Response by Roche Diagnostics Australia Pty Limited to the Review by DoHA of blood glucose test strips for people with type 2 diabetes not treated with insulin

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Introductory and Summary Remarks

Roche Diagnostics Australia Pty Limited (RDA) is pleased to provide comment to the Review by the DoHA on *Self-Monitored Blood Glucose Test Strips for people with Type 2 Diabetes Mellitus not treated with insulin.*

This document addresses each of the three Terms of References as requested starting with some remarks that attempt to capture the spirit of the overall submission. An attachment of the landmark publication is also included in support of the proposal raised in this document.

We are encouraged to learn the Department is reviewing utilisation of methods used to manage Type 2 diabetes. This is in concordance with the direction RDA has undertaken over the last three years. We have been actively promoting and supporting a process of structured self-monitoring of blood glucose (SMBG) by people with type 2 diabetes not on insulin (T2DNI) instead of the commonly applied random SMBG, as a means of improving utilization and effectiveness of self-monitoring. Our approach is supportive of current quality use of medicines policies and addresses questions of overuse, misuse and underuse of SMBG. It also takes into account the need for clinical involvement even in the presence of well utilized SMBG.

We like to highlight an unintended consequence of this Review from a patient perspective that T2DNI is not a serious condition requiring no personalised approach and that patient involvement with their health care team and their condition is not required. We are certain this is indeed not the intention of this Review since it is well known that T2D has a higher mortality and morbidity compared to T1D including higher overall costs to the payer.

RDA has invested a significant amount of resources in educating health care professionals on how to achieve excellent patient management through a clinically validated process of personalised structured SMBG, minimizing wastage and unnecessary monitoring. As an example; RDA is the only provider in Australia of an SMBG technology targeted exclusively to people using insulin. We are committed to appropriate product utilisation despite the significant reduction on the available number of potential customers for this product.

Although the positive risk/benefit profile and cost effectiveness of SMBG is now well accepted globally with people on insulin therapy, the situation is more confused with T2DNI. We suggest there are a number of reasons for this confusion including:

- Reliance on older studies and opinions that failed to link SMBG to effective therapeutic and lifestyle interventions applied to T2DNI
- Reliance on older studies that used random SMBG, that is, monitoring at random timings resulting in blood glucose data disconnected from their daily context, depriving the healthcare provider of insights into the patient's glycaemic profile
- Conducting SMBG studies in relatively well-controlled populations, limiting the ability of the intervention to provide incremental gains in control, especially with regard to the somewhat arbitrary metric of HbA1c changes of ≥0.5%.
- Failure to recognize that SMBG in T2DNI is a collaborative exercise to guide changes in daily life style, diet and exercise in this group of patients
- Focus on the physician, rather than incorporating other healthcare professionals involved in the care of people with diabetes, including diabetes nurse educators, dieticians and pharmacists
- Poor support provided to health care professionals so that they can fully appreciate and utilise SMBG in their interactions with the individual patient, hampering the translation of SMBG results into short and long term benefits.

In contrast to the above, various Guidelines and newer studies such as the Structured Testing Program (STeP) study by Polonsky *et al* (attached) emphasise the need for SMBG to be individualised, be part of an integrated care plan, and to be connected with therapeutic interventions and actively involve the patient in their own disease management programme.

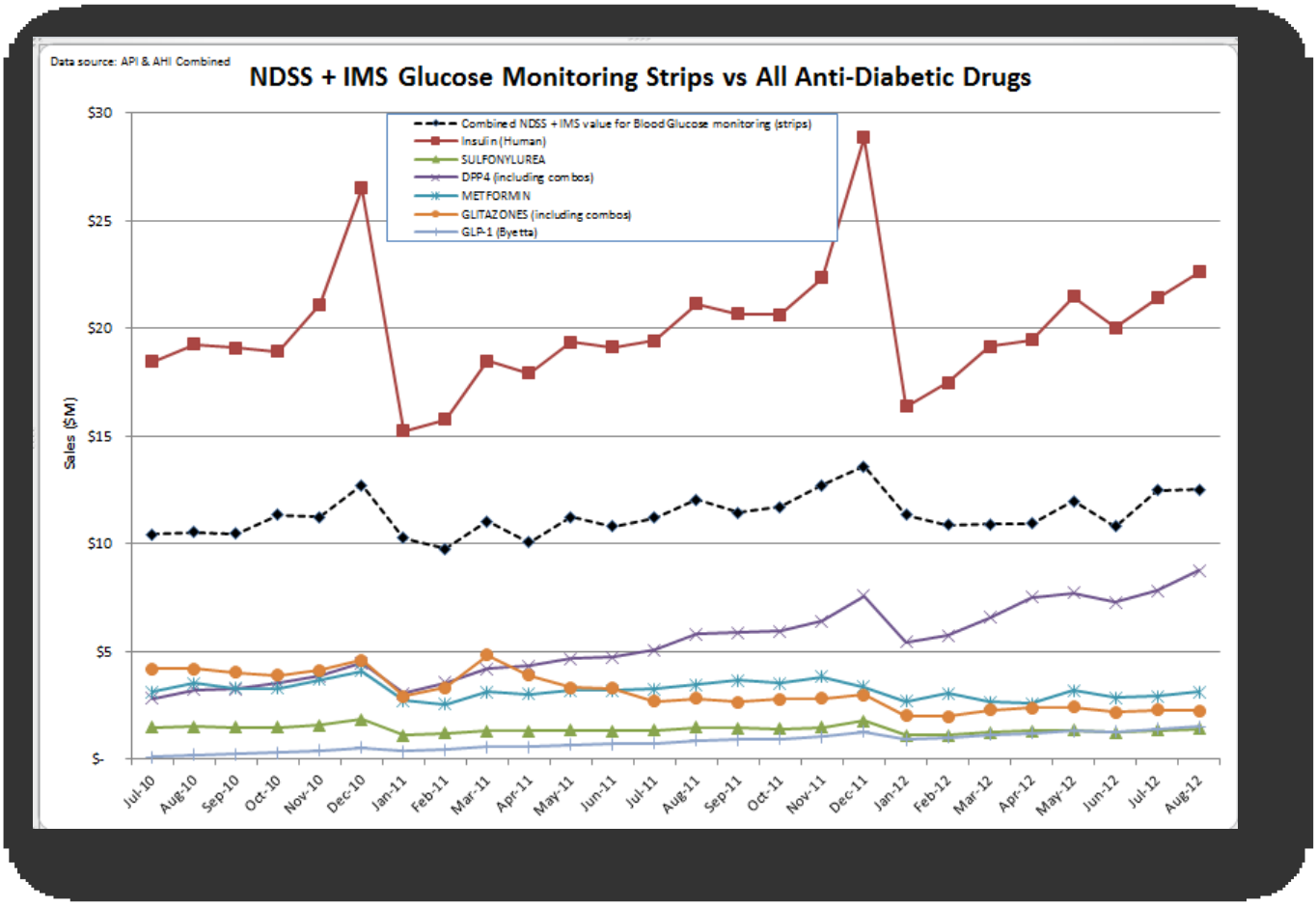
In our submission, we will assess the current status of self-monitoring of blood glucose, counsel the Review against over-reliance on HbA1c as a metric of good diabetes management, and comment on how utilisation of blood glucose monitoring resources can be further improved to support better community-based care, including better outcomes for Australians with diabetes.

We suggest that rather than trying to determine whether performance of SMBG impacts glycaemia, we need to use current resources to address whether appropriate use of SMBG data improves clinical outcomes? Recent evidence strongly suggests that it does.

Term of Reference No 5:

Describe the utilisation and patterns of use of self-monitoring of blood glucose (SMBG) by people with type 2 diabetes.

Below we offer a current extract of NDSS and IMS data incorporating insulin, anti-diabetic drugs and glucose test strips.



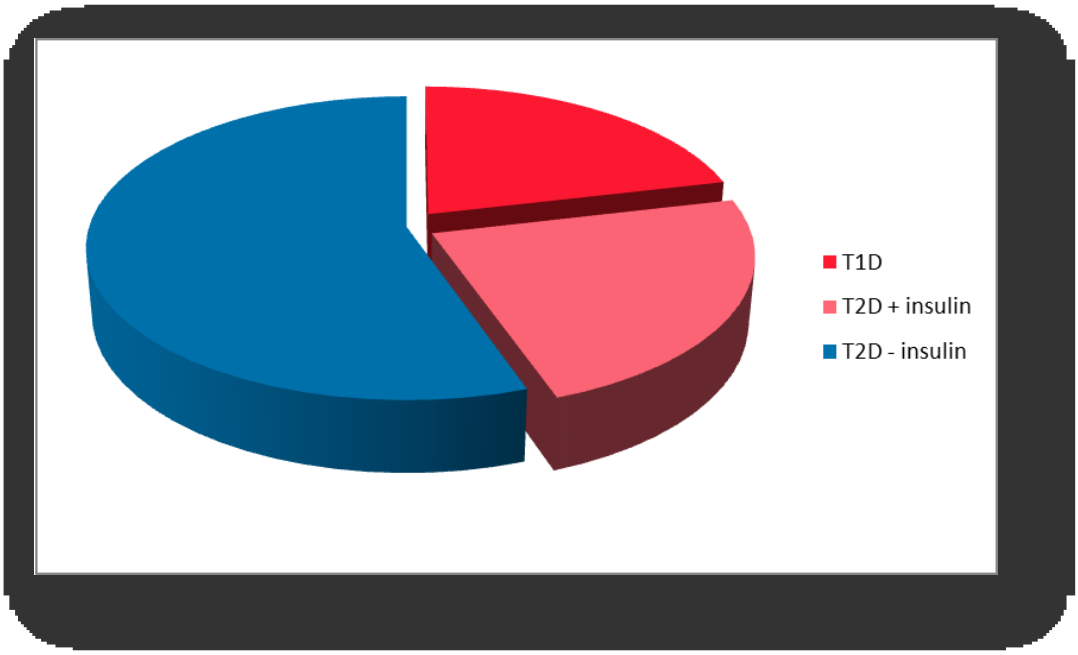
<u>Blood glucose test strip utilisation-current NDSS data (100 strips/box):</u>

- 1.1mio boxes ($44mAUD) accessed by140,000 T1 patients
- 1.0mio boxes ($39mAUD) accessed by 153,000 T2 insulin patients
- 1.1mio boxes ($44mAUD) accessed by 363,000 T2 non-insulin patients

