



Australian Government

Department of Health

MEDICAL SERVICES ADVISORY COMMITTEE

**HbA1c point of care testing for the diagnosis and
management of diabetes mellitus**

Protocol

December 2016

1. Title of application

HbA1c point of care testing for the diagnosis and management of diabetes mellitus.

2. Purpose of application

Please indicate the rationale for the application and provide one abstract or systematic review that will provide background.

Diabetes is a common chronic disease in Australia, increasing at a faster rate than other chronic diseases such as heart disease and cancer. It is estimated that around 1.7 million Australians have diabetes, with around 280 people developing it every day (1;2). This includes all types of known and registered diabetes, as well as silent, undiagnosed type 2 diabetes which is estimated to affect up to 500,000 Australians (1;2). The total annual cost impact of diabetes in Australia is estimated at \$14.6 billion (1).

It is estimated that for every 100 people with the diagnosis of diabetes there are between 25 (3) and 80 (4) people living with undiagnosed diabetes. Many patients do not seek help until they have developed complications which may be many years after diabetes actually began. The high prevalence of undiagnosed diabetes demonstrates the importance of early detection of the disease.

Diabetes is a serious complex condition resulting from defective insulin production and/or action. If left undiagnosed or poorly controlled, the chronic hyperglycaemia associated with diabetes can affect the entire body and lead to coronary artery disease (CAD), stroke, kidney failure, limb amputations and blindness (5).

The diagnosis of diabetes typically involves one or more biochemical analyses: blood glucose levels (fasting and random); the oral glucose tolerance test (OGTT); and glycated haemoglobin (HbA1c) (2). HbA1c, a marker of long-term glycaemic control, reflects the average blood glucose concentration over the preceding 3 month period.

Current guidelines recommend HbA1c tests every 3 to 6 months to assess glycaemic control as a routine component of disease management for patients with established diabetes (2). HbA1c has been endorsed as a diagnostic test for diabetes by the World Health Organization (WHO), and recently the Australian Diabetes Society, the Royal College of Pathologists of Australasia, and the Australasian Association of Clinical Biochemists confirmed its use to establish the diagnosis of diabetes (2). HbA1c testing performed in NATA accredited pathology laboratories is currently MBS listed for both the diagnosis and the management of patients with established diabetes (refer to MBS items 66551, 66554, 66841 for further details). Point of care (PoC) testing is funded by the Federal Government in a limited capacity under the Quality Assurance for the Aboriginal and Torres Strait Islander Medical Services (QAAMS) program (MBS Item 73840).

Early identification and optimal glycaemic control can slow the onset and progression of diabetes-related complications (2). Innovative HbA1c PoC tests have been developed to allow diagnostic testing at or near the site of patient care, providing clinicians and patients an alternative to laboratory testing (6). The addition of HbA1c PoC testing to usual patient management leads to improved patient outcomes (ie improved and quicker clinical decisions), and allows prevention of unnecessary healthcare resource use (ie more rational prescribing, fewer laboratory or doctor visits) (7-14).

During the recent MSAC application for HbA1c for the diagnosis of diabetes (1267) there was strong public support for the consideration of the PoC testing however this was ultimately not included in the final assessment report.

This application seeks MBS listing for the quantification of HbA1c by PoC for the diagnosis and usual management of patients with diabetes.

The proposed MSAC application will be undertaken by Optum on behalf of IVD Australia.

Please refer to Appendix 1 for background information from the Australian Government Point of Care Trial in General Practice (2009).

3. Population and medical condition eligible for the proposed medical services

Provide a description of the medical condition (or disease) relevant to the service.

Diabetes mellitus is a group of metabolic disorders characterised by hyperglycaemia resulting from defects in insulin secretion and/or action, and is categorised into three main types: type 1, type 2 and gestational. Several pathogenic processes are involved in its development ranging from autoimmune destruction of the β -cells of the pancreas to abnormalities resulting in insulin resistance. For patients with diabetes, chronic hyperglycaemia is associated with long-term damage, dysfunction and failure of various organs including eyes, kidneys, nerves, heart and blood vessels. The symptoms of hyperglycaemia include polyuria, polydipsia, weight loss and blurred vision. Long-term complications involve loss of vision due to retinopathy, renal failure, peripheral and autonomic neuropathy. The incidence of atherosclerotic cardiovascular, peripheral arterial and cerebrovascular disease, as well as hypertension and lipoprotein abnormalities in patients with diabetes is increased. Early detection and effective therapy providing good metabolic control, can delay the onset and progression of diabetes late complications, resulting in better outcomes for patients.

Define the proposed patient population that would benefit from the use of this service. This could include issues such as patient characteristics and /or specific circumstances that patients would have to satisfy in order to access the service.

The two proposed patient populations are the same as those currently funded for HbA1c testing for the diagnosis and management of diabetes (MBS items 66841, 66551 and 66554) for rural, remote and urban areas.

NHMRC guidelines (5) suggest case detection should be conducted on an opportunistic basis (eg in GP consulting rooms) in individuals who are judged to be at risk, either through a score of ≥ 12 on the AUSDRISK assessment tool, or are in one of the following population groups with a known higher risk:

- people with impaired glucose tolerance or impaired fasting glucose;
- women with a history of gestational diabetes mellitus;
- women with a history of polycystic ovary syndrome;
- people presenting with a history of cardiovascular disease event (ie myocardial infarction, stroke); and
- people on antipsychotic medication.

The proposed HbA1c PoC test will be used for the detection and diagnosis in this same at risk population.

The HbA1c POC test will also be used for ongoing management of patients with established diabetes on an as needed basis every 3-6 months to assess blood glucose control.

The HbA1c PoC test will be an alternative to the HbA1c test currently performed by a laboratory.

PASC noted that the potential benefits of the HbA1c POC test versus laboratory testing may be greater in rural, remote, disadvantaged and aged populations. Therefore these groups are listed as sub-populations of interest in the protocol. These populations will be assessed if HbA1c POC test is not cost-effective in the general population.

Indicate if there is evidence for the population who would benefit from this service i.e. international evidence including inclusion / exclusion criteria. If appropriate provide a table summarising the population considered in the evidence.

Two clinical trials were identified that recruited patients with similar criteria described above. These prospective, randomised controlled trials (RCTs) assessed the clinical effectiveness of HbA1c PoC testing in patients with established diabetes. Additionally, an RCT funded by the Australian Government investigated PoC testing in general practice. It assessed patients across three conditions (anticoagulant therapy, diabetes, hyperlipidaemia) and reported the results separately. Results from the diabetes subgroup are presented in this protocol. The eligibility criteria used to select and randomise patients in the RCTs are presented in Table 1.

