Zürcher Hochschule
für Angewandte Wissenschaften

Health Technology Assessment

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

Scoping Report V4.1

Eichler K., Tzogiou C., Knöfler F., Wieser S.

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For the attention of

Klazien W. Matter-Walstra, Dr. Phil. Nat. and
Gerhard Trunk, Dr. sc.
Bundesamt für Gesundheit BAG
Sektion Health Technology Assessment
Schwarzenburgstrasse 157
3003 Bern

Corresponding author

Simon Wieser, Prof. Dr. oec.
Winterthur Institute of Health Economics
Zürcher Hochschule für Angewandte Wissenschaften ZHAW
Gertrudstrasse 15
8401 Winterthur
058 934 768 74 / wiso@zhaw.ch

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Abbreviations

BAG	Bundesamt für Gesundheit
BIA	budget-impact analysis
BL	baseline
CEFF	cost-effectiveness analysis
CG	control group
COI	cost-of-illness study
CUA	cost-utility analysis
CVD	cardiovascular disease
DM	Diabetes Mellitus
DMP	diabetes management program
ECON	economic studies
EFF*	effectiveness* or safety studies
EN	Endnote® identifier
EQ-5D	EuroQol-5Dimensions
EUnetHTA	European network for health technology assessment
FOPH	Swiss Federal Office of Public Health
GIN	Guideline International Network
HbA1c	glycated hemoglobin
Hr-QOL	health-related quality of life
HSR	health services research
HTA	Health Technology Assessment
HUI	Health Utilities Index
ICER	incremental cost-effectiveness ratio
ICTRP	International Clinical Trials Registry Platform
IG	intervention group
KVG	Swiss social health insurance law
MA	meta-analysis
MA-SG	meta-analysis subgroups
MID	minimal important difference
MiGel	Swiss regulations for medical devices (Mittel und Gegenständeliste)
MR	meta-regression
NGC	National Guideline Clearinghouse
OAD	oral antidiabetic drug
OECD	Organisation for Economic Co-operation and Development
OLES	organizational, legal, ethical and socio-cultural issues (of this scoping report)
QALY	quality-adjusted life year

QOL	quality of life
RCT	randomized controlled trial
RQ	research question
SDSCA	Summary of Diabetes Self-Care Activities
SF-12	12-Item Short Form Survey
SF-36	36-Item Short Form Survey
SG	subgroup analysis
SMBG	self-measurement of blood glucose
SMUG	self-measurement of urine glucose
SR	systematic review
SR_npop	number of included patients in the systematic review
SR_nPS	number of primary studies included in the systematic review
T2DM	diabetes mellitus type 2
UKPDS	United Kingdom Prospective Diabetes Study
UKPDS-MO2	United Kingdom Prospective Diabetes Study Outcomes Model 2
W-BQ28	Well-Being Questionnaire 28
WIG	Winterthurer Institut für Gesundheitsökonomie
WZW	effectiveness, appropriateness and efficiency (Wirksamkeit, Zweckmässigkeit, Wirtschaftlichkeit)
ZHAW	Zurich University of Applied Sciences (Zürcher Hochschule für Angewandte Wissenschaften)

*From a knowledge generation perspective the term efficacy applies to RCTs. As we may also use health services research data with broader external validity, we will use the term effectiveness (EFF) instead of efficacy for simplification throughout the report, also for RCTs.

1 Background

The Swiss Federal Office of Public Health (FOPH) has recently installed a new section focusing on Health Technology Assessments (HTA). Its aim is to re-evaluate the effectiveness, appropriateness and efficiency (WZW) of currently reimbursed medical services and products under the Swiss social health insurance law (KVG) [1].

Self-measurement of blood glucose (SMBG) is a cornerstone of care for patients with diabetes mellitus type 1 and type 2, who are treated with insulin [2]. However, the use of SMBG in patients with non-insulin treated diabetes mellitus type 2 (T2DM) is under debate. The improvement of HbA1c due to SMBG in this patient group may be small and it may not translate into improved morbidity or mortality [3-7]. Early improvements in glycaemic control could nevertheless lead to clinical benefits in the long run by reducing, for example, the incidence of diabetes-related complications. SMBG provides information on the blood glucose levels at the time of testing. This allows immediate action to be taken, such as to prevent 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 [3].

According to the Swiss regulations for medical devices (MiGel), maximally 400 blood glucose test strips are currently reimbursed per patient per year.

The aim of the FOPH is to re-evaluate the role of SMBG in diabetes treatment of non-insulin treated T2DM [1]. Thus, the FOPH has commissioned the Winterthur Institute of Health Economics of the Zurich University of Applied Sciences (WIG/ZHAW) to perform a HTA report of SMBG for non-insulin treated patients with T2DM.

For the full HTA we will perform amendments in line with recommendations of the EUnetHTA Core Model (Section: Health Problem and Current Use of Technology).

2 Research questions of Swiss Federal Office of Public Health

The HTA commissioned by the FOPH comprises two steps:

- Scoping report (Kick-off in November 2017)
- Full HTA (to be started in 2018)

A pre-scoping report was performed by the FOPH and enclosed with the tender for the full HTA. Several research questions are of interest for the scoping report (see Table 1 with the transcript of the FOPH tender in German language).

Table 1: Research questions of the scoping report

Extract from the mandate specification by the FOPH, pages 3-4 [1]:
Im Rahmen des vom BAG bereits durchgeführten Pre-Scopings wurden die folgenden möglichen Fragestellungen erarbeitet […]. Diese sollen im Scoping-Bericht basierend auf einer systematischen Literaturrecherche durch den Auftragnehmer konkretisiert und allenfalls ergänzt werden. **3.1 Wirksamkeit** Im Bereich der Wirksamkeit ergeben sich Fragestellungen zu zwei Bereichen: a) Einfluss der SMBG auf den HbA1c-Wert bei nicht-Insulin pflichtigen T2DM-Patienten b) Zusammenhang zwischen HbA1c-Wert Senkung und harten klinischen Endpunkten zur Morbidität und Mortalität bei nicht-Insulin pflichtigen T2DM-Patienten 3.1.1 Zu a) sollen die folgenden Fragestellungen bearbeitet werden: Welchen Einfluss hat die SMBG bei nicht-Insulin pflichtigen T2DM-Patienten auf den HbA1c-Verlauf über die Studiendauer von 6, 12 und 24 Monaten sowie auf die Lebensqualität? Eventuell Stratifizierung nach Dauer der Diabeteserkrankung (T2DM < 1 Jahr; T2DM > 1 Jahr). Welche Auswirkungen auf den HbA1c-Wert hat eine „strukturierte SMBG“ im Sinne einer hinreichenden Testfrequenz zu definierten Zeitpunkten (z.B. über einen Zeitraum von mehreren Tagen durchgeführte Messungen vor und nach dem Essen, vor und nach dem Training, etc.), so dass Patienten und Ärzte Blutzuckermuster als Grundlage für notwendige Korrekturmassnahmen, wie z.B. das Vermeiden von Hyperglykämien oder das Erkennen des richtigen Zeitpunkts für eine Therapieeskalation (z.B. Wechsel auf Insulin), erkennen können? (Stöckenius, 2016).

Darauf basierend ergibt sich folgendes PICO-Schema:

P: Patienten mit nicht-Insulin pflichtigem T2DM. Dabei Berücksichtigung von HbA1c-Wert und Hypoglykämien zu Beginn der jeweiligen Studie (als sogenannte baseline), gegenwärtige Begleitmedikation, Komorbiditäten, Alter zu Beginn der jeweiligen Studie, Patienten mit oder ohne Hypoglykämie-Risiko (Stöckenius, 2016). Eventuell Stratifizierung nach Dauer der Diabeteserkrankung (T2DM < 1 Jahr; T2DM > 1 Jahr).

I: (Strukturierte) SMBG + Messung HbA1c beim Arzt. Dabei möglichst Nennung der Form der blutzuckersenkenden Therapiestrategie, z.B. im Rahmen eines therapeutischen Gesamtkonzeptes. In der Analyse kann nach verschiedenen Formen der Strukturierung, aber auch nach strukturiert oder nicht strukturiert unterschieden werden (Stöckenius, 2016).

C: Messung HbA1c beim Arzt

O: Primär: Reduktion HbA1c nach 6, 12 und 24 Monaten

Sekundär: Gesundheitsbezogene Lebensqualität und Therapiezufriedenheit; Hyper-/Hypoglykämien; Therapieänderungen, inkl. Medikationsänderungen, z.B. rechtzeitiger Wechsel auf Insulin; sonstige unerwünschte Ereignisse;

Weiter ist zu klären, ob es Subgruppen gibt, die bereits von einer geringeren HbA1c-Wert Reduktion als 0,5% in verstärktem Masse profitieren - z.B. aufgrund des Alters, des Geschlechts, der Dauer der Erkrankung, der Schwere der Erkrankung, einer instabilen Stoffwechsellage, bspw. aufgrund einer Neueinstellung von Medikamenten - und für die eine SMBG somit eher indiziert sein könnte.

Gibt es nicht-Insulin pflichtige T2DM-Patienten, für welche die SMBG aufgrund des Risikos für Hypoglykämien und einem damit verbundenen erhöhten Sicherheitsrisiko, z.B. im Strassenverkehr, beim Bedienen von Maschinen, usw. eher indiziert ist?

Welche Arten der „strukturierten SMBG“ finden in der Schweiz Anwendung? Wie viele Blutzuckerteststreifen werden pro Patient hierfür benötigt (ggf. Aufteilung in verschiedene Subgruppen)?

Welche Anzahl an Teststreifen wird von nicht-Insulin pflichtigen T2DM-Patienten tatsächlich verwendet (ggf. Aufteilung in verschiedene Subgruppen)? Wird die von Stakeholder-Seite her angesprochene „verstärkte Selbstbestimmung des Patienten“ aufgrund der SMBG durch eine hohe Anzahl an verwendeten Teststreifen untermauert?

3.1.2 Zu b) sollen die folgenden Fragestellungen bearbeitet werden:

Inwiefern besteht ein Zusammenhang zwischen einer Senkung des HbA1c-Werts und harten klinischen Endpunkten zur Morbidität und Mortalität bei nicht-Insulin pflichtigen T2DM-Patienten? Mit welcher Evidenz kann die Aussage belegt werden, dass eine HbA1c-Wert Senkung < 0,5% nicht klinisch relevant ist? (Gnägi Markus, 2015)

3.2 Sicherheit

Besteht ein Zusammenhang zwischen der SMBG und dem Auftreten von Depressionen

- in Abhängigkeit von der Zeit nach Diagnosestellung (6, 12, 24 Monate)?
- in Abhängigkeit von der Dauer der SMBG (6, 12, 24 Monate)?

