE	No; but results displayed on forest plots	3 single arm studies, and 12 month follow up of REPLACE	Not reported*
HIS [35]	Yes, but not reported	Appears to use EUnetHTA SLR and ran further searches to identify economic studies	Yes	Yes	Time spent in hypoglycaemia using the surrogate outcome of sensor glucose values <3.9 mmol/L (70 mg/dL) per 24 hour period; Rate of hypoglycaemic events <3.1 mmol/L; Events <2.5 mmol/L (45 mg/ dL) per day and over night; Hyperglycaemia > 10 mmol/L; hours per day spent in hyperglycaemia > 13.3 mmol/L; Time in 3.9 – 10 mmol/L	DTSQ and DQoL	AEs, SAEs, device-related AEs	Not reported*	No	Not reported*	Not reported*
INESSS [30]	Yes	Yes	Yes	Yes	Time in hypoglycaemia/day; HbA1c; Number of hypoglycaemias/day; Frequency of glucose measurements; r Resource utilisation	DTSQ and DQoL	AEs, SAEs, device-related AEs	GRADE	No	Unspecified number of non-randomised studies	Yes

INFARMED [39]	Yes	Unclear, search strategy not described in HTA report*	Yes	Yes	Time in hypoglycaemia/ hours/day; Time in hyperglycaemia/ hours/day; "All hypoglycaemia measures" with 6-month; Maintenance of HbA1c levels Identical doses of insulin glycaemic variability indexes	Not reported	Not reported*	Not reported*	No	Not reported*	Not reported*
HTW [31]	Yes, but not reported*	Yes	Yes	Yes	Frequency and duration of biochemical hypoglycaemia Frequency of SMBG testing	DTSQ and DQoL	AEs, SAEs, device-related AEs	No, considers quality assessment conducted by EUnetHTA	No	A sub-group analysis of data from the IMPACT trial	Not reported*
ZIN [18]	No	Yes	No	No	Not applicable	Not applicable	Not applicable	Not reported*	No	9 studies that reported technical accuracy	Not reported*

Table 2: Assessment of Clinical Studies, by Health Technology Assessment Report.

* Not reported in the final published HTA report; Unclear if this was complete and undocumented. Refers to if the manufacturer was asked to submitted evidence or answer questions as part of the HTA process

AE: Adverse Events; AQuAS: Agència Del Qualitat I Avaluació Sanitàries de Catalunya; CADTH: Canadian Agency for Drug and Technologies in Health; DDS: Diabetes Distress Scale; DTSQ: Diabetes Treatment Satisfaction Questionnaire; DQoL: Diabetes Quality of Life; EUnetHTA: European Network of Health Technology Appraisal; GRADE: Grading of Recommendations, Assessment, Development and Evaluations; HAS: Haute Autorité de Santé; HIS: Health Improvement Scotland; HTAG: Health Technology Assessment Group; HTW: Health Technology Wales; HbA1c: Haemoglobin A1c; INESSS: Institut National d'excellence en santé et en services; Man.: Manufacturer; NICE: National Institute of Health and Care Excellence; NIPH: Norwegian Institute of Public Health; RWE: Real world evidence; SAE: Serious adverse events; SESCS: Servicio de Evaluación y Planificación, Canarias; TLV: Tandvårds-och läkemedelsförmånsverket; Washington State: Washington State Health Care Authority. ZIN: Zorginstituut Nederland.

grid and MARD. Quality assessment was not applied and all five HTA reports concluded that the studies suggest that the measuring accuracy of FreeStyle Libre is acceptable according to established standards. CADTH [24], HAS [19], NICE [20], TLV [34] and EUnetHTA [16] also considered evidence from non-randomised studies which reported similar clinical outcomes as the RCTs. INESSS [30] and TLV [34] reviewed RWE to consider the clinical utility of frequent glucose monitoring.

Assessment of economic evidence

Six HTA reports produced by SESCS [23,25], Washington State [17], HTW [31] AQuAS [22], CADTH [24] and Health Improvement Scotland (HIS) [35] reviewed published economic evidence, details of which are reported in Supplementary Table 4.

