



National Evidence Based Guidelines for the Prevention and Management of Type 2 Diabetes

Overview of Guideline Development Process and Methods

**Public Consultation Draft
August 2008**

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Purpose and Structure of the Document

Purpose

This 2008 series of guidelines for type 2 diabetes updates and builds on the original suite of evidence based diabetes guidelines which were initiated in 1999 under funding from the Department of Health and Ageing to the Diabetes Australia Guideline Development Consortium. Under the initial diabetes guideline project, six evidence based guidelines for type 2 diabetes were endorsed by the NHMRC. The purpose of the initial guidelines and the current guidelines is to provide systematically derived, objective guidance to:

1. Improve quality and consistency of care and reduce inappropriate variations in practice by assisting clinicians' and consumers' understanding of and decisions about treatment and management options
2. Inform fundholders and health service planners about the effectiveness and feasibility of the various options
3. Assist researchers and research authorities to highlight i) areas of diabetes prevention and care for which there is inconclusive evidence and ii) areas of deficiency in the evidence which require further or definitive research.

The specific purpose of this current project which commenced in mid 2007 is to update two of the previous guidelines - Primary Prevention, and Case Detection and Diagnosis – and to develop two new guidelines, one for Renal Disease and one for Patient Education.

Structure

This *Overview of the Guideline Development Process and Methods* outlines the rationale for the guidelines and the organisational structure, methods and processes adopted for the project. It applies to all four guidelines being developed under the current contract. These are structured into separate documents which present the recommendations, evidence statements, documentation of search strategies and search yield and a textual account of the evidence underpinning each recommendation. The overall structure of this series of guidelines comprises:

- an Overview of the Guideline Development Process and Methods
- a guideline for Primary Prevention of Type 2 Diabetes
- a guideline for Case Detection and Diagnosis of Type 2 Diabetes
- a guideline for Diagnosis, Prevention and Management of Chronic Kidney Disease in Type 2 Diabetes
- a guideline for Patient Education for Type 2 Diabetes

Final format and implementation

The contract between the Department of Health and Ageing and the Diabetes Australia Guideline Development Consortium makes provision for locating and synthesising the available evidence on the four index areas into guideline recommendations and describing the objective justification for the recommendations. Following endorsement by the NHMRC there will need to be an independent process of consultation with potential guideline users to determine the final format of the guidelines for wide dissemination to clinicians and consumers. Once this format has been agreed, an implementation strategy to encourage and facilitate the widespread uptake of the guidelines in everyday practice will need to be developed and actioned at national and state and territory level.

1.0 Introduction and Overview

1.1 Diabetes as a health burden

Results of the national diabetes prevalence survey, AusDiab (Dunstan et al, 2002), which was conducted on representative sample of some 11,000 people across Australia, found a prevalence of type 2 diabetes of 7.4% in people aged 25 years or older. Another 16.4% of the study population had either impaired glucose tolerance or impaired fasting glucose. AusDiab also confirmed that there is one person with undiagnosed diabetes for every person with diagnosed diabetes. Findings from the second phase of AusDiab, a 5-year follow-up survey of people who participated in the baseline study, have indicated that every year eight out of every 1,000 people in Australia developed diabetes. This, together with the increasing number of new cases of pre-diabetes, obesity, the metabolic syndrome, and kidney disease, has demonstrated that abnormal glucose metabolism is exerting a major impact on the health of Australians (Magliano, 2008).

Diabetes has a demonstrably high health and cost burden (AIHW, 2008; Colagiuri S et al, 2003) resulting from its long term complications which include:

- heart disease and stroke
- foot ulceration, gangrene and lower limb amputation
- kidney failure
- visual impairment up to and including blindness
- erectile dysfunction

The health burden of diabetes is described in more detail throughout the guideline series but to put these complications in perspective, it is worth noting here that, in Australia, diabetes is the most common cause of :

- blindness in people under the age of 60 years
- end stage kidney disease
- non-traumatic amputation

Diabetes is heavily implicated in deaths from cardiovascular disease (CVD) but, due to death certificate documentation deficiencies, this link is believed to be substantially under reported. At a global level, diabetes is predicted to increase dramatically in the next decade or two (IDF, 2006). With an ageing and increasingly overweight and physically inactive population, and a cultural mix comprising numerous groups known to be at high risk of type 2 diabetes, Australia is a prime candidate for realising the projected increases.

Due to sheer numbers, the major proportion of the total diabetes burden is attributable to type 2 diabetes which is the most common form of diabetes and accounts for approximately 85% of all diabetes in Australia. Type 2 diabetes occurs predominantly in mature adults with the prevalence increasing in older age groups. However, in high risk populations such as Aboriginal and Torres Strait Islander peoples it may become manifest much earlier.

These guidelines deal exclusively with type 2 diabetes. Like type 1 diabetes, type 2 diabetes is characterised by high blood glucose levels. However, unlike type 1 diabetes, the key feature of type 2 diabetes is insulin resistance rather than insulin deficiency. Consequently, its treatment does not necessarily require insulin and in many people, particularly in the initial years following diagnosis, type 2 diabetes can be successfully managed with dietary and

general lifestyle modification alone or in combination with oral anti-diabetic medications. Insulin therapy may be required if and when oral medication becomes ineffective in lowering and maintaining the blood glucose within an acceptable range. Assiduous attention to the management of elevated blood pressure, lipid problems and overweight is also required as these common features of type 2 diabetes markedly increase the risk of long term complications.

