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Health Technology Assessment (HTA)

HTA Report v3.0

Title	**Self-measurement of blood glucose in patients with non-insulin treated diabetes mellitus type 2**
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Technology	Self-measurement of blood glucose

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Executive Summary:

Background: The value of SMBG in non-insulin treated T2DM patients is unclear. We performed a full-HTA to assess patient benefit and cost-effectiveness, as well as ethical and socio-legal aspects of SMBG.

Research question: What is the effect on HbA1c and cost-effectiveness of adding SMBG to usual care in adult non-insulin treated T2DM compared to usual care without SMBG?

Methods: We performed literature searches, quantitative and qualitative evidence synthesis. For our economic analysis we used a diabetes simulation modelling approach (UKPDS-OM2).

Results: We retrieved 2,882 records and included 24 RCTs and 10 economic studies.

Comparing several SMBG protocols of the intervention groups with no, less frequent or less structured SMBG leads to a statistically significant HbA1c decrease of -0.29%-points (95%CI: -0.40 to -0.18; 23 RCT; low certainty of evidence). Based on our model, this HbA1c decrease translates into small but statistically significant reductions in several diabetes-related complications. SMBG leads to a modelled increase in life expectancy of 18 days (95%-CI: 13 to 25) with increased total costs of CHF 2,910 (95%-CI: 2,750 to 3,021) over a time horizon of 40 years. Based on this small health benefit and on the low total additional costs, SMBG has a formal ICER of CHF 65,023 per QALY gained.

In studies without any SMBG in the control group, the HbA1c decrease is more pronounced (-0.33%-points; 95%CI: -0.45 to -0.21; 17 RCT). SMBG is more cost-effective with the ICER decreasing to CHF 41,078 per QALY gained.

SMBG was associated with a significantly increased probability of detecting hypoglycaemia (RR 2.10; 95%-CI: 1.41 to 3.15; 4 RCTs with high proportions of patients treated with sulfonylureas; episodes of mild and non-severe nature; moderate quality of evidence). SMBG increases the probability of «being in HbA1c target» (RR 2.78; 95%-CI: 1.46 to 5.31; 5 RCTs; low quality of evidence). No relevant differences were seen in the RCTs for psychological outcomes (e.g. depressive symptoms, quality of life, patient satisfaction with treatment [moderate to high certainty evidence]), morbidity, mortality, and unexpected events and harms [low certainty of evidence]).

Only 1 in 4 non-insulin treated patients with T2DM in Switzerland bought SMBG test strips in 2017 and most of those buying test strips bought substantially less than the maximum amount reimbursed. A total elimination of test strip coverage for non-insulin treated T2DM patients would lead to net savings of CHF 6.09 million per year (budget impact) from a Swiss healthcare payers' perspective.

Organisational issues of relevance are proper documentation of SMBG results by patients (possibly supported by smartphone applications) and adequate handling of SMBG by vulnerable groups (e.g. elderly persons with visual dysfunction or limited motor skills). From a *socio-legal perspective*, restricting the provision of blood glucose test strips to a certain group of patients must be based on objective reasons (WZW criteria on the basis of the HTA), but may under no circumstances be unilaterally at the expense of vulnerable groups. From an *ethical perspective*, the evidence base to question current best practices appears to be scant: SMBG is associated with a slight improvement of HbA1c levels, but it is unclear to which extent this result is also clinically relevant. At a psychological level, SMBG allows a higher degree of participation of patients in the care process, but there is no clear evidence about improved psychological outcomes in the target population.

Conclusions: SMBG shows modest efficacy on HbA1c levels in RCTs. Model calculations based on this finding suggest a resulting small increase in life expectancy. However, since this has so far not been evaluated in clinical studies, this outcome cannot be confirmed nor rebutted.

Zusammenfassung (max. 250 Wörter):

Hintergrund: Der Nutzen der Blutzuckerselbstmessung ("self-measurement of blood glucose", SMBG) bei nicht mit Insulin behandelten Typ-2-Diabetes(T2DM)-Patienten ist unklar. Wir haben ein Full-HTA durchgeführt, um den Patientennutzen, die Wirtschaftlichkeit, sowie die ethischen und sozio-rechtlichen Aspekte von SMBG zu untersuchen.

Forschungsfrage: Wie wirkt sich SMBG zusätzlich zur Standardbehandlung bei nicht mit Insulin behandeltem T2DM bei Erwachsenen im Vergleich zur Standardbehandlung ohne SMBG auf den HbA1c-Spiegel aus, und wie ist die Kostenwirksamkeit.

Methoden: Wir haben Literaturrecherchen, sowie quantitative und qualitative Evidenzsynthesen durchgeführt. Für die wirtschaftliche Analyse haben wir eine Diabetes-Simulation (UKPDS-OM2) modelliert.

Ergebnisse: Wir haben aus 2'882 Suchergebnissen 24 RCTs und 10 ökonomische Studien eingeschlossen.

Der Vergleich verschiedener SMBG-Protokolle der Interventionsgruppen mit keinem, weniger häufigem oder weniger strukturiertem SMBG führt zu einer statistisch signifikanten Senkung von HbA1c um -0.29% (95%-CI: -0.40 bis -0.18; 23 RCT; geringe Evidenzqualität). Basierend auf unserem Modell führt diese HbA1c-Abnahme zu einer geringen, aber statistisch signifikanten Verringerung mehrerer diabetesbedingter Komplikationen. SMBG führt, modelliert über einen Zeitraum von 40 Jahren, zu einer Verlängerung der Überlebensdauer um 18 Tage (95%-CI: 13 bis 25) und zu einer Zunahme

der Gesamtkosten um CHF 2'910 (95% -CI: 2'750 bis 3'021). Aufgrund dieses geringen Gesundheitsnutzens und der geringen zusätzlichen Gesamtkosten, wurde für SMBG ein ICER von CHF 65'023 pro gewonnenem QALY berechnet.

In Studien ganz ohne SMBG in der Kontrollgruppe ist die Senkung von HbA1c ausgeprägter (-0.33%; 95%-CI: -0.45 bis -0.21; 17 RCT), der ICER sinkt entsprechend auf CHF 41'078 pro gewonnenem QALY. SMBG wurde mit einer signifikant erhöhten Wahrscheinlichkeit für den Nachweis einer Hypoglykämie assoziiert (RR 2.10; 95%-CI: 1.41 bis 3.15; 4 RCTs mit hohem Anteil von mit Sulfonylharnstoffen behandelten Patienten; leichte und nicht schwere Episoden; mässige Evidenzqualität). SMBG erhöht die Wahrscheinlichkeit, «im angestrebten HbA1c-Bereich zu sein» (RR 2.78; 95%-CI: 1.46 bis 5.31; 5 RCTs; geringe Evidenzqualität).

In den RCTs wurden keine relevanten Unterschiede für psychologische Outcomes festgestellt (z.B. depressive Symptome, Lebensqualität, Patientenzufriedenheit mit der Behandlung [mässige bis hohe Evidenzqualität], Morbidität, Mortalität und unerwartete Ereignisse und Schäden [geringe Evidenzqualität]).

Nur jeder vierte nicht mit Insulin behandelte T2DM-Patient in der Schweiz kaufte 2017 SMBG-Teststreifen, und meist weniger als die maximal erstattete Menge. Eine vollständige Streichung der Rückerstattung von Teststreifen für nicht mit Insulin behandelte T2DM-Patienten würde aus Sicht der Schweizer Krankenkassen zu einer Nettoersparnis von CHF 6.09 Millionen pro Jahr führen (Budget-Impact). Relevante organisatorische Aspekte sind die sorgfältige Dokumentation der SMBG-Ergebnisse durch Patienten (möglicherweise unterstützt durch Smartphone-Apps) und der angemessene Umgang mit SMBG in schutzbedürftigen Gruppen (z.B. ältere Personen mit Sehstörungen oder eingeschränkten motorischen Fähigkeiten). Aus gesellschaftsrechtlicher Sicht muss die Beschränkung des Zugangs zu Blutzucker-Teststreifen für bestimmte Patientengruppen auf objektiven Gründen basieren (WZW-Kriterien / HTA), darf aber keinesfalls einseitig auf Kosten von schutzbedürftigen Gruppen geschehen. Aus ethischer Sicht scheint die Evidenzbasis für die Überprüfung aktueller Best Practices eher gering zu sein: SMBG ist zwar mit einer leichten Verbesserung des HbA1c-Spiegels assoziert, es ist jedoch unklar, inwieweit dieses Ergebnis auch klinisch relevant ist. Auf psychologischer Ebene ermöglicht SMBG eine stärkere Beteiligung der Patienten an der Bewältigung der Krankheit, es gibt jedoch in dieser Zielpopulation keine eindeutigen Hinweise auf verbesserte psychologische Outcomes.

Schlussfolgerungen: SMBG zeigt eine bescheidene Wirksamkeit betreffend HbA1c-Spiegel in RCTs. Modellierungen, die auf diesem Befund basieren, deuten auf eine geringfügige Verlängerung dses Überlebens hin. Da dies jedoch in klinischen Studien bisher nicht evaluiert wurde, kann dieses

Ergebnis weder bestätigt noch widerlegt werden.

Résumé (max. 250 mots):

Contexte : La valeur clinique de l'autosurveillance de la glycémie (ASG) pour les patients souffrant de diabète sucré de type 2 (T2DM) non traités à l'insuline n'est pas connue avec certitude. Nous avons procédé à une évaluation des technologies de la santé (HTA) complète afin d'évaluer les bénéfices pour les patients et le rapport coût-efficacité, ainsi que les aspects techniques et socio-légaux de l'ASG.

Question de recherche : quel effet l'ajout de l'ASG aux soins habituels des patients adultes souffrant de T2DM non traités à l'insuline a-t-il sur l'hémoglobine glyquée (HbA1c) et le rapport coût-efficacité par rapport aux soins ordinaires sans ASG ?

Méthodes : Nous avons procédé à des recherches dans la littérature et opéré une synthèse des données quantitatives et qualitatives. Pour notre analyse économique, nous avons utilisé un modèle de simulation du diabète (UKPDS-OM2).

Résultats : Nous avons recensé 2882 notices bibliographiques et inclus 24 essais randomisés contrôlés (ECR) et 10 études économiques. En comparant plusieurs protocoles d'ASG des groupes d'intervention qui n'ont pas d'ASG, une ASG moins fréquente ou une ASG moins structurée, on constate une baisse statistiquement significative de HbA1c, de -0,29 point de pourcentage (intervalle de confiance (IC) de 95 % : -0,40 à -0,18 ; 23 ECR ; faible niveau de certitude). En s'appuyant sur notre modèle, cette baisse de HbA1c se traduit par des réductions faibles, mais statistiquement significatives, de plusieurs complications liées au diabète. L'ASG conduit à une hausse modélisée de 18 jours dans l'espérance de vie (IC de 95 % : 13 à 25), avec une augmentation totale des coûts de 2910 francs suisses (IC de 95 % : 2750 à 3021) sur une période de 40 ans. Sur la base de ce léger bénéfice pour la santé et sur les faibles coûts totaux supplémentaires, l'ASG présente un rapport coût-efficacité différentiel (ICER) formel de 65 023 francs suises par année de vie pondérée par la qualité (QALY) ajoutée.

Dans les études sans ASG dans le groupe de contrôle, la baisse de HbA1c est plus prononcée (-0,33 point de pourcentage ; CI de 95 % : -0,45 à -0,21 ; 17 ECR). L'ASG est aussi plus rentable : son ICER descend à 41 078 francs suisses par QALY ajoutée.

L'ASG était associée à une hausse importante de la probabilité de détecter une hypoglycémie (RR 2,10 ; CI de 95 % : 1,41 à 3,15 ; 4 ECR avec des proportions élevées de patients traités par sulfonylurées ; épisodes de caractère bénin à non sévère ; qualité modérée des preuves). L'ASG augmente la probabilité « d'atteindre le taux cible d'HbA1c » (RR 2,78 ; CI de 95 % : 1,46 à 5,31 ; 5 ECR ; faible

qualité des preuves).

Aucune différence significative n'a été relevée dans les ECR concernant les conséquences psychologiques (p. ex. symptômes dépressifs, qualité de vie, satisfaction du patient par rapport au traitement [degré de certitude modéré à élevé], morbidité, mortalité, et événements et préjudices inattendus [faible degré de certitude]). Seul un patient sur quatre souffrant de T2DM non traité à l'insuline en Suisse a acheté des bandelettes de test ASG en 2017, et la plupart des acheteurs en ont acheté nettement moins que le montant maximum remboursé. Éliminer totalement la prise en charge des bandelettes de test pour les patients souffrant de T2DM non traités à l'insuline entraînerait une économie nette de 6,09 millions de francs suisses par an (impact budgétaire) du point de vue des payeurs de soins de santé en Suisse.

On peut relever deux enjeux organisationnels : la bonne consignation des résultats de l'ASG par les patients (éventuellement à l'aide d'applications sur smartphone) et l'utilisation adéquate de l'ASG par des groupes vulnérables (p. ex. des personnes âgées avec un dysfonctionnement de la vue ou des capacités motrices limitées). D'un point de vue socio-légal, l'idée de restreindre la mise à disposition de bandelettes de test de la glycémie à un certain groupe de patients doit se baser sur des raisons objectives (critères EAE sur la base de l'ETS), mais ne doit en aucun cas se faire de manière unilatérale aux dépens des groupes vulnérables. D'un point de vue éthique, la base de preuves permettant remettre en cause les bonnes pratiques actuelles semblent limitée : l'ASG est associée à une légère amélioration des niveaux de HbA1c, mais la pertinence clinique de ce résultat n'est pas clairement déterminée. Au niveau psychologique, l'ASG permet un degré de participation plus élevé des patients aux processus de soins, mais il n'y a pas de preuve claire de l'amélioration des résultats psychologiques dans la population cible.

Conclusions : L'ASG montre une efficacité modeste sur les niveaux de HbA1c dans les ECR. Les calculs modélisés qui se basent sur cette conclusion suggèrent une légère augmentation de l'espérance de vie. Cependant, en l'absence jusqu'ici d'évaluations dans le cadre d'études cliniques, ce résultat ne peut pas être confirmé ou infirmé.

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Abbreviations and Acronyms

AF	atrial fibrillation
ARR	absolute risk reduction
CG	control group
CHF	Swiss Francs
CE	cost-effectiveness
CG	control group
CI	confidence interval
CU	cost-utility
CPI	consumer price index
CVD	cardiovascular disease
DDD	defined daily dose
DM	diabetes mellitus
eGFR	estimated glomerular filtration rate
EQ-5D	EuroQol five dimensions questionnaire
ESRD	end-stage renal disease
FDHA	Swiss Federal Department of Home Affairs
FOPH	Swiss Federal Office of Public Health
GIN	Guideline International Network
GP	general practitioner
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
GWB	general well-being
HbA1c	glycated haemoglobin
HD	haemodialysis
HDL	high-density lipoprotein
HTA	Health Technology Assessment
HUI	Health Utilities Index
ICD	International Classification of Disease
ICER	incremental cost-effectiveness ratio
IG	intervention group
IHD	ischemic heart disease
IQR	interquartile range
LDL	low-density lipoprotein
m	million
MI	myocardial infarction
MID	minimal important difference
MiGel	Mittel und Gegenständeliste
MedStat	Swiss Medical Statistics of Hospitals
n	number
N.A.	not applicable
NGC	National Guideline Clearinghouse

NGO	non-governmental organization
NHANES	National Health and Nutrition Examination Survey
NSTEMI	non-ST-elevation myocardial infarction
OAD	oral anti-diabetic medication
OKP	Obligatorische Krankenpflegeversicherung
OLES	organizational, legal, ethical, and socio-cultural dimensions of this HTA
PCG	pharmaceutical cost group
PD	peritoneal dialysis
PICOS	Patients, Intervention, Comparator, Outcome and Study design and type
PROMs	patient-reported outcome measures
PVD	peripheral vascular disease
QALY	quality-adjusted life year
QOL	quality of life
RCT	randomized controlled trial (singular form)
RCTs	randomized controlled trials (plural form)
ROB	risk of bias
RR	relative risk
RQ	research question
SBP	systolic blood pressure
SDSCA	Summary of Diabetes Self-Care Activities Measure
SF-12/36	12-/36-item Short Form Survey
SMBG	self-measurement of blood glucose
SMUG	self-measurement of urine glucose
SR	systematic reviews
STEMI	ST-elevation myocardial infarction
T2DM	type 2 diabetes mellitus
UKPDS	United Kingdom Prospective Diabetes Study
UKPDS-OM2	United Kingdom Prospective Diabetes Study Outcomes Model version 2
WBC	white blood cells
WMD	weighted mean difference
WTP	willingness to pay
WZW	effectiveness, appropriateness, and cost-effectiveness required by social health insurance law (Wirksamkeit, Zweckmässigkeit und Wirtschaftlichkeit)

Objective of the HTA Report

The objective of this Health Technology Assessment (HTA) is the collection and analysis of existing evidence to answer the following research questions in the context of self-measurement of blood glucose (SMBG) in patients with non-insulin treated type 2 diabetes mellitus (T2DM):

– What is the **efficacy** and **safety** of adding SMBG to usual care in non-insulin treated patients with type 2 diabetes compared to usual care without SMBG?

– What is the **cost-effectiveness** of adding SMBG to usual care in non-insulin treated patients with type 2 diabetes compared to usual care without SMBG?

– Which **organizational, legal, ethical and socio-cultural issues** are of relevance from adding SMBG to usual care in non-insulin treated patients with type 2 diabetes compared to usual care without SMBG?

The methodologic steps of each of the three research questions will be presented separately in the following sections of this HTA report.

The study protocol was not registered in advance and is part of the Appendix.

1. Policy Question

Self-measurement of blood glucose (SMBG) by means of glucose test strips is a cornerstone of diabetes management. However, the supposed clinical value of SMBG in non-insulin treated type 2 diabetes patients is debated. In Switzerland, a maximum of 400 test strips per year is reimbursed over the compulsory health insurance in this patient population. This HTA evaluates patient benefits and aspects such as cost-effectiveness of SMBG to inform coverage policy makers.

2. Medical Background

Diabetes mellitus is a chronic disease characterized by the body's inability to produce sufficient insulin and/or properly use insulin, which results in high blood glucose levels. Fasting blood glucose levels up to 100 mg/dL or 5.6 mmol/L, respectively, are considered normal. Approximately 10% of patients with diabetes have type 1 diabetes mellitus, which is the result of little or no insulin being produced by the body. Around 90% of patients with diabetes have type 2 diabetes mellitus (T2DM), which is a metabolic disorder caused by varying degrees of insulin resistance, where the body usually produces insulin but is unable to use it properly. The overall prevalence of diabetes in the adult population in Switzerland has increased from 3.9% to 4.9% between 2006 and 2011. The prevalence is high especially among women (7.93%) and men (11.57%) aged >59 years. In 2011, the incidence in adults in Switzerland was 0.58%.[1] The prevalence of diabetes varies between age groups: 2.1% in people aged 35 to 49, 6.3% in people aged 50 to 64 and 10.5% in people aged 65 and older.[1]

The prevalence of diabetes in European adults reached 7.3% and is even higher globally, reaching 8.5% in 2014. As diabetes is often undiagnosed and studies to assess the number of newly occurring cases are complicated, there are almost no data on true global incidence.[2]

When inadequately managed, diabetes is likely to result in poor glycaemic control. If prolonged, this may lead to diabetes-related complications such as stroke, blindness, renal diseases or myocardial infarction. Control of blood glucose levels to reduce a patient's risk of developing these complications is an important component of diabetes management.[3] Many different teaching and training programs exist addressing the needs of specific population groups and using a broad variety of tools and approaches to enable diabetic patients to participate in their treatment and treatment decisions. In summary, approaches to improve glycaemic control include up-to-date diabetes teaching and education, lifestyle modifications such as weight control, proper nutrition, adequate exercise, and the use of medications such as oral antidiabetic drugs (OAD) and insulin.[2]

[1] https://www.obsan.admin.ch/de/indikatoren/diabetes-mellitus

3. Technology

3.1 Technology Description

Self-measurement of blood glucose (SMBG) is the measurement of blood glucose levels by patients with diabetes in their daily life.[4] Measurements can be performed fasting in the morning, before and/or after meals, or at any other time point as required. SMBG is usually performed using a glucose meter and test strips. SMBG with appropriate number of test strips forms the subject of this HTA. To measure blood glucose levels, patients prick a finger with a lancet device to obtain a blood sample. This sample is applied to a blood glucose test strip inserted into a glucose meter. Results on blood glucose concentration are determined within a few seconds by the glucose meter. Patients can store these results in the glucose meter's electronic memory, an accompanying smartphone application (app) or in a personal logbook.[5] Often glucose levels are not only used to document glucose control, but also to adjust lifestyle, diet, physical activity or drug therapy with the goal of achieving glycaemic control.[4] In all diabetes patients, doctors regularly measure patients' glycated haemoglobin (HbA1c). This laboratory test is used to identify the three-month average plasma glucose concentration and is thus used as an assessment test for glycaemic control. Thus, performing SMBG could lead to an improvement of HbA1c levels and consequently reduce diabetes-related complications.

Today, SMBG is a cornerstone of care for patients with diabetes mellitus type 1 and type 2, who are treated with insulin.[6] However, the use of SMBG in patients with non-insulin treated T2DM is under debate. The improvement of HbA1c levels due to SMBG in this patient group may be small and may not translate into reduced morbidity or mortality.[7-11] Early improvements in glycaemic control could nevertheless lead to clinical benefits in the long run by reducing the incidence of diabetes-related complications. SMBG provides information on the blood glucose levels at the time of testing. This allows to take immediate action, such as preventing hypoglycaemic events. Detection of hypoglycaemia as well as patient empowerment and improved self-management competence are important additional effects of SMBG that should be taken into account.[7]

3.2 Contraindications

No contraindications apply for this technology.

3.3 Alternative Technologies

The alternative to SMBG are 1) no self-measurement of blood glucose and 2) self-measurement of urine glucose (SMUG; as used in some older studies). However, today SMUG is very rarely practiced in Switzerland, if at all.

3.4 Regulatory Status / Provider

The reimbursement of medical devices by social health insurance is determined by the *Mittel und Gegenständeliste* [12] (MiGeL) produced by the Swiss Federal Department of Home Affairs (FDHA). Current regulation limits the number of tests strips reimbursed to patients with T2DM without insulin to a maximum of 400 test strips per year at a maximum of CHF 0.62 per test strip (MiGeL position 21.03.01.01.1). No limitation on the yearly number of reimbursed test strips applies to patients with T2DM using insulin. SMBG also requires a SMBG device (glucose meter) as well as lancets (needles) for a lancing device. An SMBG device will be reimbursed every two years at a maximum price of CHF 43.00(MiGeL position 21.02.01.00.1 for device without lancets, MiGeL position 21.02.03.00.1 for device including lancets.). The maximum reimbursed per lancet amounts to CHF 0.12 per lancet, but there is no limitation on the number of lancets reimbursed (MiGeL position 21.03.05.00.1).

Test strips, lancets and SMBG devices are mainly sold in pharmacies. Additional distribution channels include hospitals and physician offices but also regional diabetes societies. Testing equipment may also be obtained directly from producers and health insurance companies. Tests strips are available from approximately 20 different producers in packages holding 50, 51, 52 or 100 test strips. The average price per test strips in January 2019 was CHF 0.82 and thus above the maximum amount reimbursed per test strip.

Our review of recommendations on use of SMBG in eight selected European countries (Austria, Denmark, France, Germany, Italy, Netherlands, Sweden, and United Kingdom) showed that SMBG was not usually considered an integral part of diabetes care in non-insulin-treated DM (Table A 1). Generally, SMBG was recommended in non-insulin treated T2DM only if T2DM was newly diagnosed, if the antidiabetic therapy was associated with an increased risk of hypoglycaemia, if the patient suffered from concurrent illness or comorbidities, or if the patient did not achieve glycaemic targets. Notable exceptions include Austria, where SMBG was recommended for all patients with DM, and Italy, where even patients managed with dietary and lifestyle changes were recommended to conduct SMBG testing (albeit infrequently).

Reimbursement of SMBG equipment varied across populations with diabetes and across countries, reflecting both different clinical recommendations and differences in health care systems: Most countries for which reimbursement information was identified would not reimburse SMBG equipment for patients

with DM not treated with insulin, except for clearly defined circumstances and often only on prescription. Where reimbursement was possible even for patients with non-insulin-treated DM, reimbursement was restricted to cover only a fixed quantity of diabetes equipment (Table A 1).

4. Systematic Search Strategy

4.1 Databases and Search Strategy

With the support of a medical information specialist, we systematically searched for studies which assessed the effects and costs of adding SMBG to usual care compared to usual care without SMBG on HbA1c in adult non-insulin treated T2DM patients (for inclusion criteria see Table 1, for exclusion criteria see Table A 2 in the Appendix 11.2). We used the following electronic databases (imposing no language restriction): MEDLINE (see Appendix 11.4 for search strategy in OVID Interface), Embase (Embase® interface), PsycINFO and the COCHRANE-Library, including the University of York Centre for Review and Dissemination Library (from 2011 to February 2019, i.e. after the last Cochrane systematic review showing a thorough search strategy; plus update search in February 2019 after the Scoping Report). We also conducted reference screening of the included studies. We used the Cochrane review of 2011 as a reliable source of systematically searched RCTs until 2011 and screened the included RCTs of this review. By this approach, we covered the time period until 2011. From 2011 onwards we performed own systematic searches as reported in the full HTA. The 2011 Cochrane review was part of the non-systematic FOPH pre-scoping references.

Furthermore, one member of the WIG research team conducted a literature search of SMBG-related studies regarding Switzerland in the electronic databases Medline via the interface PubMed and Cochrane. Since a comprehensive search was conducted by the medical information specialist, this subsearch was more restrictive targeted at finding only Swiss studies by using only the title-field for different alternatives (see Appendix 11.3).

Additional searches were done for the efficacy of SMBG:

– International evidence-based guideline recommendations (by using the databases National Guideline Clearinghouse (NGC) and Guideline International Network (GIN) as well as NGO websites of high-income countries with a similar health service provision level as Switzerland like Canada, Australia, USA, UK)

– Ongoing clinical trials (by using clinical trials registry portal (https://clinicaltrials.gov/) and the World Health Organization International Clinical Trials Registry Platform (ICTRP) (www.who.int/trialsearch/).

– Ongoing systematic reviews (by using systematic reviews registry portal PROSPERO)

To gain the best possible understanding regarding the impact of (small) HbA1c changes in the full HTA, we scrutinised suitable publications from the database searches, as well as from other sources (e.g. websites of HTA agencies), that may have used empirical data about the relationship between HbA1c and morbidity/mortality of non-insulin-dependent T2DM, specifically the impact of small HbA1c changes:

– Guidelines of diabetes treatment

– Authoritative summaries of HTA agencies

– RCTs with long term follow-up (concerning the impact of small interventional changes of HbA1c)

– Observational studies (e.g. cohort studies; concerning the natural relationship between HbA1c and morbidity/mortality)

– Economic diabetes models (using such interventional or observational data)

4.2 Inclusion and exclusion criteria

The following inclusion criteria, concerning study designs; participants, interventions, comparators and outcomes, applied for effectiveness and safety issues (i.e. the impact of SMBG on HbA1c and defined secondary outcomes; Table 1). For exclusion criteria see Table A 2 in Appendix.

These inclusion criteria did not apply for the assessment of the relationship between HbA1c and clinical outcomes. For gaining an as good as possible understanding of the impact of (small) HbA1c changes, we accepted any reporting outcome of interest.

4.3 Search of economic studies

The objective of the literature search of economic studies was different than that on the effectiveness of SMBG. In particular, the objective was to obtain an overview of up-to-date published health economic evaluations regarding the use of SMBG in non-insulin treated patients with T2DM. Another objective was to identify a suitable health economic model that could adapted to address the economic issues posed by the FOPH.

Therefore, the systematic literature search by the medical information specialist included also specific search terms for economic studies of relevance for this HTA that were defined in collaboration with this specialist (see search strategy in Appendix 11.4). The publication date was restricted for economic studies from 2011 onwards, as we wanted to find only up-to-date health economics evaluations.

In addition, we performed focussed economic searches in EconLit without time restriction using the search strategy described in Table A 5 in the Appendix 11.5. EconLit entails a wide range of economic studies, allowing the retrieval of relevant studies that might not be included in MEDLINE / Embase or COCHRANE-Library. The retrieved studies are reported in Section 7 on costs, budget impact and cost-effectiveness.

Table 1: Inclusion criteria for efficacy **and safety studies**

	Inclusion criteria for **efficacy** ***and safety:*** **HTA SMBG**
Study design	Randomized controlled trials Observational studies (only for selected purposes)* Any length of follow up; any sample size No language restriction Year of publication: From 2011 to November 2017, i.e. after the last Cochrane systematic review showing a thorough search strategy. Publication status: published journal articles.
Setting	Any study setting (e.g. primary care sector; diabetes care in specialized centres) Geographical study location: high-income countries to ascertain health care services comparable to Switzerland
Population	Diabetes patients with non-insulin treated diabetes mellitus type 2 Age ≥ 18 years; both sexes
Intervention	Blood glucose self-measurement (SMBG; types: non-structured; structured; more intensive [as defined by primary study authors; may include teaching and education as part of a complex intervention]) plus usual diabetes care
Control intervention (comparator)	Diabetes care **without** SMBG (or with non-structured; or less intensive SMBG [as defined by primary study authors])
Outcome measures	**Primary outcomes:** HbA1c (e.g. after 6, 12, 24 months) **Secondary outcomes:** – hyper-/hypoglycaemia (with thresholds as defined by study authors) – HbA1c at the end of follow-up in target range of individual patients – change of medication (e.g. switch to insulin treatment) – morbidity (as defined by study authors; e.g. cardiovascular disease [CVD]; blindness; renal failure; foot problems) – psychological outcomes (as measured by validated instruments; e.g. anxiety; depression) – mortality – health related quality of life (QOL; as measured by validated instruments for general health related QOL [e.g. EQ-5D; SF-12; SF-36; HUI] or by validated instruments for diabetes disease specific hr-QOL) – patient satisfaction with treatment (as measured by study authors), well-being (e.g. W-BQ28), self-efficacy and mastery (e.g. SDSCA self-management performance) – other adverse events or harms (as defined by study authors)

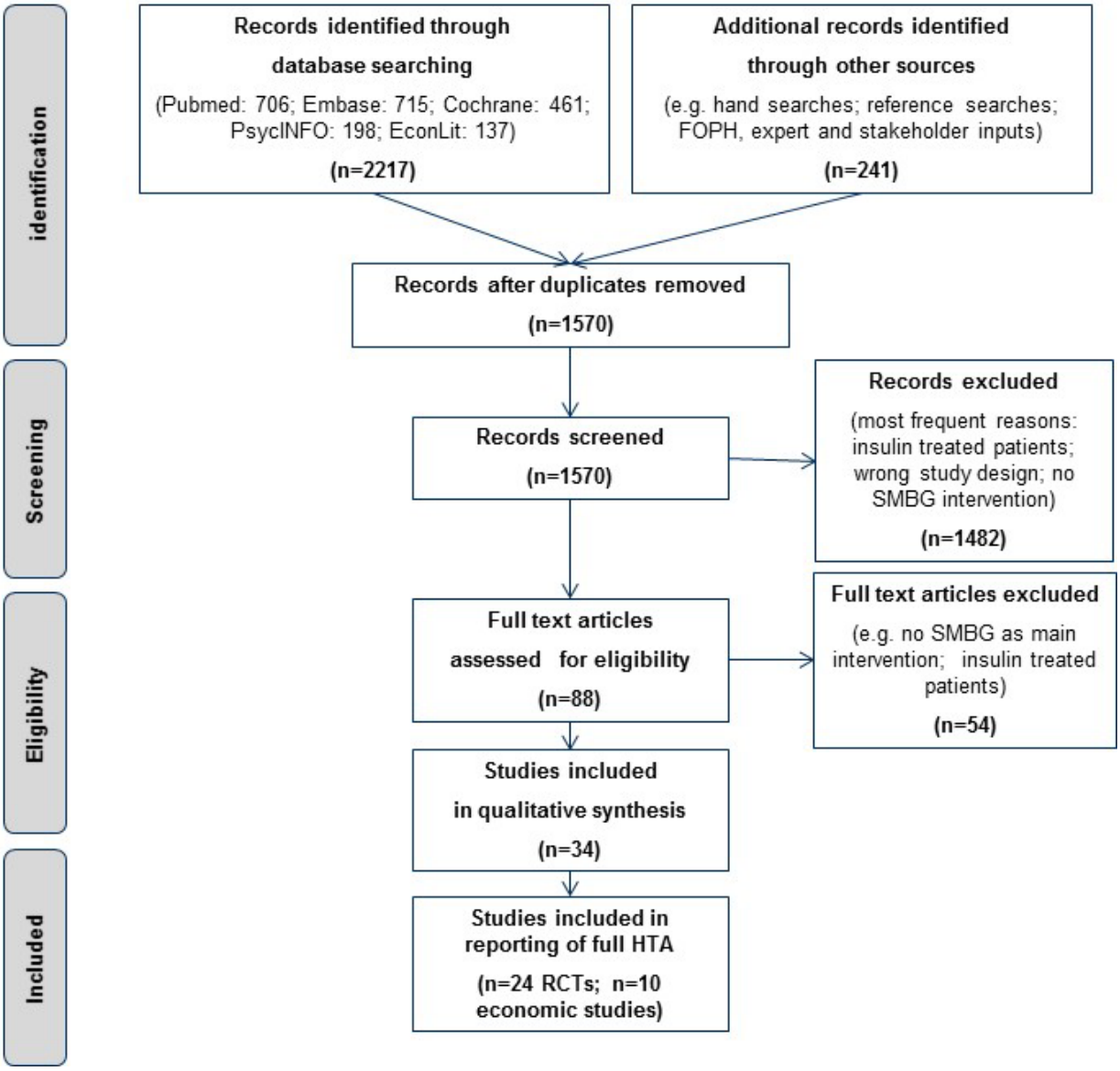
**If RCT do not provide data for (1) some secondary outcomes (observational studies: publication date: >=2004; included in prior systematic reviews) or (2) MID (minimal important difference) of HbA1c or (3) the amount of glucose sticks used*

4.4 PRISMA Flow Diagram

Our searches retrieved 2,882 potentially relevant studies.

