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The validity of recommendations from clinical guidelines: a survival analysis

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Abstract

Background: Clinical guidelines should be updated to maintain their validity. Our aim was to estimate the length of time before recommendations become outdated.

Methods: We used a retrospective cohort design and included recommendations from clinical guidelines developed in the Spanish National Health System clinical guideline program since 2008. We performed a descriptive analysis of references, recommendations and resources used, and a survival analysis of recommendations using the Kaplan–Meier method.

Results: We included 113 recommendations from 4 clinical guidelines with a median of 4 years since the most recent search (range 3.9–4.4 yr). We retrieved 39 136 references (range 3343–14 787) using an exhaustive literature search, 668 of which were related to the recommendations in our sample. We identified 69 (10.3%) key references, corresponding to 25 (22.1%) recommendations that required updating. Ninety-two percent (95% confidence interval 86.9–97.0) of the recommendations were valid 1 year after their development. This probability decreased at 2 (85.7%), 3 (81.3%) and 4 years (77.8%).

Interpretation: Recommendations quickly become outdated, with 1 out of 5 recommendations being out of date after 3 years. Waiting more than 3 years to review a guideline is potentially too long.

Competing interests: See end of article.

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Clinical guidelines are "statements that include recommendations intended to optimize patient care that are informed by systematic reviews of evidence and an assessment of the benefits and harms of alternative care options."[1] As with systematic reviews, guidelines become outdated as new evidence is published and require a periodic reassessment to remain valid.[2–4]

Updating clinical guidelines is a complex process that includes identifying new evidence, assessing whether it has an impact on the recommendations and assessing whether an update is required.[5,6] Methodological handbooks include little guidance as to how to review and update guidelines, other than to do so periodically.[5,7–9]

Despite scant research, guideline programs endorse 3 to 5 years as a reasonable period after which guidelines should be reviewed.[5,10] This generic guidance is based on a study published more than 10 years ago that investigated how often guidelines needed to be updated.[4] We therefore developed a strategy to assess the validity of recommendations and estimated how long it took before recommendations became out of date.

Methods

Design

We conducted a retrospective cohort study of recommendations from clinical guidelines. We included recommendations from English translations of guidelines developed in the Spanish National Health System clinical guidelines program since 2008. All of the guidelines are available from the GuiaSalud library (www.guiasalud.es/). We stratified guidelines by topic (cancer and palliative care, cardiovascular disease, mental health and metabolic disease) and by year of publication (2008 and 2009). When multiple guidelines per strata were available, we randomly selected one.

We classified recommendations according to topic (as stated previously), strength (A, B, C, D, or good practice point as graded using the Scot-

tish Intercollegiate Guidelines Network [SIGN] system),[11] clinical purpose (prevention, screening, treatment or other) and number of pertinent references to which it was linked (turnover).

We performed a stratified random sampling of recommendations by number of references linked per recommendation and by guideline topic. The sample size required for the study was 112 recommendations (α risk of 0.95; precision ± 0.05 units in a 2-sided test; reference population size 249; expected proportion 0.154; estimated replacement rate 1%).

Assessment of recommendations

We developed a nine-stage strategy to assess the validity of recommendations (Figure 1). Stage 1 involved the identification of clinical questions and recommendations. In stage 2, for each set of included guidelines, we conducted a baseline survey in a convenience sample of 6 clinical experts from the original guideline group (4 of whom represented the different areas covered by the guideline, and 2 of whom were external). The experts evaluated whether they considered the recommendations to be up to date and stated whether they knew of any new studies that could modify the recommendations. In stage 3, we recovered the original exhaustive literature searches for each of the clinical questions addressed in the guidelines. Information specialists, preferably from the group who worked on the original guideline, performed the database searches and filtered the results by study design (randomized controlled trial or systematic review). Stage 4 involved clustering the references obtained from the baseline survey and literature search to identify and eliminate duplicates. We then evaluated whether references were pertinent to the topic of interest, the study design and the type of publication (original article or abstract) in stage 5. In stage 6, we matched perti-