Table 1 Patient inclusion and exclusion criteria

Author and year	N	Inclusion criteria	Exclusion criteria
Khunti 2006	681	Patients with type 2 diabetes who attended participating general practices for review of their diabetes care.	Patients who were unable to attend the practice. Patients who were exclusively under hospital care.
Miller 2003	597	Patients with type 2 diabetes for at least 6 months.	
Australian Government 2009	1967	Patients with established diabetes. Patients with a fasting plasma glucose of ≥ 7.0 mmol/L or a two-hour post glucose load of ≥ 11.1 mmol/L. (This equates to 53 mmol/mol.)	Patients who were < 18 years of age. Patients whose condition was not stabilised. Patients who had dementia. Patients deemed by their GP as unable to comply with the requirements of the Trial. Patients who were unable to understand the instructions written in English.

In both trials by Khunti et al (2006) and Miller et al (2003) trials patients were randomised to receive HbA1c results either during (“rapid”) or after (“routine”) the patient visit. Khunti et al (2006) (14) found that the proportion of patients with HbA1c $< 7.0\%$ was not statistically different between either group at 12 months. Miller et al (2003) (7) reported more intensification of therapy in patients with HbA1c $\geq 7.0\%$ at baseline occurred in the PoC testing group (51 versus 32, $p=0.01$), particularly when HbA1c $\geq 8.0\%$. Additionally, a statistically significant reduction was reported in HbA1c in the PoC testing group (8.4% to 8.1%, $p=0.04$), whilst no reduction was reported in the routine care group (8.1% to 8.0%, $p=0.31$) (7). Overall no statistically significant changes in HbA1c between groups were reported, however, the trial was not powered to determine a statistically significant difference in routine care provided over the 4 month trial duration (7).

The multi-centre, cluster RCT evaluated the safety and clinical effectiveness of HbA1c PoC testing in Australian general practice (15). The main clinical outcomes of the PoC test trial findings in relation to HbA1c were:

- The median number of HbA1c tests performed was the same across treatment groups and the median HbA1c test result was similar between groups, though slightly lower in the PoC testing group (15).

- PoC testing was non-inferior compared to pathology laboratory testing in relation to the proportion of diabetes patients who have shown an improvement from baseline and are within the target range ($p < 0.0001$). Based on the adjusted analysis, the percentage of patients within target range was higher in the PoC testing group (65.48%) compared to the pathology laboratory testing group (56.18%) with a difference of 9.31%. The results of the unadjusted analysis confirmed these findings (15).
- PoC testing was non-inferior compared to pathology laboratory testing ($p < 0.0001$). Based on the adjusted analysis, the percentage of patients with a reduction in their HbA1c test from baseline was higher in the PoC testing group (57.33%) compared with the pathology laboratory group (44.91%) with a difference of 12.42% (15).
- PoC testing was non-inferior compared to pathology laboratory testing in relation to the proportion of HbA1c tests within the target range ($p < 0.0001$). Based on the adjusted analysis, the percentage of HbA1c tests within the target range was higher in the PoC testing group (64.11%) compared with the pathology laboratory group (54.74%), with a difference of 9.36%. The results of the unadjusted analysis confirm these findings (15).

This trial conducted an analysis of the comparison of PoC testing and pathology laboratory test results for HbA1c and found the mean difference in results and the 95% limits of agreement were clinically acceptable. In addition, no serious adverse events (AEs) were attributable to PoC testing (15).

Additional data from non-randomised trials were located. Kennedy et al (2006) investigated the impact of active versus usual monitoring of algorithmic insulin titration and PoC versus laboratory HbA1c measurement on glycaemic control (11). 7,893 adults with type 2 diabetes were enrolled and assigned to treatment with insulin, with either:

- Usual titration (no contact between visits) using a simple algorithm with laboratory HbA1c testing;
- Usual titration with HbA1c PoC testing;
- Active (weekly monitoring) titration with laboratory HbA1c testing; or
- Active titration with HbA1c PoC testing.

The HbA1c PoC testing arm was associated with an increase in the proportion of patients receiving active insulin titration achieving $HbA1c < 7.0\%$ (41% for PoC testing vs 36% for laboratory testing, $p < 0.0001$) (11).

Cagliero et al (1999) tested the hypothesis that immediately available HbA1c results could improve glycaemic control by changing physician or patient behaviour, or both (9). In the PoC testing group, HbA1c decreased significantly at 6 and 12 months (-0.57 ± 1.44 , and $-0.40 \pm 1.65\%$, respectively), whilst HbA1c levels did not change in the laboratory testing arm (-0.11 ± 0.79 , and $-0.19 \pm 1.16\%$, respectively, NS) (9). The difference between the two groups was statistically significant at 6 months ($p = 0.029$) but not at study end ($p = 0.346$).

Provide details on the expected utilisation, if the service is to be publicly funded.

Table 2 below shows the number of services for HbA1c MBS item numbers between March 2015 and February 2016. HbA1c pathology for diagnosis testing was made available on the MBS in November 2014. The most recent 12 months of data between March 2015 and February 2016 shows approximately 1.4 million HbA1c tests were provided. Of these the majority of tests have been in patients with established diabetes (1.1 million services).

For the diagnosis of diabetes, it is expected that POC testing would be additional testing in situations where current laboratory testing is not practical. This is based on the experience of the introduction of laboratory HbA1c testing for the diagnosis of diabetes which has results in additional testing rather than the replacement of other diagnostic tests such as OGTT. To verify this assumption the number of services provided from the OGTT were compared with the HbA1c test (MBS items 66542 and 66841). This information is shown in Table 2.

For the management of diabetes, it is estimated that PoC testing would be a combination of new testing (5%) where current laboratory testing is not practical, and replacement of laboratory testing (5%).

Table 2 Expected utilisation

MBS item description	MBS item number	Total number of services (between March 2015 and February 2016)	Uptake of HbA1c PoC testing in the first year
OGTT for the diagnosis of diabetes mellitus	66542	263,872	26,387
Quantitation of HbA1c (glycated haemoglobin) performed for the diagnosis of diabetes in asymptomatic patients at high risk. (Item is subject to rule 25)	66841	230,209	23,021
Quantitation of glycated haemoglobin performed in the management of established diabetes – (Item is subject to rule 25)	66551	1, 161,359	58,068 – New testing 58,068 – Replacement testing
Quantitation of glycated haemoglobin performed in the management of pre-existing diabetes where the patient is pregnant – including a service in item 66551 (if performed) – (Item is subject to rule 25)	66554	11,353	590 – New testing 590 – Replacement testing
Total HbA1c services		1,402,921	140,337

Ultimately, the level of uptake is uncertain. Uptake is expected to grow in with line with number of patients at risk and diagnosed with diabetes. It is anticipated that uptake will be greatest in rural and remote areas where patients are required to travel long distances for pathology services. The level of uptake would likely be affected by the implementation of the service when it is funded.