The specific results concerning the health-economic studies are reported in Section 7. In the PRISMA flow chart [13] in Figure 1, however, we report the number of efficacy/safety and economic studies together to provide an overview over the total number of retrieved studies.

Figure 1: PRISMA flow diagram of the systematic review



5. Central Research Question(s)

5.1 Central Research Question(s)

Based on our findings in the scoping stage of the HTA, we arrived at the following central research questions. The numbering of research questions (RQ) is according to the numbering of the scoping report V4.1:

RQ1: What is the effect on HbA1c of adding SMBG to usual care in adult non-insulin treated patients with T2DM compared to usual care without SMBG?

RQ2: What is the effect on other secondary outcomes (including harms) of adding SMBG to usual care in adult non-insulin treated patients with T2DM compared to usual care without SMBG?

RQ3: What is the effect on HbA1c of adding structured SMBG to usual care in adult non-insulin treated patients with T2DM compared to usual care with non-structured SMBG?

RQ4: What is the effect on other secondary outcomes (including harms) of adding structured SMBG to usual care in adult non-insulin treated patients with T2DM compared to usual care with non-structured SMBG?

(RQ5 goes with RQ9; RQ5 as formulated in the scoping report: *"Is there any subgroup of T2DM patients which has a benefit from HbA1c changes <0.5%?")*

(RQ6 goes with RQ2; RQ6 as formulated in the scoping report: *"What is the benefit of SMBG for the subgroup of T2DM patients with high risk jobs (e.g. safety concerns for public traffic workers) in reducing hypoglycaemia events?"*

RQ7: What is the number of test strips used per year in adult non-insulin treated patients with T2DM who apply a structured SMBG?

(RQ8 goes with RQ2; RQ8 as formulated in the scoping report: *"What is the benefit of SMBG on self-efficacy of T2DM patients?"*

RQ9: What is the nature of relationship between HbA1c changes and changes in morbidity/mortality in adult non-insulin treated patients with T2DM? (Is there a minimal important difference, MID, in HbA1c change?)

5.2 Patients

Diabetes patients with non-insulin treated diabetes mellitus type 2; adults; both sexes.
We have not excluded studies of populations with low HbA1c values at baseline. This HTA was designed to assess the value of SMBG for all non-insulin T2DM patients, irrespective of baseline HbA1c values. For example, also patients with low baseline HbA1c values are an important group in our HTA, as even a small HbA1c-reduction early on may be important and sustainable for health and the delay of comorbidities.

5.3 Intervention

Blood glucose self-measurement (SMBG)

Types of SMBG include: non-structured; structured; more intensive [as defined by primary study authors; may include teaching and education as part of a complex intervention]

Usual diabetes care is standard of care and part of the intervention

5.4 Comparator

Diabetes care **without** SMBG (or with non-structured; or less intensive SMBG [as defined by primary study authors])

We retrieved some studies using SMUG (self-measurement of urine glucose) as comparator. Thus, we included SMUG as an additional comparator, even though SMUG is not standard of care in Switzerland.

5.5 Outcomes

Primary outcome: HbA1c (e.g. after 6, 12, 24 months)

Secondary outcomes:

– hyper-/hypo-glycaemia (with thresholds as defined by study authors)

– HbA1c at the end of follow-up in target range of individual patients

– change of medication (e.g. switch to insulin treatment)

– morbidity (as defined by study authors; e.g. cardiovascular disease (CVD); blindness; renal failure; foot problems)

– mortality

– psychological outcomes (as measured by validated instruments; e.g. anxiety; depression)

– health related quality of life (QOL; as measured by validated instruments for general health related QOL [e.g. EQ-5D; SF-12; SF-36] or by validated instruments for diabetes disease specific hr-QOL)

– patient satisfaction with treatment (as measured by study authors), well-being (e.g. W-BQ28 psych wellbeing), self-efficacy and mastery (e.g. SDSCA self-management performance)

– other adverse events or harms (as defined by study authors)

5.6 Study design

Randomized controlled trials

Observational studies are only included for selected purposes, if RCTs do not provide data for:

(1) some secondary outcomes (criteria for included observational studies: publication date: ≥ 2004; included in prior systematic reviews), or
(2) observational studies to inform about a minimal important difference (MID) of HbA1c for a patient benefit in clinical outcomes (e.g. diabetes complications), or
(3) data to assess the amount of glucose strip use for SMBG under non-research conditions.

5.7 PICOS-Box

PICOS for RQ 1:

P	Adult diabetes patients with non-insulin treated diabetes mellitus type 2
I	Blood glucose self-measurement (SMBG, as defined by primary study authors) and standard diabetes care
C	Standard diabetes care without SMBG (as defined by primary study authors)
O	Primary Outcome: HbA1c
S	Randomized controlled trials

PICOS for RQ 2:

P	Adult diabetes patients with non-insulin treated diabetes mellitus type 2
I	Blood glucose self-measurement (SMBG, as defined by primary study authors) and standard diabetes care
C	Standard diabetes care without SMBG (as defined by primary study authors)
O	Secondary Outcomes: hyper-/hypo-glycaemia; HbA1c in target range of individual patients; change of medication (e.g. switch to insulin treatment); morbidity; psychological outcomes; mortality; health related quality of life; patient satisfaction with treatment; well-being; self-efficacy and mastery; adverse events or harms
S	Randomized controlled trials (if RCTs do not provide data: observational studies)

PICOS for RQ 3:

P	Adult diabetes patients with non-insulin treated diabetes mellitus type 2
I	Structured blood glucose self-measurement (SMBG, as defined by primary study authors) and standard diabetes care
C	Non-structured SMBG (as defined by primary study authors) and standard diabetes care
O	Primary Outcome: HbA1c
S	Randomized controlled trials

PICOS for RQ 4:

P	Adult diabetes patients with non-insulin treated diabetes mellitus type 2
I	Structured blood glucose self-measurement (SMBG, as defined by primary study authors) and standard diabetes care
C	Non-structured SMBG (as defined by primary study authors) and standard diabetes care
O	Secondary Outcomes: hyper-/hypo-glycaemia; HbA1c in target range of individual patients; change of medication (e.g. switch to insulin treatment); morbidity; psychological outcomes; mortality; health related quality of life; patient satisfaction with treatment; well-being; self-efficacy and mastery; adverse events or harms
S	Randomized controlled trials (if RCTs do not provide data: observational studies)

For RQ 7 and RQ 9 PICOS tables do not apply. A PICOS-box does not apply for RQ9 *("What is the association between HbA1c and morbidity/mortality?"*), as we found no data in the RCTs in the scoping report and non-randomized study types and modelling have to be used.

For our applied pre-specified methodological issues such as Data management, Title and abstract screening, Full text assessment, Data extraction and Risk of bias assessment see the study protocol in the Appendix 11.17.

For our applied pre-specified criteria concerning data synthesis (such as Narrative analysis; Statistical meta-analysis; Subgroup analyses; Meta-regression analysis; Assessment of publication bias) see the study protocol in the Appendix 11.17.

We used the following definitions for different categories of SMBG modes:

- no SMBG: no self-measurement of blood glucose is performed in addition to usual diabetes care (including standard diabetes educational teaching concerning nutrition, activity, psychological and medication issues)
- un-structured SMBG: SMBG with no specifications of frequency and of timing OR specifications only of frequency but not of timing
- structured SMBG: SMBG with specifications of frequency AND timing (which does not necessarily mean to use more test strips) [14]
- more frequent SMBG: SMBG with specifications of only frequency (more frequent compared to a control group (CG) with SMBG)

- more structured SMBG: SMBG with more detailed specifications of frequency and timing (compared to a CG with less structured SMBG)

6. Efficacy, Effectiveness and Safety

Twenty-four RCTs [14-37] fulfilled the inclusion criteria, provided suitable data and were included in our analysis. Two of the 24 trials were cluster-randomised trials.[14 26]

The 24 RCTs reported about n = 6,672 non-insulin treated T2DM patients, all from high-income countries (15 studies from Europe [16-18 20 22-24 26 28 30 31 33-35 37], 6 from the USA [14 19 21 27 29 36], 2 from Japan [25 32] and one multi-country study [15]). Ten [14-16 20 24 25 32-34 36] of 24 RCTs were industry funded; 13 [17-19 21-23 26-31 37] of 24 RCTs were publicly funded, 6 [17-19 22 23 37] of which in combination with industry funding; one study [35] provided no information. Most participants were recruited from endocrinology outpatient clinics (13 RCTs [15 16 22-25 29-34 36]), 10 RCTs [14 18-21 26-28 35 37] included patients from a general practitioner (GP) primary care settings and one RCT [17] provided no information.

Study population sizes varied from n = 23 [19] to n = 1,024 participants [24] (mean: n = 278). The mean age of patients at inclusion was 59.3 (SD 4.1) years (range of means: 49 to 66) with 56% male participants. Duration of diabetes was <1 year in 4 RCTs [23 26 30 31] and >1 year in 19 RCTs.[14-20 22 24 25 27-29 32-37] Ten RCTs [17 18 22 24 29-33 37] included patients treated solely with OAD, while in 11 RCTs [14-16 19-21 27 28 34-36] patients were on OAD or had no diabetes drug treatment (i.e. mixed populations). Follow-up periods were generally short (mean follow up: 10.8 months; range: 4 months to 3 years), but the completeness of follow-up was generally high (median 89%; interquartile range (IQR): 82%-97%).

Mean HbA1c values at baseline varied between 6.6% [31] and 12.1% [27] across studies (median of study values: 8.0%). The aimed frequency of SMBG measurements in the intervention groups across studies was 8.3 (median) measurements per week (IQR: 6 to 12; information from 23 RCTs). The real (performed) frequency of SMBG measurements in the intervention groups across studies was 7 (median) measurements per week (IQR: 5 to 10) with a calculated SMBG frequency compliance rate of about 83% (information from 13 RCTs [14 17 19 20 23 27 28 30-34 36]).

Further details of included RCTs are presented in the Appendix 11.6 (Table A 6).

A variety of different SMBG patterns concerning frequency and timing was applied in the intervention groups of the included RCTs. Control interventions could include “no SMBG”, “un-structured SMBG”, “less frequent SMBG” or “less structured SMBG”. Details of SMBG protocols, as well as aimed frequency of measurements per week and number of SMBG measurements performed are presented in the Appendix (Table A 7). Used devices for SMBG, sometimes for self-measurement of urine glucose (SMUG), in the intervention and control groups are also listed in the Appendix 11.8 (Table A 8).

Risk of bias and certainty of accumulated evidence

If a study described an adequate method in a specific risk of bias domain (e.g. adequate generation of random sequence for randomisation), it was judged as “low risk of bias” in this domain. Description of an in-adequate method was judged as “high risk of bias” and, if incomplete information was given, as “unclear risk of bias”.

Ten [17 18 21-25 28 33 37] of 24 studies provided enough information to conclude that both random sequence generation and allocation concealment was adequately performed (Table 2). Blinding of participants and personnel for SMBG was not possible and formally judged by the review authors as “high risk” (24 of 24 studies). Adequate blinding of outcome assessment (for example, for laboratory tests of HbA1c) was reported in 4 [14 18 32 36] of 24 studies. Attrition bias may have occurred in 6 [24 30 32 34 35 37] of 24 trials with loss to follow-up of more than 20% (a loss of 20% was defined by review authors as a pragmatic threshold to induce clinically relevant bias and pre-specified in the study protocol). For 10 [18 21-24 26 28 32 33 37] of 24 studies a study protocol was available to judge possible reporting bias. In 5 [18 23 26 32 37] of these 10 studies, outcome reporting was not complete and 5 [21 22 24 28 33] of 24 trials were judged as having a low risk of reporting bias. Finally, only 5 [18 21 22 28 33] of 24 studies were judged as having a low risk of bias in at least 4 of 6 assessed domains.

An assessment of bias across studies (publication bias) for HbA1c change was done with a funnel plot (Figure A 4, page 127 in the Appendix 11.9). Visual inspection of the funnel-plot showed some aspect of asymmetry. However, as middle-sized studies with small positive effect (as opposed to no or negative effect) may be missing, this was not interpreted as suspicious for small study effects (Egger’s test: p = 0.16; 23 RCTs).

GRADE assessment

To obtain an overall rating of confidence in estimates of effects, one reviewer applied the GRADE approach and rated the certainty of evidence of effect for relevant outcomes (Cochrane Handbook, Section 11).[38] For the specific question under study, we specified the decision rules for judging the GRADE items as follows: We judged the GRADE item “inconsistency” as serious, if (a) heterogeneity in statistical meta-analysis was at least substantial (i.e. I^2 at least 50 to 90%) and not explained by subgroup analyses; or if (b) evidence synthesis in table format showed effects in both directions (i.e. inconsistency of results) for a relevant number of studies. We judged the GRADE item “indirectness” as serious, if studies showed relevant clinical variability in study populations or SMBG and control interventions. A second reviewer checked the results. Disagreements in GRADE rating were resolved by consensus. The GRADE evidence Table 3 (page 37) was derived using the online tool (https://gdt.gradepro.org).

Table 2: Risk of bias summary table

		Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias (industry funding and recruitment in specialised endocrinology clinics can lead to specific selection bias)
author	year	selection bias	selection bias	performance bias	detection bias	attrition bias	reporting bias	selection bias
Allen[27]	1990	+	?	-	?	+	?	
Barnett[15]	2008	?	+	-	?	+	?	recruitment in endocrinology outpatient clinics; industry funded study
Bosi[24]	2013	+	+	-	?	-	+	recruitment in endocrinology outpatient clinics; industry funded study
Dallosso[26]	2014	?	+	-	-	+	-	
Davidson[36]	2005	?	?	-	+	+	?	recruitment in endocrinology outpatient clinics; industry funded study
Duran[30]	2010	?	?	-	?	-	?	recruitment in endocrinology outpatient clinics;
Farmer[28]	2009	+	+	-	?	+	+	
Fontbonne[34]	1989	?	?	-	?	-	?	recruitment in endocrinology outpatient clinics; industry funded study
Franciosi[33]	2011	+	+	-	-	+	+	recruitment in endocrinology outpatient clinics; industry funded study
Garcia de la Torre[31]	2013	?	?	-	?	+	?	recruitment in endocrinology outpatient clinics;
Guerci[35]	2003	?	?	-	?	-	?	
Harashima[32]	2013	?	?	-	+	-	-	recruitment in endocrinology outpatient clinics; industry funded study
Jaber[29]	1996	?	?	-	?	+	?	recruitment in endocrinology outpatient clinics;
Kempf[16]	2013	?	?	-	?	+	?	recruitment in endocrinology outpatient clinics; industry funded study
Kleefstra[17]	2010	+	+	-	?	+	?	

Malanda[18]	2016	+	+	-	+	+	-	
Much-more[19]	1994	?	?	-	?	+	?	
Nishimura[25]	2017	+	+	-	-	+	?	recruitment in endocrinology outpatient clinics; industry funded study
O'Kane[23]	2008	+	+	-	-	+	-	recruitment in endocrinology outpatient clinics
Parsons[37]	2019	+	+	-	-	-	-	
Polonsky[14]	2011	?	?	-	+	+	?	industry funded;
Scherbaum[22]	2008	+	+	-	?	+	+	recruitment in endocrinology outpatient clinics
Schwedes[20]	2002	?	?	-	?	+	?	Industry funded;
Young[21]	2017	+	+	-	-	+	+	

The table presents 24 studies by assessed source of bias in a cross-tabulation. Studies are sorted alphabetically by author's name.

Coding of judgements: "+": Low risk of bias (adequate method described in this risk of bias domain); "-": High risk of bias (in-adequate method described); "?": Unclear risk of bias (incomplete information was given)

Table 3: GRADE assessment

Question: SMBG compared to usual diabetes care without SMBG for adult non-insulin treated T2DM patients

Setting: primary care or diabetes outpatient clinic

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Incon-sistency**	**Indirectness**	**Imprecision**	**Other consid-erations**	**SMBG**	**Usual diabetes care without SMBG**	**Relative (95% CI)**	**Absolute (95% CI)**		
HbA1c (follow up: mean 10.8 months; assessed with: lab test; scale from: 5.0% to 12.0%)												
23	randomised trials	serious [c]	serious [d]	not serious	not serious	12 RCTs from endocrinology clinics 9 RCTs industry funded	3284	2,686	-	MD **0.29 % lower** (0.4 % lower to 0.18 % lower)	⊕⊕◯◯ LOW	CRITICAL [I]
Blood glucose (follow up: mean 11.8 months; assessed with: self-measurement; scale from: 50 mg/dL to 250 mg/dL)												
4	randomised trials	serious [a]	not serious	not serious	serious [b]	2 RCTs from endocrinology clinics 1 RCT industry funded	700	692	-	MD **4 mg/dL lower** (10.2 lower to 2.1 higher)	⊕⊕◯◯ LOW	IMPORTANT [II]
"Being in HbA1c target" (follow up: mean 11.8 months; assessed with: lab test; target thresholds as indicated by study authors)												
5	randomised trials	serious [e]	serious [f]	not serious	not serious	3 RCTs from endocrinology clinics 1 RCT industry funded	218/597 (36.5%)	41/321 (12.8%)	**RR 2.78** (1.46 to 5.31)	**227 more per 1,000** (from 59 more to 550 more)	⊕⊕◯◯ LOW	IMPORTANT [III]
Hypoglycaemia episodes (follow up: mean 11.8 months; assessed with: self-measurement)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Incon-sistency	Indirectness	Imprecision	Other consid-erations	SMBG	Usual diabetes care without SMBG	Relative (95% CI)	Absolute (95% CI)		
4 [g]	randomised trials	serious [h]	not serious	not serious	not serious	2 RCTs from endocrinology clinics 1 RCT industry funded	174/1,204 (14.5%) (mild to moderate severity; no serious events)	65/973 (6.7%) (mild to moderate severity; 1 patient requiring third party intervention)	**RR 2.10** (1.41 to 3.15)	**73 more per 1,000** (from 27 more to 144 more)	⊕⊕⊕◯ MODERATE	IMPORTANT [IV]
Depressive symptoms (follow up: mean 10.8 months; assessed with: validated instruments)												
7	randomised trials	not serious [i]	serious [j]	not serious	not serious	1 RCT from endocrinology clinics 2 RCTs industry funded	Number of patients: SMBG n=1,123; Control: n=797 In summary, ambiguous results for outcome depression (1 RCT: less depression symptoms in the intervention group; 2 RCTs: less depression symptoms in the control group; 4 RCTs: no relevant difference between intervention and control group)				⊕⊕⊕◯ MODERATE	IMPORTANT [V]
Quality of life (health related) (assessed with: validated instruments)												
6	randomised trials	not serious [k]	not serious	not serious	not serious [n]	2 RCTs from endocrinology clinics 1 RCT industry funded	Number of patients: SMBG n=1,135; Control: n=873 In summary, no relevant differences were found for the outcome health-related QOL (EQ-5D-3L; SF-36; DSQoL) between intervention and control groups.				⊕⊕⊕⊕ HIGH	IMPORTANT [VI]
Unexpected events (follow up: mean 10.8 months; assessed with: reported by study authors)												
3	randomised trials	serious [l]	not serious	not serious	not serious	1 RCT from endocrinology clinics	Number of patients: SMBG n=371; Control: n=229 In summary: scarce data with no relevant differences between groups: Mortality (info from 2 RCTs): 7 of 354 patients died in the intervention groups and 3 of 207 patients died in the control groups. Hospitalisation (info from 1 RCT): 1 Patient (intervention group) was hospitalized for an episode of chest pain; 2 patients (control group) were hospitalized, 1 for elective surgery, 1 for an unspecified leg problem.				⊕⊕◯◯ LOW	IMPORTANT [VII]
Satisfaction of patients with treatment (follow up: mean 10.8 months; assessed with: validated instruments)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Incon-sistency**	**Indirectness**	**Imprecision**	**Other consid-erations**	**SMBG**	**Usual diabetes care without SMBG**	**Relative (95% CI)**	**Absolute (95% CI)**		
8	randomised trials	serious [m]	not serious	not serious	not serious	3 RCTs from endocrinology clinics 2 RCTs industry funded	Number of patients: SMBG n=868; Control: n=665 No relevant difference in patient satisfaction with treatment was found in 7 of 8 RCTs. In one RCT satisfaction improved in both groups, but to a higher extent in the SMBG group.				⊕⊕⊕◯ MODERATE	NOT IMPORTANT [VIII]

CI: *Confidence interval;* ***MD:*** *Mean difference;* ***RCT:*** *Randomized controlled trials;* ***RR:*** *Risk ratio*

Explanations

a. unclear risk of selection bias (3 of 4 RCTs with unclear random sequence generation; 3 of 4 RCTs with unclear concealment of allocation)

b. wide 95%-CI includes both benefit and harm

c. unclear risk of selection bias (13 of 24 RCTs with unclear random sequence generation; 12 of 24 RCTs with unclear concealment of allocation)

d. unexplained heterogeneity (I-squared 67.9%)

e. unclear risk of selection bias (2 of 5 RCTs with unclear random sequence generation; 3 of 5 RCTs with unclear concealment of allocation); possibly selective reporting (4 of 5 trials with stronger SMBG effect)

f. unexplained heterogeneity (I-squared 70.1%)

g. 6 RCTs provided information about number of patients with detected hypoglycaemia events. 2 of 6 RCTs reported zero events in both groups and were excluded from meta-analysis.

h. unclear risk of selection bias (2 of 4 RCTs with unclear random sequence generation; 1 of 4 RCTs with unclear concealment of allocation); possible attrition bias in 1 of 4 RCTs

i. blinding of patients for SMBG not possible, but judged as not relevant for patient reported outcome depression

j. 7 TCTs: 1 RCT in favour of SMB; 2 RCTs in favour of control intervention; 4 RCTs with no relevant difference between groups

k. blinding of patients for SMBG not possible, but judged as not relevant for outcome QOL

l. unclear risk of selection bias (1 of 3 RCTs with unclear random sequence generation; 1 of 3 RCTs with unclear concealment of allocation); possibly reporting bias in 2 of 3 RCTs; possibly publication bias, as only 3 of 24 studies report on unexpected events beyond hypoglycaemia

m. unclear risk of selection bias (4 of 8 RCTs with unclear random sequence generation; 3 of 8 RCTs with unclear concealment of allocation); 2 of 8 RCTs with high risk of attrition bias;

n. imprecision “not serious”: this judgment is based on the 3 studies with QOL data that were well powered with n=453 [28], n=429 [21] and n=1024 [24] participants.

Overall evaluation of the certainty of the evidence:

I: HbA1c: Downgraded by one level because of serious risk of bias and by one level because of serious inconsistency.

II: Blood glucose: Downgraded by one level because of serious risk of bias and by one level because of serious imprecision.

III: “Beeing in HbA1c target”: Downgraded by one level because of serious risk of bias and by one level because of serious inconsistency.

IV: Hypoglycaemia episodes: Downgraded by one level because of serious risk of bias.

V: Depressive symptoms: Downgraded by one level because of serious inconsistency.

VI: Quality of life: No downgrading.

VII: Unexpected events: Downgraded by one level because of serious risk of bias and by one level because of scarce data from only 3 RCTs.

VIII: Satisfaction of patients with treatment: Downgraded by one level because of serious risk of bias.

6.1 Efficacy

In this Section, efficacy results (RQ 1 to 4) are presented along the central research questions as listed in Section 4. Results for RQ7 ("number of test strips used…") and for RQ9 ("relationship between HbA1c changes and changes in morbidity/mortality…") are reported in Section 7.

Results for RQ1 (primary outcome HbA1c)

RQ1: What is the effect on HbA1c of adding SMBG to usual care in adult non-insulin treated patients with T2DM compared to usual care without SMBG?

In our analysis using the full data set, adding SMBG to usual diabetes care led to a statistical significant decrease of HbA1c of -0.29%-points (95%CI: -0.40 to -0.18; 23 RCT; I^2 67.9%; Figure 2). For this analysis, we used all available data. Thus, also studies comparing, for example, structured SMBG (intervention group) with un-structured SMBG (control group) were included here.

To address RQ1 directly (the comparator for RQ1 is strictly no SMBG), we also performed an analysis including only studies with no SMBG in the CG. This means we excluded, for example, studies comparing un-structured SMBG (control group) with structured SMBG (intervention group). Adding any form of SMBG to usual diabetes without SMBG care led to a slightly more pronounced decrease of HbA1c of -0.33%-points (95%CI: -0.45 to -0.21; 17 RCT; I^2 71.2%; Figure 3).

The certainty of evidence for the outcome "HbA1c" was judged as low. It was downgraded by one level because of serious risk of bias and by one level because of serious inconsistency.

Results for RQ2 (secondary outcomes)

RQ2: What is the effect on other secondary outcomes (including harms) of adding SMBG to usual care in adult non-insulin treated patients with T2DM compared to usual care without SMBG?

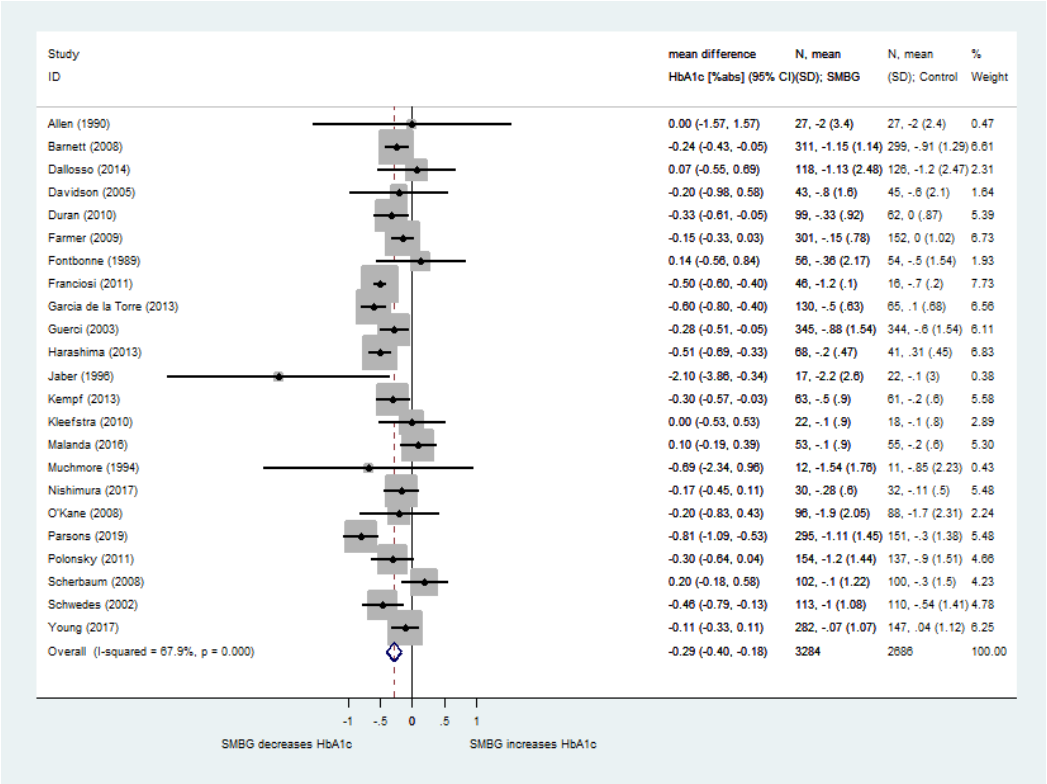
Hyper-/hypo-glycaemia

We used hyper-/hypo-glycaemia thresholds as defined by study authors. No data were available for hyper-glycaemia events.

6 RCTs [15 22 28 30 33 35] provided suitable data for analysis of the probability to detect hypo-glycaemia events (i.e. number of persons with hypoglycaemia events). Two RCTs [30 33] did not provide suitable data for the statistical meta-analysis, as no participant had a hypo-glycaemia event, neither in the IG nor in the CG. Meta-analysis of the remaining 4 RCTs [15 22 28 35] showed that SMBG was associated with a significantly increased probability of detecting hypoglycaemia events (often mild to moderate severity) compared to the CG (risk ratio, RR 2.10; 95%-CI: 1.41 to 3.15; 4 RCT; I^2 47.4%, Figure 4). It is unlikely

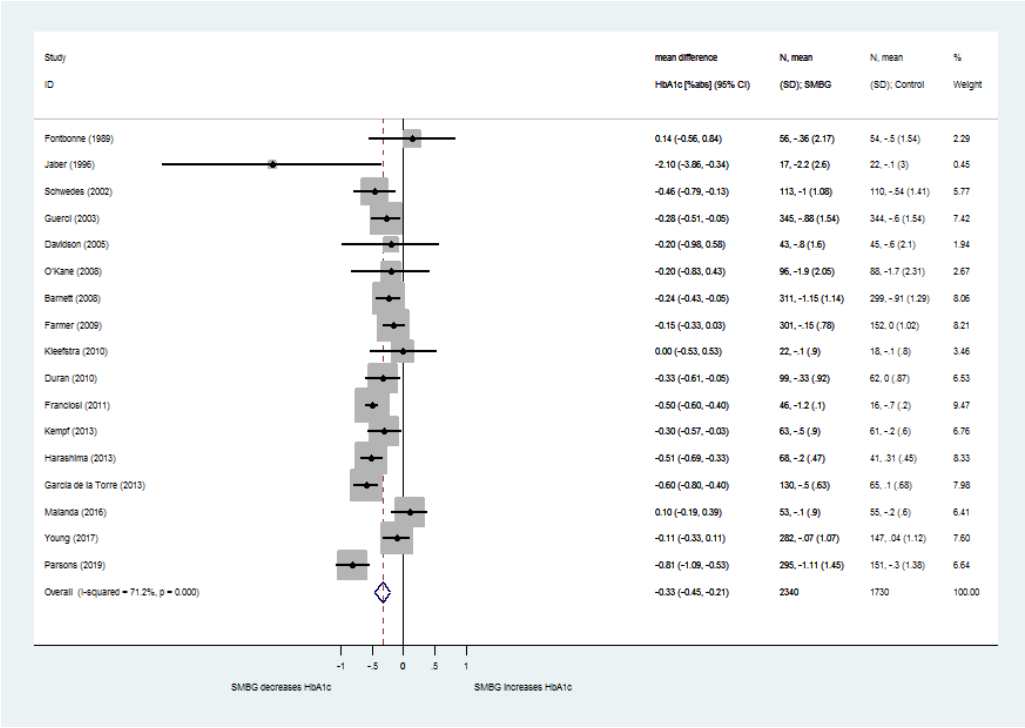
that SMBG as such increased the risk of hypoglycaemia, rather SMBG increased the probability of detecting mild to moderate hypoglycaemia events.

Figure 2: Effect of SMBG on HbA1c compared to any control group (n = 23 RCT)



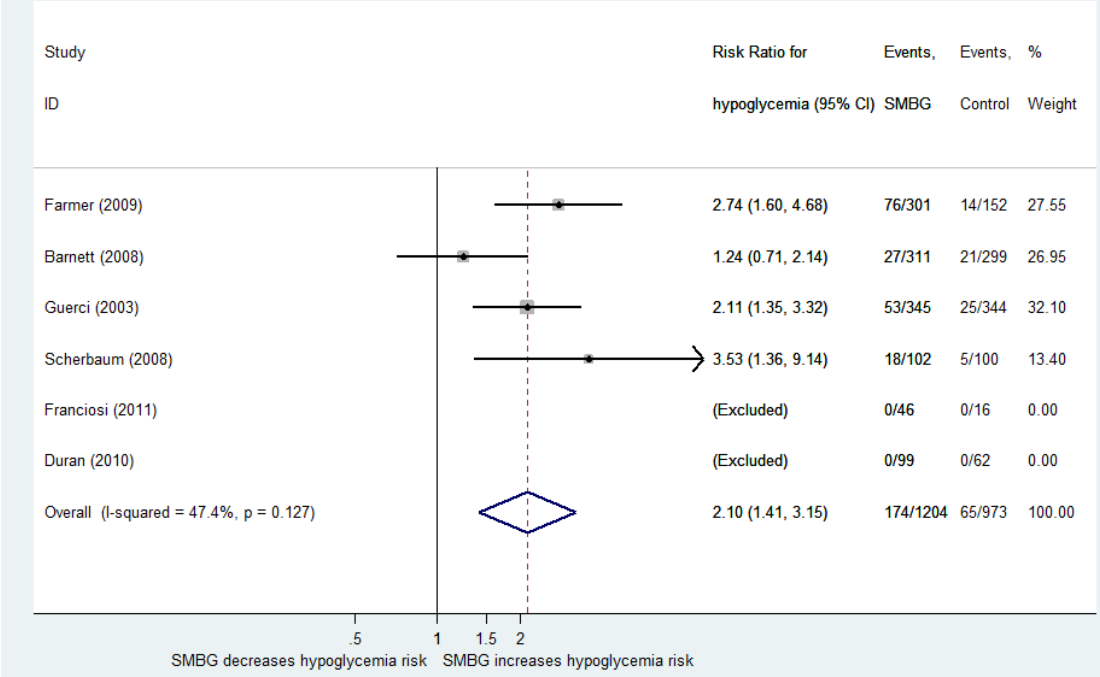
Results are provided as weighted mean difference in HbA1c (WMD: HbA1c %-points with 95%-CI) between intervention and control group.