1.2 Key components and principles of diabetes care

Key components of care

In 1995, the NSW Health Department identified three key components of diabetes care, stating that ‘there is consensus supported by published literature that diabetes care and outcomes can be improved by providing access for all people with diabetes to:

- information about their condition and self care education
- ongoing clinical care to provide optimal metabolic control
- screening for and appropriate treatment of complications’ (Colagiuri R et al, 1995).

These and the principles of care below were included in the initial suite of guidelines for type 2 diabetes and remain as valid now as they were then.

Principles of care

The particular expression of the universally accepted diabetes care principles set out below was abbreviated from those developed by the UK Clinical Advisory Group (CSAG, 1994) and later summarised by the NSW Health Expert Panel on Diabetes (NSW Health, 1996) and was further adapted for this project:

- People with diabetes should have access to timely and ongoing care from a diabetes team. This should ideally include a doctor, nurse and dietitian with specific training and experience in the management of diabetes. Additional expertise, for example in podiatry, social work, behavioural psychology and counselling, should be available as required as should referral access to specialist services for the management of identified complications
- People with diabetes are entitled to access to opportunities for information, education and skills acquisition to enable them to participate optimally in their diabetes management
- People with diabetes are entitled to access high quality health services regardless of their financial status, cultural background, or place of residence
- For people with diabetes from community groups who may have special needs eg people from Aboriginal, Torres Strait Islander or culturally and linguistically diverse backgrounds and the elderly, diabetes care should be specifically tailored to overcoming access barriers and providing opportunities for optimising diabetes care and outcomes
- Diabetes teams should routinely evaluate the effectiveness of the care they provide

1.3 Rationale for the Guidelines

The magnitude of the impact of diabetes on individuals and society in Australia is manifest in its status as a National Health Priority Area since 1996 and the current attention directed to it by the Council of Australian Governments' National Reform Agenda which seeks to address and avert a greater impact on productivity than already exists as a result of diabetes.

For tangible and lasting benefits, evidence based information is required which synthesises new and existing evidence to guide primary prevention efforts and assist clinicians to identify and treat modifiable primary risk factors, accurately diagnose type 2 diabetes, assess metabolic control, provide effective routine care, and make appropriate and timely referrals.

Since the initial suite of NHMRC diabetes guidelines was released there has been a vast improvement in both the volume and quality of the evidence about preventing type 2 diabetes which is detailed in the Primary Prevention Guideline. Nonetheless, there remain grave concerns that the rapidly increasing prevalence of obesity combined with decreasing levels of physical activity will continue to impact negatively on the incidence and prevalence of diabetes unless addressed as a matter of urgency. Consequently, the Primary Prevention Guideline also cites some of the emerging evidence about environmental influences on food consumption and physical activity.

Type 2 diabetes represents a complex interaction of pathophysiological factors and its prevention and successful management requires clinicians and public health practitioners to maintain a thorough understanding of these interactions especially since there is now irrefutable evidence that both the onset of diabetes and the onset of its complications can be prevented or significantly delayed. Given the typically long pre-clinical phase of type 2 diabetes and that half of all people with diabetes are undiagnosed, the Case Detection and Diagnosis Guideline is an important component of this suite of guidelines.

Integral to the successful management of diabetes is self care knowledge and skills, and the capacity of the person with diabetes to adapt their lifestyle to optimise their physical and psychological well being. The Patient Education Guideline presents evidence addressing these issues.

The care of type 2 diabetes is predominantly carried out by general practitioners, often under 'shared care' arrangements with local Diabetes Centres and/or private endocrinologists. In remote Australia, and even in more densely settled rural regions, the population base is insufficient to support specialist diabetes teams and the general practitioner may not have local access to specialist referral and support. Regardless of geographical factors, standards of diabetes clinical care in Australia are known to be variable. The Chronic Kidney Disease Guideline sets out diagnostic criteria and therapies for achieving the treatment targets to guide the identification, prevention and management of kidney disease in people with diabetes.

1.4 Funding source

The Type 2 Diabetes Guidelines project is funded by the Australian Department of Health and Ageing under a head contract with Diabetes Australia as convenor of the Guideline Development Consortium. The development of the guidelines is managed in partnership with Diabetes Australia by The Diabetes Unit at the University Sydney under the direction of A/Professor Ruth Colagiuri.

1.5 The Guideline Development Consortium

The Guideline Development Consortium led by Diabetes Australia Limited (DA Ltd) comprises organisations representing consumers, specialist diabetes practitioners and primary care physicians and includes:

- The Australian Diabetes Society (ADS)
- The Australian Diabetes Educators Association (ADEA)
- The Royal Australian College of General Practitioners (RACGP)
- The Diabetes Unit - Australia Health Policy Institute, the University of Sydney.

Additionally there are a number of collaborators:

- The NSW Centre for Evidence Based Health Care (University of Western Sydney)
- The Cochrane Renal Review Group (Westmead Children's Hospital)
- The Cochrane Consumer Network
- The Caring for Australians with Renal Impairment Guidelines Group (CARI),
- Kidney Health Australia.