3.3 Kosten-/Nutzen-Verhältnis

Wie gestaltet sich das Kosten-/Nutzen-Verhältnis für verschiedene Formen der (strukturierten) SMBG, welche mit einer Limitation der jährlich vergüteten Blutzuckerteststreifen (z.B. Limitation auf 50, 100, 200, 400 Teststreifen/Jahr) denkbar wären?

Lässt sich durch eine kostengünstigere Alternative, wie bspw. Limitation auf < 400 Teststreifen oder vollständige Streichung von jährlich vergüteten Teststreifen, der gleiche medizinische Erfolg erzielen?

Welche (Folge-)Kosten fallen an bei kompletter Streichung der Leistung und lediglich Vergütung bei instabiler Stoffwechsellage des nicht-Insulin pflichtigen T2DM-Patienten?

3.4 Organisatorische, rechtliche, ethische und soziokulturelle Aspekte

Welche organisatorischen, rechtlichen, ethischen und soziokulturellen Aspekte sind bei einer Fortführung der Vergütung von 400 Teststreifen jährlich, einer eingeschränkten Vergütung (z.B. Limitation auf 50, 100, 200 Teststreifen/Jahr oder Vergütung nur bei instabiler Stoffwechsellage des Patienten) oder einer kompletten Streichung für nicht-Insulin pflichtige T2DM-Patienten zu betrachten?

3 Aims of scoping report

The scoping report has the following aims:

- Re-assessment of available data concerning effectiveness and safety in published systematic reviews (SRs) and recent primary studies (randomized controlled trials, RCT).
- Refinement of the research questions formulated in the FOPH pre-scoping report, definition of methodologic approach and formulation of supplementary research questions, if necessary (e.g. concerning budget impact).

4 Effectiveness and safety (EFF)

This section comprises the domain effectiveness and safety (EFF) and reports about methods, results and conclusions for the full HTA concerning this domain.

4.1 Methods EFF

The over-arching approach ('meta-methodology') to achieve the main aims listed in section 3 is defined along the following principles:

- We will perform a systematic literature search to obtain an overview of available data and published analyses concerning the issues under examination.
- Thereafter, we will perform a systematic data mapping to learn about available data and data gaps.
- Finally, we will refine the research questions posed by the FOPH based on the data availability and feasibility analyses.

In principle, this over-arching approach will be performed for the effectiveness and safety domain and the health economic domain separately. In this section, we describe the methods for the EFF-domain.

4.1.1 Systematic literature search

Inclusion criteria

Following the criteria applied in the pre-scoping report of the FOPH, we defined the inclusion and exclusion criteria as shown in Table 2 and Table 3. These inclusion criteria apply for the EFF domain (i.e. the impact of SMBG on HbA1c and defined secondary outcomes).

These inclusion criteria do 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 will accept any reporting outcome of interest.

Several systematic reviews have already been conducted regarding the research questions of interest [3-7]. Thus, we included the following study designs:

- SRs already included in the pre-scoping report
- Recent RCTs not yet included in the SRs of the pre-scoping report
- Recent SRs not yet included in the pre-scoping report

Search strategy and electronic databases

With the support of a medical information specialist, we systematically searched for studies using the following electronic databases (imposing no language restriction): MEDLINE (see Appendix Table 1: for search strategy in OVID Interface), Embase (Embase® interface) and the COCHRANE-Library (from 2011 to November 2017, i.e. after the last Cochrane systematic review showing a thorough search strategy). We also conducted reference screening of the included studies. RCTs and SRs earlier than 2011 were extracted from the literature cited in the pre-scoping report of the FOPH.

Furthermore, one member of the WIG research team conducted a literature search of SMBG-related studies regarding Switzerland in the electronic databases PubMed and Cochrane (see Appendix Table 6 for search strategy). Since a comprehensive search was conducted by the medical information specialist, this sub-search was more restrictive targeted at finding only Swiss studies by using only the title-field for different alternatives.

Searching for economic studies:

The literature search of the medical information specialist was planned to be broader and also to inform the economic issues requested by the FOPH. Thus, a specific search term for economic studies was included in this search, as documented in our search strategy (Appendix Table 1). In this main search, the publication date was also restricted for economic studies from 2011 onwards. Our rationale was that we wanted to find current evidence reflecting up-to-date non-insulin drug treatment also for economic evaluations.

In addition, we performed focussed economic searches in EconLit without time restriction. The different economic searches and the retrieved studies are reported in more detail in the health economic evaluation section 5.

In the full HTA, we will carry out additional searches for effectiveness and safety issues (see section 4.3 on conclusions EFF for full HTA).

Table 2: Inclusion criteria for EFF

	Inclusion criteria EFF: **HTA SMBG**
Study design	Randomized controlled trials, SR Additional study types (only for selected purposes)* (Non-exclusive list of additional study types: non-randomized controlled trials, cohort studies, case-control studies; cross-sectional studies, case series; case reports)
Population	– Diabetes patients with non-insulin treated diabetes mellitus type 2 – Adults, both sexes
Intervention	Blood glucose self-measurement (SMBG; types: non-structured; structured; more intensive [as defined by primary study authors]) 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) – 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 psych wellbeing), 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 (additional study types: publication date: >=2004; included in prior systematic reviews) or (2) MID of HbA1c or (3) the amount of glucose sticks use*

EFF: effectiveness or safety studies; ECON: economic studies (CEFF: cost-effectiveness studies; CUA: cost-utility studies; COI: cost-of-illness studies)

Table 3: Exclusion criteria for EFF

	***Exclusion criteria EFF:* HTA SMBG**
Study design	Exclusion if: – non-randomized study types (unless used for selected purposes as defined in inclusion criteria) – expert opinion; abstracts
Population	Exclusion if: – diabetes patients with insulin treated T2DM – diabetes patients type 1 (per definition) – mixed diabetes populations and 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 the CG (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: **Primary outcomes:** no HbA1c

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

4.1.2 Study selection and data extraction

Study selection

Prior screening, training sessions took place to ensure high consistency between the four reviewers. Four reviewers screened titles and abstracts for relevance. Four reviewers assessed full texts for a final decision about inclusion or exclusion. For both review steps, unclear cases were discussed with a senior reviewer. Disagreements were resolved by consensus.

The particular reviewer assessed full texts for a final decision. If data from a specific population were published in several papers or if follow-up data were presented, each population was included only once to avoid double counting, but we used the most complete data set aggregated across all known publications/records.

Data were extracted in an Excel database by the particular reviewer. Unclear cases were discussed with a senior reviewer. Disagreements were resolved by consensus.

For the full HTA, additional data will be extracted for each included study and this step will be performed in duplicate by two reviewers.

Data extraction

The following data on study and participant details were extracted:

- **Included population**: age; sex; population recruitment; diabetes duration; diabetes medication at baseline, HbA1c at baseline, hypoglycaemia risk at baseline
- **Intervention**: unstructured SMBG; structured SMBG; more frequent SMBG; other forms of SMBG; number of SMBG measurements per week; length of follow-up
- **Control intervention:** no SMBG; unstructured/less structured SMBG; less frequent SMBG; other forms of SMBG; number of SMBG measurements per week
- **Outcomes, clinical**: HbA1c; blood glucose; hypoglycaemia; morbidity; depression; mortality; number of expected life years; medication change; QOL; QALYs; patient satisfaction; compliance with SMBG; other (e.g. harms)
- **Outcomes, economic**: direct medical costs; indirect costs (e.g. productivity losses after hypoglycaemia)
- **From the included SR** we also extracted the following data:
  - Definition of subgroup analyses
  - Variables used for meta-regression analyses

4.1.3 Data analysis

As a first step, a qualitative synthesis was performed to synthesize overriding information about included studies (e.g. presentation of tested SMBG types) and to judge clinical and methodological heterogeneity across studies as a step prior to a possible statistical meta-analysis.

As a second step, a systematic mapping was performed based on the extracted data to compare similarities and differences across studies:

- heterogeneity of included study populations
- range of applied diverse SMBG interventions
- diversity of applied outcome measures
- availability of already performed subgroup analyses in the RCTs or SR
- feasibility of possible additional subgroup analyses for the full HTA
- feasibility of possible meta-analyses for the full HTA

We did **not** perform meta-analyses for this scoping report. We also did **not** analyse the retrieved literature concerning a definition of the minimal important difference (MID) for haemoglobin change. Both steps will be performed in the full HTA.

To gain the best possible understanding of the impact of (small) HbA1c changes in the full HTA, we will use additional data sources. For example, the answer to *research question on the association between HbA1c and morbidity and mortality* (RQ9 in Table 13) will rely on (i) guidelines of diabetes treatment, (ii) non-randomized studies (e.g. cohort studies; assessing the natural relationship between HbA1c and morbidity/mortality) or (iii) economic diabetes models; see section Conclusions ECON for full HTA.

Evidence from selected non-randomized studies (publication date: >=2004 and included in prior systematic reviews) will also be used if RCTs do not provide data for some secondary outcomes, for example morbidity or mortality.

4.2 Results EFF

The results of the scoping report will be used to plan the full HTA. Thus, we only describe the range of available published data that may be used for analysis in the planned full HTA.

The calculation of specific measures concerning effectiveness, safety or efficiency of SMBG is also beyond the scope of this scoping report.

4.2.1 Retrieved studies

Our searches retrieved 1026 studies after duplicates were removed (see Figure 1).

We included 50 studies for the scoping report. These 50 studies comprised 16 systematic reviews (SR) [3, 5-19], 24 RCTs [20-43] and 10 health-economic studies (ECON) [20, 44-53] (Table 4).

The specific results concerning the health-economic studies are reported in the Health Economic Evaluation section. In the PRISMA flow chart in Figure 1, however, we report the number of EFF and ECON studies together for transparency reasons.

