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OREGON HEALTH AND SCIENCE UNIVERSITY
OFFICE OF CLINICAL INTEGRATION AND EVIDENCE-BASED PRACTICE

Evidence-Based Practice Summary
Appropriate Interval for Diabetic Retinopathy Screening

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BACKGROUND

Diabetic retinopathy (DR) commonly complicates diabetes mellitus and meets the World Health Organization (WHO) criteria of suitability for screening. DR is a major cause of vision loss worldwide. Approximately one third of people with diabetes have diabetic retinopathy, and a third of those with diabetic retinopathy may have sight-threatening diabetic retinopathy. The prevalence of diabetic retinopathy is projected to increase in the coming decades. The number of Americans aged 40 years or older with diabetic retinopathy and sight-threatening diabetic retinopathy is predicted to triple by 2050. The natural history of diabetic retinopathy has recognizable stages. Major risk factors for developing diabetic retinopathy include duration of diabetes, severity of hyperglycemia, hypertension and dyslipidemia. Once sight-threatening diabetic retinopathy is present, the progression is rapid and complications are unpredictable. Twenty years after diagnosis, almost all people with Type 1 diabetes mellitus and 60% of people with Type 2 diabetes mellitus will have some degree of diabetic retinopathy.(Echouffo-Tcheungui 2013)

Several national and international agencies recommend annual screening and early treatment for sight-threatening diabetic retinopathy lesions. However, given the increasing demand for ophthalmology services and costs associated with ophthalmic care, an optimal screening interval has been debated, with some suggesting the adoption of longer intervals for patients with no background retinopathy, with more frequent surveillance examinations for those at high risk Consequently, screening low-risk individuals too frequently implies an inefficient use of limited healthcare resources. (Echouffo-Tcheungui 2013)

ASK THE QUESTION

Question 1: In patients ages 18-75 with diabetes, what is the most appropriate screening interval for a diabetic eye exam?

DATE: August 2017

SEARCH FOR EVIDENCE

Databases included Ovid MEDLINE, MEDLINEinprocess, the Cochrane Central Register of Controlled Trials (CCRCT) & Cochrane Database of Systematic Reviews (CDSR).

See Appendix B for full search strategy.

CRITICALLY ANALYZE THE EVIDENCE

The literature search resulted in more than 300 articles that analyzed screening for diabetic retinopathy (DR). Only five of these 300 considered timing and interval of screening. The five studies included systematic reviews and relevant modelling studies from 2010-2017.

1. Screening Intervals for DR: Two systematic reviews examined appropriate screening intervals for DR. The first systematic review (Echouffo-Tchengui 2013), reviewed the relationship between screening intervals for DR and the incidence of vision loss in both screening and modelling studies. There was high heterogeneity in the screening studies, but an overall observed tendency that 2-year screening intervals were not associated with higher incidences of vision loss in patients with no DR at baseline. The aggregated evidence from both the natural history and cost-effectiveness modelling studies favor a screening interval >1 year, but <2 years for people without baseline DR. The second systematic review (Taylor-Phillips 2016) sought to determine whether the recommended screening interval for diabetic retinopathy (DR) in the UK can safely be extended beyond 1 year. There was also heterogeneity amongst the 29 studies included in the review, but the studies broadly supported extending screening intervals beyond 1 year for patients with Type 2 Diabetes at low risk of progression to DR, and no background retinopathy. Three studies concluded that annual screening remains the most cost-effective. The included risk stratification models showed promise in providing tailored screening intervals based on individual risk factors, but none had been externally validated.
   Overall Level of Evidence: Low

PICO Question: In patients ages 18-75 with diabetes, what is the most appropriate screening interval for diabetic eye exam?						Lower Quality Rating if: ☒ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or*
Outcome: screening interval						
Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*	
Total # of Studies: 2 # of Systematic Reviews: 2 Click here to enter text.						
Echouffo-Tcheugui et al	To systematically	Systematic Review	25 studies (15 screening studies, 3	**Screening Studies**: In evaluations of diabetic retinopathy screening	Study Limitations = ☐ None	