1.6 The scope of the Guidelines

The brief for the Guideline Development Project was to prepare a set of evidence based guidelines for type 2 diabetes to NHMRC standard.

The Type 2 Diabetes Guidelines target public health practitioners, clinicians (medical, nursing and allied health), diabetes educators and consumers and were designed to be appropriate for use in a wide variety of practice settings. The guidelines focus on care processes and interventions that are primarily undertaken in the non-acute setting ie they do not deal with highly technical procedural interventions such as renal dialysis.

1.7 Use of the Guidelines

Guidelines are systematically generated statements which are designed to assist health care clinicians and consumers to make informed decisions about appropriate treatment in specific circumstances (Field and Lohr, 1990).

Guidelines are not applicable to all people in all circumstances at all times. The recommendations contained in these guidelines are a general guide to appropriate practice and are based on the best information available at the time of their development. The clinical guidelines should be interpreted and applied on an individual basis in the light of the health care practitioner's clinical experience, common sense, and the personal judgments of consumers about what is appropriate for, and acceptable to them.

1.8 Review date

New information on type 2 diabetes is continually and rapidly becoming available. The Project Management Team and Steering Committee recommend that these guidelines are reviewed and revised no more than three years following their publication.

1.9 Economic analysis

Assessment of economic impact ie analysing the cost implications of recommendations has become a mandatory component of guideline development.

1.10 Socio economic impact

The Expert Advisory Groups for each guideline were encouraged to adopt a framework that is recommended by the NHMRC to identify, appraise and collate evidence of the impact of socioeconomic position and other markers of interest eg income, education, occupation, employment, ethnicity, housing, area of residence, lifestyle, gender.

2.0 The Guideline Development Process

2.1 Organisational structure and staffing

The organisational structure of the Guideline Development Project (Figure 1) comprises:

- A Steering Committee
- Project Management Team
- Expert Advisory Groups
- Guidelines Assessment Register (GAR) Consultant
- Research Officers
- Research team

The Steering Committee consists of a representation from each of the Consortium members, the Guideline Project's medical advisor, and the Department of Health and Ageing.

The Project Management Team. The Diabetes Unit (TDU), at the Australian Health Policy Institute, University of Sydney was subcontracted by DA Ltd to manage the project on behalf of the Consortium. The Diabetes Unit provides guidance on methods, technical support, data management, co-ordinates the input of the Expert Advisory Groups (EAGs) and supervises the project staff on a daily basis. The Project Management Team consists of the Director of TDU, the CEO of Diabetes Australia and the Medical Advisor.

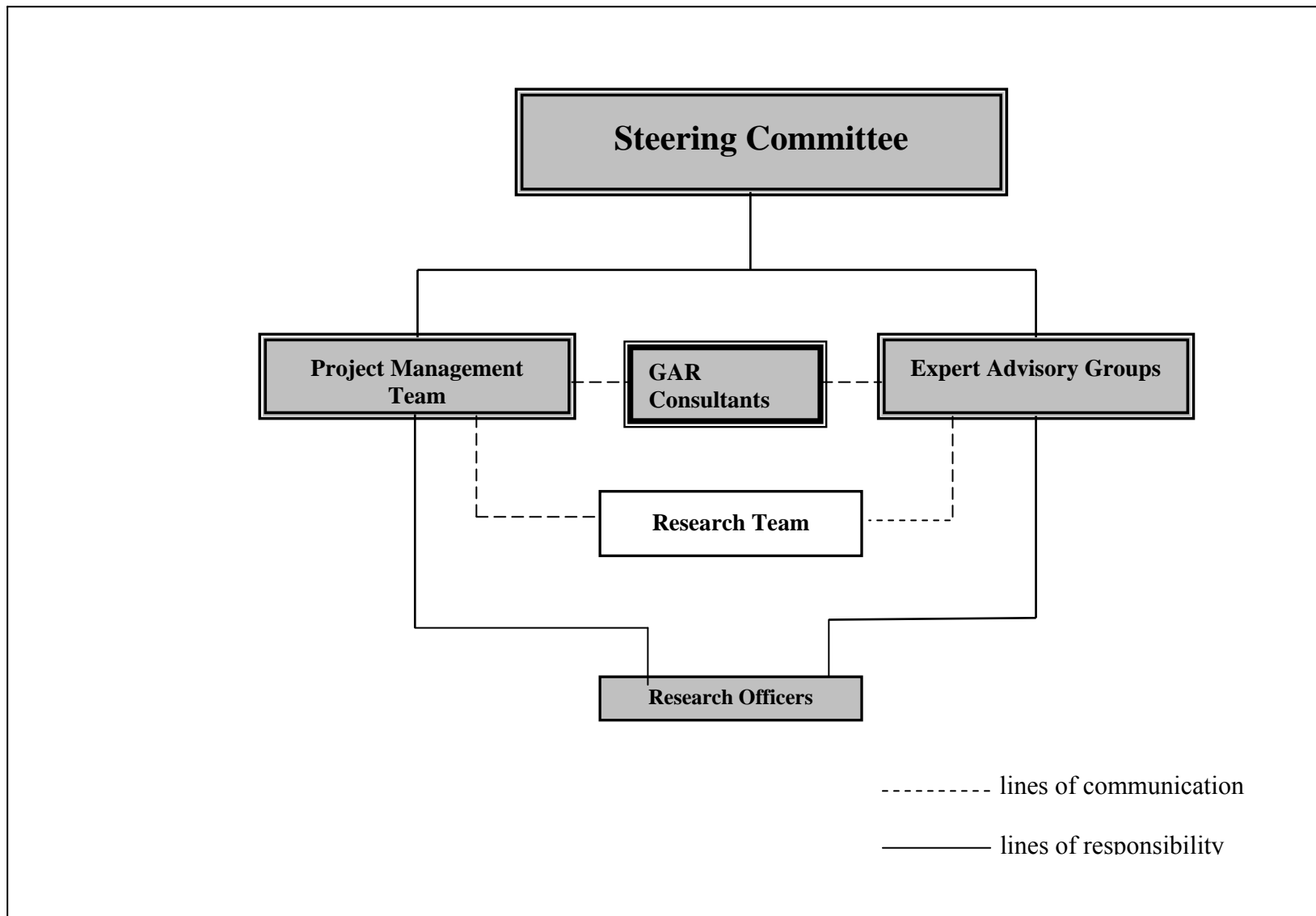
Expert Advisory Groups (EAGs) were established for each of the four guideline areas. They have a core composition of a consumer, a general practitioner, content experts, a representative of the Australian Diabetes Society and the Australian Diabetes Educators Association, and other representation as appropriate to the content area. Hence, the membership of each EAG varies slightly according to the nature of each guideline and is therefore shown at the beginning of each individual guideline.

