Universitat Autònoma de Barcelona
Facultad de Medicina
Departamento de Pediatría, de Obstetricia y Ginecología, y de Medicina Preventiva
Programa de Doctorado en Salud Pública y Metodología de la Investigación Biomédica

Actualización de guías de práctica clínica

TESIS DOCTORAL

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Memoria de tesis como compendio de publicaciones presentada por Laura Martínez García para optar al grado de doctora en Medicina por la Universitat Autònoma de Barcelona y realizada bajo la dirección del Dr. Pablo Alonso Coello.

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Cita

«Ningún esfuerzo sin éxito y ningún éxito sin esfuerzo».

Escola Virolai

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Resumen

1. Resumen

1.1. Resumen

Antecedentes

Las guías de práctica clínica (GPC) son herramientas útiles en la toma de decisiones clínicas de los usuarios, de los profesionales y de los gestores sanitarios si se mantienen actualizadas y se garantiza la vigencia de sus recomendaciones.

Objetivos

Los objetivos principales de esta tesis son: 1) identificar y describir los métodos utilizados para actualizar las GPC y 2) diseñar y evaluar nuevos métodos para actualizar las GPC.

Métodos

Se han realizado cinco estudios con diferentes metodologías: 1) una encuesta internacional sobre el proceso de actualización de GPC, 2) una revisión sistemática de los métodos de actualización de GPC, 3) un análisis de supervivencia para estimar el tiempo de vigencia de las recomendaciones, 4) una evaluación de las recomendaciones actualizadas y 5) una evaluación de dos estrategias pragmáticas de búsqueda de la literatura para identificar señales de actualización.

Resultados

En la encuesta internacional hemos observado que el 92 % (36/39) de las instituciones que elaboran GPC las actualizan. El 52,8 % (19/36) de las instituciones siguen un procedimiento formal para decidir cuándo están desactualizadas. Un 86,1 % (31/36) de las instituciones siguen un procedimiento formal para actualizarlas, pero solo un 25 % (9/36) lo ha evaluado.

En la revisión sistemática hemos identificado ocho estudios: cuatro evalúan si las GPC están vigentes, tres actualizan puntualmente las GPC y uno las actualiza de

forma continua. La etapa más explícita en los diferentes estudios está relacionada con la identificación de nueva evidencia. Un estudio comparó una búsqueda limitada de la literatura frente a otra exhaustiva y sugirió que la limitada era suficiente para identificar señales de actualización. Otro estudio evaluó el tiempo de vigencia de las GPC y sugirió que se deberían revisar cada tres años.

En el análisis de supervivencia (muestra de 113 recomendaciones incluidas en cuatro guías del Programa de GPC en el Sistema Nacional de Salud) hemos observado que el 92,0 % de las recomendaciones están vigentes un año después de su elaboración (intervalo de confianza del 95 %: 86,9 a 97,0). Esta probabilidad se reduce gradualmente (85,7 %; 81,3 %; 77,8 % a los dos, tres y cuatro años, respectivamente).

En la evaluación de recomendaciones actualizadas (muestra de 1306 recomendaciones incluidas en las guías del *National Institute for Health and Care Excellence*) hemos observado una gran heterogeneidad en la presentación de los cambios y una falta de justificación de los mismos. La muestra de recomendaciones no fue suficiente para identificar factores asociados a la actualización.

Finalmente, en la evaluación sobre estrategias pragmáticas de búsqueda de la literatura hemos observado que la búsqueda restrictiva recuperó un 68,1 % menos de referencias que la búsqueda exhaustiva (12486 frente a 39136) e identificó el 89,9 % (62/69) de las referencias clave. La búsqueda en la base de datos McMaster PLUS recuperó un 88,5 % menos de referencias que la búsqueda exhaustiva (4486 frente a 39136), aunque solo identificó el 26,1 % (18/69) de las referencias clave.

Conclusiones

Las instituciones que elaboran GPC no tienen un proceso estandarizado para actualizar sus GPC. Esto es debido, quizá en parte, a la escasa investigación metodológica sobre la actualización de las GPC.

Las recomendaciones de las GPC se desactualizan rápidamente. Utilizar una estrategia de búsqueda restrictiva y continua de la literatura, priorizando las preguntas clínicas con mayor ritmo de producción científica, podría ser una estrategia eficiente y factible para identificar las señales de actualización de GPC.

Es necesario continuar la investigación metodológica para optimizar y estandarizar el proceso de actualización de GPC, así como implementar y evaluar los resultados de dicha investigación en los programas de GPC.

1.2. Resum

Antecedents

Les guies de pràctica clínica (GPC) són útils en la presa de decisions clíniques dels usuaris, dels professionals i dels gestors sanitaris si es mantenen actualitzades i es garanteix la vigència de les seves recomanacions.

Objectius

Els objectius principals d'aquesta tesi doctoral són: 1) identificar i descriure els mètodes utilitzats per actualitzar les GPC i 2) dissenyar i avaluar nous mètodes per actualitzar les GPC.

Mètodes

S'han dut a terme cinc estudis amb diferents metodologies: 1) una enquesta internacional sobre el procés d'actualització de GPC, 2) una revisió sistemàtica sobre els mètodes d'actualització de GPC, 3) una anàlisi de supervivència per estimar el temps de vigència de les recomanacions, 4) una avaluació de les recomanacions actualitzades i 5) una avaluació de dues estratègies pragmàtiques de cerca de la literatura per identificar senyals d'actualització.

Resultats

En l'enquesta internacional hem observat que el 92,0 % (36/39) de les institucions que desenvolupen GPC les actualitzen. El 52,8 % (19/36) de les institucions tenen un procediment formal per decidir quan estan desactualitzades. Un 86,1 % (31/36) de les institucions tenen un procediment formal per actualitzar-les, tot i que només el 25 % (9/36) l'ha avaluat.

En la revisió sistemàtica hem identificat vuit estudis: quatre avaluen si les GPC són vigents, tres actualitzen puntualment les GPC i un les actualitza de manera contínua. L'etapa més explícita dels diferents estudis està relacionada amb la identificació de la nova evidència. Un estudi va comparar una cerca limitada de la literatura enfront d'una exhaustiva i va suggerir que una limitada és suficient per identificar senyals d'actualització. Un estudi va avaluar el temps de vigència de las GPC i va suggerir que s'haurien de revisar cada tres anys.

A l'anàlisi de supervivència (mostra de 113 recomanacions incloses en quatre guies del Programa de GPC del Sistema Nacional de Salut) hem observat que el 92,0 % de les recomanacions són vigents després d'un any des del seu desenvolupament (interval de confiança del 95 %: 86,9 a 97,0); aquesta probabilitat disminueix gradualment (85,7 %; 81,3 %; 77,8 % als dos, tres i quatre anys, respectivament).

En l'avaluació de les recomanacions actualitzades (mostra de 1306 recomanacions incloses en les guies del *National Institute for Health and Care Excellence*) hem observat una gran heterogeneïtat en la presentació dels canvis i una falta de justificació d'aquests canvis. La mostra de recomanacions no va ser suficient per identificar factors associats amb l'actualització de GPC.

Finalment, en l'avaluació sobre estratègies pragmàtiques de cerca de la literatura hem observat que la cerca restrictiva va recuperar un 68,1 % menys de referències que la cerca exhaustiva (12486 davant de 39136) i va identificar el 89,9 % (62/69) de les referències clau. La cerca a la base de dades McMaster PLUS va recuperar un 88,5 % menys de referències que la cerca exhaustiva

(4486 davant de 39136), tot i que només va identificar el 26,1 % (18/69) de les referències clau.

Conclusions

Les institucions que elaboren GPC no tenen un procés estandarditzat per actualitzar les seves GPC. Això es degut, possiblement, a l'escassa recerca metodològica sobre l'actualització de GPC.

Les recomanacions de les GPC es desactualitzen ràpidament. Utilitzar una estratègia de cerca restrictiva i contínua de la literatura, que prioritzi les preguntes clíniques amb un ritme de producció científica més elevat, podria ser una estratègia eficient i factible per identificar senyals d'actualització.

És necessari continuar la recerca metodològica per millorar i estandarditzar el procés d'actualització de les GPC, així com implementar i avaluar els resultats d'aquesta recerca en els programes de GPC.

1.3. Abstract

Background

Clinical practice guidelines (CPG) are useful tools to help patients, health professionals, and policymakers to make evidence-based decisions about health care; consequently, they need to be updated in order to guarantee the validity of recommendations.

Objectives

The main objectives of this thesis are: 1) to identify and describe the methods used to update CPGs and 2) to design and evaluate new methods for updating CPGs.

Methodology

We conducted five studies with different methodologies: 1) an international survey on CPG updating process; 2) a systematic review of CPG updating methods; 3) a survival analysis to estimate the length of time before recommendations become outdated; 4) an assessment of updated recommendations, and 5) an evaluation of two pragmatic search strategies to identify the need to update recommendations.

Results

In the international survey, 92.0% of the institutions (36/39) report the update of their guidelines. The 52.8% (19/36) have a formal procedure for deciding when a guideline becomes out of date. The 86.1% (31/36) have a formal procedure for updating their guidelines; nevertheless, only 25% (9/36) piloted such process.

In the systematic review, we included a total of eight studies: four studies evaluated whether CPGs were out of date; three studies were actually CPG updates; and in one study CPGs were continuously monitored and updated. The most detailed reported phase of the process was the identification of new evidence. One study compared a restricted versus an exhaustive search, suggesting that a restricted search is sufficient to assess the validity of recommendations. Another study analysed the survival time of CPGs and suggested that these should be reassessed every three years.

In the recommendations survival analysis (113 recommendations included in four guidelines from the Spanish National Health System´s CPG Programme), 92.0% of the recommendations were valid one year after their development (95% confidence interval: 86.9 to 97.0). This probability gradually decreased (85.7%, 81.3%, 77.8% at two, three and four years, respectively).

In the updated recommendations assessment (1306 recommendations produced by the *National Institute for Health and Care Excellence*), presentation formats used to indicate the changes in recommendations varied widely across CPGs. The majority of these changes were not explained. We did not perform an analysis to

identify potential predictive factors for updating, given the small sample of recommendations retrieved.

In the assessment of pragmatic search strategies, the restrictive search retrieved 68.1% fewer references than those retrieved by the exhaustive search (12,486 versus 39,136), and identified 89.9% (62/69) of key references. The use of McMaster PLUS database retrieved 88.5% fewer references than those retrieved by the exhaustive search (4,486 versus 39,136), but identified substantially fewer key references (18/69, 26.1%).

Conclusions

Institutions involved in developing CPGs do not have a standardised CPG updating process. Furthermore, there is very limited methodological research into the CPG updating process, with available research focusing mainly on evidence search strategy.

Recommendations swiftly become outdated. A restrictive and continuous search strategy, prioritizing clinical questions with a higher rate of scientific production, could be an efficient and feasible method to identify studies that signal for updating CPGs.

Methodological research must be continued in order to improve and standardise the CPGs updating process, and to implement and assess the results of this research in CPG programmes.

Introducción

2. Introducción

2.1. ¿Qué son las guías de práctica clínica?

En 1990 el *Institute of Medicine* (IOM) propuso la primera definición formal sobre las guías de práctica clínica (GPC) como «un conjunto de recomendaciones desarrolladas de manera sistemática, con el objetivo de guiar a los profesionales y a los pacientes en el proceso de la toma de decisiones sobre qué intervenciones sanitarias son más adecuadas en unas circunstancias clínicas específicas» [1].

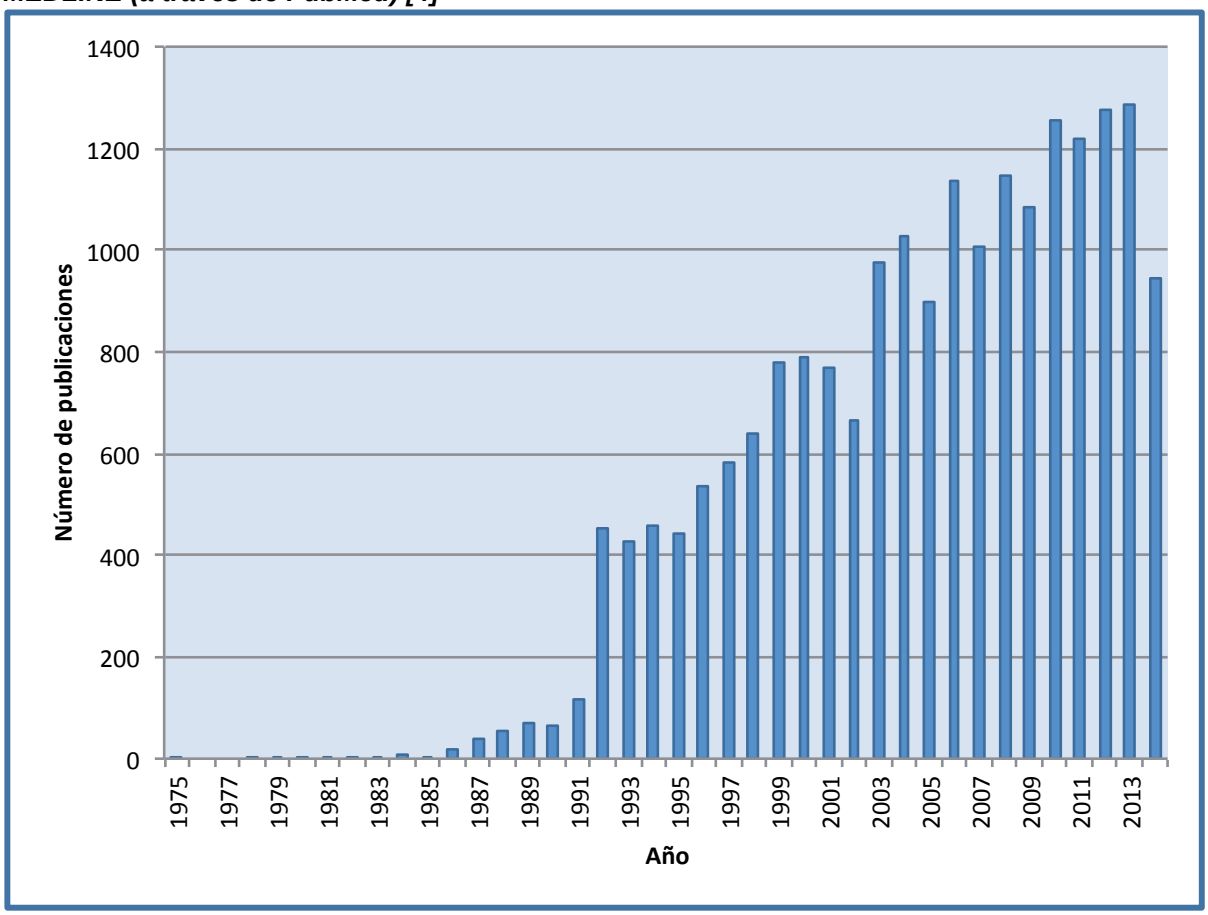
En el año 2011 el IOM actualizó la definición como «documentos que incluyen recomendaciones dirigidas a optimizar la atención a los pacientes y que se basan en revisiones sistemáticas (RS) de la evidencia científica y en una evaluación de los beneficios y riesgos de las opciones asistenciales alternativas» [2]. En la nueva definición resaltan como características esenciales de las GPC que estén basadas en RS y en la evaluación de los riesgos y beneficios de las distintas alternativas asistenciales [2].

El objetivo final de las GPC es mejorar la práctica clínica, reducir la variabilidad injustificada en la práctica clínica y mejorar la utilización de los recursos sanitarios [3].

Desde la primera definición formal en 1990, el número de GPC y de las instituciones que las elaboran ha aumentado considerablemente. El número de publicaciones relacionadas con GPC es un indicador del número de GPC elaboradas. El aumento de publicaciones se inició en los años 90 y, actualmente, se indexan, aproximadamente, 1000 documentos relacionados cada año[1] (figura 1).

[1] Búsqueda en MEDLINE a través de PubMed utilizando el término practice guideline [Publication Type].

Figura 1. Número de publicaciones relacionadas con guías de práctica clínica indexadas en MEDLINE (a través de PubMed) [4]



2.2. ¿Cómo se elaboran las guías de práctica clínica?

2.2.1. Etapas en la elaboración de guías de práctica clínica

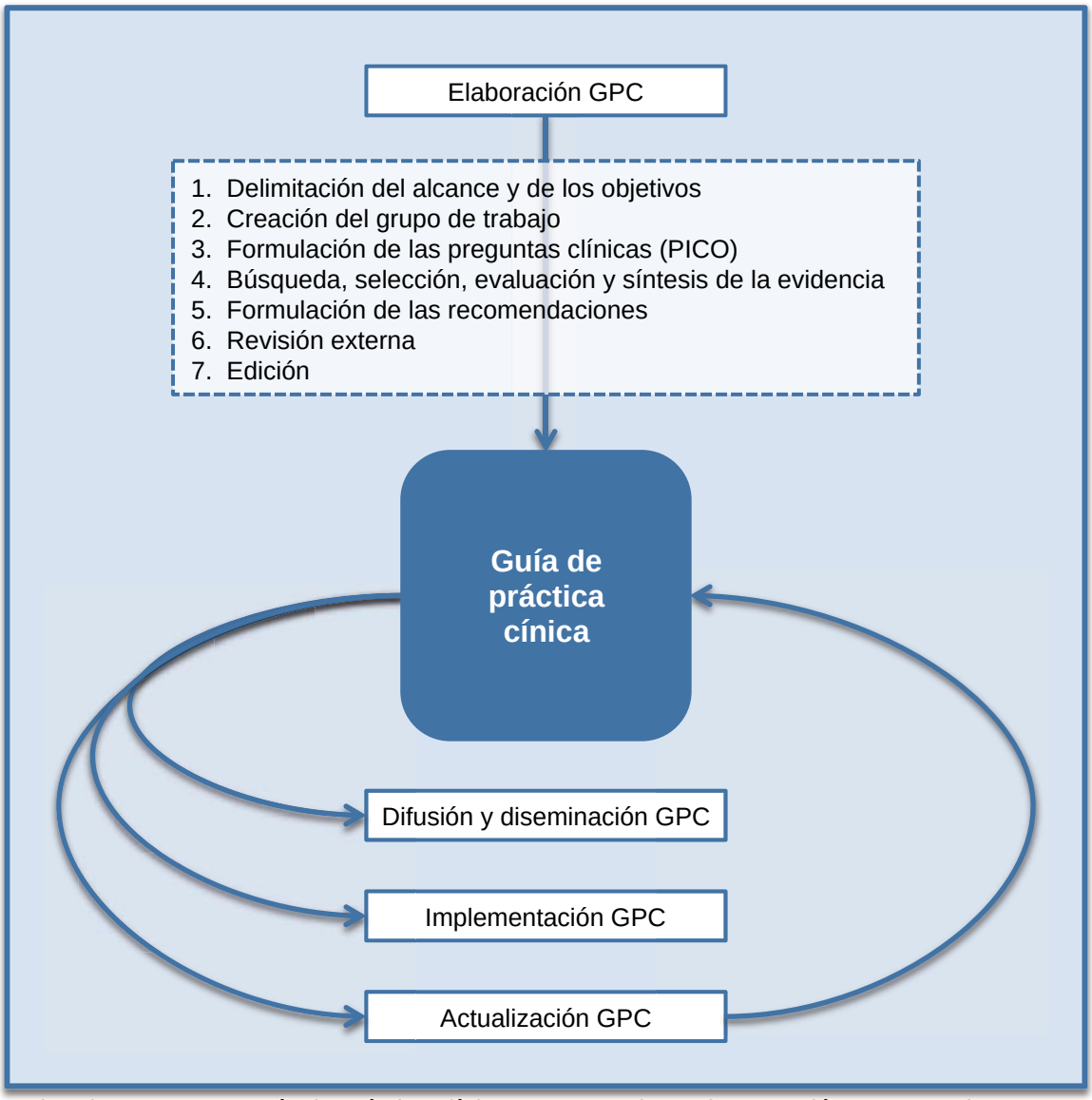
Las GPC tienen un ciclo vital que incluye diferentes etapas: 1) la elaboración, 2) la difusión y diseminación, 3) la implantación y 4) la actualización (figura 2). El proceso formal de cada etapa está ampliamente descrito en los manuales metodológicos de las diferentes instituciones que elaboran GPC [5-8]. A continuación, se describen brevemente las etapas de la elaboración:

- **Delimitación del alcance y de los objetivos:** En esta etapa se debe justificar la elaboración de la GPC, describir los objetivos generales, los aspectos de salud cubiertos y los usuarios de la GPC.
- **Creación del grupo de trabajo:** El grupo de trabajo de la GPC debe estar formado por representantes de los grupos de interés del tema de la GPC

(grupo multidisciplinario). Los perfiles que componen el grupo de trabajo generalmente: 1) están relacionados con el grupo elaborador (coordinador clínico, colaboradores clínicos y pacientes o representantes de los pacientes); 2) están relacionados con el equipo técnico (coordinador metodológico, colaboradores expertos en metodología y expertos en documentación), y 3) son revisores externos. Todos los miembros del grupo de trabajo deben realizar una cuidadosa declaración sobre potenciales conflictos de interés. Los programas de GPC deben acompañarse de actividades de formación de acuerdo con las necesidades específicas de cada grupo de trabajo.

- **Formulación de las preguntas clínicas:** En esta etapa se debe elaborar el listado de preguntas clínicas que se responderán en la GPC. Las preguntas clínicas se deben estructurar en un formato PICO (pacientes, intervención, comparación y desenlaces [*outcomes*]).
- **Búsqueda, selección, evaluación y síntesis de la evidencia:** La búsqueda y selección de la evidencia debe realizarse en base a los componentes de las preguntas clínicas (PICO) y al tipo de diseño de estudio que mejor puede darles respuesta (priorizando las RS). La calidad de la evidencia (definida como la confianza que se tiene en que la estimación del efecto que reflejan los estudios es cierta) debe evaluarse con un método explícito. Finalmente, hay que extraer y resumir la información relevante de los estudios incluidos.
- **Formulación de las recomendaciones:** En la elaboración de las recomendaciones se deben considerar de forma explícita los diferentes factores que determinan la fuerza y la dirección de las recomendaciones.
- **Revisión externa:** En esta etapa, un grupo multidisciplinario debe realizar una revisión independiente para matizar y enriquecer la GPC, así como para asegurar la exactitud de sus recomendaciones.
- **Edición:** Finalmente, en esta etapa, se debe revisar el estilo (lenguaje utilizado) y la estructura (índice de contenidos) de la GPC. Asimismo, se debe definir el formato (por ejemplo [p.ej.], en formato papel o en formato electrónico) y las versiones de la GPC (p.ej., GPC completa, GPC resumida o GPC para pacientes).

Figura 2. Ciclo vital de una guía de práctica clínica



Abreviaturas: GPC: guía de práctica clínica; PICO: paciente, intervención, comparador, desenlace.

2.2.2. Herramientas y recursos en la elaboración de guías de práctica clínica

Existen diversas herramientas y recursos para mejorar el proceso de elaboración de las GPC. Por un lado, instituciones pioneras en el campo de la elaboración de GPC han elaborado y actualizado sus manuales metodológicos [5-8]. Por otro

lado, se ha desarrollado diferentes instrumentos relacionados con la elaboración de GPC, como por ejemplo, el instrumento AGREE (*Appraisal of Guidelines for Research and Evaluation*) [9], la iniciativa GRADE (*Grading of Recommendations Assessment, Development and Evaluation*) [10] o, más recientemente, la lista de verificación del proceso de elaboración de GPC de G-I-N (*Guidelines International Network*) McMaster [11, 12].

Instrumento AGREE

El instrumento AGREE es una herramienta validada para la evaluación de la calidad de las GPC. En el año 2003, se publicó la primera versión del instrumento AGREE; en el año 2009, se publicó una nueva versión mejorada y refinada: el instrumento AGREE II [13, 14]. El objetivo del instrumento AGREE II es ofrecer un marco para evaluar la calidad de las GPC, proporcionar una estrategia metodológica para el desarrollo de las GPC y establecer qué información y cómo debe ser presentada en las GPC [15].

En los últimos años, y en especial desde la publicación del instrumento AGREE, la calidad en la elaboración de las GPC ha mejorado. No obstante, todavía existe un amplio margen para la mejora [16].

Sistema GRADE

El sistema GRADE es un marco sistemático y explícito para la evaluación de la calidad de la evidencia y la graduación de la fuerza de las recomendaciones. Desde el año 2000, el grupo de trabajo internacional GRADE (formado por elaboradores de GPC, epidemiólogos y clínicos pertenecientes a las principales instituciones que elaboran GPC) está desarrollando esta propuesta metodológica [10].

El sistema GRADE tiene tres aspectos diferenciales [17, 18]:

- En la etapa inicial de formulación de las preguntas clínicas, se deben definir los desenlaces de interés para las preguntas clínicas que se abordan, y clasificar la importancia relativa de los mismos.

- En la etapa de evaluación de la evidencia, se dispone de unos criterios explícitos para disminuir o aumentar la calidad de la evidencia por desenlace de interés. Los factores que pueden disminuir la calidad de la evidencia en ensayos clínicos son: las limitaciones en el diseño o la ejecución, los resultados inconsistentes, la ausencia de evidencia directa, la imprecisión o el sesgo de publicación. Los factores que pueden aumentar la calidad de la evidencia en estudios observacionales son: la fuerza de la asociación, la presencia de un gradiente dosis-respuesta o la consideración de los potenciales factores de confusión.
- En la etapa final de formulación de recomendaciones, se proponen varios factores que determinan la fuerza de las recomendaciones (p.ej., el balance entre los beneficios y los riesgos, la calidad de la evidencia, los valores y preferencias o los costes y el uso de los recursos).

Al utilizar el sistema GRADE los usuarios deben realizar juicios para decidir el grado de confianza que tienen en los resultados de la investigación y para decidir si adherirse a una recomendación conlleva más beneficios que riesgos [17, 18].

El sistema GRADE ya ha sido adoptado por numerosas instituciones, tanto en el ámbito internacional (Organización Mundial de la Salud [OMS], *National Institute for Health and Care Excellence* [NICE], *Scottish Intercollegiate Guidelines Netwok* [SIGN] o la Colaboración Cochrane) como en nuestro propio entorno (Programa de GPC en el Sistema Nacional de Salud [SNS]) [5-8, 19].

Para profundizar en la utilización y en la implementación del sistema GRADE se ha publicado una serie de seis artículos dirigidos a usuarios [20-25] y otra de 20 artículos dirigidos a elaboradores de GPC (actualmente se han publicado 16 de los artículos de esta serie) [26-41], que se hallan disponibles en la página web del grupo de trabajo [10].

Lista de verificación del proceso de elaboración de guías de práctica clínica de G-I-N McMaster

La lista de verificación G-I-N McMaster, desarrollada recientemente por un grupo internacional de investigadores (liderado por académicos de la Universidad

McMaster y en asociación con G-I-N), es una herramienta para que las instituciones que elaboran GPC puedan iniciar, mejorar o evaluar su proceso de elaboración de GPC [11]. Esta herramienta incluye una descripción de las diferentes etapas en la elaboración de las GPC y una página web con enlaces a publicaciones, herramientas y recursos metodológicos de apoyo [12].

2.2.3. Entidades que elaboran guías de práctica clínica

Existen múltiples instituciones que elaboran GPC, entre ellas, destacan, principalmente, las sociedades científicas y las agencias gubernamentales. Entre las más reconocidas internacionalmente se encuentran la OMS, la NICE o la SIGN, y en nuestro medio, el Programa de GPC en el SNS coordinado por GuíaSalud [42-45].

Programa de guías de práctica clínica en el Sistema Nacional de Salud – GuíaSalud

En el año 2006, el Ministerio de Sanidad puso en marcha el Programa de GPC en el SNS para promover el desarrollo, la adaptación, la actualización, la difusión y la implementación de las GPC en nuestro entorno. Este programa, en el que participan las agencias y unidades de evaluación de tecnologías sanitarias, está coordinado por GuíaSalud. En el marco del programa se elaboran GPC sobre problemas de salud prioritarios para el SNS.