(2013) *Diabetic Medicine*	review the published literature on the relationship between screening intervals for diabetic retinopathy and the incidence of visual loss.		natural history modelling studies, 7 economic modelling studies) 115977 participants	programmes, the appropriate screening interval ranged from one to four years, in people with no retinopathy at baseline. Despite study heterogeneity, the overall tendency observed in these programmes was that 2-year screening intervals among people with no diabetic retinopathy at diagnosis were not associated with high incidence of sight-threatening diabetic retinopathy **Modelling Studies (both economic and natural history):** The aggregated evidence from both the natural history and cost-effectiveness models favors a screening interval >1 year, but ≤2 years. Such an interval would be appropriate, safe and cost-effective for people with no diabetic retinopathy at diagnosis, while screening intervals ≤ l year would be preferable for people with pre-existing diabetic retinopathy. A 2-year screening interval for people with no sight threatening diabetic retinopathy at diagnosis may be safely adopted. For patients with pre-existing diabetic retinopathy, a shorter interval ≤ 1 year is warranted.	***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☒ Methods and/or results were inconsistent across studies	*outcomes varied)* ☐ Studies are indirect *(PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)* ☒ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)* ☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)* <u>Increase Quality Rating if:</u> ☐ Large Effect ☐ Dose-response gradient ☐ Plausible confounders or other biases increase certainty of effect Quality (certainty) of evidence for studies as a whole:
Taylor-Phillips, S., et al. (2016). *British Journal of Ophthalmology*	To determine whether the recommended screening interval for diabetic retinopathy (DR) in the UK can safely be extended beyond 1	Systematic Review	29 studies	Studies broadly supported extending screening intervals beyond 1 year for patients with Type 2 Diabetes at low risk of progression to DR, and no background retinopathy. Three studies concluded that annual screening remains the most cost-effective. Risk stratification models show promise in providing tailored screening intervals based on individual risk factors, but	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☒ Methods and/or results were inconsistent across	

	year.			none have been externally validated.	studies	☐ High ☐ Moderate ☒ Low ☐ Very Low

The GRADE criteria were used to evaluate the quality of evidence presented in research articles reviewed during the development of this guideline. For more detailed information, see Appendix A.

Modeling Studies Summaries			
Author/Date	*Purpose of Study*	*Study Design & Methods*	*Outcomes*
Day et al., 2016, *Computers in Biology and Medicine*	To examine the effect of changes to screening interval on the incidence of vision loss in a simulated cohort of Veterans with diabetic retinopathy (DR).	Simulated randomized controlled trial with a hybrid agent-based/discrete event simulation which incorporates a population of simulated Veterans – using abstracted data from a retrospective cohort of real-world diabetic Veterans – with a discrete event simulation (DES) eye clinic at which it seeks treatment for DR and compared vision loss under varying screening policies in a simulated population of 5000 Veterans over 50 independent ten-year simulation runs for each group.	Diabetic Retinopathy associated vision loss increased as the screening interval was extendedfrom one to five years ($p<0.0001$). This increase was concentrated in the third year of the screening interval ($p<0.01$). There was no increase in vision loss associated with increasing the screening interval from one year to two years ($p=0.98$).
Group et al., 2017, *New England Journal of Medicine*	In patients who have had type 1 diabetes for 5 years, current recommendations regarding screening for diabetic retinopathy include annual dilated retinal examinations to detect proliferative retinopathy or clinically significant macular edema, both of which require timely intervention to preserve vision. During 30 years of the Diabetes Control and Complications Trial (DCCT) and its longitudinal follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) study, retinal photography was performed at intervals of 6 months to 4 years to develop a rational screening frequency for retinopathy.	Markov modeling was used to determine the likelihood of progression to proliferative diabetic retinopathy or clinically significant macular edema in patients with various initial retinopathy levels (no retinopathy or mild, moderate, or severe nonproliferative diabetic retinopathy). The models included recognized risk factors for progression of retinopathy.	These cumulative-incidence functions provided the estimated probabilities of progression from intermediate states 1 through 4 to state 5 retinopathy over increasing screening intervals. Thus, an interval could be chosen with the goal of limiting this probability to approximately 5%. For example, patients in state 1 had only a 2.9% chance of progression to state 5 during the next 4 years, and those in state 2 had only a 3.7% chance of doing so by 3 years. The probabilities of progression to state 5 were 6.6% over 6 months in patients with state 3 and 14.4% over 3 months in patients with state 4. In patients with state 4 retinopathy, monitoring that was more frequent than quarterly would be necessary to reduce this probability to below 14.4%. This suggests that a practical schedule could use screening intervals of 4 years, 3 years, 6 months, and 3