Guidelines Assessment Register (GAR) consultant. The NHMRC nominated a GAR consultant for each guideline to provide guideline developers with support in relation to utilising evidence-based findings and applying the NHMRC criteria. Specifically, the GAR consultants provided advice on evaluating and documenting the scientific evidence and developing evidence-based recommendations based on the scientific literature and NHMRC procedures.

Research Officers were recruited or seconded from a variety of research and health care disciplines and given additional training to conduct the literature searches, and review, grade and synthesise the evidence under the supervision of the Senior Research and Project Manager, Dr Seham Girgis, the Chairs of the EAGs and the Project Management Team.

Research Team refers to the Project Director, Senior Project Manager, and Research Officers.

Figure 1: Organisational Structure



3.0 Methods

3.1 Development of Protocols

At the beginning of the project, a Methods Manual was developed for the EAGs and project staff. The Manual was based on the NHMRC *Standards and procedures for externally developed guidelines* (NHMRC, 2007) and the series of handbooks on the development, implementation and evaluation of clinical practice guidelines published by the NHMRC from 2000–03. The NHMRC Standards and procedures document (NHMRC, 2007) introduced an extended set of levels of evidence and an approach to assessing a body of evidence and grading of recommendations. These standards and handbooks have superseded *A guide to the development, implementation and evaluation of clinical practice guidelines* (NHMRC, 1999), which formed the basis of the initial suite of NHMRC guidelines for type 2 diabetes.

The NHMRC has introduced a requirement for guidelines to consider issues related to cost-effectiveness and socioeconomic impact. Two publications in the NHMRC toolkit for developing clinical practice guidelines have been used to address these issues - *How to compare the costs and benefits: evaluation of the economic evidence* (NHMRC, 2001) and *Using socioeconomic evidence in clinical practice guidelines* (NHMRC, 2003).

The Methods Manual developed for the project contains definitions, procedures and protocols, descriptions of study type classifications, checklists and examples of steps and methods for critical appraisal of the literature. It also includes the revised level of evidence and the minimum requirements for formulating NHMRC evidence based guidelines.

3.2 Guideline Development Process

From the literature and expert opinion the following steps were identified as central to the process of identifying sources of rigorously objective, peer reviewed information and reviewing, grading, and synthesising the literature to generate guideline recommendations:

1. Define specific issues and generate clinically relevant questions to guide the literature searches for each guideline topic
2. Search the literature systematically using a range of databases and search strategies
3. Sort the search yield on the basis of relevance to the topic area and scientific rigour
4. Document the search strategy and the search yield
5. Critically review, grade and summarise the evidence
6. Assess the body of evidence according to the published NHMRC standard and formulate guideline statements and recommendation/s in accordance with the evidence
7. Formulate the evidence statements and recommendations
8. Conduct quality assurance throughout all these steps

Step 1: Defining issues and questions to direct the literature searches

Each EAG was asked to define key issues for their guideline content area and to generate a set of questions focussing on clinically relevant issues to guide the literature searches. These critical clinical issues also formed the focus of each guideline recommendation and accompanying evidence statements. Some EAGs used existing diabetes and related guidelines and protocols to help identify aspects of care and currently recommended practice which needed to be confirmed, modified, or refuted and replaced with accurate new information. A generic framework for each clinical guideline area was agreed on to assist the EAGs to clarify these issues and centred on issues such as:

- What are the key treatment/management issues for this area?
- What anthropometric, clinical or behavioural parameters need to be assessed?
- Should everyone be assessed or are there particular risk factors which warrant selective testing or preventative treatment?
- What assessment techniques should be used?
- How often should the assessment be done?
- How should the results be interpreted?
- What action should follow from the results (if abnormal) eg management, further investigation, referral?
- What are the overall costs of using the intervention? (particularly in relation to changes in costs if changes to management are recommended)
- What is the impact of socioeconomic position and other markers of interest eg. income, education, occupation, employment, ethnicity, housing, area of residence, lifestyle, gender.