En el año 2007, se creó un manual metodológico para la elaboración de GPC en el SNS, con el fin de elaborar GPC basadas en un riguroso proceso centrado en el uso de la mejor evidencia disponible [5]. Posteriormente, se elaboraron los manuales para la implementación, la actualización y, más recientemente, la implicación de los pacientes en el desarrollo de GPC [46-48].

Desde el año 2008, el Programa de Guías de Práctica Clínica en el SNS ha publicado 30 GPC [42].

2.3. ¿Cómo se actualizan las guías de práctica clínica?

2.3.1. Producción e integración de la nueva evidencia científica

El volumen de información científica aumenta constantemente (p.ej., cada día se publican 75 ensayos clínicos y 11 RS) y aún no ha alcanzado la meseta en su crecimiento [49, 50]. Además, la publicación de la información científica está dispersa en cientos de revistas biomédicas [51], a veces de difícil acceso [52, 53], y no hay garantía de su calidad metodológica [54].

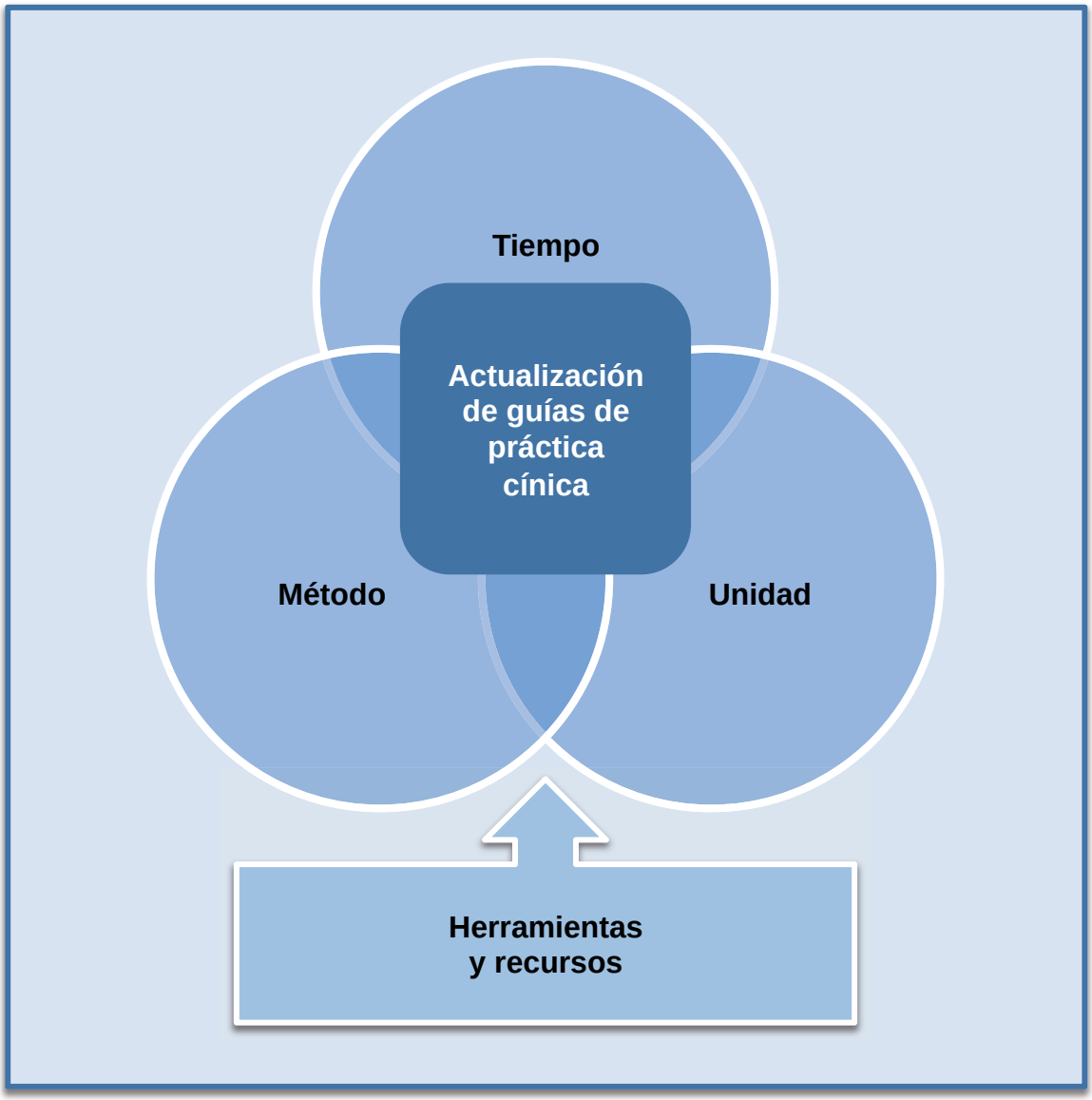
Para hacer frente a este exceso de información y con el objetivo de que la toma de decisiones clínicas se base en la mejor evidencia disponible, han tomado relevancia herramientas como las GPC [5]. No obstante, para que las GPC sean útiles en la toma de decisiones clínicas de los usuarios, de los profesionales y de los gestores sanitarios deben mantenerse actualizadas y garantizar la vigencia de sus recomendaciones.

2.3.2. Marco conceptual en la actualización de las guías de práctica clínica

La actualización de las GPC es, actualmente, un proceso complejo debido, principalmente, a la utilización de una terminología y una metodología no estandarizadas.

A continuación, se propone un marco conceptual para delimitar el proceso de actualización de GPC, centrado en los conceptos de tiempo (¿cuándo actualizar?), de método (¿cómo actualizar?), de unidad (¿qué actualizar?) y de herramientas y recursos (figura 3).

Figura 3. Marco conceptual en la actualización de guías de práctica clínica



Los principales conceptos expuestos (tiempo, método, unidad, herramientas y recursos) son útiles para describir y clasificar diferentes términos de uso frecuente en este campo; no obstante, hay que tener en cuenta que las definiciones propuestas a continuación aún no han sido consensuadas formalmente:

- **Tiempo de vigencia de las GPC[2] [concepto de tiempo]:** Es el tiempo desde la elaboración hasta la pérdida de vigencia de una GPC al identificar una señal de actualización.
- **Proceso de actualización de GPC [concepto de método]:** Entendemos la actualización de una GPC como un proceso iterativo con una metodología estructurada y explícita que incluye la identificación y la revisión de la nueva evidencia no incluida en la GPC previa[3] [55]. Si se identifica nueva evidencia relevante, se debe revisar la GPC y, en caso necesario, modificarla. Además, durante el proceso de actualización también deberían introducirse, si es necesario, mejoras metodológicas (p.ej., adaptar una GPC del sistema SIGN [56] al sistema GRADE [26]) así como mejoras de edición (p.ej., corregir erratas o mejorar la redacción del texto).

  Las tres etapas fundamentales a considerar durante el proceso de actualización de una GPC son: 1) identificación de la nueva evidencia, 2) evaluación del impacto de nueva evidencia, 3) revisión y, en caso necesario, modificación de la GPC.

  El objetivo final del proceso de actualización de GPC es minimizar el desfase entre la aparición de nuevo conocimiento y su traslación a la práctica clínica [46].
- **Señal de actualización [concepto de método]:** El término «señal de actualización» hace referencia a la nueva evidencia relevante que puede aportar cambios significativos en las preguntas clínicas (pacientes, intervención, comparación o desenlaces), en los factores que influyen en la formulación de las recomendaciones (p.ej., calidad de la evidencia, balance entre beneficios y daños, valores y preferencias, uso de recursos y costes) o en las recomendaciones.

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[2] En la mayoría de las definiciones se han utilizado las GPC como unidad de actualización. Sin embargo, las definiciones se pueden adaptar según la unidad de actualización, como por ejemplo, secciones, preguntas clínicas o recomendaciones (concepto abordado en «unidad de actualización»).

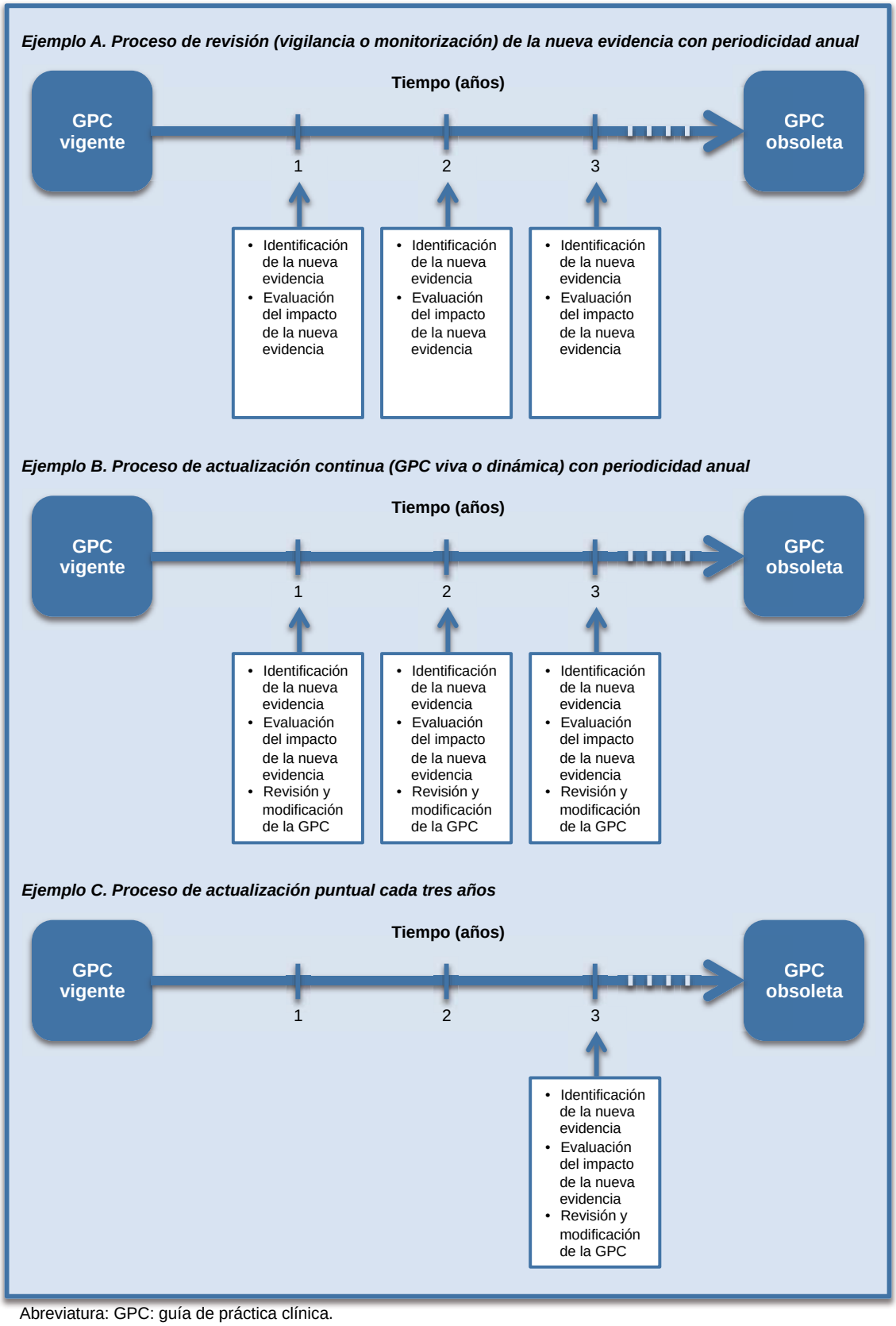
[3] Definición adaptada de la propuesta por Moher *et al*. 2006 para el proceso de actualización de las RS.

- **Ciclo de actualización de las GPC [concepto de tiempo-método]:** Cada proceso de actualización de una GPC corresponde a un ciclo de actualización y da como resultado una nueva versión de la GPC.
- **Proceso de revisión (vigilancia o monitorización) de la evidencia o identificación de la señal de actualización [concepto de tiempo-método]:** Los términos «revisión, vigilancia o monitorización» se utilizan de forma indistinta para describir el proceso de identificación de las señales de actualización. Este proceso comprende la identificación de la nueva evidencia y la evaluación de su impacto sobre la GPC. La revisión (vigilancia o monitorización) de la evidencia se asocia a un concepto de tiempo continuo (p.ej., cada seis meses o cada año) (figura 4: ejemplo A).
- **Proceso de actualización continuo (GPC vivas o dinámicas) frente a proceso de actualización puntual [concepto de tiempo-método]:** Los términos «actualización continua, GPC viva o dinámica» se diferencian del término «actualización puntual» por la periodicidad en que se realiza el proceso (identificación de la nueva evidencia, evaluación del impacto de nueva evidencia, revisión y, en caso necesario, modificación de la GPC). El concepto de actualización continua implica un intervalo más corto de tiempo entre ciclos de actualización (p.ej., cada seis meses o cada año) (figura 4: ejemplo B) que en la actualización puntual (p.ej., cada dos o tres años) (figura 4: ejemplo C).

  Además, la actualización continua implica, generalmente, una estrategia prospectiva y activa de identificación de nueva evidencia que aporte cambios significativos en la GPC; en cambio, una actualización puntual implica una estrategia retrospectiva de identificación de nueva evidencia que aporte cambios significativos, o no, en la GPC.

  Para establecer la periodicidad deben considerarse diversos factores (p.ej., el tema tratado, el volumen de nuevas publicaciones sobre el tema, la calidad de la evidencia publicada previamente o los recursos disponibles) y puede, por lo tanto, variar entre GPC.

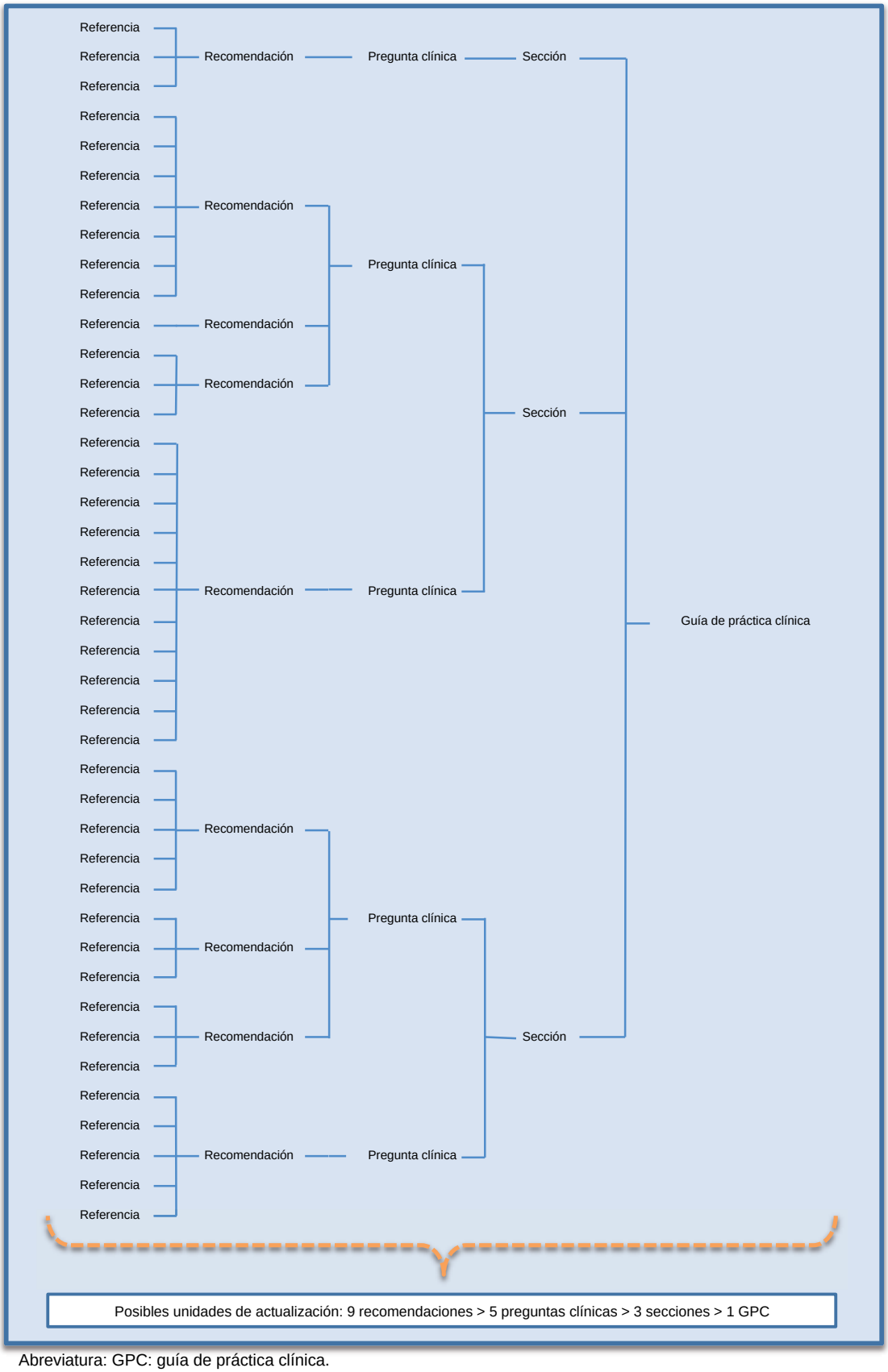
Figura 4. Periodicidad del proceso de revisión y actualización de guías de práctica clínica



Abreviatura: GPC: guía de práctica clínica.

- **Unidad de actualización [concepto de unidad]:** El proceso de actualización puede desarrollarse tomando como unidad de análisis una GPC en su conjunto, sus secciones, sus preguntas clínicas o sus recomendaciones (figura 5).

Figura 5. Unidades de actualización en una guía de práctica clínica



Abreviatura: GPC: guía de práctica clínica.

- **Proceso de actualización parcial frente a proceso de actualización completa de las GPC [concepto de método-unidad]:** Cuando se realiza una actualización completa el proceso de actualización comprende todo el conjunto de la GPC. En cambio, cuando se realiza una actualización parcial, el proceso de actualización puede incluir, por ejemplo, una sección o un conjunto de preguntas clínicas.
- **Herramientas y recursos en la actualización de las GPC**: Las herramientas y los recursos comprenden todos los elementos disponibles para sistematizar y optimizar el proceso de actualización de GPC como, por ejemplo, la aplicación de nuevos *software online* para optimizar el proceso de elaboración y actualización de las GPC [57].

2.3.3. Evidencia en el campo de la actualización de las guías de práctica clínica

Un avance significativo en el campo de la actualización de las GPC en nuestro entorno ha sido la síntesis de la investigación metodológica y de las experiencias de otras instituciones que elaboran GPC; dicha síntesis se ha incluido en el manual metodológico sobre actualización del Programa de GPC en el SNS [46]. Este manual incluye cinco secciones relevantes:

- **Evaluación de la necesidad de actualizar y tipos de actualización:** En esta sección se presentan los aspectos clave que se deben monitorizar periódicamente, desde la elaboración, para valorar la vigencia de una GPC: 1) identificación y valoración de nuevas evidencias relevantes, 2) opinión de expertos y elaboradores de la GPC, 3) percepción de los usuarios y 4) análisis del contexto. También se propone, como un criterio temporal aproximado, valorar la vigencia de una GPC, al menos, cada tres años y no sobrepasar los cinco años. Finalmente, se presentan las opciones de actualización de una GPC, que incluyen: 1) actualización completa, 2) actualización parcial, 3) actualización sin modificaciones y 4) retirada.

- **Proceso de actualización:** En esta sección se describen las etapas de actualización: 1) búsqueda de la literatura, 2) evaluación crítica y síntesis, 3) actualización del texto y de las recomendaciones, 4) revisión externa, 5) registro de las etapas y de los cambios y 6) publicación final.
- **Herramientas y recursos metodológicos para la actualización:** En esta sección se propone que: 1) para valorar la necesidad de actualizar una GPC, se realice una estrategia de búsqueda limitada a GPC, revisiones sistemáticas y estudios originales relevantes y 2) para actualizar una GPC, se editen las estrategias de búsqueda exhaustiva original y se limiten a GPC, revisiones sistemáticas y estudios originales relevantes. Como recursos metodológicos se presentan las fichas de lectura crítica, los *softwares* para la optimización de la síntesis y análisis de la literatura (Review Manager [58] o GRADE profiler [59]) y las plataformas virtuales para trabajar en red.
- **Edición de la actualización:** En esta sección se resalta que el formato de una GPC actualizada debe permitir la identificación de nuevas preguntas clínicas, nueva evidencia o nuevas recomendaciones.
- **Evaluación del proceso de actualización:** En esta sección, dado que no se identificó ninguna herramienta específicamente diseñada para evaluar el proceso de actualización de GPC, se desarrolló una lista de criterios para evaluar el proceso (tabla 1).

Tabla 1. Criterios para evaluar el proceso de actualización de guías de práctica clínica [46]

Etapa 1. Evaluación de la necesidad de actualizar	
Criterio 1	¿La actualización se realizó en el momento apropiado o bajo las circunstancias que la recomiendan?
Criterio 2	¿Es adecuado el procedimiento para decidir si la GPC requiere actualización y el tipo de actualización requerido?
Criterio 3	¿Existen mecanismos de monitorización periódica para comprobar la vigencia de las guías?
Etapa 2. Grupo de trabajo de la actualización	
Criterio 4	¿Se indica claramente qué organismos promueven la actualización, quiénes son los profesionales implicados en el proceso de actualización y cuál es la distribución de tareas y responsabilidades?
Etapa 3. Procedimiento/metodología de la actualización	
Criterio 5	¿Se ha realizado la actualización siguiendo un procedimiento explícito?

Criterio 6	¿Se realizó una búsqueda adecuada?
Criterio 7	¿Cómo se evalúa y sintetiza la evidencia?
Criterio 8	¿Cómo se formulan las recomendaciones?
Etapa 4. Edición de la actualización	
Criterio 9	¿Se presentan de forma clara los principales cambios que han tenido lugar como consecuencia de la actualización?
Criterio 10	¿Existe un archivo que recoja la documentación empleada en las versiones iniciales y sucesivas de la GPC?

Abreviatura: GPC: guía de práctica clínica.

Aunque este manual ofrece una revisión muy exhaustiva de la literatura disponible hasta el momento en este campo, no propone una estrategia explícita que pueda ser utilizada en la actualización de las GPC.

2.3.4. Evidencia en el campo de la actualización de las revisiones sistemáticas

Las RS son investigaciones científicas (investigación secundaria o investigación sobre la investigación) que utilizan un método sistemático y explícito para identificar, analizar y sintetizar la evidencia empírica y responder una pregunta específica de investigación [19]. Las RS, al igual que las GPC, deben mantenerse actualizadas y garantizar la vigencia de sus conclusiones.

Las RS y las GPC están íntimamente relacionadas: 1) ambas son herramientas útiles para la toma de decisiones clínicas de los usuarios, de los profesionales y de los gestores sanitarios, 2) las RS son la base para la elaboración de las GPC [2], 3) la metodología utilizada para actualizar las RS podría ser adaptada para actualizar las GPC y 4) las RS actualizadas (que presenten cambios en sus conclusiones) podrían ser utilizadas para actualizar las GPC.

En el área de las RS se han desarrollado diferentes estudios metodológicos relacionados con el tiempo, el método, las herramientas y los recursos para actualizar las RS (tabla 2). Principalmente, la investigación se ha basado en el proceso de actualización de RS elaboradas por la Colaboración Cochrane [60-70]

y en revisiones comparativas de la efectividad (*comparative effectiveness reviews* [CER]) elaboradas por la *Agency for Healthcare Research and Quality's* (AHRQ) [71-77].

Tabla 2. Investigación metodológica en la actualización de revisiones sistemáticas

Clasificación[#]	Primer autor y año (*orden cronológico*)	Objetivo	n
Publicaciones relacionadas con el análisis del contexto			
Encuesta sobre actualización	- Garritty 2010 [78]	Describir las prácticas y las políticas de actualización de las instituciones que elaboran RS.	114 participantes
Revisión de los métodos de actualización	- Moher 2008* [79] - Moher 2007 [80]	Identificar, describir y evaluar los métodos dirigidos a cuándo y cómo actualizar las RS.	15 publicaciones
	- Tsertsvadze 2011a* [77] - Tsertsvadze 2011b [81]	Revisar el conocimiento y las iniciativas en la actualización de RS, así como su aplicación a las CER.	-
Publicaciones relacionadas con el tiempo			
Tiempo entre la elaboración y la publicación	- Sampson 2008b [82]	Evaluar la vigencia de las RS en el momento de su publicación.	154 RS
	- Tricco 2009 [69]	Evaluar los factores asociados al tiempo de publicación en las RS Cochrane.	118 protocolos Cochrane
	- Beller 2013 [83]	Evaluar la vigencia de las revisiones en el momento de su publicación (tiempo desde la última búsqueda hasta la publicación).	300 RS
Tiempo de vigencia (análisis de supervivencia)	- Shojania 2007a* [76] - Shojania 2007b [84]	Estimar el tiempo medio para detectar cambios en la evidencia suficientemente relevantes como para justificar la actualización de RS (método Ottawa).	100 RS
	- Peterson 2011 [85]	Determinar el tiempo y los factores clave asociados a la decisión de actualizar CER de medicamentos en base a revisiones periódicas de la nueva evidencia.	41 CER
Tiempo de vigencia (cambio entre la versión original y la versión actualizada)	- French 2005 [60]	Evaluar el efecto de actualizar las RS Cochrane después de un periodo de cuatro años.	377 RS Cochrane
	- Jaidee 2010 [62]	Determinar la frecuencia de actualización de las RS Cochrane (*Cochrane Pregnancy and Chilbirth Group*), los factores asociados a la actualización y si la frecuencia de actualización es apropiada.	101 RS Cochrane

Cambio en la calidad entre la versión original y la versión actualizada	- Shea 2006 [65]	Comparar la calidad metodológica y la presentación de las versiones originales frente a las actualizadas de RS Cochrane para determinar si la actualización mejora estas dos dimensiones de la calidad.	53 RS Cochrane
Revisión (vigilancia o monitorización) de la evidencia	- Ahmadzai 2013 [71]	Desarrollar y describir los resultados iniciales de un sistema de vigilancia para evaluar las RS (método RAND y/o método Ottawa).	24 RS
	- Newberry 2013b [74]	Desarrollar e implementar un sistema de vigilancia para la identificación rápida de CER que necesitan ser actualizadas (método RAND y/o método Ottawa).	14 CER
Publicaciones relacionadas con la metodología			
Identificación de la nueva evidencia	- Sampson 2008a [86]	Analizar el rendimiento de diferentes estrategias de búsqueda de la literatura para identificar nueva evidencia y actualizar RS.	77 RS
	- Hemens 2012 [61]	Comparar el rendimiento de McMaster PLUS y *Clinical Queries* frente a *Cochrane Controlled Trials Register*, MEDLINE y EMBASE en la identificación de estudios incluidos durante la actualización de una RS.	98 RS Cochrane
	- Sagliocca 2013 [64]	Comparar una estrategia pragmática de búsqueda limitada de la literatura (número de revistas biomédicas relevantes) frente a una búsqueda exhaustiva para estimar la eficacia de los tratamientos.	27 RS Cochrane
Identificación de la nueva evidencia y evaluación del impacto de nueva evidencia	- Shekelle 2009 [75]	Evaluar la necesidad de actualizar las CER publicadas (método RAND).	13 CER
	- Pattanittum 2012 [63]	Comparación de cinco métodos estadísticos para identificar RS desactualizadas.	80 RS Cochrane
	- Chung 2012* [72] - Shekelle 2011 [87]	Aplicar y comparar dos métodos (método RAND frente a método Ottawa), que identifican señales sobre la necesidad de actualizar las RS.	4 RS
	- Shekelle 2014a* [88] - Shekelle 2014b [89]	Evaluar la vigencia predictiva de un método que evalúa las señales de actualización (método RAND).	9 CER
Priorización en la actualización	- Soll 2008 [66]	Desarrollar un método para priorizar y facilitar el proceso de revisión de las RS Cochrane (*Cochrane Neonatal Review Group*).	-
	- Sutton 2009 [67]	Evaluar la utilización de métodos estadísticos para priorizar la actualización de RS Cochrane (*Cochrane Infectious Diseases Group*) en base a búsquedas preliminares de la literatura.	12 RS Cochrane

	- Hopewell 2007 [90] - Takwoingi 2013* [68] - Takwoingi 2014 [91] - Tovey 2011 [92]	Desarrollar una herramienta multicomponente de decisión, con aspectos cualitativos y cuantitativos, para priorizar la actualización de una o más RS.	-
	- Welsh 2015 [70]	Desarrollar una técnica pragmática y explícita para identificar RS Cochrane (*Cochrane Airways Group*) altamente prioritarias a actualizar.	270 RS Cochrane
Edición de las RS actualizadas	- Newberry 2013a [73]	Describir la visión de diferentes usuarios de CER en relación con la utilidad de diferentes formatos para presentar los cambios de un documento original a un documento actualizado.	-
	- Stovold 2014 [93]	Adaptar el diagrama de flujo de los estudios para incluirlo en las revisiones actualizadas.	-
Publicaciones relacionadas con las herramientas y los recursos			
Nuevas tecnologías	- Bender 2011 [94]	Evaluar el uso de una *wiki* como herramienta de colaboración *online* para la actualización de un tipo de RS (RS de alcance o *scoping reviews*).	1 RS
	- Cohen 2012 [95]	Evaluar el impacto potencial de un sistema de aprendizaje automático para detectar alertas cuando existen nuevas publicaciones disponibles sobre un tema de RS.	11 temas de RS
	- Dalal 2013 [96]	Evaluar un sistema de aprendizaje automático (en base a términos de indexación de MEDLINE) para predecir la relevancia de las referencias.	2 CER

[#]Las publicaciones se han clasificado en función de su objetivo principal. *Publicación principal. Abreviaturas: CER: revisiones comparativas de la efectividad (*comparative effectiveness reviews*); PLUS: *Premium LiteratUre Service*; RS: revisión sistemática.