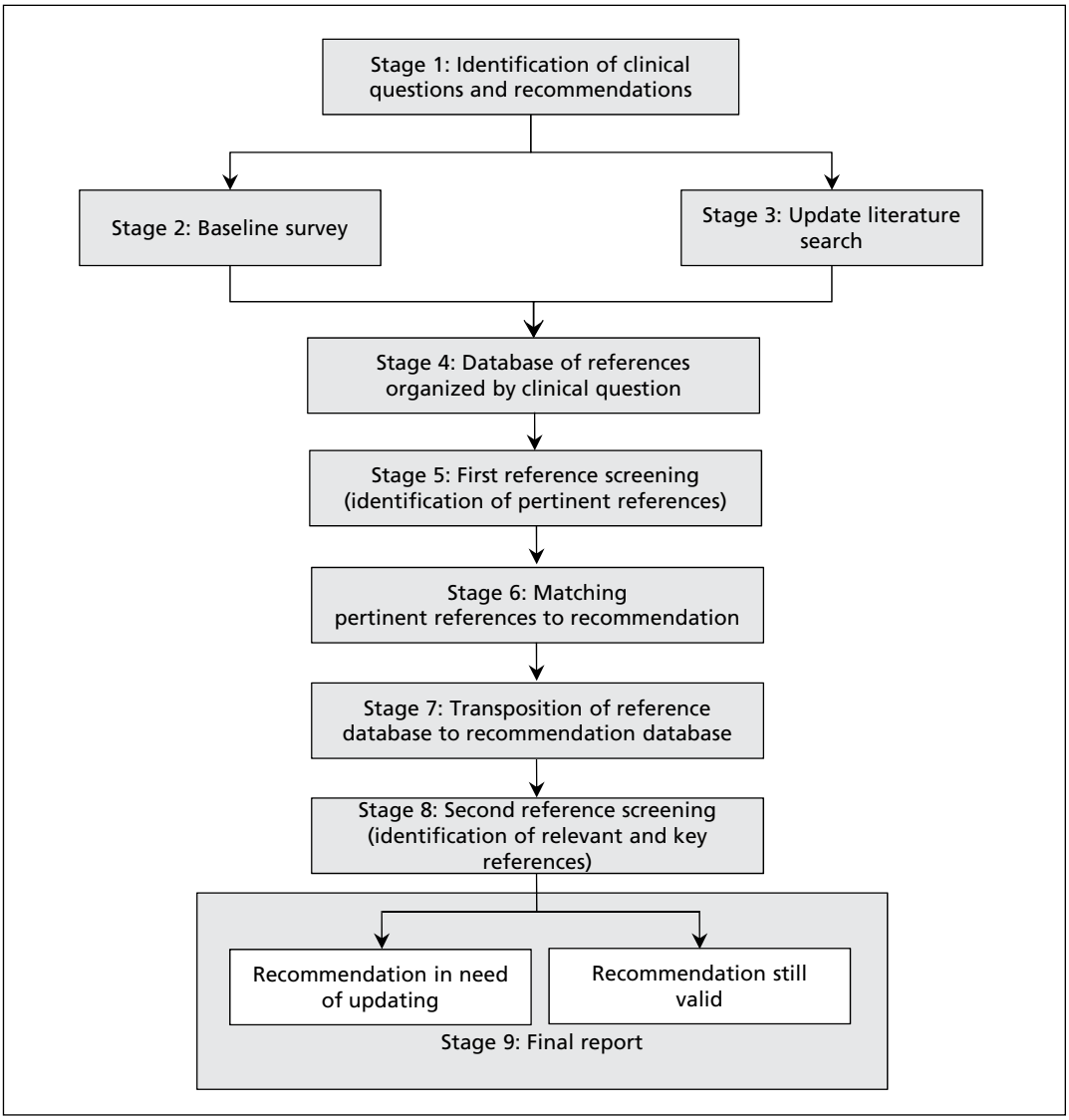

Figure 1: Strategy to assess the validity of recommendations.