EAGs also were advised to frame each question using the ‘**PICO**’ elements as follows: **P**opulation **or** **P**roblem; **I**ntervention (for a treatment intervention question), **or** **I**ndicator or exposure (for a prognosis or aetiology or question), **or** **I**ndex test (for a diagnostic accuracy question); **C**omparator; and **O**utcome

The resulting questions developed by each EAG are presented at the beginning of each guideline and again in the Search Strategy and Yield Table.

Step 2: Searching the literature

NHMRC clinical practice guidelines are required to be based on systematic identification and synthesis of the best available scientific evidence (NHMRC, 2007). A number of systematic

strategies were used in this project to identify and assess scientific information from the published literature. The search strategies were designed to reduce bias and ensure that most of the relevant data available on type 2 diabetes were included in the present review and were similar to those detailed in the Cochrane Collaboration Reviewers Handbook (Higgins, 2006). Several strategies were used to identify potentially relevant studies and reviews from the literature such as :

Electronic Databases

Searches were carried out using the following databases:

- Medline
- Cochrane Library: Databases of Systematic Reviews, DARE, Controlled Trials Register, Central, HTA.
- Additional databases searched where indicated including:
 - Embase
 - Cinahl
 - Psycho Info
 - Eric
 - Other (where appropriate) such as Internet, Expert sources, Hand searching of reference lists at the end of relevant articles.

Key words

The key words (MeSH terms and some free text terms) used when searching these electronic databases are presented in detail in the Search Strategy and Yield Table at the end of each guideline topic. The EAGs limited their searches through a number of methods including:

- specification of temporal constraints (eg 1999-2008 for the updated guideline)
- language constraints (English only)
- where there were overwhelming amounts of literature or if there was a large volume of poor quality research, some groups imposed limits by experimental design to exclude the less rigorous forms of research

Details of specific inclusion criteria for each EAG are also presented, together with the key words, at the end of each individual guideline.

Consultation with colleagues

The EAGs were encouraged to gather relevant information/articles from other experts and colleagues. The Project Management Team collated the questions developed by each EAG to direct the literature searches and highlight overlapping questions and requested EAGs and Research Officers to send any articles identified as applicable to other guideline topics to the appropriate EAG.

Step 3: Sorting the search yield

Two or more members of each EAG were responsible for sorting through the search results by

scanning the lists of titles and abstracts generated by the electronic database searches, highlighting potentially relevant articles and requesting printed full articles. Full articles were retrieved and those which were relevant were assessed for quality. Articles were considered relevant if they provided direct or indirect information addressing one or more of the specified 'clinical issues' questions and were applicable to diabetes care or prevention in Australia.

Sorting according to study design

Articles with original data were sorted according to study design. Articles with the most rigorous experimental designs were reviewed in the first instance. Articles conducted to other study designs were included if they added new information not found in the papers of highest levels of evidence. Relevant papers were sorted as follows:

- Meta-analysis, systematic review of randomised controlled trials (interventions)
- Randomised controlled trials (RCT)
- Cohort studies
- Case control studies
- Case series, pre-post or post studies

Exclusion criteria

Articles were not included for review if it was apparent that their relevance to formulating a guideline recommendation was non-existent or negligible. Examples of reasons for non review included criteria such as:

- Studies of inappropriate patient population(s) for the question being addressed (epidemiology, specific diet)
- Hypothesis/mechanism/in vitro study/animal studies
- Genetic studies that are clinically inapplicable
- Non-systematic reviews which presented the author's opinion rather than evidence

Step 4: Documenting the search strategy and its yield

The search strategy (terms and limits) and yield were documented and are available for viewing in a table at the end of each guideline. In brief, the Search Strategy and Yield Table recorded details about the:

1. Questions being investigated
2. Electronic databases searched
3. MeSH terms and key words used to search the database
4. Methods for limiting the searches
5. Number of articles identified by each search
6. Number of articles relevant from that search

7. Number of relevant articles identified through other search processes
8. Number of articles obtained for review
9. Number of relevant articles which were systematic reviews, RCTs or well designed population based studies, quasi-experimental and other (these were documented in the tables according to the updated NHMRC Evidence Levels I –IV .
10. Number of articles reviewed
11. Highest level of evidence found for each question

Step 5. Critically reviewing, grading and summarising the evidence

All relevant articles were reviewed and critically assessed using checklists recommended by the NHMRC (2000) (NHMRC, 2000a; NHMRC, 2000b). The NHMRC checklist sets out an explicit standardised approach to reviewing and incorporating scientific evidence into clinical practice guidelines.

In addition, Research Officers were asked to construct tables to summarise extraction of data and to provide a brief summary of the key results for each article.