La política de actualización de la Colaboración Cochrane consisten en que las RS se deben actualizar a los dos años de su elaboración, aunque se puede considerar que una RS no necesita ser actualizada en este plazo (p.ej., en un campo donde es probable que no se investigue o en un campo donde se obtienen resultados lentamente) [19]. Actualmente, dado el volumen creciente de RS Cochrane y la falta de recursos, cada vez hay más investigadores que abogan por una aproximación basada en la priorización de temas frente a una aproximación basada en un tiempo de vigencia predeterminado para todas las RS [66, 68, 70, 97].

La AHRQ (vinculada al Departamento de Salud y Servicios Sociales de Estados Unidos), a través del programa *Effective Health Care*, da soporte a la elaboración de RS y CER [98]. En los últimos años, ha invertido muchos recursos para desarrollar y optimizar una metodología para identificar la señal de actualización [71, 72, 74-77, 88]. En este contexto, el *Southern California Evidence-based Practice Center - Research and Development Corporation* ha desarrollado el método RAND y la Universidad de Ottawa el método Ottawa para identificar señales de actualización (tabla 3).

Tabla 3. Métodos para identificar la señal de actualización en revisiones sistemáticas

	Método RAND [75]	Método Ottawa [76]
Identificación de la nueva evidencia	- Búsqueda limitada de la literatura (identificación de revisiones, editoriales y comentarios en cinco revistas biomédicas generales y en revistas biomédicas especializadas por tema). - Consulta a expertos. - Búsqueda de alertas de medicamentos.	- Búsqueda exhaustiva de la literatura.
Evaluación del impacto de nueva evidencia	**Señales cualitativas** 1. La conclusión original sigue siendo válida y el documento original no necesita actualización. 2. La conclusión original está posiblemente obsoleta y el documento original puede	**Señales cualitativas** A1. Resultados contradictorios en ensayos claves*. A2. Riesgos importantes. A3. Nueva intervención superior. A4. Cambios importantes en la

	necesitar ser actualizado. 3. La conclusión original está probablemente obsoleta y el documento original puede necesitar ser actualizado. 4. La conclusión original está obsoleta.	eficacia menores a «A1». A5. Aumento en las indicaciones del tratamiento. A6. Riesgos clínicamente importantes. A7. «A1» en metaanálisis o en ensayos no claves*. **Señales cuantitativas** B1. Cambio en la significación estadística. B2. Cambio en el tamaño relativo del efecto de, al menos, el 50 %.

*Ensayo clave: ensayo publicado en una de las cinco principales revistas biomédicas de medicina general o ensayo cuyo tamaño de la muestra es, al menos, el triple que la del ensayo más grande incluido en la revisión sistemática original. Abreviatura: CER: revisiones comparativas de la efectividad (*comparative effectiveness reviews*).

En base a los estudios realizados sobre la factibilidad del proceso de actualización de RS [76], la comparación del método RAND y el método Ottawa [72] y la validación del método RAND [88], se ha desarrollado e implementado un sistema de vigilancia de la nueva evidencia para actualizar las RS y las CER en el programa *Evidence-based Practice Centre* de la AHRQ. El sistema de vigilancia (búsqueda limitada de la literatura, consulta a expertos y evaluación de la nueva evidencia con el método RAND y/o Ottawa cada seis meses) ha mostrado ser factible para la identificación de las señales de actualización y para priorizar la actualización de las RS y las CER [71, 74].

2.4. Justificación

2.4.1. Justificación del tema de investigación de la tesis

Las GPC, para ser útiles en la toma de decisiones clínicas, deben mantenerse actualizadas y garantizar la vigencia de sus recomendaciones.

Una GPC desactualizada puede ser causa de una práctica clínica y asistencial inadecuada al no incorporar el nuevo conocimiento disponible [46, 77, 99]. Además, las GPC y las instituciones que las elaboran pueden perder la credibilidad si estas quedan obsoletas [46].

La actualización de las GPC debe realizarse con el mismo enfoque sistemático y explícito que la elaboración *de novo*. Sin embargo, hasta el momento, la experiencia publicada sobre el proceso de actualización de GPC es limitada y es necesaria más investigación para optimizar y estandarizar el proceso de actualización de GPC [46].

2.4.2. Justificación de la tesis por compendio de publicaciones

Esta tesis, que se presenta como un compendio de publicaciones, se basa en cinco estudios sobre el proceso de actualización de GPC: 1) una encuesta internacional sobre el proceso de actualización de GPC (publicación I) [100], 2) una revisión sistemática de los métodos de actualización de GPC (publicación II) [101], 3) un análisis de supervivencia para estimar el tiempo de vigencia de las recomendaciones (publicación III) [102], 4) una evaluación de las recomendaciones actualizadas (publicación IV) [103] y 5) una evaluación de dos estrategias pragmáticas de búsqueda de la literatura para identificar señales de actualización (publicación V) [104].

Adicionalmente, en los anexos se incluyen tres publicaciones relacionadas: 1) el protocolo publicado de varios de los estudios desarrollados en la tesis (publicación VI) [105], 2) una revisión sistemática de los métodos de actualización de GPC incluidos en los manuales metodológicos de las instituciones que elaboran GPC (publicación VII) [106] y 3) un editorial sobre los retos metodológicos en la elaboración y en la actualización de las GPC (publicación VIII) [107].

El interés por realizar estos estudios surgió cuando se observó un vacío en el conocimiento sobre cuándo y cómo actualizar las GPC [46]. Además, se obtuvieron dos ayudas económicas que permitieron desarrollar varios de los proyectos: 1) la primera se recibió en el 2010, procedente del Fondo de Investigación Sanitaria del Instituto de Salud Carlos III (número de expediente PI10/00346), con el objetivo de evaluar la vigencia y las estrategias de actualización para las guías del Programa de GPC en el SNS, y 2) la doctoranda

obtuvo, en el 2011, un contrato Río Hortega del Instituto de Salud Carlos III (número de expediente CM11/00035), con el objetivo de desarrollar capacidades para identificar, analizar, sintetizar, actualizar y difundir los resultados de la investigación clínica.

La recopilación en esta tesis de los estudios publicados tiene como propósito final generar y difundir el conocimiento actual sobre el proceso de actualización de GPC, y revisar y discutir los conceptos propuestos en el marco conceptual (tiempo, método, unidad, herramientas y recursos).

Objetivos

3. Objetivos

3.1. Objetivos generales

Los objetivos generales de la tesis son:

- Identificar y describir los métodos utilizados para actualizar las GPC.
- Diseñar y evaluar nuevos métodos para actualizar las GPC.

3.2. Objetivos específicos

Los objetivos específicos de la tesis son:

- Describir la práctica habitual en la actualización de las GPC de las principales instituciones que elaboran GPC a nivel internacional.
- Identificar, describir y evaluar las estrategias propuestas para actualizar las GPC.
- Estimar el tiempo medio desde la formulación de las recomendaciones hasta la publicación de nueva evidencia para actualizarlas.
- Identificar y describir las recomendaciones actualizadas y evaluar los factores asociados a su actualización.
- Diseñar y evaluar dos estrategias pragmáticas de búsqueda de la literatura para identificar las señales de actualización de las recomendaciones.

Métodos

4. Métodos

Los métodos de la tesis son los correspondientes a cada una de las publicaciones que la conforman.

4.1. Publicación I: Encuesta internacional sobre el proceso de actualización de guías de práctica clínica

Diseño

Estudio descriptivo transversal.

Población de estudio

Se encuestó a informadores clave afiliados a instituciones nacionales e internacionales que elaboran GPC. Se seleccionaron las instituciones de los participantes según los siguientes criterios: 1) instituciones incluidas en G-I-N que elaboran GPC, 2) instituciones incluidas en *U.S. National Guideline Clearinghouse* que hubiesen publicado más de 20 GPC, o 3) instituciones seleccionadas por un comité de expertos según su relevancia.

Método de recogida de datos

Se realizó una revisión de la literatura sobre la actualización de las GPC para diseñar un cuestionario autoadministrado *online*. Se incluyeron 28 ítems agrupados en cuatro dominios: 1) características de la institución, 2) proceso de actualización, 3) información a los usuarios sobre la actualización y 4) planificación de proyectos en relación con la actualización. También se incluyeron en el cuestionario preguntas con respuesta abierta para obtener información adicional. Se pilotó el cuestionario y se mejoró a partir de las respuestas obtenidas. Entre marzo y julio de 2009, se envió el cuestionario por correo electrónico a los participantes de las instituciones incluidas. Asimismo, se enviaron, también por correo electrónico, tres cartas de recuerdo (con un intervalo de cuatro semanas), a los participantes que no respondieron.

Estrategia de análisis

Se realizó un análisis descriptivo mediante frecuencias y porcentajes. Se compararon las instituciones de los respondedores y de los no respondedores utilizando el test exacto de Fisher (variables categóricas) o el test U de Mann-Whitney (variables cuantitativas). Se evaluó el proceso de actualización según la experiencia de las instituciones en la elaboración de GPC (con más de diez años elaborando GPC o con diez o menos años elaborando GPC) mediante el test exacto de Fisher. Se consideró estadísticamente significativo un valor de p menor a 0,05. El análisis estadístico de los datos se realizó con el paquete estadístico SPSS versión 17.0 (SPSS Inc., Chicago, Illinois, Estados Unidos).

4.2. Publicación II: Revisión sistemática de los métodos de actualización de guías de práctica clínica

Diseño

Revisión sistemática.

Población de estudio

Se realizó una búsqueda de la literatura en junio de 2012 en MEDLINE (a través de PubMed) y en *The Cochrane Methodology Register* (a través de *The Cochrane Library*). No se limitó la búsqueda por idioma o tipo de publicación. De forma complementaria, se realizó una búsqueda manual en la lista de referencias de los estudios incluidos y en el libro de resúmenes de G-I-N. En caso necesario, se contactó con los autores de los estudios para obtener información adicional.

Se incluyeron estudios que evaluaban uno o más métodos para actualizar las GPC o las recomendaciones. Se excluyeron los estudios que solo describían un método de actualización (sin evaluarlo), los manuales metodológicos o las GPC actualizadas.

Dos autores revisaron de forma independiente los títulos y los resúmenes de los artículos recuperados en la búsqueda, evaluaron el texto completo de los artículos seleccionados y aprobaron su inclusión. Cualquier desacuerdo entre los autores fue inicialmente resuelto por consenso y, en caso necesario, se consultó a un tercer autor.

Método de recogida de datos

Dos autores extrajeron de forma independiente la información de los estudios incluidos utilizando un formulario *ad hoc*. Cualquier desacuerdo entre los autores fue inicialmente resuelto por consenso y, en caso necesario, se consultó a un tercer autor. De cada estudio se extrajo: 1) institución o programa de GPC y país, 2) objetivo y diseño del estudio, 3) muestra (criterios de selección y tamaño) y tema de salud, 4) tiempo hasta la actualización (número de años desde la elaboración de la GPC original), 5) etapas de la estrategia, 6) tipo de búsqueda de la literatura (restrictiva o exhaustiva, dependiendo de las bases de datos consultadas y del tipo de estudios seleccionados), 7) recursos utilizados (número de participantes y tiempo), 8) resultado de la búsqueda y de la actualización y 9) ventajas y desventajas de las estrategias descritas por los autores.

Estrategia de análisis

Se realizó una descripción narrativa de los estudios incluidos. Se calculó el rendimiento de las búsquedas de la literatura (proporción de estudios incluidos del total de documentos identificados) y el rendimiento de la actualización (proporción de recomendaciones o GPC actualizadas del total de recomendaciones o GPC evaluadas).

4.3. Publicación III: Análisis de supervivencia de las recomendaciones

Diseño

Estudio retrospectivo de una cohorte de recomendaciones de GPC.

Población de estudio

Se incluyeron recomendaciones de las guías del Programa de GPC en el SNS, traducidas al inglés y elaboradas desde el año 2008. Se estratificaron las GPC por tema (cáncer y cuidados paliativos, enfermedades cardiovasculares, salud mental y enfermedades metabólicas) y por año de publicación (2008 o 2009). Cuando se identificó más de una GPC por estrato, se realizó una selección aleatoria.

Asimismo, se llevó a cabo un muestreo aleatorio y estratificado de las recomendaciones por volumen de referencias enlazadas por recomendación y por el tema de la GPC. El tamaño de la muestra necesaria para el estudio fue de 112 recomendaciones (riesgo α 0,95; precisión ± 0,05; tamaño de la población de referencia 249; proporción esperada 0,154).

Método de recogida de datos

Se desarrolló una estrategia en nueve etapas para evaluar la vigencia de las recomendaciones:

- **Fase 1:** Se identificaron las preguntas clínicas y las recomendaciones.
- **Fase 2:** Para cada GPC, se realizó un cuestionario a un grupo de expertos clínicos (muestra de conveniencia formada por seis expertos clínicos que participaron en la elaboración o en la revisión de la GPC original). Los participantes evaluaron si las recomendaciones estaban vigentes y proporcionaron estudios recientes que podían modificarlas.
- **Fase 3:** Se recuperaron las búsquedas exhaustivas originales de la literatura para cada una de las preguntas clínicas abordadas en las GPC. Los expertos en documentación, preferiblemente del grupo de trabajo de la GPC original, revisaron y ejecutaron las búsquedas de la literatura en las bases de datos bibliográficas y filtraron los resultados por el diseño de estudio de interés (ensayos clínicos aleatorizados [ECA] o RS).
- **Fase 4:** Se agruparon las referencias obtenidas de las diferentes fuentes de información (cuestionarios a expertos clínicos y bases de datos bibliográficas) y se identificaron y eliminaron los duplicados.

- **Fase 5:** Se identificaron las referencias pertinentes (referencias relacionadas con el tema de interés y con un diseño de estudio adecuado para responder a la pregunta clínica).
- **Fase 6:** Se enlazaron las referencias pertinentes con las recomendaciones.
- **Fase 7:** Se analizó la base de datos de referencias para identificar las recomendaciones con un bajo o alto volumen de referencias enlazadas.
- **Fase 8:** Se diseñó un formulario para identificar las referencias relevantes (referencias pertinentes que se pueden utilizar para actualizar una recomendación pero que no necesariamente desencadenan una modificación por sí mismas) y las referencias clave (referencias relevantes que se considera que potencialmente podrían conllevar una modificación de las recomendaciones por sí mismas). Además, el formulario incluía la evaluación de los potenciales cambios en las recomendaciones en relación con la población, la intervención, la comparación, los desenlaces, la calidad de la evidencia, la dirección y la fuerza de la recomendación. Cada referencia fue valorada por dos expertos clínicos y un experto en metodología de GPC, los desacuerdos fueron resueltos por un algoritmo de decisión y por consenso mediante teleconferencia con los evaluadores.
- **Fase 9:** Se clasificaron las recomendaciones como: 1) recomendaciones que, potencialmente, necesitaban ser actualizadas (con una o más referencias clave enlazadas) o 2) recomendaciones vigentes (sin referencias clave enlazadas). Se realizó un informe final y se envió al grupo de expertos clínicos que había colaborado en el estudio y a las instituciones que habían elaborado las GPC.

Estrategia de análisis

Se realizó un análisis descriptivo de los datos y se calcularon las frecuencias absolutas y las relativas (variables categóricas) o las medianas y los rangos (variables cuantitativas).

Se calculó la tasa de respuesta del cuestionario inicial y se consideró válido si más del 20 % de las preguntas tenían una respuesta.

Se evaluó el grado de acuerdo entre los expertos clínicos y los expertos en metodología de GPC en la identificación de las referencias relevantes y claves. Se aplicaron los rangos, en función del índice kappa, propuestos por Landis y Koch (κ 0-0,20 insignificante; κ 0,21-0,40 bajo; κ 0,41-0,60 moderado; κ 0,61-0,80 bueno; κ mayor a 0,80 muy bueno) [108].

Se compararon las recomendaciones a actualizar con las recomendaciones válidas según el tema de la GPC (cáncer y cuidados paliativos, enfermedades cardiovasculares, salud mental y enfermedades metabólicas), la fuerza de la recomendación (A, B, C, D o buena práctica clínica) [56], el propósito clínico de la recomendación (prevención, cribado, tratamiento u otros) y el volumen de referencias enlazadas (sin referencias, menor o igual a la mediana de referencias por recomendación, mayor a la mediana de referencias por recomendación) utilizando la prueba χ^2 de Pearson.

Se calculó el tiempo de vigencia de las recomendaciones (desde la formulación de las recomendaciones hasta la publicación de nueva evidencia para actualizarlas) (tabla 4). Se utilizó el método de Kaplan-Meier para calcular la tasa de supervivencia de las recomendaciones. Se utilizó la prueba de log-rank para analizar las diferencias entre las curvas de supervivencia según el tema de la GPC, la fuerza de la recomendación, el propósito clínico de la recomendación y el volumen de referencias enlazadas por recomendación.

Tabla 4. Cálculo del tiempo de vigencia de las recomendaciones

Definiciones
- Evento: identificación de una referencia clave para una recomendación específica. - Fecha de formulación de la recomendación: fecha en que se ejecutó la búsqueda exhaustiva original de la literatura. - Fecha de la última observación de la recomendación: fecha en que se ejecutó la búsqueda exhaustiva actualizada de la literatura. - Fecha de caducidad de la recomendación: fecha de publicación de la primera referencia clave.

Cálculo

$$\text{Tiempo de vigencia para las recomendaciones que, potencialmente, necesitan ser actualizadas} = \text{fecha de caducidad} - \text{fecha de formulación}$$

$$\text{Tiempo de vigencia para las recomendaciones vigentes} = \text{fecha de última observación} - \text{fecha de formulación}$$

Se evaluaron los recursos utilizados para desarrollar la estrategia. Se registró el número de horas dedicadas a cada etapa y el número de investigadores involucrados. Se imputaron diez minutos por referencia cuando no se informó del tiempo invertido. Se calculó el número de referencias por hora evaluadas por los investigadores.

Se consideró estadísticamente significativo un valor de p menor a 0,05. El análisis estadístico de los datos se realizó con el paquete estadístico SPSS 21.0 (SPSS Inc., Chicago, Illinois, Estados Unidos) y se evaluó la concordancia (coeficiente κ) utilizando EPIDAT 4.0 [109]. Se calculó el tamaño de muestra utilizando GRANMO 7 [110].

4.4. Publicación IV: Evaluación de las recomendaciones actualizadas

Diseño

Estudio de casos y controles de recomendaciones.

Población de estudio

Se identificaron todas las GPC actualizadas de la NICE y su correspondiente versión original. Se incluyeron las GPC actualizadas si: 1) era una actualización parcial, 2) era la primera actualización de la versión original y 3) incluía una etiqueta para cada recomendación con el resultado de la actualización (p.ej.: recomendación nueva, recomendación sin cambios, recomendación suprimida, recomendación no revisada o recomendación enmendada).

Se obtuvieron las GPC actualizadas hasta mayo de 2013 mediante una búsqueda en la lista de GPC publicadas en la página web de la institución. Después de obtener la muestra de GPC actualizadas, se recuperaron las versiones originales correspondientes en la página web de la institución o contactando con el centro elaborador.

Se revisaron las GPC y se identificaron las recomendaciones. Se incluyeron todas las recomendaciones excepto las recomendaciones de investigación.

Se definieron los casos como las recomendaciones originales que habían sido modificadas tras la revisión de la nueva evidencia (recomendaciones modificadas) y los controles como las recomendaciones que estaban vigentes tras la revisión de la nueva evidencia (recomendaciones no modificadas).

Método de recogida de datos

Se mapearon las GPC originales y se extrajo la siguiente información: fecha de publicación, tema (utilizando la taxonomía de NICE) y centro elaborador de la GPC. Se mapearon las GPC actualizadas, se extrajo la misma información y, adicionalmente, las etiquetas utilizadas con el resultado de la actualización y su definición.

Se mapearon las recomendaciones originales y se extrajo la siguiente información: recomendaciones, apartado y subapartado, número de referencias enlazadas y fuerza de la recomendación. Se codificó la información de las recomendaciones según el tema de la GPC, los años entre las versiones de las GPC, el propósito y la fuerza de la recomendación (con sistema SIGN [56] o GRADE [26]). Se mapearon las recomendaciones actualizadas, se extrajo y se codificó la misma información y, adicionalmente, las etiquetas con el resultado de la actualización y la justificación del cambio.

Estrategia de análisis

Se realizó un análisis descriptivo de las GPC y las recomendaciones incluidas, se calcularon las frecuencias absolutas y las relativas (variables categóricas) o las medianas y los rangos (variables cuantitativas).

Se calculó una puntuación en base a siete ítems para valorar el registro de los cambios en las recomendaciones de las GPC actualizadas: 1) definición de las etiquetas utilizadas con el resultado de la actualización, 2) utilización de la etiqueta «recomendación modificada», 3) justificación del cambio en las recomendaciones modificadas, 4) utilización de la etiqueta «recomendación suprimida», 5) justificación del cambio en las recomendaciones suprimidas, 6) utilización de la etiqueta «recomendación enmendada» y 7) justificación del cambio en las recomendaciones enmendadas. La puntuación máxima fue de siete, aunque dependió de las etiquetas incluidas en la GPC actualizada. La puntuación final se calculó en base a una escala de diez.

Se compararon los casos (recomendaciones modificadas) y los controles (recomendaciones no modificadas) con la prueba χ^2 de Pearson (variables categóricas) o la prueba U de Mann-Whitney (variables cuantitativas). Se planeó un análisis de regresión múltiple con las variables asociadas a la actualización en el análisis bivariado y con las variables seleccionadas según su relevancia por el equipo investigador.

En todos los cálculos se aceptó como valor significativo una p menor a 0,05. El análisis se realizó con el paquete estadístico SPSS 15.0 (SPSS Inc., Chicago, Illinois, Estados Unidos).

4.5. Publicación V: Evaluación de dos estrategias pragmáticas de búsqueda de la literatura

Diseño

Estudio descriptivo.

Población de estudio

Se utilizó la muestra de la publicación previa sobre el análisis de supervivencia de las recomendaciones, que incluía una muestra aleatoria y estratificada de

recomendaciones de las guías del Programa de GPC en el SNS (publicación III) [102].

Método de recogida de datos

Se diseñaron y ejecutaron tres estrategias de búsqueda de la literatura para identificar la señal de actualización de las recomendaciones: 1) la estrategia exhaustiva (diseñada y ejecutada en la publicación III) [102], 2) la estrategia restrictiva (utilización del mínimo número de términos de búsqueda de la literatura en base a la búsqueda exhaustiva original, búsqueda en una sola base de datos bibliográfica y aplicación de filtros validados para recuperar determinados diseños de estudios) y 3) la estrategia PLUS (búsqueda en la base de datos McMaster PLUS [*Premium Literature Service*]).

- **Estrategia exhaustiva:** Expertos en metodología de GPC, con experiencia en el diseño de estrategias de búsqueda de la literatura, diseñaron y ejecutaron las búsquedas exhaustivas de la literatura para cada pregunta clínica, basándose en las búsquedas exhaustivas originales y aplicando los filtros originales para cada tipo de estudio. Además, se contactó con expertos clínicos para identificar nueva evidencia. Se obtuvo, por pregunta clínica, una base de datos de referencias. Se evaluaron las referencias para identificar las «referencias pertinentes» (referencias relacionadas con el tema de interés y con un diseño de estudio adecuado para responder a la pregunta clínica), las «referencias relevantes» (referencias pertinentes que se pueden utilizar para actualizar una recomendación pero que no necesariamente desencadenan una modificación por sí mismas) y las «referencias clave» (referencias relevantes, que se considera que, potencialmente, podrían conllevar una modificación de las recomendaciones por sí mismas). Se clasificaron las recomendaciones en función del número de referencias clave enlazadas: 1) «recomendaciones que, potencialmente, necesitaban ser actualizadas» (con una o más referencias clave enlazadas) y 2) «recomendaciones vigentes» (sin referencias clave enlazadas).
- **Estrategia restrictiva:** Expertos en metodología de GPC, tutorizados por un investigador con experiencia en el diseño de estrategias de búsqueda de la

literatura, diseñaron las estrategias de búsqueda restrictiva de la literatura por pregunta clínica. Se incluyeron aquellas preguntas clínicas con, al menos, dos componentes PICO. Las estrategias de búsqueda restrictiva se basaron en la búsqueda exhaustiva original de la literatura (mínimo número de términos MeSH [*Medical Subject Headings*] y términos en texto libre requeridos), la búsqueda en una sola base de datos bibliográfica (MEDLINE a través de PubMed) y la aplicación de filtros validados para recuperar determinados diseños de estudios (ECA y RS). Se desarrolló un proceso sistemático para diseñar y ejecutar las estrategias de búsqueda restrictiva: 1) desarrollo: se seleccionaron las palabras clave de las preguntas clínicas y se identificaron los términos MeSH y los términos en texto libre en el título; 2) validación: se ejecutaron las búsquedas restrictivas y se comprobó que recuperaban todas las referencias originales; 3) refinamiento: si las búsquedas restrictivas no recuperaban todas las referencias originales, se seleccionaban términos MeSH menos específicos y/o términos en texto libre en el título y en el resumen, y 4) aplicación de filtros: filtro extenso *Clinical Queries*, filtro limitado *Clinical Queries* y un filtro para RS [111, 112]. El límite temporal que se utilizó abarcaba desde el año completo en que se finalizó la búsqueda exhaustiva original de la literatura hasta que se finalizó la búsqueda exhaustiva actualizada de la literatura.

- **Estrategia PLUS:** Un experto en documentación, de la *Health Information Research Unit* (Universidad de McMaster, Canadá), diseñó y ejecutó una estrategia para cada GPC. Se enlazaron los términos MeSH y los términos SNOMED (*Systematized Nomenclature of Medicine*), incluidos en la base de datos McMaster PLUS, con los temas de cada GPC. Se incluyeron estudios primarios y revisiones. El límite temporal que se utilizó comprendía desde el año completo en que se finalizó la búsqueda exhaustiva original de la literatura hasta tres meses posteriores a la finalización de la búsqueda exhaustiva actualizada de la literatura, con la finalidad de considerar el proceso de evaluación de los estudios para ser incluidos en la base de datos McMaster PLUS *(critical appraisal process).*

Estrategia de análisis

Se realizó un análisis descriptivo de los datos, se calcularon las frecuencias absolutas y las relativas (variables categóricas) o las medianas y los rangos (variables cuantitativas).