Total NDSS demand: 3.2mio boxes ($126.5mAUD) accessed by 656,000 patients

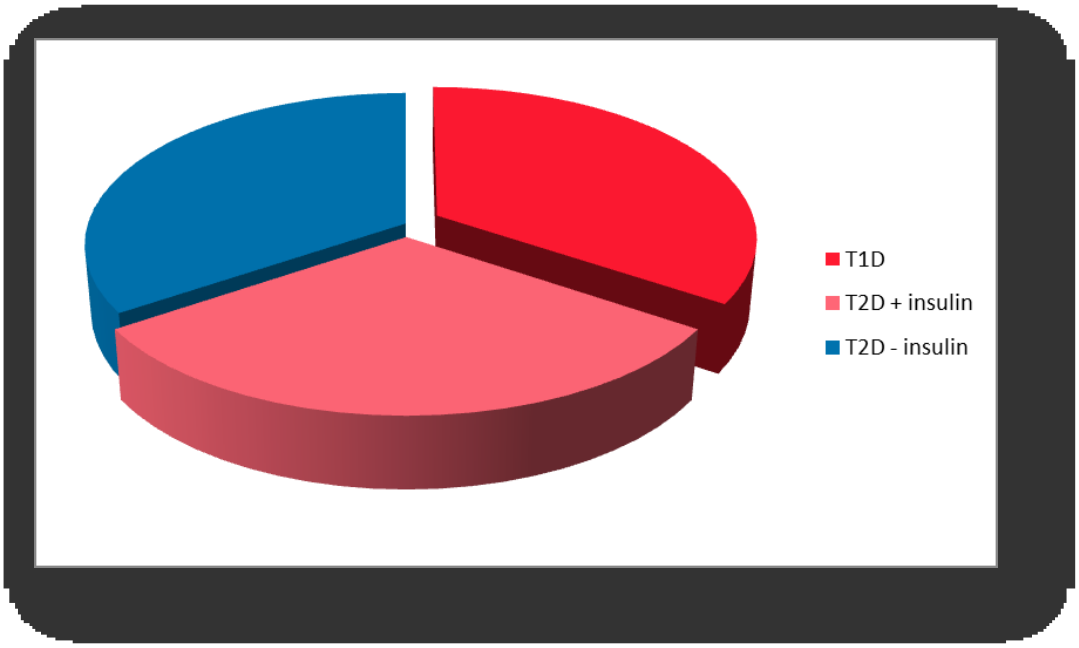
The MILES study (1) shows that blood glucose monitoring strips were the products most commonly purchased through the NDSS (90% of respondents had done so in the past year). This is concordant with sales data for NDSS versus PBS supply, where ~90% of blood glucose strips are sourced via the NDSS.

The chart below indicates the percentage of people accessing strips via **NDSS** according to treatment regimens (NDSS data, Jul-11 to Jun-12)



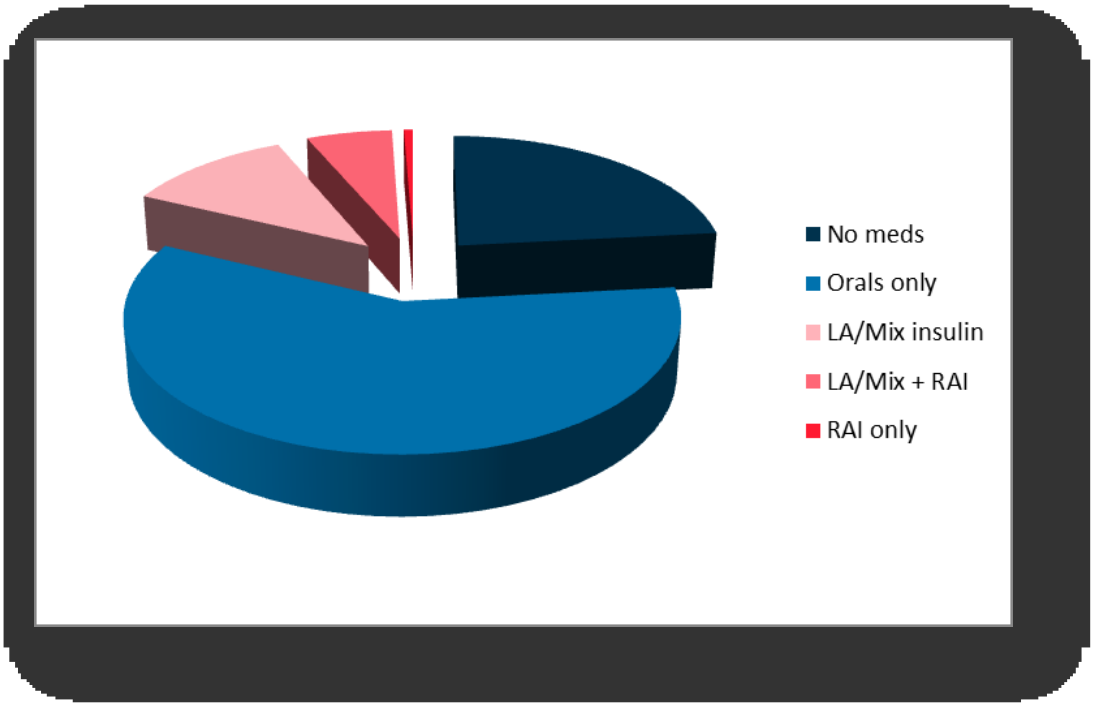
NDSS data indicate that 55% of people accessing strips via the NDSS are not using insulin.

Further, below we highlight the share of strips accessed via the NDSS by treatment regimen.



However, only around one third of the total NDSS strip volume is used by non-insulin users. This group uses, on average, less than one blood glucose strip per day (~110mio strips amongst ~360k registrants equals ~300 strips/year). This is concordant with the MILES study, wherein most type 2 respondents (59%; n=1,144) reported performing only one or two checks per day. A current analysis of PBS data indicates a similar rate of BG strip usage of around 300/strips per year, or averaging less than one strip per day, amongst those not on insulin and confirms that current systems in place by the health care professionals regarding utilisation are indeed effective in minimizing over-utilisation and wastage

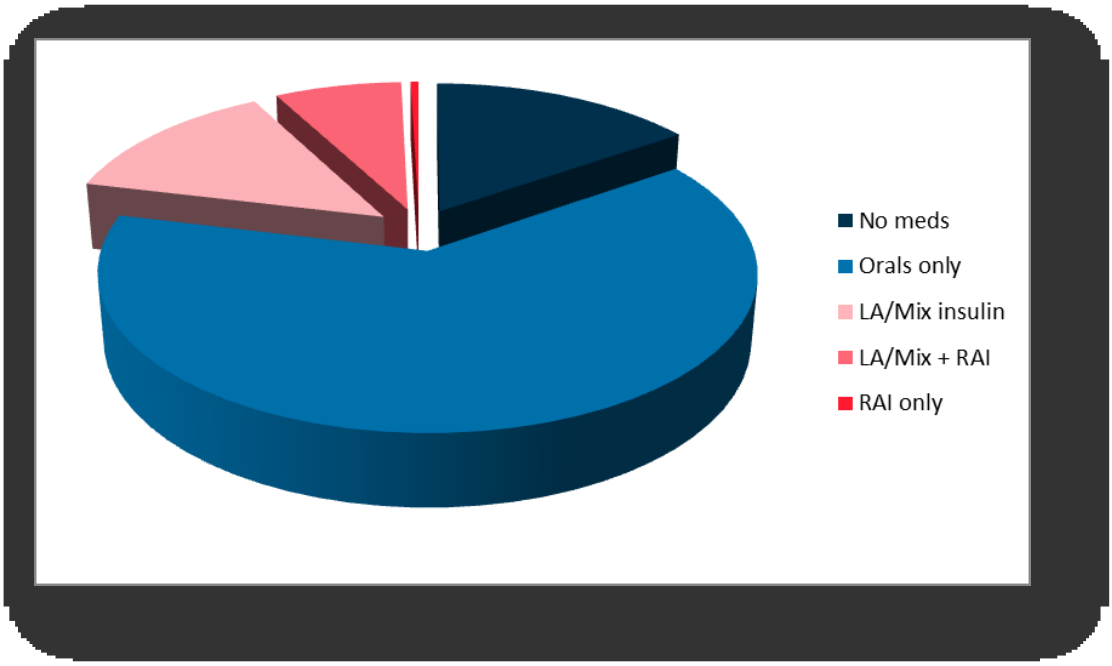
Below we also highlight the percentage of people accessing strips via **PBS** according to treatment regimens (PBS data, Jul-11 to Jun-12).



PBS data for the period June 2011 to July 2012 indicate that 82% of people accessing blood glucose strips via this channel are not using insulin (blue segments above).

These data indicate that lower intensity of disease and management is correlated with higher use of PBS sourced blood glucose strips, and presumably with higher reliance on a physician to prescribe BG strips.

The figure below illustrates the share of strips accessed via the PBS by treatment regimen.



The share of PBS-sourced strips used by those not on insulin is comparable to the population share shown immediately above. While the proportion of strips falls amongst those not on medication, this is compensated for by those on oral medication.

Term of Reference No 6:

Determine the clinical outcomes and benefits (e.g. HbA1c) of self-monitoring of blood glucose (SMBG) relative to HbA1c monitoring alone for people with type 2 diabetes not treated with insulin.

HbA_{1c}: a monitoring metric? an outcome? in competition with SMBG?

This specific term of reference causes some concerns to us due to the appearance that the Review is considering:

- HbA_{1c} to be a 'clinical outcome or benefit in itself, rather than just a protein providing information on long-term glycaemic status.
- That HbA_{1c} is not a surrogate marker and representative for all patient groups
- That SMBG only affects HbA_{1c} (rather than providing a number of other additional benefits)
- That all stakeholders are able to access and utilise HbA1c measurements to guide management when this is patently not the case.
- That SMBG *per se* should lead to therapeutic benefits
- That SMBG and HbA_{1c} are competing measurement modalities, rather than providing complementary and different information to guide diabetes management

HbA_{1c} as a metric of glycaemic control

HbA_{1c} provides information about the long-term average glycaemic status of the patient, but not what the cause of dysglycaemia is. HbA_{1c} also provides no information about the daily variability of the glycaemic profile, and cannot be used to guide daily lifestyle and therapeutic changes to optimize the glycaemic profile. Current experience with managing this group of patients shows that two individuals may have the same HbA_{1c}, but markedly different diurnal glycaemic patterns, with different risks for hyper- or hypoglycaemia. Moreover, HbA_{1c} measurements can provide misleading information based on the influence of analytical, genetic, physiological or pathological factors.

A recent review by Hinzmann *et al* (2) concludes that "The measurement of HbA_{1c} has reached a high level of analytical quality and, therefore, this biomarker is currently also suggested to be used for the diagnosis of diabetes. Nevertheless, it is crucial for people with diabetes, their treating physicians to be aware of possible interferences during its

measurement as well as physiological or pathological factors that contribute to the HbA_{1c} concentration without being related to glycaemia",

Expanding on the above Hirsch *et al* (3) also in a recent article lists such interferences:

TABLE 1. FACTORS KNOWN TO ALTER GLYCATED HEMOGLOBIN

	Factor
Hematological conditions	Anemia
	Accelerated erythrocyte turnover
	Thalassemia
	Sickle cell disease
	Reticulocytosis
	Hemolysis
Physiological states	Aging
	Pregnancy
Drugs/medications	Alcohol
	Opioids
	Vitamin C
	Vitamin E
	Aspirin
	Erythropoietin
	Dapsone
	Ribavirin
Other disease states	HIV infection
	Uremia
	Hyperbilirubinemia
	Dyslipidemia
	Cirrhosis
	Hypothyroidism
Medical therapies	Blood transfusion
	Hemodialysis
Miscellaneous	Glycation rate
	Protein turnover
	Race and ethnicity
	Laboratory assay
	Glycemic variability
	Smoking
	Mechanical heart valves

It is crucial this Review considers the limitations (as shown on the table above) of the HbA_{1c} as a replacement marker for the SMBG

HbA_{1c} as a surrogate marker for cardiovascular outcomes

There is controversy on the linkage of HbA_{1c} to clinical outcomes. While the UKPDS (4) showed reductions in a number of cardiovascular outcomes, the ACCORD (5) study saw

higher mortality rates in the intensively treated arm, and the ADVANCE (6) study saw reductions in all events, but not in major vascular events. Taken together, while these studies indicate that achieving good glycaemic control is an important goal, the linkage between HbA_{1c} and outcomes is problematic, and the ACCORD study suggests that taking a unimodal approach targeting aggressive HbA_{1c} reduction may introduce harm in some sectors of the population. This requires further elucidation but emphasises that a reliance on HbA_{1c}, and failure to consider individual circumstances and glycaemic profile would be a blunt tool approach to management.

