CODEBOOK – Evidence Synthesis

Attribute: 1. HOW – Execution of methods to develop evidence base
Sub-attribute: Systemic & Reproducible

Concept	CODEBOOK DEFINITION	OPERATIONALIZATION – *"How-to"*	CONTEXT	RELATIONSHIP WITH UPTAKE
Systemic and Reproducible	**Evidence-based:** Evidence-based clinical guidelines include a set of systematic statements, based upon current best research evidence with the aim of helping practitioners and patients make appropriate decisions about health care for specific circumstances (1). Guideline considers the best available evidence identified through a review of the literature (evidence-based) (2, 3) and is using current best evidence and multidisciplinary consensus to prioritize recommendations (4). Recommendations may be based on sound scientific evidence provided by high-quality independent original research, meta-analysis, randomized controlled trials, expert consensus, local development team, national organization (5). There are four different types of evidence available for use in clinical practice: research, clinical experience, patients, and knowledge generated in the local context (6). Recommendation is based on sound scientific evidence including, as appropriate, clinical trials or meta-analyses (7). Guidelines are classed as evidence based when there is an explicit consideration of the quality of evidence in the development of guidelines (8). The key characteristic of an evidence-based approach is the reliance on specific types of studies to reveal costs and benefits of diagnostic maneuvers and treatments, particularly over time (9); and reflect scientifically supportable practices that center on the best cost-benefit balance for the patient in both the short and long term (9). **Evidence-linked:** The explicit linkage of recommendations to the quality and strength of supporting evidence (10-18), the linking of recommendations to citations, and the use of grading systems (19). Evidence-based CPG development emphasizes the importance of linking recommendations to the scientific	**How to make recommendations evidence-based:** **1. CLEARLY ARTICULATE THE EVIDENCE IN RECOMMENDATIONS** • Report what type of evidence was considered to support recommendations o Provide supportive evidence for standard of care (including research and structure, clinical opinion, process and outcome) for each recommendation and clearly articulate (28, 35, 36) and supported by relevant comments and references (37). o Ensure that an explicit description of the scientific evidence for the recommendation is available (38). o Clearly indicate the basis of each recommendation (39). o Clearly indicate the degree to which each recommendation is supported by good evidence (39). o Include a set of systematic statements (1). o Be based on current best research evidence aimed at helping practitioners and patients make appropriate decisions about health care for specific circumstances (1, 2). o Make key data available for review (28). • Ensure that recommendations are supported with well-designed studies o Supports all decisions and recommendations, and are based on the results of well-designed clinical trials, systematic reviews and meta-analyses, and cohort or case-control studies (4, 38, 40). o The guideline is based on properly interpreted, sound scientific evidence that demonstrates improved health outcomes for patients without increasing risks (41). o Recommendations should not be based on the subjective opinion of individual practitioners (42). o Relies upon systematically identifying relevant research, reviewing the evidence using methodologically sound critical appraisal and summarizing the evidence explicitly (10). o Indicates that the quality and extent of the research on which recommendations are based are explicitly recognized (10). – The value of this approach is unquestionable as it incorporates the best available evidence, helps identify research priorities, allows for guidance on issues where evidence from randomized trials is not available and is crucial for the subsequent use of guidelines at local level (10). • Report how evidence was selected abstracted and combined (28). o Combine all relevant evidence appropriately**:** Guideline developers must bring together all the relevant evidence, and then combine it in an appropriate manner (43): o Developers should specify a particular question, define appropriate evidence using explicit criteria, conduct a comprehensive search and examine the validity of the results in a reproducible fashion (43). **2. LINK RECOMMENDATIONS TO THE SCIENTIFIC RESEARCH THAT SUPPORTS THEM** • Justify each recommendation by clearly describing the linkage between the recommendation and its supporting evidence (15, 18, 44). • o Indicate the quality of evidence, the recommendation strength (44), and grade the strength of	**Clinical Epidemiology** (7) **Cognitive Ergonomics** (29, 71, 72) **Information Science** (26) **Knowledge Translation** (34) **Medicine** (1-4, 6, 8-12, 15, 16, 20, 22, 40, 49) **Psychology** (36) **Sociology** (73) **Psychology** (36)	**Achieve validity and reliability** • Clinical practice guidelines need to be evidence-based otherwise they will never achieve the validity, reliability, and credibility required for adoption (74). • In terms of guideline development, the explicit linkage of recommendations to the quality of the supporting evidence enhances the scientific validity of the guideline (11, 12, 57). **Decision-making** • One is more confident about decisions based on evidence that offers greater protection against bias and random error (i.e., there is a hierarchy of evidence) (2). • Multiple PG, even in the areas with strong evidence base, vary considerably in their content and implications for clinical decisions and patient benefits (75). • Grading of recommendations is an important way for guideline developers to convey this level of confidence to the user (28). **Value to end users** • Evidence-based guidelines most helpful when based on the best available research evidence (2). • Users should be able to easily distinguish between recommendations based on good evidence showing large benefits vs. those based on

research that supports them (identified through a rigorous systematic identification and appraisal of all relevant research) (20). The best guidelines contain very specific linkage of findings to diagnosis, and of diagnosis to specific, proven treatments - The links should be supported by scientific evidence indicating reasonably strong sensitivity and specificity and a low false-positive rate (9).

Quality of evidence
The confidence that the recommendations are both internally and externally valid, reproducible and reliable, the results of trials are interpreted according to the user's understanding of the evidence, and are feasible for practice (3, 21, 22). A judgment about the extent to which we can be confident that the estimates of effect are correct or represents the "truth" (23, 24). Quality of evidence is a continuum - any discrete categorization involves some degree of arbitrariness - nevertheless, advantages of simplicity, transparency, and vividness outweigh these limitations (25). When the information quality is unknown, it is difficult for the user to decide on the credibility of that information (26).