Figure 3: Effect of SMBG on HbA1c compared to control groups without SMBG (n = 17 RCT)



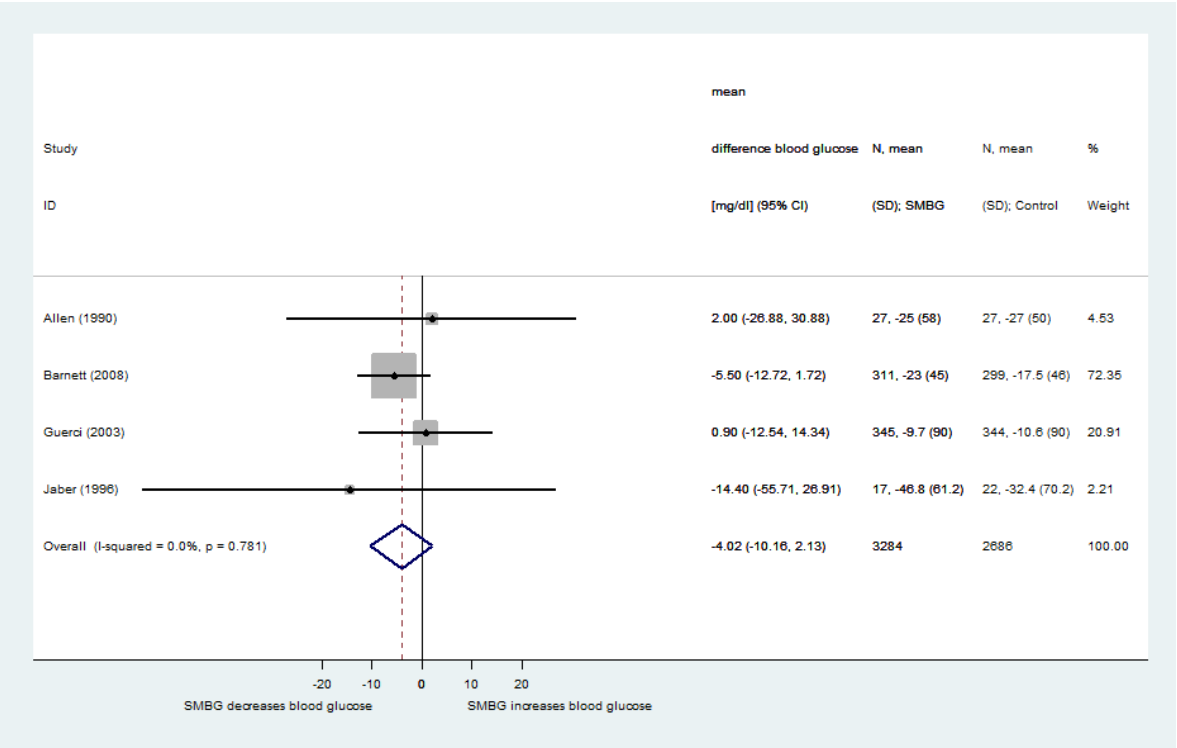
Results are provided as weighted mean difference in HbA1c (WMD: HbA1c %-points with 95%-CI) between intervention and control group

Figure 4: Effect of SMBG on detection of hypoglycaemia events compared to control groups (n = 6 RCT).



Results are provided as risk ratio (RR, 95%-CI) of suffering from hypoglycaemia in the intervention group compared with the control group.

Figure 5: Effect of SMBG on blood glucose levels compared to control group (n = 4 RCT)



Results are provided as weighted mean difference in blood glucose (WMD: mg/dL with 95%-CI) between intervention and control group.

These 4 RCTs have been published between 2003 and 2009. In 2 of the 4 RCTs information is given for drug treatment of participants: 45 to 50% of patients were treated with sulfonylureas with comparable rates between groups.[15 22] Of the 4 RCTs with reported hypoglycaemia events, 3 RCTs do not report information about adherence to the applied SMBG schemes. The remaining RCT [28] with adherence data, reports an adherence rate of 83%, which is the same as the average adherence rate as reported in 13 RCTs.

The certainty of evidence for the outcome “hypoglycaemia episodes” was judged as moderate. It was downgraded by one level because of serious risk of bias.

4 RCTs [15 27 29 35] provided data for analysis of blood glucose levels. SMBG led to a small and non-significant decrease of blood glucose levels of -4.0 mg/dl (95%CI: -10.2 to 2.1; 4 RCT; I^2 0.0%; Figure 5).

The certainty of evidence for the outcome “blood glucose levels” was judged as low. It was downgraded by one level because of serious risk of bias and by one level because of serious imprecision.

“HbA1c in target”

We used “being in target” thresholds as defined by study authors. Targets were defined as follows in the included studies: at least 25% reduction in HbA1c [27]; HbA1c <6% [30]; HbA1c <6% on metformin treatment [31]; HbA1c <7% [33 37].

Meta-analysis of 5 RCTs with data about specific targets showed a significantly increased probability of being in target with SMBG compared to the CG (risk ratio, RR 2.78; 95%-CI: 1.46 to 5.31; 5 RCT; I^2 70.1%; Figure 6, page 45).

The certainty of evidence for the outcome “HbA1c in target” was judged as low. It was downgraded by one level because of serious risk of bias and by one level because of serious inconsistency.

Change of oral medication and switch to insulin treatment

17 RCTs provided data about change of oral diabetes medication or switch to insulin therapy. In general, changes or amendments of oral diabetes medication or switch to insulin therapy were more frequent in the SMBG intervention groups. Mostly, standardised algorithms for treatment change were applied in the SMBG groups using blood glucose profiles to facilitate a more targeted approach to prescribing and to overcome the issue of clinical inertia in the treatment of hyperglycaemia in type 2 diabetes: [37]

In 6 RCTs [14 24 25 29 30 37], changes or amendments of oral diabetes medication were more frequent in the SMBG intervention groups; in 2 RCTs [27 33], this was the case in the control groups.

In 4 RCTs [14 17 30 37], switch to insulin therapy was more frequent in the SMBG intervention groups; in 1 RCT [27], this was the case in the control group.

In 8 RCTs [15 16 18 19 23 28 31 36], no relevant difference was reported concerning change of oral diabetes medication or switch to insulin therapy between SMBG intervention group and control group.

Details of results are reported in the Appendix (Table A 9, page 128).

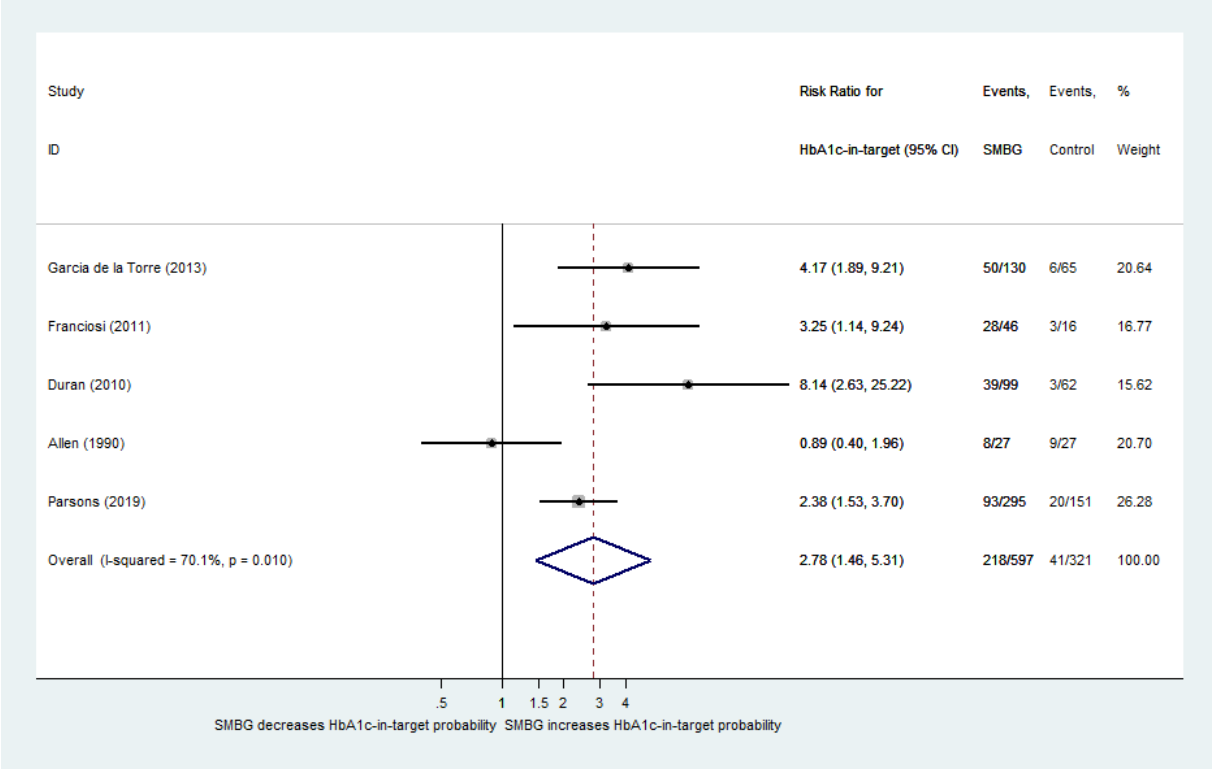
Morbidity

Results for morbidities (e.g. CVD; blindness; renal failure; foot problems) were rarely reported in the included RCTs, as follow-up was in general short (mean 10.8 months).

Most often differences in physiological parameters (for example body weight, waist circumference, blood pressure, lipid values) were reported. No clear pattern emerged in favour of intervention or control group and often no significant changes between groups were reported.

The modelling results for clinical event rates, using our HbA1c findings as one input parameter, are reported in Section 7.

Figure 6: Effect of SMBG on "being in HbA1c target" compared to control groups (n = 5 RCT).



Results are provided as probability [risk ratio (RR, 95%-CI)] of "being in HbA1c target" in the intervention group details compared with the control group.

Mortality

Results for mortality were rarely reported in the included RCTs. Some information is given about deceased patients during the often short follow-up, but no conclusions can be drawn if these events had a causal relationship to SMBG or no-SMBG.

In the study of Farmer et al. [28] 3 of 150 patients (2.0%) died in the less intensive group, 4 of 151 (2.6%) died in the more intensive group and 1 of 152 (0.6%) patients died in the control group.

In the study of Malanda et al.[18] 0 of 60 patients (0%) died in the intervention group and 2 of 62 (3.2%) died in the control group (not related to intervention according to study authors).

The Guerci et al. trial [35] reported about adverse events with outcome death, but no information was given about mortality per group (4 of 689 patients [0.6%] died due to stroke, cardiac arrest and cirrhosis with oedema).

The modelling results for mortality risk, based on our HbA1c findings, are reported in Section 7.

Psychological outcomes

We report psychological outcomes as measured by validated instruments of the primary study authors.

Outcome Depression

7 RCTs assessed the psychological outcome depression. Instruments used by study authors to assess this domain were WBQ-22, SF-36 mental component score, PHQ-8 (depressive symptoms); PHQ-9 (depressive symptoms); DDS (diabetes-related distress).

In summary, ambiguous results were found for the outcome depression (1 RCT showed less depression symptoms in the intervention group; 2 RCTs showed less depression symptoms in the control group; 4 RCTs showed no relevant difference between intervention and control group; see Table 4, page 48).

The certainty of evidence for the outcome “depression” was judged as moderate. It was downgraded by one level because of serious inconsistency.

Outcome General well-being

5 RCTs assessed the psychological outcome general well-being. Instruments used by study authors to assess this domain were WBQ-22, WHO-5; W-BQ28.

In summary, no relevant differences were found for the outcome general well-being between intervention and control groups in 5 RCTs; Table 5, page 49).

Other psychological outcomes

8 RCTs assessed other psychological outcomes (Table 6, page 50).

No differences were found for most of the assessed domains: Well-being & diabetes attitudes (Instrument: WBQ); Perceived burden of diabetes-related symptoms (DSC-r); Diabetes self-efficacy (CIDS-T2); Diabetes-related Autonomous Motivation, DRAM (TSRQ); Locus of control (LOC); Perception of diabetes (BIPQ); Emotional distress (PAID). Diabetes Symptoms Checklist (DSC); Diabetes Empowerment Scale (DES-SF); Problem Areas in Diabetes (PAID); Patient views of physician communication skills (Communication Assessment Tool).

The Young et al. study [21] found significant differences in total score and blood sugar subscale (Summary of Diabetes Self-Care Activities) in favour of SMBG, owing to the influence of the SMBG intervention. One RCT (Nishimura et al. 2017 [25]) found significantly higher change in the diet subscale (Self-management performance, SDSCA) in favour of the control group.

Health-related quality of life

6 RCTs assessed health related quality of life. Instruments used by study authors to assess this domain were generic health-related QOL instruments (EQ-5D-3L; SF-36; Health Status Questionnaire v2.0, derived from SF-36) or diabetes-specific QOL-instruments (DCCT Diabetes QOL Inventory; DSQoL).

In summary, no relevant differences were found for the outcome health-related QOL between intervention and control groups (6 RCTs showed no relevant difference between intervention and control group; see Table 7, page 52).

The certainty of evidence for the outcome “quality of life” was judged as high (no downgrading).

Patient satisfaction with treatment

8 RCTs assessed patient satisfaction with treatment (Table 8, page 53). Instruments used by study authors to assess this domain were mostly the DTSQ; but also a Global Satisfaction Scale (0-100) and an own questionnaire [32] were applied (assessing the domains: motivation to glycaemic control; willingness for treatment; encouragement to response to SMBG; perceived usefulness of SMBG; and willingness to continue SMBG)

7 RCTs found no relevant difference in patient satisfaction with treatment. In one study (Duran et al. 2010 [30]) satisfaction improved in both groups, but to a higher extent in the SMBG group.

The certainty of evidence for the outcome “patient satisfaction with treatment” was judged as moderate. It was downgraded by one level because of serious risk of bias.

Table 4: Depressive symptoms, measured with validated instruments

Author (year)	--	0	+	Intervention SMBG: Outcome Depression	Control group: Outcome Depression
Schwedes 2002 [20]			X	*Intervention: structured SMBG* *WBQ-22 (4 subscales): statstically significant difference in favour of SMBG in the depression subscale (minimal important difference?); no difference in 3 other subscales (anxiety; energy; positve well-being)*	Control: no SMBG & usual diabetes care WBQ-22 (4 subscales): statstically significant difference in favour of SMBG in the depression subscale (*minimal important difference?*); no difference in 3 other subscales (anxiety; energy; positve well-being)
O'Kane 2008 [23]	X			*Intervention: structured SMBG* *WBQ: SMBG participants were more depressed, scoring 6 points higher (that is, 6%) on the depression subscale of the WBQ at 12 months (P=0.01), and there was a trend towards increased anxiety.*	Control: no SMBG & usual diabetes care WBQ: SMBG participants were more depressed, scoring 6 points higher (that is, 6%) on the depression subscale of the WBQ at 12 months (P=0.01), and there was a trend towards increased anxiety.
Farmer 2009 [28]	X			*Intervention: structured SMBG* *30% with at least some anxiety/depression at 12 mth (EQ-5D-3L)*	Control: no SMBG & usual diabetes care 18% with at least some anxiety/depression at 12 mth (EQ-5D-3L)
Kleefstra 2010 [17]		X		*Intervention: structured SMBG* *SF-36 mental component score: no relevant difference between groups.*	Control: no SMBG & usual diabetes care SF-36 mental component score: no relevant difference between groups.
*Polonsky 2011 [14]		X		*Intervention: structured SMBG* *Depressive symptoms (PHQ-8); diabetes-related distress (DDS): significant improvement during FU with no between-group differences*	Control: (un-structured) SMBG Depressive symptoms (PHQ-8); diabetes-related distress (DDS): significant improvement during FU with no between-group differences
Malanda 2016 [18]		X		*Intervention: structured SMBG* *PHQ-9 (depressive symptoms): No relevant differences between groups.*	Control: no SMBG & usual diabetes care PHQ-9 (depressive symptoms): No relevant differences between groups.
Young 2017 [21]		X		*Intervention: un-structured SMBG* *SF-36: mental component score includes depression: no relevant difference between groups*	Control: no SMBG & usual diabetes care SF-36: mental component score includes depression: no relevant difference between groups

"--" (colour code: red): Assessment tools show more depression symptoms in the intervention group (SMBG), compared to control group;

"0" (colour code: white): Assessment tools show no relevant difference between groups;

"+" (colour code: green): Assessment tools show less depression symptoms in the intervention group (SMBG), compared to control group;

*The study by Polonsky et .al. belongs to RQ4 ("structured vs. non structured SMBG") but is also presented here to show the complete available evidence for PROMs.

Table 5: General well-being, measured with validated instruments

Author (year)	--	0	+	Intervention SMBG: Outcome PROMs: Well-being	Control group: Outcome PROMs: Well-being
Schwedes 2002 [20]		X		*Intervention: structured SMBG* *General well-being (WBQ-22): GWB improved in both groups with no significant difference.*	Control: no SMBG & usual diabetes care General well-being (WBQ-22): GWB improved in both groups with no significant difference.
O'Kane 2008 [23]		X		*Intervention: structured SMBG* *Well-being & diabetes attitudes (WBQ): no significant differences between group*	Control: no SMBG & usual diabetes care *Well-being & diabetes attitudes (WBQ): no significant differences between group*
Kleefstra 2010 [17]		X		*Intervention: structured SMBG* *Well-being (WHO-5): no relevant difference between groups.*	Control: no SMBG & usual diabetes care *Well-being (WHO-5): no relevant difference between groups.*
*Polonsky 2011 [14]		X		*Intervention: structured SMBG* *Generell well-being (WHO-5): significant increase in GWB with no (relevant) differences between groups;*	*Control: (un-structured) SMBG* *Generell well-being (WHO-5): significant increase in GWB with no (relevant) differences between groups;*
Dallosso 2014 [26]		X		*Intervention: un-structured SMBG* *Psychological well-being (W-BQ28): no significant differences between groups*	Control: SMUG *Psychological well-being (W-BQ28): no significant differences between groups*

"--" (colour code: red): Assessment tools show lower well-being levels in the intervention group (SMBG), compared to control group;

"0" (colour code: white): Assessment tools show no relevant difference between groups;

"+" (colour code: green): Assessment tools show higher well-being levels in the intervention group (SMBG), compared to control group;

**The study by Polonsky et .al. belongs to RQ4 ("structured vs. non structured SMBG") but is also presented here to show the complete available evidence for PROMs.*

Table 6: Other psychological outcomes measured with validated instruments

Author (year)	--	0	+	Intervention SMBG: Outcome PROMs	Control group: Outcome PROMs
O'Kane 2008 [23]		X		*Intervention: structured SMBG* *Well-being & diabetes attitudes (WBQ): no significant differences between group*	*Control: no SMBG & usual diabetes care* *Well-being & diabetes attitudes (WBQ): no significant differences between group*
Kleefstra 2010 [17]		X		*Intervention: structured SMBG* *Perceived burden of diabetes-related symptoms (DSC-r): no relevant difference between groups.*	*Control: no SMBG & usual diabetes care* *Perceived burden of diabetes-related symptoms (DSC-r): no relevant difference between groups.*
*Polonsky 2011 [14]		X		*Intervention: structured SMBG* *Diabetes self-efficacy (CIDS-T2); Diabetes-related Autonomous Motivation, DRAM (TSRQ): In ITT analysis significant increase in CIDS-T2 scores and DRAM with no (relevant) differences between groups;*	*Control: (un-structured) SMBG* *Diabetes self-efficacy (CIDS-T2); Diabetes-related Autonomous Motivation, DRAM (TSRQ): In ITT analysis significant increase in CIDS-T2 scores and DRAM with no (relevant) differences between groups;*
Bosi 2013 [24]		X		*Intervention: structured SMBG* *Locus of control (LOC): All domain scores improved with no (relevant) differences between groups.*	*Control: less frequent SMBG* *Locus of control (LOC): All domain scores improved with no (relevant) differences between groups.*
Dallosso 2014 [26]		X		*Intervention: un-structured SMBG* *Perception of diabetes (BIPQ): no significant differences between groups*	*Control: SMUG* *Perception of diabetes (BIPQ): no significant differences between groups*
Malanda 2016 [18]		X		*Intervention: structured SMBG* *Emotional distress (PAID), self efficacy (CIDS-2): no relevant difference between groups.*	*Control: no SMBG & usual diabetes care* *Emotional distress (PAID), self efficacy (CIDS-2): no relevant difference between groups.*
Young 2017 [21]			X	*Intervention: un-structured SMBG* *Diabetes Symptoms Checklist (DSC); diabetes Empowerment Scale (DES-SF); Problem Areas in Diabetes (PAID); Patient views of physician communication skills (Communication Assessment Tool): No significant differences between groups.* *Self Care Activities (Summary of Diabetes Self-Care Activities): Significant differences in total score and blood sugar subscale in favour of SMBG, owing to the influence of the SMBG intervention.*	*Control: no SMBG & usual diabetes care* *Diabetes Symptoms Checklist (DSC); diabetes Empowerment Scale (DES-SF); Problem Areas in Diabetes (PAID); Patient views of physician communication skills (Communication Assessment Tool): No significant differences between groups.* *Self Care Activities (Summary of Diabetes Self-Care Activities): Significant differences in total score and blood sugar subscale in favour of SMBG, owing to the influence of the SMBG intervention.*

Author (year)	--	0	+	**Intervention SMBG: Outcome PROMs**	**Control group: Outcome PROMs**
Nishimura 2017 [25]	X			*Intervention: more structured SMBG* *Self-management performance (SDSCA): Significantly higher change in the diet subscale in favour of the control group compared to intervention group; no (relevant) difference between groups in the exercise and the medication subscale.*	*Control: less structured SMBG* *Self-management performance (SDSCA): Significantly higher change in the diet subscale in favour of the control group compared to intervention group; no (relevant) difference between groups in the exercise and the medication subscale.*

"--" (colour code: red): Assessment tools show less favourite results in the intervention group (SMBG), compared to control group;

"0" (colour code: white): Assessment tools show no relevant difference between groups;

"+" (colour code: green): Assessment tools show more favourite results in the intervention group (SMBG), compared to control group;

**The study by Polonsky et .al. belongs to RQ4 ("structured vs. non structured SMBG") but is also presented here to show the complete available evidence for PROMs.*

Table 7: Quality of life measured with validated instruments

Author (year)	--	0	+	Intervention SMBG: Outcome PROMs: QOL	Control group: Outcome PROMs: QOL
Muchmore 1994 [19]		X		*Intervention: structured SMBG* *QOL (DCCT: Diabetes QOL Inventory): no (relevant) difference between groups*	*Control: no SMBG & usual diabetes care* *QOL (DCCT: Diabetes QOL Inventory): no (relevant) difference between groups*
Jaber 1996 [29]		X		*Intervention: structured SMBG* *QOL (Health Status Questionnaire v2.0; derived from SF-36): no significant differences in any of the domains tested between or within groups*	*Control: no SMBG & usual diabetes care* *QOL (Health Status Questionnaire v2.0; derived from SF-36): no significant differences in any of the domains tested between or within groups*
Farmer 2009 [28]		X		*Intervention: structured SMBG* *QOL (EQ-5D-3L): No relevant changes in QOL (utilities) between groups.*	*Control: no SMBG & usual diabetes care* *QOL (EQ-5D-3L): No relevant changes in QOL (utilities) between groups.*
Kleefstra 2010 [17]		X		*Intervention: structured SMBG* *QOL (SF-36): no relevant difference between groups.*	*Control: no SMBG & usual diabetes care* *QOL (SF-36): no relevant difference between groups.*
Bosi 2013 [24]		X		*Intervention: structured SMBG* *QOL (DSQoL): All domain scores improved with no (relevant) differences between groups.*	*Intervention: less frequent SMBG* *QOL (DSQoL): All domain scores improved with no (relevant) differences between groups.*
Young 2017 [21]		X		*Intervention: un-structured SMBG* *QOL (SF-36): no relevant difference in change of QOL between groups.*	*Control: no SMBG & usual diabetes care* *QOL (SF-36): no relevant difference in change of QOL between groups.*

"--" (colour code: red): Assessment tools show lower QOL levels in the intervention group (SMBG), compared to control group;

"0" (colour code: white): Assessment tools show no relevant difference between groups;

"+" (colour code: green): Assessment tools show higher QOL levels in the intervention group (SMBG), compared to control group;

Table 8: Satisfaction of patients with treatment, measured with validated instruments

Author (year)	--	0	+	Intervention SMBG: Outcome PROMs: Satisfaction with treatment	Control group: Outcome PROMs: Satisfaction with treatment
Schwedes 2002 [20]		X		Intervention: structured SMBG *Treatment satisfaction (DTSQ): satisfaction increased in both groups to a similar extent.*	Control: no SMBG & usual diabetes care Treatment satisfaction (DTSQ): satisfaction increased in both groups to a similar extent.
O'Kane 2008 [23]		X		Intervention: structured SMBG *Treatment satisfaction (DTSQ): no significant differences between group*	Control: no SMBG & usual diabetes care Treatment satisfaction (DTSQ): no significant differences between group
Kleefstra 2010 [17]		X		Intervention: structured SMBG *Treatment satisfaction (DTSQ): no relevant difference between groups.*	Control: no SMBG & usual diabetes care Treatment satisfaction (DTSQ): no relevant difference between groups.
Duran 2010 [30]			X	*Intervention: structured SMBG* *Treatment satisfaction (global satisfaction scale (0-100)): satisfaction scale improved, the increase was significantly greater in the SMBG group (from 30 to 90)*	Control: no SMBG & usual diabetes care Global treatment satisfaction scale (0-100) inceased from 33 to 59;
Harashima 2013 [32]		X		*Intervention: un-structured SMBG* *Satisfaction with treatment (own questionnaire): no relevant difference between groups.*	Control: no SMBG & usual diabetes care *Satisfaction with treatment (own questionnaire): no relevant difference between groups.*
Dallosso 2014 [26]		X		*Intervention: un-structured SMBG* *Treatment satisfaction (DTSQ): no significant differences between groups*	Control: SMUG Treatment satisfaction (DTSQ): no significant differences between groups
Malanda 2016 [18]		X		*Intervention: structured SMBG* *Treatment satisfaction (DTSQ): no relevant difference between groups.*	Control: no SMBG & usual diabetes care *Treatment satisfaction (DTSQ): no relevant difference between groups.*
Young 2017 [21]		X		*Intervention: un-structured SMBG* *Treatment satisfaction (DTSQ): No significant differences between groups.*	Control: no SMBG & usual diabetes care *Treatment satisfaction (DTSQ): No significant differences between groups.*

"--" (colour code: red): Assessment tools show lower satisfaction with treatment in the intervention group (SMBG), compared to control group;

"0" (colour code: white): Assessment tools show no relevant difference between groups;

"+" (colour code: green): Assessment tools show higher satisfaction with treatment in the intervention group (SMBG), compared to control group;

Results for RQ3 (primary outcome HbA1c)

RQ3: What is the effect on HbA1c of adding structured SMBG to usual care in adult non-insulin treated patients with T2DM compared to usual care with non-structured SMBG?

For this specific research question, we had only scarce data. Most studies compared a structured SMBG intervention with no SMBG or with a less structured SMBG.

Only 1 RCT[14] explicitly compared structured SMBG vs. non-structured SMBG according to our pre-specified criteria and found a reduction in HbA1c of -0.30 %-points (95%-CI: -0.64 to -0.04).

Another RCT[25] compared structured SMBG vs. less-structured SMBG according to our pre-specified criteria and found a reduction in HbA1c of -0.17 %-points (95%-CI: -0.45 to -0.11).

Results for RQ4 (secondary outcomes)

RQ4: What is the effect on other secondary outcomes (including harms) of adding structured SMBG to usual care in adult non-insulin treated patients with T2DM compared to usual care with non-structured SMBG?

Effects on secondary outcomes in the Polonsky et al. trial [14] that explicitly compared structured SMBG vs. non-structured SMBG according to our pre-specified criteria included:

– Therapy adjustments: Significantly more patients with structured SMBG received a treatment change recommendation (pharmacologic and/or lifestyle) at the month 1 visit compared with non-structured SMBG, regardless of the patient's initial baseline HbA1c level: 179 (75.5%) vs. 61 (28.0%); p< 0.0001. Between month 1 and 12, more SMBG patients (42/256; 16%) started on intermediate or long-acting insulin than control patients (23/227; 10%).

– Hypoglycaemia: No severe hypoglycaemic events occurred and incidence of hypoglycaemia (< 70 mg/dL) was similar in both groups (< 2% of downloaded SMBG readings from the glucose meter).

– Psychological outcomes: No relevant differences between groups emerged for general well-being (GWB); self-efficacy (confidence in Diabetes Self-Care for Type 2 patients, CIDS-T2), Diabetes-related Autonomous Motivation (DRAM), depressive symptoms (Patient Health Questionnaire; PHQ-8) and diabetes-related distress (Diabetes Distress Scale; DDS).

Exploring heterogeneity

Heterogeneity in our random-effects meta-analyses was often substantial (I^2 ranging between 50% and 80%). We explored heterogeneity with our pre-specified subgroup and meta-regression analysis.

In our subgroup analyses, no relevant stronger effect of SMBG on HbA1c emerged for any of our pre-defined subgroups, compared to our analysis using the complete data set or the analysis for RQ1 (Table 9).

In our multivariable meta-regression analysis, none of the independent variables was significantly associated with degree of change in HbA1c, probability of "being in HbA1c target" or probability of detecting hypoglycaemia (Table 10, page 56).

Table 9: Subgroup analyses

Outcome	24 RCT (all studies)	Change in HbA1c (weighted mean difference)	I-squared (I^2)
HbA1c (analysis of complete dataset)	23 RCT	-0.29 (95%-CI: -0.40 to -0.18)	67.9%
HbA1c (analysis for RQ1)	17 RCT	-0.33 (95%-CI: -0.45 to -0.21)	71.2%
SG: publication year < 2008 SG: publication year >= 2008	7 RCT 16 RCT	-0.32 (95%-CI: -0.54 to -0.11) -0.29 (95%-CI: -0.40 to -0.18)	12.2% 75.6%
SG: SMBG un-structured vs. no SMBG	3 RCT	-0.31 (95%-CI: -0.55 to -0.07)	74.9%
SG: SMBG structured vs. SMBG non-structured	1 RCT	-0.30 (95%-CI: -0.64 to -0.04)	0.0%
SG: SMBG ANY more complex (structured and/or frequent) vs. SMBG ANY less complex (structured and/or frequent)	2 RCT	-0.22 (95%-CI: -0.43 to -0.01)	0.0%
SG: SMBG ANY complex (structured and/or frequent) vs. no SMBG	17 RCT	-0.33 (95%-CI: -0.45 to -0.21)	71.2%
SG: SMBG more frequent vs. SMBG less frequent	1 RCT	-0.20 (95%-CI: -0.18 to 0.58)	0.0%
SG: diabetes duration < 1yr SG: diabetes duration > 1yr	4 RCT 18 RCT	-0.37 (95%-CI: -0.63 to -0.11) -0.29 (95%-CI: -0.41 to -0.16)	51.5% 69.5%
SG: diabetes drugs OAD SG: diabetes drugs (OAD or noOAD)	9 RCT 11 RCT	-0.37 (95%-CI: -0.57 to -0.17) -0.31 (95%-CI: -0.43 to -0.19)	81% 0.0%
SG: low risk of bias (>=4 of 6 ROB domains low risk) SG high risk of bias (<= 1 of 6 ROB domains low risk)	5 RCT 11 RCT	-0.12 (95%-CI: -0.39 to 0.15) -0.41 (95%-CI: -0.52 to -0.29)	88.3% 26.7%
SG: design RAN SG: design cluster RAN (corrected for clustering)	21 RCT 2 RCT	-0.30 (95%-CI: -0.41 to -0.18) -0.21 (95%-CI: -0.52 to 0.10)	70.0% 4.6%
SG: sponsor public or mixed* SG: sponsor industry only**	13 RCT 9 RCT	-0.24 (95%-CI: -0.45 to -0.03) -0.36 (95%-CI: -0.47 to -0.25)	75.1% 42.2%

OAD: oral anti-diabetic drug; SG: subgroup; RAN: randomised;

**"public or mixed": mixed funding includes industry together with public agencies or exclusive funding by public agencies or other funding sources (e.g. private foundations);*

*** Industry funding comprises exclusive industry funding;*

Table 10: Meta-regression analyses

Dependent variable	24 RCT (all studies)	Independent variables (meta-regression output)
HbA1c	12 RCT with sufficient data	HbA1c at baseline: p=0.50 SMBG frequency aim: p=0.78 SMBG frequency real: p=0.91 Follow-up months: p=0.70 Follow-up completeness: p=0.67 SMBG adherence: p=0.60
"HbA1c in target"	5 RCT with sufficient data	HbA1c at baseline: p=0.10 SMBG frequency aim: p=0.75 *(no other variables in the model due to few RCTs with relevant outcome)*
Hypoglycaemia detection	4 RCT with sufficient data	HbA1c at baseline: p=0.57 SMBG frequency aim: p=0.27 *(no other variables in the model due to few RCTs with relevant outcome)*

6.2 Effectiveness

The extent to which SMBG produces a beneficial, reproducible result under non-research conditions for non-insulin treated patients (i.e. fulfilling conditions for effectiveness) is difficult to estimate. Eleven of 24 included RCTs recruited participants on the GP level and were judged by the HTA authors as fulfilling at least some features of real-world non-research conditions.

To gain further information for the effectiveness domain, we performed two analyses:

– First, an ex-post subgroup analysis (i.e. not pre-specified) was performed according to recruitment of study participants of the RCTs (recruitment in a primary care setting vs. recruitment in a hospital, including specialised ambulatory care centres)

– Second, we assessed a selection of observational studies which explored possible effects of SMBG over a longer follow-up period. Observational studies have their own limitations, are primarily classified as “low certainty evidence” in the GRADE assessment and were not formally included in our evidence searches as we searched for RCTs. We took them into account only to gain further information for effectiveness issues. We included observational studies that had been included in earlier systematic reviews, which had also performed searches for observational studies or observational studies that had been proposed as information source by Swiss stakeholders during their review of the scoping report.

Results of our analysis in the effectiveness domain

Results correspond to RQ1 (“SMBG vs. no SMBG”: primary outcome HbA1c) and RQ2 (“SMBG vs. no SMBG”: secondary outcomes).

No relevant difference was found in our subgroup analysis of RCTs in terms of HbA1c change for studies that recruited participants in a primary care setting compared to studies that recruited participants in a hospital setting, including specialised ambulatory care centres (Table 11, page 58).

Four observational studies with longer follow-up (between 3 and 9.8 years) from 4 different countries were assessed. HbA1c change in the observational studies was difficult to interpret: Results were either poorly reported or no (non-exposed) control group existed.