Se evaluó el número de referencias clave identificadas con la estrategia restrictiva por pregunta clínica, el número de referencias clave identificadas con la estrategia restrictiva por GPC y el número de referencias clave identificadas con la estrategia PLUS por GPC. No se evaluó si las estrategias pragmáticas identificaron referencias pertinentes, relevantes o clave adicionales. En la estrategia restrictiva no se diseñaron búsquedas para preguntas clínicas con menos de dos componentes PICO; en estos casos, se imputaron los resultados de la búsqueda exhaustiva actualizada.

Se analizaron las recomendaciones que, potencialmente, necesitaban ser actualizadas (con una o más referencias clave enlazadas), identificadas por las estrategias pragmáticas. Se compararon las recomendaciones identificadas con las no identificadas según el tema de la GPC (cáncer y cuidados paliativos, enfermedades cardiovasculares, salud mental y enfermedades metabólicas), la fuerza de la recomendación (A, B, C, D o buena práctica clínica) [56], el propósito clínico de la recomendación (prevención, cribado, tratamiento u otros) y el volumen de referencias enlazadas (sin referencias, menor o igual a la mediana de referencias por recomendación, mayor a la mediana de referencias por recomendación). Se utilizó la prueba χ^2 de Pearson o el test exacto de Fisher.

Se comparó el número de horas dedicadas al diseño y a la ejecución de cada estrategia pragmática, así como el número de investigadores involucrados.

En todos los cálculos se aceptó como valor significativo una p menor a 0,05. El análisis se realizó con el paquete estadístico SPSS 21.0 (SPSS Inc., Chicago, Illinois, Estados Unidos).

Resultados

5. Resultados

Los resultados de la tesis son los correspondientes a cada una de las publicaciones que la conforman.

5.1. Resumen de resultados

5.1.1. Publicación I: Encuesta internacional sobre el proceso de actualización de guías de práctica clínica

Características de la muestra

Se seleccionaron 114 instituciones que cumplían, al menos, uno de los criterios de inclusión y se contactó a través del correo electrónico con 106 informadores clave. Cuarenta y cuatro informadores respondieron el cuestionario (tasa de respuesta 42 %; 44/106) y se incluyeron en el análisis final 39 cuestionarios correctamente completados. La mayor parte de las instituciones incluidas actualizaban sus GPC (92,3 %; 36/39).

Descripción del proceso de actualización

Las instituciones revisaban más de cinco GPC anualmente (44,4 %; 16/36) y consideraban actualizarlas de tres a cinco años de su elaboración (61,1 %; 22/36). El 52,8 % (19/36) tenían un procedimiento formal para decidir cuándo estaban desactualizadas.

El 86,1 % (31/36) de las instituciones tenían un procedimiento formal de actualización, aunque solamente el 25 % (9/36) lo habían pilotado para evaluar su viabilidad, los inconvenientes o el valor añadido en comparación con otras estrategias. El 72 % (26/36) de las instituciones describieron el proceso como moderadamente riguroso o reconocieron que podía ser más riguroso. Las instituciones con más experiencia (más de diez años elaborando GPC) aplicaban un proceso de actualización más riguroso en comparación con las instituciones con menos experiencia (diez o menos años elaborando GPC).

Las instituciones alertaban a los usuarios en su página web cuando una GPC se había elaborado desde hacía más de tres a cinco años o cuando existía el riesgo de que estuviese desactualizada (61,1 %; 22/36).

Proyectos de futuro en el proceso de actualización

El 64,1 % (25/39) de las instituciones apoyaban el concepto de «GPC viva», definido como una GPC que se revisa y actualiza continuamente [113]. Además, el 46,2 % (18/39) de las instituciones tenían planificado mejorar su proceso de actualización.

5.1.2. Publicación II: Revisión sistemática de los métodos de actualización de guías de práctica clínica

Características de los estudios

Se incluyeron un total de ocho estudios: cuatro evaluaron si las GPC estaban desactualizadas [114-117], tres actualizaron las GPC [118-120] y uno revisó y actualizó de forma continua las GPC [121].

A continuación, se describen los cinco estudios más relevantes [115, 117, 118, 120, 121]:

Estrategias para evaluar si las GPC están desactualizadas

- Shekelle *et al*. 2001 desarrollaron una estrategia para evaluar la vigencia de las GPC basada en la identificación de nueva evidencia, mediante una búsqueda limitada de la literatura (identificación de revisiones, editoriales y comentarios en cinco revistas biomédicas generales y en revistas biomédicas especializadas por tema) y un cuestionario a expertos clínicos [117]. Las GPC fueron clasificadas según el tipo de actualización que requerían: mayor (la nueva evidencia sugiere la necesidad de nuevas recomendaciones) o menor (la nueva evidencia cambia las recomendaciones, las refina o permanecen válidas). El rendimiento de la

búsqueda fue del 2,9 % (208 artículos revisados de 7150 artículos identificados inicialmente). El 76,5 % (13/17) de las GPC necesitaban ser actualizadas. Los resultados del análisis de supervivencia mostraron que el 90 % de las GPC permanecían válidas a los 3,6 años (intervalo de confianza [IC] 95 %: 2,6 a 4,6), pero el 50 % habían caducado a los 5,8 años (IC 95 %: 5,0 a 6,6).

- Gartlehner *et al*. 2004 compararon dos estrategias para identificar nueva evidencia (la estrategia modificada de Shekelle *et al*. 2001 frente a una estrategia exhaustiva) y evaluar la necesidad de actualizar seis tópicos de una GPC [115, 117]. Los investigadores modificaron en tres fases consecutivas la estrategia de búsqueda de Shekelle *et al*. 2001, principalmente eliminando algunas de las bases de datos consultadas. El rendimiento de la búsqueda fue de un 2,6 % para la estrategia modificada de Shekelle *et al*. 2001 (36 artículos potencialmente relevantes de 1382 citas inicialmente identificadas) y de un 1,2 % para la estrategia exhaustiva (45 artículos potencialmente relevantes de 3687 citas inicialmente identificadas).

Estrategias para actualizar las GPC

- Eccles *et al*. 2002 compararon el proceso de actualización con el proceso original de elaboración de dos GPC [118]. Tanto en la elaboración como en la actualización se utilizó una búsqueda exhaustiva de la literatura. Las recomendaciones se clasificaron como: nuevas (si se identificó nueva evidencia), refinadas (si se identificó evidencia complementaria) y sin cambios (si no se identificó nueva evidencia). El rendimiento de la búsqueda fue del 1,0 % en las dos GPC (p.ej., en la GPC sobre angina, 59 artículos eran relevantes de 5941 citas inicialmente identificadas). Las recomendaciones permanecieron sin cambios.
- Parmelli *et al*. 2010, de forma parecida al estudio desarrollado por Eccles *et al*. 2002, compararon el proceso de actualización con el proceso original de elaboración en 15 recomendaciones [118, 120]. Diseñaron *de novo* búsquedas exhaustivas de la literatura para la actualización. El rendimiento de la búsqueda fue del 3,5 % (24 artículos incluidos de 686 inicialmente

cribados). El 40 % (6/15) de las recomendaciones fueron completamente actualizadas.

Estrategias para revisar y actualizar de forma continua las GPC

- Johnston *et al*. 2003 desarrollaron un estudio piloto para revisar y actualizar de forma continua 20 GPC [121]. La estrategia incluyó cuatro etapas: 1) una búsqueda exhaustiva continua de la literatura (periodicidad mensual), 2) la revisión de la nueva evidencia, 3) la revisión de las recomendaciones, y 4) la edición de la nueva evidencia y de las recomendaciones modificadas. Los autores utilizaron el término «GPC viva» como la «integración de la nueva evidencia en el documento original». La estrategia se aplicó durante un año. El rendimiento de la búsqueda fue del 23,8 % (19 citas con impacto en las recomendaciones de 80 citas inicialmente identificadas). En un 30 % (6/20) de las GPC realizaron una modificación de las recomendaciones.

5.1.3. Publicación III: Análisis de supervivencia de las recomendaciones

Se identificaron 14 GPC en la página web de GuíaSalud en el año 2011. Después de un proceso de estratificación y aleatorización se incluyeron en el estudio cuatro GPC: manejo de la depresión mayor en el adulto (2008) [122], tratamiento del cáncer de próstata (2008) [123], prevención secundaria del ictus (2009) (se excluyó la prevención primaria) [124], y prevención y tratamiento de la obesidad infantojuvenil (2009) [125]. Las GPC incluidas abordaron 87 preguntas clínicas e incluyeron 249 recomendaciones.

Después de un proceso de estratificación y aleatorización se obtuvo una muestra de 113 recomendaciones vinculadas a 43 preguntas clínicas. La mayoría de las recomendaciones se graduaron como buena práctica clínica (45,1 %; 51/113) y estaban relacionadas con el tratamiento (52,2 %; 59/113) o la prevención (41,6 %; 47/113).

Cuestionario inicial a expertos clínicos

Se envió el cuestionario inicial a 24 expertos clínicos y se obtuvo una tasa de respuesta del 70,8 % (17/24). Los expertos clínicos identificaron 189 referencias, de las cuales 21 no habían sido identificadas en la búsqueda exhaustiva actualizada de la de la literatura y se incluyeron en el proceso de revisión (42,9 %; 21/189).

Actualización de la búsqueda de la literatura

Se recuperaron las estrategias de búsqueda exhaustiva original de tres GPC [122-124] y se diseñó una estrategia de búsqueda exhaustiva *de novo* para la GPC sobre la obesidad infantojuvenil [125]. Para cada GPC, se ejecutaron las búsquedas desde el inicio del año en que se realizó la búsqueda original (2007-2008) en adelante (2011-2012). Los períodos de búsqueda tuvieron una mediana de 4 años (rango: 3,9 a 4,4) y se recuperaron un total de 39136 referencias (rango: 3343 a 14787).

Evaluación de las referencias

En un primer cribado de referencias, realizado por expertos en metodología de GPC, se identificaron 951 referencias pertinentes (2,4 %; 951/39136), que se emparejaron con 187 recomendaciones (75,1 %; 187/249).

En un segundo cribado de referencias (en base a las 113 recomendaciones con 668 referencias pertinentes enlazadas), realizado por expertos clínicos y por expertos en metodología de GPC, se identificaron 69 referencias clave (10,3 %; 69/668). El acuerdo entre los expertos clínicos y los expertos en metodología en cuanto a lo que era una referencia clave fue bajo (rango κ: 0,1 a 0,2).

Evaluación de las recomendaciones

Se identificaron 25 recomendaciones que, potencialmente, necesitaban ser actualizadas (22,1 %; 25/113). La mayoría de estas recomendaciones estaban clasificadas como B o buena práctica clínica (36,0 %; 9/25 para ambos), eran sobre prevención (60,0 %; 15/25) y tenían enlazadas un mayor número de

referencias (72 %; 18/25). Las recomendaciones con mayor número de referencias enlazadas presentaron una mayor probabilidad de requerir una actualización que aquellas con menor número de referencias enlazadas. El tema de la GPC, la fuerza de la recomendación y el propósito clínico no se asociaron a la necesidad de actualizar.

La mediana del tiempo de seguimiento de las recomendaciones fue de 3,6 años (rango: 0 a 4,4). Al año, el 92,0 % de las recomendaciones seguían siendo válidas (IC 95 %: 86,9 a 97,0). Esta probabilidad se redujo gradualmente a los dos, tres y cuatro años (85,7 %; 81,3 % y 77,8 %, respectivamente). El tema de la GPC, la fuerza de las recomendaciones, el propósito clínico y el volumen de referencias enlazadas no se asociaron a diferencias en las curvas de supervivencia.

Utilización de recursos

En el estudio participaron un total de 43 profesionales (cuatro expertos en documentación, 16 expertos en metodología de GPC y 26 expertos clínicos) y se invirtió un total de 1170,9 horas.

5.1.4. Publicación IV: Evaluación de las recomendaciones actualizadas

Guías de práctica clínica y recomendaciones incluidas

Se identificaron 21 GPC actualizadas de 166 GPC publicadas en la página web de NICE en el año 2013 (12,7 %; 21/166). Se excluyeron 12 GPC actualizadas (ocho no se identificaron como una actualización parcial y cuatro no incluyeron una etiqueta para cada recomendación con el resultado de la actualización). Finalmente, se incluyeron nueve GPC actualizadas y sus correspondientes GPC originales.

Las GPC originales se publicaron desde 2003 hasta 2006; y las GPC actualizadas se publicaron desde 2007 hasta 2013. La mediana de tiempo entre versiones fue de 7,2 años (rango: 4,3 a 9,0). Las GPC originales incluyeron un total de 1106 recomendaciones y las actualizadas, 1309 recomendaciones.

Las recomendaciones incluidas fueron mayoritariamente sobre ginecología, embarazo y parto o sobre temas respiratorios, estaban relacionadas con el tratamiento o con el apoyo al paciente y a los cuidadores, y se graduaron como D o como recomendaciones débiles. No se pudieron recuperar las referencias que apoyaban las recomendaciones originales.

Estado de actualización de las recomendaciones

Las GPC actualizadas incluyeron 812 recomendaciones no revisadas (62 %; 812/1309); 294 recomendaciones nuevas-añadidas (22,5 %; 294/1309); 104 recomendaciones enmendadas (7,9 %; 104/1309); 74 recomendaciones nuevas-modificadas (5,7 %; 74/1309), y 25 recomendaciones no modificadas (1,9 %; 25/1309).

Registro y justificación de los cambios

Los formatos de presentación para indicar los cambios en las recomendaciones o en las secciones variaron según las GPC. En cinco GPC (55,6 %, 5/9) se utilizaron etiquetas en las recomendaciones con el resultado de la actualización y el texto resaltado en color; en tres (33,3 %; 3/9) se utilizaron etiquetas y una franja en el lateral de la página, y en una (11,1 %; 1/9) solo se utilizaron etiquetas.

En las GPC, los cambios en las recomendaciones se registraron de forma frecuente en los anexos (77,8 %; 7/9). Las GPC con una puntuación más alta en relación con la información registrada fueron las que incluyeron en los anexos una comparación directa entre las recomendaciones originales y las actualizadas; las puntuaciones más bajas las obtuvieron las actualizaciones más antiguas.

Factores asociados a la actualización

Después del proceso de enlace entre las recomendaciones originales y las recomendaciones actualizadas, se identificaron en las GPC originales 783 recomendaciones no revisadas (70,8 %; 783/1106), 124 recomendaciones suprimidas (11,2 %; 124/1106), 94 recomendaciones enmendadas (8,5 %; 94/1106), 78 recomendaciones nuevas-modificadas (7,1 %; 78/1106) y 27 recomendaciones sin cambios (2,4 %; 27/1106).

Se compararon las recomendaciones nuevas-modificadas (casos) con las recomendaciones no modificadas (controles) y se observaron diferencias según GPC, tema y propósito, aunque no según el tiempo entre las versiones o la fuerza de las recomendaciones. Se consideró la muestra de 105 recomendaciones inadecuada para realizar un análisis de regresión múltiple.

5.1.5. Publicación V: Evaluación de dos estrategias pragmáticas de búsqueda de la literatura

Se incluyeron en el estudio cuatro guías del Programa de GPC en el SNS (87 preguntas clínicas y 249 recomendaciones) [122-125]. Después de un proceso de estratificación y aleatorización se obtuvo una muestra de 113 recomendaciones vinculadas a 43 preguntas clínicas.

Resultados de la estrategia exhaustiva

Para las GPC incluidas, se identificaron un total de 39136 referencias. Para la muestra de recomendaciones, se identificaron 69 referencias clave y 25 recomendaciones que, potencialmente, necesitaban ser actualizadas.

Resultados de la estrategia restrictiva

Se aplicó la estrategia restrictiva al 88,5 % (77/87) de las preguntas clínicas de las GPC incluidas y al 85 % (96/113) de las recomendaciones de la muestra. Las búsquedas restrictivas abarcaron un periodo de 4,6 años (rango: 3,9 a 5,1).

Utilizando el filtro limitado *Clinical Queries* se identificaron un total de 9958 referencias para las preguntas clínicas incluidas. Utilizando el filtro limitado *Clinical Queries* y agrupando los resultados por GPC se identificaron 39 referencias clave (84,8 %; 39/46) y 17 recomendaciones que, potencialmente, necesitaban ser actualizadas (85 %; 17/20).

Cuando se incluyeron los resultados de la estrategia exhaustiva para las preguntas clínicas sin estrategia restrictiva, utilizando el filtro limitado *Clinical*

Queries y agrupando los resultados por GPC, se identificaron 12491 referencias, 62 referencias clave (89,9 %; 62/69) y 22 recomendaciones que, potencialmente, necesitaban ser actualizadas (88 %; 22/25).

No se observaron diferencias entre las recomendaciones identificadas (utilizando el filtro limitado *Clinical Queries* y agrupando los resultados por GPC) y las que no fueron identificadas según el tema de la GPC, la fuerza de la recomendación, el propósito clínico de la recomendación o el volumen de referencias enlazadas.

Resultados de la estrategia PLUS

Las búsquedas en la base de datos McMaster PLUS abarcaron un periodo de 5 años (rango: 4,1 a 5,3).

Para las GPC incluidas se identificaron un total de 4486 referencias. Para la muestra de recomendaciones se identificaron 18 referencias clave (26,1 %; 18/69) y 10 recomendaciones que, potencialmente, necesitaban ser actualizadas (40 %; 10/25).

Se identificaron más recomendaciones con un mayor volumen de referencias enlazadas, aunque no se observaron diferencias considerando otros factores (tema de la GPC, fuerza de la recomendación o propósito clínico de la recomendación).

Utilización de recursos

Tres expertos en metodología de GPC invirtieron un total de 174 horas en el diseño y la ejecución de las estrategias de búsqueda restrictiva. Un experto en documentación invirtió 28 horas en el diseño y la ejecución de las estrategias de búsqueda en la base de datos McMaster PLUS.

5.2. Publicaciones presentadas en la tesis

Publicación I: Alonso-Coello P, Martínez García L, Carrasco JM, Solà I, Qureshi S, Burgers JS, *et al*. The updating of clinical practice guidelines: insights from an international survey. Implement Sci. 2011;13;6:107.

Implement Sci 2011: factor de impacto (FI) 3,100; primer cuartil (Q1) (9/76 *health care sciences & services*).

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The updating of clinical practice guidelines: insights from an international survey

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Abstract

Background: Clinical practice guidelines (CPGs) have become increasingly popular, and the methodology to develop guidelines has evolved enormously. However, little attention has been given to the updating process, in contrast to the appraisal of the available literature. We conducted an international survey to identify current practices in CPG updating and explored the need to standardize and improve the methods.

Methods: We developed a questionnaire (28 items) based on a review of the existing literature about guideline updating and expert comments. We carried out the survey between March and July 2009, and it was sent by email to 106 institutions: 69 members of the Guidelines International Network who declared that they developed CPGs; 30 institutions included in the U.S. National Guideline Clearinghouse database that published more than 20 CPGs; and 7 institutions selected by an expert committee.

Results: Forty-four institutions answered the questionnaire (42% response rate). In the final analysis, 39 completed questionnaires were included. Thirty-six institutions (92%) reported that they update their guidelines. Thirty-one institutions (86%) have a formal procedure for updating their guidelines, and 19 (53%) have a formal procedure for deciding when a guideline becomes out of date. Institutions describe the process as moderately rigorous (36%) or acknowledge that it could certainly be more rigorous (36%). Twenty-two institutions (61%) alert guideline users on their website when a guideline is older than three to five years or when there is a risk of being outdated. Twenty-five institutions (64%) support the concept of "living guidelines," which are continuously monitored and updated. Eighteen institutions (46%) have plans to design a protocol to improve their guideline-updating process, and 21 (54%) are willing to share resources with other organizations.

Conclusions: Our study is the first to describe the process of updating CPGs among prominent guideline institutions across the world, providing a comprehensive picture of guideline updating. There is an urgent need to develop rigorous international standards for this process and to minimize duplication of effort internationally.

Background

Clinical practice guidelines (CPGs) have become increasingly popular over the last two decades. In parallel, the methodology to develop guidelines has evolved enormously [1,2]. Major attention has been given to the selection and appraisal of the available literature, becoming progressively more systematic and comprehensive. The harmonization of grading systems to classify the quality of the evidence and the strength of recommendations has been a hot issue in the guideline arena [3]. As a result, the quality of guidelines has been improved in the last decade. Nevertheless, there is still important room for improvement [4].

In guideline programs, the updating of guidelines is often scheduled irregularly [5]. Although there is no fixed lifespan for a guideline, an update every three to five years is generally recommended [6,7]. However, information about the process and methods for updating used by guideline organizations is lacking. Only few published research studies are available on this topic [6-9]. Few organizations include chapters or information on guideline updating in their handbooks on guideline development [1,2].

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A significant step forward is the synthesis of available research on updating of CPGs included in the handbook of the Programme of Clinical Practice Guidelines in the Spanish National Health System. This programme is coordinated by GuíaSalud http://www.guiasalud.es, an organization created in 2002 to promote the development and use of evidence-based guidelines and other tools for improving quality of care in the Spanish Health System. Following these objectives, a common methodology for producing, implementing , and updating CPGs has been developed [10-12]. Within this context, we conducted an international survey with the aim of identifying current practices in guideline updating, exploring the need for standardization, and, ultimately, improving the guideline-updating process.

Methods

Design

We employed a cross-sectional design for this study.

Study population

Our study population included key informants and experts affiliated with organizations dedicated to CPG development.

Study sample

We selected participant institutions in spring 2009 using the following criteria: (a) members of the Guidelines International Network http://www.g-i-n.net/ that declared that they developed CPGs, (b) institutions included in the U.S. National Guideline Clearinghouse http://www.guideline.gov/ that had published more than 20 CPGs, and (c) institutions additionally selected by an expert committee based on relevance. The expert committee was composed of 12 health professionals and methodologists with experience in the field of guideline methodology and information specialists. We sent an email to each institution through the address identified via the internet. If the person receiving this email was not the person responsible for this matter, we requested that it be forwarded to whoever they considered appropriate within that institution to answer the survey.

Intervention

We designed a self-administered survey (see Additional File 1) based on a literature review about guideline updating (unpublished). For this review, we studied websites of institutions that had published methodological handbooks and searched for published studies in MEDLINE (via PubMed) until June 2008 using a combination of descriptors (Practice Guidelines as Topic; Clinical Practice Guidelines) and free text terms (clinical guideline, practice guideline, updat*, up to date).

The survey comprised 28 items grouped into four domains. The first domain included characteristics of the organization (five items), the second was dedicated to the process of guideline updating (16 items), the third was aimed at the way users are alerted about guideline updates (two items), and the last domain focused on the future perspective on guideline updating (five items). Nineteen items included a free text area in order to gather comments or additional information.

Specific software was used to design the survey and to collect the responses http://www.surveymonkey.com. The survey was pilot tested among five institutions (three national and two international). Their feedback was used to refine the survey for optimal understanding. Between March and July 2009, we sent the survey via email to persons of selected institutions. We sent three reminders at intervals of four weeks to those institutions that had not responded. Questionnaires with no response on more than 20% of the items were returned with the request to complete the questionnaire.

Analysis

Descriptive statistics were used to analyze the data. We calculated absolute frequencies and proportions for all items. We evaluated nonresponding institutions and compared their contact source (Guidelines International Network, National Guideline Clearinghouse, or expert committee), country, and number of CPGs produced with responding institutions using Fisher's exact test or Mann-Whitney U test (alpha was set at 0.05). We finally excluded from the analysis four items (B13-B16, Additional File 1), as they were deemed to be more related to guideline development. We assessed the guideline-updating process of responding institutions by comparing the number of years developing CPGs (≤ 10 years of experience or > 10 years of experience), contact source, and number of guidelines published per year using Fisher's exact test (alpha was set at 0.05). Data analysis was performed using SPSS statistical software, version 17.0 (SPSS Inc., Chicago, IL, USA). By consensus of the three first authors, we collected and provide the most relevant themes brought up by the responders in the free text area (responses to free text questions available from the authors on request).

Ethics approval was obtained from the hospital ethics committee (Clinical Research Ethics Committee, Hospital de la Santa Creu i Sant Pau, #74/2010).

Results

Characteristics of study sample

One hundred and fourteen institutions met at least one of the inclusion criteria. We contacted 106 of these institutions by email. We received a reply from 44

institutions (42% response rate) after three reminders. In the final analysis, we included 39 questionnaires. Five questionnaires were excluded because more than 20% of the questions were not answered (Figure 1).

Characteristics of the responding institutions are presented in Table 1. The vast majority reported that they update their guidelines (n = 36, 92%). Nonresponding and excluded institutions (n = 67) did not differ from the responding institutions with regard to their contact source (Guidelines International Network, National Guideline Clearinghouse, or expert committee; Fisher's exact test p = .671), country of origin (Fisher's exact test p = .283), and the number of guidelines produced (Mann-Whitney U test p = .07).

Characteristics of the guideline-updating process

Sixteen institutions (44%) reported that they check more than five guidelines for the need for annual updating, some institutions reported variable figures (n = 10, 28%), and the remaining 10 (28%) reported that they check five or less per year (Table 2, Figure 2). Over 60% of the institutions reported a time frame for considering a guideline update between three to five years. Thirty-one institutions (86%) indicated that they have a formal procedure for updating their guidelines, but only 19 (53%) have a formal procedure for deciding when a guideline becomes out of date. Nine institutions (25%) piloted the updating process to evaluate feasibility, inconveniences, or added value compared to other strategies.

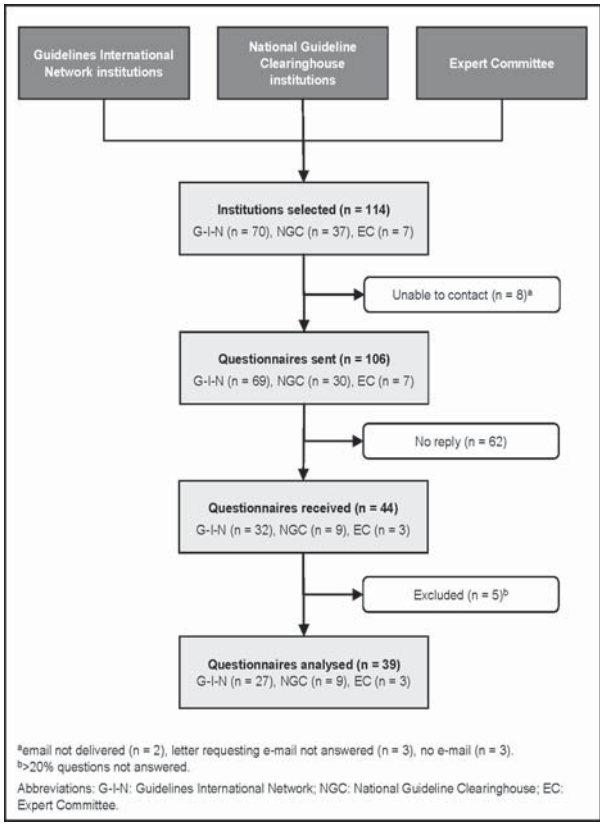


Figure 1 Participation diagram.

Table 1 Organization characteristics (n = 39)[a]

	n	(%)
Contact source		
Guidelines International Network	27	(69.2)
U.S. National Guideline Clearinghouse	9	(23.1)
Expert committee	3	(7.7)
Continent		
Europe	17	(43.6)
North America	15	(38.5)
Oceania	5	(12.8)
South America	1	(2.6)
Asia	1	(2.6)
Type of organization		
Scientific/professional society/association	20	(51.3)
Public institution	14	(35.9)
Other (Federal institute, nonprofit organization)	5	(12.8)
Number of years developing guidelines		
> 10 years	24	(61.5)
6-10 years	12	(30.8)
≤ 5 years	3	(7.7)
Number of guidelines published[b]		
≤ 5 per year	24	(61.5)
> 5 per year	14	(35.9)
Updating guidelines		
Yes	36	(92.3)
No	3	(7.7)

[a]Analysis of included institutions; [b]One institution unknown.