Quality of guidelines: The quality of the guidelines can be assessed using the AGREE instrument, in which 23 criteria in seven domains are evaluated - These include the scope and purpose of the guidelines, stakeholder participation, methodological rigour, clarity, applicability, editorial independence and overall quality (27).

Strength of recommendations
Reflect the degree of certainty (strong/weak) that the desirable effects (beneficial health outcomes, less burden, and cost savings) of adherence to a recommendation outweigh the undesirable effects (demands of adhering to a recommendation that patients or caregivers may dislike, such as having to take medication or the inconvenience of going to the doctor's office; harms, more burden, and expenses) and the belief that adherence to a particular recommendation will do more good than harm (2, 24, 28, 29).

recommendations (18).
  - Recommendations should have a statement of the level of evidence on which they are based (17) - Where there is little evidence, this needs to be explicit (17).
- All sources of evidence used to develop and inform the structure should be described and be consistent with the evidence (16, 45).
- Formally appraise the literature to create evidence based guidelines and recommendations (8).
- Identify the citation and references of the evidence used (16, 33).
- Specify the method of data extraction (33).
- Specify the method of grading or classifying scientific evidence (33).
- Use formal methods for combining evidence or expert opinion (33).

3. INDICATE AND REPORT THE QUALITY OF EVIDENCE
- Rate and Grade the quality of evidence
  - Quality of evidence is assessed (judged) based on the type of study design (randomized trials vs. observational studies), the risk of bias, the consistency of the results across studies, the precision of the overall estimate across studies, the predictive power of the study designs from which recommendations are obtained (46-48) and internal validity (19).
  - The grade of recommendation should reflect not only precision and susceptibility bias of data but also generalizability (49).
  - The level of evidence classification combines an objective description of the existence and the types of studies supporting the recommendation and expert consensus (50).
  - The classes of recommendation designation indicates the strength of a recommendation and requires guideline writers not only to make a judgment about the relative strengths and weaknesses of the study but also to make a value judgment about the relative importance of the risk and benefits identified by the evidence and to synthesize conflicting findings among multiple studies (50).
  - In general, the evidence that graded recommendations have advantages over non-graded recommendations is limited but there are strong arguments including the clear and transparent communication of how much confidence users can place in recommendations and the evidence underlying them (48).
  - Is the quality of evidence that supports the recommendation explicitly stated (51)?
- Use GRADE**:** Allows judgments about the extent to which we can be confident that the estimate of effect are correct can be made (23).
  - The GRADE system classifies recommendations (outcomes) into one of four quality of evidence categories *(high, moderate, low, or very low)*, which offers a simple and practical, yet methodologically rigorous grading system (23, 25).
  - High quality (23):
    - Further research is very unlikely to change our confidence in the estimate effect.
    - The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted.
    - High-quality evidence is linked with situations where the benefits are closely balanced with harms and burdens (2).
  - Moderate quality (23):
    - Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
    - It is evident that the probability for strong recommendation is highest when quality is moderate rather than very low or low (24).
    - It is evident that the probability for strong recommendation is highest when quality is moderate rather than very low or low. For example: Probability of making strong recommendation was 62% when evidence was moderate, while it was only 23% and 13% when evidence was low or very low (24).
  - Low quality (23):

weak evidence showing small or uncertain benefits (18).

Negative consequences
- Poor differentiation between evidence and opinion are common shortcomings of guidelines (76).
- Unless the literature is used carefully and thoroughly, and a conservative approach is taken, guidelines may create as much variance as they attempt to reduce (9).
- Only a small proportion of recommendations are based on scientific evidence while much of the remainder is derived from clinical experience or observation; owning to biased opinions, inadequate experience and skewed composition (77).
- Guidelines of variable quality and conflicting recommendation are a result of poor medical literature and development efforts (72).
- Guideline recommendations that are based on weak evidence (i.e., clinical experience or observation) can lead to wrong clinical management and could potentially result in serious harm to patients (77).

Implementability / use
- Recommendations based on evidence were used more than those that were not; Recommendations were more adhered to when an explicit description of the scientific evidence was available and when the evidence was straightforward and non-conflicting (study results) (38).
- For ensuring use of therapeutic recommendations, the strength of the evidence seems relatively more important than factors such as