nent references with the corresponding recommendations. In stage 7, we analyzed the reference database to find recommendations without references, recommendations with a low turnover (≤ median number of references per recommendation) or recommendations with a high turnover (> median number of references per recommendation). In stage 8, we designed a form to assess and classify pertinent references. Relevant references were defined as those that could be used when considering an update to a recommendation, but that would not necessarily trigger a potential update. Key references were those that could potentially trigger an update. In addition, the form asked respondents to consider potential changes in the recommendation in relation to population, intervention, comparison, outcome, quality of evidence, direction and strength of the recommendation.[12] Each form was assessed by 2 clinical experts and 1 guideline methodologist, and disagreements were resolved by consensus during online meetings. In stage 9, using the results of the second reference screening in stage 8, we classified recommendations as either in need of updating (with one or more key references linked) or still valid (without key references linked). A final report was then sent to the corresponding institutions that developed the guidelines and the clinicians who collaborated on the study.

A more complete description of our strategy is available in the previously published protocol.[13]

Outcome

Our primary outcome was the median length of time for recommendations to become out of date.

Statistical analysis

We performed a descriptive analysis of the data. We calculated either absolute and relative frequencies or median and range, as appropriate. We compared recommendations in need of updating versus those still valid by topic, strength of recommendation, clinical purpose and turnover using the Pearson χ^2 test.

We calculated the response rate for the baseline survey and considered a reply to be valid only if more than 20% of our questions had been answered.

We evaluated agreement between the opinions of the clinical experts and the methodologist as to what was a relevant or key reference. We used a decision algorithm to resolve disagreements (Appendix 1, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.140547/-/DC1). We followed the guidelines proposed by Landis and Koch[14] to evaluate agreement (κ 0–0.20, poor agreement; κ 0.21–0.40, fair agreement; κ 0.41–0.60, moderate agreement; κ 0.61–0.80, substantial agreement; κ > 0.80, almost perfect agreement).

We performed a survival analysis to determine our primary outcome. We defined an event as the identification of a key reference for a specific recommendation. We considered the inception date to be the date of the original literature search. The obsolescence date was the publication date of the first key reference. The last observation date was the date on which an updated search was started. We calculated the survival time for a potential update (obsolescence date – inception date) and for still valid recommendations (last observation date – inception date). We calculated the estimated rate of survival of recommendations using the Kaplan–Meier method. We used the log-rank test to analyze differences between survival curves according to guideline topic, strength of recommendation, clinical purpose and turnover.

We assessed the resources used to support our strategy. We recorded the number of hours spent on each stage and the number of researchers involved. We imputed 10 minutes per reference when time spent was not reported. We calculated the number of references assessed per hour per researcher and reported the median and range.

We accepted p values of less than 0.05 as significant in all calculations. We performed the analyses using SPSS 21.0 (SPSS Inc., Chicago, Illinois) and assessed the agreement (κ coefficient and the 95% confidence intervals [CIs]) using EPIDAT 4.0 (Consellería de Sanidade, Xunta de Galicia, Spain and Pan American Health Organization, Washington, DC). We calculated sample size using GRANMO 7 (www.imim.cat/ofertadeserveis/software-public/granmo).