Twenty-six institutions (72%) described the process as moderately rigorous or acknowledged that it could certainly be more rigorous. Institutions that have been developing guidelines for more than 10 years are more likely to have a formal updating procedure (Fisher's exact test p = .047) and a rigorous process for guideline updating (Fisher's exact test p = .039) than are institutions who have been developing guidelines for 10 or less years (Table 3). In general, the original guideline group or an expert committee is responsible for the decision about updating the guideline (Table 4, Figure 3). The original guideline authors are most often involved in the updating process (n = 32, 89%), followed by the institution's staff (n = 30, 83%). In 13 institutions (36%), patients are involved in the process.

Institutions tend to check and review different parts of the guideline when deciding about the need to update a guideline. Twenty-nine institutions (81%) said they check all recommendations and the full guideline text. Less frequently, key questions and recommendations, supplementary annexes, and patient information are checked.

Table 2 The guideline-updating process (n = 36)[a]

	n	(%)
Number of guidelines checked		
> 5 per year	16	(44.4)
Variable	10	(27.8)
3-5 per year	6	(16.7)
< 3 per year	4	(11.1)
Number of guidelines updated		
Unknown	14	(38.9)
≤ 5 per year	11	(30.6)
> 5 per year	7	(19.4)
Variable	4	(11.1)
Time frame to check updating		
3-5 years	22	(61.1)
< 3 years	11	(30.6)
Variable	3	(8.3)
Formal procedure to update guidelines		
Yes	31	(86.1)
No	5	(13.9)
Formal procedure to inform about guidelines being out of date		
Yes	19	(52.8)
No	17	(47.2)
Formal method to decide update section or full guideline		
No	23	(63.9)
Yes	11	(30.6)
Unknown	2	(5.6)
Pilot testing of updating process		
No	24	(66.7)
Yes	9	(25.0)
Unknown	3	(8.3)
Rigor of the updating process		
Could certainly be more rigorous	13	(36.1)
Moderately rigorous	13	(36.1)
Very rigorous	10	(27.8)

[a]Analysis of institutions updating guidelines.

- *"We are currently in the process of reviewing the currency of all our guidelines, but following this we would expect to review less than 3 per year."*
- *"We are currently updating this procedure and it will be available in our updated handbook in late 2009."*
- *"We aim to update all topics at minimum every five years, using something of a rolling process to consider all topics, and also has a process for considering 'early' updates."*
- *"Through our experience of reviewing/updating guidelines over the past seven years, no guideline recommendations have been determined to be unsafe for practice due to new evidence. However, many recommendations and supports for implementation have been further supported with updated evidence."*

Figure 2 Box of relevant comments about the characteristics of the guideline-updating process.

The institutions use several search strategies (Table 4, Figure 4). Twenty institutions (56%) ran the original search strategies and did additional horizon scanning, 14 institutions (40%) use more specific strategies than the original strategies, and seven (20%) institutions run other searches. Twenty-two institutions (61%) alert guideline users on their website when a guideline is older than three to five years or when there is a risk of being outdated.

Future plans for updating guidelines

Twenty-five institutions (64%) supported the concept of "living guidelines" (Table 5, Figure 5), defined as guidelines that are continuously monitored and updated [13]. The majority of institutions, however, reported difficulties and inconvenience in putting this concept in practice. Almost half of the institutions reported that they have plans to improve their guideline-updating process (n = 18, 46%). More than half of the institutions are willing to share resources with other organizations (n = 21, 54%). However, only 20% of the organizations reported that they would rely on other guidelines when updating or developing a guideline.

Discussion

Our study is the first international survey about the process of updating CPGs among guideline institutions across the world. Although most institutions reported having a process for updating guidelines, the process is not standardized and could be more rigorous. Many guideline developers, including those with long-standing experience, reported that they have plans to improve this process. Others are waiting for more evidence before modifying their current system.

Surprisingly, half of the organizations do not have a formal process for deciding when a guideline becomes outdated. Guideline developers need to recognize this limitation when promoting guidelines as support tools for the practice of evidence-based medicine. Similarly, guideline users should be cautious when relying on guidelines of a certain age. This lack of rigor in methodology in general was recently found in a systematic review about the quality of guidelines in the last two decades [4,14]. On the other hand, most organizations in our survey showed awareness about using insufficient methods for updating guidelines and intended to improve their processes. Up to 72% think that their updating process is only moderately rigorous or could be more rigorous. This is an issue that guideline developers need to address. This finding is consistent with the fact that only 20% of organizations in our survey would rely on other guidelines when updating or developing a guideline. This is an unfortunate paradox given the actual scenario, where most institutions would like to be

Table 3 The guideline-updating process by numbers of years developing guidelines (n = 36)[a]

	Numbers of years developing guidelines				Total		
	≤ 10 years		> 10 years				
	n	(%)	n	(%)	n	(%)	p^b
Formal procedure to update guidelines							
Yes	9	(69.2)	22	(95.7)	31	(86.1)	.047
No	4	(30.8)	1	(4.3)	5	(13.9)	
Time frame to check updating							
3-5 years	7	(53.8)	15	(65.2)	22	(61.1)	.094
< 3 years	3	(23.1)	8	(34.8)	11	(30.6)	
Varies	3	(23.1)	–		3	(8.3)	
Rigor of the updating process							
Could certainly be more rigorous	8	(61.5)	5	(21.7)	13	(36.1)	.039
Moderately rigorous	4	(30.8)	9	(39.1)	13	(36.1)	
Very rigorous	1	(7.7)	9	(39.1)	10	(27.8)	

[a]Analysis of institutions updating guidelines; [b]Fisher's exact test.

Table 4 Characteristics of the guideline-updating process (n = 36)[a]

	Answers					
	Yes		No		Unknown	
	n	(%)	n	(%)	n	(%)
Who decides the need for updating[b]						
Guideline group	18	(50.0)	18	(50.0)	–	
Expert committee	15	(41.7)	21	(58.3)	–	
Guideline coordinator	9	(25.0)	27	(75.0)	–	
Other	9	(25.0)	27	(75.0)	–	
Standing editorial staff	6	(16.7)	30	(83.3)	–	
Who participates in the updating process[c]						
Original guideline authors	32	(88.9)	–		4	(11.1)
Staff of organization	30	(83.3)	–		6	(16.7)
New group of experts	25	(69.4)	4	(11.1)	7	(19.4)
Original information managers/specialist	21	(58.3)	5	(13.9)	10	(27.8)
Original external reviewers	20	(55.6)	6	(16.7)	10	(27.8)
Patients	13	(36.1)	11	(30.6)	12	(33.3)
Others	7	(19.4)	5	(13.9)	24	(66.7)
Which part of the guidelines get checked[c]						
Full text	29	(80.6)	2	(5.6)	5	(13.9)
All recommendations	29	(80.6)	1	(2.8)	6	(16.7)
Key questions	25	(69.4)	1	(2.8)	10	(27.8)
Key recommendations	25	(69.4)	–		11	(30.6)
Annexes	20	(55.6)	3	(8.3)	13	(36.1)
Patient information	19	(52.8)	5	(13.9)	12	(33.3)
Which kind of search run[b]						
Original search strategies plus some horizon scanning	20	(55.6)	16	(44.4)	–	
Original searches strategies modified to be specific rather than sensitive	14	(38.9)	22	(61.1)	–	
Original search strategies	10	(27.8)	26	(72.2)	–	
Other	7	(19.4)	29	(80.6)	–	

[a]Analysis of institutions updating guidelines; [b]Closed-ended questions yes/no; [c]Aggregation responses yes/partially.

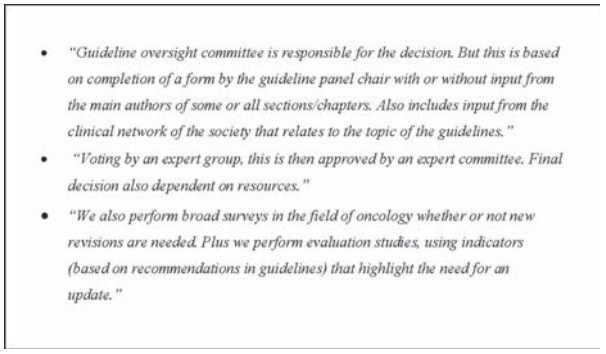


Figure 3 Box of relevant comments about decision-making process of the need of updating.

able to share the burden of the development process. There is a perceived need for international collaboration, but the product to be exchanged needs to be more mature.

The majority of institutions support the concept of living guidelines. However, this type of guideline development is regarded as very labour intensive and resources may be insufficient. This modality could make more sense in fast-changing fields such as AIDS, cardiovascular risk management, and breast cancer. Guidelines on other topics, such as venous ulcer or sinusitis, may need less frequent updating. Some responders emphasized that guideline updating should be tailored to the topic in order to optimize the efficient use of resources (Figure 5).

A noted limitation of frequent updating of guidelines is that notifications of each update could be burdensome for developers and users (Figure 5). Users' interests may vary for different kinds of updates, some being interested in any change made to the guideline, some just being concerned about major modifications. Ideally, web-based organizations could have personalized systems of alerts that could be tailored to each user group.

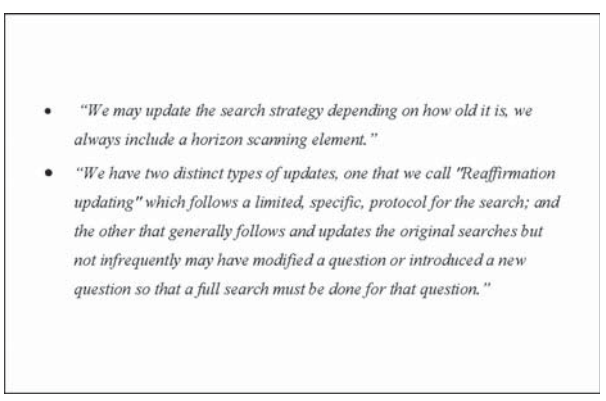


Figure 4 Box of relevant comments about the characteristics of the search process.

Sufficient funding is important for appropriate guideline updating. Guideline organizations that are structurally embedded within the countries' healthcare system and funded by the government, such as the National Institute for Health and Clinical Excellence (NICE) and the Scottish Intercollegiate Guidelines Network (SIGN), have more rigorous updating procedures. In organizations with fewer resources, funding is only available for developing *de novo* guidelines. Research in the field of guideline updating is scarce. There is an urgent need for valid tools to estimate the rate of new relevant findings related to the topic of the guideline and for efficient search strategies to track new research evidence. In addition, more knowledge is needed about the best method to reach end users when guidelines are out of date and when guidelines are updated.

Our survey shows that institutions consider guideline updating to be time consuming and resource intensive. Despite the limitations described above, over half of the institutions surveyed are eager to share the burden and work with peer institutions. International collaboration could further help to avoid duplication of effort. Some institutions suggested that a forum to discuss and share updating experiences would be helpful (Figure 5). The Guidelines International Network could provide these facilities, in the same way that they support other groups active in guideline methodology.

Work is being duplicated around the world, with institutions failing to work jointly, consolidating networks around health topics or fields. Timidly but progressively, international collaboration on guideline development and updating for chronic obstructive pulmonary disease (COPD) has been initiated recently [15]. In the field of oncology, a European collaboration of guideline institutions (CoCanCPG) has been active [16]. To increase the efficient use of existing guidelines in guideline updating, the ADAPTE methodology could be helpful [17]. In addition, a standardized format for evidence tables and for grading the evidence could help with sharing evidence worldwide [3,18]. Finally, international databases of gaps in evidence could be developed, which could feed the agenda of healthcare researchers and reviewers, such as the Cochrane Collaboration.

This study has a few limitations. First, the response rate was rather low, despite sending three reminders. Nevertheless, our survey included the most prominent guideline organizations, like NICE, SIGN, the United States Preventive Services Task Force, and the New Zealand Guidelines Group (Additional File 2). We did not find essential differences between responding and nonresponding institutions. Second, bias cannot be excluded due to the nature of the survey being self-reported. Although we contacted a key informant from each institution, other responders from the same institutions

Table 5 The guideline-updating process in the future (n = 39)[a]

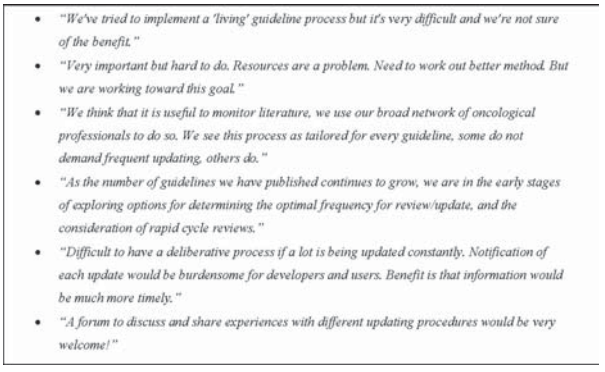
	Answers					
	Yes		No		Not sure/unknown	
	n	(%)	n	(%)	N	(%)
It is worth having living guidelines[b]	25	(64.1)	6	(15.4)	8	(20.5)
Plans to set up a protocol to improve the updating process	18	(46.2)	10	(25.6)	11	(28.2)
Share resources with other organizations	21	(53.8)	1	(2.6)	17	(43.6)
Resources to share (n = 21)						
- References	20	(95.2)	–		1	(4.8)
- Evidence synthesis	19	(90.5)	–		2	(9.5)
- Key questions	18	(85.7)	–		3	(14.3)
- Search strategies	18	(85.7)	–		3	(14.3)
- Evidence tables	18	(85.7)	1	(4.8)	2	(9.5)
- Considered judgement forms[c]	14	(66.7)	–		7	(33.3)

[a]Analysis of included institutions; [b]Considering "living guidelines" as those that are continuously being monitored and updated; [c]Document that explicitly includes the factors taken into account when grading recommendations.

might have provided different answers. In some institutions, the person initially contacted referred us to another person more able to answer the questions, which increases the likelihood of appropriate answers.

Conclusions

Our study provides the first comprehensive picture of guideline updating around the world. This stage in guideline development has not benefited from the same rigor of methodological development that has been applied to the initial development of a guideline. Our study shows that it is an area that needs increasing attention. Our main findings include the urgent need to develop a rigorous standard for this process, initially by funding research into how to optimize the process, share the burden, and minimize duplication of effort internationally. We believe that these changes will improve the quality and impact of guidelines and, ultimately, patient care.



- *"We've tried to implement a 'living' guideline process but it's very difficult and we're not sure of the benefit."*
- *"Very important but hard to do. Resources are a problem. Need to work out better method. But we are working toward this goal."*
- *"We think that it is useful to monitor literature, we use our broad network of oncological professionals to do so. We see this process as tailored for every guideline, some do not demand frequent updating, others do."*
- *"As the number of guidelines we have published continues to grow, we are in the early stages of exploring options for determining the optimal frequency for review/update, and the consideration of rapid cycle reviews."*
- *"Difficult to have a deliberative process if a lot is being updated constantly. Notification of each update would be burdensome for developers and users. Benefit is that information would be much more timely."*
- *"A forum to discuss and share experiences with different updating procedures would be very welcome!"*

Figure 5 Box of relevant comments about future plans for updating guidelines.

Additional material

Additional file 1: Survey. This document shows the survey designed, based on a literature review about guideline updating.

Additional file 2: Organizations. This document shows information about the organizations that participated in this survey (name, country and source of contact).

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Authors' contributions
PAC, LMG, JMC, IS, SQ, and JSB participated in the conception and design of the study. LMG, PAC, and JMCG analyzed the data. PAC and LMG drafted a first version. All members of the Updating Guidelines Working Group participated in the design of the study and revising the draft critically for important intellectual content and all authors have given final approval of the version to be published.

Competing interests
The authors declare that they have no competing interests.

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Implement Sci 2012: FI 2,372; Q1 (20/83 *health care sciences & services*).

IMPLEMENTATION SCIENCE

SYSTEMATIC REVIEW Open Access

Strategies for monitoring and updating clinical practice guidelines: a systematic review

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Abstract

Background: Scientific knowledge is in constant change. The flow of new information requires a frequent re-evaluation of the available research results. Clinical practice guidelines (CPGs) are not exempted from this phenomenon and need to be kept updated to maintain the validity of their recommendations. The objective of our review is to systematically identify, describe and assess strategies for monitoring and updating CPGs.

Study design and setting: We conducted a systematic review of studies evaluating one or more methods of updating (with or without monitoring) CPGs or recommendations. We searched MEDLINE (PubMed) and The Cochrane Methodology Register (The Cochrane Library) from 1966 to June 2012. Additionally, we hand-searched reference lists of the included studies and the Guidelines International Network book of abstracts. If necessary, we contacted study authors to obtain additional information.

Results: We included a total of eight studies. Four evaluated if CPGs were out of date, three updated CPGs, and one continuously monitored and updated CPGs. The most detailed reported phase of the process was the identification of new evidence. As opposed to studies updating guidelines, studies evaluating if CPGs were out of date applied restricted searches. Only one study compared a restricted versus an exhaustive search suggesting that a restricted search is sufficient to assess recommendations' Validity. One study analyzed the survival time of CPGs and suggested that these should be reassessed every three years.

Conclusions: There is limited evidence about the optimal strategies for monitoring and updating clinical practice guidelines. A restricted search is likely to be sufficient to monitor new evidence and assess the need to update, however, more information is needed about the timing and type of search. Only the exhaustive search strategy has been assessed for the update of CPGs. The development and evaluation of more efficient strategies is needed to improve the timeliness and reduce the burden of maintaining the validity of CPGs.

Keywords: Clinical practice guidelines, Diffusion of innovation, Evidence-based medicine, Information storage and retrieval, Methodology, Updating, Implementation science, Dissemination and implementation, Knowledge translation

Background

Scientific knowledge is in constant change, and new information requires frequent assessment to determine whether it changes the knowledge base [1]. A clinical practice guideline (CPG) may be considered out of date if it does not include all recent, valid, and relevant evidence or does not reflect current clinicians' experience and patients' values and preferences [2]. CPGs, hence, need to be updated regularly to remain valid.

Shekelle et al. evaluated the validity of a cohort of CPGs [3]. Survival analysis indicated that 90% of CPGs were still valid in 3.6 years, but 50% were out of date in 5.8 years [3]. Based on these results, most methodological handbooks for the development of CPGs propose three years as a reasonable time frame to update their guidelines [1,4].

In 2007, Moher et al. conducted a study about when and how to update systematic reviews [5]. Although not included in the objectives, the authors identified and described several methods for updating CPGs. In their conclusions the authors argue that the methodology for

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updating CPGs, as opposed to systematic reviews, is well established. Nevertheless, a recent international survey showed high variability and a lack of standardization in the CPGs updating processes [6].

A few studies have evaluated different strategies for the CPGs updating process [3,7,8], however, no systematic reviews have been conducted about this topic. We therefore undertook a systematic review of the studies that assessed strategies for monitoring and updating CPGs.

Methods

Information sources and search

We performed a search in June 2012 in MEDLINE (accessed through PubMed, from 1966 onwards) and The Cochrane Methodology Register (accessed through *The Cochrane Library*, Issue 6 2012). We included studies regardless of their language or publication status. The search strategy is available as supplementary data (Additional file 1). Additionally, we hand searched reference lists of the included studies and in the Guidelines International Network book of abstracts (available online from 2009 until 2011 in http://www.g-i-n.net/). If necessary we contacted study authors to obtain additional information. Two authors were in charge of performing all searches (IS, LMG).

Eligibility criteria

1. Type of study: We included studies evaluating one or more methods of updating (with or without monitoring) evidence-based CPGs or recommendations. We excluded studies that only reported updating methods (without actually testing them), methodological handbooks or CPGs updates. We made no restriction by health topic.
2. Type of design: We included studies assessing strategies for evaluating if CPGs are out of date; for updating CPGs; for continuous monitoring and updating of CPGs (Figure 1).

Study selection

Two authors independently reviewed the titles and abstracts, as well as the full text of the selected articles for a more detailed evaluation and approved their final inclusion (LMG, IAR). Any disagreement among the authors was initially resolved by consensus, and if necessary, we consulted a third author (IS).

Data extraction strategy

Two authors independently extracted information from the included studies using an ad hoc form (LMG, IAR) that can be requested from the authors. Disagreements among the authors were resolved by consensus and, if required, by a third author (IS). We contacted study authors by email when more information was needed.

We extracted the following information from each study: institution or guideline program and country; objective and design of the study; sample (selection and size) and health topic; time to update (number of years since the development of the original CPG); stages of the strategies; type of search (restricted or exhaustive, classified depending on databases consulted and types of studies searched); resource use (number of participants and time spent); search and update results; and advantages and limitations of strategies reported by the authors.

Data synthesis and presentation

We describe included studies both individually and narratively. We calculated the search performance of the strategies (as a proportion of included documents from all documents identified); and update performance of the strategies (as a proportion of updated recommendations or CPGs from all evaluated recommendations or CPGs).

Results

Study selection

The screening process is summarized in the flow diagram (Figure 2). We initially identified 2,923 references from our search strategy, and excluded 141 duplicates and 2,731 references after examining the title and abstract. We reviewed 51 full texts and we excluded 39 references (Additional file 2). We finally included eight studies corresponding to 12 original references [3,7-17]. Three studies were only available as abstracts [9,14,15]. We successfully contacted two of the first abstracts' authors to obtain additional information of these studies [14,15].

Study characteristics

Four studies assessed strategies evaluating if CPGs were out of date [3,7,9,15], three studies assessed strategies for updating CPGs [10,14,16], and one study assessed a strategy for continuous monitoring and updating CPGs [8] (Table 1). Five studies assessed a single strategy for: evaluating if CPGs were out of date [3,9,15], for updating CPGs [14] or for continuous monitoring and updating of CPGs [8]; three studies compared two strategies: two different strategies for evaluating if CPGs were out of date [7] or 'de novo' development versus updating strategies [10,16]. Most of the studies evaluated full CPGs (range from one to 20 CPGs) [3,8-10,14,15], however none of them included a random sample. The topics included varied widely, with cancer being the most frequent [8,9,16]. The time to update source documents ranged from one to eight years. The common

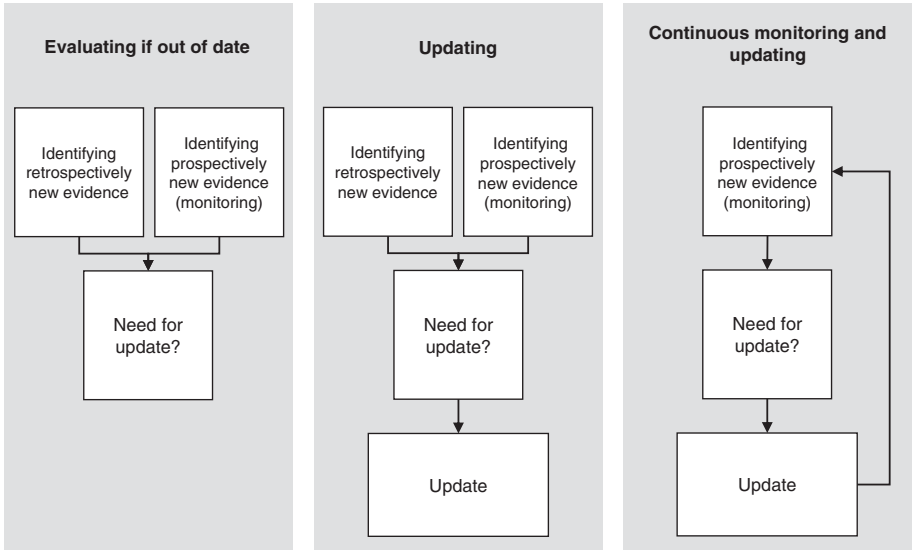

Figure 1 Updating Clinical Practice Guidelines Strategies.

stages identified in the strategies were: assessment of need to update; scope definition of the update; working group composition; search strategy; selection, assessment, and synthesis of the evidence; recommendations update (only for updating and continuous monitoring); and presentation format of the updates (for strategies for updating and continuous monitoring) (Table 2).

Strategies for evaluating if CPGs are out of date

Shekelle et al. [3] developed a strategy to assess the validity of CPGs based on identified new evidence through restricted searches (reviews, editorials, or commentaries in general or specialised journals) and through a survey of clinical experts (Table 2). The CPGs were classified by the type of update required as: major update—new evidence suggests the need for new recommendations; minor update—new evidence supports changes to recommendations or refinement of existing recommendations; and the recommendations remain valid. The participants in this updating process were two methodologists and 146 clinical experts. The clinical experts participated in a survey to assess current validity of the guideline recommendations and to identify new evidence (71% of response rate). The search performance was 2.9% (208 articles reviewed from 7,150 articles initially identified) (Table 3). The authors concluded that 76.5% of the guidelines needed to be updated (13/17 CPGs) (Table 3). The results of survival analysis indicated that 90% of CPGs were still valid at 3.6 years (95% confidence interval (CI) 2.6 to 4.6 years), but 50% of CPGs were out of date at 5.8 years (95% CI 5.0 to 6.6 years). The main reported limitation of the study included no previous validation of the method of assessing obsolescence.

Bosquet et al. [9] monitored the literature to assess the need for updating a CPG (Table 2). This approach applied an exhaustive search and evaluated the impact of new studies on existing guidelines (consistent, inconsistent or concern new topics) by consultation with the original working group (mail and meetings). The search performance was 45.2% (118 references submitted to the working group from 261 references initially identified) (Table 3).

Gartlehner et al. [7] compared two search strategies to identify new evidence for assessing the need to update six topics of one CPG: a modified Shekelle et al. [3] search versus an exhaustive search (Table 2). The researchers modified in three consecutive phases the literature search developed by Shekelle et al. [3], mainly by eliminating some of the databases (omitting a general web site search and confining the MEDLINE search to Abridged Index Medicus journals). The participants were 10 methodologists (five for each model) and 13 clinical experts. The clinical experts participated in a survey similar to the one carried out in Shekelle et al. [3] (28% response rate). The search performance was 2.6% for the modified Shekelle et al. [3] search (36 eligible studies from 1,382 citations initially identified) and 1.2% for the exhaustive search (45 eligible studies from 3,687 citations initially identified) (Table 3). The reported strength of the modified Shekelle et al. [3] method was that it offered a search strategy that detected fewer citations to review and identified all studies that triggered an update. However, the study only included prevention topics; the comparison of the number of abstracts and full texts between the two approaches was limited because the Shekelle et al. [3] search was an integral part of the exhaustive search; and the experts who

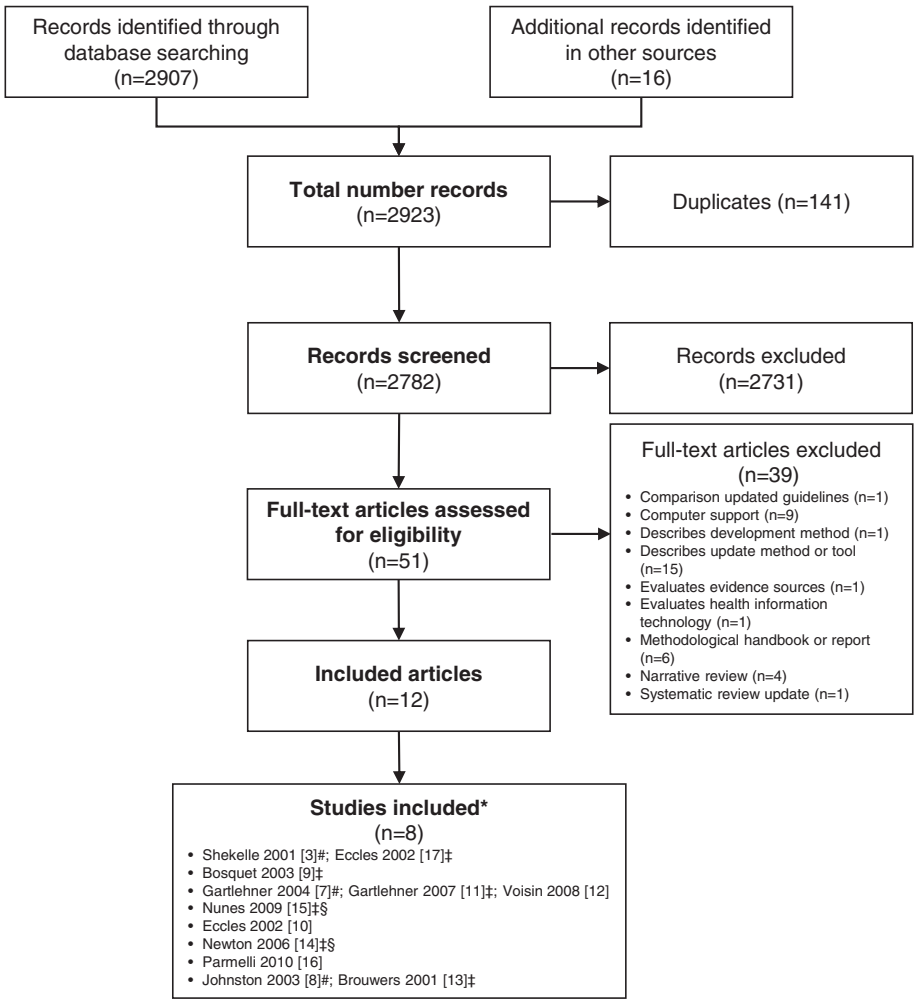

Figure 2 Flow diagram for the identification of studies. *Ordered by type of strategy and chronology; #Main publication for the study; ‡Only abstract available; §Information provided by the author.

assessed the importance of the studies not identified were not blinded to the type of search approach.