			months for the four retinopathy states, respectively.
Scalon et al., 2015, *Health Technology Assessment*	To determine whether personalized screening intervals are cost-effective	Risk factors were identified in Gloucestershire, UK using survival modelling. A probabilistic decision hidden (unobserved) Markov model with a misgrading matrix was developed. This informed estimation of lifetime costs and quality-adjusted life-years (QALYs) in patients without STDR. Two personalized risk stratification models were employed: two screening episodes (SEs) (low, medium or high risk) or one SE with clinical information (low, medium-low, medium-high or high risk). The risk factor models were validated in other populations. Data were obtained in Gloucestershire from 12,790 people with diabetes with known risk factors to derive the risk estimation models, from 15,877 people to inform the uptake of screening and from 17,043 people to inform the health-care resource-usage costs.	The rate of progression to STDR was 5 per 1000 person-years (PYs) in the lowest decile of risk and 75 per 1000 PYs in the highest decile. In the absence of personalised risk stratification, the most cost-effective screening interval was to screen all patients every 3 years, with a 46% probability of this being cost-effective at a 30,000 per QALY threshold. Using either risk stratification models, screening patients at low risk every 5 years was the most cost-effective option, with a probability of 99-100% at a 30,000 per QALY threshold. For the medium-risk groups screening every 3 years had a probability of 43-48% while screening high-risk groups every 2 years was cost-effective with a probability of 55-59%.

The two published clinical guidelines were evaluated for this review using the **University of Pennsylvania's Center for Evidence-Based Practice Trustworthy Guideline rating scale.** The scale is based on the Institute of Medicine's "Standards for Developing Trustworthy Clinical Practice Guidelines" (IOM), as well as a review of the AGREE Enterprise and Guidelines International Network domains.

Guideline Issuer	International Council of Ophthalmology 2017	American Academy of Ophthalmology 2016
1. Transparency	C	A
2. Conflict of interest	NR	A
3. Development group	NR	B
4. Systematic Review	C	B
5. Supporting evidence	C	A
6. Recommendations	C	A
7. External Review	C	A

DATE: August 2017

8. Currency and updates	B	A

See appendix C for full description of the Trustworthy Guideline grading system.

Guideline Recommendations:

In 2017, the **International Council of Ophthalmology** released an updated guideline for diabetic eye care. Recommendations are given based on the resources available for a given setting, and are noted below:

Table 2a. Re-examination and Referral Recommendations Based on International Classification of Diabetic Retinopathy* and Diabetic Macular Edema for High Resource Settings.

Diabetic Retinopathy (DR)		
Classification	**Re-examination Or next screening schedule**	**Referral to Ophthalmologist**
No apparent DR, mild nonproliferative DR and no DME	Re-examination in 1-2 year	Referral not required
Mild nonproliferative DR	6-12 months	Referral not required
Moderate nonproliferative DR	3-6 months	Referral required
Severe nonproliferative DR	< 3-months	Referral required
PDR	< 1 month	Referral required
Diabetic Macular Edema (DME)		
Classification	**Re-examination Or next screening schedule**	**Referral to Ophthalmologist**
Noncentral-involved DME	3 months	Referral required
Central-involved DME	1 month	Referral required

* In cases where diabetes is controlled.