Results

We identified 14 clinical guidelines in March 2011 (www.guiasalud.es/). We excluded 6 guidelines that were not available in English and stratified the remaining guidelines by topic and year of publication. Our selection process is summarized in Appendix 2 (available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.140547/-/DC1). Because multiple guidelines were available for the stratum "mental health 2008," we randomly selected a single publication. We included 4 guidelines in our final cohort: management of major depression in adults (2008);[15] prostate cancer treatment (2008);[16] secondary prevention of stroke (2009) (primary prevention was excluded);[17] and prevention and treatment of obesity in childhood and adolescence (2009).[18]

The included guidelines addressed 87 clinical questions and made 249 recommendations (Appendix 3, available at www.cmaj.ca/lookup

/suppl/doi:10.1503/cmaj.140547/-/DC1). In 3 guidelines, the original literature search started in 2007;[15–17] the literature search for the guideline on obesity in childhood and adolescence began in 2008.[18]

Our random sample of recommendations included 43 clinical questions and 113 recommendations (Table 1). Most of the recommendations were classified as a good practice point (n = 51 [45.1%]) and were about treatment (n = 59 [52.2%]) or prevention (n = 47 [41.6%]). These proportions were similar independent of turnover (Table 1).

Baseline survey

We contacted a total of 24 clinical experts for our baseline survey and had a response rate of 70.8% (17 respondents) (Appendix 3). Respondents reported that they were aware of new and relevant studies for 140 recommendations (56.2%), but they considered this new evidence to be sufficient to warrant an update in only 68 recommendations (27.3%) (Appendix 3). After screening for pertinence, we selected 49 of the 189 references suggested by the clinical experts (25.9%). In addition, we included 21 (42.9%) references that were not identified in the updated literature search (Appendix 3).

Literature search

We recovered the original search strategy for 3 clinical guidelines[15–17] and developed a new search for the remaining set of guidelines.[18] Searches were done by different information specialists, with the exception of the clinical guidelines on secondary prevention of stroke,[17] for which the original information specialist was available (Appendix 3).

For each set of guidelines, we ran exhaustive literature searches for the complete year in which the original search was completed (2007–2008) onward (2011–2012). Search periods had a median of 4 years (range 3.9–4.4 yr). We retrieved a total of 39 136 references (range 3343–14 787) (Table 2).

Table 1: Characteristics of recommendations

Characteristic	Guidelines topic and year of publication: Major depression in adults, 2008[15]	Obesity in childhood and adolescence, 2009[18]	Prostate cancer treatment, 2008[16]	Secondary prevention of stroke, 2009[17]	Total
Sample size, no.					
Clinical questions	8	10	16	9	43
Recommendations	26	29	36	22	113
SIGN strength of recommendations, no. (%)					
A	4 (15.4)	0 (0.0)	5 (13.9)	9 (40.9)	18 (15.9)
B	8 (30.8)	6 (20.7)	3 (8.3)	5 (22.7)	22 (19.5)
C	2 (7.7)	3 (10.3)	2 (5.6)	2 (9.1)	9 (8.0)
D	1 (3.8)	1 (3.4)	11 (30.6)	0 (0.0)	13 (11.5)
Good practice point	11 (42.3)	19 (65.5)	15 (41.7)	6 (27.3)	51 (45.1)
Clinical purpose, no. (%)					
Prevention	0 (0.0)	25 (86.2)	0 (0.0)	22 (100.0)	47 (41.6)
Screening	3 (11.5)	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.7)
Treatment	23 (88.5)	0 (0.0)	36 (100.0)	0 (0.0)	59 (52.2)
Other	0 (0.0)	4 (13.8)	0 (0.0)	0 (0.0)	4 (3.5)
Turnover, no. (%)					
No references	4 (15.4)	7 (24.1)	11 (30.6)	6 (27.3)	28 (24.8)
Low	12 (46.2)	11 (37.9)	13 (36.1)	8 (36.4)	44 (38.9)
High	10 (38.5)	11 (37.9)	12 (33.3)	8 (36.4)	41 (36.3)

Note: SIGN = Scottish Intercollegiate Guidelines Network.

Assessment of references

First screening

We identified 951 (2.4%) pertinent references, which could be matched to 187 (75.1%) recommendations (Table 2). The number of pertinent references per recommendation was between 2 and 7 (Appendix 3).