The linkage between SMBG and HbA_{1c}

It is now well accepted by those directly involved with managing T2DNI that an individual with otherwise well-controlled diabetes may be experiencing regular periods of hypoglycaemia. Their HbA1c provides no insight into this, and the person with diabetes and their healthcare provider would need to undertake personalised structured SMBG to determine and address this serious risk.

In such (common) cases, a net reduction in HbA_{1c} is unlikely, but an important clinical outcome may be achieved by addressing that person's hypos, and preventing further incidents (including hospitalisations) subsequent to recurring hypos and hypo unawareness.

Access to HbA_{1c} measurement and result versus SMBG

At present a patient's HbA_{1c} result is only available to physicians able to request its determination by a pathology laboratory with access to the relevant Medicare Benefit Schedule item.
Neither people with diabetes, nor other healthcare professionals - such as diabetes educators, dieticians and pharmacists - are able to request or access this information unless they can source it through a physician. Instead, they are able to engage in diabetes patient management through informed usage of SMBG.

It is important to note that a very large proportion of T2DNI present at visits without a recent HbA_{1c} result. Personal communications and experience indicates that it is not uncommon for a patient to present to their GP with a gap of at least 6 months since their last HbA_{1c} was measured. In most instances this leads to repeat referrals for blood collection and HbA_{1c} testing and a return visit to the requesting physician in order to discuss the results.

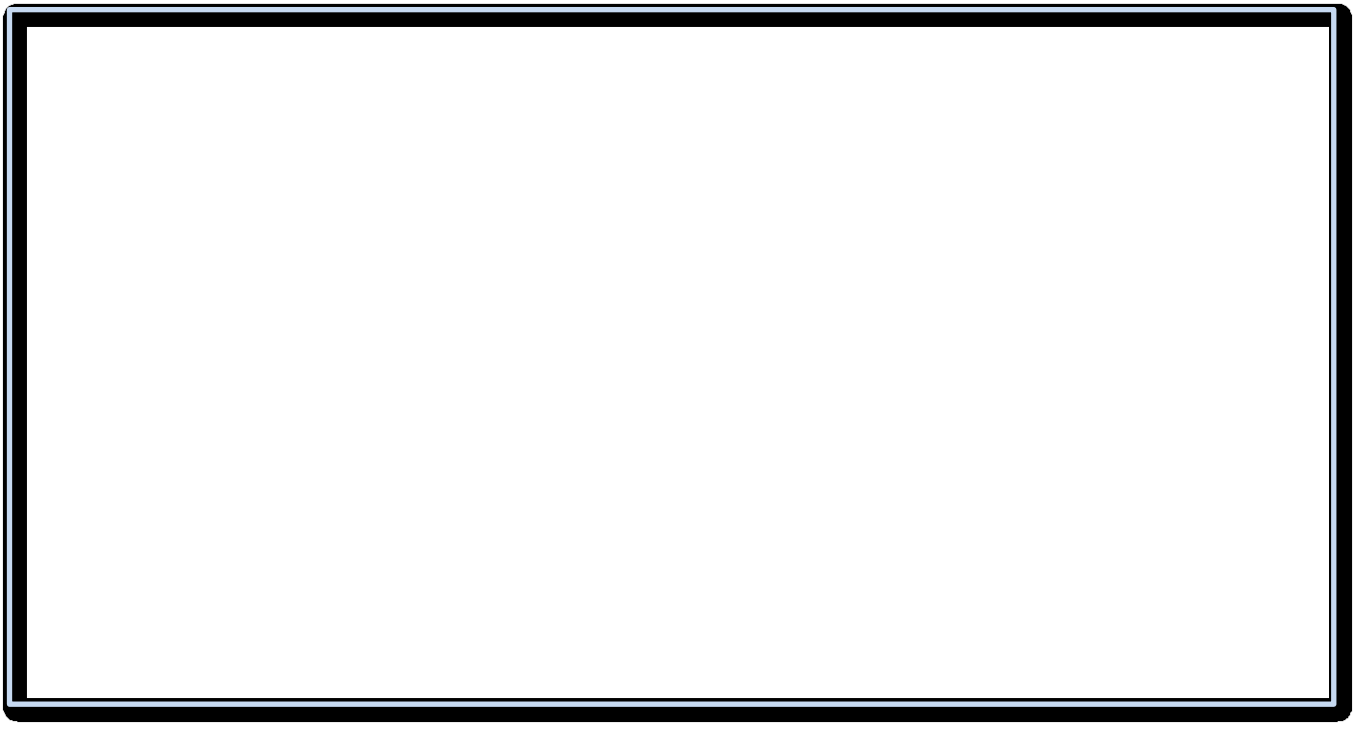
The Australian Federal Government has put in place a number of programs to improve management of diabetes in the community. Restricting diabetes monitoring to HbA_{1c} would serve to undermine these programs, and the engagement of other frontline healthcare practitioners in diabetes management.

<u>Monitoring without action cannot lead to therapeutic benefits</u>

"Knowledge without action is futile" – Abu Bakr

SMBG is but one component of a complex intervention aimed at improving overall glycemic control and well-being. Prescribing or evaluating the effects of monitoring without using the data to make therapeutic adjustments is a waste of healthcare resources.

Unfortunately early studies on SMBG - including those commonly incorporated in a number of meta-analyses – have either used random monitoring (so the data cannot be interpreted in their daily context), or have failed to provide guidance to study participants on how to use the SMBG data for patient management.



Our position is aligned to the *International Diabetes Federation's* (IDF) guidelines for use of SMBG in non-insulin treated diabetes. These guidelines recommend that SMBG

should be used only when patients and/or their clinicians "*have the knowledge, skills and willingness to incorporate SMBG monitoring and therapy adjustment into their diabetes care plan in order to attain agreed treatment goals*."

This approach has been clinically validated in the Structured Testing Program (STeP) Study, by Polonsky *et al* (7) published in *Diabetes Care* in 2011, and which has been the basis of a comprehensive educational effort by Roche Diagnostics in Australia over the last three years. This will be discussed in greater depth later in this Submission.

SMBG and HbA1c are complementary not competing monitoring modalities

Scientific literature reflects that while HbA_{1c} can be a valid surrogate marker for long-term diabetes control, in contrast to SMBG it cannot provide insight into the daily glucose variability that an individual may be subject to, and does not alone provide insight into the daily and long-term risk profile of an individual person with diabetes.

HbA_{1c} and structured blood glucose measurements complement each other and one cannot be abandoned in favor of the other.

Studies assessing SMBG in non-insulin treated T2DM

Unfortunately, appropriate structured SMBG criteria are absent from many of previous studies (e.g., DiGEM (8), ESMON (9)) that have subsequently been incorporated in recent reviews (e.g. Clar *et al.* (10), Farmer *et al* (11)- *Please see Appendix A for additional information*) making findings difficult to interpret often leading to the wrong conclusions due to:

- A failure to recognise that SMBG is not an intervention itself but a guide to inform decision-making on an interventions applied. If these interventions are not taken, it is not surprising there is little benefit to any monitoring modality (including HbA_{1c}) that is not used to support management changes. This is confirmed by the STeP study, where structured monitoring led to more frequent treatment changes and improved glycaemic control

- A failure to recognize that diabetes is a lifestyle disease that requires the person living with the disease to self-manage and make numerous daily decisions regarding food, activity and medications. T2DNI patients need to be proficient in a number of self-care skills supported by SMBG, including diet and exercise choices, medication adjustment, timing of medication administration, and understanding when and why they are at most risk of hyper- and hypoglycaemia.

In the STeP study, this educational process was supported for both patients and healthcare practitioners.

- Even where SMBG may not be linked to significant changes in HbA_{1c}, it can provide substantial information to guide changes to treatment (both pharmacological and behavioral), and subsequent reductions in the risk of hyperglycaemia and hypoglycaemia. Unfortunately, most reported studies have failed to identify and measure this benefit.

- Reliance on HbA_{1c}, presupposing that key healthcare professionals have access to this measure when counseling patients under their care. As mentioned previously, in the current framework key stakeholders do not have access to this measure, including diabetes educators, dieticians and pharmacists.

- Treating people with diabetes as a homogenous population, rather than needing tailored interventions in response to the factors underlying and driving their condition and daily management. Most current guidelines emphasise the need for individualized care in diabetes and patient engagement in a daily self-management process.

- An over-emphasis on HbA_{1c} and cardiovascular outcomes, understating the critical role of daily management in addressing education, patient empowerment and self-efficacy, quality of life and the high rates of depression and distress endured by people with diabetes. In the STeP study, patients in the structured monitoring arm saw significant improvements in all these metrics, as well as in their glucose control, *while decreasing strip consumption*.

RDA suggests to the Review that structured SMBG in people with diabetes provides the data foundation for self-management and informed therapeutic interventions.

Structured monitoring of blood glucose and the STeP Study

The STeP study was a large prospective, cluster-randomized, multi-center trial evaluating the use of structured SMBG in 483 poorly controlled (HbA_{1c} ≥7.5%, insulin-naïve T2DM patients from 34 US primary care practices. The primary endpoint was change in HbA_{1c} over time.

Patients in the structured testing group used a simple paper tool that facilitates collection and interpretation of 7-point glucose profiles over 3 consecutive days. These patients completed the tool on a quarterly basis, brought to the completed tools to medical visits, and discussed findings with their physicians. Structured testing group patients received training in blood glucose measurement, including instructions for how to identify problematic glycemic patterns and how best to address such problems

through changes in physical activity, portion sizes, and/or meal composition; structured testing group physicians received an algorithm describing various pharmacologic/lifestyle treatment strategies that could be used in response to the specific SMBG patterns identified.

Active control group patients received enhanced usual care only and were instructed to use their meter following their physicians' recommendations but received no additional SMBG prompting, training, or instruction.

At 12 months, intent-to-treat (ITT) analysis revealed that structured testing group patients (n=256) experienced significantly greater improvement in mean HbA_{1c} than active control group patients (n=227): -1.2% vs. -0.9%; P=0.04. Per protocol (PP) analysis revealed an even greater HbA_{1c} reduction (- 0.5%) in the experimental (n=130) vs. control (n=161) patients (-1.3% vs. -0.8%; P<0.003).

Further analyses of data from the STeP study have revealed improvements in several other parameters, including clinicians' intensification of treatment; depression and diabetes-related distress; and patient self-efficacy and autonomous motivation in managing their diabetes.