Overall assessment of individual studies

At the conclusion of reviewing each article, the reviewers rated the evidence in a summary form as shown in (Table 1) using the following criteria:

- *Levels of evidence*
The ‘interim’ NHMRC levels of evidence (NHMRC, 2007) was used in this project to assess levels of evidence for a range of study designs (Appendix 1).
- *Quality of evidence*
- *Magnitude of effect*
- *Relevance of evidence*

Criteria for quality of evidence, magnitude of effect, and relevance of evidence were based on those provided by the NHMRC (2000a &b). These criteria are presented in Appendix 2.

Table 1: Example of an Overall Assessment Report

Assessment Category	Rating			
	Value	Low	Medium	High
Level of evidence				
Quality of evidence				
Magnitude of effect				
Relevance				

These assessments were then used in the evidence tables which summaries basic information about **Each Study** reviewed, including an overall assessment of the evidence (Table 2).

Table 2. Example of an evidence table with overall study assessment

Author	Evidence				
	<i>Level of Evidence</i>		<i>Quality Rating</i>	<i>Magnitude of effect Rating</i>	<i>Relevance Rating</i>
	<i>Level</i>	<i>Study Type</i>			
Author X(1999)	III-2	Cohort	High	Low	High

Step 6. Assessing the body of evidence and formulating guideline evidence statements and recommendations

In addition to considerations of the rigour of the research providing the evidence (Tables 1 and 2), principles for formulating guideline evidence statements and recommendations were derived consistent with the NHMRC recommended standard *'The NHMRC Standards for External Developers of Guidelines'* (NHMRC, 2007).

For each identified clinical question, evidence statements are based on an assessment of all included studies for that question (**the Body of Evidence**). The NHMRC considers the following five components in judging the overall body of evidence (NHMRC, 2007) as specified in the *'NHMRC Body of Evidence Matrix'* (Table 3):

- The evidence base, in terms of the number of studies, level of evidence and quality of studies (risk of bias).
- The consistency of the study results.
- The potential clinical impact of the proposed recommendation.
- The generalisability of the body of evidence to the target population for the guideline.
- The applicability of the body of evidence to the Australian healthcare context.

Based on the body of evidence, recommendation/s were formulated to address each of the identified clinical questions for the area. Recommendation/s were written as an action statement.

Principles for formulating the guideline recommendation/s

In the course of the face to face meetings of the EAGs, and from published sources, principles were identified re-affirming the need for guideline recommendations to:

- be developed systematically and objectively by synthesising the best available evidence

- have potential to improve health and related outcomes whilst minimising possible harms
- be clinically relevant and feasible
- take account of ethical considerations, and acceptability to patients
- centre on interventions which are accessible to those who need them
- propose activities within the scope of the role of those expected to use the guidelines eg interventions which could be expected to be conducted in routine general practice

Grading of recommendation/s

The grading of each recommendation reflects the strength of the recommendation (Table 4) and is based on ‘The *NHMRC Standards for External Developers of Guidelines* (NHMRC, 2007).

In face-to-face meetings, the EAGs, initially graded each of the five components of the NHMRC Body of Evidence Matrix (Table 3) for each recommendation and then determined the overall grade for the body of evidence by summing the individual component grades (Appendix 3).

Cost effectiveness analyses are usually based on modelling and therefore cannot be evaluated using the NHMRC ‘Body of Evidence Matrix’. Hence, cost-effectiveness recommendations were not graded.

Table 3: NHMRC Body of Evidence Matrix

Component	A	B	C	D
	Excellent	Good	Satisfactory	Poor
Evidence base	several level I or II studies with low risk of bias	one or two level II studies with low risk of bias or a SR/multiple level III studies with low risk of bias	level III studies with low risk of bias, or level I or II studies with moderate risk of bias	level IV studies, or level I to III studies with high risk of bias
Consistency	all studies consistent	most studies consistent and inconsistency may be explained	some inconsistency reflecting genuine uncertainty around clinical question	evidence is inconsistent
Clinical impact	very large	substantial	moderate	slight or restricted
Generalisability	population/s studied in body of evidence are the same as the target population for the guideline	population/s studied in the body of evidence are similar to the target population for the guideline	population/s studied in body of evidence different to target population for guideline but it is clinically sensible to apply this evidence to target population ³	population/s studied in body of evidence different to target population and hard to judge whether it is sensible to generalise to target population
Applicability	directly applicable to Australian healthcare context	applicable to Australian healthcare context with few caveats	probably applicable to Australian healthcare context with some caveats	not applicable to Australian healthcare context

Table 4: Definition of NHMRC grades of recommendation

Grade of recommendation	Description
A	Body of evidence can be trusted to guide practice
B	Body of evidence can be trusted to guide practice in most situations
C	Body of evidence provides some support for recommendation(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution

Step 7. Articulate the guidelines

For each guideline, clinical questions identified by EAGs are addressed in separate sections in a format presenting:

- *Recommendation(s)* - including grading
- *Practice Point (s)* – including experts’ consensus in absence of gradable evidence
- *Evidence Statements* - supporting the recommendations
- *Background* - to issues for the guideline
- *Evidence* - detailing and interpreting the key findings
- *Evidence tables* - summarising the evidence ratings for the articles reviewed
- At the end of the guideline, references were provided
 - *Evidence references*
 - *General references*
 - *Search Strategy and Yield Tables* documenting the identification of the evidence sources

To ensure consistency between the guidelines, a template was designed.