Concerning association of SMBG with morbidity and mortality in observational studies with longer follow-up, ambiguous results emerged (Table 12, page 58):

1 retrospective cohort study from Germany [39] comparing SMBG with no SMBG found lower morbidity and all-cause mortality for SMBG patients (also for T2DM patients without insulin).

1 observational study from Australia [40 41] performed a longitudinal analysis comparing SMBG with no SMBG found no association of SMBG with all-cause mortality, but an association of SMBG with a 79% increased cardiovascular mortality. This unexpected result may be due to chance after multiple testing. SMBG was also associated with a 48% reduced risk of retinopathy.

2 of 4 observational studies did not report morbidity or mortality data.

Table 11: Ex-post subgroup analysis according to population recruitment.

Outcome	24 RCT (all studies)	Change in HbA1c (weighted mean difference)
SG: population **recruitment primary care** (GP)	10 RCT	-0.26 (95%-CI: -0.44 to -0.08)
SG: population **recruitment hospital** (including specialised outpatient clinics)	13 RCT	-0.33 (95%-CI: -0.47 to -0.19)

Table 12: Observational studies and morbidity/mortality outcomes

Author (year) Country	Acronym Design	Population age (mean)	Observed patients	Intervention (exposure)	Control (non-exposure)	Outcome
Franciosi 2005 [42-44] ITA	QuED case series (register?)	Age (mean): 61 to 63yr Follow-up in observational study: 3 (years)	n=2,661 (data of n=1,896)	SMBG frequency	n.a.	HbA1c-change: SMBG frequency did not predict metabolic control Morbidity, mortality: no info MID HbA1c: no info
Martin 2006 [39] GER	ROSSO retrospective cohort	Age (mean): 62yr Follow-up in observational study: 6.5 (years)	n=3,268	SMBG	no SMBG	HbA1c-change: no info Morbidity, mortality: lower morbidity and all-cause mortality for SMBG (also for T2DM patients without insulin) MID HbA1c: no info
Karter 2006 [45-47] USA	KAISER cohorts (longitudinal analysis)	Age (mean): 59 to 67yr Follow-up in observational study: 3 (years)	n=16,091 (new user) 15,347 (prevalent user)	SMBG new user	SMBG prevalent user	HbA1c-change: New users: -0.35% to -0.42%; prevalent users: no info Morbidity, mortality: no info MID HbA1c: no info
Davis 2007 [40 41] AUS	FREMANTLE observational longitudinal study	Age (mean): no info Follow-up in observational study: 9.8 (years)	n=1,280 + 531	SMBG	*no SMBG*	HbA1c-change: no significant difference between groups Morbidity, mortality: no association of SMBG with all-cause mortality, SMBG associated with 79% increased cardiovascular mortality; SMBG associated with 48% reduced risk of retinopathy MID HbA1c: no info

Colour code: GREEN: HbA1c change/morbidity/mortality in favour of exposure SMBG

Colour code: RED: HbA1c change/morbidity/mortality in favour of control exposure

6.3 Safety

Other adverse events or harms

Other adverse events or harms were rarely reported in the RCTs.

In the Jaber et al. study [29] 1 of 17 patients in the intervention group was hospitalized for an episode of chest pain. 2 of 22 patients in the control group were hospitalized (1 for elective surgery, 1 for an unspecified leg problem).

Also hypoglycemia is considered a safety issue, but is reported in the Chapter Efficacy 5.1 to stick to our secondary outcomes definition.

6.4 Summary Statement Efficacy, Effectiveness and Safety

Adding (may be more frequent or more structured) SMBG to usual diabetes care leads to a statistical significant decrease of HbA1c of -0.29%-points (95%CI: -0.40 to -0.18; 23 RCT; low certainty of evidence). In studies without any SMBG in the control group, the decrease of HbA1c is more pronounced (-0.33%-points; 95%CI: -0.45 to -0.21; 17 RCT). The clinical relevance of this HbA1c improvement is assessed via modelling in Section 7.

SMBG leads to a significantly increased probability of detecting hypoglycaemia events compared to the CG (risk ratio, RR 2.10; 95%-CI: 1.41 to 3.15; 4 RCTs with high sulfonylurea rates; hypoglycaemia episodes mostly of mild to moderate severity; moderate certainty evidence).

SMBG increases the probability of «being in HbA1c target» (risk ratio, RR 2.78; 95%-CI: 1.46 to 5.31; 5 RCTs; low certainty evidence).

No relevant differences were seen for psychological outcomes (e.g. depressive symptoms), quality of life, patient satisfaction with treatment (moderate to high certainty evidence) or morbidity, mortality, unexpected events and harms.

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7. Costs, Budget Impact and Cost-Effectiveness

7.1 Current evidence from economic studies

The searches retrieved 137 economic studies, 9 of which were duplicates. Two researchers of the research team screened the remaining 128 studies and identified 10 relevant studies: 6 cost-effectiveness studies [48-53], 2 cost-utility studies [28 54], 1 budget-impact study [55] and 1 financial impact study [56] (see Table A 10, page 129 in Appendix 11.11). Two studies referred to Switzerland [50 55], 2 to USA [51 53], 3 to the UK [28 54 56], 2 to Canada [48 49] and 1 to France, Germany, Italy and Spain [52]. A flow chart or quality assessment of the retrieved studies was not conducted, as the studies were not used in our analysis but are used to provide an overview of the current literature on this topic.

Cost-effectiveness and cost-utility studies applied two main diabetes simulation models: the UKPDS Outcomes Model 1 (UKPDS-OM1) was applied in 3 studies [28 48 49] and the IQVIA CORE Diabetes Model was applied in 5 studies [50-54]. Of these studies, 5 [48 49 51-53] used a simulation period of 40 years, 1 [50] of 30 years and in 2 studies[28 54] the “lifetime horizon” was not defined. The discount rates applied ranged from 3% to 5% per year. The gains of a daily SMBG frequency ranged from 0.028 [49] to 0.371 [54] life years and from -0.004 [28] to 0.165 [54] QALYs (see Table A 10 in the Appendix). The wide range of results is explained by variations in the clinical, economic and model assumptions among the studies.

SMBG in non-insulin treated T2DM patients may increase or lower the cost of treating patients with diabetes when the benefits of potentially avoided diabetes-related complications are considered. A study for Switzerland compared the annual treatment costs, *including* costs of complications, between non-insulin treated T2DM patients using and non-insulin treated T2DM patients not using SMBG and found a cost difference of CHF –514 per patient year for those using SMBG.[55] This study assumed a yearly average number of test strips of 38.8, based on German data. A study for the UK compared annual treatment costs, *without including* costs of complications, and found that £ 17.12 m per year could be saved if non-insulin treated T2DM patients would use less SMBG and follow the UK consensus. According to this study approximately 54% of non-insulin treated T2DM patients practiced SMBG with a frequency of 130 to 213 per year.[56]

7.2 Cost-Effectiveness

Cost-effectiveness evaluations of SMBG build on the insights generated by effectiveness (or efficacy) evaluations of SMBG. However, the time horizon of the effectiveness evaluation of SMBG differs from the time horizon of the health economic evaluation of SMBG. Typical primary outcomes of effectiveness evaluations are changes in HbA1c levels within a time span of 3 to 12 months and short-term complication of diabetes. Conversely, cost-effectiveness evaluations aim to assess the lifetime consequences of

improved glucose control,[57] as prevention and delay of long-term consequences may have substantial effects on health and cost outcomes. As this type of information is not available from clinical trials, the consequences of changes in SMBG must be estimated with health economic models simulating the lifetime consequences of changes in HbA1c triggered by changes in SMBG. Also included observational studies did not provide information about a minimal important difference (MID) of HbA1c to result in patient relevant differences in clinical outcomes.

7.2.1 Methods of cost-effectiveness analysis

Cost-Effectiveness Model

We evaluated the cost-effectiveness and cost-utility of SMBG compared to using no SMBG. The clinical efficacy of SMBG was derived from our meta-analyses described in Section 6.1 (–0.29%-points (95%CI: –0.40 to –0.18) corresponding to 365 SMBG per year and –0.33%-points (95%CI: –0.45 to –0.21) corresponding to 260 SMBG per year [2]). We performed this analysis from the healthcare payers' perspective. The well-known and validated United Kingdom Prospective Diabetes Study Outcomes Model Version 2 (UKPDS-OM2) was used and adapted to the context of the Swiss healthcare system. We used a 40-year simulation period, which is common in cost-effectiveness analyses regarding diabetes,[48 49 51-53] to fully capture the long disease progression and mortality of the diabetes population and to measure the long-term cost implications. This long simulation period also ensures that patients with a long life expectancy are not excluded, considering the relatively high figures in Switzerland.

The UKPDS-OM2 was provided for free by the University of Oxford. A detailed description of the model and its validation has been previously published.[57] The model uses a patient-level approach to model adult populations with no restrictions on diabetes duration.[57] The model simulates the lifetime progression of T2DM and projects the clinical and economic outcomes in T2DM over the patient's lifecycle (see Figure 7, page 63). These outcomes include gains in life expectancy and quality-adjusted life-years (QALYs), long-term treatment costs of diabetes-related complications, and costs of SMBG. Using these

2 The number of strips corresponds to the median (because the distributions were skewed) of actual testing frequencies in the intervention group, based on the data from the randomized controlled trials in our literature review. This median was equal to 7 test strips per week in the intervention group when the HbA1c change of -0.29%-points was estimated, and equal to 5 test strips per week in the intervention group when the HbA1c change of -0.33%-points was estimated. The observed stronger HbA1c decrease with fewer number of test strips is due to the inclusion of different primary studies in the two meta-analyses (-0.29%-points: 23 RCTs with SMBG vs any control group; -0.33%-points: 17 RCTs with SMBG vs no SMBG) and should be regarded as a chance effect. The median of actual testing frequencies in the control group for both efficacy estimates is equal to zero.

outcomes we also estimate the incremental cost-effectiveness ratio (ICER) comparing the additional net cost of SMBG versus no SMBG with its additional health benefits.

The UKPDS-OM2 model uses the UKPDS 82 [57] risk regression equations for the first occurrence of 8 diabetes-related complications and death (Table 13) and for the second occurrence of myocardial infarction, stroke and amputation, based on the demographic characteristics and on a number of risk factors of each single modelled patient, including HbA1c. According to these equations and the patients' baseline characteristics, the probability of experiencing a diabetes-related complication or death is calculated for each patient in the cohort for every simulated year. The model accounts for the interdependence of complications in individual patients. Complications may also cluster or interact in a patient due to shared risk factors. Therefore, one patient could experience more than one complication and if a complication is predicted to occur in a given year it could affect a patient's risk of experiencing other complications or death in the same or in following years, e.g. if the risk of experiencing a complication in the future is associated with the presence of a specific complication.[58] If an individual is predicted to die, then this person exits the simulation and her total years lived and QALYs are calculated. If the individual remains in the simulation, his or her baseline characteristics are updated for the next simulated year.

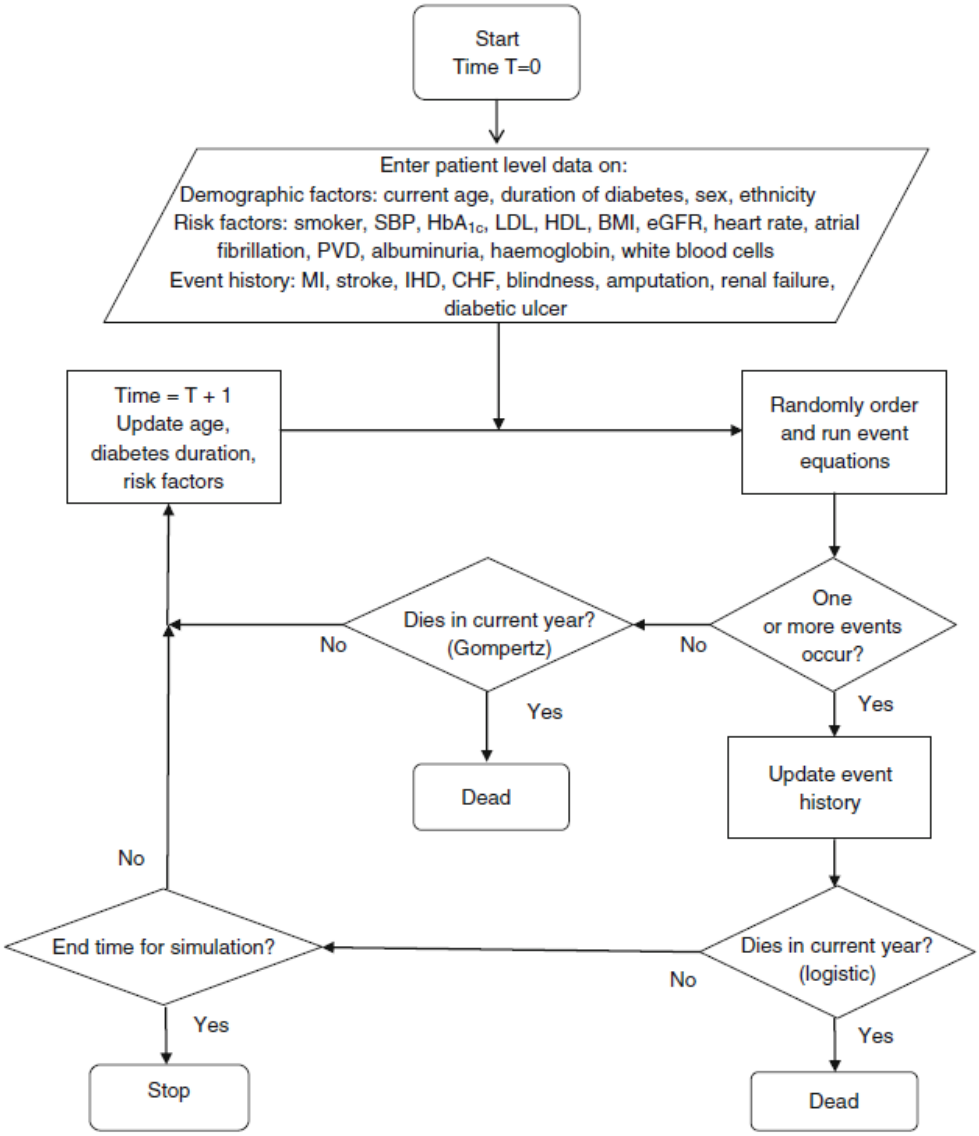
Although the user cannot modify the coefficients of these equations, a number of input parameters and modelling assumptions can be modified. For example, all continuous risk factors can be specified as a continuous variable on a year-by-year basis, either by holding the initial values constant for the simulation period or by using linear regression. This allows to model the effects of small changes in HbA1c on the diabetes-related complications.57 We assumed that all risk factors other than HbA1c levels remain constant over the simulation period. Regarding the initial HbA1c level in the intervention group, we decreased its value by the estimated efficacy of SMBG in the first year and then assumed that HbA1c increases linearly by 1% in relative terms every year over the simulation period. For HbA1c in the control group, we assumed that HbA1c increases linearly by 1% every year in relative terms from the first year of the simulation. We thus implicitly also assume that the HbA1c decrease achieved with SMBG is maintained over the simulation period. Due to lack of clinical evidence this pragmatic assumption was based on the clinical experience of our advising diabetologist.

Table 13: Clinical outcomes in UKPDS-OM2

Diabetes-related Complications	Types of death
Ischaemic heart disease (IHD)	All death
Myocardial infarction (MI)	Cardiovascular diseases (CVD) death
Heart failure	Other death
Stroke	
Amputation	
Blindness in one eye	
Renal failure	
Ulcer (diabetic foot)	

Source: Hayes et al. 2013 [57]

Figure 7: Overview of the UKPDS-OM2



Source: Hayes et al. 2013

Gompertz refers to the regression model used for estimating mortality in the UKPDS-OM2, named after Benjamin Gompertz (1779-1865) (for more information see the statistical appendix in Hayes et al. (2013) [57]

Parameters of model cohort

The analysis was run over 40 years in one-year intervals, for 2,000 patients (1,000 in the intervention and 1,000 in the control group), 10,000 loops and 500 bootstraps. The number of 1,000 simulated patients per group is typically used in evaluations with this type of models (see for example [50-52]). In order to obtain stable results we performed 10,000 loops. This allowed to achieve a relative error of the difference in life expectancy of below 5% (i.e. first order uncertainty), as recommended by the model developers.[59] The number of bootstraps is associated with second order uncertainty and used to estimate

confidence intervals of life expectancy, QALYs and costs.[59] Each bootstrap run uses a different set of model equation parameters that were estimated from bootstrapping with replacement the original UKPDS trial population.[59] Larger number of internal loops and bootstraps leads to more precise confidence intervals but at the costs of very long simulation times. Accounting for first and second order uncertainty, as well as the simulation time, we conducted 10,000 loops and 500 bootstraps for the main results and 10,000 loops and 200 bootstraps for the sensitivity analyses. No race distinctions were made, because 98.5% of the population in Switzerland are Caucasian.

We simulated a 1,000-patient cohort using the baseline demographics and risk factor profiles of non-insulin treated T2DM in Switzerland supplemented with data from the US National Health and Nutrition Examination Survey (NHANES)[60] 2015-2016 (Table 14). We name this cohort *SimCombined*. The Swiss data were obtained from a Swiss general practitioner (GP) network. NHANES entails information regarding the health and nutritional status of adults and children in the United States based on interviews and physical examinations. For the simulation of the patient cohort we applied the Cholesky decomposition to generate a multivariate random sample, using the correlations between the baseline demographics and risk factors. The Cholesky decomposition allowed us to not only draw random values from the characteristics' distribution, but we also accounted for the correlations between these characteristics. These correlations were based on the UKPDS trial and were provided by the Health Economics Research Centre, University of Oxford. We also generated two additional cohorts, to test the robustness of our results, based on only the NHANES dataset. *SimNHANES* entails also 1,000 simulated patients but this time using only data from NHANES and the correlations from the UKPDS trial. *RawNHANES* was the raw dataset of the non-insulin treated T2DM in NHANES (n = 595).

Table 14: Cohort characteristics

Characteristics	Unit	Mean value (sd)		
		Switzerland N = 241	USA N = 595	SimCombined N = 2,000
female	%	40.66	44.87	40.66
age	years	64.57 (13.23)	60.93 (13.54)	64.57 (13.23)
diabetes duration	years		10.12 (9.52)	9.30 (8.80)*
weight	kg	86.31 (17.18)	89.06 (23.21)	86.31 (17.18)
height	m	1.67 (0.09)	1.66 (0.10)	1.67 (0.09)
Atrial fibrillation	%			0.75**
Peripheral vascular disease	%		12.77	12.77
smoker	%	35.00	20.67	35.00
albuminuria	%		25.04	25.04
high-density lipoprotein cholesterol	mmol/l		1.28 (0.42)	1.28 (0.42)
low-density lipoprotein cholesterol	mmol/l	3.29 (1.03)	2.62 (0.56)	3.29 (1.03)
systolic blood pressure	mmHg	143.42 (18.16)	131.93 (19.12)	143.42 (18.16)
HbA1c	%	7.11 (1.18)	7.18 (1.67)	7.11 (1.18)
heart rate	bpm		73.25 (12.32)	73.25 (12.32)
white blood cells	x10^9/l		7.62 (2.06)	7.62 (2.06)
haemoglobin	g/dl		13.69 (1.52)	13.69 (1.52)
eGFR CKD-EPI	ml/min/1.73m^2		82.31 (22.41)	82.31 (22.41)
ischaemic heart disease	number of years since event		8% ≥ 1 years 5% = 0 years 91% = no event	8% ≥ 1 years 5% = 0 years 91% = no event
	%		8.83	8.83
heart failure	number of years since event		8% ≥ 1 years 5% = 0 years 91% = no event	8% ≥ 1 years 5% = 0 years 91% = no event
	%		8.77	8.77
amputation	%		0.91***	0
blindness	%		12.79****	0
renal failure	%		8.08	0
stroke	number of years since event		6% ≥ 1 years 1% = 0 years 93% = no event	6% ≥ 1 years 1% = 0 years 93% = no event
	%		7.06	7.06
myocardial infarction	number of years since event		9% ≥ 1 years 1% = 0 years 90% = no event	9% ≥ 1 years 1% = 0 years 90% = no event
	%		9.95	9.95
ulcer	%		10.71***	0

Sources: Swiss general practitioner (GP) network and NHANES [60] 2015-2016.
eGFR: estimated glomerular filtration rate. Albuminuria was defined as urinary albumin-to-creatinine ratio > 30 mg/g. Peripheral vascular disease was defined based on the presence of intermittent claudication or ankle brachial pressure index < 0.9. Information on this index was last extracted in NHANES 2003-2004. We, therefore, calculated PVD in NHANES 2003-2004 and predicted whether an individual in NHANES 2015-2016 would have PVD using random draws, based on the drivers of PVD estimated in NHANES 2003-2004. We could not use the mean, because the UKPDS-OM2 does not allow numerical values for binary variables. eGFR was calculated based on the 2009 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation, (p.7 in [61]).

** This is a Swiss parameter extracted from Lamine et al.[62]. ** Atrial fibrillation could not be directly extracted from the dataset of the Swiss GP network or NHANES 2015-2016 and was therefore extracted from Pollock et al [50]. Other studies have also shown that the prevalence of AF is very low in T2DM ranging from 0.4 [63] to 1.3 [64]. *** These parameters were extracted from NHANES 2003-2004, because they were not available in NHANES 2015-2016. **** Blindness in NHANES 2015-2016 also includes "serious difficulty seeing even when wearing glasses?" [60].*

Additional assumptions

Due to lack of data, the patient cohort was assumed to have no history with pre-existing amputation, blindness, renal failure and ulcer. Hayes et al.[57] have shown that pre-existing ulcer and blindness are not associated with mortality in the current year. Pre-existing ulcer is only associated with the probability of heart failure and blindness is only associated with the probability of renal failure. Pre-existing amputation is associated with the probability of mortality, heart failure, IHD, MI in males, stroke and renal failure. However, the prevalence of amputation in non-insulin treated T2DM is very low (0.91% in NHANES 2003-2004 (Table 14, page 65), 2.6% according to Pollock [50]). Additionally, only 8.1% of the non-insulin treated T2DM patients in NHANES 2015-2016 reported having weak or failing kidney, while 0.0% to 0.9% had baseline renal complications according to Brändle et al. 2009.[64] The prevalence of blindness and ulcer in non-insulin treated T2DM patients in the USA is 12.8% and 10.7% respectively (Table 14). Finally, the annual event rate for these complications is relatively low ranging from 0.0006 events/total patient-years for second amputation to 0.003 events/total patient-years for blindness.[57] In Canada, less than 1% of T2DM patients have a history of stroke, blindness, amputation or renal disease.[49]

Utility decrements and costs of diabetes-related complications

All costs of diabetes complications were drawn from Swiss data sources and expressed in 2016 Swiss Francs. Future costs and health outcomes were discounted with a 3% rate. The cost and utility decrements of the 8 diabetes-related complications considered in the UKPDS-OM2 are shown in Table 15. The initial utility value of diabetes without complications is equal to 0.807.[65] Table 16 on page 68 shows the parameters used for the calculation of the cost in the absence of complications and the therapy costs of SMBG. More information on the cost and utility parameters can be found in Sections 11.12-11.16 of the Appendix.

Table 15: Costs and utility decrements diabetes complications per patient per year (CHF, 2016)

Diabetes complications	At time of event			In subsequent years		Sources
	Fatal cost	Non-fatal cost	Utility Decrement*	Cost	Utility decrement*	
Ischaemic heart disease	7,497	22,160	0.000	2,979	0.000	Brändle et al. 2011 [66]
Myocardial infarction	8,707	33,877	–0.065	2,794	0.000	Authors' calculation based on Wieser et al. 2012[67]
Heart failure	10,825	43,021	–0.101	14,958	–0.101	Brändle et al. 2011 [66]
Stroke	11,153	34,814	–0.165	12,388	–0.165	Authors' calculation based on Pletscher et al. 2013[68]
Amputation	29,106	31,997	–0.172	1,523	–0.172	Brändle et al. 2011 [66]
Blindness		6,667	0.000	6,667	0.000	Brändle et al. 2011 [66]
Renal failure	0.00	97,895	–0.330	90,258	–0.330	Authors' calculation based on Eichler et al. 2013[69] and Sandoz et al. 2004 [70]
Ulcer		4,367	–0.210	220	–0.210	Brändle et al. 2009 [64]

** The utility decrements are drawn from Alva et al..[65] The utility decrements for renal failure and for ulcer are drawn from Lung et al..[71] The cost in the subsequent years regards surviving subjects and is applied in all subsequent years until the end of the simulation period or until the subject dies.*

Sensitivity Analyses

All modelling studies are based on assumptions regarding the population, costs and other model parameters. In order to test the robustness of our results, we conducted univariate and multivariate sensitivity analyses. In the univariate sensitivity analysis we selected particular model parameters based on our model assumptions and assessed how the results changed when these parameters were modified. In particular, the key model assumptions were evaluated by testing the effect of varying the cohort, the HbA1c efficacy estimates, the number of test strips, the discounting rate, the simulation period and the therapy costs (number of SMBG lancets and cost of SMBG device). In the multivariate sensitivity analysis, we assessed how the results changed when multiple parameters were modified simultaneously. The multivariate sensitivity analysis used 500 full sets of equation parameters estimated by the model developers [57] [59] with bootstrapping (with replacement) the original UKPDS trial population. The resulting cost-effectiveness scatter plots and cost-effectiveness acceptability curves show the probability of SMBG being cost-effective at different hypothetical willingness-to-pay (WTP) thresholds.

Table 16: Other cost parameters

Type of cost	CHF (2016)	Frequency[72]	Source
Cost in the absence of complications	**569**		Authors' calculation based on the following parameters:
Cost per consultation in GP including laboratory costs	96	3 times per year	SWICA
Additional cost from feet examination	34	Once per year	TARMED* Position 00.0415 (19.76 TP) was applied twice and multiplied with the mean tax point value in 2016 (CHF 0.87)
Cost per consultation in Ophthalmologist	246	Once per year	SASIS Datapool
Therapy cost prior to complication for:	**Intervention**	**Control**	
ΔHba1c = –0.29 %P (95%CI: –0.40 to –0.18)	**292** for 365 SMBG/ year	**0** for 0 SMBG/year	Authors' calculation based on number of strips and on the following parameters:
ΔHba1c = –0.33 %P (95%CI: –0.45 to –0.21)	**215** for 260 SMBG/year	**0** for 0 SMBG/year	
SMBG strip	0.62		MiGEL 2019 [12] (21.03.01.01.1)
SMBG lancet	0.12		MiGEL 2019 [12] (21.03.05.00.1)
SMBG device	43.00		MiGEL 2019 [12] (21.02.01.00.1; 1 device every two years)

*Frequency of healthcare utilization was based on the diabetes treatment guidelines.[72] * TARMED refers to the Swiss official medical tariff. The efficacy estimates are based on our meta-analyses described in Section 6.1. The number of strips corresponds to the median (because the distributions were skewed) of actual testing frequencies in each group, based on the data from the randomized controlled trials in our literature review. MiGeL 2019 [12] refers to the list of the medical aids and appliances covered by the compulsory health insurance. Deviations may occur due to internal rounding.*

7.2.2 Results of cost-effectiveness analysis

Table 17 shows the predicted cumulative event rates of the 8 diabetes-related complications and death examined in the UKPDS-OM2 over a period of 40 years for 2 SMBG efficacy estimates. Using SMBG compared to control interventions leads to small reduction in diabetes-related complications. For example, for the efficacy estimate ΔHba1c = –0.29%-points:

– In 5 (MI, stroke, amputation, blindness and CVD death) of 11 modelled cumulative event rates of diabetes-related complications, SMBG leads to a small absolute risk reduction ranging from 0.29% to 0.65%. The number needed to treat to avert one of these complications over the examined period ranges from 153 to 343.

– In 1 (event "other death") of 11 modelled cumulative event rates the SMBG group exhibits a small yet higher risk of 0.53% compared to the control group. This might be explained by the fact that a higher number of people in the SMBG group die of non-diabetes-related complications.

A similar pattern holds for the HbA1c efficacy of –0.33%-points.

According to the model, SMBG is associated with increased life expectancy and QALYs. Both SMBG efficacy rates lead to an increase of 0.05 years in life expectancy (95%-CI: 0.04 to 0.), which corresponds to 18 to 20 days and 0.04 to 0.05 QALYs (ΔHba1c = –0.29%-points 95%-CI: 0.03 to 0.06; ΔHba1c = –0.33%-points 95%-CI: 0.04 to 0.06) (Table 18, page 71).

The modelled ICER decreases with higher SMBG efficacy. For example, the cost-utility ICER drops from CHF 65,023 (ΔHba1c = –0.29%-points) to CHF 41,078 (ΔHba1c = –0.33%-points) per QALY gained. This can be explained by the drop in the difference of the total costs from CHF 2,910 (for ΔHba1c = –0.29%-points) to CHF 2,013 (for ΔHba1c = –0.33%-points), which is mainly driven by the decreasing therapy costs.

Table 17: Cumulative event rates of diabetes-related complications for base case estimates

		ΔHba1c = –0.29%-points			ΔHba1c = –0.33%-points		
			95% CI			*95% CI*	
		event rate	*lower*	*upper*	event rate	*lower*	*upper*
Ischaemic heart disease	Intervention group	14.32%	12.64%	16.44%	14.33%	12.66%	16.44%
	Control group	14.25%	12.59%	16.34%	14.25%	12.59%	16.34%
	ARD	**0.07%**	**-0.11%**	**0.26%**	**0.08%**	**-0.10%**	**0.28%**
	NNT						
Myocardial infarction	Intervention group	28.56%	25.90%	32.10%	28.49%	25.83%	32.03%
	Control group	29.22%	26.53%	32.72%	29.22%	26.53%	32.72%
	ARD	**-0.65%**	**-1.04%**	**-0.26%**	**-0.73%**	**-1.14%**	**-0.31%**
	NNT	153			138		
Heart failure	Intervention group	9.67%	8.24%	11.54%	9.68%	8.25%	11.55%
	Control group	9.62%	8.20%	11.48%	9.62%	8.20%	11.48%
	ARD	**0.05%**	**-0.11%**	**0.21%**	**0.06%**	**-0.10%**	**0.21%**
	NNT						
Stroke	Intervention group	18.80%	16.19%	22.13%	18.75%	16.15%	22.10%
	Control group	19.22%	16.57%	22.52%	19.22%	16.57%	22.52%
	ARD	**-0.41%**	**-0.77%**	**-0.05%**	**-0.47%**	**-0.84%**	**-0.08%**
	NNT	242			215		
Amputation	Intervention group	5.42%	4.00%	7.58%	5.37%	3.96%	7.52%
	Control group	5.90%	4.38%	8.23%	5.90%	4.38%	8.23%
	ARD	**-0.48%**	**-0.80%**	**-0.28%**	**-0.53%**	**-0.88%**	**-0.32%**
	NNT	208			190		
Blindness	Intervention group	5.35%	4.31%	6.31%	5.30%	4.28%	6.28%
	Control group	5.64%	4.59%	6.63%	5.64%	4.59%	6.63%
	ARD	**-0.29%**	**-0.47%**	**-0.12%**	**-0.33%**	**-0.52%**	**-0.15%**
	NNT	343			299		
Renal failure	Intervention group	0.46%	0.22%	0.72%	0.46%	0.22%	0.72%
	Control group	0.46%	0.22%	0.72%	0.46%	0.22%	0.72%
	ARD	**0.00%**	**-0.03%**	**0.03%**	**0.00%**	**-0.03%**	**0.03%**
	NNT						
Ulcer	Intervention group	2.86%	2.20%	3.52%	2.85%	2.19%	3.51%
	Control group	3.01%	2.31%	3.69%	3.01%	2.31%	3.69%
	ARD	**-0.16%**	**-0.30%**	**0.01%**	**-0.17%**	**-0.32%**	**0.00%**
	NNT						
All death	Intervention group	99.77%	94.45%	105.06%	99.77%	94.44%	105.06%
	Control group	99.78%	94.51%	105.03%	99.78%	94.51%	105.03%
	ARD	**-0.01%**	**-0.60%**	**0.57%**	**-0.01%**	**-0.61%**	**0.58%**
	NNT						
Cardiovascular diseases death	Intervention group	38.72%	35.91%	43.42%	38.69%	35.85%	43.38%
	Control group	39.26%	36.42%	43.94%	39.26%	36.42%	43.94%
	ARD	**-0.53%**	**-0.88%**	**-0.14%**	**-0.57%**	**-0.95%**	**-0.17%**
	NNT	187			177		
Other death	Intervention group	61.05%	54.92%	65.47%	61.08%	54.96%	65.51%
	Control group	60.52%	54.45%	64.94%	60.52%	54.45%	64.94%
	ARD	**0.53%**	**0.02%**	**0.95%**	**0.56%**	**0.07%**	**1.02%**

ARD: Absolute risk difference between intervention and control groups. NNT: number needed to treat. NNT is only reported for significant negative ARDs, for which the incidence rate is higher in the control compared to the one in the intervention group. For ΔHba1c = –0.29%-points the intervention group used a median of 365 SMBG/year and the control group 0 SMBG/year. For ΔHba1c = –0.33%-points the intervention group used a median of 260 SMBG/year and the control group 0 SMBG/year.

Table 18: Cost-effectiveness and cost-utility for the two base case efficacy estimates

		Life expectancy (years)			Total QALE (QALYs)			Therapy costs (CHF, 2016)			Cost of complications (CHF, 2016)			Total cost (CHF, 2016)			CE ICER CHF/year	CU ICER CHF/QALY
			95% CI			95% CI			95% CI			95% CI			95% CI				
			Lower	Upper		Lower	Upper		Lower	Upper		Lower	Upper		Lower	Upper		
ΔHba1c = –0.29%-points																		
SimCombined	Intervention	10.81	10.61	11.19	8.55	8.40	8.84	3,156	3,098	3,266	48,899	46,076	51,728	52,055	49,218	54,932		
	Control	10.76	10.57	11.14	8.51	8.36	8.79	0	0	0	49,145	46,405	52,047	49,145	46,405	52,047		
	Difference	**0.05**	0.04	0.07	**0.04**	0.03	0.06	3,156	3,098	3,266	-245	-410	-188	**2,910**	2,750	3,021	**58,195**	**65,023**
ΔHba1c = –0.33%-points																		
SimCombined	Intervention	10.82	10.62	11.20	8.56	8.40	8.85	2,322	2,280	2,404	48,835	46,059	51,684	51,157	48,372	54,039		
	Control	10.76	10.57	11.14	8.51	8.36	8.79	0	0	0	49,145	46,405	52,047	49,145	46,405	52,047		
	Difference	**0.05**	0.04	0.07	**0.05**	0.04	0.06	2,322	2,280	2,404	-310	-448	-216	**2,013**	1,882	2,144	**36,900**	**41,078**

For ΔHba1c = –0.29%-points the intervention group used a median of 365 SMBG/year and the control group 0 SMBG/year.