As noted by PASC, due to ‘episode coning’ which limits the payment of pathology services within a patient episode, it is difficult to determine the total number of HbA1c tests that were performed based on MBS data. HbA1c tests that are not paid for by Medicare due to episode coning are not captured in MBS data. The Sponsor notes this coning effect and will attempt to account for this in the economic and budget impact models within the SBA based on available data.

4. Intervention – proposed medical service

Provide a description of the proposed medical service.

The proposed medical service is for the use of an *in vitro* diagnostic test instrument that meets defined accepted performance criteria equivalent to laboratory based testing being performed at or near the site of patient care (eg within GP consulting rooms) for the quantification of HbA1c in human whole blood.

If the service is for investigative purposes, describe the technical specification of the health technology and any reference or “evidentiary” standard that has been established.

Generally accepted performance criteria for an HbA1c PoC test system are (16):

- a total coefficient of variation (CV) <3.0%; and

- a National Glycohemoglobin Standardization Program (NGSP) manufacturer certification.

The CV specification ensures that the instrument or system provides reproducible results.

NGSP certification is a widely recognised international certification program for both laboratory-based and point of care HbA1c assays. .

The aim of the NGSP program is to standardise HbA1c test results to those of the Diabetes Control and Complications Trial (DCCT) and United Kingdom Prospective Diabetes Study (UKPDS) which established the direct relationships between HbA1c levels and outcome risks in patients with diabetes.

For NGSP certification, a particular assay (laboratory or point of care) is compared against a reference method in an independent laboratory. Test specimens must be distributed over the clinically meaningful range of concentrations and the assay must meet the internationally accepted specification for agreement with the reference method in order to obtain certification. Certification is valid for 1 year.

The analytical performance of NGSP certified laboratory assays and point of care assays with external proficiency samples (QAP samples) is comparable. The bias compared to the mean result, and %CV of laboratory assays is comparable to those of point of care assays.

NGSP certification indicates appropriate analytical accuracy across the range of clinically relevant HbA1c values, including the diagnostic cut-off of 48 mmol/mol (6.5%), compared to a globally accepted standard and allows comparison of results between different test methodologies.

HbA1c tests are Class 2 *in vitro* diagnostics and must be included on the ARTG by the TGA before being supplied in Australia. All PoC instruments undergo mandatory technical review by the TGA which assesses the test's analytical performance and suitability for use at the PoC.

The proposed medical services have analytical performance which meet quality specifications for both trueness and imprecision, and their performance is comparable to that of laboratories.

Indicate whether the service includes a registered trademark with characteristics that distinguish it from any other similar health technology.

The service will be available for all appropriate PoC tests that meet the performance criteria described above, irrespective of registered trademark.

Below are examples of ARTG listed PoC test devices that meet the proposed performance criteria:

- Afinion Test System:
 - ARTG identifier 204479: Instrument/analyser IVD
 - ARTG identifier 204476: Clinical chemistry substrate IVDs
- cobas b 101system
 - ARTG identifier 202785: Instrument/analyser IVD
 - ARTG identifier 201876: Clinical chemistry substrate IVDs

Indicate the proposed setting in which the proposed medical service will be delivered and include detail for each of the following as relevant: inpatient private hospital, inpatient public hospital, outpatient clinic, emergency department, consulting rooms, day surgery centre, residential aged care facility, patient's home, laboratory. Where the proposed medical service will be provided in more than one setting, describe the rationale related to each.

The proposed medical service will be delivered at the point of patient care, primarily within health care professionals consulting rooms.

Describe how the service is delivered in the clinical setting. This could include details such as frequency of use (per year), duration of use, limitations or restrictions on the medical service or provider, referral arrangements, professional experience required (e.g.: qualifications, training, accreditation etc.), healthcare resources, access issues (e.g.: demographics, facilities, equipment, location etc.).

The details of the PoC HbA1c testing depend on the test instrument or system that is used, with a number of appropriate instruments available in Australia.

Typically, a lancet is used to perform a fingerstick and a small (1 – 10 µl) sample of whole blood is obtained. The whole blood is added to a disposable test cartridge or device which contains the reagents required for the analysis. The test cartridge is inserted into an analyser which provides the HbA1c test result in 3 – 10 min. Most systems require minimal maintenance (if any) and calibration is typically via bar code or chip inserted into the device.

In terms of frequency of use and duration of use, the proposed medical service would reflect current MBS reimbursement criteria (MBS items 66841, 66551 and 66554):

- Diagnosis of diabetes: a limit of HbA1c diagnostic test once in a 12 month period for the diagnosis of diabetes in asymptomatic patients at high risk.
- Management in established diabetes: not more than four times in a 12 month period.
- Management in pre-existing diabetes (pregnant patients): not more than six times in a 12 month period.

PoC testing is proposed to be an alternative to laboratory testing where appropriate and that current limits on frequency of HbA1c testing would continue to apply whether the test is performed in a laboratory or at the point of care e.g. HbA1c testing for management in established diabetes would be limited to not more than four times (laboratory and/or PoC) in a 12 month period.

For clarity, testing outside the direct supervision of a medical or nurse practitioner, such as in pharmacy or other settings, is outside the scope of this application. Per PASC recommendations, the MBS item descriptor will be implicit in stating that the test result interpretation will be conducted by the treating medical or nurse practitioner.

The HbA1c PoC test can be performed in a non-laboratory clinical setting by appropriately trained device operators that may include registered nurses, nurse practitioners, general practitioners or practice staff who meet a required competency level to perform PoC testing. These device operators can perform the test and analyse the data output with the results reported to the treating practitioner for interpretation and action (where the test is not performed by a GP).

It is proposed that a practical framework would be used for the accreditation of sites performing point of care testing. Requirements would include appropriate quality control

testing, enrolment an external proficiency program, and staff training requirements. This point of care accreditation would be conducted as part of overall Practice Accreditation.

Healthcare resources required to utilise the proposed medical service will vary depending on the instrument or system that is used but would typically consist of: an appropriate test system and any associated reagents or cartridges; a small amount of space in the consulting rooms for the instrument and equipment required for collecting fingerstick samples such lancets, swabs, etc. Aside from the test system and reagents the costs of additional equipment is not considered to be significant.

The use of PoC testing by health care professionals is likely to significantly improve access to HbA1c testing for the diagnosis and ongoing management of patients with diabetes, particularly in patients in rural and remote areas. Patients in these areas may have limited access to pathology services due to issues of transportation and the distance to approved pathology laboratories.