Three HTA reports, produced by SESCS [23], NIPH [29] and the TLV [34] appraised a cost utility analysis (CUA) submitted by the manufacturer. All three submissions used the CORE diabetes model (CDM) and shared similar characteristics. Further details of the models submitted by manufacturers are provided in Supplementary Tables 5 and 6.

The HTA reports' conclusions on the manufacturer's models were mixed. SESCS [23] concluded that the results should be interpreted with caution because of model parameter uncertainty, the NIPH [29] were unable to draw conclusions due to the model's lack of transparency and the TLV [34] concluded that the manufacturer's submission may have overestimated the clinical utility but agreed with the assumption that FreeStyle Libre was associated with a utility gain and therefore likely to be cost-effective.

Seven HTA reports, produced by AQuAS [22], Health *Technology Assessment* Group (HTAG) [36], NIPH [29], the TLV [34], HIS [35], INESSS [30] and HTW [31] reported the results of an economic analysis produced or modified by the HTA bodies, as detailed in Table 3. All of these were conducted from a health service perspective and the time horizons were between 1-5 years, with the exception of two CUAs [34,35] which applied a lifetime time horizon. The TLV's [34] CUA applied assumptions based on the literature and the HIS [35] CUA extrapolated data from IMPACT [10] and REPLACE [11]. The HTW analysis [31] applied assumptions from a published FreeStyle Libre cost calculator [12].

The results of the HTA bodies' economic analyses were mixed and are reported in Table 3. AQuAS [22], HTAG [36] and INESSS [30] reported that FreeStyle Libre is not cost-saving in an aggregate population, but may be cost-saving in populations that had a high test frequency. The NIPH [29] reported that FreeStyle Libre is more expensive in T1DM MDI but could be cost-saving in T2DM MDI populations. The CUA analysis developed by HIS [35] reported that FreeStyle Libre was cost-effective at the current willingness-to-pay threshold of £20,000 per quality adjusted life year gained (QALY) gained. Similarly, the TLV [34] reported a cost per QALY below the generally accepted willingness-to-pay threshold in Sweden of SEK 700,000 (€ 68,278 at January 2019 exchange rate) [37].

Engagement with stakeholders

Eight HTA reports produced by HAS [19], SESCS [23], HTAG [36], NICE [20], NIPH [29], Regione Lombardia [21], HIS [35], and INESSS [30] reported consultations with HCP. EUnetHTA [16] also consulted with HCPs but the findings were not reported in the final HTA report. The consultation approach varied by HTA body and included focus groups, invitation to comment and submission of letters as detailed in Table 4.

Where HCP feedback on the clinical or patient was described, it was largely in favour of FreeStyle Libre. HCPs that contributed to the HAS's HTA report [19] concluded that FreeStyle Libre was likely to result in public health benefit due to the expected reduction in diabetes related complications and severe hypoglycaemia [38]. Similarly the TLV report [34] noted that HCPs advised that a reduction of events and time in hypoglycaemia has significant clinical benefit. A HCP in Ireland [36] commented that they believed FreeStyle Libre improved the consultation process by providing a clinically actionable result.

In addition to clinical and patient benefits some HTA processes asked HCPs to review aspects of methodology. HIS [35] asked HCPs to validate the model assumptions and the NIPH [29] asked HCPs to comment on the methods and assessment applied in their HTA report.

Eight HTA reports included feedback from patients, as described in Table 3. AQuAS [22] reviewed patient blogs, SESCS [23], NICE [20] NIPH [29] and HAS [19] consulted with patient associations, Regione Lombardia [21] and HIS [35] reviewed submissions from patient groups, EUnetHTA [16] and INESSS [30] conducted focus groups and HTW [31] considered patient feedback reported in other HTAs.