For ΔHba1c = –0.33%-points the intervention group used a median of 260 SMBG/year and the control group 0 SMBG/year.

CU: cost-utility, CE: cost-effectiveness.

Cost-utility ICER shows the amount of money spend for one QALY gained. Cost-effectiveness ICER shows the amount of money spent for one year of life expectancy gained.

Results of sensitivity analysis

We obtain very similar results when using the SimNHANES or RawNHANES cohort instead of the SimCombined or when using a higher SMBG efficacy compared to the base cases. In particular, the cumulative incidence rates of MI, stroke, amputation, blindness and CDV death slightly decrease with SMBG over a time horizon of 40 years (Table 19, page 74). These reductions are statistically significant for all sensitivity analyses, besides the reduction of stroke when the cohort is RawNHANES. As a result, a statistically significant reduction in life expectancy ranges from 14 days, with the RawNHANES cohort, to 51 days, with an HbA1c change of –1.00%-points (Table 20, page 75). The smallest gain in life expectancy equal to 11 days is observed with an HbA1c change of –0.18%-points (Table 20). The effect of SMBG on the difference of total costs remains small ranging from CHF 2,337 to CHF 3,641 compared to CHF 2,910 for an HbA1c change of –0.29%-points (Table 20) and from CHF 1,495 to CHF 2,579 compared to CHF 2,013 for an HbA1c change of –0.33%-points (Table 21, page 76). The largest change in the ICER is observed when the SMBG efficacy increases from the base cases to an HbA1c change of –1.00% leading to a 71% decrease in the ICER per year and per QALY gained. A comparison of Table 20 with Table 21 shows that the ICER drops by 36% when the number of test strips is reduced from 365 to 260 per year for a SMBG efficacy of ΔHbA1c of –1%-points.

Table A 18 and Table A 19 show the effect of a reduced simulation period. Reducing the simulation period from 40 years to 5 and 10 years leads to a relative reduction of 40% in the cumulative event rates of the diabetes-related complications to 86%. Considering that the total costs also reduce with a smaller simulation period, the ICERs increase by 6 to 8 times and by approximately twice for a simulation period of 5 and 10 years respectively, thus reducing the cost-effectiveness of SMBG,

Removing the SMBG devices from the intervention costs, and assuming a lower consumption of lancets (ratio of lancets to test strips assumed equal to 21% based on data from diabetesschweiz regarding all diabetes patients), reduces the difference in therapy cost between the intervention and control group. In particular, over a period of 40 years, the difference in therapy cost reduces from CHF 3,156 (Table 18) to CHF 2,546 and from CHF 2,322 (Table 18) to CHF 1,820 for a HbA1c change of -0.29%-points and -0.33%-points respectively. This leads to a drop in the ICERs by 21% and 25% respectively.

Figure 8 (page 77) shows the cost-effectiveness scatter plot for 500 different set of model parameters, for the two base case efficacy estimates and a hypothetical WTP threshold of CHF 100,000 per QALY gained. This WTP threshold has been frequently used in health economic evaluations for Switzerland but is not in official use. All points are concentrated in the northeast quadrant indicating higher costs, but also QALY gains. The cost-effectiveness acceptability curves Figure 9 (page 77) shows that the probability that SMBG would be cost-effective at a WTP threshold of CHF 100,000 is 100% for both

SMBG base case efficacies. It is important to note, that this cost effectiveness scatter plot is modelled using (1) the effects of SMBG on clinical endpoints that in turn lead to small increased life expectancy and QALYs over 40 years and (2) small increased total cost for SMBG of CHF 2,013 to CHF 2,910 over 40 years.

7.2.3 Limitations of cost-effectiveness estimation

Study limitations include the cohort and model assumptions. Due to lack of data we combined Swiss with US cohort baseline data. In contrast to other studies, both datasets include only information on non-insulin treated T2DM and are thus comparable. We also had to make assumptions regarding the history of pre-existing complications. As this information is very scarce, previous studies [48] [49] applying the UKPDS-OM1 have made similar assumptions. Furthermore, we had to make assumptions regarding the progression of the risk factors over the simulation period, especially regarding HbA1c and the maintained effect of SMBG over this period.

Table 19: Univariate sensitivity analysis on type of cohort and degree of SMBG efficacy regarding diabetes-related complications

	SimNHANES			RawNHANES			SimCombined					
	ΔHba1c = –0.29%-points						ΔHba1c = –0.50%-points			ΔHba1c = –1.00%-points		
		95% CI			95% CI			95% CI			95% CI	
		Lower	Upper		Lower	Upper		Lower	Upper		Lower	Upper
Ischaemic heart disease												
Intervention	13.29	11.51	15.41	12.88	11.15	15.04	14.36	12.62	16.48	14.48	12.71	16.62
Control	13.22	11.46	15.35	12.85	11.11	14.97	14.24	12.50	16.33	14.24	12.50	16.33
ARD	0.06	-0.12	0.24	0.02	-0.19	0.29	0.13	-0.06	0.31	0.24	0.02	0.44
Myocardial infarction												
Intervention	24.49	21.69	27.17	22.93	20.78	25.54	28.21	25.38	31.61	27.37	24.51	30.75
Control	25.05	22.20	27.77	23.49	21.32	26.13	29.20	26.41	32.50	29.20	26.41	32.50
ARD	-0.56	-0.95	-0.25	-0.56	-1.00	-0.19	-0.99	-1.54	-0.55	-1.83	-2.75	-1.13
Heart failure												
Intervention	9.42	7.77	11.22	9.78	8.28	11.74	9.71	8.22	11.50	9.76	8.26	11.59
Control	9.38	7.75	11.17	9.77	8.28	11.71	9.63	8.15	11.40	9.63	8.15	11.40
ARD	0.04	-0.12	0.19	0.01	-0.18	0.24	0.08	-0.08	0.24	0.13	-0.03	0.32
Stroke												
Intervention	13.76	11.70	16.22	13.80	12.12	16.12	18.58	16.19	21.82	17.99	15.61	21.37
Control	14.06	12.00	16.55	14.14	12.44	16.41	19.20	16.89	22.39	19.20	16.89	22.39
ARD	-0.31	-0.60	-0.03	-0.34	-0.67	0.01	-0.63	-1.11	-0.14	-1.21	-1.98	-0.33
Amputation												
Intervention	6.64	4.49	9.34	7.88	5.61	11.17	5.14	3.65	7.31	4.55	3.18	6.48
Control	7.26	4.97	10.22	8.63	6.14	12.22	5.90	4.27	8.35	5.90	4.27	8.35
ARD	-0.62	-1.03	-0.36	-0.75	-1.19	-0.41	-0.77	-1.23	-0.47	-1.36	-2.14	-0.87
Blindness												
Intervention	5.08	3.90	6.03	5.26	4.15	6.29	5.16	4.10	6.10	4.78	3.74	5.75
Control	5.38	4.13	6.37	5.57	4.40	6.67	5.64	4.54	6.55	5.64	4.54	6.55
ARD	-0.30	-0.49	-0.13	-0.32	-0.53	-0.10	-0.47	-0.69	-0.23	-0.85	-1.19	-0.47
Renal failure												
Intervention	0.44	0.22	0.69	2.04	1.47	2.59	0.46	0.24	0.75	0.46	0.24	0.75
Control	0.44	0.22	0.68	2.03	1.46	2.59	0.46	0.24	0.75	0.46	0.24	0.75
ARD	0.00	-0.03	0.03	0.00	-0.08	0.08	0.00	-0.03	0.03	0.00	-0.03	0.04
Ulcer												
Intervention	3.13	2.26	3.88	3.27	2.38	4.34	2.79	2.13	3.39	2.58	1.94	3.20
Control	3.29	2.38	4.11	3.46	2.48	4.62	3.00	2.30	3.69	3.00	2.30	3.69
ARD	-0.16	-0.35	0.01	-0.19	-0.41	0.02	-0.22	-0.45	0.00	-0.42	-0.77	-0.02
All death												
Intervention	98.86	92.57	104.50	91.17	87.93	93.62	99.77	94.19	105.09	99.76	94.07	105.09
Control	98.89	92.62	104.52	91.30	88.09	93.76	99.78	94.31	105.01	99.78	94.31	105.01
ARD	-0.03	-0.62	0.52	-0.12	-0.85	0.50	-0.01	-0.67	0.63	-0.02	-0.94	0.85
Cardiovascular diseases death												
Intervention	32.40	29.23	36.25	30.67	28.52	34.14	38.45	35.47	43.01	37.78	34.77	42.36
Control	32.88	29.67	36.71	31.09	28.91	34.59	39.24	36.28	43.75	39.24	36.28	43.75
ARD	-0.47	-0.81	-0.12	-0.42	-0.87	-0.04	-0.78	-1.25	-0.38	-1.45	-2.15	-0.86
Other death												
Intervention	66.45	59.94	71.53	60.50	56.17	62.89	61.31	55.24	65.84	61.97	55.81	66.61
Control	66.01	59.58	71.09	60.21	55.85	62.61	60.54	54.45	64.99	60.54	54.45	64.99
ARD	0.44	-0.08	0.88	0.29	-0.30	0.83	0.77	0.26	1.31	1.43	0.74	2.19

ARD: Absolute risk difference between intervention and control groups.

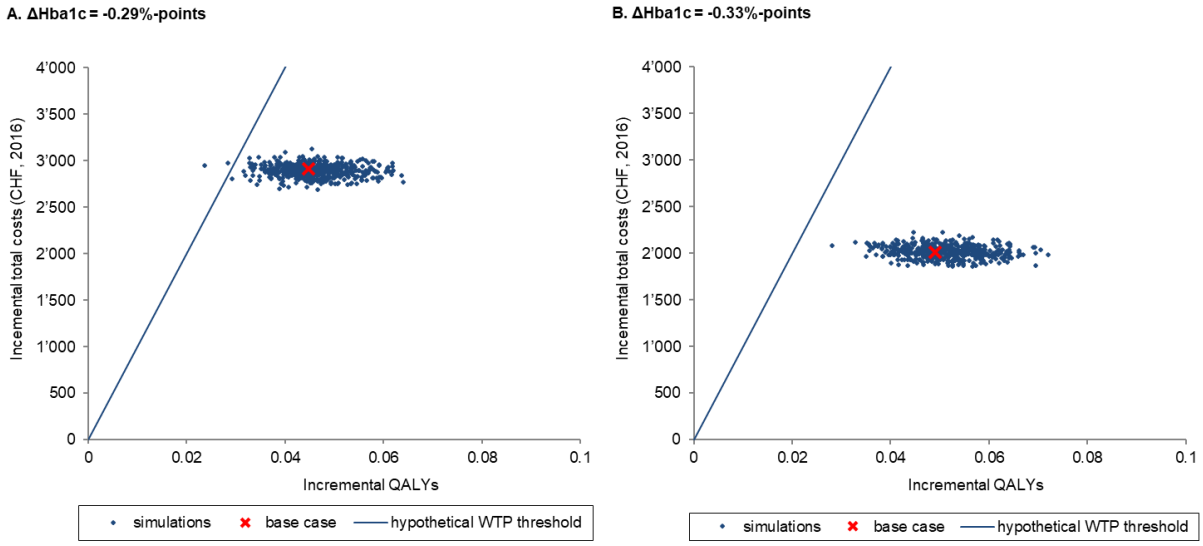
Table 20: Univariate sensitivity analysis on ICER with SMBG efficacy of ΔHba1c = –0.29%-points

		Life expectancy (years)			Total QALE (QALYs)			Total cost (CHF, 2016)			CE ICER CHF/year	%-Change	CU ICER CHF/QALY	%-Change
			95% CI			95% CI			95% CI					
			Lower	Upper		Lower	Upper		Lower	Upper				
Base case: ΔHba1c = –0.29%-points (365 SMBG/year vs 0 SMBG/year), SimCombined, discounting = 3.0%, CE ICER = 58,195, CU ICER = 65,023														
SimNHANES	Intervention Group	12.80	12.54	13.22	10.15	9.96	10.49	55,408	51,876	58,225				
	Control Group	12.75	12.49	13.17	10.10	9.91	10.44	51,929	48,549	54,720				
	Difference	**0.05**	0.04	0.06	**0.04**	0.03	0.06	**3,478**	3,319	3,568	**71,175**	22%	**78,085**	20%
RawNHANES	Intervention Group	12.78	12.59	13.08	10.12	9.98	10.35	55,567	52,849	58,502				
	Control Group	12.74	12.54	13.04	10.08	9.93	10.32	52,252	49,462	54,998				
	Difference	**0.04**	0.03	0.06	**0.04**	0.03	0.06	**3,315**	3,272	3,561	**84,348**	45%	**84,913**	31%
ΔHba1c = –1.00%	Intervention Group	10.90	10.69	11.32	8.63	8.47	8.95	51,497	48,853	54,573				
	Control Group	10.76	10.56	11.13	8.51	8.35	8.79	49,160	46,539	52,033				
	Difference	**0.14**	0.11	0.19	**0.13**	0.10	0.17	**2,337**	2,075	2,654	**16,704**	-71%	**18,557**	-71%
ΔHba1c = –0.50%	Intervention Group	10.84	10.63	11.23	8.57	8.41	8.87	51,842	49,252	54,885				
	Control Group	10.76	10.56	11.13	8.51	8.35	8.79	49,160	46,539	52,033				
	Difference	**0.07**	0.06	0.11	**0.07**	0.05	0.09	**2,681**	2,561	2,899	**36,829**	-37%	**40,800**	-37%
ΔHba1c = –0.40%	Intervention Group	10.83	10.62	11.21	8.56	8.40	8.86	51,923	49,292	54,965				
	Control Group	10.76	10.56	11.13	8.51	8.35	8.79	49,160	46,539	52,033				
	Difference	**0.06**	0.05	0.09	**0.06**	0.04	0.08	**2,763**	2,659	2,971	**43,548**	-25%	**48,367**	-26%
ΔHba1c = –0.18%	Intervention Group	10.79	10.59	11.17	8.54	8.38	8.82	52,091	49,479	55,114				
	Control Group	10.76	10.56	11.13	8.51	8.35	8.79	49,160	46,539	52,033				
	Difference	**0.03**	0.03	0.05	**0.03**	0.02	0.04	**2,930**	2,858	3,080	**95,182**	64%	**104,378**	61%
No discounting	Intervention Group	13.89	13.58	14.59	10.96	10.74	11.50	67,139	63,378	71,859				
	Control Group	13.82	13.51	14.49	10.90	10.67	11.42	63,498	59,691	67,959				
	Difference	**0.07**	0.06	0.11	**0.06**	0.06	0.10	**3,641**	3,537	3,932	**52,334**	-10%	**58,036**	-11%

Table 21: Univariate sensitivity analysis on ICER with SMBG efficacy of ΔHba1c = –0.33%-points

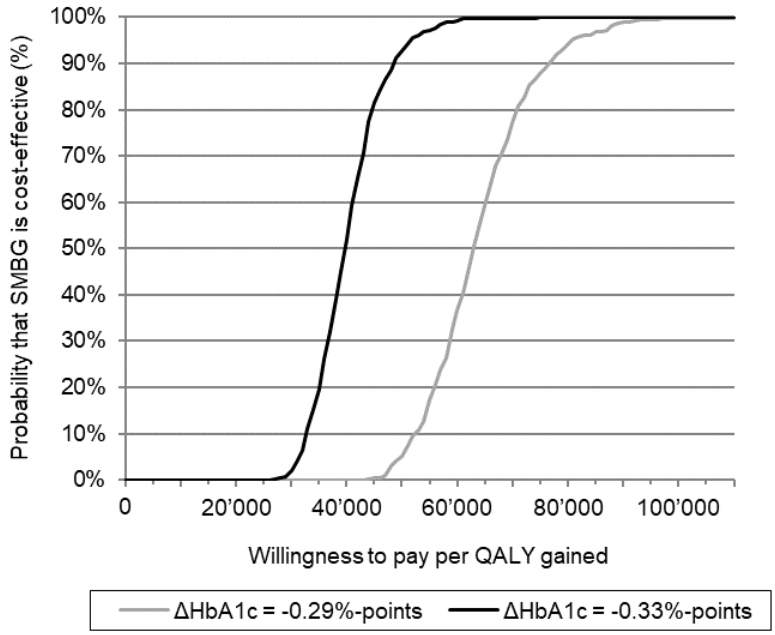
		Life expectancy (years)			Total QALE (QALYs)			Total cost (CHF, 2016)			CE ICER CHF/year	%-Change	CU ICER CHF/QALY	%-Change
			95% CI			*95% CI*			*95% CI*					
			Lower	*Upper*		*Lower*	*Upper*		*Lower*	*Upper*				
Base case: ΔHba1c = –0.33%-points (260 SMBG/year vs 0 SMBG/year), SimCombined, discounting = 3.0%, CE ICER = 36,900, CU ICER = 41,078														
ΔHba1c = –1.00%	Intervention Group	10.90	10.69	11.32	8.63	8.47	8.95	50,655	48,009	53,713				
	Control Group	10.76	10.56	11.13	8.51	8.35	8.79	49,160	46,539	52,033				
	Difference	**0.14**	0.11	0.19	**0.13**	0.10	0.17	**1,495**	1,242	1,812	**10,688**	-71%	**11,874**	-71%
ΔHba1c = –0.50%	Intervention Group	10.84	10.63	11.23	8.57	8.41	8.87	51,005	48,413	54,029				
	Control Group	10.76	10.56	11.13	8.51	8.35	8.79	49,160	46,539	52,033				
	Difference	**0.07**	0.06	0.11	**0.07**	0.05	0.09	**1,845**	1,719	2,052	**25,342**	-31%	**28,074**	-32%
ΔHba1c = –0.45%	Intervention Group	10.83	10.63	11.22	8.57	8.41	8.86	51,044	48,469	54,078				
	Control Group	10.76	10.56	11.13	8.51	8.35	8.79	49,160	46,539	52,033				
	Difference	**0.07**	0.05	0.10	**0.06**	0.05	0.09	**1,883**	1,768	2,080	**26,715**	-28%	**29,761**	-28%
ΔHba1c = –0.21%	Intervention Group	10.80	10.60	11.17	8.54	8.38	8.83	51,217	48,620	54,252				
	Control Group	10.76	10.56	11.13	8.51	8.35	8.79	49,160	46,539	52,033				
	Difference	**0.04**	0.03	0.05	**0.03**	0.03	0.05	**2,057**	1,992	2,212	**56,091**	52%	**61,669**	50%
No discounting	Intervention Group	13.90	13.59	14.60	10.97	10.74	11.51	66,078	62,275	70,781				
	Control Group	13.82	13.51	14.49	10.90	10.67	11.42	63,498	59,691	67,959				
	Difference	**0.08**	0.07	0.12	**0.08**	0.06	0.11	**2,579**	2,425	2,798	**30,689**	-17%	**34,344**	-16%

Figure 8: Cost-effectiveness scatter plot for ΔHba1c = –0.29%-points and ΔHba1c = –0.33%-points



WTP: Willingness to pay threshold of CHF 100,000

Figure 9: Cost-effectiveness Acceptability Curves



7.3 Costs of SMBG

The current yearly cost of SMBG in non-insulin treated patients with T2DM, from the healthcare payers' perspective, corresponds to the yearly total SMBG costs reimbursed by health insurers for these patients. Current regulation limits the number of tests strips reimbursed to a maximum of 400 test strips per year at a maximum of CHF 0.62 per test strip (MiGeL position 21.03.01.01.1).[12] SMBG also requires a SMBG device (glucose meter), as well as lancets (needles) for a lancing device. A SMBG device will be reimbursed every two years at a maximum price of CHF 43.00, if a patient is eligible for the reimbursement of blood glucose test strips (MiGeL position 21.02.01.00.1). The maximum reimbursed price amounts to CHF 0.12 per lancet, but there is no limitation on the number of lancets reimbursed (MiGeL 21.03.05.00.1).

The total maximum cost of SMBG per non-insulin treated patient with T2DM thus corresponds to the cost of 400 test strips and lancets and one SMBG device every two years.[73] This corresponds to a maximum of CHF 317.50 per year and per patient in Switzerland (400 × (CHF 0.62 + CHF 0.12) + CHF 43.00 / 2). However, not all patients eligible for the reimbursement will actually buy the test strips, lancets and SMBG device at the maximum amounts. The actual costs of SMBG must take account of the amounts actually bought by these patients. Furthermore, patients may buy a smaller amount of lancets than test strips and SMBG devices are sometimes provided for free.

7.3.1 Methods of SMBG cost estimation

The current cost of SMBG in non-insulin treated patients with T2DM for social health insurance was assessed based on claims data for the year 2017 provided by the SWICA health insurance. SWICA is a large health insurance with a market share of 8.11% in 2017.[74]

The number of test strips acquired by the relevant SWICA population was assessed in two steps:

First, non-insulin treated patients with T2DM were identified based on type of diabetes mellitus medication. We made use of the pharmaceutical cost groups (PCGs) introduced by the FOPH for the new risk adjustment scheme between social health insurers, which will come into effect in 2020. The sum of "PCG 11 (DM)" and "PCG 35 (DM + hyp)" include all diabetes mellitus patients which acquired oral diabetic drugs in the reference year, but no insulin. As patients must acquire a minimum of 180 defined daily doses (DDD) of diabetic medications to qualify for a PCG, we included patients which bought diabetic drugs for at least half a year.

Second, the identified patients were assigned to groups defined by the number of test strips bought in the reference year: *no test strips*, *1-110 test strips*, *111-210 test strips*, and so forth with intervals of 100 test strips up to the last group with *511 and more test strips*. These intervals were chosen because the

number of test strips in the various packages sold in Switzerland hold 50, 51, 52 or 100 test strips. The average number of test strips bought by each group was also assessed.

We then calculated the cost of SMBG by multiplying the number of patients in each group with the average number of test strips bought by this group and the maximum reimbursed price for a test strip and a lancet. To this we added a third of the maximum reimbursed price of the SMBG device multiplied with the number of patients that bough at least one package of test strips in the reference year.

Finally, we extrapolated these cost of the SWICA health insured population to the overall population in Switzerland by using the information on the overall number of individuals included in the relevant PCGs in total population, according to the first test run of the PCG based risk adjustment scheme in 2017.[75]

7.3.2 Results for RQ7: amount and cost estimation of SMBG

Table 22 and Figure 10 (page 80) illustrate our results regarding the number of patients using test strips, as well the number of test strips used and their cost. We estimated a total of 124,494 non-insulin treated patients with T2DM in the Swiss population in 2017. Of these, 75.0% did not buy any test strips, 21.3% bought 1 to 410 test strips, and 3.8% bought over 411 test strips. Most of those buying test strips, bought substantially less strips than the maximum reimbursed amount of 400 test strips. While the total number of test strips bought amounted to CHF 8.4 million (m), health insurance reimbursed only 6.5 m test strips, as those buying more than 400 test strips payed the additional test strips out-of-pocket.

The total cost of tests strips for health insurers are estimated at CHF 4.0 m. Figure 10 shows that this is only a relatively small proportion of the costs that would occur if all eligible patients bought the maximum amount of test strips. This maximum cost would correspond to CHF 49.8 m and is equal to the area below the maximum line multiplied by the maximum reimbursed price per test strip in Figure 10.

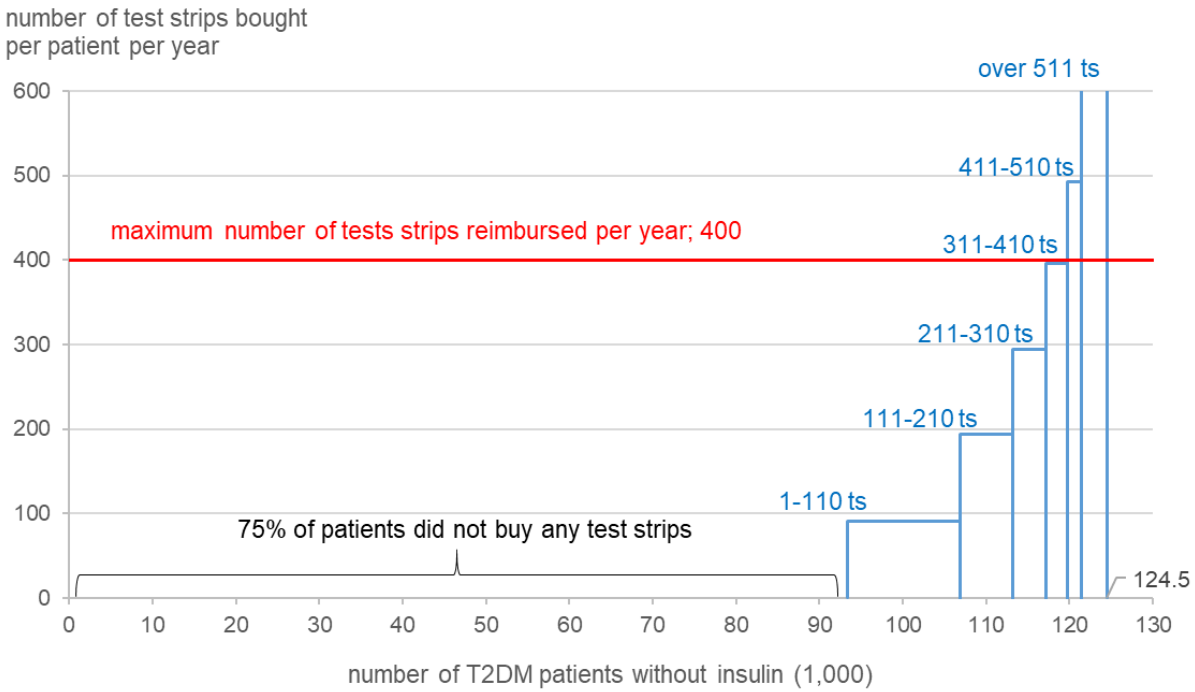
Table 22: Number of patients by number of test strips and cost of test strips

n of test strips per patient per year	n of patients	share of patients (%)	average number of test strips	n of test strips	n of test strips covered by health insurance	cost for health insurance at limit of 400 strips per year (CHF)
0	93,354	74.99	0	0	0	0
1 to 110	13,588	10.91	91	1,231,362	1,231,362	763,444
111 to 210	6,292	5.05	194	1,217,670	1,217,670	754,955
211 to 310	3,908	3.14	294	1,148,005	1,148,005	711,763
311 to 410	2,668	2.14	397	1,058,185	1,058,185	656,075
411 to 510	1,675	1.35	493	826,051	669,920	415,351
over 511	3,009	2.42	956	2,875,737	1,203,586	746,223
total	**124,494**	**100.00**		**8,357,010**	**6,528,728**	**4,047,811**

n: number

Source: authors' calculation based on SWICA data for 2017

Figure 10: Number of test strips acquired by non-insulin treated patients with T2DM



n: number; ts: test strips

Source: authors' calculation based on SWICA health insurance data for 2017

The total cost of SMBG in T2DM patients without insulin for social health insurance amounted to CHF 7.5 m in 2017 (baseline scenario in Table 23). Test strips were the largest cost component (54% of total cost), followed by SMBG devices (36%) and lancets (10%). A comparison may be useful to evaluate the magnitude of these costs: This yearly cost of SMBG corresponds to 0.027% of total net spending by social health insurance, or CHF 0.90 per insured person, or 1.047% of total cost of social health insurance for devices (MiGeL products) in 2017.

Table 23: Estimated total yearly cost of SMBG for social health insurance in Switzerland in 2017

	Baseline scenario		**Sensitivity analysis** assuming that all SMBG devices are for free and a 21% ratio of lancets to test strips	
cost component	**CHF**	**% of total**	**CHF**	**% of total**
test strips	4'047'811	53.91	4'047'811	96.09
lancets	783'447	10.44	164'524	3.91
SMBG devices	2'676'611	35.65	0	0.00
total	**7'507'869**	**100**	**4'212'335**	**100**

Estimation for T2DM patients without insulin

Source: authors' calculation based on SWICA health insurance data for 2017

We also carried out a sensitivity analysis, assuming that all SMBG devices are provided for free and that lancet consumption is substantially lower, with a 21% ratio of lancets to test strips. This ratio is based on diabetesschweiz data regarding all diabetes patients, including those treated with insulin. Table 23 illustrates that yearly costs of SMBG decrease by 44% in this sensitivity analysis. This decrease is mainly driven by the removal of the cost of SMBG devices. The cost of SMBG is thus virtually equal to the cost of test strips.

7.4 Budget Impact

The budget impact analysis assesses the impact of a complete or partial removal of the current yearly reimbursement of 400 test strips by social health insurance for T2DM patients without insulin. A complete budget impact analysis should not only consider the reduced costs of test strips and the cost of the associated lancets and SMBG devices (see Section 7.3), but also the costs due to changes in the use of other health care services and products. These changes could arise due to an increase of diabetes-related complications triggered by the reduction of SMBG.

7.4.1 Methods of budget impact analysis

We carried out two types of budget impact analyses:

The *first* budget impact analysis considered only the direct effect on the reduction of SMBG-related costs. We simulated the effects of a reduction of the maximum amount of the yearly reimbursed test strips to 300, 200 and 100 and strips, as well as the complete elimination of test strips. This simulation was based on our assessment of the levels of test strip use in Switzerland in 2017, as illustrated by Figure 10 in Section 7.3.2.

The *second* budget impact analysis additionally considered the possible impact on health care costs triggered by increased diabetes-related complications due to the removal of SMBG coverage. These complications and their costs must be assessed with a health economic simulation model combining information on disease progression, effectiveness of SMBG, and costs. The UKPDS Outcomes Model 2 (UKPDS-OM2) developed by the University of Oxford is such a model (see Section 7.2 for a detailed description of the model). We adapted the UKPDS-OM2 for the cost-effectiveness evaluation of SMBG This model does not allow the direct calculation of the budget impact of changes in SMBG levels. However, we used the model's estimated diabetes-related complication costs for our *second* budget impact analysis, by comparing the additional diabetes complication costs with costs saved by the removal of SMBG. We ran the UKPDS-OM2 with an SMBG efficacy of –0.33%-points of HbA1c reduction according to the subgroup analysis of SMBG vs. no SMBG (see Section 6.1). This comparison best reflects a total elimination of SMBG coverage in the current Swiss healthcare situation. This *second* budget impact analysis did not include a simulation of different test strip reimbursement volumes, as we had no information on the dose-response relationship between the number of test strips and HbA1c changes.

The *second* budget impact analysis required a number of additional assumptions: 1) We assumed that the number of test strips bought was identical to the Swiss situation in 2017 according to Section 6.1. The patients in the intervention groups of the SMBG vs. no SMBG used an average of 5 test strips per week, corresponding to a total of 260 strips per year. 2) We assumed that the yearly cost of diabetes complications corresponded to their average undiscounted cost in the first 10 years of the UKPDS-OM2

run with the SMBG efficacy according to the SMBG vs. no SMBG studies, as the vast majority of costs occur in this period. These average costs amounted to CHF 45.61 per patient year and were multiplied by the number of patients buying at least one package of strips.

7.4.2 Results of budget impact analysis

Table 24 illustrates the results of the *first* budget impact analysis limited to the direct effect on SMBG related costs. The table shows the savings for social health insurance at lower maxima of test strip reimbursement and separates savings for strips only, and from savings also including the reduced use of lancets and SMBG devices. Lowering the maximum reimbursed number of strips to 300 or 200 strips led to relatively small savings, because the majority of test strips buyers buy less than 200 test strips per years and because reimbursement for SMBG devices does not change. Even at maximum level of 100 test strips per year, savings amounted to only a third of the savings achievable with a total elimination of test strip coverage.

Table 24: Budget impact analysis 1 – limited to costs of strips, lancets and SMBG devices

maximum of test strips reimbursed per year	**cost of SMBG coverage (million CHF)**		**saving (million CHF) with lower maximum of test strips**	
	strips only	test strips, lancets and SMBG devices	strips only	test strips, lancets and SMBG devices
400	4.05	7.51	0.00	0.00
300	3.60	6.97	0.45	0.54
200	2.91	6.16	1.13	1.35
100	1.85	4.89	2.20	2.62
0	0.00	0.00	4.05	7.51

Source: authors' calculation based on SWICA data (2017)

Table 25 illustrates the results of the second budget impact analysis. The additional costs due to increased diabetes complications are estimated at CHF 1.42 m yearly corresponding to 20% of the costs saved due to the elimination of SMBG coverage. The net budget thus amounts to savings of CHF 6.09 m. Table 25 also illustrates the results of the sensitivity analysis assuming that SMBG costs are virtually limited to the costs of test strips (see Table 23). In this case savings amount to CHF 2.79 m.

Table 25: Budget impact analysis 2 – including effect of increased diabetes complications

cost components considered	baseline scenario (million CHF)	sensitivity analysis according to Table 23 (million CHF)
costs saved (test strips, lancets and SMBG devices)	– 7.51	**–** 4.21
additional costs due to increased diabetes complications	1.42	1.42
net budget impact	**– 6.09**	**– 2.79**

Source: own calculation based on SWICA data (2017), output of UKPDS model for subgroup analysis of SMBG vs. no SMBG (see Section 6.1)

7.4.3 Limitations of budget impact analysis

The budget impact analysis has a number of limitations: (1) We do not consider the time lag between the removal of SMBG coverage and the resulting increase in health care costs due to increased diabetes-related complications. However, our approach of taking the average undiscounted costs of diabetes complications in the first 10 years after coverage removal fits well with the relatively short time horizons considered in budged impact analyses. (2) The magnitude of the costs of diabetes complications is affected by the limitations of the UKPDS-OM2 to the context of the Swiss health care system (see Section 7.2.3)

7.5 Discussion of health and economic effects of SMBG

Health implications of SMBG

Results for RQ9: What is the nature of relationship between HbA1c changes and changes in morbidity/mortality in adult non-insulin treated patients with T2DM? (Is there a minimal important difference, MID, in HbA1c change?)