Step 8. Methods for Quality Assurance across the project

To ensure optimal accuracy and consistency within and between guideline areas, the Project Management Team conducted a range of quality assurance activities throughout the project:

Quality Assurance - Procedures and protocols

- the provision of a Methods Manual which provide written instructions to the Chairs of EAGs and research staff identifying the steps and processes to be followed
- the provision to the EAGs of a selection of key published resource material relevant to the development of the guidelines (NHMRC tool kit 2000-2003; NHMRC, 2007).

- specification and training of research staff on the search process

Quality Assurance - Methods

- the appointment of a Senior Research Officer to the Project Management Team to advise on research methods, and provide a resource and support service to the research staff
- the establishment of a Methods Advisory Group
- the development of questions based on key clinical issues for each guideline topic to focus and guide the literature searches and the formulation of the guideline recommendations. As previously indicated, these are listed at the beginning of each guideline and the Search Strategy and Yield Table at the end of the guideline
- the Project Management Team collated and reviewed the questions and undertook a Delphi - like process with the Chairs of EAGs to refine these questions. In addition, all EAGs and the Project Management Team reviewed the combined questions during one of the three face to face meetings.
- the design and provision to Chairs of EAGs and Research Officers of standardised forms documenting aspects of the search strategy used, the search yield, and the inclusion and exclusion of articles for review. A completed Search Strategy and Yield Table follows each guideline topic
- the Senior Research Officer reviewed:
 - all search terms used to ensure that the searches were comprehensive and that the approach was similar across groups
 - the documentation of the search process
- the GAR Consultants worked closely with the Senior Research Officer and EAGs. The GAR Consultants provided advice on evaluating and documenting the scientific evidence, developing evidence-based recommendations based on the scientific literature, and NHMRC procedures.
- double culling of the search yield for each guideline topic by project staff and members of the EAG
- double reviewing of a sample of completed reviews for each guideline topic by the Senior Research Officer or an experienced Research Officer, or by a member of the relevant EAG.
- review of the completed recommendations and written description of the literature review for each guideline area was undertaken to check for:
 - appropriate use of references
 - accurate application of evidence ratings
 - congruence between the recommendations and evidence statements
 - consistency between recommendations
 - clarity of the literature review findings

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APPENDICES

APPENDIX 1

NHMRC Evidence Hierarchy: designations of 'levels of evidence' according to type of research question (NHMRC 2007)

Level	Intervention	Diagnostic accuracy	Prognosis	Aetiology	Screening Intervention
I	A systematic review of level II Studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among consecutive persons with a defined clinical presentation	A prospective cohort study	A prospective cohort study	A randomised controlled trial
III-1	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among non-consecutive persons with a defined clinical presentation	All or none	All or none	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)
II-2	A comparative study with concurrent controls: <ul style="list-style-type: none"> ▪ Non-randomised, experimental trial ▪ Cohort study ▪ Case-control study ▪ Interrupted time series with a control group 	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst persons in a single arm of a randomised controlled trial	A retrospective cohort study	A comparative study with concurrent controls: <ul style="list-style-type: none"> ▪ Non-randomised, experimental trial ▪ Cohort study ▪ Case-control study
III-3	A comparative study without concurrent controls: <ul style="list-style-type: none"> ▪ Historical control study ▪ Two or more single arm study ▪ Interrupted time series without a parallel control group 	Diagnostic case-control study	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: <ul style="list-style-type: none"> ▪ Historical control study ▪ Two or more single arm study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard)	Case series, or cohort study of persons at different stages of disease	A cross-sectional study or case series	Case series

(Source: NHMRC 2007)

Study Assessment Criteria

I. Study quality criteria

Systematic reviews

1. Were the questions and methods clearly stated?
2. Is the search procedure sufficiently rigorous to identify all relevant studies?
3. Does the review include all the potential benefits and harms of the intervention?
4. Does the review only include randomised controlled trials?
5. Was the methodological quality of primary studies assessed?
6. Are the data summarised to give a point estimate of effect and confidence intervals?
7. Were differences in individual study results adequately explained?
8. Is there an examination of which study population characteristics (disease subtypes, age/sex groups) determine the magnitude of effect of the intervention?
9. Were the reviewers' conclusions supported by data cited?
10. Were sources of heterogeneity explored?

Randomised controlled trials

1. Were the setting and study subjects clearly described?
2. Is the method of allocation to intervention and control groups/sites independent of the decision to enter the individual or group in the study ?
3. Was allocation to study groups adequately concealed from subjects, investigators and recruiters including blind assessment of outcome?
4. Are outcomes measured in a standard, valid and reliable way?
5. Are outcomes measured in the same way for both intervention and control groups?
6. Were all clinically relevant outcomes reported?
7. Are factors other than the intervention e.g. confounding factors, comparable between intervention and control groups and if not comparable, are they adjusted for in the analysis?
8. Were >80% of subjects who entered the study accounted for at its conclusion?%
9. Is the analysis by intention to intervene (treat)?
10. Were both statistical and clinical significance considered?
11. Are results homogeneous between sites? (Multi-centre/multi-site studies only).