Figure 1: PRISMA study flow chart

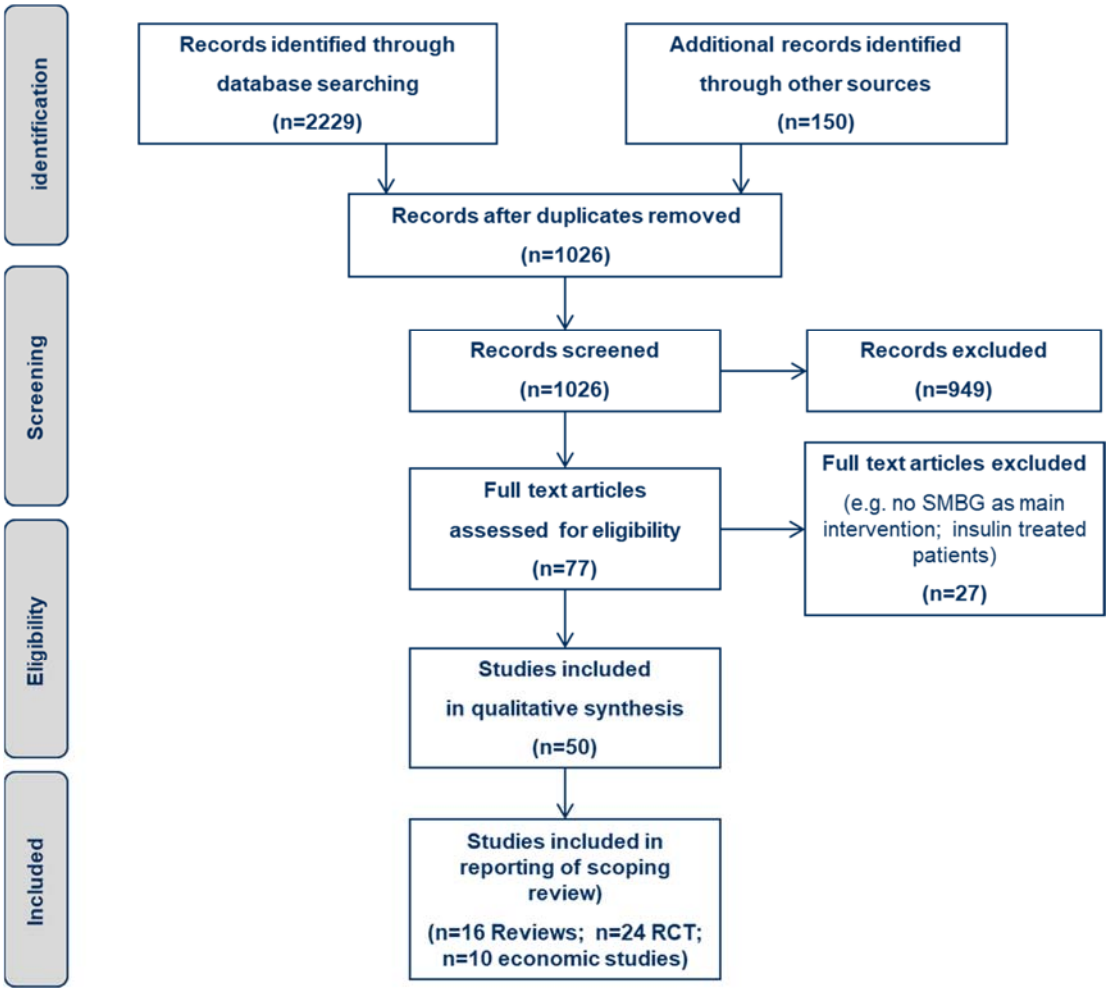


Table 4: EFF studies included for the scoping report

Number	Design	Content
16	Systematic reviews* (SR)	Mostly effectiveness and safety
24	RCTs (19 in the reviews + 5 by new searches)	Mostly effectiveness and safety

**Not all of the 16 reviews strictly fulfil the requirements of a systematic review, but for simplification, we refer to them as systematic reviews in our report.*

There is a big overlap for primary studies (RCTs) across the 16 SRs (see Table 5).

The 24 included RCTs comprise 19 single RCTs from the 16 relevant SRs (see Appendix Table 2 for a list of the 24 included RCTs and Appendix Table 3 for a list of the 16 relevant SRs). In addition, we retrieved 5 RCTs in our electronic searches from 2011 up to November 2017 (last search of the Cochrane systematic review Malanda [6] with a thorough search strategy: July 2011).

Some core features of the 16 relevant SRs are shown in the Appendix Table 4.

Core features of the 5 RCTS not yet included in the 16 relevant SRs are shown in Appendix Table 5.

Table 5: Relationship between relevant SRs and included RCTs

16 Systematic reviews / 24 Randomized controlled trials	Faas (1997)	Coster (2000)	Sarol (2005)	Welschen (2005)	Jansen (2006)	McGeoch (2007)	Poolsup (2008)	Towfigh (2008)	Allemann (2009)	IQWiG (2009)	St. John (2010)	Farmer (2012)	**Malanda (2012) CSR**	Lobè (2013)**	Hou (2014)	Zhu (2016)
Fontbonne (1989)	x	x	x	x	x		x	x	x				**x**			x
Allen (1990)	x	x		x	x								**x**			
Muchmore (1994)		x	x	x	x		x	x	x				**x**			x
Jaber (1996)			x		x		x	x	x							
Schwedes (2002)			x	x	x	x	x	x	x	x	x	x	**x**		x	x
Guerci (2003)			x	x	x	x	x	x	x	x	x	x	**x**		x	x
Davidson (2005)			x	x	x	x	x	x	x		x	x	**x**		x	x
Siebolds (2006)										x			**x**			
Barnett (2008)									x	x	x	x	**x**		x	x
O'Kane (2008)									x	x	x	x	**x**		x	x
Scherbaum (2008)									x	x						
Farmer (2009)							x*	x*		x		x*	**x***			x*
Durán (2010)													**x**			
Kleefstra (2010)													**x**		x	x
Franciosi (2011)													**x**		x	x
Polonsky (2011)																
Bosi (2013)																
Garcia de la Torre (2013)																x
Harashima (2013)																x
Kempf (2013)																x
Dallosso (2015)																
Malanda (2015)																x
Nishimura (2017)																
Young (2017)																

The systematic literature search using electronic databases for this scoping report was performed for the period 2011 to 2017 (i.e. after the Cochrane systematic review, CSR, Malanda 2012, in bold).

See Appendix Table 2 for a list of the 24 included RCTs and Appendix Table 3 for a list of the 16 relevant SRs.

** Farmer (2007) included, the preceding study of Farmer (2009)*

*** HTA including following reviews: McGeoch (2007), Towfigh (2008), Poolsup (2009), Allemann (2009), St. John (2010), Farmer (2012), Malanda (2012). Five more recent RCTs, which are not yet covered by reviews, are highlighted in red.*

4.2.2 Mapping of available data

We performed a systematic mapping to gain an overview over the available data to be used for analysis in the full HTA. This provides important information regarding the feasibility of planned analyses. The data are reported along several domains and sometimes only reported for RCTs due to the big population overlap in the systematic reviews.

Range of population features

We report population features for the included 24 RCTs. Almost complete information is given for gender, age, setting, diabetes duration and HbA1c at baseline. Information is somewhat less complete for diabetes medication classes at baseline and nearly inexistent for hypoglycaemia risk of participants at baseline (Table 6).

Table 6: Range of population features in 24 included RCTs

Population features	Information available	n RCTs with information
Gender (male ratio; %; range)	31 to 100	24
Age (years, range)	49 to 66	24
Setting (population recruitment)	General practitioner: 11 studies (Ambulatory) diabetes center: 13 studies	24
Diabetes duration (months)*	New onset diabetes: 1 study Diabetes <1yr: 2 studies Diabetes >1yr*: 19 studies	22
Diabetes medication	All on OAD: 6 studies No drugs or OAD: 14 studies	20
HbA1c at baseline (%; range)	6.6 to 12.1	24
Hypoglycemia risk (at baseline) (%)	3.5% of participants: 1 study	1
Study features		
Length of follow-up (months; range)	4 to 36	24

OAD: oral antidiabetic drug

**For the full HTA we will further stratify for diabetes duration > 1 year (may be 1- 5 years, > 5 years) However, this approach depends on the data available.*

Comparison of SMBG modes

We report on compared SMBG modes in the included 24 RCT. The most often assessed comparison in the RCTs (18/24) were structured SMBG vs. no SMBG (or SMUG) (Table 7).

Only few RCTs were retrieved for structured SMBG vs. un-structured SMBG (2/24), more frequent SMBG vs. less frequent SMBG (1/24) and more structured SMBG vs. less structured SMBG (1/24).

The number of SMBG measurements in the RCTs with structured SMBG (i.e. number of measurements per day/week and relationship to daytime and/or meals) varied over a wide range. We will describe these SMBG features in the full HTA more precisely.

Table 7: Comparison of SMBG modes as used in included RCTs

SMBG mode (intervention group)	SMBG mode (control group)	studies with information
Unstructured SMBG	No self-measurement	1
	SMUG	1
Structured SMBG	No self-measurement	15
	CG1: No self-measurement CG2: SMUG	2 (three arm trials)
	SMUG	1
	Un-structured SMBG	2
More frequent SMBG	Less frequent SMBG	1
More structured SMBG	Less structured SMBG	1

CG: control group; SMUG: Self-measurement of urine glucose

Range of outcome measures

We report outcome measures for the 16 relevant SRs and the 24 included RCTs. As defined by our inclusion criteria, all 16 relevant SR and 24 included RCTs reported about HbA1c as outcome measure (Table 8). The magnitude of observed HbA1c reduction due to SMBG in 13 of 16 included SR/Reviews with suitable data was in a range from -0.21% to -0.41%.

Depression was assessed in 4 RCTs, medication change in 10 RCTs, quality of life in 6 RCTs, patient satisfaction in 8 RCTs and compliance with SMBG was reported in different ways in 11 RCTs.

Table 8: Outcome measures as used in relevant SRs and included RCTs

Outcome measures (according to categories)	type of study	
	n SR	n RCT
1: HbA1c	16	24
2: blood glucose (includes: [fasting] plasma glucose)	3	7
3: hypoglycemia	5	7
4: morbidity (example diseases: CVD; blindness; renal failure; foot problems)	1	4
5: depression	0	4
6: mortality	0	0
7: number of expected life years	0	0
8: medication change (e.g. change of oral drugs; initiation of insulin)	2	10
9: quality of life	4	6
10: patient satisfaction	10	8
11: compliance with SMBG	1	11
12: other outcome measures, for example: weight change, BMI, cholesterol, triglyceride, microalbumin, general well-being, anxiety, energy, physician satisfaction; impact on beliefs about diabetes and SMBG, impact self-reported behavior; adverse events such hyperglycemia	4	19

Numbers indicate the number of studies in each category (16 SRs; 24 RCTs) reporting an outcome measure of the defined category (left column).