Patient feedback was consistently positive across all HTA reports. The benefits of FreeStyle Libre included personal convenience and providing greater flexibility to manage their illness [30]. Patients reported that FreeStyle Libre helped to remove some of the many limitations and restrictions caused by diabetes [29] and was described as life-changing [35]. Comments in the NIPT report [29] highlighted that as T1/T2DM MDI are chronic diseases, even a small improvement in their daily routines would have a large impact over their lifetime.

Specific needs of some populations were also considered by patient associations, including people in jobs where finger-prick testing is not

Agency	Type of Analysis	Model perspective	Time horizon	Comparators	Base case results	Sensitivity analysis	Conclusions
AQuAS [22]	CEA & BIM	Health care payer	1 year	SMBG	At 3 tests /day: the ICER is €42,052.15 / QALY	One-way, varying number of tests	FSL is cost neutral when compared to 17 or 18 SMBG tests/day, which is considered an unrealistic scenario
					At 6 tests /day: ICER is € 33,221.51/QALY		FSL is cost effective (ICER between €21,000 and €24,000) in patients with ≥ 10 determinations of glucose per day.
					At 9 tests per/day: ICER is € 24,390.86/ QALY		
					Cost-effectiveness is achieved (ICER<€ 24,000) at 6 tests/day, a reduced price of € 48.91		
HTAG [36]	Manufacturer's BIM, modified by agency	Health care payer	1 year	SMBG	Cost per patient / year increases by €62.60 or €980 in best and worst case scenarios respectively	Considers best and worst-case scenarios	There is insufficient evidence to support the claim that the FSL could yield savings to the health service
NIPH [29]	Manufacturer's BIM, modified by agency	Health care payer	5 years	SMBG	NIPH budget impact in T1DM:	None reported	The NIPH's budget impact model indicates FSL is more expensive in T1DM and cost-saving in T2DM.
					Total ***added*** cost after 5 years of NOK 913 million or, average annual cost of NOK 186 million		
					NIPH budget impact in T2DM:		
					Total ***decrease*** in cost after 5 years of NOK 433 million, or average annual cost-saving of NOK 91.7 million		
					NIPH budget impact in T1DM & T2DM:		
					Total ***added cost*** after 5 years of NOK 480 million, or average annual added cost of NOK 94 million		
TLV [34]	Supplementary analysis to manufacturer's CUA	Health care payer	Lifetime	SMBG	Difference in cost (FSL vs SMBG): SEK 132,404	Conducted a number of one-way sensitivity analyses on the following	The cost per QALY gained is SEK 389,424 for people with T1DM and these results are expected to be transferable to T2DM populations with similar insulin use*
					Difference in QALYs: 0.34		
					Cost per QALY gained SEK 389,424		
HIS [35]	CUA developed by agency	Health care payer	Lifetime	SMBG	The ICER for FSL compared with SMBG ranged from £2,459 to £12,340 per QALY in T1DM and from £4,498 to £18,125 in T2DM, depending on the modelling approach considered.	One-way and PSA	FSL is likely to be cost-effective compared to SMBG

INESSS [30]	CMA, developed by agency	Health care payer	1 year	SMBG	FSL was more expensive than SMBG in all populations.	PSA	In all populations considered the cost of using FSL is higher than the average cost of SMBG; FSL is therefore a nonefficient option
					Average annual cost of FSL and SMBG per patient, was respectively estimated as:		The PSA showed that FSL has zero probability of being efficient for a population with T2DM and near-zero probability of being efficient for a population with T1DM (0.15% and 0.3% respectively). However, it reports a 17% probability that FSL is efficient for patients using at least 8 test strips daily.
					$2,717 and $803, for patients under insulin treatment;		
					$2,748 and $1,080 for patients with T1DM under intensive insulin treatment;		
					$2,717 and $895 for patients with T2DM under intensive insulin treatment;		
					$2,748 and $2,397 for patients under intensive insulin treatment using more than 8 test strips daily.		
HTW [31]	Reviewed the HIS model and built a Budget impact model	Health care payer	5 years	SMBG	5 Year Budget Impact: £11,847,390 if 5.6 SMBG tests are assumed and savings over £9,485,828 if 10 SMBG tests per day is assumed	None reported	FSL may be cost-saving in patients that test more than 10 times per day

Table 3: Health Technology Assessment Bodies Economic Analysis.