	Key considerations that determine/influence the strength of a recommendation include the quality of the evidence, the necessary resources, the balance between desirable and undesirable consequences of alternative management strategies, the degree of uncertainty or variability of patient values and preferences for which the guideline document is intended, the magnitude & consistency of positive outcomes relative to negative outcomes (AE, burdens to patient & HC system), and relative value placed on different outcomes and finally, the associated costs (28, 30, 31). The strength, grade, confidence or force of a recommendation (31). The use of scientific evidence and reporting of the strength of evidence to support each recommendation (29, 32). Recommendations are graded according to the strength of evidence (33). There is a need for higher-level evidence accompanied by descriptions of the strength of the evidence (Van der Weijden, 1998). Each recommendation directly reflects the strength of underlying evidence (13). **Evaluation of evidence:** Proper performed evaluation of the scientific evidence (33). How the evidence was graded, which may or may not include a statement about the strength of the evidence (16). This dimension included use of evidence, method for combining evidence, risk-benefits issues, and cost concerns (33). Example: The methodological standards on the identification and summary of evidence were poorly adhered to in this study's evaluation of 279 guidelines, with an overall mean adherence of 33.6% (33). **Quality of guideline development** The confidence that the potential biases inherent of guideline development have been addressed adequately (21). **Communicability of evidence:** Clearly communicate evidence related to the intervention (34). Theoretical meaning of communicability: Communication gap with regards to perceived effectiveness - failure to communicate information about effectiveness of an intervention in a comprehensible manner to bridge the	– 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. – Low quality evidence usually leads to weak recommendations because of uncertainty about the balance between risks and benefits (2). – Locally developed study samples and case studies are the least persuasive forms of medical evidence (5). – In various nursing specialties, there is a lack of intervention studies and the prominent use of descriptive studies within nursing generates evidence that is rated low on the continuum of evidence strength (52) - Some have claimed that the evidence developed by experimental research (primarily randomized controlled trials), systematic reviews, and meta-analysis may be unsuitable (53) or unavailable (54, 55) for specific areas of nursing practice. ○ Very low quality (23): – Any estimate of effect is very uncertain. – Low or very low quality evidence usually leads to weak recommendations because the uncertainty about the balance between risks and benefits (2). ○ Downgrading of evidence – The most frequent reason for RCT-based recommendations to be down-graded was that the RCT was conducted to answer a particular question in a restricted study population but was then extrapolated in the guideline to justify using the tested intervention in a related, but different, clinical scenario and/or in a more general population (19). – The intervention may be associated with costs, discomforts, or impracticalities that downgrade the strength of a summary recommendation about what clinicians should do (31). – Example of the effects of downgrading: While two-thirds of cardiovascular risk management therapy recommendations made in the nine different guidelines we examined were based on RCT evidence, less than half of these RCT-based recommendations were deemed "high quality" using an evidence grading scheme that went beyond considerations of internal validity alone to take into account clinical relevance and direct applicability of the RCT to that recommendation - As a result, less than one-third of recommendations that advocated specific cardiovascular risk management therapies in these evidence-based guidelines were actually based on high quality evidence (19). • What to do with the “expert opinion” category of evidence: ○ Systems that classify "expert opinion" as a category of evidence create confusion - Judgment is necessary for interpretation of all evidence, whether that evidence is high or low quality (25). ○ Develop guidelines that are evidence based instead of consensus based (56); many experts feel that evidence-based guidelines are the "gold standard". It is important to state when the origin of the recommendations shifts from various classes of evidence to opinion and to consensus (9). ○ An absence of high quality evidence (e.g. randomized trials) however does not preclude a structured use of expert consensus if an important quality concern needs to be addressed. Despite increasing acceptance of an evidence-based approach to clinical decision making, much clinical practice is still not based on the best available evidence (4). ○ Formal consensus provides greater structure to the analytical process (10). Formal consensus may fail to provide an explicit link between recommendations and the quality of evidence (10). Informal consensus occurs when the development group has poorly defined criteria (subjective judgment) for decision making (10). ○ With a structured approach to achieving agreement, consensus may avoid some problems, particularly if combined with prior preparation and documentation condensing the underlying		complexity and patient expectations (40). • Evaluating guidelines - this seems both a necessary element of appropriate monitoring of practice policy and PG, and also a stimulus to more effective implementation (10). • Grading systems that are simple with respect to judgments both about the quality of the evidence and the strength of recommendations facilitate use by patients, clinicians, and policy makers (25). • Reassurance that a guideline is of good quality is needed prior to implementation (22). **Understandability** • Rating of the evidence quality and the grading of the recommendation strength helps clinicians understand the guideline’s summary message (2). **Agreement** • When the source of evidence used to support decision were of high quality, they found a higher level of full agreement among the guidelines' recommendations (8). **Adherence / Compliance** • Grading can affect concerns with compliance; Authors argue that adherence to grade A recommendations is clearly more important than adherence to lower-grade recommendations (46). **Acceptability** • Acceptability of recommendations may be strongly related to the quality assessments so that quality beliefs add little above acceptability beliefs (I.e.

communication gap (34). Empirical meaning of communicability: evidence of effectiveness, treatment effect, proportion of users who might benefits, cost-effectiveness (34). Example: This paper explored a sample of GPs' views of the notion of effectiveness of medical interventions, and found that this was underpinned by "size of impact" needed (34). Size of impact appears closely related to the estimates of effect size reported by trials, and is captured by constructs such as "small treatment effect for users", "a small proportion of users will benefit" or "weak/minimal evidence of effectiveness". Whether the intervention appealed to patients in the bottom-right quadrant of the map suggests that GPs perceived such interventions as characterized by high patient effort and small impact (34).

evidence (10).
  - Example: The Delphi method and adaptation of the RAND method for combining the strength of the evidence together with expert opinion (10).

4. INDICATE AND REPORT THE STRENGTH OF RECOMMENDATIONS

- Indicate and Grade the strength of recommendations (including cost-effectiveness) (44, 49)
  - Practice guidelines and recommendations should be accompanied by descriptions of the strength of the evidence, whether the evidence is high quality and the desirable effects clearly outweigh the undesirable effects or there is a close or uncertain balance, and indicate the expert judgment behind them (12, 25, 57).
  - The strength of evidence provided by a study is also influenced by how well the study was designed and carried out (12).
- Use GRADE: An approach that classifies recommendations for or against treatments into two grades (2, 25):
  - Strong:
    - When the desirable effects of an intervention clearly outweigh the undesirable effects or clearly do not - If guideline developers are confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects, they will make a strong recommendation within the context of a described intervention (2).
    - The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted.
    - A strong recommendation indicates that use of a decision aid is unnecessary - almost all informed patients would make the same choice.
    - The higher the costs of an intervention (i.e., the greater the resources consumed), the lower the likelihood that a strong recommendation is warranted.
    - It is possible to have methodologically sound (category 1) evidence about a clinically irrelevant area of practice or one with such a small effect that it is of little practical importance and therefore attracts a lower strength of recommendation; Also, a statement of evidence may cover only one part of an area in which a recommendation is made, or evidence of similar quality may be contradictory (49).
    - Guideline developers us the terms "we recommend" to denote strong recommendations; Strong recommendations receive grade 1 classification (2).
  - Weak:
    - When the trade-offs are less certain, either because of low quality evidence or because evidence suggests that desirable and undesirable effects are closely balanced.
    - The narrower the gradient, the higher the likelihood that a weak recommendation is warranted.
    - A weak recommendation indicates that a decision aid could be useful.
    - The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted.
    - Guideline developers us the terms “we suggest” for weak recommendations; weak recommendations receive a grade 2 classification (2).
  - Factors that can weaken the strength of a recommendation (48):
    - Lower quality of evidence.
    - Uncertainty about the balance of benefits and harms and burdens.
    - Uncertainty or difference in values.
    - Marginal net benefits or downsides.
    - Uncertainty about whether the net benefits are worth the costs.
- Other considerations in strength of the recommendations
  - If one combines the strength and heterogeneity of the primary studies with the magnitude and precision of the treatment effect as it relates to the threshold NNT, one can decide on the strength of the recommendation to treat or not to treat (58).