Subgroup analyses concerning population

We report outcome measures for the 16 relevant SRs and the 24 included RCTs. The most often performed subgroup analyses were for HbA1c at baseline and diabetes duration (Table 9).

Table 9: Subgroup analyses as used in relevant SRs and included RCTs

Population subgroup analyses	type of study	
	n SR	n RCT
1: age groups	1	3
2: HbA1c categories (at BL)	2	4
3: diabetes treatment categories (e.g. no drugs vs. OAD at BL)	1	3
4: diabetes duration	4	5
5: SMBG experience (e.g. naiveness [i.e. new to testing] vs. former SMBG)	1	3
6: other population subgroups (e.g.: health literacy, number of baseline comorbidities; adherence rates)	5	7

BL: baseline; OAD: oral antidiabetic drugs

Subgroup analyses concerning mode of SMBG

We report subgroup analyses for the 16 relevant SRs. Subgroup analyses concerning mode of SMBG in systematic reviews are scarce. Two SRs assessed the difference in effect of pure SMBG vs. SMBG with adjustment of diabetes management plan (Table 10).

Table 10: SMBG subgroup analyses as used in relevant SRs

Subgroup analyses concerning intervention SMBG	n SR
1: more frequent SMBG vs. less frequent SMBG	1
2: structured vs. non-structured SMBG	1
3: other SMBG comparisons (2 SR: pure SMBG vs. SMBG with adjustment of diabetes management plan)	2

Subgroup analyses concerning study features of RCTs

We report subgroup analyses for the 16 relevant SRs. Three SRs assessed the influence of length of follow-up on the outcome and one SR assessed the influence of industry sponsorship of RCTs (Table 11).

Table 11: Subgroup analyses in SRs concerning study features of included RCTs

Subgroup analyses in SR concerning study features of included RCT	n SR
sponsorship (industry funded vs not industry funded)	1
length of follow-up	3

Meta-regression analyses

In our retrieved 16 relevant SRs, meta-regression analyses to assess the specific influence of single factors on results are scarce (Table 12). In one additional SR, meta-regression analysis was planned but not reported.

Table 12: Meta-regression analyses as used in relevant SRs

Meta-regression analyses in SRs	n SR
Independent variables: all stratified analyses (univariate meta-regression)	1
Independent variables: follow up, diabetes duration,	1
Dependent variables: (3 separate meta-regressions performed in this SR): HbA1c; body mass index (BMI); total cholesterol (TC) Independent variables: sample size, publication year, history of diabetes, follow up	1

4.3 Conclusions EFF for full HTA

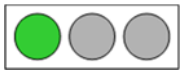
Based on our findings in the scoping project, we come to a number of conclusions for the full HTA. This section summarises our conclusions:

- **Feasibility judgement** of solving the research questions as formulated in the FOPH mandate specification
- Proposed **final research questions** to be answered by the full HTA (related to effectiveness and safety issues)
- Definition of available **outcome measures** as used for the full HTA (concerning effectiveness; safety) and assignment to final research questions

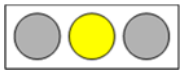
4.3.1 Feasibility of addressing FOPH research questions regarding EFF issues

This section examines the feasibility of solving the research questions formulated in the FOPH mandate specification. This feasibility is evaluated based on the data retrieved in our scoping review and on our experience in synthesizing evidence and performing meta-analyses.

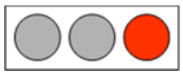
For each FOPH research question, we estimate feasibility using a traffic light colour code (Table 13):



green: suitable primary data available → analysis is feasible



yellow: only some data available (or data availability unclear)
→ feasibility of analysis is unclear

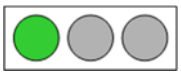
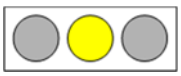
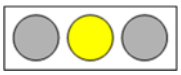
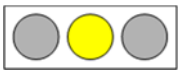
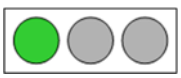
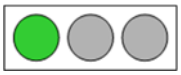


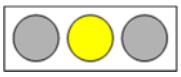
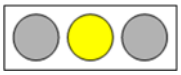
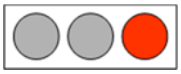
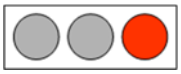
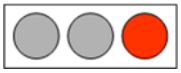
red: no or almost no data available → analysis is not possible

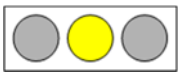
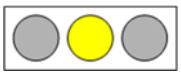
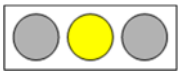
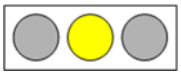
The rationale for the proposed traffic light code is to communicate the envisaged feasibility of analyses for each research question (RQ), based on our own judgment. Thus, our estimation is not based on clear-cut criteria or scientific definitions of categories, but on our experience with similar RQ and analyses.

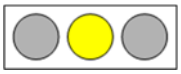
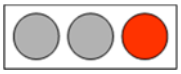
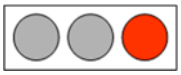
Some health services research questions may be assessed relying on data other than RCTs, such as non-randomized study types or modelling studies.

Table 13: Feasibility of addressing RQs on effectiveness and safety in the HTA

	Research questions	**Comment WIG based on scoping report**
Section of FOPH mandate	3.1a Effectiveness: outcome HbA1c	
RQ1 	What is the impact of **SMBG** on **HbA1c**?	Several follow-up periods available Planned analysis: MA, MR
RQ1-SG 	Subgroup analysis: Stratification for **duration of T2DM** < 1year; > 1year	Only 5 RCTs with data; in case of a meta-regression some RCTs may not provide sufficient independent variables to be included for adjusted analyses; Planned analysis: MA-SG; MR
RQ2 	What is the impact of **SMBG** on **QOL**?	Only 4 SRs and 6 RCTs with data Planned analysis: MA
RQ2-SG 	Subgroup analysis: Stratification for **duration of T2DM** < 1year; >1 year	Scarce data; in case of a meta-regression some RCTs may not provide sufficient independent variables to be included for adjusted analyses; Planned analysis: MA-SG; MR
RQ3.1 	What is the impact of structured **SMBG** compared to **non-structured SMBG** on **HbA1c**?	3 RCTs with data; some heterogeneity of interventions Planned analysis: MA-SG
RQ3.2 	What is the impact of more frequent **SMBG** compared to **less frequent SMBG** on **HbA1c**?	1 RCT with data; Planned analysis: Tabulation

RQ4 	What is the impact of structured **SMBG** compared to **non-structured SMBG** on **medication changes**?	10 RCTs with data for medication changes but possibly not in combination structured SMBG vs non-structured SMBG Planned analysis: MA-SG
RQ5 	Is there any subgroup of T2DM patients which has a benefit from **HbA1c changes < 0.5%**?	No data in the RCT; to be answered with non-randomized study types and modelling; relates to the minimal important difference (MID) question (RQ 10) Planned analysis: table format; qualitative summary
RQ6 	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**?	Presumably no data in the RCT. Laws may require SMBG for people who work for public transport agencies. Planned analysis: table format; qualitative summary
RQ7.1 	Which different **types of structured SMBG** are used in daily routine in **Switzerland**?	We will contact health services experts/perform interviews Planned analysis: table format; qualitative summary
RQ7.2 	Which **number of test strips** is used to comply with the modes of **structured SMBG** in daily routine in Switzerland?	We will contact health services experts/perform interviews Planned analysis: table format; qualitative summary

RQ7.3 	Which **number of test strips** is used in daily routine in **Switzerland**? (“**real use**”; not “real claim”)	To be answered by health services research methods (e.g. health insurance database analyses); however, some evidence is available from international studies that can be used for an approximation. [44, 46, 54, 55] Planned analysis: table format
RQ8 	What is the impact of **SMBG** on **self-efficacy** and **quality of self-management of T2DM patients**?	Unclear database in the primary studies Planned analysis: table format
Section of mandate	**3.1b Effectiveness: outcome morbidity and mortality**	
RQ9 	What is the **association** between **HbA1c** and **morbidity** and **mortality**?	No data in the RCT; to be answered with non-randomized study types and modelling; relates to the MID question (RQ 10) Planned analysis: table format
RQ10 	Is there a minimal important difference **(MID) of HbA1c**?	No data in the RCT; to be answered with non-randomized study types Planned analysis: table format; qualitative summary

Section of mandate	**3.2 Safety**	
RQ11 	What is the **association** between **SMBG** and **depression**?	Only 4 RCTs with data Planned analysis: MA; table format
RQ11-SG1 	Subgroup analysis: stratification for diabetes duration (6, 12, 24 months)	Possibly no or few strata reported in studies that report about depression as outcome measure. Planned analysis: MA-SG; table format
RQ11-SG2 	Subgroup analysis: stratification for duration of SMBG (6, 12, 24 months)	Possibly no or few strata reported in studies that report about depression as outcome measure. Planned analysis: MA-SG; table format

SG: subgroup analysis; MA: meta-analysis; MA-SG: meta-analysis subgroups; MR: meta-regression

Based on the results of the scoping process, we have refined the FOPH research questions. A summary table of the proposed PICO after the scoping process for all domains and the planned methods for analysis is shown in Table 14 below. The table provides an overview of proposed changes for the full HTA regarding the pre-scoping questions specified by FOPH.