PASC agreed with the description of the proposed intervention and requested that the following specifications be included in the Protocol:

- Provider of service – The PoC testing component will be undertaken within General Practice (registered nurses, nurse practitioners, general practitioners or practice staff who meet a required competency level to perform PoC testing). Test results interpretation will be conducted by the treating medical or nurse practitioner.
- Proposed training – The device manufacturer, device supplier or appropriate training organisation will provide training on use of HbA1c PoC testing devices to practice staff.
- Accreditation, quality control (QC) and quality assurance (QA) – The Sponsors of this application are currently drafting a proposed guidance document and framework for accreditation, QC and QA. The complete framework will be included in the Submission Based Assessment (SBA). In brief, the framework will include requirements for:
 - Clinical governance
 - Quality control (QC) procedures and external proficiency (external QA) requirements
 - Staff training and competency checks
 - Incorporation of POC testing into the practice's quality framework with a nominated person responsible for POC testing.

5. Co-dependent information (if not a co-dependent application go to Section 6)

Please provide detail of the co-dependent nature of this service as applicable

Not applicable

6. Comparator – clinical claim for the proposed medical service

Please provide details of how the proposed service is expected to be used, for example is it to replace or substitute a current practice; in addition to, or to augment current practice.

The proposed medical service will be a new MBS item for a PoC test conducted at or near the site of patient care (within consulting rooms and excluding the laboratory setting) using a PoC instrument that meets defined performance criteria for the quantification of HbA1c in human whole blood.

It is proposed that the appropriate comparator for HbA1c PoC testing will be HbA1c testing performed in a laboratory (MBS items 66841, 66551 and 66554). Currently, HbA1c tests are predominantly performed in NATA accredited laboratories. Point of care testing has been funded in a limited capacity under the Quality Assurance for the Aboriginal and Torres Strait Islander Medical Services (QAAMS).

The current clinical pathways for diagnosis and management of diabetes are based on recommendations in the NHMRC case detection guidelines (5) and general practice guidelines (2).

The three new proposed MBS items will be similar to the currently listed diagnostic tests for HbA1c currently used to diagnose diabetes in asymptomatic patients at high risk (see MBS item 66841) and to monitor the effectiveness of diabetes treatment and long-term blood glucose in people with established diabetes (see MBS items 66551 and 66554 in pregnant patients).

For the proposed medical service, practitioners would perform the test under the same circumstances as they would order the existing HbA1c tests.

As with current HbA1c testing arrangements the medical practitioner may request alternative tests such as fasting blood glucose (FBG) or OGTT if they are clinically indicated.

PASC agreed with the comparator being HbA1c test as analysed in an accredited pathology laboratory. PASC also agreed that provision of HbA1c PoC testing via QAAMS is not an appropriate comparator.

PASC agreed that the reference standard is the HbA1c test analysed in an accredited pathology laboratory at the diagnostic cut-off of 48 mmol/mol (6.5%).

7. Expected health outcomes relating to the medical service

Identify the expected patient-relevant health outcomes if the service is recommended for public funding, including primary effectiveness (improvement in function, relief of pain) and secondary effectiveness (length of hospital stays, time to return to daily activities).

Improvements in therapeutic control, even slight, can prevent or delay the onset of diabetes-related complications, including kidney failure, heart disease and diabetic retinopathy, lowering associated healthcare costs and resource use.

Immediate availability of HbA1c results at the time of consultation can increase the frequency of intensification of therapy (7), lowers HbA1c levels in type 2 diabetes (8;14), positively impact on medication adherence (10) and assist in the better management of chronic conditions (7-14). The avoidance of diabetes-related diseases and complications leads to both an increase in quality and quantity of life for patients, and a consequent reduction in the healthcare burden associated with diabetes-related death, disability and decline in quality of life when compared to no intervention.

The RCT performed in Australian general practice (15) reported the following patient-relevant health outcomes:

- GP visits: The number of GP visits per person-year in the diabetes sub-analyses were similar between both treatment groups. The total number of tests per person-year for HbA1c in Phase II was slightly higher for the HbA1c PoC test group (1.8) compared to the pathology laboratory group (1.5) (15).

- Process of care actions: Across both treatment groups, a total of 3014 (55.03%) HbA1c tests were within target range and 2463 (44.96%) tests were outside the target range (15).
 - For HbA1c test results within the target range:
 - the most common process of care actions for patients with diabetes, which were not part of the diabetes annual cycle of care, were review of the results (94.01%), a GP consultation (91.10%) and a review of all medications (59.32%).
 - the least common action was change or cessation of medication (8.31%).
 - when viewed by treatment group, the proportion of actions in all areas was greater in the HbA1c PoC test group than in the pathology laboratory group. More tests in the HbA1c PoC test group were associated with a GP consultation (94.48%) compared with the pathology laboratory group (83.39%) as well as review of all medications (61.22%) and other actions (45.62%).
 - For HbA1c tests outside the target range:
 - the most common actions were similar to those reported for the tests within range being review of test results (93.61%), GP consultation (85.06%) and review of all medications (61.18%)
 - when comparing treatment groups the HbA1c PoC test group had a larger proportion of actions in terms of GP consultations (90.83% versus 78.56%), review of all medications (64.18% versus 57.81%) and other actions (42.49% versus 27.94%). However, the pathology laboratory group reported a slightly higher proportion of changes in medication (19.73% versus 17.01%).
 - In terms of impact on processes of care:
 - More GPs changed or ceased diabetes medication if the test was outside the target range (18.3%) than within range (8.3%).
 - More GP consultations were noted (90.1%) within range than outside the range (85.1%). This was an interesting finding, as it would be expected that those patients outside the range would require additional GP follow-up visits.
 - Larger number of follow-up HbA1c test for those outside the range than within range (20.2% v 15.0%). Interestingly, GPs in the pathology laboratory group were more likely to order an HbA1c follow-up test than the HbA1c PoC test group GPs despite having access to a PoC testing device.
- Medication compliance: Based on all Trial participants, using the adjusted analysis, the percentage of MARS-5 questionnaire responses indicating compliance with disease management (use of medicines), was higher in the HbA1c PoC test group (39.27%) compared to the pathology laboratory group (36.98%), with a difference of 2.29% and a 90% confidence interval for the difference of (-0.06, 4.64) (10;15). The lower limit of the 90% confidence interval is greater than the non-inferiority limit of -3.70%, indicating PoC testing is non-inferior to pathology laboratory testing in relation to the proportion of MARS-5 questionnaire responses indicating compliance with disease management ($p < 0.0001$) (10;15). The results of the unadjusted analysis confirm these findings. Over 50% of diabetes patients reported forgetting to take their medicines with approximately 10-15% of both treatment groups altering the dose, missing out a dose or stopping taking them for a while (10;15).
- Patient satisfaction: No subgroup analysis for diabetes patients was provided. However, the Trial findings overall found strong statistical evidence that PoC testing patients on average were more satisfied than patients in the pathology laboratory

group in regards to the PoC testing process, the convenience of not travelling to an outside laboratory and to disease management (12;15).