Second screening

From the 668 pertinent references linked to our random sample of 113 recommendations, we identified 69 key references (10.3%) (Table 2 and Appendix 4, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.140547/-/DC1]. Agreement between clinical experts and the methodologist as to what was a key reference was poor (range 0.1–0.2) (Appendix 3). Forty-four of the key references (63.8%) were randomized controlled trials and 46 (66.7%) changed the quality of the evidence supporting the corresponding recommendation (Table 2). We identified 9 references that changed the direction of one recommendation about the pharmacological treatment of depression (Table 2).

Assessment of recommendations

We identified 25 (22.1%) recommendations that were considered in need of updating. Most of these recommendations were graded B for strength or considered a good practice point (n = 9

Table 2: Results of the updated literature search, reference screening and reference classification

Characteristic	Guidelines topic and year of publication: Major depression in adults, 2008[15]	Obesity in childhood and adolescence, 2009[18]	Prostate cancer treatment, 2008[16]	Secondary prevention of stroke, 2009[17]	Total
References found during updated exhaustive literature search, no.	11 243	9 763	3 343	14 787	39 136
First reference screening from all recommendations, no. (%)					
Duplicate	3 846 (34.2)	2 445 (25.0)	286 (8.6)	1 582 (10.7)	8 159 (20.8)
Excluded	6 976 (62.0)	6 981 (71.5)	2 901 (86.8)	12 940 (87.5)	29 798 (76.1)
Included (pertinent references)	260 (2.3)	334 (3.4)	102 (3.1)	255 (1.7)	951 (2.4)
New*	161 (1.4)	3 (0.0)	54 (1.6)	10 (0.1)	228 (0.6)
Second reference screening from sample recommendations, no. (%)	n = 192	n = 292	n = 106	n = 78	n = 668
Pertinent references	73 (38.0)	93 (31.8)	22 (20.8)	12 (15.4)	200 (29.9)
Relevant references†	106 (55.2)	167 (57.2)	73 (68.9)	53 (67.9)	399 (59.7)
Key references‡	13 (6.8)	32 (11.0)	11 (10.4)	13 (16.7)	69 (10.3)
Key references, type of study, no. (%)	n = 13	n = 32	n = 11	n = 13	n = 69
Randomized controlled trial	8 (61.5)	23 (71.9)	9 (81.8)	4 (30.8)	44 (63.8)
Systematic review	5 (38.5)	9 (28.1)	2 (18.2)	9 (69.2)	25 (36.2)
Key references, recommendation change, no. (%)§					
Population	1 (7.7)	4 (12.5)	–	1 (7.7)	6 (8.7)
Intervention	12 (92.3)	5 (15.6)	2 (18.2)	7 (53.8)	26 (37.7)
Comparison	–	2 (6.3)	2 (18.2)	1 (7.7)	5 (7.2)
Outcome	9 (69.2)	2 (6.3)	3 (27.3)	–	14 (20.3)
Quality of the evidence	11 (84.6)	25 (78.1)	5 (45.5)	5 (38.5)	46 (66.7)¶
Direction of the recommendation	9 (69.2)	–	–	–	9 (13.0)
Strength of the recommendation	11 (84.6)	14 (43.8)	7 (63.6)	6 (46.2)	38 (55.1)

*References that may be related to new recommendations.
†All relevant references were also pertinent.
‡All key references were also pertinent and relevant.
§One reference may change more than one issue.
¶Fourteen key references changed the quality of evidence.

[36.0%] for both), were about prevention (n = 15 [60.0%]) and included a high number of linked references (n = 18 [72.0%]) (Table 3). Recommendations with a high turnover were more likely to require a potential update than those with a low turnover. Guideline topic, the strength of recommendations and clinical purpose were not associated with the need to update.

The median follow-up time of recommendations was 3.6 years (range 0–4.4 yr). At 1 year, 92.0% (95% CI 86.9%–97.0%) of the recommendations were still valid. This probability gradually decreased at 2, 3 and 4 years (85.7%, 81.3% and 77.8%, respectively) (Figure 2 and Appendix 3). The guideline topic, strength of the recommendations, clinical purpose and recommendation turnover were not associated with differences between survival curves.