Table 14: Proposed PICO after the scoping process and planned methods for analysis

Domain: EFF Research questions (RQ) FOPH-No.:	RQ1	RQ2	RQ3	RQ4	RQ5	RQ6	RQ7.1 & 7.2 & 7.3	RQ8	RQ9	RQ10	RQ11
Population	adults DM Type2	adults DM Type2	adults DM Type2	adults DM Type2	adults DM Type2	adults DM Type2 & high risk jobs	adults DM Type2	adults DM Type2	adults DM Type2	adults DM Type2	adults DM Type2
Intervention	SMBG	SMBG	structured SMBG	structured SMBG	exposition: <0.5% change in HbA1c	SMBG	exposition: structured SMBG and number of used test strips in Switzerland	SMBG	exposition: HbA1c	MID for HbA1c?	SMBG
Control	no SMBG	no SMBG	non-structured SMBG	non-structured SMBG	n.a.	no SMBG	n.a.	no SMBG	n.a.	n.a.	no SMBG
Outcome	primary outcome: HbA1c	secondary outcome*: hyper-/hypoglycemia etc. (see below*)	primary outcome: HbA1c	secondary outcome: Medication changes	morbidity; mortality	hypoglyc events	n.a.	self-efficacy; Q of self-management	morbidity; mortality	morbidity; mortality	depression
additional analysis	RQ1-SG[#]: diabetes duration; high risk jobs;	RQ2-SG: diabetes duration; high risk jobs;	if data available: more frequent vs less frequent SMBG	if data available: more frequent vs less frequent SMBG					which type of association? (linear; threshold; MID); SG with benefit?		
type of analysis[$]	MA; MA-SG; MR;	MA; MA-SG; MR; table format	MA-SG; Tabulation	MA-SG			HSR-data and interviews: table format; qualitative summary		assessment of observational studies; table format; qualitative description		
change in RQ after scoping process	RQ-1 for all SG	RQ-2 for all secondary outcomes and for all SG	none	none	RQ5 goes with RQ9	RQ6 goes with RQ2	none	RQ8 goes with RQ2	none	RQ10 goes with RQ9	RQ11 goes with RQ2

**secondary outcomes include: hyper-/hypoglycemia; change in medication; morbidity; psychological outcomes (e.g. depression); mortality; QOL; patient satisfaction (incl. self-efficacy; self-management performance); other adverse events or harms; **depending on availability of data; [#]SG: subgroup analysis; [$]MA: meta-analysis; MA-SG: meta-analysis subgroups; MR: meta-regression; HSR: health services research*

4.3.2 Relevant outcome measures EFF

Based on the primary data available, we propose the following outcome measures (numbered according to our mapping table) for the full HTA (Table 15).

We will not directly use information from SRs. However, we have also provided the outcome measures as used in the relevant SRs, as the figures give some important insight why it is justified to rely on RCTs rather than on published SRs. For example, none of the SRs, that we have retrieved, reports about depression as (synthesized) outcome measure, while 4 of the retrieved RCTs report this outcome.

Table 15: Proposed outcome measures for the full HTA

Proposed outcome measures for the full HTA (according to categories, as used in the mapping section)	n SR	**n RCT**	**Used for refined RQ**
1: HbA1c;	16	**24**	RQ1; RQ3
2: blood glucose (includes: [fasting] plasma glucose); represented by No1	3	**7**	---
3: hypoglycaemia;	5	**7**	RQ2
4: morbidity (example diseases: CVD; blindness; renal failure; foot problems);	1	**4**	RQ2
5: depression;	0	**4**	RQ2
6: mortality*; possibly, only assessed by modelling; represented by No7	0	**0**	(RQ2*); RQ9
7: number of expected life years;	0	**0**	RQ9
8: medication change (e.g. change of oral drugs; initiation of insulin);	2	**10**	RQ4
9: quality of life	4	**6**	RQ2
10: patient satisfaction;	10	**8**	RQ2
11: compliance with SMBG;	1	**11**	RQ2
12: other outcome measures (selected examples): weight change, BMI, cholesterol, triglyceride, anxiety, physician satisfaction; impact on beliefs about diabetes and SMBG, impact self-reported behaviour; adverse events such hyperglycemia;	4	**19**	RQ2 (selection according to defined secondary outcome)

**Mortality: During full HTA, we will check included publications on data for death (from any cause) which may provide some information on mortality in the RCTs.*

4.3.3 Other conclusions for full HTA

The following issues will also be part of the full HTA.

a) Additional searches will be done for the EFF domain during the full HTA:

- PsychInfo database
- international evidence-based guideline recommendations (by using the databases National Guideline Clearinghouse (NGC) and Guideline international network (GIN) as well as NGO websites of evidence-based medicine advanced countries 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)

b) To gain the best possible understanding regarding the impact of (small) HbA1c changes in the full HTA:

We will scrutinise suitable publications that may have used empirical data about the relationship between HbA1c and morbidity/mortality of non-insulin-dependent type 2 diabetes, specifically the impact of small HbA1c changes:

- Guidelines of DM treatment
- Authoritative summaries of HTA agencies
- RCTs with long term follow-up (concerning the impact of small interventional changes of HbA1c)
- Non-randomized study types (e.g. cohort studies; concerning the natural relationship between HbA1c and morbidity/mortality)
- Economic diabetes models (using such randomized or non-randomized study type data)

c) Additional study types beyond RCT

- Evidence from non-randomized study types (publication date: >=2004 and included in prior systematic reviews) will also be used if RCTs do not provide data for some secondary outcomes, for example morbidity or mortality.

d) Specific points to consider for data extraction:

- Medication of study population: To document drug types that may lead to an increased risk of hypoglycaemia, for example beta-blocker. For some drug combinations, it is recommended to perform SMBG more frequently.
- Information, if HbA1c at the end of follow-up was in target range of individual patients (yes/no); not only absolute HbA1c values
- Information, which technological generation of SMBG measurement devices was used
- Crucial parameters of SMBG Intervention: (1) SMBG frequency and timing; (2) patient's knowledge and skills, (3) clinicians knowledge and skills, (4) display of SMBG data
- Information about adherence to medication and SMBG protocols

e) Specific points to consider for analysis:

- Subgroup-analysis for publication date of included studies (publication year before 2008 vs. from 2008 onwards) and meta-analysis sorted for publication year (to enable graphical inspection of possible time trends)
- Subgroup-analysis of cluster-randomized RCT vs non-cluster-randomized RCT

5 Health economic evaluation (ECON)

This section comprises the domain health economic evaluations (ECON) and reports about methods, results and conclusions for the full HTA concerning this domain.

5.1 Research questions of HTA

In order to address the health economic related research questions posed by the FOPH (3.3 in Table 1) the health economic evaluation included in the planned HTA may cover the following aspects:

1) What is the **cost-effectiveness of the currently reimbursed SMBG** in non-insulin treated T2DM versus no SMBG in Switzerland? This cost-effectiveness analysis should compare the net monetary costs of SMBG with the potential net benefit of SMBG in terms of better health and longer life expectancy. Net monetary costs would include the costs of SMBG as well as the potentially prevented or delayed costs of diabetes-related complications.
2) What is the **costs-effectiveness of possible variations in SMBG** in non-insulin treated T2DM in Switzerland? These variations may concern specific patient populations (e.g. newly diagnosed T2DM patients) or specific variations of SMBG (e.g. structured SMBG, reduced number of reimbursed glucose test strips per year). We will specify the subgroups of SMBG and of the population upon analysis of the literature review results in the full HTA and in agreement with FOPH.
3) What is the **budget impact** of the currently reimbursed SMBG and of possible variation of SMBG in Switzerland?

Health economic evaluations build on the insights generated in the effectiveness evaluation of SMBG. However, the time horizon of the effectiveness evaluation of SMBG may differ 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, the prevention and delay of the long-term consequences of poor glycemic control are the main drivers of the results of health economic evaluation. As this type of information is usually not available from clinical trials, it must be estimated with health economic models simulating the health and cost consequences of SMBG over a lifetime horizon.

The development of a heath economic model evaluating the lifetime consequences of changes in HbA1c levels would require a substantial financial effort and time, exceeding the resources and timelines of the planned HTA. We thus plan to use and adjust one of the existing health economic models of T2DM. Such a model must be adaptable to the context of the Swiss healthcare system and to the estimation of the cost-effectiveness of SMBG versus no SMBG as well as of different variations of SMBG and the budget impact of SMBG. The identification

of such a model for the HTA of SMBG in non-insulin treated T2DM in Switzerland is part of this report.

5.2 Methods ECON

The methodologic approach for the full HTA in the ECON domain is designed along the following principles:

- We will perform a literature search to obtain an overview of available published health economic analyses concerning the use of SMBG in non-insulin treated T2DM and to identify a suitable health economic model to be adapted to the research questions of the HTA.
- We will examine the available health economic models in terms of their suitability, adjustability and accessibility.
- We will examine the input parameters required for the health economic model.

5.2.1 Literature search ECON

We conducted three literature searches:

1) *External*: In addition to the literature search regarding EFF, the medical information specialist conducted a literature search in MEDLINE / Embase and COCHRANE-Library (including the CRD-Database) using specific search terms for economic studies (see OVID Interface in Appendix Table 1). The aim of this search was to find up-to-date economic evaluations. Hence, following the same strategy as for EFF, the publication date of this search was restricted from 2011 onwards.
2) *Internal*: A researcher of the WIG team performed a literature search in the electronic database EconLit (ProQuest interface) using the search strategy described in the Appendix Table 7, without imposing any time or language restrictions. 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.
3) *Internal*: A researcher of the WIG team screened all the health economic diabetes models presented at the Mt Hood Challenge Meetings[1] [56] and looked for studies that apply these models on the research question of the HTA, without imposing any time or language restrictions. For the comprehensiveness of the results, a further hand search was performed based on the reference of relevant studies.

[1] The aim of the Mt Hood Diabetes Challenge Network is to bring the developers and users of the health economic diabetes simulation models together to exchange ideas and compare the predictions of various diabetes complications using different models and settings.

The inclusion and exclusion criteria applied for the evaluation of the retrieved economic studies are shown in Table 16 and Table 17. No restrictions were imposed on the study design or the comparison group. Cost effectiveness studies comparing SMBG with other self-management methods are relevant only in terms of the methodology and model applied.

Table 16: Inclusion criteria for ECON

	***Inclusion criteria ECON:* HTA SMBG**
Study design	All health economic studies, including CEFF, CUA, BIA, COI, cost comparison, SR of economic studies
Population	– diabetes patients with non-insulin treated diabetes mellitus type 2 – adults, both sexes
Intervention	blood glucose self-measurement (SMBG; types: non-structured; structured; more intensive [as defined by primary study authors]) 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:** direct, indirect costs, generic measures of health (e.g. QALYs, life expectancy) **Secondary outcomes:** ICER

ECON: economic studies (CEFF: cost-effectiveness studies; BIA: budget impact analysis; CUA: cost-utility studies; COI: cost-of-illness studies; ICER: Incremental cost-effectiveness ratio)

Table 17: Exclusion criteria for ECON

	***Exclusion criteria ECON:* HTA SMBG**
Study design	Exclusion if no journal article
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
Control intervention (comparator)	Exclusion if: **See intervention**
Outcome measures	Exclusion if: no economic outcomes

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

5.2.2 Study selection and data extraction

In addition to study and participant details, we extracted also the following data from the included economic studies:

- Information on the health economic model applied
- Definition of subgroup analyses
- Categories of cost outcomes

5.3 Results ECON

5.3.1 Retrieved studies

The searches retrieved 137 economic studies, 9 of which were duplicates. Two researchers of the WIG team screened the remaining 128 studies. Ten relevant studies were identified: seven cost-effectiveness studies [45-51], one cost-utility study [52], one budget-impact study [53] and one financial impact study [44].