PASC advised that the proposed outcomes should include the following:

- Analytical performance (% coefficient of variation, trueness, imprecision);
- Clinical performance (diagnostic accuracy, sensitivity, specificity in proposed setting (GP));
- Clinical effectiveness (safety and effectiveness);
- Health resources (number of HbA1c tests, total tests per year, number of GP consultations, and other healthcare resource use).

These are included in Table 5 and Table 6, which summarise the PICO for the diagnosis and management of diabetes, respectively.

Describe any potential risks to the patient.

A 2014 study found that four HbA1c PoC test systems met generally accepted performance criteria (16). This is supported by other studies reporting that PoC testing met the desired goals for imprecision (9-12), although the study of Schwartz et al (17) showed the mean HbA1c result of the PoC testing device to be significantly higher compared to the laboratory.

The RCT performed in Australian general practice (15) conducted in 2006 reported weighted estimates of the number of serious adverse events (SAEs), the number and percentage of patients experiencing one or more SAE and the number of SAEs per 10,000 person-years were calculated both overall and by treatment group. Descriptive analysis of Trial incidents was also undertaken. Issues of under-reporting were noted where reports were made direct by Trial staff or patients/carers using the appropriate SAE form.

Of patients with diabetes, there were 372 SAEs, with the most common being inpatient hospitalisations (64.54%), followed by other important medical events (17.55%) (15). A higher percentage of SAEs within the pathology laboratory group were inpatient hospitalisations (80.59%) compared with the HbA1c PoC test group (53.76%) (15). The HbA1c PoC test group had a higher percentage of events classified as 'other important medical events, compared to the pathology laboratory group (25.19% vs 6.18%) (15). Table 3 presents the type of SAE for the diabetes treatment group (weighted estimates).

Table 3 Type of SAE for the diabetes treatment group (weighted estimates)

Type of SAE	Treatment group				Total	
	Laboratory test		HbA1c PoC test		N	%
	N	%	N	%		
Death	10	6.50	26	11.59	36	9.55
Inpatient hospitalisation or prolongation of existing hospitalisation	120	80.59	120	53.76	240	64.54
Life threatening	0	0.0	11	5.01	11	3.00
Newly diagnosed cancer	10	6.73	3	1.56	14	3.63
Other important medical event	9	6.18	56	25.19	65	17.55
Permanent or significant disability or incapacity	0	0.0	6	2.89	6	1.73
Total	149	100.00	222	100.00	372	100.00

Reference: Australian Government PoCT report (2009)

Specify the type of economic evaluation.

A cost-effectiveness/ cost-utility analysis will be conducted to extrapolate costs associated with patients who receive the proposed medical service (HbA1c PoC testing) and those who receive the comparator (HbA1c testing via pathology lab), and associated gains in patient outcomes ie responder (controlled diabetes) and QALYs. This analysis is based on the following clinical claim: HbA1c PoC testing is non-inferior (same or better) in terms of clinical effectiveness and clinical utility for the diagnosis and management of patients with diabetes when compared with pathology laboratory testing. In areas with limited access to pathology laboratory services HbA1c testing is likely to be superior. HbA1c PoC testing is non-inferior and comparable in terms of diagnostic performance, clinical validity and analytical performance compared to pathology laboratory testing.

8. Fee for the proposed medical service

Explain the type of funding proposed for this service.

Public funding via the MBS is proposed for this service. It is proposed that the medical service will be listed as an additional medical service similar to the existing MBS items 66551, 66554 and 66841 (the quantification of HbA1c in established diabetes, management of pre-existing diabetes where the patient is pregnant, and the diagnosis of diabetes in asymptomatic patients at high risk respectively) with specific reference to conducting the test at the point of patient care.

Please indicate the direct cost of any equipment or resources that are used with the service relevant to this application, as appropriate.

Direct costs associated with the proposed medical service consist of:

- Instrument and reagent costs
- Training, accreditation and quality requirements

These costs will depend on the instrument that is used and the quality framework that is adopted.

To enable PoC tests to be accessible to patients, costs associated with accreditation, quality assurance and training need to be at an appropriate level to remove barriers to access. Different cost models will be included in the economic evaluation.

An indication of the costs of the medical service (including the device, consumables (test cartridge) and operating costs are included in Table 4 per PASC advice. The items described in this table are adapted from those presented in the Australian Government PoCT GP trial report (2009).

Final Protocol 1431 – HbA1c PoC testing in diabetes

Table 4 Costs of the medical service

Item	Cost per year	Cost per test (based on 260 tests per practice per year) ^a	Source/ Comments
Establishment and annual costs			
Device	\$1,000	\$3.85	Sponsor. Based on a range of upfront device costs between \$2,000 to \$8,000 over 5 years
Training	\$280	\$1.08	Sponsor. Based on \$600 in the first year, \$200 per year thereafter, over 5 years.
Accreditation	\$350	\$1.35	Sponsor estimate based on proposed accreditation framework
QA program	\$420	\$1.62	Cost of enrolment in POC QAP program.
Subtotal	\$2,050	\$7.88	Calculations
Monthly costs			
QA/QC consumables	\$430	\$1.65	Sponsor market estimate of QC material. QA material is included in QA program.
QA/QC Device Operator time	\$130	\$0.50	Based on 20 tests per year at \$6.53 / test (15)
Subtotal	\$560	\$2.15	Calculations
Per test costs			
Consumables	\$2,860	\$11.00	Sponsor market estimate
Device Operator time	\$1,698.80	\$6.53	Based on PoCT GP Trial (15)
Subtotal	\$4,557.80	\$17.53	Calculations
Total	\$7,167.80	\$27.57	Calculations

Notes: ^a Cost per test is based on practices using the device 260 times per year (ie assuming practices operate 5 days per week and use the POC test device once per day).

Provide details of the proposed fee.

The proposed fee is to be determined based on the direct costs of performing delivering the service and the value provided by the service through improved diagnosis and management of diabetes.

In a pivotal clinical trial of the effectiveness and safety of HbA1c PoC testing, the estimated MBS item fee was AUD\$91.42, which included an operating margin as well as the full cost of the analyser, all training, accreditation, and maintenance requirements (15). It should be noted that this fee is high as it was only based on the number of times the HbA1c PoC test was used over the 18 month trial period, ie 73 times (approximately \$18 per test). This cost was based on the within trial analysis, and is a significant overestimate of the cost if the PoC test was made available on the MBS.

An indication of the proposed MBS item fee is included per PASC advice. This is approximately \$27 per test, and is based on an approximate of the total cost of the testing over 12 months (ie \$7,168) and on an assumption of 260 tests conducted per practice per year. The items included in this total cost are based on those described in the PoCT GP trial, as listed in Table 4.

The Sponsors remains open to further discussions with PASC and MSAC regarding a suitable fee.