Use of resources

A total of 43 people (4 information specialists, 16 guidelines methodologists and 26 expert clinicians) participated in our process, for a total of 1170.9 hours (Appendix 3). The most time-consuming task was the first reference screening and matching of the references with recommendations (566.5 h) (Appendix 3).

Interpretation

We evaluated the validity of a random sample of recommendations from clinical guidelines produced by a national guideline development program. Previous studies that have analyzed the survival time of clinical guidelines have suggested that guidelines should be reassessed every 3 to 5 years.[4,19] However, these studies considered the guidelines as the unit of analysis rather than the individual recommendations, and the authors did not use an exhaustive search strategy. Our analysis of recommendation-level data showed that recommendations quickly became outdated (about 20% of the recommendations were out of date within 3 years).

Recommendations with a high turnover were more likely to require an update than those with a low turnover, which suggests that fields with high research activity are likely areas in which effects

Table 3: Status of 113 recommendations included in the sample

Variable	Status, no. (%)		p value*
	Still valid	Potential for update	
Guidelines topic			
Mental health, n = 26	23 (88.5)	3 (11.5)	0.32
Metabolic disease, n = 29	21 (72.4)	8 (27.6)	
Cancer and palliative care, n = 36	29 (80.6)	7 (19.4)	
Cardiovascular disease, n = 22	15 (68.2)	7 (31.8)	
SIGN strength of recommendations	n = 88	n = 25	
A	15 (17.0)	3 (12.0)	0.11
B	13 (14.8)	9 (36.0)	
C	6 (6.8)	3 (12.0)	
D	12 (13.6)	1 (4.0)	
Good practice point	42 (47.7)	9 (36.0)	
Clinical purpose			
Prevention	32 (36.4)	15 (60.0)	0.14
Screening	3 (3.4)	0 (0.0)	
Treatment	49 (55.7)	10 (40.0)	
Others	4 (4.5)	0 (0.0)	
Turnover			
Without references	28 (31.8)	0 (0.0)	0.00
Low turnover	37 (42.0)	7 (28.0)	
High turnover	23 (26.1)	18 (72.0)	

Note: SIGN = Scottish Intercollegiate Guidelines Network.
*Pearson χ^2 test.

are not conclusive or where alternative interventions are being developed. Guideline developers should hence tailor their strategies accordingly. Factors such as topic, strength of the recommendation and clinical purpose were not predictors of the need for updating.

Previous work studying the lifespan of systematic reviews showed that an updating signal appeared in 23% of the publications within 2 years, and that cardiovascular medicine had the shortest time before an updating signal.[2] In addition, a recent evaluation of guidelines for interventions developed by the UK's National Institute for Health and Care Excellence (NICE) showed that updated recommendations generally had a larger body of evidence published since they were originally published.[20] Our results agree with these findings, with similar signals for the speed of decay and topics with a high turnover. Recent studies showed that recommendations based on scarce evidence were more likely to be updated,[21,22] and a large proportion of good practice points in our sample of recommendations needed to be updated (36% [9/25]).

Finally, empirical investigations of the speed of updating evidence-based point of care summaries shows that these resources undergo more frequent surveillance than clinical guidelines do.[3] These resources are popular among clinicians, and being up to date is a possible reason for their success. Thus, clinical guidelines should be updated more frequently if they are to be useful to clinicians.

Limitations

We did not implement our strategy prospectively in newly published guidelines, we limited our search by type of study, including only randomized controlled trials and systematic reviews, and we defined obsolescence date as the date when the first key reference was published.

Our sample is limited to recommendations from 4 guidelines developed by the Spanish National Health System's clinical guideline program, and our findings might not be generalizable to other settings. However, this potential limitation is mitigated because our sample covers broad areas such as cancer, cardiovascular diseases, mental health and lifestyle and behavioural issues.