quality may not be viewed as unique or distinct from other attributes) (3).

Adoptability

- Low rating of evidence affects practitioners' inclinations to adopt recommendations outlined in the guideline, particularly in specialties where RCTs are not possible for research such as in various nursing specialties (78).
- In general, the stronger and more consistent the research evidence, supporting a particular guideline, the more likely that guideline will be adopted (65).

Potential for improving clinical outcomes / Translation to practice

- Clearly guidelines based on recommendations for treatments for which there is proven evidence of benefit should at least have the potential for improving clinical outcomes and the quality of health care for patients, although success is certainly not guaranteed and evidence-based guidelines are only one option for improving the quality of health care (27).
- The grading assigned to a recommendation is related to the likelihood that, if that recommendation is implemented, the predicted outcome will be achieved (46).
- Translation to clinical practice is more likely to occur when the guidelines are based on solid data resulting in high-grade recommendation (79).

Evaluability of guidelines

- If developers do not include information about how they chose options and outcomes,

		○ To produce comprehensive recommendations, a guideline group has to extrapolate from available evidence and this sometimes leads to lower strength recommendations based on category 1 evidence; Applying a strength of recommendation to cost information presents some difficulties (49). • What to do if have limited or clear evidence ○ Areas of limited evidence can be highlighted as areas for future research (17). ○ Areas without clear evidence can also be drawn up as a practice point as opposed to a full recommendation (17). **5. OTHER** • Include Evidence profiles**:** ○ All guideline action statements should ideally be supported by evidence profiles that summarize clearly the decision-making process in terms of aggregate evidence quality, harm-benefit assessment, development group values, and the rile of patient preferences; Section in a guideline that provides transparency in how recommendations were developed and classified. They list all the decisions made by the group under the following titles: aggregate evidence quality, benefit, harm, cost, benefit-harm assessment, value judgments, intentional vagueness, role of patient preferences, exclusions (4); Evidence profiles assist guideline writers and users by 1) encouraging an explicit and transparent approach to guideline writing, 2) forcing guideline developers to discuss and document the decision-making process; 3) creating "organizational memory" to avoid re-discussing already-agreed-upon issues; 4) allowing guideline users to rapidly understand how and why statements were developed - See Table 13 (page S29) for evidence profile constructs for key action statements - this outlines the construct (i.e., benefit, harm, cost, etc.), what to include in the profile, and comments (4). • Develop guidelines by describing underlying assumptions and beliefs (56). ○ Users were not convinced when they thought that the recommendations were consensus based rather than evidence based. Moreover, the effectiveness of the guideline had not been tested in general practice and the underlying assumptions and beliefs were not described. (56). • Evaluate guidelines: ○ The evidence on which PG are based can change over time - Good PG should be reviewed regularly (10). ○ The criteria by which to judge whether guideline developers have done an adequate job in accumulating and synthesizing the evidence are similar to those that apply to systematic review (59). • If there is a lack of evidence**:** ○ PG may have lack of evidence when it comes to making recommendations (60). ○ Because guideline developers must deal with inadequate evidence, they may have to consider a variety of studies (other than RCTs) as well as reports of expert or consumer experience (43). ○ Gaps in the research evidence for many types of therapy (36). – Example: Nurses and physicians indicated a lack of evidence for several recommendations; Respondents emphasized the need for research to further develop standardized clinical protocols to assist medical practitioners to implement best practice care; respondents noted that there was a lack of evidence for the majority of recommendations in the pressure ulcer CPG. Only 8 or the 32 recommendations had level 1 evidence (i.e. large, randomized trials with clear cut results and low risk of error) (60). ○ Recommendations with an absence of supporting evidence often require elaboration in the text to explain their rationale, which may be as extensive as the paragraphs reviewing the results of various clinical trials (50). Example: ○ The increase in the number of recommendations included in the ACC/AHA guidelines is likely due to greater complexity of patient management decisions (50). Extensive documents		selected evidence, and decided on values, you might suspect that these steps were not done systematically (43) - In any case, you cannot evaluate such guidelines, and their recommendations should not influence your decision-making (43). **Credibility of information** • When the information quality is unknown, it is difficult for the user to decide on the credibility of that information - Unknown quality of enormous amount of information also leads to overload; grading recommendations is helpful in this regard (26). **Tradeoffs:** • There are significant gaps in the research evidence and some have questioned whether results from randomize trials can be used to assist practice decisions (36). • Reporting of strength of recommendations may range from A to D, but categories of evidence may not always map simply onto a certain strength of recommendation (49). • Categorizing quality into 4 categories may oversimplify complex healthcare recommendations, but guideline users are likely to benefit from this simplification, as they are most interested in which recommendations to follow (48). **Miscellaneous** • Few guidelines have been scientifically proven to maintain quality while controlling costs (71). • Unknown quality of enormous amount of information also leads to overload (26).