The modelled HbA1c benefit of self-monitoring in adult non-insulin treated patients with T2DM corresponds to small significant absolute reductions (ranging from 0.29% to 0.73%) in the cumulative incidence of 5 diabetes-related complications (MI, stroke, amputation, blindness, CVD death) over a time horizon of 40 years (Table 17). At the same time, it also corresponds to a small increase of non-CVD death by 0.53% to 0.56%. The model also shows a statistically significant increase in life expectancy by 18 days to 20 days and of 0.05 QALYs. The association between the decreasing diabetes-related complications and the increasing life expectancy is explained by the causal effect of MI, stroke and amputation on mortality reflected in the probability of mortality equation of UKPDS-OM2.

Our findings are within the range observed in other studies regarding the absolute incidence rate of most of the diabetes-related complications (e.g. ischaemic heart disease, MI, heart failure, stroke, amputation). For example, we find a cumulative incidence rate of approximately 28.5% in the SMBG group in the two base cases. This is slightly higher compared to another Swiss study,[50] which finds 26%, and much lower than the cumulative incidence rates of 36% and 39% found by 2 Canadian studies.[48 49] Regarding blindness, renal failure and ulcer we find lower incidence rates. Disparities could be explained by differences in the cohort characteristics, such history of diabetes-related complication, baseline HbA1c and age, as well as differences in the model characteristics, such as SMBG efficacy and time horizon. We cannot make comparisons regarding the relative risk difference, because previous studies did not evaluate the statistical significance of these reductions.

Our findings are also within the range observed in other studies regarding the effect of SMBG on life expectancy and QALYs. Table A 10 (page 129) provides an overview of the cost-effectiveness and cost-

utilities studies identified in our health economic literature review. Our results of gains in life expectancy between 18 to 20 days are in line with 2 studies reporting discounted life expectancy gains between 10 to 25 days. Table A 10 also shows that in all but one study [28] SMBG leads to QALY gains. These gains vary between 0.024 and 0.165 QALYs, which is in line our finding between 0.04 and 0.05 QALYs. A systematic review [76] of cost-effectiveness studies of glycaemic control interventions in T2DM patients found that an 1% absolute reduction in HbA1c was associated with gains of 0.642 life years and 0.371 QALYs, when adjusted for a variety of metabolic risk factors. This is a substantial difference with regards to our results. However, there is a substantial heterogeneity in the results across the included studies of this systematic review and our results are quite similar to some of these included studies.

We did not find any literature indicating the value of MID regarding the probability of experiencing diabetes-related complications and life expectancy. However, we find that with increasing SMBG efficacy from ΔHbA1c = -0.18%-points to ΔHbA1c = -1.00%-points life expectancy increases from 11 days to 51 days. Further research with patient focused groups is required to precisely define MID for different outcomes.

Economic Results

SMBG has a formal ICER of CHF 65,023 and CHF 41,078 per QALY gained for an HbA1c change of –0.29%-points and –0.33%-points respectively over a time horizon of 40 years (Table 18). The modelled ICER decreases with a higher SMBG efficacy, and with the number of test strips (Table 20 and Table 21). The sensitivity analyses show that the results are robust under a number of assumptions, indicating that a similar pattern holds for all analyses, but also showing that the modelled ICER is most sensitive to the SMBG efficacy reflected through the HbA1c change.

Our results regarding the cost-utility ICER are in the range of the results found in previous health economic studies (min: CHF 1,633 per QALY gained in Germany [52] and max: CHF 113,643 per QALY gained in Canada [49]). This may be explained by differences in the cohort and model characteristics but could also be attributed to differences in the healthcare system and treatment costs between the countries.

An important limitation of our results is related to the assumptions we had to make regarding the progression of HbA1c. In particular, we assumed that HbA1c increases in both intervention and control groups relatively by 1% per year and that the HbA1c improvement in the intervention group is maintained over the examined time horizon. Shorter maintenance periods would most probably lead to higher cost-effectiveness ratios due to the length of time it takes for HbA1c improvements to translate into reduced diabetes-related complications and in turn higher life expectancy and improvements in costs.[54] Pollock

et al.,[50] for example, find that cost-utility ICER would decrease by 9% if the HbA1c values in the intervention and control groups would converge over a time horizon of 30 years.

A total of 124,494 non-insulin treated patients with T2DM were estimated in Switzerland in 2017. 75% of these did not buy any test strips, 21% bought 1 to 410 test strips, and 4% bought over 411 test strips. Most of those buying test strips, bought substantially less strips than the maximum reimbursed amount of 400 test strips. The net budget impact of eliminating the test strip coverage amounts to savings of CHF 6.09 m per year from the healthcare payers' perspective in Switzerland (CHF 2.79 m if the cost of SMBG devices is excluded and lancet use is assumed at a 21% ratio of lancets to test strips).

7.6 Summary Statement Costs, Budget Impact and Cost-Effectiveness

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Based on the UKPDS-OM2 model, the HbA1c efficacy decrease of -0.29%-points with SMBG translates into small but statistically significant reductions in several diabetes-related complications. This leads to an increase in life expectancy due to SMBG of 18 days (95%-CI: 13 to 25) and increased total costs of CHF 2,910 (95%-CI: 2,750 to 3,021) over a time horizon of 40 years according to the model. Based on this small modelled health benefit and on the low total additional costs, SMBG has a formal ICER of CHF 65,023 per QALY gained.

Using the more pronounced HbA1c decrease of -0.33%-points in studies without any SMBG in the control group, SMBG becomes formally more cost-effective with the respective ICER decreasing to CHF 41,078 per QALY gained.

Only 1 in 4 non-insulin treated patients with T2DM in Switzerland bought SMBG test strips in 2017 and most of those buying test strips bought substantially less than the maximum amount reimbursed. A total elimination of test strip coverage would lead to savings equal to maximum CHF 7.51 m per year for the healthcare payers. Deducting the avoided diabetes-related complications from these savings leads to a net budget impact of savings equal to CHF 6.09 m.

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8. Legal, Social and Ethical Issues

Legal, social and ethical issues were elaborated in close cooperation with experts in the field (one expert in socio-legal issues in the Swiss context; one clinical ethicist).

Experts had a draft version of our HTA report at hand. In addition, open question were resolved via telephone calls to ensure a best possible understanding of the HTA results in the domains efficacy, effectiveness, safety, costs, cost-effectiveness and budget impact. Furthermore, a two-hour workshop discussed relevant socio-legal and ethical questions together with the HTA-team. Finally, experts provided their written statement to the relevant Core Model Assessment Elements, which is reported in this section of the HTA report.

8.1 Legal Issues

Departing from the research questions, the scope of this Section of the report is to describe salient legal issues at stake by following the EUnetHTA / HTA Core Model legal issues Section and by considering also additional aspects (Table 26).

The legal situation in Switzerland concerning the relevant questions at stake is covered in different Core Model Assessment Elements.

Table 26: Topics and issues in the legal issues domain

Topic	Issue	Core Model Assessment Element ID
Autonomy of the patient	*What kind of legal requirements are there for providing appropriate information to the user or patient and how should this be addressed when implementing the technology?* According to Swiss law, diabetes patients with OAD, who carry an increased hypoglycaemia risk (for example patients with adjustment problems or drugs with hypoglycaemia risk), must perform SMBG before driving with their own car; in addition, no relevant hyperglycaemia is permitted for car drivers; no data available to judge whether this procedure reduces road accidents. A Swiss working group has summarised relevant Swiss legal requirements for diabetes and driving in guidelines that were updated in 2017 and inform medical professionals and their diabetic patients. [77] In addition, a German guideline exists that obligates diabetic drivers to be informed about their current blood glucose level before driving.[78]	I0002
Autonomy of the patient	*Who is allowed to give consent for minors and incompetent persons?* Patients in fully informed about the facts must be capable of making a decision so that they can legally consent to their treatment. Maturity or majority does not play a role in this matter. The ability to judge does not depend on the age of the patients but on their mental ability. The capacity to act is assessed on the specific case in question and the mental ability of the person concerned.	I0034

Topic	Issue	Core Model Assessment Element ID
	In specific cases, it must be determined whether the person concerned – despite a possible mental impairment with regard to a specific question – is able to assess the scope of his/her decision correctly, express his/her will, and act accordingly. If the ability to judge applies to an adult, that person's legal representative decides on his/her behalf (Art. 19c (2) Swiss Civil Code).	
Privacy of the patient	*Is there a possibility that the use of the technology produces additional information that is not directly related to the current care of the patient and may violate their right to privacy?* With this method, only medical information concerning blood glucose is collected. Additional information (such as sports activities or car driving) is closely related to the purpose of the therapy, which is why there is no interference with personal rights – or this is justified by legal regulations (e.g., traffic licensing regulations) and by the consent of the patients within the scope of the treatment contract, which is why there is generally no infringement of personal rights. An example for additional information collected is the so-called “Diabetes Pass”. With this document, the patients get a standardised overview concerning recommended diet, physical activity and performed measurements to increase self-competency in dealing with this chronic illness. This document is now also available as an electronic App (Diabetes Pass App; Android and iOS version).	I0007
Privacy of the patient	*What do laws/binding rules require with regard to informing relatives about the results?* The above stated (I0034) has implications for the overall doctor-patient relationship. To the extent that patients are able make a judgement, the doctor may not disclose personal information to relatives or other persons or ask them for their opinion regarding a treatment without the patient's expressed or implied consent.	I0008
Privacy of the patient	*What do laws/binding rules require with regard to appropriate measures for securing patient data and how should this be addressed when implementing the technology?* Personal data processed in a doctor's office belong to the category of “particularly sensitive data” under the Data Protection Act. Details regarding state of health are extremely confidential, and the handling of this data must be carried out responsibly. Particular attention must also be paid to adequate technical installations. Concerning data processing in connection with blood glucose measurements, the same requirements of the Data Protection Act and the federal laws regarding electronic patient dossiers apply as to other patient data.	I0009
Equality in health care	*What do laws/binding rules require with regard to appropriate processes or resources which would guarantee equal access to the technology?* Restricting the provision of blood glucose test strips to a certain group of patients must be based on objective reasons. The WZW criteria are objective reasons (WZW stands for the effectiveness, appropriateness, and cost-effectiveness required by social health insurance law for services covered by social health insurance). Moreover, the restriction of provision or the complete cessation of this service by the social health insurance company may under no circumstances be unilaterally	I0011

Topic	Issue	Core Model Assessment Element ID
	at the expense of vulnerable groups (e.g. the elderly, geriatric patients, dementia patients or patients unable to form a judgement, patients with a migration background, or patients with rare diseases, etc.). However, there is hardly any danger of discrimination if the blood glucose test strips are only partially administered or removed from social health insurance for objective reasons (differentiated assessment of the WZW criteria on the basis of the HTA) and do not concern unilaterally vulnerable groups.	
Equality in health care	*What are the consequences of various EU-level and national regulations for the equal access to the technology?* As explained above, quantitative and cost-limitation measures by social health insurers must not have a one-sided effect to the detriment of vulnerable groups, otherwise the regulation would not be lawful. With regard to the blood glucose test strips, however, this is hardly questionable under the prerequisite of WZW criteria.	I0012
Ethical aspects	*Does the implementation or use of the technology affect the realization of basic human rights?* No, as long as the technology meets WZW criteria.	F0014
Ethical aspects	*Can the use of the technology pose ethical challenges that have not been considered in the existing legislations and regulations?* No, as long as the technology meets WZW criteria.	F0016
Authorization and safety	*What authorizations and register listings does the technology have?* The test strips must meet the requirements of the Medical Devices Ordinance of 17 October 2001 (MepV); Classified Compilation of Federal Legislation 812.213) with regard to approval for the Swiss market (Art. 23 Swiss Health Insurance Benefits Ordinance (KLV)). The supervision and enforcement of MepV is the responsibility of Swissmedic, the Swiss Agency for Therapeutic Products, Medical Devices Division.	I0015
Regulation of the market	*What kinds of legal price control mechanisms are there that are relevant to the technology?* The official prices and tariffs are valid. SMBG strip prices in Switzerland are regulated according to Swiss MiGeL list.	I0023
Regulation of the market	*What kind of regulation exists for the acquisition and use of the technology?* SMBG strip prices in Switzerland are regulated according to Swiss MiGeL list (Anhang 2 KLV).	I0024
Regulation of the market	*What legal restrictions are there for marketing the technology to the patients?* Principles regarding the permissibility of advertising medical devices are described in the Therapeutic Products Act (HMG) and MepV; there are no special features for this technology.	I0025

8.2 Social Issues

Departing from the research questions, this Section of the report described salient social issues at stake by following the EUnetHTA / HTA Core Model social issues Section and by considering also additional aspects (Table 27).

Table 27: Topics and issues in the social issues domain

Topic	Issue	Core Model Assessment Element ID
Patients' perspectives	*What are the experiences of living with the condition?* See medical background Section	H0200
Patients' perspectives	*What expectations and wishes do patients have with regard to the technology and what do they expect to gain from the technology?* According to literature and clinical experience, patients expectations with regard to the technology may be improved prognosis via better blood glucose control; sufficient autonomy; better quality of life; less hypoglycaemic incidences; compliance with Swiss legislation concerning car driving;	H0100
Patients' perspectives	*How do patients perceive the technology under assessment?* See Section 5: Synthesis of semi-quantitative information from included studies concerning depressive symptoms; general well-being; other psychological outcomes (for example self-efficacy); health-related quality of life; patient satisfaction with treatment	H0006
Patients' perspectives	*What is the burden on care-givers?* For nursing staff and physicians, duties of care and clarification to the usual extent (contract law) apply.	H0002
Social group aspects	*Are there groups of patients who currently do not have good access to available therapies?* No.	H0201
Social group aspects	*Are there factors that could prevent a group or person from gaining access to the technology?* No.	H0012
Communication aspects	*How are treatment choices explained to patients?* Current standard of care: basic diabetes teaching programs for all diabetes patients; this includes treatment choices, such as healthy life style, daily physical levels, nutrition, drug treatment (oral anti-diabetic drugs; insulin). Subgroups which don't speak the official languages in Switzerland should be considered when designing suitable communication strategies.	H0202
Communication aspects	*What specific issues may need to be communicated to patients to improve adherence?* To improve adherence to SMBG, specific teaching and training programs are documented in the included studies of this HTA.	H0203

8.3 Ethical Issues

Departing from the research questions, the scope of this Section of the report is to describe salient ethical issues at stake by following the EUnetHTA / HTA Core Model ethics Section and by considering also additional aspects. According to the involved clinical ethicist, the following points have to be considered:

General ethical aspects of SMBG in non-insulin treated T2DM patients

Enhancing the health literacy of the non-insulin treated T2DM population through targeted interventions and empowerment is paramount to an effective medical care, since the attenuation of disease-related risk factors directly impacts morbidity, mortality, quality of life and life expectancy, but also the social and economic burden of disease. This holds particularly true for the target population of the present report, where diabetic complications have to be prevented as long as possible. Given the possible modification both of the onset and the course of T2DM, securing the access of non-insulin treated T2DM patients to SMBG has to respond to three ethical requirements which are closely related to each other:

– Social justice in distributing health resources fairly, i.e. according to effective needs and – in the face of resource constraints – imposing limits to the extent that they are reasonable, do not threaten safety or impose serious additional risks.[79]

– Maximization of opportunity in order to pursue other valuable social goods besides health, like education, wealth, social inclusion, offspring, etc..[80]

– Self-determination, agency, and independence through participation and quality of life through choices that enable the best possible standard of health as well as the largest possible degree both of independency and safety.

The extent to which SMBG contributes to meet these ethical requirements can be seen as *the central ethical issue* within this HTA report. As shown by the previous sections of this report, there is no clear-cut reply to it. Nevertheless, these sections show the broad range of outcomes that should be assessed in order to fully capture the ethical dimension of the research question and the type of research needed to answer it from an ethical perspective. They range from the monitoring of physiological parameters (e.g. HbA1c, blood glucose, blood pressure and lipids), to social and ethical aspects (sense of independence, safety and self-efficacy, perceived quality of life).[81]

Specific effects

<u>Best attainable health, autonomy and perceived self-efficacy</u>

Achieving the best attainable health for patients with T2DM through active participation in the management of the disease rests on different ethical values: It fosters patient autonomy through the sharing of

knowledge, enables deliberate choices and facilitates the experience of independence, control and self-efficacy in the management of T2DM. Interventions aimed at implementing these values foster patients' capabilities of self-monitoring, early detection of short-term risks (hypo- or hyperglycaemia) and prevention of long-term complications.

Economic burden of disease and SMBG

Health is both an individual and a social good, which is built on a complex system of solidarity and cooperation in the repartition of burdens and risks between individuals, service providers, insurers and society. In the light of the observed prevalence patterns of T2DM, societies and healthcare systems are faced with considerable challenges as to the economic burden of T2DM imposed to society. They call for a careful evaluation both of the utility and the effectiveness of interventions and services that represent the standard of due care and are therefore to be offered to patients and covered by the social insurance system. The value of SMBG for non-insulin treated T2DM patients has been put under critical scrutiny within the scientific community. The UK spent 158 m pounds for SMBG in non-insulin treated T2DM patients in 2011.[11] Up to now, the discrete amount of research – previously presented in this report – was not able to give a sufficiently clear answer whether SMBG in non-insulin treated T2DM patients was effective in order to reach pre-established clinical endpoints and therefore justify its costs. The economic analysis included in this HTA departing from a database combining Swiss and US data shows a relevant net benefit of non-insulin treated T2DM patients in terms of life expectancy (Table 18), QALYs and costs of complications, which is also mirrored in the cumulative event rates (Table 17).

However, a judgement based solely on the results derived from such data can be problematic for several reasons: (1) Any criterion for a “relevant benefit” in life expectancy is influenced by normative values; (2) the number of gained 18days in life expectancy generated by the UKPDS-OM2 model are of course uncertain and is on average. However, it is clear that the true gain would not be 18 days in all patients. It would most likely be null in most patients and much more (possibly years) in those in whom clinical events are avoided; (3) small average gains in life expectancy are seen in many cost-effectiveness analyses (including some on cancer drugs), and the interventions are not discarded on this basis; (4) in the light of the estimated ICERs, the analysis indicates reasonable value of SMBG for money. It is a general discussion, and certainly not clear by today, how much weight this should be given in the presence of small effects.

Evidence base of coverage policy recommendations

The evidentiary base to question current coverage practices appears to be scant in terms of solid cohort studies describing illness trajectories of the T2DM population with and without SMBG. One important comparator could be the insulin-free interval of this population with and without SMBG, translated in

terms of preserved independence and thus quality of life. Also the psychological outcomes of SMBG compared to control interventions do not show a net benefit of SMBG as to prevalence of depression, quality of life, general wellbeing and other psychological outcomes. Also here, long term longitudinal data would be needed in order to assess long term outcomes.

Identification of specific risk groups

A roadmap to the required research could be inspired by the "Choosing Wisely"-recommendations issued by the US-Endocrine Society in October 2013 in order to avoid routine multiple daily self-glucose monitoring in adults with stable T2DM on agents that do not cause hypoglycaemia and listing possible situations at risk.[82] The recommendations list situations of acute illness, change of medication, weight fluctuation, drifting HbA1c levels and other clinical circumstances needing adjustment, which could also be expanded to non-insulin treated T2DM patients with professional risks needing narrow monitoring of blood glucose levels in situations of instability (e.g. pilots or bus drivers).

Table 28: Topics and issues in the ethics issues domain

Topic	Issue	Core Model Assessment Element ID
Benefit-harm balance	*What are the symptoms and the burden of disease or health condition for the patient?* The onset of T2DM can be postponed and its course can be attenuated through a multimodal approach entailing behavioural aspects (dietary measures, weight loss, physical exercise, avoidance of alcohol and nicotine), monitoring of glucose levels (blood and urine, short and long term), blood pressure and fats as well as the prevention and treatment of long-term complications. As shown in the scoping report, the benefit of SMBG for non-insulin treated T2DM has been questioned, especially as to the HbA1c improvement and unclear effects on morbidity or mortality of this population. However, early improvements in glycaemic control could reduce the incidence of diabetes-related complications and empower patients' self-management abilities.	F0005
Benefit-harm balance	*What are the known and estimated benefits and harms for patients when implementing or not implementing the technology?* See Section “Evidence base of coverage policy recommendations” of this ethics report. SMBG is associated with a slight and statistically significant improvement of HbA1c levels. However, it is unclear to which extent this result is also clinically relevant as to the prevention of morbidity, late complications of T2DM, mortality and the duration of the insulin-free interval of diabetes care. At a psychological level, the possibility of direct monitoring through SMBG allows a bigger degree of participation of patients in the care process and supports behavioural adaptation as to nutrition and lifestyle. However, there is no clear evidence about improved psychological outcomes in the target population (see Section Efficacy). As to possible harms of SMBG, this intervention provides information on the blood glucose levels at the time of testing. It may be possible that non-insulin treated T2DM patients trying to "adjust" SMBG derived elevated blood glucose levels with longer-acting anti-diabetic oral medication with endogen hypoglycaemia risk (e.g. sulfonylureas), thus exposing themselves to a significant risk of hypoglycaemia (see risk ratio, RR, for detecting hypoglycaemia: 2.1; Section Efficacy). When weighing up these risks against possible benefits, it can be argued that the former can be prevented through suitable educational measures.	F0010
Benefit-harm balance	*What are the benefits and harms of the technology for relatives, other patients, organisations, commercial entities, society, etc.?* Fear of hypoglycaemia is a major concern for some patients on OAD and their relatives. [83] SMBG can contribute to reducing the fear of hypoglycaemia. The uses of SMBG in the target population has no benefits for other stakeholders which are commensurable with the benefits for patients and relatives. Of course there are secondary interests of the industry and of service providers.	F0011
Benefit-harm balance	*Are there any other hidden or unintended consequences of the technology and its applications for patients/users, relatives, other patients, organisations, commercial entities, society etc.?*	F0003

Topic	Issue	Core Model Assessment Element ID
	See F0010	
Benefit-harm balance	*Are there any ethical obstacles for evidence generation regarding the benefits and harms of the intervention?* As highlighted in the ethics Section “Evidence base of coverage policy recommendations», it is necessary to define which type of evidence is needed in order to inform policymakers about coverage decisions. A too narrow reliance on physiological parameters may not capture all the relevant aspects and has to be correlated with other aspects like patients' perceived self-efficacy, insulin-free interval of the course of the illness and sense of influenceability of the health situation.	F0104
Autonomy	*Is the technology used for individuals that are especially vulnerable?* The prevalence of T2DM is constantly rising. Its incidence is attributable to genetic predispositions, but also lifestyle and nutrition patterns. Although T2DM cannot be cured, its onset can be postponed and its course can be attenuated through a multimodal approach entailing behavioural aspects, clinical care measures (monitoring) and treatment of complications. The extent of morbidity and mortality of T2DM follows the same social determinants of health (and especially health literacy) for which socio-economic and literacy gradients have been observed also in Switzerland (FOPH 2018, p. 16 ff) [84].	F0005
Autonomy	*Does the implementation or use of the technology affect the patient´s capability and possibility to exercise autonomy?* See following sections of the ethics Section: “General ethical aspects of SMBG in non-insulin treated T2DM patients” “Best attainable health, autonomy and perceived self-efficacy” One of the possible benefits of SMBG is giving non-insulin treated T2DM patients a "locus of control" in managing their medical condition. However, there might also be a psychological burden or pressure of constantly being reminded to measure SMBG and being confronted with results. Thus, “control” can be handled as a positive characteristic, but it may as well be experienced as a negative pressure. If the latter, in case of only a small clinical benefit due to SMBG, this side of the coin should also be kept in mind. The legal requirements in Switzerland already now affect the autonomy of some non-insulin treated T2-DM patients: Diabetic patients on specific OAD (sulfonylureas; exception: Gliclazid) have to perform SMBG before driving.	F0004
Autonomy	*Is there a need for any specific interventions or supportive actions concerning information in order to respect patient autonomy when the technology is used?* There is only a scant evidentiary basis for judging the effects of teaching and patient instruction as to structuration and frequency of SMBG as well as perceived self-efficacy and sense of safety in the	F0006

Topic	Issue	Core Model Assessment Element ID
	self-management of non-insulin treated T2DM. Research addressing these issues would be very valuable.	
Autonomy	*Does the implementation or withdrawal of the technology challenge or change professional values, ethics or traditional roles?* Some professionals argue that withdrawal of SMBG is counterproductive for patient autonomy, as they see SMBG as a cornerstone in diabetes self-management. No quantitative data found yet in the included studies to refute or confirm this. Possibly, further qualitative data may arise by stakeholder consultation.	F0007
Respect for persons	*Does the implementation or use of the technology affect human dignity?* Question not applicable, as long as patients are treated in accordance with current clinical standards.	F0008
Justice and Equity	*How does implementation or withdrawal of the technology affect the distribution of health care resources?* See Section “Economic burden of disease and SMBG” of the ethics Section. SMBG in the non-insulin treated T2DM population contributes to the significant economic burden of disease of T2DM.	F0012
Justice and Equity	*How are technologies with similar ethical issues treated in the health care system?* Patients with the same medical condition who take subcutaneous insulin medication are granted access to SMBG. In the light of the general ethical aspects (see Section “General ethical aspects…”), the rationale of the insulin medication as necessary condition for SMBG hast to be critically evaluated.	F0013
Legislation	*Does the implementation or use of the technology affect the realisation of basic human rights?* Question not applicable as long as patients are respected in their entitlement to attain the best possible standard of health according to the Universal Declaration of Human Rights and the Federal Constitution.	F0014
Legislation	*Can the use of the technology pose ethical challenges that have not been considered in the existing legislations and regulations?* See Section “Evidence base of coverage policy recommendations” of the ethics Section. There is a need to identify specific risk groups (patients with adjustment problems or new medical conditions). According to Swiss law, diabetes patients with OAD, which carry a hypoglycaemia risk, must perform SMBG before driving with their own car.	F0016

Topic	Issue	Core Model Assessment Element ID
Ethical consequences of the HTA	*What are the ethical consequences of the choice of endpoints, cut-off values and comparators/controls in the assessment?* See Section “Evidence base of coverage policy recommendations” of the ethics report. The evidentiary base to question current best practices appears to be to scant in order to be translated in recommendations for change of current coverage policies. Further research should focus on a broad range of evidence, entailing the onset of insulin medication and the perceived self-efficacy and safety of patients. It is to be hoped that multiple outcome measures will enable a sharper distinction of subgroups with a clearer risk-benefit ratio of SMBG from those with an only marginal benefit (that might be statistically relevant, but not clinically significant) and could also be reached by alternative and more cost-effective measures.	F0017
Ethical consequences of the HTA	*What are the ethical consequences of conducting the technology assessment at this point of time?* See F0017. The existing data focusing predominantly on physiological endpoints may not capture all the aspects relevant to the ethical evaluation.	F0103

8.4 Summary Statement on Legal, Social and Ethical Issues

Socio-legal issues: Restricting the provision of blood glucose test strips to a certain group of patients must be based on objective reasons (WZW criteria on the basis of the HTA). Moreover, it may under no circumstances be unilaterally at the expense of vulnerable groups.

However, there is hardly any danger of discrimination if the blood glucose test strips are only partially administered or removed from social health insurance for objective reasons and do not concern unilaterally vulnerable groups.

Ethical issues:

The extent to which SMBG contributes to meet three ethical requirements can be seen as *the central ethical issue* within this HTA report: (1) social justice in distributing health resources fairly**;** (2) maximization of opportunity in order to pursue other valuable social goods besides health**;** (3) choices that enable the best possible standard of health, independency and safety.

The evidence base to question current best practices appears to be to scant in order to be translated in recommendations for change of current coverage policies. SMBG is associated with a slight improvement of HbA1c levels. However, it is unclear to which extent this result is also clinically relevant. At a psychological level, the possibility of direct monitoring through SMBG allows a bigger degree of participation of patients in the care process and supports behavioural adaptation as to nutrition and lifestyle. However, there is no clear evidence about improved psychological outcomes in the target population.

A roadmap could be inspired by the "Choosing Wisely"-recommendations to avoid routine multiple daily SMBG in adults with stable T2DM on agents that do not cause hypoglycaemia and listing possible situations at risk (acute illness, change of medication, weight fluctuation, drifting HbA1c levels and other clinical circumstances needing adjustment), which could also be expanded to non-insulin treated T2DM patients with professional risks (e.g. pilots or bus drivers).

9. Organisational Issues

Organisational issues have been judged by the experts as being relevant aspects for this technology. These organisational issues are treated in this HTA within ethical and social aspects, but also together with efficacy and effectiveness issues.

In the efficacy domain, for example, adherence to therapy was documented in the RCTs by T2DM patients keeping a personal logbook; patients had to carry the glucose meter, needles, and test strips with them when they were away from home; people had to remember to measure the blood sugar. In addition, people could use a smartphone application to remember the measurement, but teaching was necessary to download it before, read and understand the instructions. Furthermore, there exist many self-management education and support programmes for diabetic patients. These programmes can use some form of SMBG to increase the patients' health competencies and therefore their abilities to participate in their treatments. Such educational programmes, however, were not the topic of this HTA.

In the effectiveness domain (observational studies), patients had to get used to SMBG in their everyday life; patients had to see a doctor to get a prescription, and with this prescription they had to go to a pharmacy.

Ethical and socio-legal reasoning of the experts, for example, took into account that vulnerable groups, such as people of older ages with T2DM, have to do the SMBG; they may have visual dysfunction or limited fine motor skills, so that the handling of needles and test strips may be difficult for them.