Patients using the structured monitoring methodology experienced these benefits, but had a ***lower*** utilisation of blood glucose strips.

McAndrew et al. (12) showed patient-provided SMBG data contributes to glycaemic improvement when blood glucose patterns are easy to detect, and well-trained physicians take timely action. Collaborative use of structured SMBG data leads to earlier, more frequent, and more effective treatment modification recommendations for poorly controlled, non-insulin-treated T2DM subjects

Cost-effectiveness of structured monitoring

The STeP study confirmed that introducing a structured SMBG approach versus unstructured SMBG was cost-neutral even if treatment is intensified. An explorative analysis of the STeP data showed that structured SMBG in participants who did not actively test before the start of the study, was associated with higher reductions in HbA_{1c} compared to standard SMBG use. The use of structured SMBG may be especially cost-effective in terms of HbA1c reduction per test strips used in patients with poorly controlled non-insulin-dependent diabetes mellitus who do not show a history of consistent SMBG use.

According to Schramm (13) structured testing represents a cost-effective approach to improve diabetes care from the perspective of U.S. third party payers over life-time. This is based on combining STeP outcomes with US cost of diabetes utilizing a well-established Markov model. STeP offers an intervention that reduces HbA_{1c} through better utilization of existing management principles. This STeP protocol enables a healthcare system to use an existing resource (test strips, supplies) more effectively.

Term of Reference No 7:

Consider the clinical criteria for eligibility for subsidised access to blood glucose test strips under the PBS and NDSS, accounting for clinical benefits offered through SMBG compared to HbA1c monitoring.

Clinical criteria for eligibility for subsidised access to blood glucose test strips under the PBS and NDSS:

SMBG utilisation is endorsed by a number of current guidelines. The recent global Guidelines for Type 2 Diabetes by the *International Diabetes Federation (2012)* make the following recommendations:

- Self-monitoring of blood glucose (SMBG) should only be made available to people with diabetes when they have the knowledge, skills and willingness to use the information obtained through testing to actively adjust treatment, enhance understanding of diabetes and assess the effectiveness of the management plan on glycaemic control.
- The purpose(s) of performing SMBG and using SMBG data should be agreed between the person with diabetes and the health-care provider.
- SMBG should be considered for people using oral glucose lowering medications as an optional component of self-management, and in association with HbA_{1c} testing:
- To provide information on, and help avoid hypoglycaemia
- To assess changes in blood glucose control due to medications and lifestyle changes.
- To monitor the effects of foods on postprandial glycaemia.
- To monitor changes in blood glucose levels during intercurrent illness.
- Regular use of SMBG should not be considered part of routine care where diabetes is well controlled by nutrition therapy or oral medications alone.
- SMBG protocols (intensity and frequency) should be individualised to address each individual's specific educational/behavioural/clinical requirements, and provider requirements for data on glycaemic patterns to monitor therapeutic decision making.

- Structured assessment of self-monitoring skills, the quality and use made of the results obtained, and of the equipment used, should be made annually.
- Provision should be made for the supply of glucose strips on a continuing basis to people with diabetes. When providing meters, education in their use and in interpretation of the results should be given. Review of technique, data interpretation and meter function should be a part of the Annual Review

In addition, the importance of post-meal glucose (through SMBG) in patients with diabetes has been highlighted in the 2011 IDF guidelines "*Guideline for Management of Post-Meal Glucose in Diabetes*"

- Post-meal hyperglycaemia is harmful and should be addressed
- Implement treatment strategies to lower post-meal glucose in people with post-meal hyperglycaemia (SMBG is the only tool capable of achieving this, HbA_{1c} cannot achieve this)
- A variety of both non-pharmacologic and pharmacologic therapies should be considered to target post-meal plasma glucose
- Post-meal plasma glucose should be measured 1-2 hours after a meal
- The target for post-meal glucose is 9.0 mmol/L
- SMBG should be considered because it is currently the most practical method for monitoring post-meal glycaemia

Similar recommendations are made by the NHMRC Guidelines "*National Evidence Based Guideline for Blood Glucose Control in Type 2 Diabetes*"

- Blood glucose control should be optimised because of its beneficial effects on the development and progression of microvascular complications. (Grade A)
- The potential harmful effects of optimising blood glucose control in people with type 2 diabetes should be considered when setting individual glycaemic targets. (Grade A)
- Glycated haemoglobin measurement should be used to assess long term blood glucose control. (Grade A)

- SMBG should be considered in all people with type 2 diabetes but the decision to perform SMBG, and the frequency and timing of testing, should be individualised. (Grade C)

- The general HbA_{1c} target in people with type 2 diabetes is ≤ 7%. Adjustment to diabetes treatment should be considered when HbA_{1c} is above this level. (Grade A)

- Targets for self-monitored blood glucose levels are 6–8 mmol/L fasting and preprandial, and 6–10 mmol/L 2 h postprandial. (Grade C)

- Interventions to achieve target glycated haemoglobin should begin with lifestyle modification followed by pharmacological options selected on the basis of individual clinical circumstances, side effects and contraindications. (Grade A)

- Routine care of people with type 2 diabetes should address disparities associated with socio-economic status and ethnicity. (Grade C)

Similar call to action on individualizing treatment is also recommended by the *Diabetes Management in General Practice, Diabetes Australia Guidelines 2012* where it is recommended that Self-monitoring needs to be individualised and assist people with diabetes to understand the impact of medication, food and physical activity on blood glucose control. Frequency of self-monitoring can be determined according to the individual's self-management goals."

The recent meta-analysis by Farmer et al (11) of SMBG concluded that the surveyed literature did not support routine self-monitoring of blood glucose, however, in an incisive response to this review by J Speight (BMJ, March 2012) noted that:

> *"None of the studies included in Farmer's review took a wholly structured approach to SMBG, and many did not include up-skilling or education on blood glucose level pattern analysis as part of the SMBG intervention (for the patients or the doctors). Most did not include psychosocial outcomes in their intervention evaluation, which limits the capacity to weigh the benefits of SMBG against the costs…*
>
> *We draw an alternative conclusion from this review:* ***current approaches to SMBG are sub-optimal but current evaluations are limited by their focus on biomedical outcomes and their reliance on unstructured approaches to monitoring, which many patients and health professionals find confusing, frustrating and pointless.***

Further, rather than abandoning SMBG for people with non-insulin-treated T2DM, we should instead seek to trial alternate approaches, improve education and training for those initiating SMBG and for their health professionals…",

The IDF Guidelines also state:

In some cases more tests are necessary dependent on disease state and behavior of the patient, e.g. on meals, illnesses, sport, travel, amount of insulin intake and how the person is feeling.

The Guideline Development Group (GDG) within NICE states clearly that "the frequency of monitoring that is useful to someone with diabetes is highly individual and it is inappropriate to put an artificial restriction on this". Further:

- Patients managed with sulphonylurea are at risk of hypoglycaemia and therefore they need access to monitoring their blood glucose.
- All women contemplating or with established pregnancy will need to monitor blood glucose levels regardless of type of diabetes or mode of management.
- Patients with haemoglobinopathies and on medications which alter red blood cell survival will require an alternative method (to HbA_{1c}) of assessing glycaemic control.

SMBG provides the patient who is not treated with insulin with insights into the impact of diet and exercise upon their blood glucose levels which would not be apparent from HbA_{1c}. This would be of educational value and may motivate lifestyle changes.

<u>Additional points regarding eligibility:</u>

- The patient's needs for blood glucose self-monitoring depend on diabetes type, treatment, and individual patient factors. A consistent message in current guidelines is that diabetes management and self-monitoring needs to be individualized between the person with diabetes and their healthcare provider. Increasingly, that healthcare provider will be someone who cannot access HbA_{1c} as a monitoring measure, but is able to incorporate structured SMBG into a monitoring plan.

- Restricting SMBG use would disempower people with diabetes and allied healthcare professionals, could delay progression of treatment and ultimately increase the burden of the disease, complications related to diabetes and increase the burden on the healthcare system.

Clinical benefits offered through SMBG compared to HbA1c monitoring

- In contrast to HbA_{1c}, SMBG provides accurate real-time information about the patient's current glycaemic status. As a core component in diabetes management, it provides immediate feedback on the impact of behavioral and pharmacological interventions on glucose levels. However, if people with diabetes are not educated on how to improve glucose levels through diet, exercise, or medication, the effect of SMBG on HbA_{1c} will be minimal. Thus, SMBG helps people with diabetes associate eating behaviors to blood glucose levels. Results of several studies confirm that people with diabetes who are taught to change their diet to lose weight increase adherence to dietary recommendations subsequently resulting in better blood glucose control. The integration of a structured SMBG-based lifestyle intervention program into the therapy scheme of diabetes results in beneficial long-term weight loss, increased quality of life, and a greater reduction of HbA_{1c}.

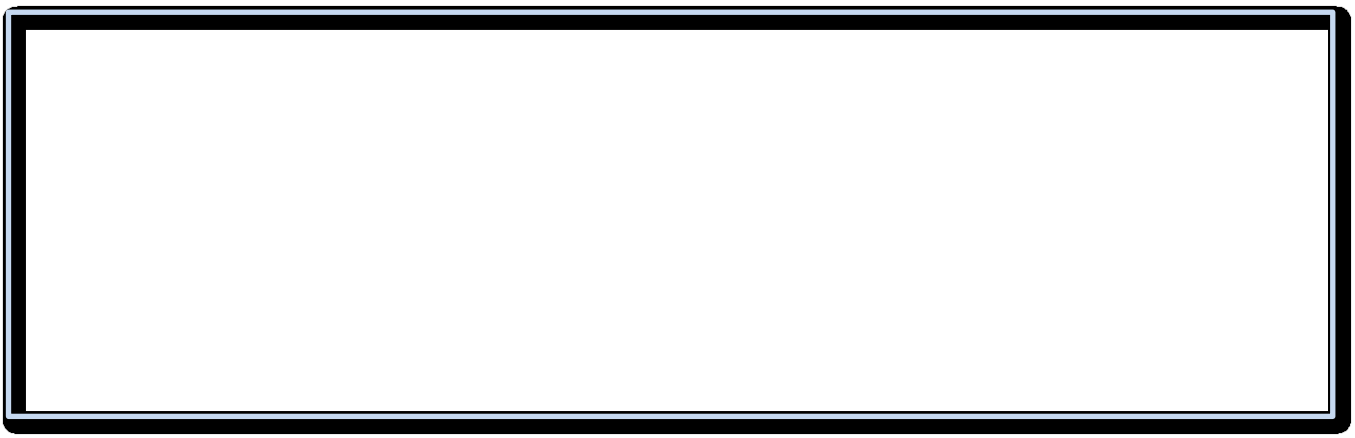
- Taken together, SMBG is of value as a supportive tool in behavioral programs targeting a holistic approach in diabetes self-management. Roche Diagnostics Australia is especially committed and engaged to improve diabetes care in Australia. Structured SMBG in people with diabetes over pre-defined days provides the data foundation for a pattern analysis of blood glucose profiles. In a tightly linked collaboration between physicians and people with diabetes, these data allow to achieve treatment optimization resulting in improved glycemic control without increasing strip consumption.