		including a large proportion of uncertain or non-evidence-based recommendations may make it increasingly difficult, when referring to a guideline, to locate the most important and/or evidence-based information relevant to an individual patient. Thus, they may reduce the implementation of evidence-based recommendations because the length of the documents may interfere with prompt access to guideline information (61-63). • Consider checklist for WHO treatment guidelines - evidence section (64): o What percent of recommendations are evidence-based? o Are the recommendations, which are not evidence-based explicitly, labeled as "expert opinion" based? o Is there explicit consideration of issues of cost-effectiveness? o Is the strength of the recommendation linked to the evidence? o Do recommendations take into account potential resource constraints? **EXAMPLES:** Examples of guidelines with high quality evidence • One of the successes of the AHCPR algorithm is that it is straightforward, cutting through the mountain of sometimes conflicting literature and the flood of proprietary interests bombarding clinicians (29). • Overall, evidence based guidelines had higher [quality] scores than consensus based guidelines and consensus based-and evidence based category ranked in the middle. No major disagreement in recommendations was detected among guidelines regardless of the method used for development, but the evidence-based guidelines had a better agreement with the benchmark guideline for any decision point (8). • Study found consistently that (5) physicians indicated that RCTs are the most persuasive medical evidence that could be included in PG and that locally developed study samples and case studies generally do not sway their treatment strategies; and so RCT should be the primary medical evidence used in PG development whenever possible. • Just 77 (18%) guidelines used explicit criteria to grade the strength of the scientific evidence in support of their recommendations - the number of guidelines satisfying this criterion increased from 6% in 1988-1991 to 27% in 1996-98 (32). • The guideline (checklist) to reduce catheter-related bloodstream infections was supported by a large body of evidence and was widely adopted - conversely, guidelines to tightly control blood glucose are not well-supported, and this clinical practice is less supported (65). Examples of guidelines with low or poor quality evidence or contradictory evidence: • Scores for overall quality of guidelines were 28%, 41%, and 51% for opinion-based, evidence-base, and hybrid PGs, respectively. Scores for different quality criteria varied but apart from applicability, opinion-based PG tended to have lower scores; overall quality was better in evidence-based than opinion-based PG, and significantly better still in the hybrid PG that combined research evidence with expert opinion (27). • For many reasons, the methodologic quality of diagnostic guidelines is poorer than that of therapeutic guidelines, particularly in the field of laboratory medicine (66, 67) (68) - One major difference is that therapeutic recommendations tend to have a higher quality evidence based (rigourous RCTs) as compared with diagnostic recommendations (generally poorer level of evidence) (69). • Less than half the guidelines in the recent period graded the quality of the evidence and 6% did not even review the scientific literature and both at lower rates than that of guidelines produced in the earlier period; While the authors did not study the quality of the guidelines in the CMA Infobase, previous work has revealed that the quality of drug guidelines in this database is less than optimal. (47). • Guidelines based on informal consensus are more likely to be flawed because they fail to use an approach that is structured, repeatable and scientifically sound to incorporate evidence ("systematic		• The findings of website evaluations in Norway (Clare Glenton, personal communication) found that users preferred graded over non-graded recommendations (48). • Detailed and explicit criteria for ratings of quality and grading of strength will make judgments more transparent to those using guidelines in recommendations (80). • The evidence-based methodology, consensus of experts in the field, and the aura of the professional organization enhance the normativity of the guideline. (73).

approach") rely upon the potentially restricted knowledge of the individuals involved, and may be distorted by the 'who shouts loudest' phenomenon (10).
- Users were not convinced when they thought that the recommendations were consensus based rather than evidence based. Moreover, the effectiveness of the guideline had not been tested in general practice and the underlying assumptions and beliefs were not described (56).
- "False positive" means a finding that is present but is uncorrelated pathologically because of its high prevalence in asymptomatic individuals. Many guidelines present very general algorithms and then lists of questions and physical maneuvers to consider, without defining the answers that would pathognomonically indicate a correlation (9).
- The scientific validity of cholesterol guidelines has not gone unquestioned and have been contradictory over the years (70).
- Within wound care, there are a number of PG in which most of the recommendations are based on the weakest grade of evidence - This is due to the lack of high-quality RCTs (42) and has been blamed for undermining the reliability of many PG (42).

<u>Examples of alternative evidence assessment / grading tools</u>
- Evidence assessments, such as CHEP and GRADE, incorporate external validity, applicability, and clinical relevance into evidence appraisal, which helps improve the link between the recommendations and practice (19).
    - For instance, evidence of a recommendation based on an RCT may be classified as B instead of A if the relevance and applicability to the general population is sufficiently uncertain (see downgrading).
- Different groups have used different hierarchies to describe both the level of the evidence (I-III) and the strength of the overall recommendation (A-E).
    - For e.g., AHCPR panels have used simpler A-B-C categories to distinguish recommendations based on definitive trial evidence, those based on weaker, and expert opinion evidence (13).
- The authors developed three "grades" of recommendation: standard, recommendation, option.
- Recommendations were labeled standard if the panel concluded that it should be followed by virtually all health care providers for virtually all patients; However, few of the recommendations were considered standards which are intended to provide strong guidance for clinical decision making (28).