5.3.2 Health economic models

We identified two models that could be applied for the HTA of non-insulin treated T2DM patients:

1) The *UKPDS Outcomes Model 2* (*UKPDS-OM2)* described in [57] and applied in three studies [20, 46, 47] to estimate the cost-effectiveness of SMBG in non-insulin treated T2DM.
2) The *IQVIA CORE Diabetes Model* described in [58] and applied in six studies [45, 48-52] to estimate the cost-effectiveness of SMBG in non-insulin treated T2DM.

Model platform and fee for model use

UKPDS Outcomes Model version 2 (UKPDS-OM2)

- The UKPDS-OM2 can operate on Windows. It uses Microsoft Excel workbooks to store input and output data [59].
- No charge is made to academic organizations but commercial organizations must pay an appropriate fee [60].

IQVIA CORE Diabetes Model

- The IQVIA CORE Diabetes Model is accessible via the internet and operates with an executable code linked to a user front-end [58].
- The fee depends on the type of license. Options include annual licenses, single-project licenses or licenses combined with consulting support [61].

The two models differ mainly in the diabetes-related complications considered (Table 18) and in their mode of operation.

We were able to obtain a license for the UKPDS-OM2 model. Table 19 provides an overview of its structure. The model simulates the lifetime progression of T2DM and projects the clinical and economic outcomes in T2DM over the patient's lifecycle. These outcomes include gains in life expectancy and quality-adjusted life-years (QALYs), long-term treatment costs of diabetes-related complications, and cost of monitoring strips. The model also estimates incremental cost-effectiveness ratio (ICER) comparing the additional net cost of SMBG versus no SMBG

with its additional health benefits. Furthermore, it allows to perform univariate and multivariate sensitivity analyses. Univariate sensitivity analyses explore how results change when single model assumptions are modified (e.g. compliance with SMBG or the price of blood glucose strips). Multivariate sensitivity analysis explores the overall robustness of the results and allows to calculate confidence intervals of the results [59].

The UKPDS-OM2 model uses the UKPDS 82 [57] risk regression equations for the prediction of the probability of diabetes-related complications and death due to a number of risk factors, including HbA1c. These parametric proportional hazard models are currently the most validated set of equations [62]. Although the user cannot modify the coefficients of these equations with UKPDS-OM2, a number of input parameters and modelling assumptions can be modified. For example, HbA1c values 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.

The clinical impact of SMBG may vary with diabetes duration, baseline HbA1c, across non-insulin diabetes treatments (e.g. diet and exercise vs OAD), SMBG frequencies, and adherence rates, cost parameters, time horizon of the model, and changes in the level of these risk factors over time [48, 56, 59]. Cost-effectiveness can therefore be assessed in different cohorts of the non-insulin T2DM (e.g. in terms of treatment, baseline risk profiles) and for different SMBG interventions (e.g. structured SMBG vs non-structured, different frequencies of SMBG).

Table 18: Comparison of diabetes related complications in UKPDS and CORE model

	UKPDS Outcome Model 2	IQVIA CORE Diabetes Model
1. death	x	x
2. myocardial infarction	x	x
3. angina	x	x
4. stroke	x	x
5. heart failure	x	x
6. amputation	x	x
7. renal failure	x	x
8. diabetic ulcer	x	x
9. blindness in one eye	x	
10. peripheral vascular disease		x
11. diabetic retinopathy		x
12. macular edema		x
13. cataract		x
14. hypoglycemia		x
15. ketoacidosis		x
16. nephropathy		x
17. neuropathy		x

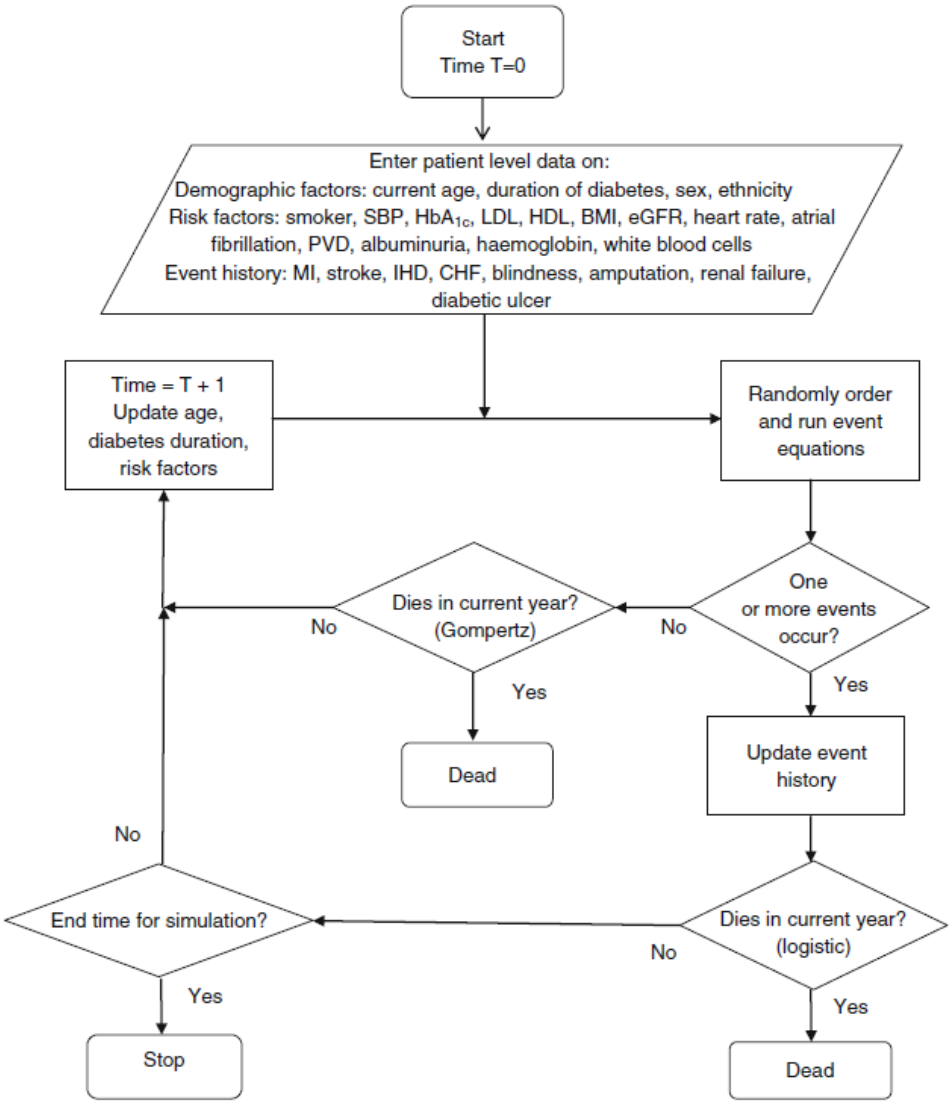
Source: [57] Mt Hood Challenge network [56]

Table 19: Overview of UKPDS Outcome Model 2

Excerpts from publications describing the model:

"UKPDS-OM2 integrates separate risk equations for eight diabetes-related complications and death"[57]

"UKPDS-OM is based on an integrated system of parametric equations that predict the annual probability of any of the above complications and Monte Carlo methods to predict the occurrence of events. The likelihood of the events is based on patient demographics, duration of diabetes, risk factor levels, and history of diabetes-related complications. Different treatment and management strategies are evaluated through their impact on risk factor levels. A key aspect of the model is its ability to capture the clustering or interaction of different types of complications at the individual patient level. The model is a probabilistic discrete-time multi-state model. Patients start with a given health status (e.g., age, sex, duration of diabetes, risk factor values, and no complications) and can have one or more nonfatal complications and/or die in any model cycle. When a patient experiences a complication, their utility is permanently decremented such that they accumulate quality-adjusted life-years at a slower rate. Utility decrements and costs associated with events are estimated from the same patient-level data set." [56]



Source: [57]

5.3.3 Input Parameters for health economic model

The adaption of the UKPDS-OM2 to the Swiss healthcare system will include the following input variables, provided their availability:

- Clinical effects of SMBG on HbA1c for different sub-groups will be drawn from the studies identified in our literature review on the effectiveness of SMBG. For the full HTA, we will carefully plan the best meta-analytic approach to analyze the data. Based on the results of the scoping report, we judge the clinical and methodological heterogeneity of the included studies as sufficiently low to justify a statistical meta-analysis, employing a random-effects meta-analysis.
- Cohort characteristics regarding baseline demographics and risk factor profiles of non-insulin treated T2DM will be based on Swiss data sources where available (e.g. population statistics, Swiss Health Survey, health insurance claims data) and if necessary supplemented with data from the Kaiser Permanente study [63].
- The actual number of test strips used by non-insulin treated T2DM patients in Switzerland is currently unknown. However, health insurance claims data may be used to assess the number of blood glucose measurement strips purchased in a given year by non-insulin treated diabetes patients using oral antidiabetic drugs. The Helsana health insurance group, one of the largest Swiss health insurers, has confirmed that it could undertake such an analysis on our behalf. This result would provide the upper bound of the number of strips used, as the patients may not use part of the purchased strips.[2]
- Cost unit parameters (e.g. treatment costs in different healthcare setting) will be drawn from Swiss data sources (e.g. Swiss Federal Statistical Office), while the price of test strips will be drawn from the list with the Swiss regulations for medical devices (MiGEL). The most recent unit prices according to MiGEL for test strips will be used. Future costs and health outcomes will be discounted with a 3% rate.
- Utility values for the assessment of QALYs will be drawn from the UKPDS 68 [64].

[2] The number of measurements by a single patient could be derived from the patient's self-monitoring device using a dedicated software. The treating physicians might thus be able to obtain the information on the number of strips used during a consultation. However, these data will not be available for this HTA.