AQuAS: Agència del Qualitat I Avaluació Sanitàries de Catalunya; BIM: Budget Impact Model; CUA: Cost-effectiveness analysis; CUA: Cost utility analysis; CMA: Cost minimisation analysis; FSL:the FreeStyle Liber System; HIS: Health Improvement Scotland; HTAG: Health Technology Assessment Group; HTW: Health Technology Wales; INESSS: Institut national d'excellence en santé et en services; NIPH: Norwegian Institute of Public Health; RCT: Randomised Controlled Trials; SMBG: Self-monitoring blood glucose; PSA: Probabilistic sensititivity analysis; T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus; TLV: Tandvårds-och läkemedelsförmånsverket; QALY: Quality adjusted life year.

practical [29], pregnant women, people with highly variable blood glucose, people with poor peripheral circulation, older people and hospital in-patients who need regular monitoring [20]. Feedback in the EUnetHTA [16] and INESSS [30] reports highlight that FreeStyle Libre may be particularly beneficial to children where SMBG is painful and disruptive if glucose monitoring is required overnight.

HTA bodies' conclusions and recommendations

The conclusions on the clinical efficacy of FreeStyle Libre were relatively consistent. A majority of HTA reports concluded that, compared to SMBG, FreeStyle Libre is more effective at reducing events and time in hypoglycaemia and improving patient satisfaction. However, conclusions typically highlighted that there were uncertainties in the evidence base and note that there is no evidence of an effect on HbA1c.

Many of the HTA reports called for more research to address uncertainties around the clinical efficacy of FreeStyle Libre. Specifically, there were calls to assess the long-term efficacy and the impact on sub-groups such as children and young people as well as to conduct further real-world studies in local populations. A study of FreeStyle Libre in paediatric patients [27] was published in July 2018, however this was after the majority of the HTA reports had been published, as illustrated in Figure 1. There were mixed conclusions regarding the economic case for FreeStyle Libre, as illustrated in Figure 2, with the balance of evidence suggesting the FreeStyle Libre is likely to be cost-effective but unlikely to be cost-saving.

Eight HTA reports [HAS [19], SESCS [23,25], HTAG [36], Regione Lombodia [21], HIS [35], INESSS [30], INFARMED [39] and HTW [31] concluded with a statement on reimbursement, all of which made either a partial, conditional or unrestricted recommendation, as illustrated in Figure 2. Where a recommendation was not made, this was out of scope of the assessment process to do so. Further details of the HTA bodies' conclusions and recommendations are described in Supplement 1.

Discussion

The present study has shown that there is a lot of heterogeneity across the assessment methodologies, which led to variation in their conclusions. At a European level work is on-going coordinated by the European Commission to foster more cooperation and develop common methodologies and to develop common tools to reduce variation [40]. Our analysis has shown similarities in selecting studies and reporting the results of RCTs, which mostly followed best practice guidelines [5]. The methodological differences that contributed to variation in conclusions and recommendations included: the approach to quality assessment, the consideration of early evidence, the type of evidence reviewed outside of RCTs, assessment of the economic case and consideration of stakeholder feedback.