Cohort studies

1. Are study participants well-defined in terms of time, place and person?
2. What percentage (%) of individuals or clusters refused to participate?
3. Are outcomes measured in a standard, valid and reliable way?
4. Are outcomes measured in the same way for both intervention and control groups?
5. Was outcome assessment blind to exposure status?
6. Are confounding factors, comparable between the groups and if not comparable, are they adjusted for in the analysis?
7. Were >80% of subjects entered accounted for in results and clinical status described?
8. Was follow-up long enough for the outcome to occur
9. Was follow-up complete and were there exclusions from the analysis?
10. Are results homogeneous between sites? (Multicentre/multisite studies only).

Case-control studies

1. Was the definition of cases adequate?
2. Were the controls randomly selected from the source of population of the cases?
3. Were the non-response rates and reasons for non-response the same in both groups?
4. Is possible that over-matching has occurred in that cases and controls were matched on factors related to exposure?
5. Was ascertainment of exposure to the factor of interest blinded to case/control status?
6. Is exposure to the factor of interest measured in the same way for both case and control groups in a standard, valid and reliable way (avoidance of recall bias)?
7. Are outcomes measured in a standard, valid and reliable way for both case and control groups?
8. Are the two groups comparable on demographic characteristics and important potential confounders?

- and if not comparable, are they adjusted for in the analysis?
9. Were all selected subjects included in the analysis?
 10. Was the appropriate statistical analysis used (matched or unmatched)?
 11. Are results homogeneous between sites? (Multicentre/multisite studies only).

Diagnostic accuracy studies

1. Has selection bias been minimised
2. Were patients selected consecutively?
3. Was follow-up for final outcomes adequate?
4. Is the decision to perform the reference standard independent of the test results (ie avoidance of verification bias)?
5. If not, what per cent were not verified?
6. Has measurement bias been minimised?
7. Was there a valid reference standard?
8. Are the test and reference standards measured independently (ie blind to each other)
9. Are tests measured independently of other clinical and test information?
10. If tests are being compared, have they been assessed independently (blind to each other) in the same patients or done in randomly allocated patients?
11. Has confounding been avoided?
12. If the reference standard is a later event that the test aims to predict, is any intervention decision blind to the test result?

(Sources: adapted from NHMRC1999, NHMRC 2000a, NHMRC 2000b, Liddle et al 96; Khan et 2001)

Study quality – Rating

The following was used to rate the quality of each study against the study type criteria listed above.

High: all or all but one of the criteria were met

Medium: 2 or 3 of the criteria were not met

Low: 4 or more of the criteria were not met

II. Classifying magnitude of the effect

Ranking	Statistical significance		Clinical importance of benefit
High	Difference is statistically significant	AND	There is a clinically important benefit for the full range of estimates defined by the confidence interval.
Medium	Difference is statistically significant	AND	The point estimate of effect is clinically important BUT the confidence interval includes some clinically unimportant effects
Low	Difference is statistically significant OR Difference is not statistically significant (no effect) or shows a harmful effect	AND AND	The confidence interval does not include any clinically important effects The range of estimates defined by the confidence interval includes clinically important effects.

(Source: adapted from the NHMRC classification (NHMRC 2000b))

III. Classifying the relevance of the evidence

Ranking	Relevance of the evidence
High	Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival <i>Or</i> Evidence of an effect on a surrogate outcome that has been shown to be predictive of patient-relevant outcomes for the same intervention
Medium	Evidence of an effect on proven surrogate outcomes but for a different intervention <i>Or</i> Evidence of an effect on proven surrogate outcomes but for a different intervention and population
Low	Evidence confined to unproven surrogate outcomes.

(Source: adapted from the NHMRC classification (NHMRC 2000b))

NHMRC Evidence Statement

Key question(s):		Evidence table ref:
1. Evidence base <i>(number of studies, level of evidence and risk of bias in the included studies)</i>		
	A	Several Level I or II studies with low risk of bias
	B	one or two Level II studies with low risk of bias or SR/multiple Level III studies with low risk of bias
	C	Level III studies with low risk of bias or Level I or II studies with moderate risk of bias
	D	Level IV studies or Level I to III studies with high risk of bias
2. Consistency <i>(if only one study was available, rank this component as 'not applicable')</i>		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact <i>(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)</i>		
	A	Very large
	B	Moderate
	C	Slight
	D	Restricted
4. Generalisability		
	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability		
	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation))*

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EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base		
2. Consistency		
3. Clinical impact		
4. Generalisability		
5. Applicability		

Indicate any dissenting opinions

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RECOMMENDATION

What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.

GRADE OF RECOMMENDATION

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IMPLEMENTATION OF RECOMMENDATION	
<i>Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.</i>	
Will this recommendation result in changes in usual care?	YES
	NO
Are there any resource implications associated with implementing this recommendation?	YES
	NO
Will the implementation of this recommendation require changes in the way care is currently organised?	YES
	NO
Are the guideline development group aware of any barriers to the implementation of this recommendation?	YES
	NO