Nunes et al. [15] described a restricted search and a review of new CPGs to decide whether their guideline required an update (Table 2). The participants were three methodologists and two experts. The search performance was 28% (seven guidelines reviewed from 25 guidelines initially identified) (Table 3). No recommendations needed to be updated because identified recommendations in other CPGs were consistent with the existing CPG (Table 3). Less time was required to perform the update strategy than the time estimated to perform an exhaustive search. The need to judge the applicability of recommendations from other guidelines was one of the difficulties reported.

Strategies for updating CPGs

Eccles et al. [10] compared the updating process with the original development process of two CPGs (Table 2). In both the development and updating process new evidence was identified by exhaustive search. Recommendations were classified as: new (if new evidence was identified); refined (if supplementary evidence was identified); and unchanged (if no new evidence was identified). Two methodologists and 14 clinical experts participated. The search performance was 1.0% for each guideline (e.g., for angina there were 59 acceptable papers from 5,941 citations initially identified) (Table 3). Recommendations remained unchanged (Table 3). Among the reported strengths were that some members also had participated in the original development of the guidelines and were better trained and were more familiar with the literature. These members also identified other relevant evidence. The main reported limitation of the updating strategy was that it was as burdensome, time consuming, and costly.

Newton et al. [14] updated an existing CPG (by updating and expanding the original search) and adapted it to the local context (by adding research questions for the

Table 1 Characteristics of included studies*

Author and year	Institution or guideline program (country)	Objective	Design	Sample	Health topic	Time to update
Shekelle 2001 [3]	AHRQ (USA)	Evaluating if out of date	One strategy	17 CPGs	Several topics	4-8 years
Bosquet 2003 [9]‡	FNCLCC (France)	Evaluating if out of date	One strategy	1 CPG	PET scanning in cancer	NS
Gartlehner 2004 [7]	RTI-UNC EPC, USPSTF, AHRQ (USA)	Evaluating if out of date	Two strategies	6 topics	Prevention topics	6 years
Nunes 2009 [15]‡§	NCGC, NICE (UK)	Evaluating if out of date	One strategy	1 CPG	Obesity	3 years
Eccles 2002 [10]	North of England Evidence Based Guideline Development Programme (UK)	Updating	Two strategies (development vs updating)	2 CPGs	Angina and asthma in adults	4-5 years
Newton 2006 [14]‡§	AHTA (Australia)	Updating (updating by adapting)	One strategy	1 CPG	Posttraumatic stress disorder	1-3 years
Parmelli 2010 [16]	ERHCA (Italy)	Updating	Two strategies (development vs updating)	15 recommendations	Anticancer drugs for breast, colorectal and lung cancer	3 years
Johnston 2003 [8]	CCOPGI (Canada)	Continuously monitoring and updating	One strategy	20 CPGs	Cancer	NS

*Ordered by type of strategy and chronology; ‡Only abstract available; §Information provided by the author.
Abbreviations: AHRQ: Agency for Healthcare Research and Quality; AHTA: Adelaide Health Technology Assessment; CCOPGI: Cancer Care Ontario Practice Guidelines Initative; CPG: Clinical practice guideline; ERHCA: Emilia-Romagna Health Care Agency; FNCLCC: Fédération Nationale des Centres de Lutte Contre le Cancer; NCGC: National Clinical Guidelines Centre for Acute and Chronic Conditions; NICE: National Institute for Health and Clinical Excellence; NS: Not stated; PET: Positron Emission Tomography; RTI-UNC EPC: RTI International–University of North Carolina Evidence-based Practice Center; UK: United Kindom; USA: United States of America; USPSTF: US Preventive Services Task Force; vs: Versus.

local setting) (Table 2). The participants were nine methodologists and six experts. The search performance was 0.2% (43 studies included from 19,423 citations initially identified) (Table 3). The authors spent nine months to update 11 research questions and to develop seven new research questions (Table 3). The authors acknowledged that they were uncertain whether the process was more time efficient due to the additional search needed to cover local adaptation issues.

Parmelli et al. [16], similarly to Eccles et al. [10], compared an updating method with the original development process in a set of 15 recommendations (Table 2). The GRADE framework was used in both developing and updating recommendations [18]. For the updating process, new exhaustive searches were designed. The number of participants was not specified, but they described the main characteristics of its coordinator, methodological, and expert group. The researchers spent eight months to update 15 recommendations. The search performance was 3.5% (24 papers included from 686 records initially screened) (Table 3). Forty per cent of the recommendations (6/15) were completely updated due to identification of new evidence, leading to a change in recommendation classification or to redefinition of the original clinical questions (Table 3). The advantages of this updating strategy, as reported by the authors, were better collaboration among the members of the updating group, and improved methodology, leading to more relevant recommendations for clinical practice. On the other hand, the updating process was neither time nor resource saving.

Strategies for continuous monitoring and updating of CPGs

Johnston et al. [8] carried out a pilot study of a monitoring strategy in 20 CPGs (Table 2). The strategy included four steps: continuous and exhaustive searching; reviewing the new evidence; revising recommendations; and announcing new evidence and modified recommendations. The researchers used the term 'living' practice guideline, defined as 'integrated evidence update into the original report.' The information about the participants was limited. The researchers applied this strategy during a year. The search performance was 23.75% (19 citations with impact on recommendations from 80 citations initially identified) (Table 3). In 30% (6/20) of the guidelines, a change in their clinical recommendations was made (Table 3). The reported advantages of this method were that often the experts identified new evidence before it was available in electronic databases, and they therefore proposed that the literature search could be done quarterly and limited to Medline, the Cochrane library, and meeting proceedings. The authors described the process as intensive, and they foresaw that the updating process would need to change if many more guidelines had to be updated.

Discussion

Our systematic review shows that the available research about the monitoring and updating of CPGs is scarce,

Table 2 Stages of the strategies*

Author and year	Assessing the need to update	Scope definition	Update group (number of participants)	Evidence search strategy	Evidence selection, assessment and synthesis	Update recommendations	Presentation of updates
Shekelle 2001 [3]	Within specific timeframe	Identification of main recommendations	Reviewers (2) Chairs of the original CPG expert panel (15) Members related with original CPGs (2) Members of the original CPG expert panel (121) Nonpanel experts (8)	**Restricted search** 5 key medical journals and key specialty journals Reviews, editorials, commentaries Additional search in NGC and web sites of CPGs publishing organizations Surveyed experts by mail	Reviewed references (title, abstract and articles) Reviewed the relevance of selected references Based on new evidence and judgment guidelines were classified in to: major update, minor update or still valid	NA	NA
Bosquet 2003 [9]‡	Monitoring	Discussion about priority of topics to be updated	Methodologist (NS) Original working group (NS)	**Exhaustive search** MEDLINE, EMBASE, SBU and APM web sites	Selection of references Evaluation the impact of reference on existing guideline: consistent with existing guidelines, inconsistent or concern new topics	NA	NA
Gartlehner 2004 [7]	Within specific timeframe	Developed analytic framework, critical key questions and eligibility criteria Survey to national/ international experts	Clinicians (4) Health services researchers (2) Reviewers (4) Librarians (NS) National or international experts (13)	**Modified Shekelle et al. [Shekelle2001] search** AIM journals and non-AIM speciality journals Reviews, editorials, commentaries, guidelines Additional search in PreMedline, HSTAT, The Cochrane Library and selected NIH websites Surveyed to national or international experts **Exhaustive search** MEDLINE, The Cochrane Library Reviews, meta-analysis, RCTs Surveyed to national or international experts	Assessed the relevance of abstracts, full-text articles and original studies Used of update memos with studies that judged as eligible and addressed a critical key question	NA	NA
Nunes 2009 [15]‡§**	Within specific timeframe	NS	Methodologist (3) Clinicians (3)	**Restricted search** Guidelines	Selection and assessment guidelines with AGREE Narrative summary of the methodological aspects and major findings of each guideline	NA	NA
Eccles 2002 [10]	Within specific timeframe	NS	General practitioners (8) Consultants (2) Nurses (2) Health economists (2) Guideline methodologist (2)	**Exhaustive search** MEDLINE, EMBASE, The Cochrane Library	Systematic review Evidence tables or text summaries	3 situations: new recommendations; refinement recommendations; and unchanged recommendations	NS
Newton 2006 [14]‡§	NS	Additional research questions	Methodologist (9) Clinicians (6)	**Exhaustive search** NS	Verification of results and study quality from the original review	Integrating a qualitative and quantitative data on the prior review and developing recommendations	NS
Parmelli 2010 [16]	Within specific timeframe	Mail consultation to experts from development group Relevant evidence	Coordinating group (10) 3 multidisciplinary panels (NS) External methodological group (NS)	**Exhaustive search** MEDLINE, EMABASE, central and databases for conference (ASCO) SRs, meta-analysis, RCTs	Evidence selection Application GRADE methodology Evidence tables Informed and discussed with panellist in meetings	Classified strength of recommendation in 4 levels: strong positive, weak positive, weak negative and strong negative Voted by experts in meeting	NS

Table 2 Stages of the strategies* *(Continued)*

Johnston 2003 [8]	Monitoring	NS	Health information specialist (3) Lead author of the original guideline (NS) DSG who developed guideline: chair, members and research assistant (NS)	**Exhaustive search** MEDLINE (monthly), CancerList (monthly), HealthStar (monthly), The Cochrane Library (quarterly) Guidelines, SRs, RCTs Additional search in key journals and proceedings meeting Notifications by DSG members	Identified potentially relevant new trials, meta-analyses an evidence-based guidelines or update results from trials included in original guideline Reviewed abstracts and articles Considered relevance of each reference to original guideline question Interpreted new evidence in the context of original guideline Descriptive and summaries of new evidence	DSG choose implications of new evidence on clinical recommendations: unchanged recommendation, strength recommendation, change recommendation	Notice linked to each guideline to keep practitioners aware that regular update search conduced Update bulletin with new evidence emerged Notice at the top of the guideline to alert practitioners that guideline was review Removed obsolete guidelines Integrated evidence update into original report (dynamic 'living' practice guidelines)

*Ordered by type of strategy and chronology; ‡Only abstract available; §Information provided by the author.
Abbreviations: *AIM* Abridged Index Medicus, *APM* Agence de Presse Médicale, *ASCO* American Society of Clinical Oncology, *CPG* Clinical practice guideline, *DSG* Disease site group, *GRADE* Grading of Recommendations Assessment, Development and Evaluation, *HSTAT* Health Service/Technology Assessment Text, *NGC* National Guideline Clearinghouse, *NIH* National Institutes of Health, *NA* Not applicable, *NS* Not stated, *RCT*. Randomized controlled trials, *SBU* Swedish Council on Health Technology Assessment, *SR* Systematic review.

Table 3 Results of the strategies*

Author and year	Search performance (%)	Update performance (%)
Shekelle2001 [3]	208 articles reviewed/7150 articles initially identified (2,9)	13/17 CPGs (76,5)
Bosquet 2003[9]‡	118 references submitted to the working group/261 references initially identified (45,2)	NS
Gartlehner 2004 [7]	Modified Shekelle et al. search: 36 eligible studies/1382 citations initially identified (2,6)	NS
	Exhaustive search: 45 eligible studies/3687 citations initially identified (1,2)	NS
Nunes 2009 [15]‡§	7 guidelines reviewed/25 guidelines initially identified (28)	0/NS recommendations
Eccles 2002 [10]	Angina CPG: 59 acceptable paper/5941 citations initially identified (1)	0/NS recommendations
	Asthma CPG: 79 acceptable paper/7560 citations initially identified (1)	0/NS recommendations
Newton 2006 [14]‡§	43 studies included/19423 citations initially identified	11/NS questions
Parmelli 2010 [16]	24 papers included/686 records initially screened (3,5)	6/15 recommendations (40)
Johnston 2003 [8]	19 citations with impact on recommendation/80 citations initially identified (23,8)	6/20 CPGs (30)

*Ordered by type of strategy and chronology; ‡Only abstract available; §Information provided by the author.
Abbreviations: *CPG* Clinical practice guideline, *NS* Not stated.

and little is known at present about the most efficient way of keeping guidelines valid. Furthermore, the suboptimal reporting and the wide variability in the design, choice of outcomes, type of search strategy, and breadth of topics makes the assessment of the included studies difficult.

We identified eight studies with three main different objectives: evaluation if guidelines are out of date and, hence, how often they need updating [3,7,9,15], and the evaluation of updating strategies without [10,14,16] or with continuous monitoring new evidence [8]. Regardless of the goal, the included studies followed similar stages in their process. However, authors generally did not describe the process in enough detail to clearly identify the different stages.

The most detailed phase of the studies was the literature search method. Strategies evaluating if CPGs were out of date [3,7] used more restricted searches (limited to reviews, editorials or commentaries of specific journals and expert collaboration) than updating strategies. These approaches aim to identify the relevant new evidence without performing an exhaustive search; however, they risk omitting key references (references that trigger a modification of a recommendation). The evidence for their performance is so far limited [3,7], with only one single head-to-head comparison available between a restricted search and an exhaustive search [7]. According to the results observed in Gartlehner et al. [7], the evidence identified by this more restricted search would be enough to assess the need to update a CPG. However, it remains unclear whether these search results would be a sufficient way to actually update recommendations.

Strategies that aimed to update [10,16] or continuously monitor and update CPGs [8] used more exhaustive searches and were generally very similar to the ones used in the development processes. These exhaustive search strategies are more time-consuming than restricted searches as the searches trade what is hoped will be higher sensitivity for low specificity. However, the study of Gartlehner et al. [7] suggests that sensitivity for key studies is not increased by an exhaustive search process.

Although search strategies were specified in the included studies, search results were difficult to compare across studies due to the variability of the search performance outcomes (e.g., Shekelle*et al.* [3] reported the articles reviewed and Gartlehner et al. [7] reported just the eligible studies). Furthermore, reported results would need to be adjusted by the number of CPGs or recommendations updated and the time to update them. Unfortunately, this information was not available for most of the studies.

Only three studies [3,8,16] reported updating performance results. For example, Parmelli et al. updated 40% of the recommendations about breast, colorectal, and lung cancer treatment three years after the development of the recommendations [16]. The update process should focus on the recommendations, instead of the full guideline, because it could provide an opportunity to make the process more efficient. The GRADE system [19], already used by Parmelli et al. [16], could provide a framework to systematically and explicitly assess to what extent the new evidence can modify the different factors that ultimately influence the direction and strength of the recommendations (quality of the evidence, balance between benefits and harms, patients' values and preferences, and resource use) [18].

Future research studies should standardize outcomes of interest. In relation to the search performance, authors should report the number of key references (references that triggered a modification of a recommendation) from the number of references initially identified. In relation to the updating performance, measures should include the number of recommendations updated from total of the CPG recommendations. Finally, regarding resource use,

studies should report the number of participants and the time spent in the updating process.

All the studies described the composition of the updating working group involved in the process; however, the total number of participants and their roles was generally unclear. In general, similarly to the development of guidelines, there was a core method group and a larger group of clinical experts (with a variable degree of involvement). Only three studies included the time devoted to the process (range eight to ten months) [8,14,16]. Nevertheless, this information is difficult to generalise because it is highly dependent on the goal of the strategy, the scope of the guideline, the methodological expertise of the group members or the economic resources of the different institutions involved, among other possible factors. Had this information been more detailed, it could have been used as a guide to assist in the development and updating of CPGs programs.

There is a need to develop more efficient monitoring and updating strategies for CPGs and, for this, rigorous research is crucial. The gold standard strategy to update CPGs should include the identification of new evidence by an exhaustive search and the update of the recommendations [10,16]. One of the most resource-intensive phases where there is more room for improvement is the literature search. Other restricted search strategies or resources like McMaster Premium LiteratUre Service or Clinical Queries, have shown to improve the efficacy of keeping systematic reviews up to date [20]. This remains to be replicated in guidelines. Other areas to explore are the performance of databases (e.g., EMBASE) or the role of clinical experts as a source of references, with these more limited strategies [21].

In relation to survival time, Shekelle et al. [3] proposed, as a general rule, to assess the validity of CPGs every three years. Regardless of the time frame, which is highly dependent on the health topic, it would be desirable to develop a dynamic warning system to identify new relevant evidence (monitoring) and evaluate the need to update. A potential tool that could be easily implemented to monitor the new evidence is the automated periodic searches in MEDLINE, using their Selective Dissemination of Information service [22]. Complementary, guideline groups could monitor publication rate of specific MeSH terms in relation with a CPG topic. At the moment this information is not readily available in biomedical databases (e.g., MEDLINE).

Our study has several strengths. We performed an exhaustive systematic review including contacting authors for additional information. In our review, we proposed a novel classification of CPGs updating strategies according to their objective: evaluation CPGs obsolescence, updating, and continuously monitoring and updating CPGs. Finally, we also propose standardised reporting framework, including outcomes, for research purposes.

Our study has limitations. First, it is possible that we did not identify all studies due to publication bias or to the omission of some more specialised information sources (e.g., conference proceedings). Second, the difficulty of synthesizing, evaluating, and comparing complex methodological studies, without a standardized reporting, as opposed to systematic reviews [23] or comparative effectiveness reviews [24], makes the analysis and interpretation of results challenging.

Conclusions

There is limited evidence about the optimal strategies for monitoring and updating CPGs. A restricted search is likely to be sufficient to monitor new evidence and assess the need to update; however, more information is needed about the timing and type of search. Only the exhaustive search strategy has been assessed for the update of CPGs.

Our review highlights suboptimal reporting, and wide variability in the design, choice of outcomes, and type of search strategy of the available studies. The development and evaluation of more efficient strategies is needed to improve the timeliness and reduce the burden of maintaining the validity of CPGs. Future research studies should adequately report their methods and results.

Additional files

Additional file 1: Search strategy. This document shows the search strategy in MEDLINE and The Cochrane Methodology Register.

Additional file 2: Excluded studies. This document shows a list with excluded studies and the reason for exclusion.

Abbreviations

CI: Confidence interval; CPG: Clinical practice guideline.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Conceiving the review: LMG, PAC. Undertaking searches: IS, LMG. Screening search results: LMG, Ingrid IAR. Screening retrieved papers against inclusion criteria: LMG, IAR, IS. Extracting data from papers: LMG, IAR. Data management for the review: LMG. Writing the review: LMG, PAC. Comment and editing of review drafts: LMG, PAC, IAR, IS, R Brian Haynes, Per Olav Vandvik, Petra Díaz del Campo Fontecha, Maria Dolors Estrada Sabadell, Elvira García Álvarez, Javier Gracia San Román, Anna Mariyanova Kotzeva, Flavia Salcedo Fernandez, María del Mar Trujillo Martín. Responsible for reading and checking review before submission: LMG, PAC. All authors read and approved the final manuscript.

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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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*The complete list of members of the Updating Guidelines Working Group appears at the end of the 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-

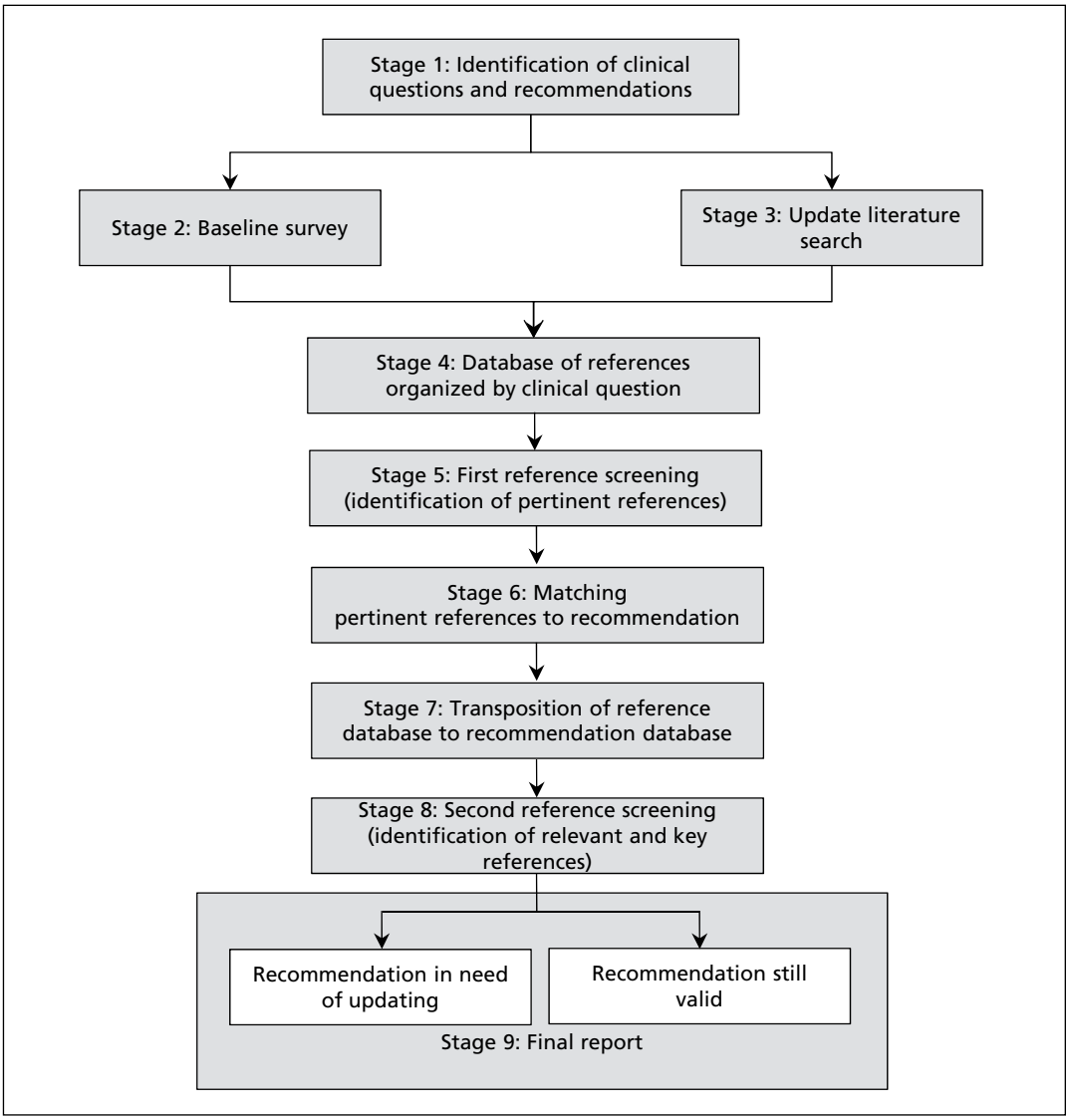

Figure 1: Strategy to assess the validity of recommendations.

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

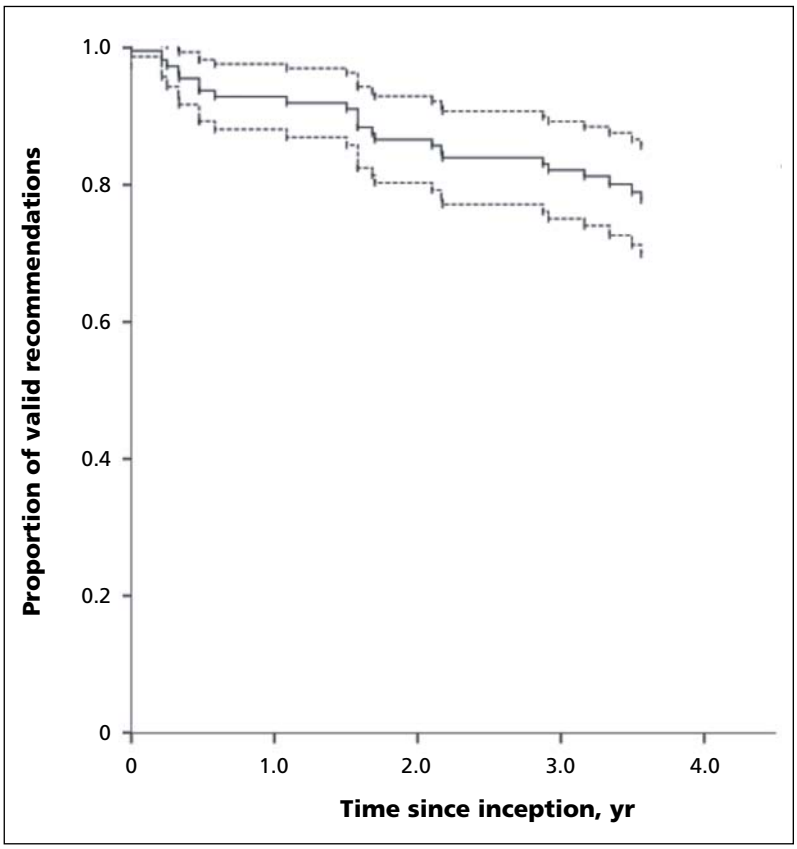

Figure 2 : Kaplan–Meier survival curve (solid line) of clinical guideline recommendations with 95% confidence intervals (dashed lines).

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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IMPLEMENTATION SCIENCE

METHODOLOGY Open Access

Updated recommendations: an assessment of NICE clinical guidelines

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Abstract

Background: Updating is important to ensure clinical guideline (CG) recommendations remain valid. However, little research has been undertaken in this field. We assessed CGs produced by the National Institute for Health and Care Excellence (NICE) to identify and describe updated recommendations and to investigate potential factors associated with updating. Also, we evaluated the reporting and presentation of recommendation changes.

Methods: We performed a descriptive analysis of original and updated CGs and recommendations, and an assessment of presentation formats and methods for recording information. We conducted a case-control study, defining cases as original recommendations that were updated ('new-replaced' recommendations), and controls as original recommendations that were considered to remain valid ('not changed' recommendations). We performed a comparison of main characteristics between cases and controls, and we planned a multiple regression analysis to identify potential predictive factors for updating.