Table 2b. Re-examination and Referral Recommendations Based on Simplified Classification of Diabetic Retinopathy* and Diabetic Macular Edema for Low-/Intermediate Resource Settings.

Diabetic Retinopathy (DR)		
Classification	**Re-examination Or next screening schedule**	**Referral to Ophthalmologist**
No apparent DR, mild nonproliferative DR and no DME	Re-examination in 1-2 year	Referral not required
Mild nonproliferative DR	1-2 year	Referral not required
Moderate nonproliferative DR	6-12 months	Referral required
Severe nonproliferative DR	< 3 months	Referral required
PDR	< 1 month	Referral required
Diabetic Macular Edema (DME)		
Classification	**Re-examination Or next screening schedule**	**Referral to Ophthalmologist**
Noncentral-involved DME	3 months	Referral not required (referral recommended if laser resources available)
Central-involved DME	1 month	Referral required

* In cases where diabetes is controlled.

In 2016, the **American Academy of Ophthalmology** released an updated set of Diabetic Retinopathy Preferred Practice Pattern guidelines:

- Recommendation 1: People with Type 1 diabetes should have annual screenings for diabetic retinopathy beginning 5 years after the onset of their disease, whereas those with Type 2 diabetes should have a prompt examination at the time of diagnosis and at least yearly examinations thereafter. *Strong Recommendation – Good Quality Evidence*

REFERENCES

1. American Academy of Ophthalmology Retina/Vitreous Panel. Preferred Practice Pattern®Guidelines. Diabetic Retinopathy. San Francisco, CA: American Academy of Ophthalmology; 2016. Available at: www.aao.org/ppp.
2. Day et al. (2014) "Sensitivity of diabetic retinopathy associated vision loss to screening interval in an agent-based/discrete event simulation model." Computers in biology and medicine 47(1): 7-12.
3. Echouffo-Tcheugui, J. B., et al. (2013). "Screening intervals for diabetic retinopathy and incidence of visual loss: a systematic review." Diabetic Medicine 30(11): 1272-1292.
4. Group, D. E. R., et al. (2017). "Frequency of Evidence-Based Screening for Retinopathy in Type 1 Diabetes." New England Journal of Medicine 376(16): 1507-1516.
5. International Council of Opthamalogy.(2016). “Guidelines for Diabetic Eye Care.” http://www.icoph.org/downloads/ICOGuidelinesforDiabeticEyeCare.pdf.
6. Scanlon, P. H., et al. (2015). "Development of a cost-effectiveness model for optimisation of the screening interval in diabetic retinopathy screening." Health Technology Assessment (Winchester, England) 19(74): 1-116.
7. Taylor-Phillips, S., et al. (2016). "Extending the diabetic retinopathy screening interval beyond 1 year: systematic review." British Journal of Ophthalmology 100(1): 105-114.

Appendix A. GRADE criteria for rating a body of evidence on an intervention

Developed by the GRADE Working Group

Grades and interpretations:

High: Further research is very unlikely to change our confidence in the estimate of effect. Moderate: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low: Any estimate of effect is very uncertain.

Type of evidence and starting level

Randomized trial–high Observational study–low Any other evidence–very low

Criteria for increasing or decreasing level

Reductions Study quality has serious (–1) or very serious (–2) problems Important inconsistency in evidence (–1) Directness is somewhat (–1) or seriously (–2) uncertain Sparse or imprecise data (–1) Reporting bias highly probable (–1) **Increases** Evidence of association† strong (+1) or very strong (+2) †Strong association defined as significant relative risk (factor of 2) based on consistent evidence from two or more studies with no plausible confounders Very strong association defined as significant relative risk (factor of 5) based on direct evidence with no threats to validity.