9. Clinical Management Algorithm - clinical place for the proposed intervention

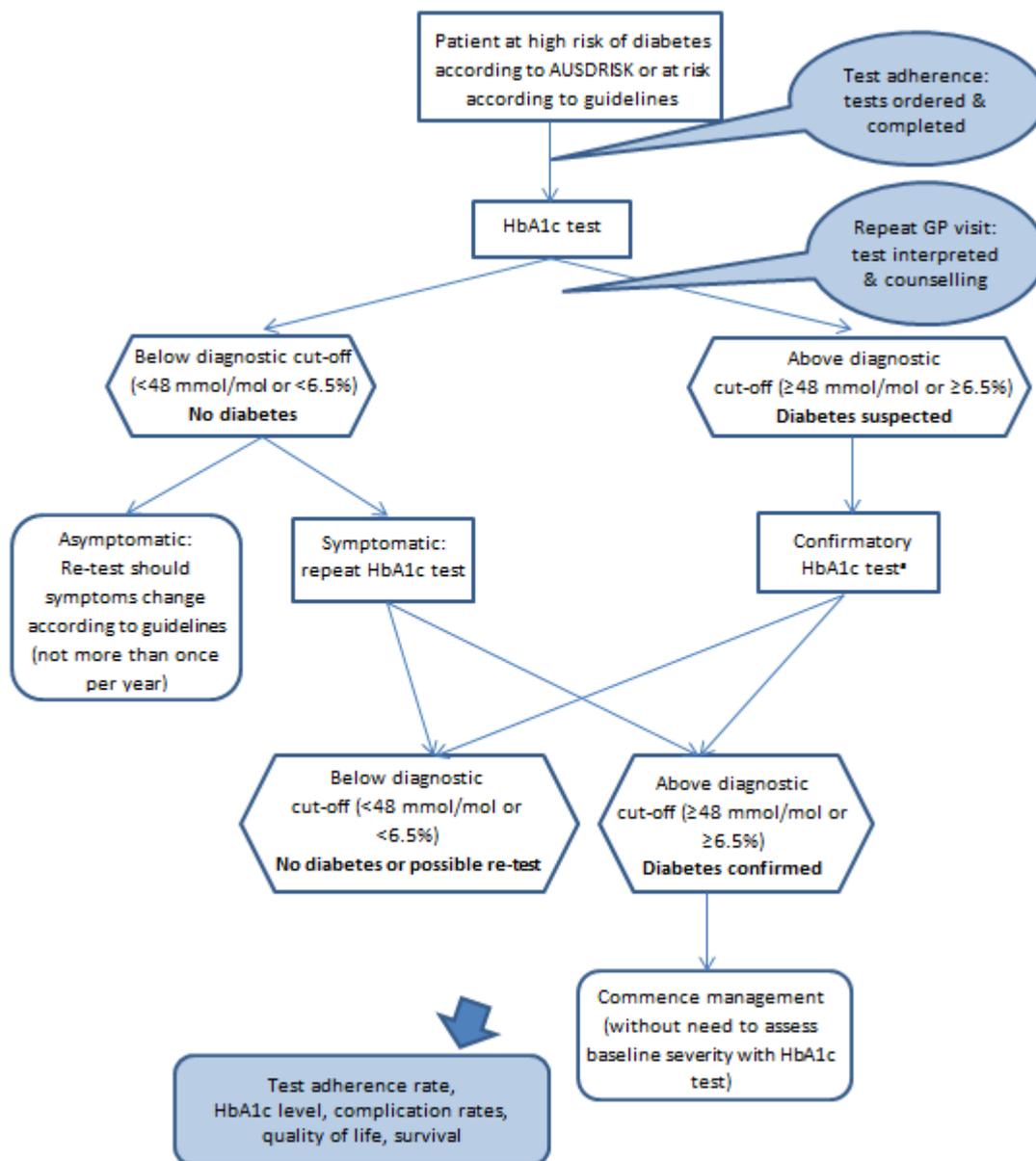
Provide a clinical management algorithm (e.g.: flowchart) explaining the current approach (see (6) Comparator section) to management and any downstream services (aftercare) of the eligible population/s in the absence of public funding for the service proposed preferably with reference to existing clinical practice guidelines.

Provide a clinical management algorithm (e.g.: flowchart) explaining the expected management and any downstream services (aftercare) of the eligible population/s if public funding is recommended for the service proposed.

Practitioners would perform the proposed medical service under the same circumstances as they would order the existing HbA1c tests and hence the clinical management algorithm will remain the same as current practice.

Figure 1 presents the diagnostic algorithm using HbA1c testing for diabetes. Patients who are referred for an HbA1c test (either via laboratory or PoC device) may present to the GP with known issues related to diabetes, or may present to the GP for unrelated issues.

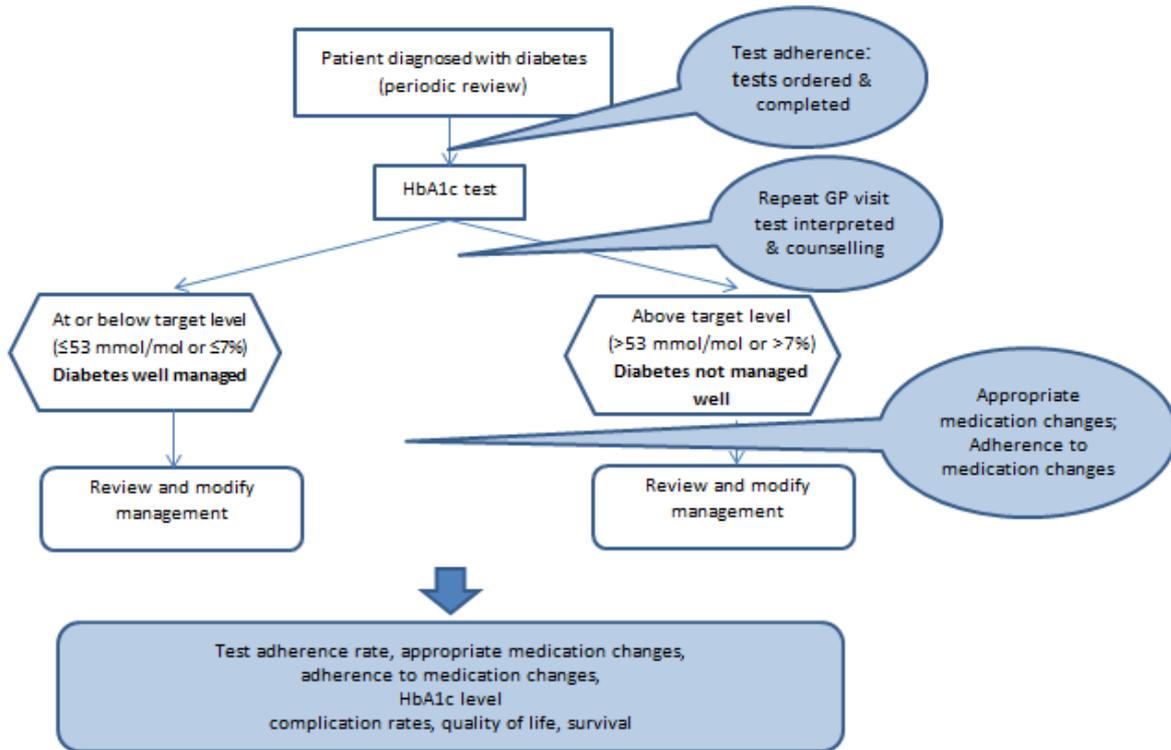
Figure 1 Diagnostic algorithm using HbA1c testing (laboratory or point of care) for diabetes



Note: ^a Whilst the confirmatory HbA1c test is recommended in the NHMRC practice guidelines (Colagiuri et al, 2009), this is not routinely performed in practice and confirmatory testing is not MBS funded.