Results: We included nine updated CGs (1,306 recommendations) and their corresponding original versions (1,106 recommendations). Updated CGs included 812 (62%) recommendations 'not reviewed', 368 (28.1%) 'new' recommendations, 104 (7.9%) 'amended' recommendations, and 25 (1.9%) recommendations reviewed but unchanged. The presentation formats used to indicate the changes in recommendations varied widely across CGs. Changes in 'amended', 'deleted', and 'new-replaced' recommendations (n = 296) were reported infrequently, mostly in appendices. These changes were recorded in 167 (56.4%) recommendations; and were explained in 81 (27.4%) recommendations. We retrieved a total of 7.1% (n = 78) case recommendations ('new-replaced') and 2.4% (n = 27) control recommendations ('not changed') in original CGs. The updates were mainly from 'Fertility CG', about 'gynaecology, pregnancy and birth' topic, and 'treatment' or 'prevention' purposes. We did not perform the multiple regression analysis as originally planned due to the small sample of recommendations retrieved.

Conclusion: Our study is the first to describe and assess updated CGs and recommendations from a national guideline program. Our results highlight the pressing need to standardise the reporting and presentation of updated recommendations and the research gap about the optimal way to present updates to guideline users. Furthermore, there is a need to investigate updating predictive factors.

Keywords: Clinical practice guidelines, Information dissemination, Evidence-based medicine, Knowledge translation, Methods, Updating

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Background

Clinical Guidelines (CGs) 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]. Scientific knowledge is in constant change, and new information requires frequent assessment to determine whether it changes clinical practice. Therefore, CGs require a periodic review of new scientific research that may change the influencing factors in the formulation of their recommendations (quality of the evidence, balance between benefits and harms, patients' values and preferences, or resource use and cost [2]). Any decision to update a guideline must balance the need to reflect changes in the evidence against the need for stability, because frequent changes to guideline recommendations would make implementation difficult [3-6]. Furthermore, a requirement to maintain a clinically relevant library of guidelines and the resource use this requires may also be a deciding factor.

Updating CGs is a complex process and includes three main stages: identifying important new evidence; assessing if the new evidence has an impact on the current guideline recommendations and whether an update is required; and the updating process [7]. Some research has been published about the identification and assessment of new evidence (encompassed sometimes as review, surveillance or monitoring process), [8,9]. Less attention has been paid to the process of updating CGs *per se*, making the assumption that it is similar to the development process [7,8].

The role of the National Institute for Health and Care Excellence (NICE) is to improve outcomes for people using the National Health Service in England and Wales and other public health and social care services. Since 2005, NICE has developed CGs which are systematically-developed statements to assist professional and patient decisions about appropriate care for specific clinical circumstances. As advances in medicines and technologies may lead to guideline recommendations becoming obsolete, CGs developed by NICE are published with the expectation that they will be regularly reviewed and updated as necessary [3].

These processes have evolved in different versions of NICE manuals [3-5]. At present, NICE has suspended the routine review process every three years and an interim surveillance programme is being implemented, which alternates rapid (two, six, and ten years after publication) or full reviews (four and eight years after publication) [6]. Also, rapid updates of guidelines are being piloted [10].

Although the updating process is not yet standardised, some institutions try to keep their CG program up to date [11]. An analysis of current practice would provide relevant information about CG review and update process, and also highlight existing gaps in the process. For example, the identification of recommendations with high or low turnover or clinical questions with a greater proportion of updated recommendations will help to focus evidence surveillance systems and, consequently, will improve the distribution of resources in the CG updating process.

Therefore, we evaluated updated CGs from NICE to identify and describe updated recommendations and to investigate factors associated with updating (predictive factors). Also, we assessed presentation formats and methods for recording information when presenting the changes from the original to updated recommendations.

Methods

Study design

We performed a descriptive study of original and updated CGs and recommendations. Also, we conducted a case-control study to identify potential predictive factors for updating.

Setting and participants

We included all updated CGs from NICE; and their corresponding original version. We included an updated CG if: it was partially updated; it was the first updated version of the original; it included the updating status of each recommendation; and it was published on the NICE website up to May 2013. Updated CGs were obtained from the NICE website in May 2013 by searching the list of published CGs (http://guidance.nice.org.uk/CG/Published). After we obtained the sample of the updated CGs, we retrieved the originals from internal sources within NICE as the original versions of the CGs are no longer available on the website.

Finally we reviewed CGs and selected the recommendations. We included all the recommendations from both original and updated CGs, except research recommendations because these are unanswered research questions or areas of uncertainty that emerge during guidance development as opposed to recommendations for clinical practice.

We defined cases as original recommendations that were updated ('new-replaced' recommendations), and controls as original recommendations that were still valid after an updating process ('not changed' recommendations).

Variables and data sources

We mapped original and updated CGs and extracted the following metrics: publication date, topic area (using NICE taxonomy), and guideline development centre (centres that are contracted to develop the guidelines on behalf of NICE). We also extracted from the updated CGs the information about update status labels and definitions (Table 1). We mapped the corresponding original recommendations

Table 1 Update status labels and definitions

Update status label*			Definition*	Recommendations included in case-control study
Reviewed	New	New-replaced	Recommendation from original guideline that has been changed following review of evidence.	Cases
		New-added	New recommendation following review of evidence.	
	Not changed		Recommendation from the original guideline where evidence has been reviewed but the recommendation is not changed.	Controls
	Deleted		Recommendation from original guideline that has been removed.	
Not reviewed			Recommendation from the original guideline where the evidence has not been formally reviewed for the update.	
Amended			A small amendment has been made to the original recommendation but the evidence has not been updated or reviewed.	

*Adapted from NICE manual [5].

and extracted: recommendations, heading and subheading, and their strength (with SIGN or GRADE system [2,12]). We coded the recommendations by: CG topic area, years between versions, purpose (using key words), and strength [Additional file 1].

We mapped and recoded the updated recommendations and extracted similar information plus: update status (Table 1); change recorded (whether changes in the recommendations were registered) [Additional file 1] and justification of the change. For example, the recommendation in Fertility CG 2004 [13], 'Women who are undergoing *in vitro* fertilisation treatment using gonadotrophin-releasing hormone agonists for pituitary down regulation should be informed that luteal support using human chorionic gonadotrophin or progesterone improves pregnancy rates'; was replaced in Fertility CG 2013 [14] with 'Offer women progesterone for luteal phase support after *in vitro* fertilisation treatment'; the change was recorded in the guideline as 'new 2013′ label; and the change was justified as follows 'New evidence shows that only progesterone is useful as a luteal phase support, so the recommendation has been changed'.

We matched original and updated recommendations; firstly using the changes recorded in the updated CGs, and secondly matched recommendation with recommendation, to obtain the updating status. One reviewer mapped, extracted, and recoded the data. A second evaluator checked the coding and the link processes.

Data analysis

We performed a descriptive analysis of included CGs and recommendations and calculated absolute and relative frequencies (purpose of recommendations and update status) or median and range (number of recommendations per CG and time between versions of original and updated CGs), as appropriate. We also conducted a descriptive analysis of the update status of recommendations, changes recorded and justification for the change. We assessed the reported information about the change in recommendations per CG based on seven issues (recording information score): recommendation update status defined; changes recorded for 'amended' recommendations; changes explained for 'amended' recommendations; changes recorded for 'deleted' recommendations; changes explained for 'deleted' recommendations; changes recorded for 'new-replaced' recommendations; and changes explained for 'new-replaced' recommendations. For each of the seven issues the selection was one (yes) or zero (no), and the summation was the numerator. The maximum points score were seven (denominator), but depended on the type of update status included in CGs (for example, lung cancer CG 2011 [15] did not have 'amended' or 'new' recommendations so the denominator was three). The final score was reported on a scale of ten (sum points obtained/highest score possible * 10 = final score).

We compared cases ('new-replaced') and controls ('not changed') recommendations using Pearson chi-square test (for categorical variables) or Mann-Whitney U test (for quantitative variables), as appropriate. We planned to perform a multiple regression analysis with variables associated with updating in bivariate analysis and with relevant variables agreed by the research group [16]. In addition, we aimed to link recommendations with references supporting them with a view to exploring the association between number of references linked per recommendation and its vulnerability to change.

We accepted p value ≤0.05 as significant in all calculations. We performed the analysis with SPSS 15.0 (SPSS Inc., Chicago, Illinois, United States).

Results

Included CGs and recommendations

We retrieved 21 (12.7%) updated CGs out of a total of 166 current CGs (Figure 1); and linked them with 24 original CGs (three CGs about type 2 diabetes were merged into one during an update). We excluded 12 updated CGs: eight were not reported as partial update, and four did not record the update status of each recommendation (Additional file 2). Finally, we included nine

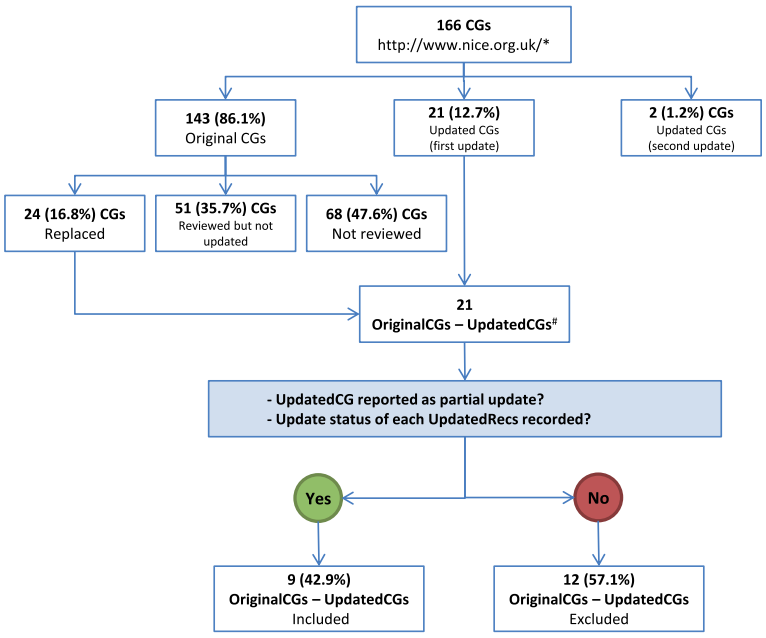

Figure 1 Flow diagram of included clinical guidelines. Abbreviations: CG: Clinical guideline. *Accessed 15 May, 2013. #Four OriginalCGs about Type 2 diabetes were updated in one UpdatedCG.

updated CGs and their corresponding original CGs (Table 2) [13-15,17-31]. Of the study sample, original CGs were published from 2003 to 2006; and updated CGs were published from 2007 to 2013 [Table 2]. The median time between versions was 7.2 years (range 4.3 – 9.0).

Original CGs included a median of 99 recommendations per CG (range 50 – 220), and 126 (range 52 – 285) for updated CGs (Table 3). The majority of recommendations across all CGs were about 'gynaecology, pregnancy and birth' (24.9% of original recommendations and 25.7% of updated recommendations) or 'respiratory' topics (25.9% of original recommendations and 23.8% of updated recommendations); were most commonly related to 'treatment' purpose or 'supporting patients or carers' (27.9% and 19.2% of original recommendations and 28.4% and 18.3% of updated recommendations respectively); and most were graded as 'D' or as 'weak' recommendations (39.8% of original recommendations and 42.7% of updated recommendations) (Table 3). The references from recommendations to evidence could not be retrieved.

Recommendations updating status

Updated CGs included 812 (62%) recommendations 'not reviewed'; 368 (28.1%) 'new' recommendations ('new-added' and 'new-replaced'); 104 (7.9%) 'amended' recommendations; and 25 (1.9%) recommendations that were reviewed but remained unchanged (Table 3).

'Reviewed' recommendations ('new' plus 'not changed'; 393, 30%) were included in 45 sections of the CGs with recommendations (61.6%).

'New' recommendations were mainly 'new-added' (294, 79.9%), from 'gynaecology, pregnancy and birth' topic (115, 31.3%), had a 'treatment' purpose (146, 39.7%), and were graded as 'weak' (308, 83.7%). The main reasons for the changes in the 'new-replaced' were the identification of new evidence (21/33; 63.6%) and changes in writing style (11/33; 33.3%) (Additional file 3).

Presentation formats and information recording

The presentation formats used to indicate the changes in recommendations or sections varied across updated CGs. Five (5/9, 55.6%) updated CGs used update status labels for recommendations plus highlight colour [25,26,28,30,31]; three (3/9; 33.3%) used update status labels for recommendations plus a bar down the side of the page [15,29,14]; and one (1/9; 11.1%) only indicated the recommendations' update status [27]. Updating status labels were defined in seven CGs (77.8%) [14,15,25,27,29-31] (definitions are available in Additional file 4).

The updated CGs with highest recording information score were for those that included a head to head comparison between original and updated recommendations in an appendix (10 points for both Caesarean section CG – 2011 [29] and Fertility CG – 2013 [14]); and the lowest scores were for the oldest updates (1.4 points for Head injury CG – 2007 [25] and 2.9 points for Chronic heart failure CG - 2010 [27]). An illustration of presentation formats is available in Additional file 5 and scores are available in Additional file 6.

Table 2 Included clinical guidelines

Original clinical guidelines			Updated clinical guidelines		
Title	**Development centre**	**Publication date**	**Title**	**Development centre**	**Publication date**
- Anaemia management in chronic kidney disease (CG39) (replaced by CG114) [24]	NCC-CC	Sep-06	- Anaemia management in people with chronic kidney disease (CG114) [28]	NCGC	Feb-11
- Caesarean section (CG13) (replaced by CG132) [21]	NCC-WCH	Apr-04	- Caesarean section (CG132) [29]	NCC-WCH	Nov-11
- Chronic heart failure (CG5) (replaced by CG108) [19]	NCC-CC	Jul-03	- Chronic heart failure (CG108) [27]	NCGC-ACC	Aug-10
- Chronic obstructive pulmonary disease (CG12) (replaced by CG101) [20]	NCC-CC	Feb-04	- Chronic obstructive pulmonary disease (updated) (CG101) [26]	NCGC-ACC	Jun-10
- Epilepsy (CG20) (replaced by CG137) [22]	NCC-PC	Oct-04	- Epilepsy (CG137) [30]	NCGC-ACC	Jan-12
- Fertility (CG11) (replaced by CG156) [13]	NCC-WCH	Feb-04	- Fertility (CG156) [14]	NCC-WCH	Feb-13
- Head injury (CG4) (replaced by CG56) (withdrawn) [18]	NCC-AC	Jun-03	- Head injury (CG56) [25]	NCC-AC	Sep-07
- Infection control (CG2) (replaced by CG139) [17]	National Collaborating Centre for Nursing & Supportive Care and Thames Valley University	Jun-03	- Infection control (CG139) [31]	NCGC-ACC	Mar-12
- Lung cancer (CG24) (replaced by CG121) [23]	NCC-AC	Feb-05	- Lung cancer (CG121) [15]	NCC-C	Apr-11

Abbreviations: NCC-AC National Collaborating Centre for Acute Care, *NCC-C* National Collaborating Centre for Cancer, *NCC-CC* National Collaborating Centre for Chronic Conditions, *NCC-PC* National Collaborating Centre for Primary Care, *NCC-WCH* National Collaborating Centre for Women and Children's Health, *NCGC* National Clinical Guideline Centre, *NCGC-ACC* National Clinical Guideline Centre for Acute and Chronic Conditions.

Documented changes in recommendations were reported frequently in updated CGs appendices (n = 7; 77.8%) (Additional file 4). The changes in 'amended', 'deleted' and 'new-replaced' recommendations (n = 296) were recorded in 167 (56.4%) recommendations; and were explained in 81 (27.4%) recommendations. The most common change factor in 'amended' recommendations was 'change in writing style (accuracy, clarity, consistency, or terminology)' (n = 23, 65.7%), in 'deleted' recommendations was 'recommendation outside the scope' (n = 4; 30.8%); and in 'new-replaced' recommendations was 'incorporation of new evidence' (n = 21; 63.6%) (Additional file 3).

Predictive factors for updating

After the linking process, we identified in original CGs: 229 (20.7%) 'reviewed' ('deleted' plus 'new-replaced' plus 'not changed'), 783 (70.8%) 'not reviewed' and 94 (8.5)'amended' recommendations [Table 3]. A total of 7.1% (n = 78) had been 'new-replaced' (cases) and 2.4% (n = 27) were 'not changed' (controls) recommendations. More than one updated recommendation could correspond to one original recommendation and vice versa. For this reason, the absolute overall numbers of update status do not match between versions (Table 2).

There were differences between 'new-replaced' (cases) versus 'not changed' (controls) recommendations by CGs, topic and purpose, but not by time between publication versions or strength of recommendations (Table 4).

The 'new-replaced' recommendations (cases) were mainly from 'Fertility (CG11) 2004′ CG [13], about 'gynaecology, pregnancy and birth' topic, and 'treatment' or 'prevention' purposes [Table 4].

We considered the sample of 105 recommendations inadequate to perform a multiple regression analysis [16].

Discussion

Our study evaluated a cohort of updated recommendations in one of the leading national CG development programs. We identified 368 (28.1%) 'new' recommendations in the updated CGs; of these, 7.1% (78/1106) being 'new-replaced' recommendations from the original CGs. The changes were mainly due to the identification of new evidence and were topic and purpose related.

We included in the study partially updated guidelines; defined as CGs that include some recommendations that required updating in the light of new evidence, or because they were unclear [4]. The reason to include only partial updates is that in full updates there is no information about the modifications made with respect to the previous versions. Inclusion of only partial updates resulted in the majority of original recommendations not being reviewed. In some instances updated CGs can have the same original scope (no new areas were

Table 3 Recommendations characteristics

	Original recommendations (n = 1106)		Updated recommendations (n = 1309)	
CGs, n (%)				
- Anaemia management in chronic kidney disease	50	(4.5)	52	(4.0)
- Caesarean section	108	(9.8)	124	(9.5)
- Chronic heart failure	92	(8.3)	95	(7.3)
- Chronic obstructive pulmonary disease	193	(17.5)	182	(13.9)
- Epilepsy	220	(19.9)	285	(21.8)
- Fertility	167	(15.1)	213	(16.3)
- Head injury	83	(7.5)	126	(9.6)
- Infection control	99	(9.0)	102	(7.8)
- Lung cancer	94	(8.5)	130	(9.9)
CGs topic, n (%)				
- Blood and immune system/ Urogenital	50	(4.5)	52	(4.0)
- Cardiovascular	92	(8.3)	95	(7.3)
- Central nervous system	220	(19.9)	285	(21.8)
- Gynaecology, pregnancy and birth	275	(24.9)	337	(25.7)
- Injuries, accidents and wounds	83	(7.5)	126	(9.6)
- Public health	99	(9.0)	102	(7.8)
- Respiratory	287	(25.9)	312	(23.8)
Recommendations purpose, n (%)				
- Access to services - Referral and approach to care - Service organisation	168	(15.2)	226	(17.3)
- Diagnostic	188	(17.0)	223	(17.0)
- Monitoring - Follow up	64	(5.8)	68	(5.2)
- Prevention practices	153	(13.8)	164	(12.5)
- Supporting patients and carers	212	(19.2)	239	(18.3)
- Treatment	309	(27.9)	372	(28.4)
- >1 purpose or others	12	(1.1)	17	(1.3)
Recommendations strength - SIGN, n (%)				
- A	194	(17.5)	133	(14.1)
- B	98	(8.9)	87	(9.2)
- C	140	(12.7)	118	(12.5)
- D	440	(39.8)	402	(42.7)
- GPP	214	(19.3)	187	(19.9)
- Others	20	(1.8)	14	(1.5)
Recommendations strength - GRADE, n (%)				
- Legal	-	-	11	(3.0)
- Strong	-	-	49	(13.3)
- Weak	-	-	308	(83.7)
Update status, n (%)				
- Amended	94	(8.5)	104	(7.9)
- Deleted	124	(11.2)	-	-
- New – added	-	-	294	(22.5)
- New – replaced	78	(7.1)	74	(5.7)
- Not changed	27	(2.4)	25	(1.9)
- Not reviewed	783	(70.8)	812	(62.0)

Abbreviations: CG Clinical guidelines, *GPP* Good practice point.

included), or in others a new scope is reported (where new key areas were identified) [4]. We did not assess the differences in scopes or included clinical questions between guidelines versions. It would have been useful for the analysis that all updated CGs recorded these issues. Only a minority of updated CGs included appendices highlighting how recommendations had changed between versions of the CG. Similarly there was no information reported about the methods undertaken for the review, surveillance or monitoring process.

The identification of the updated CGs was sometimes difficult because occasionally two or more CGs were merged, titles were modified, and some guidelines had went through more than one updating process. The expected increase of guideline updates in the future makes it necessary to improve labelling to avoid confusion. To further complicate the analysis, access to the original version of the CG was not straightforward, as they had been removed from the website. Nevertheless, we managed in all cases to obtain the original CGs as copies of the original guidelines are stored internally within NICE.

There was not a prioritisation for updating particular sections of the included CGs, hence, the distribution of reviewed recommendations was from across all guidelines and sections.

The proportion of 28.1% (368) 'new' recommendation over a median time frame of seven years since their development is similar to a recent survival analysis of the validity of recommendations (22.1 % recommendations were considered to need a potential update, median time frame of four years) [32]. A standardised process for conducting surveillance reviews every three years was introduced in August 2010 therefore; the median time frame of seven years between versions of CGs included in this study may be attributed partly because these CGs were reviewed for update on an *ad hoc* basis.

We observed unclear definition about update status labels, variability in the presentation formats for recommendation changes and poor reporting for the justification for change. Only two CGs included an appendix with a detailed comparison of the original and updated recommendations [14,29]. There is scant research in these

Table 4 Differences between recommendations by change status

	New-replaced recommendations (cases, n = 78)		Not changed recommendations (controls, n = 27)		p[a]
CGs, n (%)					
- Anaemia management in chronic kidney disease	1	(1.3)	-	-	
- Caesarean section	10	(12.8)	1	(3.7)	
- Chronic heart failure	4	(5.1)	4	(14.8)	
- Chronic obstructive pulmonary disease	-	-	-	-	0.036
- Epilepsy	2	(2.6)	5	(18.5)	
- Fertility	34	(43.6)	10	(37.0)	
- Head injury	3	(3.8)	-	-	
- Infection control	24	(30.8)	7	(25.9)	
- Lung cancer	-	-	-	-	
Time between publication versions, median (range)					
- Years	8.8	(4.3-9.0)	8.8	(7.1-9.0)	0.296
CGs topic, n (%)					
- Blood and immune system/Urogenital	1	(1.3)	-	-	
- Cardiovascular	4	(5.1)	4	(14.8)	
- Central nervous system	2	(2.6)	5	(18.5)	
- Gynaecology, pregnancy and birth	44	(56.4)	11	(40.7)	0.027
- Injuries, accidents and wounds	3	(3.8)	-	-	
- Public health	24	(30.8)	7	(25.9)	
- Respiratory	-	-	-	-	
Recommendations purpose, n (%)					
- Access to services - Referral and approach to care - Service organisation	3	(3.8)	2	(7.4)	
- Diagnostic	7	(9.0)	1	(3.7)	
- Monitoring - Follow up	1	(1.3)	5	(18.5)	0.027
- Prevention practices	23	(29.5)	7	(25.9)	
- Supporting patients and carers	17	(21.8)	2	(7.4)	
- Treatment	23	(29.5)	9	(33.3)	
- >1 procedure - Others	4	(5.1)	1	(3.7)	
Recommendations strength - SIGN, n (%)					
- A	25	(32.1)	6	(22.2)	
- B	5	(6.4)	2	(7.4)	
- C	11	(14.1)	5	(18.5)	0.296
- D	19	(24.4)	7	(25.9)	
- GPP	16	(20.5)	6	(22.2)	
- Others	2	(2.6)	1	(3.7)	

Abbreviations: CG Clinical guidelines, *GPP* Good practice point.
[a]Pearson Chi-Square or Mann-Whitney Test, as appropriate.

areas with most focusing either on the presentation of original recommendations or in the field of systematic reviews [33-35].

An important area to highlight is the coexistence of two systems of strength of recommendations in the same updated CG. This is due to the relatively recent decision to move from the SIGN system to GRADE to rate the quality of the evidence and formulate the recommendations. At the moment, the impact of this potential confusion for users is unknown.

Strengths and limitations

Our study has several strengths. First, we followed a structured and rigorous approach and developed a protocol that is available from the authors. Second, we explored all CGs from a national program that has a well-established reviewing and updating process. Finally, we explored several issues that have not been assessed until now (*e.g.*, updating reporting and presentation formats and predictive factors for updating recommendations).

Our study also has some limitations. We were not able to link recommendations with references supporting them, as originally planned. This could have led us to explore the association between number of references linked per recommendation and its vulnerability to change [35]. Furthermore, the identification of individual recommendations was difficult because, for example, more than one updated recommendation could correspond to an original recommendation, and vice versa. We might have therefore underestimated the real proportion of recommendations that were changed. Although the results suggest there were differences between changed versus not changed recommendations by CGs, topic and purpose, it was not possible to define predictive factors for updating recommendations. Additional work is needed to define changes to CG recommendations because this will help to focus evidence surveillance systems and, consequently, will improve the distribution of resources in the CG updating process. Finally, we only included the first update of each guideline and excluded later versions if available.

Implications of our results for practice and research

Our study is the first to describe and assess updated CGs and recommendations from a national guideline program. Our results highlight the pressing need to standardise the reporting and presentation of updated recommendations. We have also identified a research gap about the optimal way to present updates to the users. Furthermore, there is a need for larger studies to investigate updating predictive factors.

Availability of supporting data

The dataset is available from the corresponding author.

Additional files

Additional file 1: Information about recoding. We listed the key words used for recoding purpose, SIGN or GRADE system or update status recommendations.

Additional file 2: Sample selection. We listed included and excluded CGs from NICE.

Additional file 3: Documented changes in recommendations. We listed the documented changes by type of recommendation (amended, deleted or new).

Additional file 4: Presentation formats. We listed the update status definition and the how and where the change were recorded and/or explained by CGs.

Additional file 5: Presentation formats examples. We captured images form included updated clinical guidelines to illustrate different presentation formats.

Additional file 6: Reporting information score. We listed the score by CGs.

Abbreviations

CG: Clinical guideline; GRADE: Grading of recommendations assessment, development and evaluation; NICE: National institute for health and care excellence; SIGN: Scottish intercollegiate guidelines network.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

LMG (Laura Martínez García) and PAC (Pablo Alonso-Coello) participated in the conception of the study. LMG, EM (Emma McFarlane), SB (Steven Barnes) and PA (Philip Alderson) designed the study protocol. LMG carried out the data extraction and analysis and EM checked the coding and the link processes. LMG and EM wrote the first draft of the paper. All authors revised the article for important intellectual content and approved the final version of the submitted manuscript.

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RESEARCH ARTICLE Open Access

Efficiency of pragmatic search strategies to update clinical guidelines recommendations

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Abstract

Background: A major challenge in updating clinical guidelines is to efficiently identify new, relevant evidence. We evaluated the efficiency and feasibility of two new approaches: the development of restrictive search strategies using PubMed Clinical Queries for MEDLINE and the use of the PLUS (McMaster Premium Literature Service) database.

Methods: We evaluated a random sample of recommendations from a national guideline development program and identified the references that would potentially trigger an update (key references) using an exhaustive approach.
We designed restrictive search strategies using the minimum number of Medical Subject Headings (MeSH) terms and text words required from the original exhaustive search strategies and applying broad and narrow filters. We developed PLUS search strategies, matching Medical Subject Headings (MeSH) and Systematized Nomenclature of Medicine (SNOMED) terms with guideline topics. We compared the number of key references retrieved by these approaches with those retrieved by the exhaustive approach.

Results: The restrictive approach retrieved 68.1 % fewer references than the exhaustive approach (12,486 versus 39,136), and identified 89.9 % (62/69) of key references and 88 % (22/25) of recommendation updates. The use of PLUS retrieved 88.5 % fewer references than the exhaustive approach (4,486 versus 39,136) and identified substantially fewer key references (18/69, 26.1 %) and fewer recommendation updates (10/25, 40 %).

Conclusions: The proposed restrictive approach is a highly efficient and feasible method to identify new evidence that triggers a recommendation update. Searching only in the PLUS database proved to be a suboptimal approach and suggests the need for topic-specific tailoring.