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11. Appendices

11.1 SMBG Regulation in other European countries

Table A 1: SMBG reimbursement for T2DM patients in different European countries

Country	Recommendations regarding SMBG	Reimbursement of SMBG
Austria	SMBG should always be structured and be available for all patients (both for type 1 and type 2 diabetes mellitus).[85]	Sickness funds reimburse, on prescription:[86 87] – For all patients: 3-month supply for consumables (lancets, test strips, etc.), with supply dependent on treatment modalities (e.g. 100 test strips per 3 months if on OAD, 650 test strips per 3 months if treated with basal-bolus therapy). – Non-insulin treated patients pay glucose meter out-of-pocket.
Denmark	No current evidence/recommendations identified. A 2005 HTA identified little evidence on and likely little value in SMBG for T2DM, with the exception of insulin-treated patients who adapt their insulin doses themselves and as a tool for training in self-care.[88]	No specific reimbursement data identified but SMBG equipment would likely be covered by general reimbursement thresholds in Denmark, which vary by personal annual expenditure.[89]
France	SMBG restricted to non-insulin-treated patients [90 91] – with therapies with high risk of hypoglycaemia (2 times per week to 2 times per day) – planned insulin therapy in the near future (2-4 times per day) – not achieving therapeutic targets (2 times per week to 2 times per day)	Reimbursement only on prescription:[90 91] – 1 glucose meter every 4 years – 1 lancing device every year – Test strips: 200 per year for patients with T2DM not treated with insulin; test strips reimbursed “under usual conditions” for all other patients with SMBG
Germany	SMBG (may be) required in patients with T2DM [92] – if T2DM is newly diagnosed – in case of frequent hypoglycaemia – comorbidities, planned surgery, mental illness, or disease-related changes to diet – if T2DM is treated with insulin (including pumps) or OAD with elevated risk of hypoglycaemia	– No reimbursement in non-insulin-treated diabetes; exceptions include cases specified in previous column [93]
Italy	SMBG is recommended for patients (number of measurements per month):[94] – On OAD with elevated risk of hypoglycaemia: 15–20 (30–40 if patient at high risk of hypoglycaemia; 75–100 if therapy change for 3–6 months) – on diet/lifestyle management: 10–15 initially, 3–5 if well-adjusted	Responsibility for reimbursement rests with regions/provinces but a nationwide reimbursement code (“Codice 013”) applies:[95 96] – *Non-insulin-treated diabetes*: up to 200 test strips (and corresponding quantity of lancets) per year dispensed free of charge to patient
Nether-lands	Guidelines mention but do not provide any detail on SMBG; in 2010, benefits of SMBG in non-insulin-treated T2DM were deemed to be clinically irrelevant [97 98]	Blood glucose meters and test strips not reimbursed for non-insulin-treated patients with diabetes, no data identified on reimbursement quantities [99] Recent data indicate a perceived need among patients for increased reimbursement of SMBG equipment [100]
Sweden	SMBG [101] – should be offered to patients with T2DM not treated with insulin in case of treatment changes, acute glycemic variability or for educational purposes – can be offered to patients with T2DM not treated with insulin	Dental and Pharmaceutical Benefits Agency (TLV) database on consumables does not specify reimbursement restrictions [102]

Country	Recommendations regarding SMBG	Reimbursement of SMBG
United Kingdom	SMBG should *not* be routinely offered to patients with T2DM no treated with insulin unless:[103] – there is a history of hypoglycaemia – patient is on OAD with increased risk of hypoglycaemia while driving or operating machinery – patient is or is planning to become pregnant SMBG should be accompanied by structured assessment (at least 1 per year)	Specific reimbursement set by Clinical Commissioning Groups, dependent on NICE recommendations and treatment modalities, but are similar across different jurisdictions. Clinical Commissioning Groups also specify preferences for make of blood glucose meters, test strips and lancets. Example on “typical annual usage” specified by Greater Manchester Clinical Standards Board: [104 105] – Non-insulin-treated T2DM: 4–8 packs with 50 test strips – Newly diagnosed T2DM: SMBG not necessary

OAD: oral antidiabetic medications

11.2 Exclusion criteria for RCTs

Table A 2: Exclusion criteria for efficacy and safety studies

	***Exclusion criteria effectiveness and safety issues:* HTA SMBG**
Study design	Exclusion if: – non-randomized controlled trials, – observational studies (unless used for selected purposes as defined in inclusion criteria)expert opinion; abstracts Exclusion if: – Studies only available as abstracts, as well as editorials, grey literature and unpublished material.
Population	Exclusion if: – diabetes patients with insulin treated T2DM – diabetes patients type 1 (per definition) – for mixed diabetes populations: no separate data for non-insulin treated patients – patients with impaired fasting glucose only (i.e.no diagnosis of clinically manifest diabetes) – women with gestational diabetes – populations from middle and low-income countries (according to OECD definitions)
Intervention	Exclusion if: – no SMBG – SMBG with a co-intervention in the IG, which is not offered in a CG using SMBG (e.g. [SMBG & nutrition intervention] vs SMBG); rationale for exclusion: effect of technology SMBG cannot be assessed – main intervention is a technology, which is tested in combination with the co-intervention SMBG (e.g. [mHealth & SMBG] vs SMBG); rationale for exclusion: effect of technology SMBG cannot be assessed; possibly, a separate HTA can make sense for this technology (additional examples: e-health; pharmacist interventions; DMP; integrated care interventions);
Control intervention (comparator)	Exclusion if: **See intervention**
Outcome measures	Exclusion if: No HbA1c as primary or secondary outcome (for RCT)

DMP: diabetes management program; IG: intervention group; CG: control group

11.3 Search strategy for SMBG-related studies regarding Switzerland

Table A 3: Search strategy of additional search regarding Switzerland

Search terms	Results
Pubmed	
self-monitor* [Title/Abstract] AND “diabetes“ [Title] AND “type 2“ [Title/Abstract] AND "Switzerland"[Mesh]	3
self-monitor* [Title/Abstract] AND “diabetes“ [Title] AND “type 2“ [Title/Abstract] AND Switzerland [Title/Abstract]	2
(glyc*[Title] OR glucose[Title]) AND “diabetes“ [Title] AND "Switzerland"[Mesh]	9
(glyc*[Title] OR glucose[Title]) AND “diabetes“ [Title] AND Switzerland [Title/Abstract]	16
“self”[Title] AND manag*[Title] AND “diabetes“ [Title] AND "Switzerland"[Mesh]	1
“self”[Title] AND manag*[Title] AND “diabetes“ [Title] AND Switzerland [Title/Abstract]	1
Cochrane	
self-monitor* [Title, Abstract, Keywords] AND “type 2 diabetes” [Title, Abstract, Keywords] AND "Switzerland“ [Title, Abstract, Keywords]	1
"glucose" in Record Title and "diabetes" in Title, Abstract, Keywords and "Switzerland" in Title, Abstract, Keywords in Trials	11
"glucose" in Record Title and "diabetes" in Title, Abstract, Keywords and "Swiss" in Title, Abstract, Keywords	0
"glycaemic" in Record Title and "diabetes" in Title, Abstract, Keywords and "Switzerland" in Title, Abstract, Keywords in Trials	5
"glycaemic" in Record Title and "diabetes" in Title, Abstract, Keywords and "Swiss" in Title, Abstract, Keywords in Trials	3
"glycemic" in Record Title and "diabetes" in Title, Abstract, Keywords and "Switzerland" in Title, Abstract, Keywords in Trials'	6
"'glycemic" in Record Title and "diabetes" in Title, Abstract, Keywords and "Swiss" in Title, Abstract, Keywords	0
Total (including duplicates)	**58**

11.4 Search strategy for Pubmed

Figure A 1: Pubmed search strategy (Ovid interface)

Ovid: Search Results

Ovid®

Wolters Kluwer

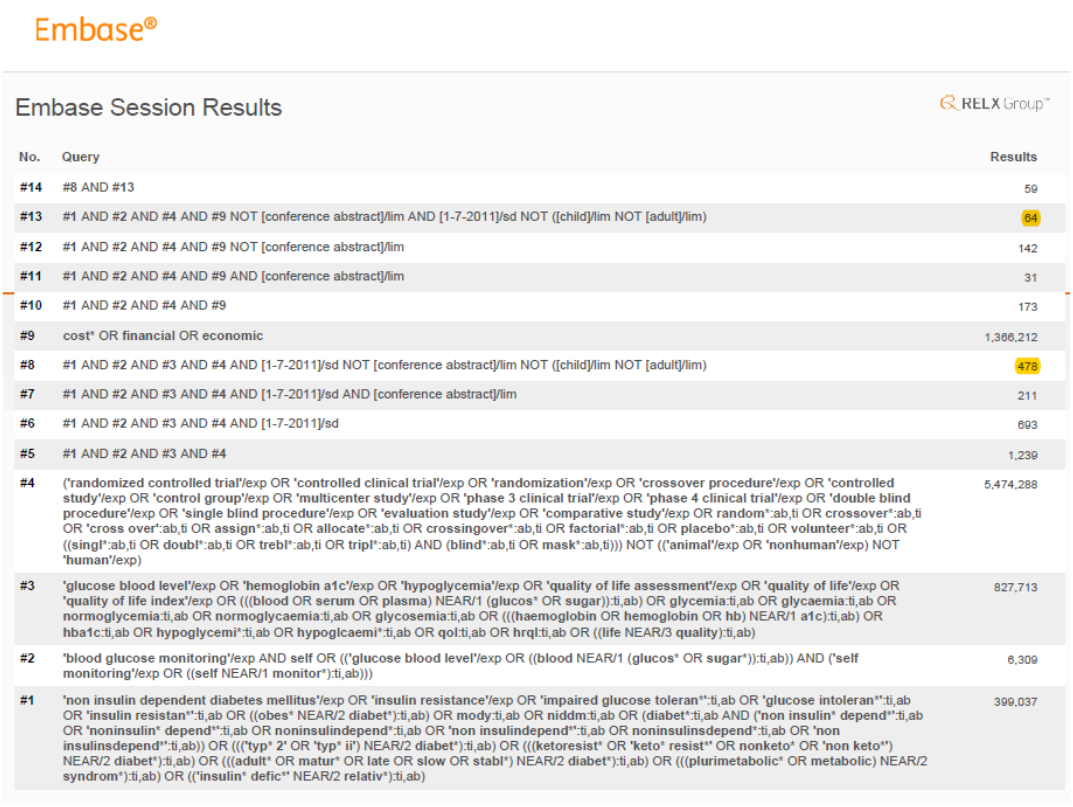
Support & Training Close

Database(s): **Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present

Search Strategy:

#	Searches	Results
1	exp Diabetes Mellitus, Type 2/ or exp Insulin Resistance/ or ("impaired glucose toleran*" or "glucose intoleran*" or "insulin resistan*").ti,ab. or (obes* adj2 diabet*).ti,ab. or (mody or niddm).ti,ab. or (diabet* and ("non insulin* depend*" or "noninsulin* depend*" or noninsulindepend* or "non insulindepend*" or noninsulinsdepend* or "non insulinsdepend*")).ti,ab. or (("typ* 2" or "typ* II") adj2 diabet*).ti,ab. or ((ketoresist* or "keto* resist*" or nonketo* or "non keto*") adj2 diabet*).ti,ab. or ((adult* or matur* or late or slow or stabl*) adj2 diabet*).ti,ab. or ((plurimetabolic* or metabolic) adj2 syndrom*).ti,ab. or ("insulin* defic*" adj2 relativ*).ti,ab.	282082
2	exp Blood Glucose Self-Monitoring/ or ((exp Blood Glucose/ or (blood adj1 (glucos* or sugar*)).ti,ab.) and (self adj1 monitor*).ti,ab.)	7264
3	exp Blood Glucose/ or Hemoglobin A, Glycosylated/ or exp Hypoglycemia/ or "Quality of Life"/ or ((blood or serum or plasma) adj1 (glucos* or sugar)).ti,ab. or (glycemia or glycaemia or normoglycemia or normoglycaemia or glycosemia).ti,ab. or ((Haemoglobin or hemoglobin or hb) adj1 a1c).ti,ab. or (hba1c or hypoglycemi* or hypoglcaemi* or qol or hrql).ti,ab. or (life adj3 quality).ti,ab.	555900
4	1 and 2 and 3	2219
5	(RANDOMIZED CONTROLLED TRIAL/ or CONTROLLED CLINICAL TRIAL/ or RANDOM ALLOCATION/ or DOUBLE BLIND METHOD/ or SINGLE BLIND METHOD/ or exp clinical trial/ or PLACEBOS/ or RESEARCH DESIGN/ or COMPARATIVE STUDY/ or exp EVALUATION STUDIES/ or FOLLOW UP STUDIES/ or PROSPECTIVE STUDIES/ or (clin$ adj25 trial$).ti,ab. or ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab. or (placebo$ or random$ or crossover* or "cross over" or assign* or allocate* or crossingover* or factorial*).ti,ab. or (control$ or prospectiv$ or volunteer$).ti,ab.) not (ANIMALS not HUMANS).sh.	5887047
6	4 and 5	1642
7	(2011107* or 201108* or 2011109* or 201110* or 201111* or 201112* or 2012* or 2013* or 2014* or 2015* or 2016* or 2017*).ep.	4648039
8	6 and 7	516
9	8 not (child not adult).sh.	508
10	(cost* or financial or economic).af.	956433
11	1 and 2 and 5 and 7 and 10	51
12	11 not (child not adult).sh.	50
13	9 and 12	48
14	9 not 12	460
15	12 not 13	2

Figure A 2: Embase search strategy



Embase®

Embase Session Results

RELX Group™

No.	Query	Results
#14	#8 AND #13	59
#13	#1 AND #2 AND #4 AND #9 NOT [conference abstract]/lim AND [1-7-2011]/sd NOT ([child]/lim NOT [adult]/lim)	64
#12	#1 AND #2 AND #4 AND #9 NOT [conference abstract]/lim	142
#11	#1 AND #2 AND #4 AND #9 AND [conference abstract]/lim	31
#10	#1 AND #2 AND #4 AND #9	173
#9	cost* OR financial OR economic	1,366,212
#8	#1 AND #2 AND #3 AND #4 AND [1-7-2011]/sd NOT [conference abstract]/lim NOT ([child]/lim NOT [adult]/lim)	478
#7	#1 AND #2 AND #3 AND #4 AND [1-7-2011]/sd AND [conference abstract]/lim	211
#6	#1 AND #2 AND #3 AND #4 AND [1-7-2011]/sd	693
#5	#1 AND #2 AND #3 AND #4	1,239
#4	('randomized controlled trial'/exp OR 'controlled clinical trial'/exp OR 'randomization'/exp OR 'crossover procedure'/exp OR 'controlled study'/exp OR 'control group'/exp OR 'multicenter study'/exp OR 'phase 3 clinical trial'/exp OR 'phase 4 clinical trial'/exp OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR 'evaluation study'/exp OR 'comparative study'/exp OR random*:ab,ti OR crossover*:ab,ti OR 'cross over':ab,ti OR assign*:ab,ti OR allocate*:ab,ti OR crossingover*:ab,ti OR factorial*:ab,ti OR placebo*:ab,ti OR volunteer*:ab,ti OR ((singl*:ab,ti OR doubl*:ab,ti OR trebl*:ab,ti OR tripl*:ab,ti) AND (blind*:ab,ti OR mask*:ab,ti))) NOT ('animal'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	5,474,288
#3	'glucose blood level'/exp OR 'hemoglobin a1c'/exp OR 'hypoglycemia'/exp OR 'quality of life assessment'/exp OR 'quality of life'/exp OR 'quality of life index'/exp OR (((blood OR serum OR plasma) NEAR/1 (glucos* OR sugar)):ti,ab) OR glycemia:ti,ab OR glycaemia:ti,ab OR normoglycemia:ti,ab OR normoglycaemia:ti,ab OR glycosemia:ti,ab OR (((haemoglobin OR hemoglobin OR hb) NEAR/1 a1c):ti,ab) OR hba1c:ti,ab OR hypoglycemi*:ti,ab OR hypoglcaemi*:ti,ab OR qol:ti,ab OR hrql:ti,ab OR ((life NEAR/3 quality):ti,ab)	827,713
#2	'blood glucose monitoring'/exp AND self OR (('glucose blood level'/exp OR ((blood NEAR/1 (glucos* OR sugar*)):ti,ab)) AND ('self monitoring'/exp OR ((self NEAR/1 monitor*):ti,ab)))	6,309
#1	'non insulin dependent diabetes mellitus'/exp OR 'insulin resistance'/exp OR 'impaired glucose toleran*':ti,ab OR 'glucose intoleran*':ti,ab OR 'insulin resistan*':ti,ab OR ((obes* NEAR/2 diabet*):ti,ab) OR mody:ti,ab OR niddm:ti,ab OR (diabet*:ti,ab AND ('non insulin* depend*':ti,ab OR 'noninsulin* depend*':ti,ab OR noninsulindepend*:ti,ab OR 'non insulindepend*':ti,ab OR noninsulinsdepend*:ti,ab OR 'non insulinsdepend*':ti,ab)) OR (((typ* 2' OR 'typ* ii') NEAR/2 diabet*):ti,ab) OR (((ketoresist* OR 'keto* resist*' OR nonketo* OR 'non keto*') NEAR/2 diabet*):ti,ab) OR (((adult* OR matur* OR late OR slow OR stabl*) NEAR/2 diabet*):ti,ab) OR (((plurimetabolic* OR metabolic) NEAR/2 syndrom*):ti,ab) OR (('insulin* defic*' NEAR/2 relativ*):ti,ab)	399,037

Table A 4: Cochrane Library search strategy:

Search number	*Search terms*
excl backgr legal driving (29-07-2019) medica lcond#1	*("impaired glucose toleran*" or "glucose intoleran*" or "insulin resistan*"):ti,ab,kw or (obes* near/2 diabet*):ti,ab,kw or (mody or niddm):ti,ab,kw or (diabet* and ("non insulin* depend*" or "noninsulin* depend*" or noninsulindepend* or "non insulindepend*" or noninsulinsdepend* or "non insulinsdepend*")):ti,ab,kw or (("typ* 2" or "typ* II") near/2 diabet*):ti,ab,kw or ((ketoresist* or "keto* resist*" or nonketo* or "non keto*") near/2 diabet*):ti,ab,kw or ((adult* or matur* or late or slow or stabl*) near/2 diabet*):ti,ab,kw or ((plurimetabolic* or metabolic) near/2 syndrom*):ti,ab,kw or ("insulin* defic*" near/2 relativ*):ti,ab,kw*
#2	*(blood near/1 (glucos* or sugar*)):ti,ab,kw and (self near/1 monitor*):ti,ab,kw (blood near/1 (glucos* or sugar*)):ti,ab,kw and (self near/1 monitor*):ti,ab,kw*
#3	*((blood or serum or plasma) near/1 (glucos* or sugar)):ti,ab,kw or (glycemia or glycaemia or normoglycemia or normoglycaemia or glycosemia):ti,ab,kw or ((Haemoglobin or hemoglobin or hb) near/1 a1c):ti,ab,kw or (hba1c or hypoglycemi* or hypoglcaemi* or qol or hrql):ti,ab,kw or (life near/3 quality):ti,ab,kw*
#4	*#1 and #2 and #3*
#5	*#1 and #2 and #3* *Publication year from 2011*
#6	*(cost* or financial or economic):ti,ab,kw*
#7	*#1 and #2 and #6*
#8	*#1 and #2 and #6* *Publication year from 2011*
#9	*#5 and #6*
#10	*#5 NOT #6*

Figure A 3: PsycINFO search strategy

EBSCOhost

Thursday, February 14, 2019 6:34:12 AM

#	Query	Limiters/Expanders	Last Run Via	Results
S6	S3 not S5	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	21
S5	S3 AND S4	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	177
S4	DE "Depression Emotion" OR DE "Major Depression" OR DE "Anaclitic Depression" OR DE "Dysthymic Disorder" OR DE "Endogenous Depression" OR DE "Late Life Depression" OR DE "Postpartum Depression" OR DE "Reactive Depression" OR DE "Recurrent Depression" OR DE "Treatment Resistant Depression" OR DE "Atypical Depression" OR DE "Self-Efficacy" OR DE "Client Attitudes" OR DE "Client Satisfaction" OR DE "Client Participation" OR DE "Treatment Compliance" AND DE "Health Attitudes" OR DE "Behavioral Intention" OR DE "Commitment" OR DE "Motivation" OR DE "Problem Solving" OR DE "Coping Behavior" OR DE "Self-Care Skills" OR DE "Self-Management" OR DE "Well Being" OR DE "Quality of Life" OR TX (self N1 (efficacy OR care OR managment)) OR TX	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	2,266,034

(PsycINFO search strategy, continued):

	(depression OR barrier* OR facilitat* OR intention OR behaviour OR behavior OR acceptance OR attitude OR commitment OR motivation OR reflection OR coping OR "problem solving" OR "patient perspective*" OR "treatment satisfaction" OR "well-being" OR "quality of life" OR SF-36 OR SF36 OR EQ-5D OR EQ5D OR WHO-5)			
S3	S1 AND S2	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	198
S2	(DE "Blood Sugar" OR TX (blood N1 (glucos* OR sugar*))) AND (self N1 monitor*) OR MA Blood Glucose Self-Monitoring	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	387
S1	DE "Type 2 Diabetes" OR MA Diabetes Mellitus, Type 2 OR TX ("impaired glucose toleran*" OR "glucose intoleran*" OR "insulin resistan*") OR TX (obes* N2 diabet*) OR TX (mody OR niddm) OR TX (diabet* and ("non insulin* depend*" OR "noninsulin* depend*" OR noninsulindepend* OR "non insulindepend*" OR noninsulinsdepend* OR "non insulinsdepend*")) OR TX (("typ* 2" OR "typ* II") N2 diabet*) OR TX ((ketoresist* OR "keto* resist*" OR nonketo* OR "non keto*") N2 diabet*) OR TX ((adult* OR matur* OR late OR slow OR stabl*) N2 diabet*) OR TX ((plurimetabolic* OR metabolic) N2 syndrom*) OR TX ("insulin* defic*" N2 relativ*)	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	15,689

11.5 Search strategy for health economic evaluations in EconLit

Table A 5: EconLit search strategy

Search terms	Results
EconLit	
self-monitor	6
ti(self) AND ti(monitor)	4
ti(self-monitoring) AND (type 2)	2
ti(self) AND ti(monitor) AND ti(diabetes)	1
ti(glucose) AND ti(diabetes)	1
ti(glycemic) AND ti(diabetes)	1
ti(self) AND ti(management) AND ti(diabetes)	1
Total (including duplicates)	**16**

11.6 Details of included RCTs

Table A 6: Details of included RCTs

Author; year	Study	Population	Outcome (primary)	n IG	Intervention SMBG	n CG	Control group Intervention	Comment
Fontbonne 1989 [34]	Country: FRA Design: RCT Follow-up: 6 mth Setting: endocrinology center	Age (mean): 55yr Diabetes duration: >1yr HbA1c baseline: 8.2 %	HbA1c	n=56	structured SMBG	n=54	no SMBG & usual diabetes care	
Allen 1990 [27]	Country: USA Design: RCT Follow-up: 6 mth Setting: general practitioner	Age (mean): 58yr Diabetes duration: >1yr HbA1c baseline: 12.1 %	HbA1c, blood glucose	n=27	structured SMBG	n=27	SMUG (self-measurement of urine glucose)	Funding: Veterans Administration Health Services Research and Development Service with additional funds from the A.W. Mellon Foundation.
Muchmore 1994 [19]	Country: USA Design: RCT Follow-up: 10.2 mth Setting: general practitioner and newspaper	Age (mean): 59yr Diabetes duration: >1yr HbA1c baseline: 10.4 %	HbA1c	n=12	structured SMBG	n=11	no SMBG & usual diabetes care	
Jaber 1996 [29]	Country: USA Design: RCT Follow-up: 4 mth Setting: endocrinology center	Age (mean): 62yr Diabetes duration: >1yr HbA1c baseline: 11.9 %	HbA1c	n=17	structured SMBG	n=22	no SMBG & usual diabetes care	

Author; year	Study	Population	Outcome (primary)	n IG	Intervention SMBG	n CG	Control group Intervention	Comment
Schwedes 2002 [20]	Country: GER/AUT Design: RCT Follow-up: 6 mth Setting: general practitioner	Age (mean): 60yr Diabetes duration: >1yr HbA1c baseline: 8.4 %	HbA1c; quality of life	n=113	structured SMBG	n=110	no SMBG & usual diabetes care	
Guerci 2003 [35]	Country: FRA Design: RCT Follow-up: 6 mth Setting: general practitioner	Age (mean): 62yr Diabetes duration: >1yr HbA1c baseline: 8.9 %	HbA1c	n=345	un-structured SMBG	n=344	no SMBG & usual diabetes care	
Davidson 2005 [36]	Country: USA Design: RCT Follow-up: 6 mth Setting: endocrinology center	Age (mean): 50yr Diabetes duration: >1yr HbA1c baseline: 8.5 %	HbA1c	n=43	structured SMBG	n=45	no SMBG & usual diabetes care	
O'Kane 2008 [23]	Country: IRL Design: RCT Follow-up: 12 mth Setting: endocrinology center	Age (mean): 59yr Diabetes duration: <1 yr HbA1c baseline: 8.7 %	HbA1c, psycho-logical indices, hypoglycaemia	n=96	structured SMBG	n=88	no SMBG & usual diabetes care	
Barnett 2008 [15]	Country: 7 countries worldwide Design: RCT Follow-up: 6.2 mth Setting: endocrinology center	Age (mean): 56yr Diabetes duration: >1yr HbA1c baseline: 8.1 %	HbA1c	n=311	structured SMBG	n=299	no SMBG & usual diabetes care	DINAMIC 1 study; sponsor: Servier pharmaceutical company

Author; year	Study	Population	Outcome (primary)	n IG	Intervention SMBG	n CG	Control group Intervention	Comment
Scherbaum 2008 [22]	Country: GER Design: RCT Follow-up: 12 mth Setting: endocrinology center	Age (mean): 61yr Diabetes duration: >1yr HbA1c baseline: 7.2 %	HbA1c	n=102	more frequent SMBG	n=100	less frequent SMBG	Diabetes drugs: 43 to 49% of patients on sulfonylureas.
Farmer 2009 [28]	Country: GBR Design: RCT Follow-up: 12 mth Setting: general practitioner	Age (mean): 66yr Diabetes duration: >1yr HbA1c baseline: 7.5 %	HbA1c	n=301	structured SMBG	n=152	no SMBG & usual diabetes care	Three arm trial: Two intervention groups combined: 1) Less and 2) more intensive SMBG Medication: no info about sulfonylurea rates
Kleefstra 2010 [17]	Country: NED Design: RCT Follow-up: 12 mth Setting: no info	Age (mean): 59yr Diabetes duration: >1yr HbA1c baseline: 7.5 %	HbA1c	n=22	structured SMBG	n=18	no SMBG & usual diabetes care	
Duran 2010 [30]	Country: ESP Design: RCT Follow-up: 12 mth Setting: endocrinology center	Age (mean): 64yr Diabetes duration: <1 yr HbA1c baseline: 6.6 %	regression of T2DM (HbA1c <6.0%) remission of T2DM (HbA1c 6.0 to 6.4%)	n=99	structured SMBG	n=62	no SMBG & usual diabetes care	Funding: Ministerio de Sanidad from Spain (Fondos de Cohesion 2008) and the Fundacio´ n de Estudios Endocrinometabo´ licos.
Franciosi 2011 [33]	Country: ITA Design: RCT Follow-up: 6 mth Setting: endocrinology center	Age (mean): 49yr Diabetes duration: >1yr HbA1c baseline: 7.9 %	HbA1c	n=46	structured SMBG	n=16	no SMBG & usual diabetes care	

Author; year	Study	Population	Outcome (primary)	n IG	Intervention SMBG	n CG	Control group Intervention	Comment
Polonsky 2011 [14]	Country: USA Design: cRAN Follow-up: 12 mth Setting: general practitioner	Age (mean): 56yr Diabetes duration: >1yr HbA1c baseline: 8.9 %	HbA1c	n=256	structured SMBG	n=227	(un-structured) SMBG	
Harashima 2013 [32]	Country: JPN Design: RAN Follow-up: 6 mth Setting: endocrinology center	Age (mean): 64yr Diabetes duration: >1yr HbA1c baseline: 7.4 %	HbA1c	n=68	un-structured SMBG	n=41	no SMBG & usual diabetes care	Three arm trial: 2 IG combined: IGa (fingertip) and IGb (palm)
Kempf 2013 [16]	Country: BUL Design: RAN Follow-up: 18 mth Setting: endocrinology center	Age (mean): 57yr Diabetes duration: >1yr HbA1c baseline: 7.5 %	HbA1c	n=63	structured SMBG	n=61	no SMBG & usual diabetes care	
Garcia de la Torre 2013 [31]	Country: ESP Design: RAN Follow-up: 36 mth Setting: 3	Age (mean): 58yr Diabetes duration: <1 yr HbA1c baseline: 6.7 %	regression rate of T2DM (HbA1c <6%)	n=130	structured SMBG	n=65	no SMBG & usual diabetes care	Three arm trial: 2 IG combined: Ia (SMBG without exercise) and Ib (SMBG + excercise);
Bosi 2013 [24]	Country: ITA Design: RAN Follow-up: 12 mth Setting: endocrinology center	Age (mean): 60yr Diabetes duration: >1yr HbA1c baseline: 7.4 %	HbA1c; beeing in target (low/high blood glucose index)	n=501	structured SMBG	n=523	less frequent SMBG	PRISMA trial (psychological outcomes: Russo 2016 [106])
Dallosso 2014 [26]	Country: GBR Design: cRAN Follow-up: 18 mth Setting: general practitioner	Age (mean): 58yr Diabetes duration: <1 yr HbA1c baseline: 8.2 %	HbA1c	n=135	un-structured SMBG	n=144	SMUG (self-measurement of urine glucose)	DESMOND SMBG trial

Author; year	Study	Population	Outcome (primary)	n IG	Intervention SMBG	n CG	Control group Intervention	Comment
Malanda 2016 [18]	Country: NED Design: RAN Follow-up: 12 mth Setting: general practitioner	Age (mean): 61yr Diabetes duration: >1yr HbA1c baseline: 7.4 %	diabetes-specific emotional distress; perception of self-efficacy	n=53	structured SMBG	n=55	no SMBG & usual diabetes care	
Young 2017 [21]	Country: USA Design: RAN Follow-up: 12 mth Setting: general practitioner	Age (mean): 61yr Diabetes duration: no info HbA1c baseline: 7.6 %	HbA1c; quality of life	n=282	un-structured SMBG	n=147	no SMBG & usual diabetes care	Three arm trial: 2 IGs were combined IG1 (no messaging SMBG) and IG2 (SMBG with messages).
Nishimura 2017 [25]	Country: JPN Design: RAN Follow-up: 5.5 mth Setting: endocrinology center	Age (mean): 66yr Diabetes duration: >1yr HbA1c baseline: 7.2 %	HbA1c	n=30	more structured SMBG	n=32	less structured SMBG	Funding: This work was supported by Roche Diagnostics K.K., Japan.
Parsons 2019 [37]	Country: GBR Design: RAN Follow-up: 12 mth Setting: general practitioner	Age (mean): 62yr Diabetes duration: >1yr HbA1c baseline: 8.6 %	HbA1c	n=295	structured SMBG	n=151	no SMBG & usual diabetes care	Three arm trial: IG1 (SMBG alone) and IG2 (SMBG + TeleCare) were combined. Funding: European Foundation for the Study of Diabetes; additional support by way of SMBG monitoring equipment and an unrestricted grant by Roche Diabetes Care GmbH.

11.7 Details of SMBG patterns

Table A 7: Details of SMBG patterns as applied in the RCTs.

Author (year)	Protocol: SMBG patterns for intervention group	SMBG aim (intervention group; per week)	SMBG actual (intervention group; per week; compliance with protocol)
Fontbonne 1989 [34]	*SMBG: twice every other day (fasting and two hours after the evening meal)+ 1 extra test 2 hours after lunch on sundays*	7	7.15
Allen 1990 [27]	*SMBG: at least 36 blood glucose determinations per month; instruction: "each other day before each meal" (=45 pm);* *goal: <7.7 mM fasting and <8.8 mM before lunch and dinner for all blood glucose levels.*	8.3	7.5
Muchmore 1994 [19]	*SMBG: 6 times daily (pre and 2 h postprandially) for 4 w then reduced to pre and postprandial testing of single meal per day for the next 16 w, after week 20 SMBG was at the ind choice and expense*	42	33
Jaber 1996 [29]	*SMBG: 4 times per day at 2 days per week. Detailed written instrictions for specific testing times relative to meal consumption were provided.*	8	no info
Schwedes 2002 [20]	*SMBG: requested to measure blood glucose six times (before and 1 h after main meals) on 2 days per week (one weekday and on Sunday) and to record the values obtained in a combined diary for blood glucose data and documentation of eating habits and their state of well-being (all entries were counted and checked for plausibility)*	12	24.8
Guerci 2003 [35]	*SMBG: 6 times a week, at 3 different days, including weekend*	6	no info
Davidson 2005 [36]	*SMBG: Patients were instructed to measure glucose levels before and between 1 and 2 hours after eating meals 6 days a week; 2 breakfasts, 2 lunches, and 2 suppers, and to record what they ate at those meals.*	36	no info
O'Kane 2008 [23]	*SMBG: patients were asked to monitor 4 fasting and 4 postprandial capillary BGM each weak*	8	63 carried out more than 80% of the requested blood glucose monitoring
Barnett 2008 [15]	*SMBG: 2 days per week and 6 times per day: before each meal (breakfast, lunch and dinner), 2 h after the main meal and before bedtime; once per month, postprandial measurements after each of the three main meals.*	12	no info

Author (year)	Protocol: SMBG patterns for intervention group	SMBG aim (intervention group; per week)	SMBG actual (intervention group; per week; compliance with protocol)
Scherbaum 2008 [22]	*SMBG: four measurements a week on Tuesdays, Thursdays and one day of the weekend before dinner and one additional measurement before lunch, and also additional measurement in the event of suspected hypoglycaemia or severe hyperglycaemia.*	4	no info
Farmer 2009 [28]	*SMBG: 3 times daily on 2 days a week (one fasting and the other two pre meal or 2 hours post meal)* *More intensive: frequency not specified (see also comments)*	6	5
Kleefstra 2010 [17]	*SMBG: 4x/day (one fasting glucose and three post-meal, 1.5 hours after the meal), twice weekly, on one weekday and one day in the weekend for a period of one year.*	8	17 (77%) performed at least 80% of the requested glucose registrations
Duran 2010 [30]	*SMBG: six-point profiles every 3 days, before and 2 h after breakfast, lunch, and dinner as well as after any change in pharmacological therapy*	18	4.8
Franciosi 2011 [33]	*SMBG: 1st day: before and 2 hours after breakfast, 3rd day: before and 2h after lunch and 5th day: before and 2h after dinner, repeated 2 weeks every month*	3	2.7
Polonsky 2011 [14]	*SMBG: 7-point SMBG profile (fastig, preprandial/2h postprandial at each meal, bedtime) on3 consecutive days prior to each scheduled study visit*	2	5.4
Harashima 2013 [32]	*SMBG: At least 3 times daily at 3 days/week + 7 times daily at 2 days/week in the week before physician visit*	9.8	13.4
Kempf 2013 [16]	*SMBG: 4 x 7-point x day at baseline + after 4, 8, and 12 weeks, as well as event-driven SMBG (e.g.1.5–2 h after chocolate consumption,...).*	9.3	no info
Garcia de la Torre 2013 [31]	*SMBG: Six-point profiles were initially recommended every 3 days. After stabilization, defined as five complete SMBG profiles on target in two consecutive visits, patients were recommended to perform at least one 6-point profile every 2 weeks if they were on metformin or metformin plus pioglitazone or at least one profile per week if they were receiving any treatment other than metformin and/or pioglitazone*	6-12	no info
Bosi 2013 [24]	*SMBG: 4-point profile before breakfast and lunch, 2h after lunch, and 5h after lunch but before dinner, 3 days/week, every week (2 working days and 1 weekend day) for 12 months.*	12	median 10

Author (year)	Protocol: SMBG patterns for intervention group	SMBG aim (intervention group; per week)	SMBG actual (intervention group; per week; compliance with protocol)
Dallosso 2014 [26]	*SMBG: were free to change their method of monitoring or to stop*	were free to change their method of monitoring or to stop	83% monitoring
Malanda 2016 [18]	*SMBG: 3 pre-and 3 postprandial measurements a day on 2 separate days each week; allowed to adjust freq ad libitum from8 weeks after baseline*	12	no info
Young 2017 [21]	*SMBG: 2 groups: 1) standard once-daily 2) enhanced once-daily with automated tailored messages*	7	no info
Nishimura 2017 [25]	*SMBG: SMBG 7 times per day on 3 consecutive days; once every 2mth without daily testing (but <25pm)*	2.4	no info