  Structured blood glucose monitoring provides insights especially into patterns of hyperglycaemia that would not be apparent from HbA_{1c} measurements (i.e. fasting vs. post-prandial) in T2D patients managed with oral agents and may guide the selection of the optimal agent to add when intensifying therapy.

- Roche Diagnostics Australia appreciates the efforts and objectives of this Review if it will help in adding to our understanding of diabetes management and leads to improvements in patient care, especially when used for decision making of patients and their physicians.

We cannot ignore evidence that structured SMBG has an impact to T2DNI:

- Polonsky et al (7) state that structured SMBG significantly improves glycaemic control and facilitates more timely/aggressive treatment changes in non-insulin treated type 2 people with diabetes.
- SMBG helps people with diabetes associate eating behaviors to blood glucose levels. Results of several studies confirm that people with diabetes who are taught to change their diet to lose weight increase adherence to dietary recommendations subsequently resulting in better blood glucose control. The integration of a structured SMBG-based lifestyle intervention program into the therapy scheme of diabetes results in beneficial long-term weight loss, increased quality of life, and a greater reduction of HbA_{1c}.
- Suggestions that SMBG has a negative effect on patients have been settled by Fisher et al (14) who showed structured SMBG leads to reductions in depressive symptoms and diabetes distress over time in moderately depressed or depressed insulin-naïve type 2 patients with poor glycaemic control
- Collaborative (patient and healthcare professional) use of structured SMBG data leads to earlier, more frequent, and more effective treatment modification recommendations for poorly controlled, non-insulin treated type 2 people with diabetes (7).



Roche Diagnostics Australia is especially committed and engaged in improving diabetes care in Australia, Structured SMBG in people with diabetes provides the foundation for a collaborative approach between physicians and people with diabetes, improving self-management and supporting better glycemic control with better utilization of healthcare resources. Please see Appendix B for an account of RDA activities in Australia regarding structured testing.

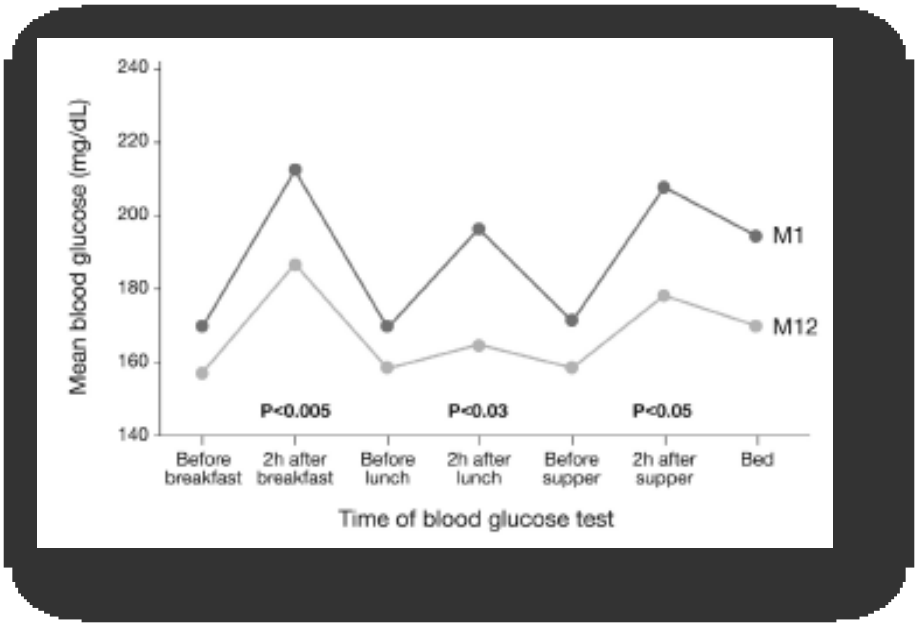
<u>Structured SMBG data as the basis for decision making in medication dose adjustments or medication class change</u>

Although HbA_{1c} is commonly recognized and used for monitoring long term glycaemia, it does not provide any information about day-to-day and within-day changes of an individual's blood glucose level

SMBG is one of the core components in diabetes management recommended by leading international medical organizations. Unlike HbA1c, SMBG, when appropriately applied, provides fasting, before-meal, after-meal, and before-bedtime blood glucose values. Using this immediate real-time feedback about the effect of foods, meals, and physical activities, people with diabetes are enabled to identify hyper- and hypoglycemia and take action steps to prevent large blood glucose swings (glycemic excursions).

An analysis of blood glucose information provides further information for therapy optimization. For the analysis to be most meaningful, blood glucose measurements should be done and documented in a structured way over the course of specified days, e.g., one structured monitoring scheme requires 7 blood glucose measurements per day for 3 days. An abnormal pattern can be identified, for example, if several blood glucose values repeatedly lie beyond the target range at different points of time during the day. This could be caused by meal size variations, sporting activities, and low or high doses of prescribed medications. Based upon such a pattern analysis, appropriate actions including medication dose changes are agreed upon Different medication classes do have characteristic blood glucose lowering effects on fasting or after-meal blood glucose levels. Physicians need to recognize the pattern of blood glucose profiles in order to properly adjust the dose and, if needed, change to another, more eligible medication class

In the STeP study, people with diabetes in the structured testing group showed significant reductions in average, pre-prandial, postprandial and bedtime blood glucose levels at Month 12 ($p<0.01$). The degree of glycemic excursions at breakfast, lunch and supper was also significantly improved (intent-to-treat analysis). (Please see figure below-Abbr.: M1 (Month 1), M12 (Month 12)).



The STeP study results were able to demonstrate that using pattern recognition of blood glucose levels by means of SMBG profiles and subsequent early treatment modifications by involving physicians or other healthcare professionals lead to significant reduction of HbA_{1c}, and simultaneously, of glycaemic variability in the study participants.

APPENDIX A

A critical look at the evidence

Clar et al (10).

- Including subjects into a trial which subjects had relatively low baseline HbA_{1c} values limits the effect that can be achieved. Including the same trial in a systematic review like by Clar et allimits the effect within the review. For example, subjects in all arms of the DiGEM trialhad mean baseline HbA_{1c} values ranging from 7.41% to 7.53%. At the time this trial was conducted, <7.5% HbA_{1c} was considered acceptable glycemic control according to UK diabetes treatment guidelines This, would certainly explain why treatment intensification was so minimal; use of oral diabetic agents was increased in only one third of DiGEM patients. As a result, little improvement in HbA_{1c} was seen at study end.

- Roche Diagnostics Australia acknowledges the importance of education and feedback components for successful impact of SMBG in health care and that by the time Clar et al conducted their review there was little evidence in the literature regarding the way in which Healthcare Professionals (HCPs) collaborate with patients regarding how to interpret and act on readings.

- Furthermore, the authors state "*most trials did not give any details on changes made to therapy or life style based on SMBG*" and no trials reported patients being actively encouraged to make behaviour/lifestyle changes based on results of SMBG. No feedback on results was given to patients. There appears to be a difference in expectation between HCPs and patients, in that patients expect HCPs to decide based on the readings they provide, whereas HCPs see SMBG as a tool for patients to make behaviour/ lifestyle changes. SMBG readings were taken at inappropriate times and so it was impossible to gain meaningful results. ".

- Setting a clinical relevance threshold of 0.5% reduction in HbA_{1c} may not be appropriate to assess the value of SMBG for the following reasons:

  - According to Clar et al setting a relevance threshold of 0.5% reduction in HbA_1 appears to be “somewhat arbitrary”, especially in diagnostics.

  - The UKPDS investigators found that every 1.0% reduction in HbA_{1c} was associated with a 37.0% decrease in risk for microvascular complications and a 21.0% decrease in the risk of any end point or death related to diabetes. Furthermore, they did not observe any thresholds of glycaemia for any type of complication of

diabetes. This suggests that there is no specific target value of haemoglobin HbA_{1c} for which one should aim but that the nearer to normal the haemoglobin HbA1c concentration the better. Thus, the statistically significant reduction of HbA_{1c} 0.25 % at 6 months reported in the meta-analysis should not be dismissed as a clinically not significant improvement in patient care.

- According to Clar et al. enhanced vs. no SMBG is clinically relevant. Structured SMBG like in the STeP study has the potential to be even more clinically relevant.
- The observed higher frequency of hypoglycaemia in patients performing SMBG is not necessarily caused by SMBG. On the contrary: most likely more hypoglycemic episodes are detected by SMBG.
- With regards to quality of life, one also needs to consider that Clar et al. states that
  - "In some patients, SMBG caused adverse psychological effects, including depression and self-chastisement, whereas others found it a useful tool for reassurance, assessing effects of behaviour and empowerment."
  - The authors have found in a survey of confirmed SMBG users that they clearly benefit from SMBG in order to adjust diet, physical activity or medications. Furthermore, they pose the question if "increased anxiety has more to do with having type 2 diabetes than the mechanism of self-monitoring of blood glucose. Furthermore, when readings are high and anxiety is increased, this emotion may encourage a person to act in response to that high reading."

Extract from a Report by the Canadian Agency for Drugs and Technologies in Health[1]

…Due to methodological problems regarding the DiGEM trial (8) no one could expect a significant impact of SMBG. The report provides a sensitivity analysis of subgroups, i.e. "good quality studies". It would be of considerable interest to carry out a sensitivity analysis including only those studies, where patients had "room for improvement (e.g. HbA_{1c} over 8 %) AND the possibility to react appropriately in view of their SMBG results. This view is also shared by the British NICE (National Collaborating Centre for Chronic Conditions. *Type 2 diabetes: national clinical guideline for management in primary and secondary care (update).*

[1] Canadian Agency for Drugs and Technologies in Health. Systematic review of blood glucose test strips for the management of diabetes mellitus. Ottawa; 2009.(15)

The presented meta-analysis and sensitivity analysis are undoubtedly very comprehensive. It should however also be mentioned, that the Cochrane review on the same topic from 2005 (17) stated, that "because of differences in baseline data of the patients and type of interventions between the studies, it was not possible to perform either a meta-analysis and/or subgroup or sensitivity analyses". A meta-analysis of studies could suggest that the interventions were homogenous. The studies being pooled within the CERC[2] review in the NIDDM section do only have in common that SMBG as a technology has been used. The technology does, however – in contrast to a drug – not have an intrinsic effect. The process of how the technology – here SMBG – is used in the therapy does significantly impact its value and effectiveness. This aspect puts more emphasis on the question of "How can SMBG be used most effectively?" rather than "Is SMBG effective (in average)?".

In any other insulin or non-insulin therapy SMBG provides information on hypo- or hyperglycemic states for instant action. Furthermore, SMBG is the basis for life-style adjustments – initiated either by the patient himself or a health care professional. In these applications SMBG becomes part a wider therapeutic concept. It can only work if this is trained, understood and actions are implemented.

The Canadian Diabetes Association comments on CERC's report (18) as follows: "SMBG should not be viewed as an intervention, but rather as an aid to assessing interventions. There are scientific concerns with the studies that have been chosen for review by CERC and form the basis of the CERC recommendations. Further, the meta-analysis methodology used by CERC serves to present diabetes as a homogeneous condition, which it is not. Subsets of patients with diabetes cannot be fully accounted for within a meta-analysis. CERC did not differentiate between the numerous oral anti-hyperglycaemic agents prescribed for type 2 diabetes. Some oral anti-hyperglycaemic agents place individuals at higher risk for hypoglycaemia than others. We believe that some differentiation between these oral agents is necessary."