Sub-attribute: Valid and reliable

Concept	CODEBOOK DEFINITION	OPERATIONALIZATION – *"How-to"*	CONTEXT	RELATIONSHIP WITH UPTAKE

Valid / Validity
 	
Internal consistency = Reliability
	Validity: Guideline is valid if when followed or implemented, will lead to the health and cost outcomes projected by them or was intended to achieve (11, 16, 22, 57, 77, 81). A valid guideline includes all the relevant literature and has explicit links between decisions and scientific evidence (4). Valid guidelines have explicit links between decisions and scientific evidence (4). Validity is also influenced by how well the authors assess the evidence and translate it into recommendations (22). Also of importance is how and by whom the guideline has been developed, for example guidelines can be developed by expert consensus guidelines, which are based on clinical experts opinions when scientific evidence is weak or lacking (82). It is also possible to use certain prospective indicators to judge guideline validity before outcomes are known, for example, substance and quality of the evidence used to formulate the guideline, the methods used, strength of evidence (77). Validity is a guideline's interpretation of the evidence (83); however it depends on how well the evidence has been identified (i.e. the substance and quality of the evidence cited), synthesized (i.e., the means used to evaluate the evidence), and incorporated in the guideline (I.e., the relationship between the evidence and recommendations (57, 84).
	
	Apparent/face validity: The degree to which the recommendation reflects the intent of the developer and the strength of evidence (GLIA) (Rosenfeld, 2009).
	
	Scientific validity: The method of developing the guideline determines its scientific validity (43, 85).
	
	Generalizability (External validity): How generalizable the results of a trial are to the populations, interventions, and outcomes specified in the recommendations. Also described as external validity ("a neglected dimension in evidence ranking") (19, 36). Definition: Extent to which the research is generalizable to the patients (36).
		To achieve / increase validity of guidelines:
		• Valid recommendations are those supported with consistent research evidence or sufficient consensus among the guideline development team when evidence is conflicting or lacking (69); Invalid recommendations are those that are not supported with consistent research evidence or sufficient consensus among the guideline development team when evidence is conflicting or lacking (69).
		• The evidence should be identified, summarized and presented such that the quality of the evidence and quantity of the evidence are apparent, easily reviewed, understood and in interpreted (16, 84, 88).
		• Use of rigorous methodology and recommendations are based on best available evidence (where possible, systematic reviews of research evidence) (37, 84) and ensuring involvement of stakeholder groups affected by PG (37).
		  ○ Specify how evidence was synthesized; and structured literature review with specific inclusion and exclusion criteria (4).
		• Specified criteria for assessing quality of studies (4).
		• Rated level of supporting evidence for each recommendation (4).
		• The references to evidence which the recommendations were based on and the number of distinct recommendations are clearly cited (16, 88).
		• The evidence used is graded - Graded evidence helps categorize quality of evidence that supports each recommendation (16, 88).
		• Validity is dependent on how many guideline users and key disciplines were included in guideline development group and specifically how it was developed (84) - Involvement of all stakeholders in guideline development panels and through the explicit linkage of recommendations with evidence is important (84).
		• Guideline developers should include enough information that allows potential users to make informed judgments on relevance and validity (39).
		• Health benefits, harms/risk, costs and outcomes are stated (16).
		• Clearly distinguish and justify where expert judgment or group consensus was used to support recommendation (4).
		• Physicians felt that they needed substantial information about the process used, literature reviewed, and financial support received to assess the validity of the guideline (89).
		• Characteristics measured/evaluated:
		  ○ Structure literature review with specific inclusion and exclusion criteria.
		  ○ Specified criteria for assessing quality of studies.
		  ○ Specified how evidence was synthesized.
		  ○ Rated level of supporting evidence for each recommendation (4).
		
		Examples
		<u>Examples of valid guidelines</u>
		• In the study, most of the nurse managers reported the PG to be appropriate and suitable for use (37). Validity and reliability are probably the most important attributes of CPGs: a guideline that lacks sufficient validity or reliability is likely to be ignored by medical practitioners
		• Most PG we examined contained a large volume of graded evidence; a recent analysis recommended that the reliability, relevance and readability of knowledge resources be improved to support evidence-based decision making (90).
		• Research suggests that individual clinicians value guidance on how to blend experience with evidence when applying the recommendations to individual patients, and engage patients in shared
			Medicine
			(11, 16, 22, 43, 57, 81-84)
			
			Psychology
			(36)
				Implementability
				• One possible explanation for implementation problems could be the perceived problem with the adequacy or validity of PG (38).
				
				Relevance to practice
				• Physicians' questioning a guideline's interpretation of the evidence (its validity) is one of the most fundamental of the "unfavorable attributes" of CPGs.
				• If physicians question the relevance or validity of a guideline, they may not even consider other issues. Panelists often found guidelines' statements to be only somewhat consistent with their understandings of the literature and opinions (83).
				• Some maintain that guidelines lack validity and relevance to the variety and complexity of primary care practice (96).
				
				Confidence of guideline users
				• Guideline users should be confident that these recommendations are the product of a rigorous evidence driven development process, that the recommendations address clinically relevant issues and are applicable to the patient for which guidance is being sought (28).
				
				Miscellaneous
				• Whereas many GPs believe that good practice is not always necessarily based on scientific evidence (97), the scientific validity of the guideline has not gone unquestioned (98).

	Acceptability: absence of controversy (86). Acceptability describes whether the recommendation should be put into practice (ADAPTE Collaboration) and providers' views about how useful each guideline would be in clinical practice (83). Acceptability is predicted by the endorsement and intent to use a guideline (87). Evaluated based on: (1) perceived comprehensiveness and (2) perceived validity (83). Acceptability of recommendations may be strongly related to the quality assessments so that quality beliefs add little above acceptability beliefs (3).	decision making (38, 83, 91-93); Examples of invalid guidelines • Saturno et al. (2003 in Tan, 2006)) found that neck pain treatment CPGs in Spain were largely invalid as most guidelines were not supported by scientific evidence. • Most guidelines also do not consider how generalizable (applicable) the results of a trial are to the populations, interventions, and outcomes specified in the guideline recommendations. The evidence underlying 64 of the guideline recommendations failed to achieve a high CHEP grade because the RCT data were collected in a population of people with different characteristics to those covered by the guideline. Thus, even evidence arising from internally valid RCTs may not be directly applicable to the populations, interventions, and outcomes specified in guideline recommendations (19). • Research on the effectiveness of psychotherapy has most commonly been carried out on relatively tightly defined populations in order to maximize internal validity (94). This leaves the guideline developer and user of a guideline uncertain to the extent to which the research is generalizable to patients who might have been excluded from a typical efficacy trial because of multiple co-morbidities (95).		