We used the original exhaustive literature searches to identify new evidence. These searches yielded many off-target references and were resource intensive. Previous research suggests that restrictive search strategies are sufficient to monitor the literature for updating clinical guidelines and systematic reviews.[23,24] Nevertheless, available research is limited, and more studies about the performance of restrictive strategies are needed.[13]

The baseline surveys among clinical experts to assess which recommendations were considered to be out of date or to suggest relevant references had different response rates for each of the clinical guidelines, and the surveys did not provide additional useful information. However, this strategy could be useful if implemented prospectively.

For the purpose of this study, we manually built our own databases of references and recommendations. All of the Guidelines were available through a Web portal (www.guiasalud.es/) and were accessible as PDF files. However, we did not have a guideline-authoring tool or a common electronic platform with the functionalities needed to automate the process, increasing the burden of the work.

Conclusion

Guideline developers should implement strategies to survey the validity of the recommendations. A time line of 6 to 12 months for the surveillance of new evidence could be reasonable and should be tailored depending on the speed with which new research is published. This

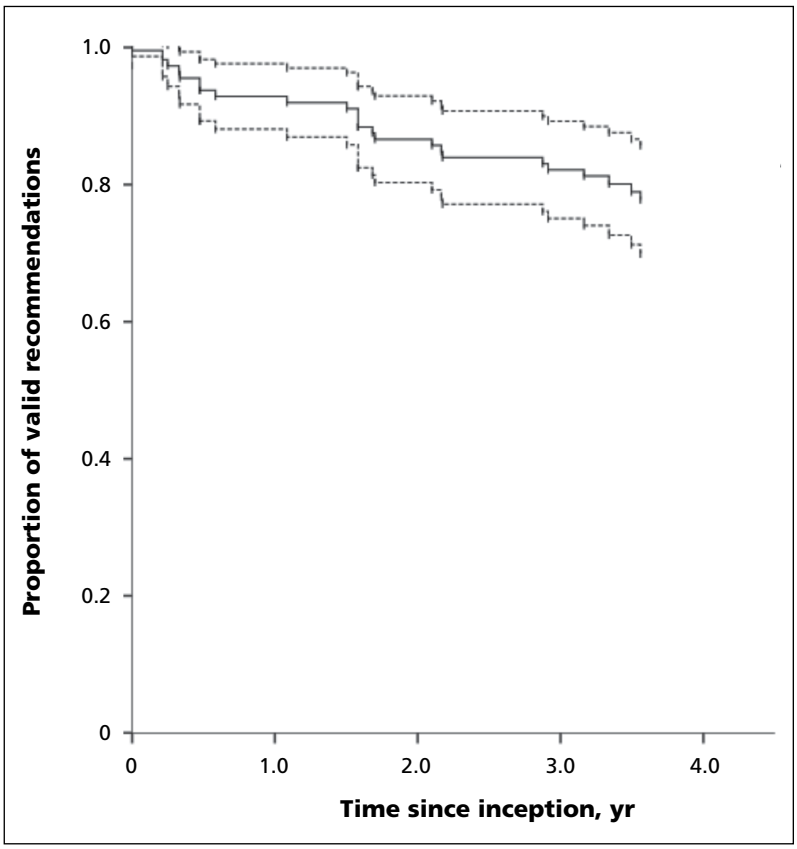

Figure 2 : Kaplan–Meier survival curve (solid line) of clinical guideline recommendations with 95% confidence intervals (dashed lines).

approach would likely decrease the workload for each update and, most importantly, assure the validity of recommendations.

Institutions that develop guidelines may benefit from working with online platforms that organize the guidelines, recommendations, references and searches in databases. Ideally, this technology would semiautomate the updating process, thereby optimizing efficiency.[25–27]

Finally, our framework provides a structured strategy to assess the validity of recommendations and provides detailed guidance for replicating the process. Our strategy could also be used to develop and evaluate more efficient ways of maintaining the validity of guidelines.[13]

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