Farmer *et al* (11).

In an article "Meta-analysis of individual patient data in randomised trials for self-monitoring of blood glucose in people with non-insulin treated type 2 diabetes", the

[2] http://www.cadth.ca/en/advisory-bodies/cerc (accessed on October 16th 2012): "The CERC Expert Review Committee (CERC) is an advisory body that makes recommendations related to the identification, evaluation, and promotion of optimal drug prescribing and use in Canada. The approach is evidence-based, and the advice reflects current medical and scientific knowledge, as well as clinical practice in the Canadian health care system."

authors conclude: "Evidence from this meta-analysis of individual patient data was not convincing for a clinically meaningful effect of clinical management of non-insulin treated type 2 diabetes by self monitoring of blood glucose levels compared with management without self monitoring." Whilst the authors concede that subjects in the studies analyzed who used SMBG did achieve statistically significant improvement in HbA_{1c}, we are concerned that the authors' conclusions may be misinterpreted by both healthcare providers and payers, and, potentially, lead to under-utilization of self-monitoring of blood glucose (SMBG), which has been shown to have a significant positive impact on clinical and psychosocial outcomes when used appropriately.

Additionally, we feel that arbitrarily setting a relevance threshold of 0.5% reduction in HbA_{1c} to assess the value and utility of SMBG may not be appropriate for the following reasons:

- Setting a relevance threshold of 0.5% reduction in HbA1c is "somewhat arbitrary" as the corresponding reference by Clar et al. (11) states and there is not scientific consensus about applying on a diagnostic like SMBG which has no direct effect on HbA1c.

- The relevance threshold was applied post-hoc because it was not mentioned in the protocol publication[3]. This is not an internationally accepted approach.

For example, the UKPDS investigators found that every 1.0% reduction in HbA1c was associated with a 37.0% decrease in risk for microvascular complications and a 21.0% decrease in the risk of any end point or death related to diabetes. Thus, the statistically significant reduction of HbA1c 0,25 % at 6 months reported in the meta-analysis should not be dismissed as a clinically insignificant improvement in patient care.

Despite our differing views regarding the methodologies and efficacy standards used in the meta-analysis, we agree with the authors' statement that "*self monitoring of blood glucose is not simply a diagnostic tool but one component of a complex intervention aimed at improving overall glycemic control and well-being.*" Moreover, we agree that prescribing SMBG without the intention to interpret and utilize the data to make therapeutic adjustments is wasteful of healthcare resources. The majority of studies included in the meta-analysis clearly illustrate this construct.

Malanda *et al* (16).

In their review, the authors concluded "with the present findings" that "self-monitoring of blood glucose (SMBG) in newly diagnosed type 2 diabetes patients who are not using

insulin is beneficial in lowering HbA_{1c}. However, when diabetes duration is over one year, the overall glycemic effects of SMBG are small at short-term and subside after one year."

It is important to note that we fully agree that *simply performing SMBG per se does not affect blood glucose levels. Nor, would we expect it to – anymore than we would expect performance of HbA1c testing to affect blood glucose levels*. It is our position that SMBG and HbA1c are only measures of glycaemic control, and that the clinical utility and cost effectiveness of these tests are dependent solely upon the degree to which the resulting data are appropriately and consistently utilized to adjust pharmacologic therapies and/or modify lifestyle behaviors.

Mentioned with regards to the report by CERC, the IDF criteria for appropriate SMBG use are absent from the interventions used in many of the studies (e.g., DiGEM, ESMON, Davidson) analyzed in the Cochrane Review. The authors, themselves, conclude: "Because subgroup meta-analyses could not fully take the presence of clinical heterogeneity into account, clinical interpretation and translation into practice of these results is difficult and should be done with caution. Different levels of probability and estimates of outcome variables of included studies might account for differences in presented subgroups. In addition, differences in requested monitoring frequency, HbA_{1c} level at baseline and SMBG and diabetes education may have contributed to the differences as well."

While it is not our intention to question the scientific discipline and diligence that the authors clearly exercised in their review of the evidence, we feel that the research question, itself, should be reconsidered. Rather than assessing whether *performance* of SMBG in general impacts glucose levels, perhaps the more pertinent question is "What is the impact on glycemic status when SMBG data generated in a structured manner, accurately interpreted and then used by both patients and clinicians to guide treatment decisions?" in order to find the best way of using SMBG data by patients and clinicians

Unfortunately, the authors of the Cochrane Review did not include the STeP study results into their meta-analysis due to the lack of a control group of type 2 diabetes patients treated with usual care but without SMBG. Nevertheless, similar findings as in the STeP study were seen in those studies included in the review that did utilize structured SMBG in their interventions.

APPENDIX B

Please Note: This Appendix (only) is classified as "COMMERCIAL IN CONFIDENCE" and must not be published on the internet.

Please see separate attachment

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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

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OBJECTIVE—To assess the effectiveness of structured blood glucose testing in poorly controlled, noninsulin-treated type 2 diabetes.

RESEARCH DESIGN AND METHODS—This 12-month, prospective, cluster-randomized, multicenter study recruited 483 poorly controlled (A1C ≥7.5%), insulin-naïve type 2 diabetic subjects from 34 primary care practices in the U.S. Practices were randomized to an active control group (ACG) with enhanced usual care or a structured testing group (STG) with enhanced usual care and at least quarterly use of structured self-monitoring of blood glucose (SMBG). STG patients and physicians were trained to use a paper tool to collect/interpret 7-point glucose profiles over 3 consecutive days. The primary end point was A1C level measured at 12 months.

RESULTS—The 12-month intent-to-treat analysis (ACG, n = 227; STG, n = 256) showed significantly greater reductions in mean (SE) A1C in the STG compared with the ACG: −1.2% (0.09) vs. −0.9% (0.10); $\Delta = -0.3\%$; $P = 0.04$. Per protocol analysis (ACG, n = 161; STG, n = 130) showed even greater mean (SE) A1C reductions in the STG compared with the ACG: −1.3% (0.11) vs. −0.8% (0.11); $\Delta = -0.5\%$; $P < 0.003$. Significantly more STG patients received a treatment change recommendation at the month 1 visit compared with ACG patients, regardless of the patient's initial baseline A1C level: 179 (75.5%) vs. 61 (28.0%); <0.0001. Both STG and ACG patients displayed significant ($P < 0.0001$) improvements in general well-being (GWB).

CONCLUSIONS—Appropriate use of structured SMBG significantly improves glycemic control and facilitates more timely/aggressive treatment changes in noninsulin-treated type 2 diabetes without decreasing GWB.

Diabetes Care 34:262–267, 2011

Self-monitoring of blood glucose (SMBG) is widely recognized as a core component of effective diabetic self-management (1–3). Although most evidence indicates that SMBG contributes to good glycemic control among type 1 (4,5) and type 2 diabetic (6,7) patients, it remains uncertain whether SMBG use is efficacious in insulin-naïve type 2 diabetic patients. Current evidence in this latter population is mixed, with some studies pointing to significant glycemic benefits resulting from SMBG use (8–10), while others have shown no significant benefits (11–13). Given the growing cost of current type 2 diabetic care, it is important to determine whether resources devoted to SMBG in the insulin-naïve population are justified and are effectively applied.

Inconsistent findings seen in studies of insulin-naïve type 2 diabetic patients may be due, in part, to differences in key design issues, such as subject selection criteria (e.g., whether or not patients had poor glycemic control at study entry), critical content differences in the actual SMBG intervention (e.g., whether physicians were privy to patient SMBG data), fidelity of treatment delivery (e.g., the same physicians cared for patients from multiple study groups), and/or intervention adherence (e.g., whether patients actually completed the SMBG study protocol as directed). A review of these issues was published previously (14). We developed a comprehensive, structured SMBG intervention package that addresses these design issues and encourages patients and physicians to work collaboratively to collect, interpret, and appropriately use structured SMBG data. Our study was designed to investigate the effect of this intervention on glycemic control in poorly controlled, insulin-naïve type 2 diabetic patients compared with enhanced usual care. Additionally, we assessed the effect of this intervention on SMBG frequency, timing and intensity of treatment modification, and general well-being (GWB).

RESEARCH DESIGN AND METHODS

—The Structured Testing Program (STeP) is a 12-month, cluster-randomized, multicenter comparison between poorly controlled (A1C ≥7.5%), noninsulin-treated type 2 diabetic patients using structured SMBG in conjunction with enhanced usual care (structured

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See accompanying editorial, p. 527.

testing group [STG]) and an active control group (ACG) that received enhanced usual care only. Enhanced usual care included quarterly clinic visits that focused specifically on diabetes management, free blood glucose meters and strips, and office point-of-care A1C capability.

Patients were recruited from primary care practice sites across the eastern U.S., which were stratified to STG or ACG. This included both small and large practices serving communities with a range of patient education, social class, and ethnicity that reflected the diversity of primary care settings in the U.S. The use of a stratified, cluster-randomized design ensured that physicians cared for patients from one study group only. Each site generated a list of all patients who met age, diagnosis, and A1C inclusion criteria from their patient databases or chart review. Participating physicians reviewed the list and eliminated patients whom they felt should not participate in the study (e.g., dementia, psychosis, recent emotional trauma). Patients were then randomly selected from the list using a study-defined protocol until the predetermined sample size was reached.

Inclusion criteria were: duration of type 2 diabetes >1 year; aged ≥25 years; A1C level 7.5–12.0%; currently treated by diet, exercise, oral diabetes medication, and/or injectable incretin mimetic; able to read and write English without assistance; and had not participated in any other research protocol within the last 30 days. Exclusion criteria were: type 1 diabetes; managed with insulin at the start of the study; C-peptide level ≤0.50 ng/mL; used systemic oral or inhaled steroids more than 14 days within the last 3 months; treated with chemotherapy or radiation therapy; pregnant or breast-feeding; or had severe depression or other severe psychological conditions.

The study protocol was approved by the Copernicus Group (Central Institutional Review Board) and is in compliance with the Helsinki Declaration (15). Written informed consent was obtained from all subjects.

Procedures

The study's duration was 12 months with patient visits occurring at initial screening and baseline followed by visits at months 1, 3, 6, 9, and 12. At screening, investigators recorded demographics, collected relevant medical history, performed physical examinations, collected laboratory samples (e.g., A1C, lipids), and documented all current medications. Patients completed the STeP questionnaire, which included measures of self-care, diabetes-related distress, depression, and GWB. A description of these measures was previously published (14). A baseline visit was scheduled within 14 days. At the baseline visit, laboratory results were reviewed. Patients in both arms received a free blood glucose meter and test strips (Accu-Chek Aviva meter system; Roche Diagnostics, Indianapolis, IN), and they were instructed in their use.

At all subsequent visits (months 1, 3, 6, 9, and 12), ACG and STG clinic staff collected laboratory samples, recorded changes in medications, and performed brief physical examinations. Point-of-care A1C equipment (A1CNow+ test kit; Bayer Healthcare, Tarrytown, NY) was provided to all practices for clinical use only to assure that differential availability of the equipment did not affect outcomes. Patients in both groups brought their meters to each subsequent visit for electronic data uploading; physicians and clinic staff were blinded to these data and all other study-collected measures. Patients also reported all changes made to their diabetes regimen since their last visit. All patients completed the STeP questionnaire and a post-visit questionnaire to record physician discussion of SMBG results and recommendations for pharmacologic and lifestyle changes that occurred during the visit.