Sub-category: Transparent

Concept	CODEBOOK DEFINITION	OPERATIONALIZATION – *"How-to"*	CONTEXT	RELATIONSHIP WITH UPTAKE
Transparent	**Transparency:** Makes clear the purpose and basis of recommendations to end-users (4). They must formulate recommendations, but they should be candid about the type and quantity of evidence on which those recommendations are based (43). We do believe that transparency about any extrapolation of RCT evidence is critical, particularly in light of studies demonstrating that the composition and interpersonal dynamics of a guideline panel influence the extent to which their consensus recommendations diverge from the available evidence base (19). **Transparent methodology:** Transparent methodology is explicitly, reproducible, and applied consistently so guideline users can link recommendations to the corresponding level of evidence, benefit-harm-cost relationship, and the roles of values and patient preferences in decision making (4). **Transparency of evidence:** Lack of transparency in both the quality of evidence and strength of recommendations makes prioritization and strength of recommendations difficult (76).	**HOW-TO** • Potential conflicts of interest should be clearly disclosed because they could inappropriately affect how recommendations were formulated (18). • Funding sources ought to be reported and the guideline should provide enough detail for users to determine whether and how the views or interests of the funding source may have influenced final recommendations (18). • Recommendations must be transparent to the target audience (49). • Because guideline developers must deal with inadequate evidence, they may have to consider a variety of studies (other than RCTs) as well as reports of expert or consumer experience (1st point). They must formulate recommendations, but they should be candid about the type and quantity of evidence on which those recommendations are based (2nd point) (43). • Transparency about any extrapolation of RCT evidence is critical, particularly in light of studies demonstrating that the composition and interpersonal dynamics of a guideline panel influence the extent to which their consensus recommendations diverge from the available evidence base (19).	**Health Policy** (49) **Medical Informatics** (76) **Medicine** (4, 19, 43)	• None.

CODEBOOK – Evidence Synthesis

Attribute: 2. WHAT – Completeness of reporting evidence base

Concept	CODEBOOK DEFINITION	OPERATIONALIZATION – *"How-to"*	CONTEXT	RELATIONSHIP WITH UPTAKE
Consistent and Comprehensive	Guidelines should report on a number of different things. They should be consistent and comprehensive. Consistency Consistency among guideline recommendations (99). Methodology concordance and consistency to formulate recommendations (79). Discrepancies can arise from methodology difference used to formulate recommendations (79). Comprehensiveness Comprehensive guidelines address more phases of the illness, discuss a wider variety of treatment modalities, and make greater numbers of specific recommendations. They also have greater depth, with recommendations reflecting previous treatment trials and responses. Ideally, costs and resource allocation are also considered (82, 100).	**HOW-TO (Consistent)** • Guideline consistency can be assessed by the following three evaluations (101): (1) search strategy and selection of evidence supporting the recommendations; (2) consistency between the evidence, as well as how developers summarized and interpreted the evidence; and (3) consistency between evidence interpretation and recommendations (ADAPTE) (this is linked to considered judgment) **HOW-TO (Comprehensive**) (82, 100). Characteristics measured/evaluated: • number of recommendations. • recommendations contingent on patient's history. • phases of illness. • variety of treatment modalities. • comorbid conditions. • cost and resource considerations.	**Medicine** (79, 82, 99, 100)	• Confusion arises when there are discrepancies within the guideline such as in diagnostic and treatment recommendations (79).
Alternatives (Options)	Alternative interventions to those recommended or dealt with by the CPG to deal with this topic (11). Amount of options to choose from (102). To understand why a particular practice is recommended you should consider whether the guideline developers included all reasonable practice options and important consequences (28). Number of options provided to a consumer considering a purchase (103, 104).	**HOW-TO** • Whether developers present guidelines for prevention, diagnosis, therapy or rehabilitation, they should specify both the interventions of interest and sensible alternative practice (43). • Were all the reasonable practice options and important potential outcomes clearly considered and specified (105)? **EXAMPLES** The ACP guideline offers recommendations about medical interventions for preventing strokes (106). While caratoid endarterectomy is mentioned as a possible surgical intervention in the preamble to the guideline, the procedure is not considered in the recommendations themselves. This guideline could have been strengthened if medical intervention for TIAs had been placed in the management context that included the highly effective surgical procedure (43).	**Medicine** (11, 43)	• None.
Comorbid conditions	Whether the guideline addresses or ignores comorbid conditions (29).	**EXAMPLES** Heart failure is frequently not an isolated phenomenon and dealing with comorbid conditions is perhaps the most difficult aspect of caring for such patients. Yet, AHCPR guidelines ignore comorbid conditions (29).	**Cognitive Ergonomics** (29)	• None.