Agency	Healthcare Professionals (HCP) Involvement	Patient Involvement
AQuAS [22]	None reported	Did not explicitly consult patient groups but considered patient feedback reported on social networks and civil society
HAS [19]	Yes, consulted with a leading national HCP association	Consulted with national patient diabetes association
SESCSa/b* [23,25]	Consulted with 3 HCPs and 1 person from the Spanish Medicines Agency	One representative from a patient association reviewed the document
CADTH [[24]	Not reported**	Not reported**
HTAG [36]	Considered letters from 7 HCPs working in the area of diabetes in Ireland	Not reported**
NICE [20]	Consulted with 4 HCPs that regularly use FreeStyle Libre with patients; 1 was a self-user	A patient group provided comments on user experience
NIPH [29]	Consulted with 6 HCPs (consultants or professors) who were asked to provide feedback on draft documents	Representatives from a patient group are listed as contributors but involvement is unclear
Regione Lombadia [21]	Considered written letters from 6 HCPs	Three contributions were received respectively from the coordination of patient associations
TLV [[34]	Not reported**	Not reported**
Washington State [17]	Not reported**	Not reported**
EUnetHTA [16]	Feedback from 2 HCPs reported on website but not reported in the HTA report	A focus group (with individual patients) was held in Croatia, one for adults and one for children with informal caregivers (i.e. two separate focus groups were held). Also considered feedback from Patient Group Submission templates which were sent to the Inter-national Diabetes Federation European Region, Brussels and Diabetes Scotland, Scotland.
HIS [35]	A panel of HCPs were requested to review the model and validate assumptions and estimates used.	A patient organisation submission was received from Diabetes Scotland
INESSS [30]	Considered feedback from a panel meeting with 8-12 HPs	Considered feedback from a panel meeting with 8-12 health patients and carers
INFARMED [39]	Not reported**	Not reported**
HTW [31]	Consulted with HCPs but feedback not reported	Consulted with a patient organisation and the Diabetes Scotland submission to the HIS HTA
ZIN [18]	HCP bodies consulted in the process, but feedback not explicitly reported	Patient groups were consulted in the process, but feedback is not explicitly reported

Table 4: Approach to Stakeholder Engagement, by Health Technology Assessment Report.

* No additional stakeholder data considered in updated HTA by SESCS; ** Not reported in the final published HTA report; Unclear if this was complete and undocumented

AQuAS: Agència del Qualitat I Avaluació Sanitàries de Catalunya; EUnetHTA: European Network of Health Technology Appraisal; HAS: Haute Autorité de Santé; HCP healthcare Professionals; HIS: Health Improvement Scotland; HTAG: Health Technology Assessment Group; HTW: Health Technology Wales; INESSS: Institut national d'excellence en santé et en services; NICE: National Institute of Health and Care Excellence; NIPH: Norwegian Institute of Public Health; PICO: Population Intervention Comparator Outcomes; SESCS: Servicio de Evaluación y Planificación, Canarias; TLV: Tandvårds-och läkemedelsförmånsverket; Wasington State : Washington State Health Care Authority. ZIN: Zorginstituut Nederland.

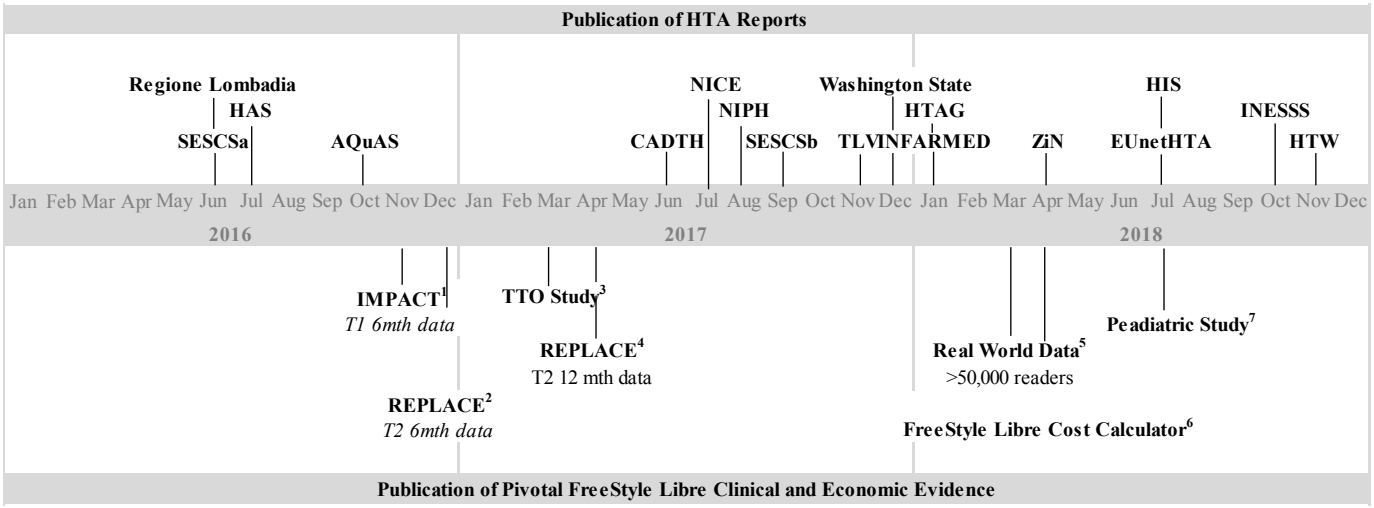
Differences in the approach to assessing risk of bias led to variation in the conclusions regarding the robustness of the evidence base. Many of the limitations of IMPACT [10] and REPLACE [11] highlighted within the HTA reports were unavoidable, and inherent problems of HTA in medical devices. Blinding patients or assessors to FreeStyle Libre was not possible given the nature of the device, and the provision of additional clinical visits was necessary to facilitate smooth adoption.