Figure 2 presents the algorithm for the management and review (cycle of care) of patients with diabetes using HbA1c (either laboratory or PoC).

Figure 2 Management algorithm using HbA1c testing (laboratory or point of care) for patients with diabetes



Note: This figure is adapted from the NHMRC practice guidelines (Colagiuri et al, 2009)

10. Regulatory Information

Please provide details of the regulatory status. Noting that regulatory listing must be finalised before MSAC consideration.

There are several HbA1c PoC tests available in Australia that meet the defined acceptable performance criteria comparable to laboratory based testing as described in Section 4.

In Australia, HbA1c tests are Class 2 *in vitro* diagnostics and must be included on the ARTG by the TGA before being supplied in Australia. All PoC instruments undergo mandatory technical review by the TGA which assesses the test's analytical performance and suitability for use at the point of care.

Below are examples of ARTG listed PoC test devices that meet the proposed performance specifications:

- Afinion Test System:
 - ARTG identifier 204479: Instrument/analyser IVD
 - ARTG identifier 204476: Clinical chemistry substrate IVDs
- cobas b 101system

- ARTG identifier 202785: Instrument/analyser IVD
- ARTG identifier 201876: Clinical chemistry substrate IVDs

11. Decision analytic

Provide a summary of the PICO as well as the health care resource of the comparison/s that will be assessed, define the research questions and inform the analysis of evidence for consideration by MSAC (as outlined in Table 5).

Table 5 and Table 6 provide a summary of the PICO criteria for the proposed medical service. Patients are reflective of the criteria currently funded for HbA1c testing for the diagnosis and management of diabetes (MBS items 66551, 66554, 66841). Intervention options include usual practice laboratory testing or PoC HbA1c testing with a system of appropriate analytical performance. Patient outcomes reflect the pivotal trial evidence described in Section 7.

Table 5 Summary of PICO to define research question for the diagnosis of diabetes

PICO	
<i>Is HbA1c POC testing for the diagnosis of diabetes in at risk patients safe and effective, and cost-effective compared to HbA1c analysed in a pathology laboratory?</i>	
Patients	Patients who are judged to be at risk, either through a score of ≥ 12 on the AUSDRISK assessment tool, or are in one of the following population groups with a known higher risk: <ul style="list-style-type: none"> • people with impaired glucose tolerance or impaired fasting glucose; • women with a history of gestational diabetes mellitus; • women with a history of polycystic ovary syndrome; • people presenting with a history of cardiovascular disease event (i.e. myocardial infarction, stroke); and • people on antipsychotic medication.
Intervention	HbA1c point of care test analysed in clinical PoC setting
Comparator	HbA1c testing analysed in an accredited laboratory
Outcomes	Claim of non-inferiority based on PASC advice <ul style="list-style-type: none"> • Safety (adverse events of test procedure). • Diagnostic accuracy, sensitivity, specificity in proposed setting (GP). • % coefficient of variation, trueness, imprecision. • Clinical effectiveness: <ul style="list-style-type: none"> ▪ Test adherence ▪ Diagnosis of diabetes ▪ Health outcomes: patient-relevant health outcomes including retinopathy, limb amputation, ischaemic heart disease, stroke), patient satisfaction, acceptability and convenience, quality of life). ▪ Impact of false negative- side effects of taking medication unnecessarily, captured in health outcomes ▪ Impact of false positive- unnecessary treatment, side-affects from treatment, unnecessary visits to GP and specialists • Health care resources: number of HbA1c tests, total tests per year, number of GP consultations, other healthcare resource use

Table 6 Summary of PICO to define research question for the management of diabetes

PICO	
<i>Is HbA1c POC testing for the monitoring of diabetes control in established diabetes patients safe and effective, and cost-effective compared to HbA1c analysed in a pathology laboratory?</i>	
Patients	Patients with established diabetes.
Intervention	HbA1c point of care test analysed in clinical PoC setting
Comparator	HbA1c testing analysed in an accredited laboratory
Outcomes	<p>Claim of non-inferiority based on PASC advice</p> <ul style="list-style-type: none"> • Safety (adverse events of test procedure). • % coefficient of variation, trueness, imprecision. • Clinical effectiveness: <ul style="list-style-type: none"> ▪ Test adherence. ▪ Intermediate outcomes (test adherence, change in patient management including changes in intensification of therapy if above range; frequency of intensification of therapy at baseline; amount of change in dosage of oral agents only, oral agents plus insulin, insulin only), time from testing to intervention or treatment change; medication adherence; HbA1c levels at follow-up (% within range, mean HbA1c), hospitalisations (any major complications)). ▪ Health outcomes: patient-relevant health outcomes including retinopathy, limb amputation, ischaemic heart disease, stroke), patient satisfaction, acceptability and convenience, quality of life). ▪ Impact of false negative- side effects of taking medication unnecessarily, captured in health outcomes ▪ Impact of false positive- unnecessary treatment, side-affects from treatment, unnecessary visits to GP and specialists • Health care resources: number of HbA1c tests, total tests per year, number of GP consultations, other healthcare resource use

12. Healthcare resources

Using Table 7, provide a list of the health care resources whose utilisation is likely to be impacted should the proposed intervention be made available as requested whether the utilisation of the resource will be impacted due to differences in outcomes or due to availability of the proposed intervention itself.

Table 7 List of resources to be considered in the economic analysis

	Provider of resource	Setting in which resource is provided	Proportion of patients receiving resource	Number of units of resource per relevant time horizon per patient receiving resource	Disaggregated unit cost					
					MBS	Safety nets*	Other government budget	Private health insurer	Patient	Total cost
Resources provided to deliver proposed intervention (HbA1c PoC test)										
Initial GP consultation. (Treatment initiated if POC test indicates diabetes)	GP	Outpatient		1	37.05					37.05
HbA1c test	GP	Outpatient		1	Approx. \$27					Approx. \$27
Resources provided to deliver comparator										
Initial GP consultation ^a	GP	Outpatient		1	37.05					37.05
Patient episode initiation fee ^b	Pathology	Laboratory		1	6.00					6.00
HbA1c test	Pathology	Laboratory		1	16.80					16.80
GP consultation for results and initiation of treatment if appropriate.	GP	Outpatient		1	37.05					37.05

Notes: ^aFor diagnosis only. ^bPatient episode initiation item (from Group 10 of the pathology services table) Fees range from \$2.40 to \$17.60. For the purpose of this protocol a fee of \$6.00 is used.