Healthcare burden	Detailed information from primary sources on incidence, point prevalence, cumulative or lifetime prevalence, patient-based outcomes (e.g., quality of life), direct and indirect costs, and outcomes considered in the guideline (4).	**HOW-TO** Suggested template for major section in a guideline (4).	**Medicine** (4)	• None.
Benefits and harms	Potential benefits and risks associated with recommendations (COGS) (4, 16, 107). Benefits and harms of specific practices are specified; benefits and harms are quantified (33). The recommendation is supported with a discussion of the benefits (e.g. health gains), and the harms and risks (e.g. drug side effects) (40). The "ultimate" PG may incorporate a full account of the risks and benefits of treatment, patients' estimates of their quality of life, and the cost effectiveness of alternative treatment options potential (10). Recommendations to administer, or not administer, an intervention, should be based on the tradeoffs between benefits on the one hand, and risks, burden and, potentially, costs on the other. If benefits outweigh risks and burden, experts will recommend that clinicians offer a treatment to typical patients. The uncertainty associated with the tradeoff between the benefits and risks and burdens will determine the strength of recommendations (23).	**HOW-TO** • "Harm" should be included in the evidence profile - List the adverse events or other unfavourable outcomes that may occur if the action statement were followed (4). • These guidelines should include declarations of acceptable levels of risks and costs per benefit achieved, so that comparisons can be made across guidelines. (43). • Qualitative and quantitative information should be included (4). • Does it consider all relevant harms and benefits of the interventions discussed (105)?	**Medicine** (4, 10, 16, 23, 31, 33, 40, 43, 105, 107)	• To be clinically important, a guideline should convince you that the benefits of following the recommendations are worth the expected harms and costs (31).
Costs	Costs should be included in the evidence profile (4, 33, 98). Costing and discounting methods should accord with standard guidelines for economic evaluation (45).	**EXAMPLE** Guidelines rely on epidemiologic, or population-based evidence to determine effectiveness over a range of anatomy and physiology and physiologic findings and response. A dual viewpoint considering both individual and population costs and benefits is critical. - In the context of occupational medicine (9).	**Medicine** (4, 33, 45, 98)	• None.
Outcome Data	The presence of outcome data in the guideline or in connection to the guideline (43) and whether it includes outcomes that patients care about (89).	**EXAMPLE** Respondents in this study stated that outcome data that take into account patients' health status and well-being need to be included in guideline development (89).	**Medicine** (43, 89)	• None.
Scope and purpose	Patient population eligible for guideline plus exclusion criteria (COGS) (4).	**HOW-TO** • Contain a specific description about the overall objective(s), the health question(s) covered by the guideline and the population (patients, public, etc.) to whom the guideline is meant to apply (17, 108). **EXAMPLES** • A focused and narrow scope is beneficial. For example: (a) We limited the scope of the guideline to secondary prevention to minimize complexity and to maximize consensus (72). (b) Guidelines with a narrow scope had significantly higher mean domain scores for "rigour of development" and "clarity of presentation" compared with those with a broad scope (109).	**Medicine** (4, 108-110) **Cognitive Ergonomics** (72)	• None.

Patient Information	Patient information (16) and “Role of patient preferences” should be included in the evidence profile. Information is included to support discussion with patients, or patient involvement in decision making (88).	**HOW-TO** • Specify “role of patient preferences” as large, moderate, small or none, based on the opportunity for shared decision making with the patient or Proxy (4). • Include patient education or involvement (informational or educational resources for patients/caregivers, questions for clinicians to facilitate discussion, or contact information (phone, fax, email or URL) to acquire information or educational resources) (88).	**Medicine** (4, 16, 88)	• None.
Ethnicity Information	Ethnic specific information should be specified in the PG and their recommendations. Ethnic differences between patients exist between country (111).	**EXAMPLE** The results of the study show that PG from the four western countries do contain ethnic specific information and recommendations, but to a varying extent (111).	**Medicine** (111)	• Disregarding scientific evidence about ethnic difference in PG could compromise the quality of care for ethnic minorities and could lead to unnecessary health problems in this group (111).

CODEBOOK – Evidence Synthesis

Attribute: 3. WHEN – Currency of evidence base

Concept	CODEBOOK DEFINITION	OPERATIONALIZATION – *"How-to"*	CONTEXT	RELATIONSHIP WITH UPTAKE
Updating	With rapidly changing body of literature, guidelines can rapidly become outdated (18). Users should consider potential effects of new information when assessing guidelines, particularly for rapidly evolving topics (18). The duration (i.e. period of time) to which the change is applicable and intended to persist (112).	**HOW-TO:** • Practice guidelines must include statements about when they should be reviewed to determine whether revisions are warranted, given new clinical evidence or professional consensus (or the lack of it) (57). • Guidelines should describe methods for monitoring new evidence and updating recommendations when needed (113). • Continually and periodically update a guideline according to the evidence base (1, 79). **EXAMPLES** • One GP stated "you read the guidelines, in the absolute certain knowledge that they're at lest two years out of date"'; One GP stated "of course, the asthma guidelines that we use at the moment are not based on terribly good evidence; evidence base is not representative of "real world" patients; Use of the guideline with individual patients depends if deemed suitable by the health care professional (114). • Guidelines for the management of benign prostatic hyperplasia may be more susceptible to becoming obsolete b/c the field is characterized by extremely rapid accumulation of new evidence and emergence of evolving technology (79). • Study suggests that change in recommendations may hinder implementations. "And you then begin to wonder how long before it changes again and for what reason?" [participant]- This is extremely important since the development of evidence based PG requires changed in recommendations (because of change in evidence or our understanding of evidence) (91).	**Medicine** (1, 18, 57, 79, 91, 112, 114)	• Guidelines that reflect current state of practice or suggest minor changes found their way into practices easier (91). • Some have reservations about the evidence base of guidelines; specifically how up to date they are (114). • Change in recommendations evoked skepticism and negatively influenced implementation (91). • Noticeable changes in recommendations affected patient-doctor relationships as patients because skeptical of the quality of care they received (91). GP welcomed PG if they were changes in practice and they felt "they needed update on them" [participants] (91).

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