Where the quality of the FreeStyle Libre RCTs was appraised using the GRADE quality assessment tool [33], the evidence was mostly rated as low and lack of blinding appeared to be a primary reason. Arguably studies should not be marked down on this dimension where blinding is unethical or impossible to implement because ranking evidence as low irrespective of the soundness of planning, data collection, analysis, and scientific interpretation makes it difficult for decision-makers to consider study quality in the context of what is possible.

Where the HTA reports did not apply a formal assessment tool, a pragmatic approach was applied. This involved listing aspects of the study design and providing commentary on whether decisions that might have adversely affected study quality were avoidable, and the level of uncertainty that the study design introduced [HAS [19], TLV [34], NICE [20] and HIS [35]]. This method is arguably more appropriate for assessing medical devices because it helps decision-makers differentiate between intentional and unavoidable risk of bias.

Only two of the HTA reports [NICE [20] and HAS [19]] assessed FreeStyle Libre under a medical device-specific program. These HTA bodies appeared to draw more positive conclusions regarding the evidence base, with NICE referring to the RCTs as being of good quality and HAS rating the evidence as ASA III; a rating of ASA I, II or III has been achieved by only 12% of medical devices assessed by HAS between 2013 and 2017 [40]. These HTA bodies' drew on broader forms of evidence, including HCP and patient feedback, when considering areas of uncertainty. Accounting for MD specific issues in this way are likely to be more useful to decision-makers tasked with making trade-offs between investments in alternative medical devices.

While NICE and HAS were the only HTA bodies to assess FreeStyle Libre under medical device-specific programs, other bodies applied pragmatic approaches to evidence appraisal that accounted for the medical device-specific issues in their consideration of the risk of bias in the study protocol [NICE [20] TLV [34], HIS [35], HTAG [36]]. The TLV [34] and HIS [35]], also took pragmatic approaches to considering the uncertainty in utility benefit in their economic models, seeking HCP feedback on plausible ranges and testing these in sensitivity analyses.



Abbreviations: AQuAS: Agència del Qualitat I Avaluació Sanitàries de Catalunya; CADTH: Canadian Agency for Drug and Technologies in Health; EUnetHTA: European Network of Health Technology Appraisal; HAS: Haute Autorité de Santé; HIS: Health Improvement Scotland; HTAG: Health Technology Assessment Group; HTW: Health Technology Wales; INESSS: Institut national d'excellence en santé et en services; Mth: month; NICE: National Institute of Health and Care Excellence; NIPH: Norwegian Institute of Public Health; SESCS: Servicio de Evaluación y Planificación, Canarias; TLV: Tandvårds-och läkemedelsförmånsverket; TTO: Time trade off study Washington State Health Care Authority. ZIN: Zorginstituut Nederland