13. Questions for public funding

Please list questions relating to the safety, effectiveness and cost-effectiveness of the service / intervention relevant to this application, for example:

- *Which health / medical professionals provide the service*
- *Are there training and qualification requirements*
- *Are there accreditation requirements*

- Will this service meet an unmet clinical need?
- What will be the primary health benefits to patients?
- What will be the key benefits to the health sector?

PASC noted that consultation feedback was received from one GP practice manager, one specialist, one QAAMS program manager, one organisation from the IVD industry, three peak bodies and one medical student. Overall positive feedback was received regarding:

- Greater accessibility (particularly in regional/rural areas);
- Decreased GP visits;
- Decreased loss of patients to follow-up;
- Increased patient convenience;
- Education and management;
- Increased health outcomes; and
- Improved quality of life.

Uncertainties were noted regarding:

- Increase in practice time;
- Increase in patient costs;
- Changed model of care;
- Requirement for other pathology tests; and
- Potential duplicate testing.

Reference List

- (1) Diabetes Australia. Diabetes in Australia: Facts. 2015(29 September 2015)
- (2) RACGP. General practice management of type 2 diabetes 2014-15.
- (3) Australian Bureau of Statistics. Australian Health Survey: Biomedical Results for Chronic Diseases, 2011-12. 2013 Jan 1.
- (4) Valentine N, Alhawassi T, Roberts G, Vora P, Stranks S, Doogue M. Detecting undiagnosed diabetes using glycated haemoglobin: an automated screening test in hospitalised patients. *MJA* 2011 Feb 21;194(4):160-4.
- (5) Colagiuri, Davies D, Girgis S, Colagiuri R. National Evidence Based Guideline for Case Detection and Diagnosis of Type 2 Diabetes. Canberra; 2009.
- (6) Shephard M. Point-of-care testing comes of age in Australia. *Australian Prescriber* 2010 Jan 2;33(1):6-9.
- (7) Miller CD, Barnes CS, Phillips LS, Ziemer DC, Gallina DL, Cook CB, et al. Rapid A1c availability improves clinical decision-making in an urban primary care clinic. *Diabetes Care* 2003;26(4).
- (8) Bubner T, O Laurence C, Gialamas A, Yelland L, Ryan P, Willson K, et al. Effectiveness of point-of-care testing for therapeutic control of chronic conditions: results from the PoCT in General Practice Trial. *MJA* 2009 Jan 6;190(11):624-6.
- (9) Cagliero E, Levina E, Nathan DM. Immediate Feedback of HbA1c Levels Improves Glycaemic Control in Type 1 and Insulin-Treated Type 2 Diabetic Patients. *Diabetes Care* 1999 Jan 11;22(11):1785-9.
- (10) Gialamas A, Yelland L, Ryan P, Willson K, O Laurence C, Bubner T, et al. Does point-of-care testing lead to the same or better adherence to medication? A randomised controlled trial: the PoCT in General Practice Trial. *MJA* 2009 Feb 2;191(9):487-91.
- (11) Kennedy L, Herman W, Tideman P, Harris A, for the GOAL A1c Team. Impact of Active Versus Usual Algorithmic Titration of Basal Insulin and Point-of-Care Versus Laboratory Measurement of HbA1c on Glycaemic Control in Patients With Type 2 Diabetes. *Diabetes Care* 2006 Jan 1;29(1):1-8.
- (12) O Laurence C, Gialamas A, Bubner T, Yelland L, Willson K, Ryan P, et al. Patient satisfaction with point-of-care testing in general practice. *British Journal of General Practice* 2010 Jan 3;DOI: 10.3399/bjgp10X483508:e98-e104.
- (13) Thaler L, Ziemer DC, Gallina DL, Cook CB, Dunbar V, Phillips L, et al. Diabetes in Urban African-Americans. XVII. Availability of Rapid HbA1c Measurements Enhances Clinical Decision-Making. *Diabetes Care* 1999 Jan 9;22(9):1415-21.

- (14) Khunti K, Stone MA, Burden AC, Turner D, Raymond NT, Burden M, et al. Randomised controlled trial of near-patient testing for glycosylated haemoglobin in people with type 2 diabetes mellitus. *The British journal of general practice : the journal of the Royal College of General Practitioners* 2006;56(528).
- (15) Australian Government. Point of care testing in general practice trial: Final Report. Canberra; 2009.
- (16) Lenters-Westra E, Slingerland RJ. Three of 7 hemoglobin A1c point-of-care instruments do not meet generally accepted analytical performance criteria. *Clinical chemistry* 2014;60(8).
- (17) Schwartz KL, Monsur JC, Bartoces MG, West PA, Neale AV. Correlation of same-visit HbA1c test with laboratory-based measurements: a MetroNet study. *BMC family practice* 2005;6.

Appendix 1

Australian Government Point of Care Trial in General Practice (2009)

Conclusion in relation to clinical effectiveness of point of care testing in general practice for diabetes (Section 9.6).

Diabetes

At both the patient and test level PoCT was found to be non-inferior to pathology laboratory testing for diabetes, therefore therapeutic control for PoCT patients is the same or better compared to control patients. The Trial also found a significantly higher percentage of patients in the intervention group with a reduction in their HbA1c test results from baseline. The results indicated that HbA1c testing in the intervention group was more in line with diabetes management guidelines which recommend that testing be at least six monthly (Appendix 3). More interestingly, the results found that patients in the intervention group were having urine microalbumin tests performed every 12 months compared to control patients, who were having the test every 2 years. Again, this indicates that intervention GPs were following diabetes management guidelines. From the case note audit data the Trial found that GPs using PoCT results, overall, provided a greater number of processes of care actions compared to GPs in the control group when managing their patients with diabetes. While there was little evidence that PoCT influenced GPs to undertake the actions related to the diabetes annual cycle of care, overall, GPs in both treatment groups showed poor adherence to these actions. However, PoCT GPs did provide a higher rate of testing of urine microalbumin, eye examinations and measurement of BMI. These findings could be an indication that the annual cycle of care actions are being performed either outside the consultation regarding the test result and/or by someone else in the practice, such as the practice nurse. From a patient perspective the Trial found that only a small percentage of people reported that they intentionally failed to take their medication. In addition, only a small percent indicated that they participated in any specific exercise session in the previous seven days.