Appendix B. Search Strategy

Search strategy included:

1 exp Glucose Metabolism Disorders/co [Complications] (45574)
2 exp eye/ (156307)
3 exp eye diseases/ (268442)
4 exp Vision, Ocular/ (10319)
5 2 or 3 or 4 (341001)
6 exp Mass Screening/ (81391)
7 1 and 5 and 6 (111)
8 exp Diabetes Complications/di, dg, pa, pc [Diagnosis, Diagnostic Imaging, Pathology, Prevention & Control] (25065)
9 5 and 6 and 8 (686)
10 5 and 8 (5949)
11 ((screen* or ((routin* or frequen*) adj5 (test* or exam* or visit* or consult*))) adj10 (eye or eyes or retina* or vision* or visual* or opthalm* or ophthalm* or macula*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (8369)
12 10 and 11 (715)
13 9 or 12 (950)
14 7 or 13 (966)
15 exp Diabetes Complications/ (73777)
16 5 and 6 and 15 (741)
17 14 or 16 (1009)
18 exp Preventive Health Services/ (338765)
19 exp Diabetes Mellitus/ (243719)
20 exp Eye Diseases/di, dg, pa, pc [Diagnosis, Diagnostic Imaging, Pathology, Prevention & Control] (125836)
21 18 and 19 and 20 (701)
22 17 or 21 (1143)
23 6 and 19 and 20 (707)
24 22 or 23 (1146)
25 ((prevent* or diagnos* or uncover* or screen* or discover* or monitor* or exam or exams or examin* or observ* or check* or track* or surveill* or telemedic* or tele-medic*) adj10 ((eye or eyes or retina* or vision* or visual* or opthalm* or ophthalm* or macula* or optic*) adj5 (diseas* or disorder* or pathol* or physiopath* or degener* or neurodegenerat* or worse*))).mp. (8542)
26 10 and 25 (284)
27 24 or 26 (1300)

28 limit 27 to (english or abstracts) (1278)
29 limit 28 to yr="2010 -Current" (528)
30 exp Prognosis/ (1146545)
31 exp "Outcome and Process Assessment (Health Care)"/ (855588)
32 exp "sensitivity and specificity"/ (457054)
33 exp Vital Statistics/ (645298)
34 exp Cost-Benefit Analysis/ (54234)
35 exp attitude to health/ (290229)
36 exp health behavior/ (120216)
37 30 or 31 or 33 or 34 or 35 or 36 (1999668)
38 29 and 37 (172)
39 exp Epidemiologic Studies/ (1662464)
40 29 and 39 (178)
41 (systematic* adj review*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (80362)
42 limit 29 to (controlled clinical trial or guideline or meta analysis or randomized controlled trial or systematic reviews) (41)
43 29 and 41 (6)
44 42 or 43 (41)
45 38 or 40 or 44 (295)
46 29 not 45 (233)
47 exp Glucose Metabolism Disorders/co [Complications] (45574)
48 exp eye/ (156307)
49 exp eye diseases/ (268442)
50 exp Vision, Ocular/ (10319)
51 48 or 49 or 50 (341001)
52 exp Mass Screening/ (81391)
53 47 and 51 and 52 (111)
54 exp Diabetes Complications/di, dg, pa, pc [Diagnosis, Diagnostic Imaging, Pathology, Prevention & Control] (25065)
55 51 and 52 and 54 (686)
56 51 and 54 (5949)
57 ((screen* or ((routin* or frequen*) adj5 (test* or exam* or visit* or consult*))) adj10 (eye or eyes or retina* or retinogra* or electroretin* or vision* or visual* or opthalm* or ophthalm* or macula*)).mp. [mp=title, abstract, original title, name of substance word,

subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (8420)
58 56 and 57 (722)
59 55 or 58 (953)
60 53 or 59 (969)
61 exp Diabetes Complications/ (73777)
62 51 and 52 and 61 (741)
63 60 or 62 (1012)
64 exp Preventive Health Services/ (338765)
65 exp Diabetes Mellitus/ (243719)
66 exp Eye Diseases/di, dg, pa, pc [Diagnosis, Diagnostic Imaging, Pathology, Prevention & Control] (125836)
67 64 and 65 and 66 (701)
68 63 or 67 (1146)
69 52 and 65 and 66 (707)
70 68 or 69 (1149)
71 ((prevent* or diagnos* or uncover* or screen* or discover* or monitor* or exam or exams or examin* or observ* or check* or track* or surveill* or telemedic* or tele-medic*) adj10 ((eye or eyes or retina* or retinogra* or electroretin* or vision* or visual* or opthalm* or ophthalm* or macula* or optic*) adj5 (diseas* or disorder* or pathol* or physiopath* or degener* or neurodegenerat* or worse*))).mp. (8556)
72 56 and 71 (284)
73 70 or 72 (1303)
74 limit 73 to (english or abstracts) (1281)
75 limit 74 to yr="2010 -Current" (530)
76 exp Prognosis/ (1146545)
77 exp "Outcome and Process Assessment (Health Care)"/ (855588)
78 exp "sensitivity and specificity"/ (457054)
79 exp Vital Statistics/ (645298)
80 exp Cost-Benefit Analysis/ (54234)
81 exp attitude to health/ (290229)
82 exp health behavior/ (120216)
83 76 or 77 or 79 or 80 or 81 or 82 (1999668)
84 75 and 83 (173)
85 exp Epidemiologic Studies/ (1662464)

86 75 and 85 (180)
87 (systematic* adj review*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (80362)
88 limit 75 to (controlled clinical trial or guideline or meta analysis or randomized controlled trial or systematic reviews) (41)
89 75 and 87 (6)
90 88 or 89 (41)
91 84 or 86 or 90 (297)
92 75 not 91 (233)

Filters/limits included articles published in English in the last 7 years.

Appendix C. Trustworthy Guideline rating scale

The University of Pennsylvania's Center for Evidence-Based Practice Trustworthy Guideline rating scale is based on the Institute of Medicine's "Standards for Developing Trustworthy Clinical Practice Guidelines" (IOM), as well as a review of the AGREE Enterprise and Guidelines International Network domains.

The purpose of this scale is to focus on the weaknesses of a guideline that may reduce the trust a clinical user can have in the guideline, and distinguish weaknesses in documentation (e.g. guide-line does not have a documented updating process) from weaknesses in the guidance itself (e.g. recommendations are outdated). Current quality scales like AGREE emphasize documentation. They are important checklists for developers of new guidelines, but are less useful for grading existing guidelines. These scales also are harder for clinicians and other persons who are not methodology experts to apply, and their length discourages their use outside formal technology assessment reports. This new scale is brief, balanced, and easy and consistent to apply.

We do not attempt to convert the results of this assessment into a numeric score. Instead we present a table listing the guidelines and how they are rated on each standard. This facilitates qualitative understanding by the reader, who can see for what areas the guideline base as a whole is weak or strong as well as which guidelines are weaker or stronger.

1. Transparency

A	Guideline development methods are fully disclosed.
B	Guideline development methods are partially disclosed.
C	Guideline development methods are not disclosed.

The grader must refer to any cited methods supplements or other supporting material when evaluating the guideline. Methods should include:
Who wrote the initial draft
How the committee voted on or otherwise approved recommendations
Evidence review, external review and methods used for updating are not addressed in this standard.

2. Conflict of interest

A	Funding of the guideline project is disclosed, disclosures are made for each individual panelist, and financial or other conflicts do not apply to key authors of the guideline or to more than 1 in 10 panel members).
B	Guideline states that there were no conflicts (or fewer than 1 in 10 panel members), but does not disclose funding source.
C	Lead author, senior author, or guideline panel members (at least 1 in 10) have conflict of interest, or guideline project was funded by industry sponsor with no assurance of independence.
NR	Guideline does not report on potential conflict of interests.