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2) Haak, T., Hanaire, H., Ajjan, R., Hermanns, N., Riveline, J.P., & Rayman, G. (2016). Flash Glucose-Sensing Technology as a replacement for blood glucose monitoring for the management of insulin-treated type 2 diabetes: A multicenter, open-label randomized controlled trial. *Diabetes Therapy* ,

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7) Campbell FM, Murphy NP, Stewart C, Biester T, Kordonouri O. Outcomes of using flash glucose monitoring technology by children and young people with type 1 diabetes in a single arm study. Pediatr Diabetes. 2018;1–8

Figure 1: Timeline for Publication of Health Technology Assessment Reports and Pivotal FreeStyle Libre Manuscript.

This suggests that a pragmatic approach to conducting HTA of medical device that accounts for medical device-specific issues and considers early evidence in the context of the stage of product development may be more helpful to decision-makers tasked with the question of whether to adopt new medical devices.

This review has also demonstrated wide variability in the type of evidence considered, particularly with respect to stakeholder feedback. The approach to collecting feedback and influence this had on conclusions varied widely. Patient or HCPs' feedback was frequently acknowledged in the closing remarks and recommendations of many of the HTAs and appeared to help bridge the gap where there were uncertainties in the evidence. As stakeholder feedback appears to be an increasingly important aspect of HTA, HTA bodies may need to consider the optimal approach for collecting and utilising this type of evidence.

As many of the conclusions regarding the clinical, patient and economic benefit were broadly similar, variation in reimbursement recommendations appear to be a linked to the HTA bodies approach to managing uncertainty associated with early adoption. The HTA report by HAS [19] was the first to make a broad, unrestricted recommendation. This decision was based on achieving a clinical evidence rating of ASA III after appraisal of published and unpublished evidence and HCP feedback that recognised high unmet need in this area, as well as the clinical value of improved glycaemic control [38-40]. In contrast SESCS [23,25] also assessed FreeStyle Libre before REPLACE was published and as this review did not appraise the REPLACE results, it made a restricted recommendation. SESCS [25] reviewed the evidence again, after the results from REPLACE were published, and made a broader recommendation that included T2DM MDI users and concluded that the potential benefit of the device outweighs its risks, noting high acceptance of the device by patients. Other HTA bodies made unrestricted recommendations but proposed some form of risk-sharing agreement [21,36]. In contrast, HTW [31] made a restricted recommendation to only reimburse FreeStyle Libre where cost-savings were achievable and noted that a broader reimbursement would be considered when the evidence was more developed (i.e., coverage with evidence development).

These contrasting decisions reflect different approaches to sharing the risk of early adoption. In addition to HTA bodies conclusions, there