Intervention

STG participants used the Accu-Chek 360° View blood glucose analysis system (Roche Diagnostics), a validated tool (16) that enabled patients to record/plot a 7-point SMBG profile (fasting, preprandial/2-h postprandial at each meal, bedtime) on 3 consecutive days prior to each scheduled study visit (months 1, 3, 6, 9, and 12), to document meal sizes and energy levels, and to comment on their SMBG experiences. STG participants received training in the use of the Accu-Chek system, including instructions for how to identify problematic glycemic patterns and how best to address such problems through changes in physical activity, portion sizes, and/or meal composition. STG patients and physicians reviewed the completed form at each of the scheduled visits and noted areas of needed medication and lifestyle change. Completion of the Accu-Chek system was prompted via a telephone call from their physician's office one week prior to their next appointment. ACG subjects did not receive the Accu-Chek system. ACG patients were instructed to use their meter following their physicians' recommendations but received no additional SMBG prompting, training, or instruction.

STG physicians/staff received training on interpreting the structured data and were provided with an algorithm that described various pharmacologic/lifestyle treatment strategies that could be used in response to the specific SMBG patterns identified. Physicians were free to select from these options based on patient/physician preferences. All STG physicians were contacted regularly over the 12 months of the study to ensure consistency of the intervention over time. ACG physicians and staff received no additional training. STeP Study tools and resources are available at www.behavioraldiabetes.org/studies/STeP-Study.html.

Measurements

The primary end point was change in A1C from screening to 12 months. A1C analysis was conducted by a central laboratory (Covance, Indianapolis, IN) using the Variant II and Variant II Turbo hemoglobin testing systems (Bio-Rad Laboratories, Hercules, CA).

Treatment intensification was calculated using information entered into patient medical records at each clinic visit. These included recommended pharmacologic modification (defined as the initiation of a new medication, increase or decrease in the dose of an existing medication, or termination of an existing medication) and recommended lifestyle modification (defined as any change in diet, exercise, or other self-care behavior). The total number of visits with medication or lifestyle modifications and the time to the first treatment change was recorded for all patients.

Frequency of SMBG for all patients was calculated from blood glucose meter data that were uploaded electronically by the site coordinator directly to a web server at each study visit via the Accu-Chek Smart Pix device (Roche Diagnostics).

GWB was measured using the WHO-5 Well-Being Index assessment tool (17), a widely used, five-item questionnaire with a total score range of from 0–100 (higher scores indicating more positive well-being). Findings regarding other patient-reported outcomes will be presented in subsequent reports.

Statistical analysis

The study was designed to have a 90% power to detect a difference of 0.5% in

A1C levels. This was determined using a two-sample *t* test (two-sided, $\alpha = 0.05$), assuming a common SD of 1.5%. The estimate of SD in A1C values was inflated from 1.15 to 1.50 because of the clustering effect (18,19). We required a total of 408 patients (204 per study arm) to achieve the specified statistical power. A larger STG sample was initially recruited to account for potentially greater attrition expected in this group over time.

The analysis of change in A1C and other dependent variables was performed using linear mixed models (LMM) analysis with SAS PROC MIXED (20,21). LMM allows for comparisons between groups across study waves over time, along with analyses of moderator and mediator variables within the same analytic frame (20,21). Control variables in all analyses included: baseline dependent variable (A1C); patient age, gender, and race (white/nonwhite) as fixed effects; and practice site and subject as random effects. Missing data were estimated using maximum likelihood methods (22). Based on the mixed model, the least-square estimates of the group differences were obtained and tested for statistical significance. Additional analyses of patient attrition at each step in the protocol also were undertaken.

LMM was performed in two ways using values from all study visits across the 12 months. In the first approach, the analysis focused on the intent-to-treat (ITT) population, which was defined as ACG and STG subjects who completed the baseline and at least one postbaseline visit. The second approach was a per protocol (PP) analysis, which included all ACG and STG patients who adhered to the study protocol. Adherence in the ACG was defined as those who completed the study (with ≥4 visits) and did not use structured SMBG records that were similar to the Accu-Chek 360° View blood glucose analysis system intervention tool. Adherence in the STG was defined as those who completed at least 80% of all blood glucose values on the intervention tool, brought their completed tool to the clinic visit, and reported that their physicians looked at the tool and discussed the results (via the Post-Visit Questionnaire) at ≥4 of the 5 clinic visits.

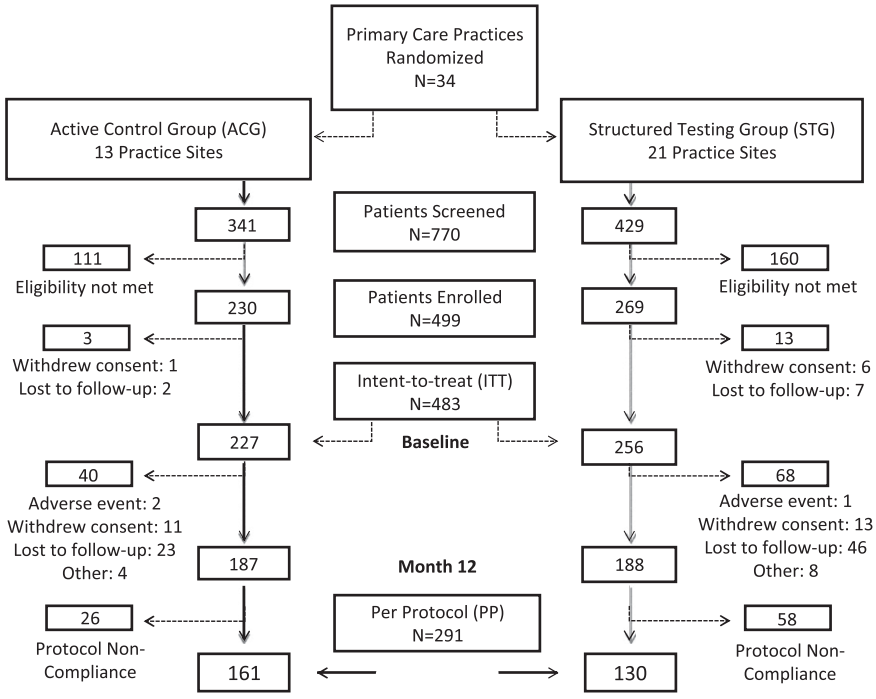


Figure 1—*Consort diagram.*

RESULTS—We recruited 34 primary care practices that were then randomized with stratification to ACG ($n = 13$) or STG ($n = 21$) (Fig. 1). Of the 770 patients screened, 499 patients were eligible and enrolled in the study. Of these, 7 patients (ACG, $n = 1$; STG, $n = 6$) withdrew consent, and 9 patients (ACG, $n = 2$; STG, $n = 7$) were lost to follow-up. The remaining 483 patients (ACG, $n = 227$; STG, $n = 256$) were included in the ITT cohort. During the study, 15 patients discontinued, 24 withdrew consent, and 69 were lost to follow-up, all primarily because of time or other life demands. Dropouts were slightly younger ($P < 0.02$), more likely to be African American ($P < 0.02$), had a higher A1C ($P < 0.01$), and had fewer comorbid conditions at baseline ($P < 0.02$). Characteristics of the dropouts were not significantly different between the two study groups. An additional 84 patients (ACG, $n = 26$; STG, $n = 58$) were excluded from the PP analyses because of protocol nonadherence. Thus, the PP cohort included 161 (71%) ACG patients and 130 (51%) STG patients.

Site and patient characteristics are summarized in Table 1. Patient demographic and disease-related characteristics at baseline between the two study groups differed only by age and ethnicity. These differences were controlled in all subsequent analyses. There were no intervention-related adverse events. Over the 12 months, no severe hypoglycemic events were reported. The incidence of hypoglycemia (<70 mg/dL), based on downloaded meter data, was 1.9% in the ACG and 1.8% in the STG (P = NS). There were no significant differences between the groups in number of total visits (scheduled study visits plus follow-up visits) over the 12 months (ACG = 5.1 [2.2]; STG = 4.9 [2.6], $P = 0.56$)

A1C findings

ITT analysis revealed that both groups showed significant reductions in A1C levels; however, STG subjects evidenced significantly greater mean (SE) reductions in A1C than ACG subjects over the 12 months: −1.2% (0.09) vs. −0.9% (0.10); $\Delta = -0.3\%$; $P = 0.04$ (Fig. 2*A*). PP analysis revealed an even greater mean (SE) A1C reduction among those STG subjects who adhered to the intervention compared with ACG subjects: −1.3% (0.11) vs. −0.8% (0.11); $\Delta = -0.5\%$; $P < 0.003$ (Fig. 2*B*). It is noteworthy that A1C reductions in nonadherent STG subjects were not significantly different than reductions seen in ACG subjects.

Seven-point blood glucose profile findings

STG subjects showed significantly lower average preprandial and postprandial glucose levels at all meals and at bedtime from month 1 to month 12 (in all cases, $P < 0.001$). More importantly, there was a significant drop from month 1 to month 12 in preprandial to postprandial glucose excursions at all meals: breakfast (44 to 35 mg/dL, $P < 0.005$), lunch (25 mg/dL

Table 1—*Baseline characteristics of practice sites and patients with type 2 diabetes by randomization group*

Practice sites	All sites	ACG	STG	*P*
n	34	13	21	
Physician age: mean (SD) age (years)	44.8 (7.7)	43.3 (6.4)	45.7 (8.4)	0.3867
Gender: male	27 (79.4)	11 (84.6)	16 (76.2)	0.5549
Years in practice: mean (SD) (years)	13.1 (7.9)	11.3 (7.2)	14.1 (8.3)	0.3441
Type of practice				0.4289
Primary care	27 (79.5)	10 (76.9)	17 (81.0)	
Multispecialty care	6 (17.6)	2 (15.4)	4 (19.0)	
Primary care/multispecialty care	1 (2.9)	1 (7.7)	0 (0.0)	
Number of type 2 diabetic patients: mean (SD)	1,084 (1,483)	1,250 (2,023)	978 (1,065)	0.6276
Primary location of practice				0.3024
Rural setting	10 (29.4)	2 (15.4)	8 (38.1)	
Suburban	17 (50.0)	9 (69.2)	8 (38.1)	
Urban	6 (17.6)	2 (15.4)	4 (19.0)	
Urban and suburban	1 (3.0)	0 (0.0)	1 (4.8)	

Patients	All patients	ACG	STG	*P*
n	483	227	256	
Patient age: mean (SD) age (years)	55.8 (10.7)	57.0 (11.2)	54.8 (10.1)	0.0197
Gender: male	257 (53.2)	122 (53.7)	135 (52.7)	0.8243
Ethnicity				0.0004
African American	150 (31.1)	72 (31.7)	78 (30.5)	
Caucasian	305 (63.1)	152 (67.0)	153 (59.8)	
Other	28 (5.8)	3 (1.3)	25 (9.8)	
Highest level of education				0.1002
No college	253 (52.7)	114 (50.9)	139 (54.3)	
Some college	98 (20.4)	40 (17.9)	58 (22.7)	
College graduate	129 (26.9)	70 (31.3)	59 (23.0)	
A1C: mean (SD) A1C (%)	8.9 (1.2)	8.9 (1.2)	8.9 (1.2)	0.8751
BMI: mean (SD) BMI (kg/m^2)	35.1 (7.3)	35.1 (6.7)	35.0 (7.8)	0.8851
Diabetes duration: mean (SD) (years)	7.6 (6.1)	7.7 (6.1)	7.5 (6.1)	0.6547

Values are *n* (percentages) unless stated otherwise.

to 17 mg/dL, $P < 0.03$), and supper (34 to 26 mg/dL, $P < 0.05$). Measurements of mean amplitude of glucose excursions indicated significant ($P = 0.0003$) mean (SE) reductions in glycemic variability among STG subjects from 38.5 mg/dL (0.9) at month 1 to 34.3 mg/dL (1.0) at month 12. There were no changes in these findings when insulin-using patients were excluded from the analyses.