5.4 Conclusions ECON for full HTA

This section summarises the conclusions for the compilation of the full HTA related to the **health-economic methods** to be applied in the full HTA (modelling; outcome measures).

5.4.1 Feasibility

Despite the fact that HbA1c changes due to SMBG are expected to be small for non-insulin treated diabetes mellitus type 2, SMBG can have important advantages (e.g. avoiding hypoglycemia and its complications, better control of diet and sport routines, better diabetes therapy) that should not be ignored, while there are considerable ethical aspects that need to be addressed. At the same time, as explained in section 5.3.2, with UKPDS-OM2 we are able to to model the effects of small changes in HbA1c on the diabetes related complications. Therefore, the HTA will be conducted even with a small effect of SMBG on HbA1c.

5.4.2 Health economic method

Based on the aims of the FOPH we developed three health economic questions for the HTA (section 5.1). We will answer these questions by adapting the UKPDS-OM2 model to the context of the Swiss healthcare system with the parameters described in section 5.3.3.

The main outcomes of the cost-effectiveness analysis will be the cost and effect differences of currently reimbursed SMBG in non-insulin treated T2DM versus no SMBG, as well as the resulting ICERs. Possible variations in the patient population and the type of SMBG will also be evaluated if sufficient evidence on the effectiveness will be available. In case of identical effects in comparator and intervention, we will carry out a cost minimisation analysis. The budget impact analysis will assess the impact on overall healthcare spending in Switzerland for the different scenarios of the SMBG.

The health economic outcomes will be evaluated from a healthcare payer perspective. This perspective includes all payers according to Swiss National Health Accounts (mandatory health insurance, public contributions, out-of-pocket, etc.).

6 Organizational, legal, ethical and socio-cultural issues (OLES)

The global consensus conference on SMBG in 2005 suggested that diabetes patients should be able to determine the SMBG practices according to their needs [52]. Self-monitoring is useful in providing personal feedback about the impact of changes in eating patterns and physical activity to support self-management [20] and may be required by law for people who work for public transport agencies. Nevertheless, empirical evidence may be useful to assess if the concept of improved self-efficacy via SMBG also holds for non-insulin treated patients with T2DM.

In this section, we describe, as far as possible, the planned approach in the OLES domain during the full HTA.

6.1 Methods OLES for full HTA

The research question for organisational, legal, ethical and socio-cultural issues formulated in the mandate specification by the FOPH is shown in Table 20.

Table 20: Research question for organisational, legal and socio-cultural issues

Section of mandate	**3.4 Organisational, legal, ethical and socio-cultural issues**
	Which organisational, legal, ethical and socio-cultural issues are of relevance for each of the four scenarios? – No change in reimbursement of the maximum possible 400 test strips per year in Switzerland – Limitation of reimbursement of test strips per year in Switzerland (e.g. 50, 100, 200 strips/year) – Reimbursement only in case of decompensated blood glucose levels – Stop of reimbursement of blood glucose strips for all patients with non-insulin treated T2DM

The relevance of the organisational, legal, ethical and socio-cultural issues will be discussed in the full HTA and will be influenced by the results regarding the effectiveness, safety and health economic aspects of SMBG.

We will apply the following methodological steps:

- Refinement/Re-evaluation of the FOPH research questions, after the results of the effectiveness and cost-effectiveness evaluation are at hand.
- Definition of the range of reimbursement scenarios considered feasible within the legal framework in Switzerland, based on the findings in the domains EFF and ECON.
- Judgement, if the results of the full HTA are also applicable to vulnerable groups (for example elderly people). Other decisions may apply for the reimbursement of test strips for such patient groups, in order to sufficiently adhere to the Swiss legal framework and ascertain appropriate health care.

6.2 Conclusions OLES for full HTA

The conclusions will depend on the results of the effectiveness and cost-effectiveness evaluation as performed in the full HTA.

The following issues will also be part of the OLES section of the full HTA.

a) Which organisational, legal, ethical and socio-cultural issues are of relevance for the following scenario: Reimbursement only in case of newly diagnosed diabetes mellitus?
b) Which organisational, legal, ethical and socio-cultural issues may arise from a claimed earlier switch to insulin therapy, if SMBG test strips are not (fully) reimbursed?

7 Strategy and depth of analysis for the full HTA

Effectiveness and safety issues

There is a big overlap for primary studies (RCTs) across the 16 relevant SRs. In addition, 5 RCTs are not yet covered by the relevant last Cochrane systematic review (Malanda 2012: last search JUL-2011 [6]). Thus, it may make sense for several research questions, to base the synthesis of evidence on the 24 included RCTs rather than only on the retrieved systematic reviews, as this may result in biased findings.

Such a procedure has implications for the workload of the full HTA: As we do not recommend using the results of other review groups, full data extraction of the 24 included RCTs has to be performed. This approach enables flexible meta-analyses and maybe meta-regression analyses to answer the research questions, where existing reviews do not cover the full range of published RCTs up to 2017.

Health economic evaluation

We propose a health economic evaluation assessing the direct medical costs, life expectancy and quality adjusted life-years associated with diabetes-related complications depending on the variation of SMBG and of the characteristics of the non-insulin treated T2DM population. In case of identical effects in comparator and intervention, we propose a cost minimisation analysis instead. In addition, we propose a budget impact analysis comparing the impact of different reimbursement policies of blood glucose test strips on the net costs of each policy.

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54. Tavares, R., et al., *Differences in self-monitored, blood glucose test strip utilization by therapy for type 2 diabetes mellitus.* Acta Diabetologica, 2016. **53**(3): p. 483-492.

55. Cameron, C., et al., *Utilization and Expenditure on Blood Glucos Test Strips in Canada.* Canadian Journal od Diabetes, 2010. **34**(1): p. 34-40.

56. Mt Hood Diabetes Challenge Network, *Diabetes simulation modeling database.* 2017. **2017**(19 September).

57. Hayes, A., et al., *UKPDS outcomes model 2: a new version of a model to simulate lifetime health outcomes of patients with type 2 diabetes mellitus using data from the 30 year United Kingdom Prospective Diabetes Study: UKPDS 82.* Diabetologia, 2013. **56**(9): p. 1925-1933.

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60. University of Oxford and Diabetes Trials Unit. *UKPDS Outcomes Model. Conditions of use and copyright. Licensing the software*. [cited 2017 20. November]; Available from: https://www.dtu.ox.ac.uk/outcomesmodel/download.php.

61. IQVIA. *Services*. [cited 2017 20. November]; Available from: http://www.core-diabetes.com/Index.aspx?Page=Services.

62. IQVIA. *Incorporation of UKPDS 82 Risk Equations into the IQVIA CORE Diabetes Model*. [cited 2017 18. December]; Available from: http://www.core-diabetes.com/Index.aspx?Page=News#n8.

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64. Clarke, P., et al., *A model to estimate the lifetime health outcomes of patients with type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model (UKPDS no. 68).* Diabetologia, 2004. **47**(10): p. 1747-1759.

Appendix

Appendix Table 1: Example search strategy

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

MEDLINE search strategy using Ovid interface.

We will also report the search strategies for Embase and the Cochrane Library in the full HTA.

Appendix Table 2: 24 included RCTs (in alphabetical order)

1. Allen, B.T.D., Elizabeth R; Feussner, John R, Impact of Glucose Self-Monitoring on Non-Insulin-Treated Patients With Type II Diabetes Mellitus: Randomized Controlled Trial Comparing Blood and Urine Testing. Diabetes Care, 1990. 13(10): p. 1044-1050.
2. Barnett, A.K., AJ; Strojek, K; Sieradzki, J; Azizi, F; Embong, M; Imamoglu, S; Perušičová, J; Uličiansky, V; Winkler, G, The efficacy of self-monitoring of blood glucose in the management of patients with type 2 diabetes treated with a gliclazide modified release–based regimen. A multicentre, randomized, parallel-group, 6-month evaluation (DINAMIC 1 study). Diabetes, Obesity and Metabolism, 2008. 10(12): p. 1239-1247.
3. Bosi, E., et al., Intensive structured self-monitoring of blood glucose and glycemic control in noninsulin-treated type 2 diabetes: The PRISMA randomized trial. Diabetes Care, 2013. 36(10): p. 2887-2894.
4. Dallosso, H.M., et al., Self-monitoring of blood glucose versus self-monitoring of urine glucose in adults with newly diagnosed Type 2 diabetes receiving structured education: A cluster randomized controlled trial. Diabetic Medicine, 2015. 32(3): p. 414-422.
5. Davidson, M.B.C., Maria; Kain, Don; Duran, Petra, The effect of self monitoring of blood glucose concentrations on glycated hemoglobin levels in diabetic patients not taking insulin: a blinded, randomized trial. The American journal of medicine, 2005. 118(4): p. 422-425.
6. Durán, A.M., Patricia; Runkle, Isabelle; Pérez, Natalia; Abad, Rosario; Fernández, Mercedes; Del Valle, Laura; Sanz, Maria Fuencisla; CALLE-PASCUAL, Alfonso Luis, Benefits of self-monitoring blood glucose in the management of new-onset Type 2 diabetes mellitus: The St Carlos Study, a prospective randomized clinic-based interventional study with parallel groups. Journal of Diabetes, 2010. 2(3): p. 203-211.
7. Farmer, A.J.W., A. N.; French, D. P.; Simon, J.; Yudkin, P.; Gray, A.; Craven, A.; Goyder, L.; Holman, R. R.; Mant, D.; Kinmonth, A. L.; Neil, H. A.; Di, G. E. M. Trial Group, Blood glucose self-monitoring in type 2 diabetes: a randomised controlled trial. Health Technol Assess, 2009. 13(15): p. iii-iv, ix-xi, 1-50.
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9. Franciosi, M.L., G; Pellegrini, F; Cantarello, A; Consoli, A; Cucco, L; Ghidelli, R; Sartore, G; Sciangula, L; Nicolucci, A, ROSES: role of self-monitoring of blood glucose and intensive education in patients with Type 2 diabetes not receiving insulin. A pilot randomized clinical trial. Diabetic Medicine, 2011. 28(7): p. 789-796.
10. Garcia de la Torre, N.G.D., Alejandra; Del Valle, Laura; Fuentes, Manuel; Barca, Idoya; Martín, Patricia; Montañez, Carmen; Perez-Ferre, Natalia; Abad, Rosario; Sanz, Fuencisla, Early management of type 2 diabetes based on a SMBG strategy: the way to diabetes regression—the St Carlos study. Acta Diabetologica, 2013. 50(4): p. 607-614.
11. Guerci, B.D., P; Grange, V; Bougneres, P; Fontaine, P; Kerlan, V; Passa, P; Thivolet, Ch; Vialettes, B; Charbonnel, B, Self-monitoring of blood glucose significantly improves metabolic control in patients with type 2 diabetes mellitus: the Auto-Surveillance Intervention Active (ASIA) study. Diabetes & metabolism, 2003. 29(6): p. 587-594.
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13. Jaber, L.A.H., Henry; Fernet, Mireille; Tummalapalli, Suresh; Diwakaran, Hariharan, Evaluation of a pharmaceutical care model on diabetes management. Annals of Pharmacotherapy, 1996. 30(3): p. 238-243.