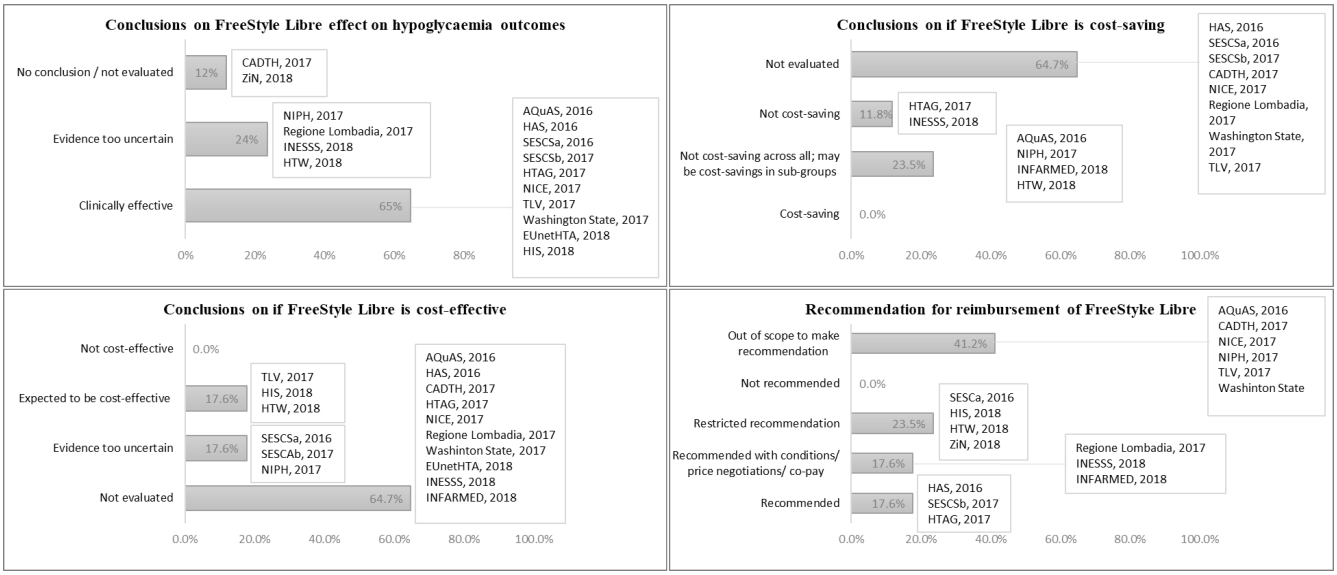

Figure 2: Health Technology Assessment Reports Conclusions & Recommendations.

Abbreviations: AQuAS: Agència del Qualitat I Avaluació Sanitàries de Catalunya; CADTH: Canadian Agency for Drug and Technologies in Health; EUnetHTA: European Network of Health Technology Appraisal; HAS: Haute Autorité de Santé; HIS: Health Improvement Scotland; HTAG: Health Technology Assessment Group; HTW: Health Technology Wales; INESSS: Institut national d'excellence en santé et en services; Mth: month; NICE: National Institute of Health and Care Excellence; NIPH: Norwegian Institute of Public Health; SESCS: Servicio de Evaluación y Planificación, Canarias; TLV: Tandvårds-och läkemedelsförmånsv; Washington State Health Care Authority. ZIN: Zorginstituut Nederland.

are also broader factors that will contribute to payor's decisions to reimburse medical devices, including budgetary and political pressures. The present study suggests that there are opportunities for HTA bodies, payers and manufacturers to work together to develop solutions that both support early adoption and help to manage the risks associated with uncertain evidence, maximizing the balance of risk-benefit to both patients and society.

Conclusion

This review provides a comprehensive summary of all HTAs published on FreeStyle Libre by October 2018 which were used to compare and contrast different HTA processes for medical devices in 45 countries where FreeStyle Libre had market authorisation at the time of this paper redaction. FreeStyle Libre is now reimbursed in 33 of these countries, as detailed in Supplementary Table 1.

While the HTA reports differed in terms of their remit and methodologies, they shared a common goal to objectively assess the evidence and consider if FreeStyle Libre represents good value to patients, physicians and payers. Despite uncertainties in the evidence base, a majority of HTA bodies concluded that compared to SMBG, FreeStyle Libre reduces the frequency and time in hypoglycaemia and improved patient satisfaction. Across all HTAs that considered patient and HCP feedback, there was strong support for the adoption of FreeStyle Libre.

The majority of HTA reports that considered cost-effectiveness evidence reported that FreeStyle Libre is a cost-effective intervention. There was greater uncertainty regarding whether FreeStyle Libre is cost-saving, with the balance of evidence suggesting that FreeStyle Libre is more expensive but may be cost-saving amongst patients with a high-test frequency.

This review has also demonstrated wide variation across HTA processes and highlighted some important issues that should be considered by HTA bodies as the role of HTA of medical devices evolves. Aspects that contributed to variation that warrant further consideration in future programs aimed at developing common methodologies include the approach to quality assessment, the assessment of early evidence and incorporating stakeholder feedback. This review suggests that some of the challenges to conducting HTA in medical devices can be overcome by applying pragmatic approaches to adjusting HTA processes. These include more appropriate use of quality grading tools that adjust for what is feasible in the context of testing medical devices and drawing on broader sources of evidence to fill evidence gaps.

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