For purposes of this checklist, conflicts of interest include employment by, consulting for, or holding stock in companies doing business in fields affected by the guideline, as well as related financial conflicts. This definition should not be considered exclusive. As much as anything,

this is a surrogate marker for thorough reporting, since it may be assumed that guideline projects are funded by the sponsoring organization and many authors think it unnecessary to report a non-conflict.

3. Guideline development group

A	Guideline development group includes 1) methodological experts and clinicians and 2) representatives of multiple specialties.
B	Guideline development group includes one of the above, but not both.
C	Guideline developers all from one specialty or organization, and no methodologists.
NR	Affiliations of guideline developers not reported

The purpose of this standard is to ensure that supporters of competing procedures, or clinicians with no vested interest in utilization of one procedure or another, are involved in development of the guideline. Both AGREE II and IOM call for patient or public involvement: very few guideline panels have done so to date, so this is not necessary for guidelines to be rated A. Involvement of methodologists or HTA specialists in the systematic review is sufficient involvement in the guideline development group for our purposes. In the absence of any description of the guideline group, assume the named authors are the guideline group.

4. Systematic review

A	Guideline includes a systematic review of the evidence or links to a current review.
B	Guideline is based on a review which may or may not meet systematic review criteria.
C	Guideline is not based on a review of the evidence.

In order to qualify as a systematic review, the review must do all of the following:
Describe itself as systematic or report search strategies using multiple databases
Define the scope of the review (including key questions and the applicable population)
Either include quantitative or qualitative synthesis of the data or explain why it is not indicated

Note: this element does not address the quality of the systematic review: simply whether or not it exists. Concerns about quality or bias of the review will be discussed in text, where the analyst will explain whether the weaknesses of the review weaken the validity or reliability of the guideline.
Note: a guideline may be rated B on this domain even if the review on which it is based is not available to us. This potential weakness of the guideline should be discussed in text of the report.

5. Grading the supporting evidence

A	Specific supporting evidence (or lack thereof) for each recommendation is cited and graded
B	Specific supporting evidence (or lack thereof) for each recommendation is cited but the recommendation is not graded.
C	Recommendations are not supported by specific evidence.

To score a B on this domain there should be specific citations to evidence tables or individual references for each relevant recommendation in the guideline, or an indication that no evidence was available. Any standardized grading system is acceptable for purposes of this rating. If a guideline reports that there is no evidence available despite a thorough literature search, it may be scored B on this domain, or even A if evidence for other recommendations is cited and graded.

6. Recommendations

A	Considerations for each recommendation are documented (i.e. benefits and harms of a particular action, and/or strength of the evidence); and recommendations are presented in an actionable form.
B	Either one or the other of the above criteria is met.
C	Neither of the above criteria are met

In order to be actionable, the guideline should specify the specific population to which the guideline applies, the specific intervention in question, and the circumstances under which it should be carried out (or not carried out). The language used in the recommendations should also be consistent with the strength of the recommendation (e.g. directive and active language like “should” or “should not” for strong recommendations, and passive language like “consider” for weak recommendations). A figure or algorithm is considered actionable as long as it is complete enough to incorporate all the applicable patients and interventions. Please see the forthcoming NICE manual (24) for a good discussion of actionability in guidelines.

7. External review

A	Guideline was made available to external groups for review.
B	Guideline was reviewed by members of the sponsoring body only.
C	Guideline was not externally reviewed.
NR	No external review process is described.

8. Updating and currency of guideline

A	Guideline is current and an expiration date or update process is specified.
B	Guideline is current but no expiration date or update process is specified.
C	Guideline is outdated.

A guideline is considered current if it is within the developers’ stated validity period, or if no period or expiration data is stated, the guideline was published in the past three years (NOTE: the specific period may be changed at the analyst’s discretion, based on whether the technology is mature and whether there is a significant amount of recent evidence). A guideline must address new evidence when it is updated. A guideline which is simply re-endorsed by the panel without searching for new evidence must be considered outdated.