14. Kempf, K.T., Tsvetalina; Martin, Stephan, ROSSO-in-praxi-international: long-term effects of self-monitoring of blood glucose on glucometabolic control in patients with type 2 diabetes mellitus not treated with insulin. Diabetes technology & therapeutics, 2013. 15(1): p. 89-96.

15. Kleefstra, N.H., J; Logtenberg, SJJ; Slingerland, RJ; Groenier, KH; Houweling, ST; Gans, ROB; van Ballegooie, E; Bilo, HJG, self-monitoring of blood glucose in tablet-treated type 2 diabetic patients (ZODIAc-17). Neth J Med, 2010. 68(7/8): p. 311-6.

16. Malanda, U.B., SDM; Kostense, PJ; Snoek, FJ; Dekker, JM; Nijpels, G, Effects of self-monitoring of glucose on distress and self-efficacy in people with non-insulin-treated Type 2 diabetes: a randomized controlled trial. Diabetic Medicine, 2016. 33(4): p. 537-546.

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18. Nishimura, A., et al., Effects of structured testing versus routine testing of blood glucose in diabetes self-management: A randomized controlled trial. Journal of Diabetes and its Complications, 2017. 31(1): p. 228-233.

19. O'Kane, M.J.B., B.; Copeland, M.; Coates, V. E.; Esmon study group, Efficacy of self monitoring of blood glucose in patients with newly diagnosed type 2 diabetes (ESMON study): randomised controlled trial. BMJ, 2008. 336(7654): p. 1174-7.

20. Polonsky, W., et al., *Structured self-monitoring of blood glucose significantly reduces A1C levels in poorly controlled, noninsulin-treated type 2 diabetes: results from the Structured Testing Program study.* Diabetes care, 2011. **34**(2): p. 262-267.

21. Scherbaum, W.A.O., Christian; Abholz, Heinz-Harald; Dragano, Nico; Lankisch, Mark, Effect of the frequency of self-monitoring blood glucose in patients with type 2 diabetes treated with oral antidiabetic drugs—a multi-centre, randomized controlled trial. PLos one, 2008. 3(8): p. e3087.

22. Schwedes, U.S., Markus; Mertes, Gabriele, Meal-related structured self-monitoring of blood glucose. Diabetes Care, 2002. 25(11): p. 1928-1932.

23. Siebolds, M.G., Oliver; Schwedes, Ulrich; SMBG Study Group, Self-monitoring of blood glucose—Psychological aspects relevant to changes in HbA 1c in type 2 diabetic patients treated with diet or diet plus oral antidiabetic medication. Patient education and counseling, 2006. 62(1): p. 104-110.

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Appendix Table 3: 16 relevant systematic reviews (in alphabetical order)

1. Allemann, S.H., C.; Diem, P.; Stettler, C., Self-monitoring of blood glucose in non-insulin treated patients with type 2 diabetes: a systematic review and meta-analysis. Curr Med Res Opin, 2009. 25(12): p. 2903-13.
2. Coster, S.G., MC; Seed, PT; Powrie, JK; Swaminathan, R, Self-monitoring in Type 2 diabetes mellitus: a meta-analysis. Diabetic Medicine, 2000. 17(11): p. 755-761.
3. Faas, A.S., FG; Van Eijk, JTM, The efficacy of self-monitoring of blood glucose in NIDDM subjects: a criteria-based literature review. Diabetes care, 1997. 20(9): p. 1482-1486.
4. Farmer, A.J.P., R.; Ward, A.; Heneghan, C.; Oke, J.; Barnett, A. H.; Davidson, M. B.; Guerci, B.; Coates, V.; Schwedes, U.; O'Malley, S., Meta-analysis of individual patient data in randomised trials of self monitoring of blood glucose in people with non-insulin treated type 2 diabetes. BMJ, 2012. 344: p. e486.
5. Hou, Y.Y., et al., Efficacy of blood glucose self-monitoring on glycemic control in patients with non-insulin-treated type 2 diabetes: A meta-analysis. International Journal of Nursing Sciences, 2014. 1(2): p. 191-195.
6. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG), Urin- und Blutzuckerselbstmessung bei Diabetes mellitus Typ 2. 2009.
7. Jansen, J.P., Self-monitoring of glucose in type 2 diabetes mellitus: a Bayesian meta-analysis of direct and indirect comparisons. Current medical research and opinion, 2006. 22(4): p. 671-681.
8. Lobè, C., et al. Self-monitoring of blood glucose in adult patients with Type 2 Diabetes not using insulin (Structured abstract). Health Technology Assessment Database, 2013.
9. Malanda, U.L.W., L. M.; Riphagen,, II; Dekker, J. M.; Nijpels, G.; Bot, S. D., Self-monitoring of blood glucose in patients with type 2 diabetes mellitus who are not using insulin. Cochrane Database Syst Rev, 2012. 1: p. CD005060.
10. McGeoch, G.D., Sheena; Moore, R Andrew, Self-monitoring of blood glucose in type-2 diabetes: what is the evidence? Diabetes/metabolism research and reviews, 2007. 23(6): p. 423-440.
11. Poolsup, N.S., Naeti; Jiamsathit, Warisara, Systematic review of the benefits of self-monitoring of blood glucose on glycemic control in type 2 diabetes patients. Diabetes technology & therapeutics, 2008. 10(S1): p. S-51-S-66.
12. Sarol Jr, J.N.N.J., Nemencio A; Tan, Kathryn M; Grava, Maritess B, Self-monitoring of blood glucose as part of a multi-component therapy among non-insulin requiring type 2 diabetes patients: a meta-analysis (1966-2004). Current medical research and opinion, 2005. 21(2): p. 173.
13. St John, A.D., Wendy A; Price, Christopher P; Davis, Tim ME, The value of self-monitoring of blood glucose: a review of recent evidence. Journal of Diabetes and its Complications, 2010. 24(2): p. 129-141.
14. Towfigh, A.R., Maria; Weinreb, Jane E; Munjas, Brett; Suttorp, Marika J; Zhou, Annie; Shekelle, Paul G, Self-monitoring of blood glucose levels in patients with type 2 diabetes mellitus not taking insulin: a meta-analysis. 2008.
15. Welschen, L.M.B., E.; Nijpels, G.; Dekker, J. M.; Heine, R. J.; Stalman, W. A.; Bouter, L. M., Self-monitoring of blood glucose in patients with type 2 diabetes who are not using insulin: a systematic review. Diabetes Care, 2005. 28(6): p. 1510-7.

16. Zhu, H.Z., Y.; Leung, S. W., Is self-monitoring of blood glucose effective in improving glycaemic control in type 2 diabetes without insulin treatment: a meta-analysis of randomised controlled trials. BMJ Open, 2016. 6(9): p. e010524.

Appendix Table 4: Core features of the 16 relevant reviews

EN	author	year	SR_last_search	SR_nPS	SR_npop
86	Faas	1997	1996_FEB	6	592
85	Coster	2000	1999_X	3	419
106	Welschen	2005	2004_SEP	6	1285
104	Sarol	2005	2004_X	8	1307
87	Jansen	2006	2005_X	13	2160
88	McGeoch	2007	2006_NOV	3	1000
105	Towfigh	2008	2007_JUL	9	1862
103	Poolsup	2008	2007-SEP	7	1625
1	Allemann	2009	2009_JAN	15	3270
38	IQWIG	2009	2009_JUN	5	2485
107	St John	2010	2008_JUN	6	2573
4	Farmer	2012	2010_JUN	6	2552
5	Malanda	2012	2011_JUL	12	3259
1016	Lobé	2013	2011_JUL	14	n.a.
394	Hou	2014	2012_JUN	7	1896
8	Zhu	2016	2015_OCT	15	3383

EN: Endnote® identifier; SR: systematic review; SR_nPS: number of primary studies included in SR; SR_npop: number of included patients in the SR

Reviews are sorted by year of publication

Appendix Table 5: Core features of the 5 RCTs not yet included in the 16 reviews

EN	**author**	**year**	**country**	**study design**	**n_pop**	**sex male** (%)	**age** (mean; years)	**HbA1c** (at BL in %)	**Follow-up** (months)	**inter-vention**	**control**
928	Polonsky	2011	USA	RCT	483	53	55.8	8.9	12	struc-tured SMBG	unstruc-tured SMBG
429	Bosi	2013	ITA	RCT	1024	60	60.3	7.35	12	struc-tured SMBG	less struc-tured SMBG
347	Dallosso	2014	GBR	Cluster RCT	292	54	58	8.15	18	unstruc-tured SMBG	SMUG
7	Young	2017	USA	RCT	450	46	61	7.55	12	unstruc-tured SMBG	no SMBG
223	Nishimura	2017	JAP	RCT	62	61	66	7.21	5.5	struc-tured SMBG	unstruc-tured SMBG

EN: Endnote® identifier

Appendix Table 6: Additional search for SMBG-related studies regarding Switzerland

Search terms	Results
Pubmed	
self-monitor* [Title/Abstract] AND “diabetes“ [Title] AND “type 2“ [Title/Abstract] AND "Switzerland"[Mesh]	3
(glyc*[Title] OR glucose[Title]) AND “diabetes“ [Title] AND "Switzerland"[Mesh]	9
“self”[Title] AND manag*[Title] AND “diabetes“ [Title] AND "Switzerland"[Mesh]	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	**39**

In the full HTA we will extend this search by adding the term “Switzerland” in the [Title, Abstract] fields as well.

Appendix Table 7: Additional search for SMBG-related studies in EconLit

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	**16**