11.8 Details of SMBG devices as used in the included RCTs

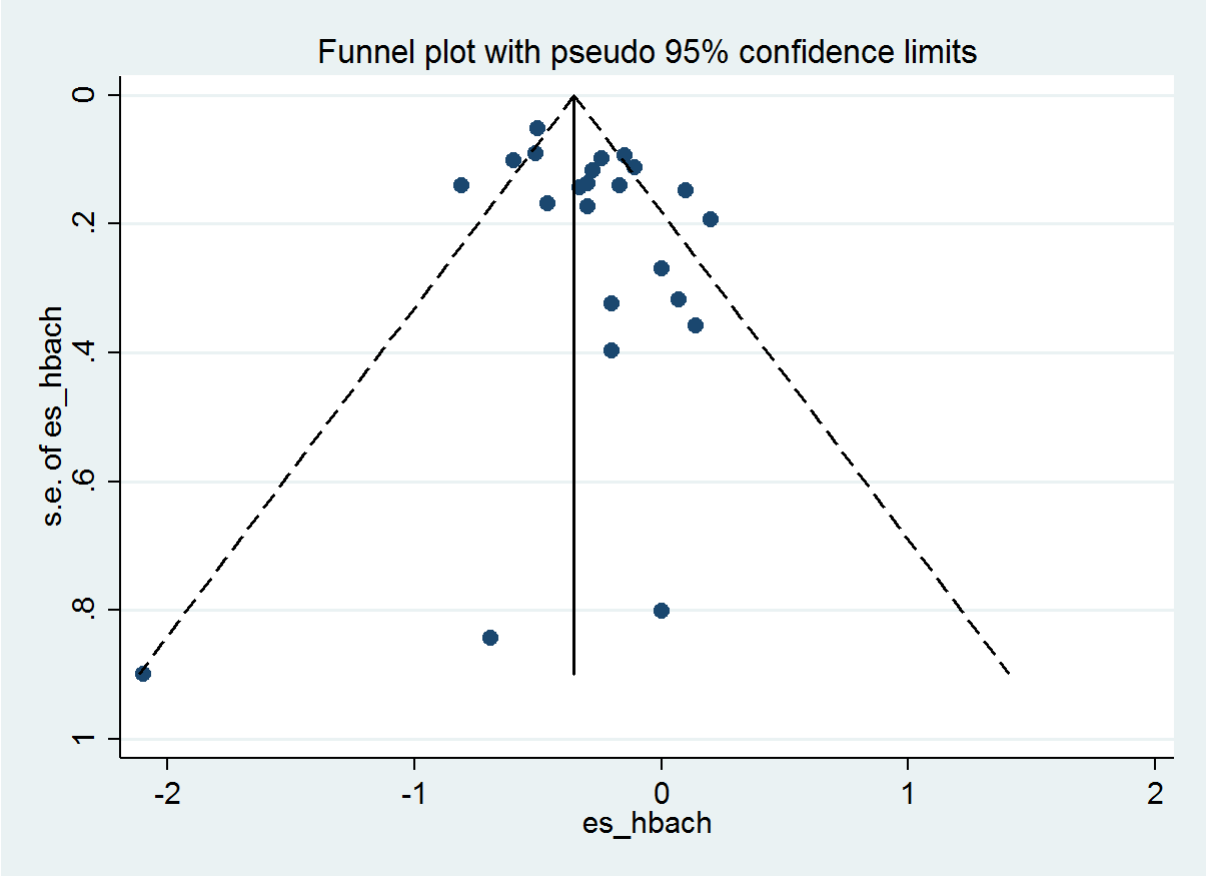
Table A 8: Details of SMBG devices as applied in the RCTs

Author (year)	Intervention SMBG: Device	Control group: Device
Fontbonne 1989 [34]	Intervention: Glucometer reflectance-meter (Ames Division, Miles Laboratory) + Dextrostix	Control: no SMBG
Allen 1990 [27]	Intervention: Accu-Chek I (Bio-Dynamics, Indianapolis, IN) reflectance meter + Chemstrips bG	Control: Tes-Tape (Lilly, Indianapolis) (Urine testing)
Muchmore 1994 [19]	Intervention: One Touch (LifeScan)	Control: no SMBG
Jaber 1996 [29]	Intervention: One Touch Basic glucose reflectance meter (LifeScan)	Control: no SMBG
Schwedes 2002 [20]	Intervention: sensor disc Glucometer Dex	Control: no SMBG
Guerci 2003 [35]	Intervention: Ascensia Esprit Discmeter (Bayer)	Control: no SMBG
Davidson 2005 [36]	Intervention: Glucometer + strips (Lifescan)	Control: no SMBG
O'Kane 2008 [23]	Intervention: Lifescan OneTouch Ultra (Johnson and Johnson)	Control: no SMBG
Barnett 2008 [15]	Intervention: Glucometers from Bayer Diagnostics, Roche Diagnostics, Hypoguard, LifeScan and Medisense	Control: no SMBG
Scherbaum 2008 [22]	Intervention: glucometers from Roche Diagnostics	Control: glucometers from Roche Diagnostics
Farmer 2009 [28]	Intervention: Glucometer (Optimum, Abbott Diabetes Care)	Control: no SMBG

Author (year)	Intervention SMBG: Device	Control group: Device
Kleefstra 2010 [17]	Intervention: Accu-check Aviva (Roche Diagnostics)	Control: no SMBG
Duran 2010 [30]	Intervention: no info	Control: no SMBG
Franciosi 2011 [33]	Intervention: Lifescan OneTouch Ultra 2 (Johnson and Johnson)	Control: no SMBG
Polonsky 2011 [14]	Intervention: Accu-Chek Aviva meter system + Accu-Chek 360° View blood glucose analysis system (Roche Diegnostics)	Control: ACG subjects did not receive the Accu-Chek system.
Harashima 2013 [32]	Intervention: One touch Ultra Blood Glucose Monitoring System Kit (Johnson & Johnson)	Control: no SMBG
Kempf 2013 [16]	Intervention: Accu-Chek Performa (Roche Diagnostics)	Control: no SMBG
Garcia de la Torre 2013 [31]	Intervention: no info	Control: no SMBG
Bosi 2013 [24]	Intervention: Accu-Chek Smart-Pix system (Roche Diagnostics)	Control: no info
Dallosso 2014 [26]	Intervention: no info	Control: no info (Urine testing)
Malanda 2016 [18]	Intervention: Lifescan OneTouch Ultra 2 (Johnson and Johnson)	Control: no SMBG
Young 2017 [21]	Intervention: IG 1: glucometer IG2: telecare meter	Control: no SMBG
Nishimura 2017 [25]	Intervention: Accu Check Aviva Nano™ (Roche Diagnostics) + 360° viewsheet to record BG-levels	Control: Self-monitoring notes of the Japan Association for Diabetes Education and Care (JADEC), commonly used by patients to record blood glucose levels in Japan
Parsons 2019 [37]	Intervention: Accu-Chek Aviva meter and Accu-Chek 360° View Paper Tool.	Control: no SMBG

11.9 Assessment of bias across studies (publication bias)

Figure A 4: Funnel plot to assess publication bias



11.10 Medication changes and switch to insulin

Table A 9: Changes of oral diabetes medications and new insulin therapy (17 RCTs).

Author (year)	Medication changes (intervention group)	Medication changes (control group)
Allen 1990 [27]	changes in 36% of monthly visits – 1 started insulin, 2 new OAD, 9 had changes in dose of OAD or changed to second generation OAD	changes in 41% of monthly visits – 2 started insulin, 4 new OAD, 14 had changes in dose of OAD or changed to second generation OAD
Muchmore 1994 [19]	Medication changes up or down occurred with equal frequency in the control and experimental groups. OAD was initiated in 1 patient. OAD dosage increase occured in 3 patients. Elimination of OAD occured in 1 patient.	Medication changes up or down occurred with equal frequency in the control and experimental groups. OAD was initiated in 1 patient. OAD dosage increase occured in 3 patients. Dosage reduction occured in 1 patient. Elimination of OAD occured in 1 patient.
Jaber 1996 [29]	38 pharmacotherapeutic interventions were made.	9 pharmacotherapeutic interventions (mean of 0.4 interventions per patient) were reported in the control group.
Davidson 2005 [36]	Medications at end of study were similar in both groups, indicating that the two were treatedsimilarly by the nurse	Medications at end of study were similar in both groups, indicating that the two were treatedsimilarly by the nurse
O'Kane 2008 [23]	There were no differences between groups in use of oral hypoglycaemic drugs at any time points. No drugs (b:86, after 12m: 34), 1 drug (b: 8, after12m: 44), 2 drugs (b:0, after 12m: 11)	There were no differences between groups in use of oral hypoglycaemic drugs at any time points. No drugs (b:78, after 12m: 29), 1 drug (b: 7, after12m: 40), 2 drugs (b:2, after 12m: 6)
Barnett 2008 [15]	no significant difference between groups in duration and dosage of treatment intake at wk18;	no significant difference between groups in duration and dosage of treatment intake at wk18;
Farmer 2009 [28]	no differences between groups regarding change in OAD or statin treatment.	no differences between groups regarding change in OAD or statin treatment.
Kleefstra 2010 [17]	3 patients progressed to insulin therapy	no patient progressed to insulin therapy
Duran 2010 [30]	Medication changes were earlier and more frequent in the intervention group; remained on metformin alone: 65% (64 of 99); 23% on insulin at end of study;	Medication changes were earlier and more frequent in the intervention group; remained on metformin alone: 59.7% (37 of 62); 5% on insulin at end of study;
Franciosi 2011 [33]	13 therapy changes were made in 10 out of 46 patients (21.77%) between randomization and last visit. Overall 16 patients (35%) required therapy adjustment.	4 therapy changes were made in 4 out of 16 patients (25.0%) between randomization and last vist. Overall 9 patients (59%) required therapy adjustments.

Author (year)	Medication changes (intervention group)	Medication changes (control group)
Polonsky 2011 [14]	Significantly more IG patients received a treatment change recommendation at the month 1 visit compared with CG-patients, regardless of the patient,s baseline A1C level. Almost twice as many IG patients were started on intermediate or long-acting insulin	Significantly more IG patients received a treatment change recommendation at the month 1 visit compared with CG-patients, regardless of the patient,s baseline A1C level. Almost twice as many IG patients were started on intermediate or long-acting insulin
Kempf 2013 [16]	there was a significant increase of metformin use within both groups, but medication was not significantly different between groups	there was a significant increase of metformin use within both groups, but medication was not significantly different between groups
Garcia de la Torre 2013 [31]	54% of the patients in the IG remained on metformin alone.	50% of the patients in the CG remained on metformin alone.
Bosi 2013 [24]	medication change at visit 4: 32%	medication change at visit 4: 20%
Malanda 2016 [18]	No differences between groups	No differences between groups
Nishimura 2017 [25]	50% (15 of 30): oral hypoglycemic agents were increased in dosage and/or more combination; no subjects whose medication was decreased in dosage or in frequency.	21% (7 of 32): oral hypoglycemic agents were increased in dosage and/or more combination; no subjects whose medication was decreased in dosage or in frequency.
Parsons 2019 [37]	Rate of patients with increased number of diabetes medication: IG (combined) 48% Rate of patients with prescribed insulin during study: IG (combined) 8/295 (3%)	Rate of patients with increased number of diabetes medication: CG 28% Rate of patients with prescribed insulin during study: IG (combined) CG (3/151 (2%)

Colour code: BLUE: More changes / amendments of oral diabetes medications, OAD (compared to other group, may be intervention group (SMBG) or control group);

Colour code: GREEN: More switches to insulin therapy (compared to other group, may be intervention group (SMBG) or control group);

EN: Endnote® study identifier

11.11 Literature review of cost-effectiveness and cost-utility studies

Table A 10: Methods and results from existing cost effectiveness and cost utility studies

Author; year	Country	Model	Simula-tion years	N	Mean age	History of complications [a]	Discount rate	ΔHba1c (%-points)	SMBG frequency [b]	ΔLE	ΔQALY	Δcost	CHF/ life-years	CHF/ QALY	Unit
Cost-effectiveness studies															

Tunis 2011[48]	Canada	UKPDS-OM1	40	100	60	assumed no history	5%	-0.25	1.29 vs 0	-	0.039	2,451	-	63,664	2008 Canadian dollars
Cameron 2010[49]	Canada	UKPDS-OM1	40	1,000	61	assumed no history	5%	-0.24	1.29 vs 0	0.028	0.024	2,711	97,729	113,643	2008 Canadian dollars
Pollock 2010[50]	Switzer-land [c]	CORE	30	2,270	63	-	3%	-0.32	1.00 vs 0	0.068	0.058	528 [d]	7'731	9,177	2006 Swiss francs
Tunis 2010[51]	USA	CORE	40	1,000	61	-	3%	-0.14	1.00 vs 0	0.097[e]	0.047	1,225	-	26,208	2006 US dollars
Tunis 2010[52]	France Germany Italy Spain	CORE	40	1,000	63	-	3% 3% 3% 6%	-0.32	1.00 vs 0	0.148 [e] 0.255 [e] 0.211 [e] 0.240 [e]	0.079 0.130 0.109 0.089	959 213 1,386 325	-	12,114 1,633 12,694 3,661	2007 Euros
Tunis 2008[53]	USA	CORE	40	1,000	63	-	3%	-0.32	1.00 vs 0	0.205 [e]	0.103	808	-	7,856	2006 US dollars
Cost-utility studies															
Farmer 2009[28]	UK	UKPDS-OM1	patient-lifetime	453[f]	66	-	3.5%	-0.14 -0.17	less intensive vs control / more intensive vs control [g]	-	-0.004 -0.020	59 56	-	-	2006 UK pounds
Palmer 2006[54]	UK	CORE	patient-lifetime	1,000	60	-	3.5%	-0.3	1.00 vs 0 [h]	0.371 [e]	0.165	2,564	-	15,515	2004 UK pounds

UKPDS-OM1: UKPDS Outcomes Model Version 1. LE: life expectancy. QALY: quality-adjusted life-years. N: number of patients. All cost-effectiveness and cost-utility analyses were conducted from the healthcare payers' perspective

[a] Referred to diabetes-related complications [b] in strips per day [c] based on an American patient cohort. [d] Δ treatment costs – Δcost of complications = (2,203+28)-1,624 = 528 (CHF, 2006) [e] undiscounted [f] control group = 152, [g] "less intensive self-monitoring = 150, more intensive monitoring = 151 (1) (1) standardised usual care with 3-monthly measurement of HbA1c by health professionals (control group); (2) use of a meter with training focused on clinician interpretation of results (less intensive self-monitoring); and (3) use of a meter with training in self-interpretation and application of the results to diet, physical activity and medication adherence (more intensive selfmonitoring)"[28] [h] results regarding patients on diet and exercise are reported in this table, because this groups is assumed to use one SMBG test per day compared to the patients on oral agents, which are assumed to use twice a day, and can thus be better compared to our results.

11.12 Cost and utility parameters

The parameters were adjusted to 2016 CHF by using the development of per capita healthcare costs in Switzerland, published by the Swiss Federal Statistical Office.[107] We used the per capita healthcare costs instead of the consumer price index (CPI) in order to account for the change in the type and intensity of treatment of the diabetes-related complications. The cost in absence of complications were calculated following the disease management of diabetes guideline published by the Swiss society of endocrinology and diabetes.[72] The SMBG costs were calculated based on the information in Section 7.2.1. [72]

The utility decrements are based on UKPDS patients and were drawn from Alva et al..[65] The utility decrements for renal failure and ulcer were drawn from a meta-analysis of quality of life studies.[71]

The direct medical costs of IHD, heart failure, amputation and blindness were drawn from a Swiss study by Brändle et al..[66] These costs were assessed from the healthcare payers' perspective. The calculations are presented in Table A 11 to Table A 14.

The direct medical costs of myocardial infarction (MI) and stroke were calculated based on two studies [67] [68] conducted by the Winterthur Institute of Health Economics. Detailed cost information was available for the calculations. We identified the relevant diagnosis of MI and stroke by matching the International Classification of Disease (ICD) codes with the respective ones defined in the UKPDS (ESM Table1 in Hayes et al.2013[57]). For MI we used the cost-of-illness study of acute coronary syndrome by Wieser et al..[67] Using the translated ICD-9 codes of MI from the UKPDS,[57] we selected the ST-elevation MI (STEMI) (ICD-10: I21.0, I21.1-3, I22.0-1, I22.8) and Non-ST-elevation MI (NSTEMI) (ICD-10: I21.4, I21.9, I22.9), in order to calculate the fatal, non-fatal and maintenance cost (for every subsequent year) per MI event. The specified cost calculation and the included services are presented in Table A 15. For stroke we used the cost-effectiveness study of dabigatran for stroke prevention by Pletscher et al..[68] Using the translated ICD-9 codes of stroke from the UKPDS[57], we selected the diagnosis ischemic stroke (IS) (ICD-10: I63.0-I63.9, I64) and haemorrhagic stroke (HS) (ICD-10: I60.0-I62.1, I62.9) in order to calculate the fatal, non-fatal and maintenance cost per stroke event. The event costs comprised of inpatient and outpatient costs. The specified cost calculation and the included services are presented in Table A 16.

The direct medical costs for treating renal failure were based on two sources. We drew the dialysis costs from a Swiss study by Eichler et al..[69] and the cost of renal transplantation from a Swiss study by Sandoz et al..[70] The specified cost calculation is presented in Table A 17.

Costs for treating ulcer were drawn from Brändle et al..[64] These cost were assessed based on published costs and Swiss expert opinions (a detailed description of the calculation could not be found). The cost at the time of the event was calculated as the mean between the cost for treating an infected (CHF 6,300) and a standard uninfected (CHF 2,435) ulcer. The cost for every subsequent year after the ulcer is healed is equal to CHF 220.

11.13 Cost of ischemic heart disease, heart failure, amputation and blindness

The direct medical fatal, non-fatal and maintenance costs of ischemic heart disease, heart failure, amputation and blindness were drawn from a Swiss study by Brändle et al..[66] The cost parameters used to asses these costs are extracted from the Appendix of this study. The costs presented in the following Tables are in CHF 2006. For our calculations they were adjusted to CHF 2016.[107]

Table A 11: Cost parameters of ischemic heart disease

Services	Cost per event
Fatal	**5,694**
Emergency physician	500
Ambulance transport	1,000
Hospitalization in 50% of cases	4,194
Non-Fatal	**16,831**
Hospitalization with PTCA (16.6% of patients) and CABG (10.1%) procedures	8,734
Rehabilitation	5,555
Examination by specialist once after discharge	87
Outpatient physician visits (4 times)	163
Electrocardiography (ECG) (3 times)	200
Electroencephalography (EEG)	376
Medication consisting of platelet aggregation inhibitors	182
Beta blockers	238
Angiotensin-converting enzyme (ACE) inhibitors	714
Statins	581
Maintenance	**2,263**
Physician visits twice a year	82
Physical examination every third year	30
Electrocardiography (ECG) once a year	67
Electroencephalography (EEG) every fifth year	75
Medication consisting of platelet aggregation inhibitors	578
Beta blockers	245
ACE inhibitors	671
Statins	599

PTCA: Percutaneous Transluminal Coronary Angioplasty, CABG: Coronary Artery Bypass Grafting

Source: Brändle et al. 2011 [66] (costs adjusted to the year 2006)

Table A 12: Cost parameters of heart failure

Services	Cost per event
Fatal	**8,222**
Emergency physician	500
Ambulance transport	1,000
Hospitalization in 50% of cases	6,722
Non-Fatal	**32,676**
Inpatient treatment	25,119
Cardiac rehabilitation	5,555
Examination by specialist once after discharge	87
Outpatient physician visits (2 times)	82
Electrocardiography (ECG) (6 times)	400
Electroencephalography (EEG)	376
Medication consisting of platelet aggregation inhibitors	555
Beta blockers	241
Angiotensin-converting enzyme (ACE) inhibitors	261
Maintenance	**11,361**
"based on a study from Szucs [49] in 1999 indexed to the year 2006."	

Source: Brändle et al. 2011 [66] (costs adjusted to the year 2006)

Table A 13: Cost parameters of amputation

Services	Cost per event
Fatal	**22,107**
Event comprising hospitalization	22,107
Non-Fatal	**24,303**
Event comprising hospitalization	22,107
First fitment of orthopedic appliances	2,079
Maintenance	**1,157**
orthopedic supervision twice a year	117
renewal of orthopedic appliances every second year	1,040

Source: Brändle et al. 2011 [66] (costs adjusted to the year 2006)

Table A 14: Cost parameters of blindness

Services	Cost per event
Non-Fatal	**5,064**
Maintenance	**5,064**
"Subjects were assumed to incur severe vision loss/blindness in both eyes simultaneously and therefore the event of blindness occurred only once. Cost values of initial costs (CHF 5,064) and subsequent annual maintenance costs (CHF 5,064) derived from published data [108]."	

Source: Brändle et al. 2011 [66] (costs adjusted to the year 2006)

11.14 Costs of myocardial infarction

The cost-of-illness study of acute coronary syndrome [67] separately assessed the cost of STEMI and NSTEMI into outpatient before hospital, inpatient and outpatient after hospital care. For fatal events, we calculated the cost of outpatient before hospital and inpatient and considered events as fatal, when the patient eventually died in the hospital. For non-fatal events, we calculated the cost of outpatient before hospital, inpatient and outpatient after hospital. For maintenance, we included the event cost of outpatient after hospital care of those who survived. To finally retrieve the cost for MI, the costs were weighted by the share of patients with STEMI and NSTEMI and summed up. Table A 15 shows the services included and the corresponding cost for fatal, non-fatal and follow-up events. The data sources used in the cost-of-illness study of acute coronary syndrome [67] to calculate these costs are the following: The number of hospitalized patients, deaths in the hospital and inpatient costs were calculated based on the Swiss Medical Statistics of Hospitals (MedStat),[109] the Cause of Death Statistic [110] and the Statistics of Case-Related Costs [111] provided by the Federal Statistical Office FSO. The number of patients treated in outpatient rehabilitation centres were extracted from the Swiss ACS registry AMIS Plus.[112] The tariff data on cardiac rehabilitation were received from santésuisse,[113] the Swiss health insurer association. Outpatient drug consumption was calculated based on AMIS plus registry data[112] and a German expert survey.[114] Remaining outpatient healthcare utilization was calculated based on the German survey [114] and adapted for Switzerland based on Swiss experts' interviews.

Table A 15: Cost parameters of myocardial infarction

Services	Cost per event
Fatal	**8,707**
Emergency physician	596
Ambulance transport (including Helicopter)	3,048
Acute care hospital	5,063
Non-Fatal	**33,877**
Emergency physician	154
Ambulance transport (including Helicopter)	814
Acute care hospital	27,777
Inpatient rehabilitation	2,983
Physician	432
Cardiologist	456
Long-term ECG	41
Medication*	867
Outpatient rehabilitation (Phase II)	304
Outpatient rehabilitation (Phase III) Heart group	49
Maintenance	**2,794**
Physician Cardiologist Long-term ECG Medication* Outpatient rehabilitation (Phase III) Heart group	

** Medication: Beta Blocker, ACE Inhibitor, ATII-Antagonist, Statins, Platelet aggregation inhibitor, Platelet aggregation inhibitor (Cox-1/Cox-2 Inhibitor)*

Source: authors' calculation based on Wieser et al. 2012 [67] (costs adjusted to the year 2006)

11.15 Costs of stroke

In the cost-effectiveness study of dabigatran for stroke prevention [68] the event costs and long-term follow-up costs were calculated separately in 3-month intervals for independent, moderate disability and totally dependent patients and fatal events. Patients discharged to go home and labelled as “healed” in MedStat [109], were classified as independent patients. Patients not labelled as “healed” but discharged to go home were classified as moderately dependent. Patients transferred to nursing homes after inpatient care were classified as totally dependent patients. The event costs were distinguished between costs due to fatal and due to non-fatal events. For non-fatal event, we calculated the event and follow-up costs from the independent, moderately disability and totally dependent patients. For the cost of maintenance, we calculated the follow-up costs from the three aforementioned disability groups. The costs were weighted by the share of the patients in each disability group. Table A 16 shows the services included and corresponding cost for fatal, non-fatal and follow-up events. The data sources used in the cost-of-illness study of dabigatran for stroke prevention [68] to calculate these costs are the following: Patient characteristics were based on sub-samples of the RE-LY trial.[115 116] Information on services used in inpatient care were extracted from MedStat.[109] “The cost of inpatient rehabilitation was calculated by multiplying the length of stay from MedStat and CHF 655, which represents the average daily tariff of three major rehabilitation clinics (Aar Schinznach- Bad, Reha Rheinfelden and Rehaklinik Bellikon) in 2008.[117] The cost of inpatient nursing homes was represented by medical expenditures in the Statistics of Social Medical Institutions [118] of CHF 42,360 per year.[68] Ambulance cost was estimated based of invoices from two ambulance services. Outpatient healthcare utilization (e.g. number of doctor visits after an inpatient visit), diagnostic and laboratory tests, as well as medication use were calculated based on a German survey [114] and adapted for Switzerland based on Swiss experts’ interviews. The unit costs of these services and medication were obtained from various Swiss sources.[119-121] The annual cost of outpatient rehabilitation was estimated as the cost of physiotherapy of CHF 2,167 from Mahler et al..[122] The annual cost of outpatient nursing of CHF 2,807 from Mahler et al.[122] was doubled to account for contributions by local governments [123] and corrected to reflect 12% inflation in health care from 2003 to 2008.[124]

Table A 16: Cost parameters of stroke

Services	Cost per event
Fatal	**11,153**
Emergency physician	41
Ambulance transport	437
Acute hospital care	10,168
Inpatient rehabilitation	507
Non-Fatal	**34,814**
Ambulance transport	384
Emergency physician	103
Acute care hospital	21,120
Inpatient rehabilitation	6,918
Inpatient nursing home	2,852
Outpatient nursing	2,116
Outpatient rehabilitation	482
Physician	88
Specialist*	173
Examination (including diagnosis)**	230
Medication***	247
Therapy (Physio)	101
Maintenance	**12,388**
Inpatient nursing home	8,476
Outpatient nursing	2,013
Physician	193
Specialist*	210
Examination (including diagnosis)**	534
Medication***	556
Therapy (Physio)	404

** Specialist: Rehabilitation neurologist, psychiatrist.*

*** Examination: LDL, cholesterol, hematogram I, potassium, glucose, creatinine, blood sample, rest electrocardiography, holter electrocardiography, magnetic resonance imaging, neuroangiography.*

**** Medication: Metoprolol-Mepha ZOK, Accuretic, Esidrex, Cosaar, Lioresal, Orfiril, Cymbalta*

Source: authors' calculations based on Pletscher et al. 2013 [68] (costs adjusted to the year 2006)

11.16 Costs of renal failure

The costs of dialysis and renal transplantation were calculated in CHF 2008 and CHF 2001 respectively. All costs were inflated to CHF 2016.[107] Dialysis costs were calculated based on routine claims data of dialysis patients of a large Swiss health Insurer, Helsana, combined with data from the central data pool (SVK).[69] Transplantation costs were calculated based on patients with renal transplantation as a consequence of end-stage renal disease (ESRD) in 6 transplantation centres in Switzerland. Renal transplantation from both a deceased and a living donor were included in the calculation, while almost all recipients in 2001 were out-patients.[70]

Table A 17: Cost parameters of renal failure

	Non-fatal cost	Maintenance	Sources
Costs of renal failure	**97,895**	**90,258**	Authors' calculations based on the following parameters:
Cost of haemodialysis (HD)	80,764	80,764	Eichler et al. 2013 [69]
Cost of peritoneal dialysis (PD)	69,079	69,079	Eichler et al. 2013 [69]
Cost of renal transplantation	86,420	19,615	Sandoz et al. 2004 [70]
Share of patients with ESRD dialysed		91%	Sandoz et al. 2004 [70]
Share of HD in dialysed patients		93%	Eichler et al. 2013 [69]
Share of HD in dialysed patients		7%	Eichler et al. 2013 [69]
Share of patients with ESRD that underwent transplantation		9%	Sandoz et al. 2004 [70]

ESRD: end-stage renal disease

(costs adjusted to the year 2006)

11.17 Results from sensitivity analysis on simulation period

Table A 18 Univariate sensitivity analysis on simulation period on diabetes-related complications

SimCombined													
diabetes related complications		ΔHba1c = –0.29%-points						ΔHba1c = –0.33%-points					
		5 years			10 years			5 years			10 years		
			95% CI			95% CI			95% CI			95% CI	
			Lower	Upper		Lower	Upper		Lower	Upper		Lower	Upper
Ischaemic heart disease	Intervention	4.83	4.37	5.33	8.44	7.58	9.39	4.82	4.37	5.33	8.46	7.58	9.39
	Control	4.82	4.37	5.33	8.44	7.56	9.38	4.82	4.37	5.33	8.44	7.56	9.38
	ARD	0.01	-0.04	0.04	0.00	-0.07	0.09	0.00	-0.04	0.04	0.02	-0.07	0.09
Myocardial infarction	Intervention	9.06	8.38	9.97	16.30	14.99	17.87	9.04	8.37	9.95	16.23	14.94	17.84
	Control	9.25	8.58	10.16	16.65	15.39	18.23	9.25	8.58	10.16	16.65	15.39	18.23
	ARD	-0.18	-0.29	-0.10	-0.35	-0.58	-0.22	-0.21	-0.32	-0.11	-0.42	-0.64	-0.24
Heart failure	Intervention	3.03	2.74	3.31	5.24	4.63	5.87	3.03	2.73	3.31	5.23	4.63	5.87
	Control	3.03	2.74	3.30	5.25	4.62	5.86	3.03	2.74	3.30	5.25	4.62	5.86
	ARD	-0.01	-0.03	0.03	-0.01	-0.06	0.06	0.00	-0.03	0.03	-0.02	-0.06	0.06
Stroke	Intervention	5.17	4.61	5.72	9.65	8.49	10.81	5.18	4.60	5.71	9.59	8.46	10.79
	Control	5.28	4.70	5.81	9.85	8.68	11.00	5.28	4.70	5.81	9.85	8.68	11.00
	ARD	-0.11	-0.16	-0.02	-0.20	-0.36	-0.06	0.00	0.00	0.00	-0.26	-0.39	-0.08
Amputation	Intervention	0.87	0.65	1.09	2.03	1.57	2.57	0.85	0.65	1.08	2.03	1.55	2.55
	Control	0.93	0.72	1.16	2.23	1.72	2.78	0.93	0.72	1.16	2.23	1.72	2.78
	ARD	-0.07	-0.10	-0.04	-0.20	-0.27	-0.11	-0.08	-0.11	-0.04	-0.20	-0.29	-0.13
Blindness	Intervention	1.62	1.28	1.89	2.95	2.35	3.44	1.60	1.27	1.89	2.93	2.33	3.43
	Control	1.69	1.35	1.97	3.11	2.50	3.60	1.69	1.35	1.97	3.11	2.50	3.60
	ARD	-0.08	-0.12	-0.04	-0.16	-0.24	-0.08	-0.10	-0.13	-0.05	-0.18	-0.27	-0.09
Renal failure	Intervention	0.15	0.07	0.23	0.27	0.13	0.42	0.15	0.07	0.23	0.27	0.13	0.42
	Control	0.15	0.07	0.23	0.27	0.13	0.42	0.15	0.07	0.23	0.27	0.13	0.42
	ARD	0.00	-0.01	0.01	0.00	-0.01	0.01	0.00	-0.01	0.01	0.00	-0.01	0.01
Ulcer	Intervention	0.90	0.68	1.10	1.63	1.24	1.99	0.90	0.68	1.10	1.62	1.24	1.98
	Control	0.94	0.72	1.14	1.72	1.32	2.07	0.94	0.72	1.14	1.72	1.32	2.07
	ARD	-0.04	-0.07	0.00	-0.09	-0.15	-0.01	-0.04	-0.08	0.00	-0.10	-0.16	-0.01
All death	Intervention	18.20	17.23	19.22	38.04	36.11	39.61	18.19	17.20	19.21	38.02	36.10	39.57
	Control	18.34	17.37	19.34	38.33	36.42	39.91	18.34	17.37	19.34	38.33	36.42	39.91
	ARD	-0.14	-0.23	-0.05	-0.28	-0.49	-0.12	-0.15	-0.25	-0.06	-0.31	-0.53	-0.15
Cardiovascular diseases death	Intervention	9.35	8.71	10.18	18.32	17.00	19.89	9.35	8.70	10.17	18.26	16.98	19.88
	Control	9.49	8.84	10.31	18.61	17.32	20.20	9.49	8.84	10.31	18.61	17.32	20.20
	ARD	-0.14	-0.21	-0.06	-0.29	-0.45	-0.15	-0.14	-0.22	-0.07	-0.35	-0.49	-0.18
Other death	Intervention	8.85	7.89	9.62	19.73	17.75	21.02	8.84	7.90	9.61	19.76	17.74	21.03
	Control	8.85	7.90	9.62	19.72	17.75	21.04	8.85	7.90	9.62	19.72	17.75	21.04
	ARD	0.00	-0.06	0.05	0.01	-0.13	0.12	-0.01	-0.06	0.05	0.04	-0.13	0.12

ARD: Absolute risk difference between intervention and control groups.

Table A 19 Univariate sensitivity analysis on simulation period regarding the ICERs

		Life expectancy (years)			Total QALE (QALYs)			Total cost (CHF, 2016)			CE ICER CHF/year	%-Change	CU ICER CHF/QALY	%-Change
			95% CI			95% CI			95% CI					
			Lower	Upper		Lower	Upper		Lower	Upper				
Base case: ΔHba1c = –0.29%-points (365 SMBG/year vs 0 SMBG/year), SimCombined, discounting = 3.0%, CE ICER = 58,195, CU ICER = 65,023														
Simulation time of 5 years	Intervention Group	4.30	4.27	4.32	3.43	3.41	3.45	19'841	19'351	20'237				
	Control Group	4.29	4.27	4.32	3.43	3.41	3.45	18'673	18'201	19'060				
	Difference	**0.00**	0.00	0.00	**0.00**	0.00	0.00	**1'168**	1'138	1'191	**506'461**	770%	**471'185**	625%
Simulation time of 10 years	Intervention Group	7.24	7.16	7.31	5.76	5.70	5.82	34'165	32'937	35'248				
	Control Group	7.22	7.15	7.30	5.75	5.69	5.81	32'234	31'005	33'312				
	Difference	**0.01**	0.01	0.02	**0.01**	0.01	0.01	**1'931**	1'863	1'982	**166'180**	186%	**169'660**	161%
Base case: ΔHba1c = –0.33%-points (260 SMBG/year vs 0 SMBG/year), SimCombined, discounting = 3.0%, CE ICER = 36,900, CU ICER = 41,078														
Simulation time of 5 years	Intervention Group	4.30	4.27	4.32	3.43	3.41	3.45	19'493	19'006	19'885				
	Control Group	4.29	4.27	4.32	3.43	3.41	3.45	18'673	18'201	19'060				
	Difference	**0.00**	0.00	0.00	**0.00**	0.00	0.00	**819**	792	852	**313'444**	749%	**293'449**	614%
Simulation time of 10 years	Intervention Group	7.23	7.16	7.31	5.76	5.70	5.82	33'559	32'354	34'666				
	Control Group	7.22	7.15	7.30	5.75	5.69	5.81	32'234	31'005	33'312				
	Difference	**0.01**	0.01	0.02	**0.01**	0.01	0.02	**1'325**	1'282	1'408	**115'589**	213%	**115'158**	180%

11.18 Study protocol of full HTA

(see following pages)