Changes in treatment

ITT analysis showed that patients in both study groups who received a treatment change recommendation (pharmacologic and/or lifestyle) at the month 1 visit experienced significantly ($P < 0.0005$) greater reductions in A1C than patients who did not receive a treatment change recommendation at the month 1 visit. However, significantly more STG patients received a treatment change recommendation at the month 1 visit compared with ACG patients, regardless of the patient's baseline A1C level: 179 (75.5%) vs. 61 (28.0%); $P < 0.0001$. Of note, almost twice as many STG patients were started on intermediate or long-acting insulin than ACG patients between the month 1 and month 12 visits: 42 vs. 23; $P = 0.046$. ITT analyses excluding patients who began insulin during the study period also indicated significant decreases in A1C for both the ACG and the STG, with STG patients still demonstrating significantly greater reductions in A1C by month 12 than ACG patients: −1.3% (0.10) vs. −1.0% (0.10); $\Delta = -0.3\%$; $P = 0.03$. Similar between-group differences occurred using last observation carried forward analysis (last A1C before insulin start carried forward): −1.0% (0.10) vs. −0.7% (0.10); $\Delta = -0.3\%$; $P = 0.03$. Thus, the observed group difference in glycemic outcomes was not accounted for by those patients who started insulin during the course of the study.

The mean (SD) number of scheduled visits at which a treatment change was recommended was significantly higher in STG patients than in ACG patients: 2.7 (1.5) vs. 1.1 (1.0); $P < 0.0001$. PP analyses showed that the mean (SD) number of clinic visits where treatment change recommendations occurred was almost three times greater in STG patients than in ACG patients: 3.1 (1.4) vs. 1.1 (1.0), $P < 0.0001$.

SMBG frequency

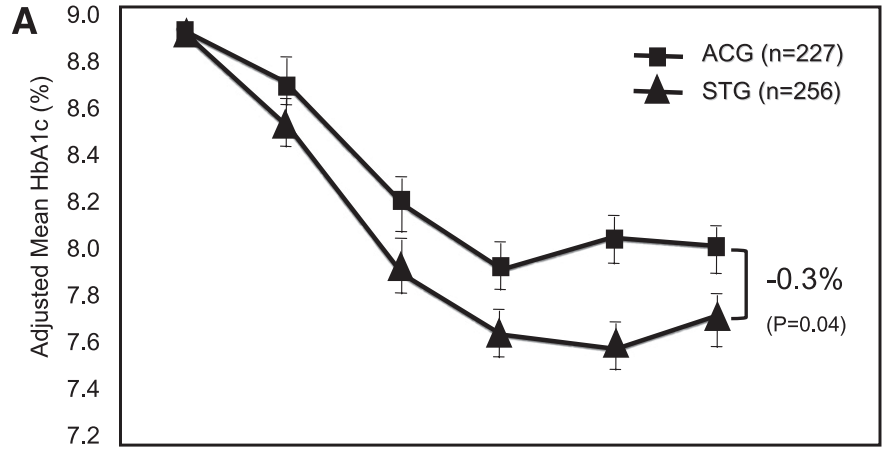
ITT analyses showed that the mean (SD) number of daily blood glucose tests, even when including the 7-point Accu-Chek 360° View blood glucose analysis system profiles for the STG, was significantly lower for the STG than for the ACG at month 6 (0.97 [0.81] vs. 1.21 [1.00], $P = 0.007$); month 9 (0.85 [0.72] vs. 1.11 [0.84], $P = 0.001$); and month 12 (0.77 [0.69] vs. 1.05 [0.80], $P < 0.0001$). PP analysis showed no significant between-group differences in SMBG frequency.

General well-being

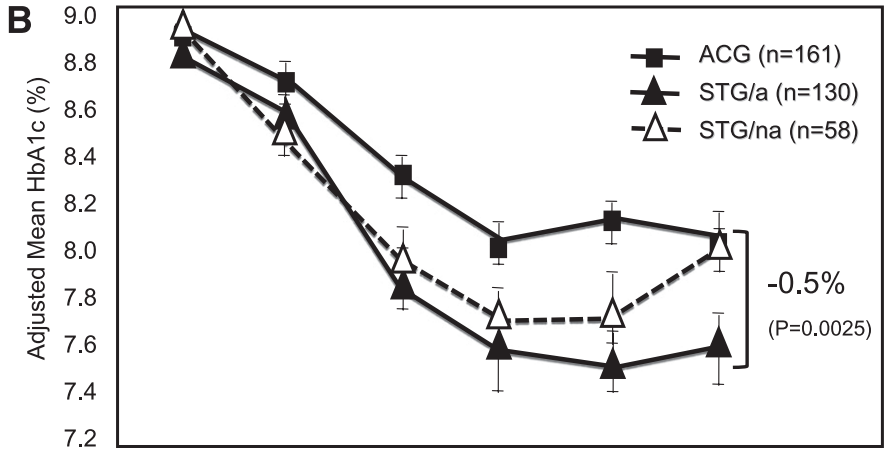
There was a significant increase in GWB over the study period in both the ACG ($P < 0.007$) and the STG ($P < 0.0001$), as assessed by the WHO-5 (16), with no significant between-group differences over time. In the ACG, mean (SD) WHO-5 scores rose from 58.0 (20.7) at study start to 62.0 (20.8) at month 12. In the STG, mean (SD) WHO-5 scores rose from 57.3 (23.6) at study start to 65.5 (21.3) at month 12. PP analyses revealed that adherent STG subjects reported a significantly greater improvement in GWB than adherent ACG subjects ($P < 0.04$).

CONCLUSIONS—We found that programmatic, structured SMBG contributes to significant improvement in glycemic control in insulin-naïve type 2 diabetic patients compared with patients who did not receive structured SMBG. Further, this significant between-group difference occurs even though there is a significant A1C reduction of 0.9% achieved by the ACG during the 12-month study period. Glycemic improvement was even greater in STG patients who adhered to the protocol. Of note, patients in the structured SMBG group also show improvement in mean amplitude of glucose excursions and in 7-point blood glucose profiles over the 12-month period.

We suspect that the significant A1C improvement in the ACG over time is due mainly to the heightened attention paid to



	Baseline	M1	M3	M6	M9	M12
ACG	8.9% (0.08)	8.7% (0.1)	8.2% (0.1)	7.9% (0.1)	8.0% (0.1)	8.0% (0.1)
STG	8.9% (0.07)	8.5% (0.09)	7.9% (0.09)	7.6% (0.09)	7.6% (0.09)	7.7% (0.09)



	Baseline	M1	M3	M6	M9	M12
ACG	8.9% (0.1)	8.7% (0.1)	8.3% (0.1)	8.0% (0.1)	8.1% (0.1)	8.0% (0.1)
STG/a	8.8% (0.1)	8.5% (0.11)	7.9% (0.11)	7.6% (0.11)	7.5% (0.11)	7.6% (0.11)
STG/na	8.9% (0.14)	8.5% (0.15)	7.9% (0.15)	7.7% (0.15)	7.7% (0.16)	8.0% (0.15)

Figure 2—A*: ITT analysis: mean (± SE) A1C over 12 months (M) in patients with noninsulin-treated type 2 diabetes according to randomization group.* B*: PP analysis: mean (± SE) A1C over 12 months (M) in patients with noninsulin-treated type 2 diabetes, comparing ACG patients, adherent STG (STG/a) patients, and nonadherent STG (STG/na) patients.*

study subjects, the use of free meters and strips, the requirement that subjects bring their meters to all study visits, and the more frequent than usual medical visits. Thus, the observed differences between the STG and the ACG may be a conservative estimate compared with what might be obtained with similar patients in most clinical settings.

We also found significant differences between the STG and the ACG in the frequency and intensity of the treatment change recommendations made by physicians. This suggests that when patients bring structured SMBG information to clinic visits, and when physicians know how to interpret and respond to SMBG information, timely and appropriate treatment changes are more likely to occur than in cases in which structured SMBG data are not available, as occurred in the ACG.

Another possible explanation is that the treatment changes made by the STG physicians, and the resulting improvements in A1C, occurred because only the STG physicians were trained on a treatment algorithm and were encouraged to follow it. However the PP analyses show that the glycemic advantage occurred only among the STG patients who adhered to the intervention. Therefore, physician training alone does not sufficiently explain these findings.

Additionally, the greater improvement in A1C over time in the STG than in the ACG occurred with less (ITT) SMBG frequency. This finding has important policy implications, suggesting that it may be appropriate to shift the current focus from SMBG quantity (testing frequency) to SMBG quality (meaningful test results that contribute to positive action), utilizing protocols that place more emphasis on when patients test and how they and their physicians organize and make clinically relevant use of the resulting data.

Study strengths and weaknesses

We used a comprehensive approach to address the design limitations of previous studies (23): a cluster-randomized design; an A1C inclusion criterion of ≥7.5%; a highly structured protocol that led to actionable outcomes for both patients and physicians; and a set of PP analyses to determine the effects of protocol completion.

Several limitations are noteworthy. First, the study did not include a third study arm that would have assessed the effect of the increased attention paid to both study groups over the 12-month period. Thus, the enhanced usual care received by the ACG resulted in a conservative estimate of between-group differences. Second, we could not determine if the treatment changes initiated by the physicians and the patients were clinically appropriate; our measures examined the number of changes, rather than the type of change recommended. Third, we could not determine how many of the recommended treatment changes actually occurred. Fourth, there was more attrition of the STG patients than the ACG patients over the 12-month period (though this difference was not statistically significant), suggesting that some patients may have found the structured SMBG intervention too burdensome, which may have biased the findings.

Our findings demonstrate that appropriate use of SMBG in poorly controlled, insulin-naïve type 2 diabetic patients can

be efficacious and clinically meaningful. This suggests that most patients and physicians will make appropriate use of SMBG data when there is a well-defined testing protocol, a tool for organizing the data, and the knowledge to interpret the data. It is evident that physicians can be trained to use well-organized SMBG data and to collaborate with patients to make timely and effective treatment decisions to improve glycemic control. Integrating SMBG into a collaborative program of care may lead to improved glycemic control without increasing strip consumption.

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