Keywords: Clinical guidelines, Diffusion of innovation, Dissemination and implementation, Evidence-based medicine, Information storage and retrieval, Knowledge translation, Methods, Updating

Background

Clinical guidelines, like systematic reviews and other evidence summaries, require periodic reassessment of research evidence to remain valid [1–4]. Current guidance usually recommends revision and update within two to three years of their publication [5, 6]. New evidence to update clinical guidelines is generally identified using the original exhaustive search strategies [7].

A major challenge for guideline developers is to efficiently screen for new, relevant evidence that justifies a clinical guideline update. Unfortunately, little empirical work has been conducted to date to test the effectiveness and efficiency of searching processes [7]. More than a decade ago, Shekelle et al. developed a strategy based on retrieving reviews, editorials, and commentaries in high impact general journals and specialised journals, complemented with a survey by clinical experts [8].

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Gartlehner et al. compared a modified version of this strategy versus an exhaustive search strategy [9]. The results so far have shown that restrictive approaches are promising, but more information is needed about the timing and type of search [7].

Similarly, researchers are testing alternative search strategies to update systematic reviews [10–13]. Haynes et al. developed the McMaster Premium Literature Service (PLUS) database, from the McMaster Health Knowledge Refinery [14, 15]. PLUS contains a searchable subset of pre-appraised primary studies and systematic reviews from more than 120 journals and it can identify key articles needed to update systematic reviews [14, 15]. Clinical Queries search filters in MEDLINE and EMBASE have also shown a high sensitivity to detect key articles [11].

We designed a study to evaluate the efficiency and feasibility of two approaches to identify the need to update clinical guidelines recommendations: 1) restrictive search strategies using PubMed Clinical Queries search filters for MEDLINE and 2) the use of PLUS database.

Methods

Design

We conducted a descriptive study of search strategies to identify the references that update recommendations from clinical guidelines. We developed three search strategies to identify the need to update the recommendations: an exhaustive approach, a restrictive approach, and a PLUS approach.

The sample was obtained from a previous study and included a stratified random sample of recommendations from the Spanish National Health System Clinical Guidelines Program [1, 16]. The selection process involved two phases: 1) we stratified guidelines by topic and by year of publication; when multiple guidelines per strata were available, we randomly selected one; 2) we performed a stratified random sampling of recommendations by guideline topic and by turnover (number of pertinent references linked per recommendation in the updating process).

1) Exhaustive approach

Guideline methodologists with experience designing search strategies developed exhaustive literature search strategies for each clinical question: 1) based on the original searches; and 2) applying the filters of the original study. An example of the exhaustive search strategy is available in Additional file 1. We also contacted clinical experts to identify new studies. We obtained a reference database of clinical questions. We screened the references and assessed them qualitatively as: 1) *Pertinent references:* Randomised controlled trials or systematic reviews related to the topic of the clinical guideline; 2) *Relevant references:* pertinent references that could be used when considering an update to a recommendation, but that would not necessarily trigger a potential update; and 3) *Key references:* relevant references that would potentially trigger an update because of their impact on the population, the intervention, the comparison, the outcome, the quality of the evidence, the direction and/or the strength of the recommendation. Using the results of the reference screening we classified recommendations as: 1) need for updating*:* with one or more key references linked; or 2) still valid: without key references linked.

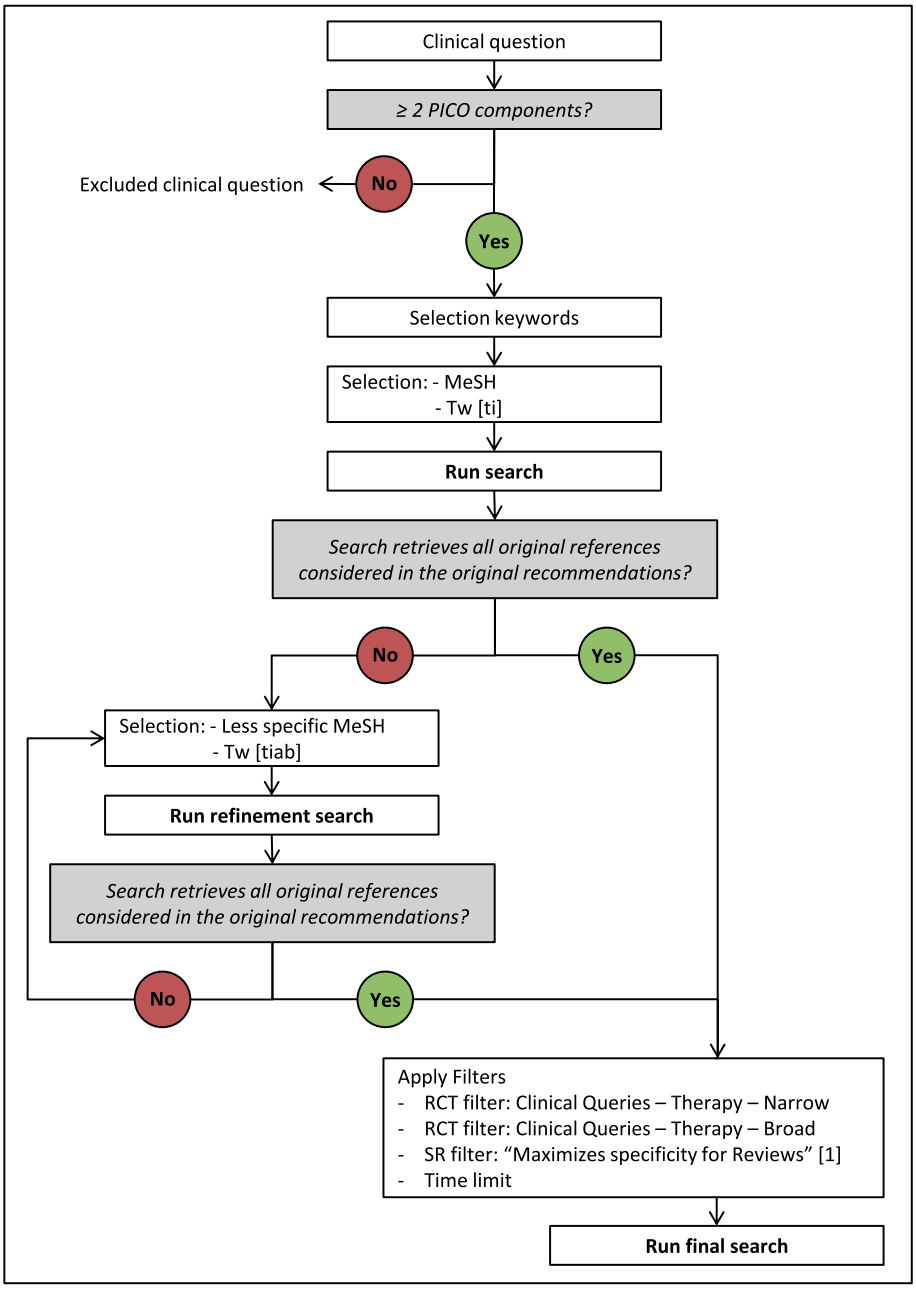
A more complete description of this approach is available in the previously published protocol and survival analysis results [1, 16].

2) Restrictive approach

Guideline methodologists, trained by researchers with experience designing search strategies, developed restrictive search strategies for each clinical question using the PubMed Clinical Queries search filters for the MEDLINE database. We considered clinical questions that had at least two PICO (population, intervention, comparator or outcome) components. We developed the restrictive search strategies considering the minimum number of Medical Subject Headings (MeSH) terms and text words required from the original exhaustive searches strategies. The search strategies were designed in four stages [Fig. 1]: 1) Development: we selected keywords from the clinical questions and identified Medical Subject Headings (MeSH) terms and text words in titles; 2) Validation: we evaluated whether each search retrieved all the original references for its corresponding recommendation; 3) Refinement: If a search did not retrieve all the original references, we selected and searched less specific Medical Subject Headings (MeSH) and/or text words in the title or abstract; and 4) Application of each of a broad and a narrow treatment Clinical Queries filter (www.ncbi.nlm.nih.gov/pubmed/clinical), and a systematic review filter [17]. We used the same date limits as with the exhaustive approach (from the complete year in which the original exhaustive searches was completed onwards). An example of a restrictive search strategy is available in Additional file 1.

3) PLUS approach

An information specialist from the Health Information Research Unit developed a PLUS search strategy for each guideline topic. We matched Medical Subject Headings (MeSH) and Systematized Nomenclature of Medicine (SNOMED) indexing terms in the PLUS database with clinical guideline topics. Both primary and review papers were included. To take into account the time delay associated with the critical appraisal process (CAP) the articles go through, we ran the PLUS searches strategies from the beginning of the year in which



Abbreviations: MeSH: Medical Subject Headings; RCT: Randomized controlled trial; SR: Systematic review; Ti: Title; Tiab: Title or abstract; Tw: Text words

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Fig. 1 Restrictive approach algorithm. Figure01_RestrictiveApproachAlgorithm. Microsoft PowerPoint presentation

the original exhaustive searches were run, until approximately three months beyond the latest date of the exhaustive searches. An example of a PLUS search strategy is available in Additional file 1.

Outcome

Our primary outcome was the number of key references identified by each alternative approach.

Statistical methods

We performed a descriptive analysis of the data. We calculated absolute and relative frequencies or median and range, as appropriate.

Two investigators independently retrieved the key references (identified in the exhaustive approach) in each of the alternative approach results. We analysed the number of key references in: 1) the results of restrictive

search strategies per clinical question; 2) restrictive search strategies results per clinical guideline (clustering all references identified by clinical question) [Fig. 2]; and 3) results of PLUS strategies per clinical guideline. We did not identify additional pertinent, relevant or key references from the alternative approaches. We did not develop restrictive search strategies for clinical questions with less than two of the four PICO components, prognosis or diagnostic clinical questions. In these instances we used the updated exhaustive search strategies.

We identified the recommendations that needed an update (with one or more key references) retrieved by each alternative approach. We compared the recommendations identified with those that were not identified according to clinical guideline topic (cancer, cardiovascular disease, mental health or metabolic disease), strength of recommendation (A, B, C, D or good practice point [18]), clinical purpose (prevention, screening, diagnosis, treatment or other), and turnover. Each recommendation was classified according to the number of linked pertinent references: none, ≤ median number (low turnover), or > median number (high turnover). We used Pearson's chi-square test or Fisher's exact test, as appropriate.

We recorded the number of hours spent on designing each approach and the number of researchers involved.

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).

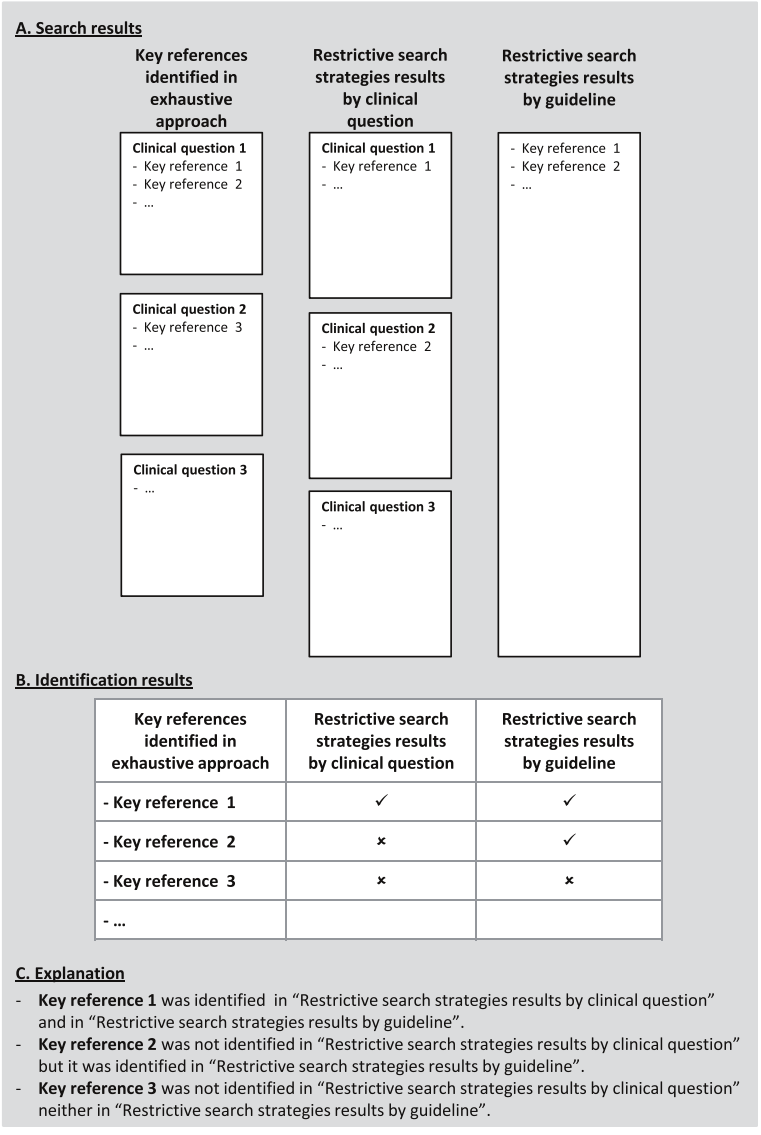


Fig. 2 References analysis. Figure02_ReferencesAnalysis. Microsoft PowerPoint presentation

Results

We included a cohort of four clinical guidelines from the Spanish National Health System Clinical Guidelines Programme, corresponding to 87 clinical questions and 249 recommendations [19–22]. After the random selection process, the final recommendation sample included 43 clinical questions and 113 recommendations.

Exhaustive approach results

This approach retrieved a total of 39,136 references from the four clinical guidelines included. From the recommendations sample, we identified a total of 69 key references and 25 recommendations that potentially needed an update [Table 1].

Restrictive approach results

We applied the restrictive approach to 88.5 % (77/87) clinical questions from the included clinical guidelines, corresponding to 85 % (96/113) of the recommendations from our recommendation sample. We excluded eight questions that did not present a minimum of two PICO components (population, intervention, comparator or outcome) and one diagnostic question.

The restrictive searches covered a mean of 4.6 years (range 3.9 – 5.1 years) from 2008–2009 to 2011 – 2012 [Table 2].

For the clinical guidelines included, we retrieved a total of 40,021 references using the broad filter and 9,958 references using the narrow filter [Table 2]. We retrieved more key references when we clustered results of references per guideline rather than per question (40 [87 %] and 39 [84.8 %] compared with 26 [56.5 %] and 25 [54.3 %] using the broad and narrow filters, respectively) [Table 2, Additional file 2]. Similarly, clustered results of references per guideline identified a higher number of recommendations that were considered to potentially need an update (18 [90.0 %] and 17 [85 %] compared with 15 [75 %] and 14 [70 %] respectively [Table 2].

When we used exhaustive search strategies for the clinical questions not developed by the restrictive approach (narrow filter and clustering by all questions), we retrieved a total of 12,486 references, and we identified a total of 62 (89.9 %) key references and 22 (88.0 %) recommendations that potentially needed an update [Table 4].

The restrictive approach (narrow filter and clustering by all questions) failed to identify seven key references (15.2 %): four (57.1 %) references were systematic reviews and three references (42.9 %) were congress abstracts (not indexed in MEDLINE) [Fig. 3].

The recommendations that potentially needed an update not identified by the restrictive approach were similar to those that were identified in terms of topic, strength of the recommendations, clinical purpose, and turnover [Additional file 3].

PLUS approach results

The PLUS searches covered a median of 5.0 years (range 4.1 – 5.3 years) from 2008–2009 to 2011 – 2012 [Table 3].

For the clinical guidelines included, we retrieved a total of 4,486 references (range 137 – 3,059) [Table 3]. For the recommendation sample, we retrieved 18 (26.1 %) key references; these references potentially update 10 (40 %) recommendations [Table 3, Additional file 2].

The PLUS approach failed to identify 51 key references (73.9 %); most (41 references, 80.4 %) were from journals not included in PLUS database [Fig. 4].

Recommendations with a high turnover were more likely to be identified by the PLUS approach. The remaining factors (clinical guideline topic, strength of the recommendations, and clinical purpose) were not significantly associated with the need to update [Additional file 3].

Resource use

Three guideline methodologists spent a total of 174 h in designing and running the restrictive search strategies [Table 4]. The PLUS search strategies were developed by an information specialist who designed and ran the searches in 28 h [Table 4].

Discussion

We evaluated two search strategies to identify signals for updating recommendations and compared them to an

Table 1 Exhaustive approach results

	Major depression in adults 2008 [19]	Obesity in childhood and adolescence 2009 [20]	Prostate cancer treatment 2008 [21]	Secondary prevention of stroke 2009 [22]	Total
Search period (years)	4.8	3.9	4.5	5.1	
References retrieved in search for clinical guidelines, n	11243	9763	3343	14787	39136
Key references identified from recommendation sample, n	13	32	11	13	69
Potential update recommendations identified from recommendation sample, n (%)	3	8	7	7	25

Table 2 Restrictive approach results

	Major depression in adults 2008 [19]		Obesity in childhood and adolescence 2009 [20]		Prostate cancer treatment 2008 [21]		Secondary prevention of stroke 2009 [22]		Total	
Search period (years)	4.8		3.9		4.5		5.1			
References retrieved in search for clinical guidelines, n										
- Broad filter	9223		10561		6939		13294		40017	
- Narrow filter	2814		3976		976		2187		9953	
Key references identified from recommendation sample, n (%)[a]										
- Exhaustive approach[b]	13		16		4		13		46	
- Broad filter										
by individual clinical questions	5	38.5	11	68.8	4	100.0	6	46.2	26	56.5
by clustering all clinical questions	11	84.6	16	100.0	4	100.0	9	69.2	40	87.0
- Narrow filter										
by individual clinical questions	4	30.8	11	68.8	4	100.0	6	46.2	25	54.3
by clustering all clinical questions	10	76.9	16	100.0	4	100.0	9	69.2	39	84.8
Potential update recommendations identified from recommendation sample, n (%)[a]										
- Exhaustive approach[b]	3		6		4		7		20	
- Broad filter										
by individual clinical questions	3	100.0	4	66.7	4	100.0	4	57.1	15	75.0
by clustering all clinical questions	3	100.0	6	100.0	4	100.0	5	71.4	18	90.0
- Narrow filter										
by individual clinical questions	2	66.7	4	66.7	4	100.0	4	57.1	14	70.0
by clustering all clinical questions	2	66.7	6	100.0	4	100.0	5	71.4	17	85.0

[a]Percentage of references and recommendations identified regarding the exhaustive strategy
[b]Exhaustive strategy results without clinical questions and recommendations not included in ReSe strategy

exhaustive search strategy using a random sample of recommendations from a cohort of clinical guidelines from a national guideline development program.

The restrictive approach (using a narrow PubMed Clinical Queries filter, clustering results per clinical guideline and imputing exhaustive search results for clinical questions not developed) retrieved 68.1 % fewer references than the exhaustive approach, and identified most of the key references (62/69, 89.9 %) and recommendations updates (22/25, 88.0 %). We developed search strategies for each clinical question but obtained better results by considering the results across all questions included in a clinical guideline. The restrictive approach proved to be relatively simple to develop, not needing the expertise of information retrieval specialists. Over half of the very few missing key references with this approach were systematic reviews. Three references were missed due to a mistake in the design of restrictive searches, and one was missed by the filter used [17], reflecting the need to pay more attention to the design and quality check of search strategies. Additional searches for systematic reviews in specific databases, like Epistemonikos, could prove useful [www.epistemonikos.org/]).

Our results show that PLUS approach retrieved 88.5 % fewer references than the exhaustive approach but identified a substantially lower number of key references (18/69, 26.1 %) and potential updates (10/25, 40 %) than the restrictive approach. These results were similar independently of the searches being performed by a PLUS information specialist (using search strategies) or directly using the PLUS interface using topic

Why Restrictive Approach (narrow filter and clustering all questions) did not identify 7 key references?

4 (57.1%) references were SRs

3 (42.9%) references were congress conferences (without PMID)

Abbreviations: PMID: PubMed Unique Identifier; ReSe: Restrictive Search; SR: Systematic review.

Fig. 3 Key references not identified by restrictive approach. Figure03_RefNotIdentifiedRestrictive. Microsoft PowerPoint presentation

Table 3 PLUS approach results

	Major depression in Adults 2008 [19]		Obesity in childhood and adolescence 2009 [20]		Prostate cancer treatment 2008 [21]		Secondary prevention of stroke 2009 [22]		Total	
Search period (years)	5.3		4.1		4.8		5.3			
References retrieved in search for clinical guidelines, n	973		317		137		3059		4486	
Key references identified from recommendation sample, n (%)[a]										
- Exhaustive strategy	13		32		11		13		69	
- PLUS strategy	4	(30.8)	9	(28.1)	1	(9.1)	4	(30.8)	18	(26.1)
Potential update recommendations identified from recommendation sample, n (%)[a]										
- Exhaustive strategy	3		8		7		7		25	
- PLUS strategy	2	(66.7)	4	(50.0)	1	(14.3)	3	(42.9)	10	(40.0)

[a]Percentage of references and recommendations identified regarding the exhaustive strategy

synonyms (*post-hoc analysis*). This poor performance was mainly due to most of these key references (80.4 %) being from journals not included in PLUS database.

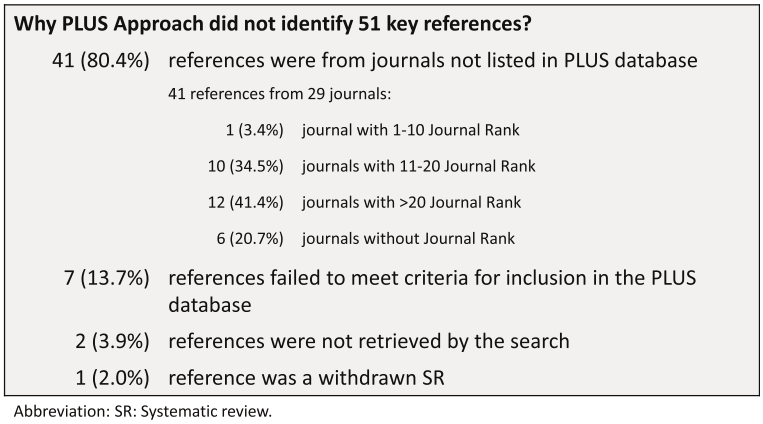
The PLUS approach performed differently across topics with major depression performing best (66.7 % of key references retrieved) and prostate cancer worst (14.3 %). This poor performance in the prostate cancer guideline is explained by the fact that the PLUS database does not include a large number of urology journals. This resource includes a limited number of journals with a stronger focus on a limited number of specialties and health topics. Given these findings and building on previous research in the systematic reviews and clinical guidelines fields, post-hoc we explored a potential approach of tailoring the PLUS approach by adding a limited number of journals for each specialty (e.g. those with a higher impact factor) [8, 9, 12, 13]. However, missing key references were published in a highly heterogeneous sample of journals, with only 3.4 % being in the first decile [Fig. 4].

The two search strategies we tested were far less time consuming than the exhaustive search strategy. The restrictive approach needs initial tailoring and takes each original guideline, question, search and references into account. In contrast, the PLUS approach could be potentially executed directly in its interface simply using topic synonyms from clinical guidelines.

Our results in the context of previous research

Only one previous study of clinical guidelines compared a different type of restrictive approach versus an exhaustive approach [9]. However, this study considered prevention topics as the unit of analysis rather than the individual recommendations. Furthermore, the authors restricted the search to MEDLINE, using publication types (review articles, editorials, guidelines and commentaries) and limiting the search to core and specialty clinical journals [9].

A recent evaluation of NICE clinical guidelines for interventional procedures also showed that updated recommendations that required a modification generally had a



Abbreviation: SR: Systematic review.

Fig. 4 Key references not identified by PLUS approach. Figure04_RefNotIdentifiedPLUS. Microsoft PowerPoint presentation

Table. 4 Summary results by approach

	Exhaustive approach		Restrictive approach[a]		PLUS approach	
	n	%	n	%[b]	n	%[b]
References identification						
References retrieved in search for clinical guidelines	39136		12486	31.9	4486	11.5
Key references identified from recommendation sample	69		62	89.9	18	26.1
Recommendation identification						
Potential update recommendations identified from recommendation sample	25		22	88.0	10	40.0
Resource use						
Guidelines methodologists	4		3	75.0	-	
Information specialist	-		-		1	25.0
Time to perform the search (hours)	279		174.3	62.5	28	10.0

[a]Narrow filter, clustered by all questions, and imputed exhaustive search results for the clinical questions not included in the restrictive approach
[b]Percentage regarding the exhaustive approach

greater increase in their evidence base (number of patients included in observational studies published) than non-updated recommendations [23]. Our results are consistent with this finding, showing a higher efficiency of the PLUS approach in recommendations with a higher turnover.

There is indirect evidence about the performance of PLUS for clinical guidelines from a previous study that evaluated the updating of systematic reviews [11]. Only 13 out of 87 systematic reviews (14.9 %) included all the new studies in PLUS. In 39 (44.8 %) reviews there was no statistically significant difference between PLUS and non-PLUS new studies (ROR: 0.99; 95 % confidence interval: 0.87-1.14). Thirty-five updated reviews (40.2 %) had no new studies indexed in PLUS (although conclusions were seldom altered by addition of new studies) [11]. Despite these results in systematic reviews, the PLUS database did not perform similarly in the context of clinical guidelines. However, we did not routinely determine the change in effect sizes with key references, so we could not assess their quantitative relationship. Neither did we assess whether references identified in the PLUS database could have reliably signalled the need to update for topics that were in the journals that are included.

The same study by Hemens et al. confirmed the high sensitivity of Clinical Queries filters for MEDLINE and EMBASE in detecting randomized controlled trials [11]. This is consistent with our results showing that incorporating Clinical Queries filters (to identify randomized controlled trials) and Montori's et al. filter (to identify systematic reviews) significantly reduces the citation screening burden [17].

Strengths and limitations

We used a rigorous and explicit methodology building on previous research in this area, improving its deficiencies, and implementing an innovative solution. We also used the exhaustive approach as a standard, improving the validity of the results and, hence, the strength of our inferences. We independently screened and extracted the data in pairs and included methodologists and panel members from the original guidelines as far as possible. Finally, we laid out a structured framework (e.g., outcome definitions) that could prove useful in the future for other researchers in the field.

Our study has some limitations. We did not assess all references retrieved by each alternative approach, so we were not able to evaluate whether other key references were identified by any of these approaches. Our sample is limited to recommendations from four guidelines topics. However, this potential limitation is mitigated because our sample covers broad areas such as cancer, cardiovascular diseases, mental health and lifestyle and behavioural issues. Additionally, we based our exhaustive search strategies on searches specifically designed during the original guidelines development. A post-hoc analysis revealed several mistakes and inconsistencies in search strategies that could have been avoided through peer review process [24]. However, the validation of the accuracy of the original search strategies was beyond the scope of our study. We are unable to estimate how this issue could affect the recall of the exhaustive search strategies, although we think that these deficiencies are minor and that they do not alter our conclusions. We included only randomised controlled trials and systematic reviews and did not incorporate observational studies, diagnostic questions or evidence about values and preferences or resource use considerations. Finally, some authors had conflicts of interest due to their involvement in the PLUS database and Clinical Queries filter development. However, they did not participate in the identification of key references.

Conclusions

Our results have important implications both for the updating of guidelines and for future research in this field. The proposed method of developing restrictive search strategies, using PubMed Clinical Queries filters in the MEDLINE database, provides a feasible and efficient method for guideline developers to identify significant new studies that are likely to trigger a recommendation update. Searching only in the PLUS database was a suboptimal approach that needs topic specific tailoring.

Our results highlight the need for additional methodological research in this field. For this future work, investigators are likely to find our framework helpful.

Additional files

Additional file 1: Search strategies examples. We reported an example of exhaustive strategy, restrictive strategy, PLUS strategy. (PDF 82 kb)

Additional file 2: Key references by approach. We reported key references by strategy, according to their clinical guidelines and linked to recommendation. (PDF 62 kb)

Additional file 3: Additional tables. We reported complementary results (PDF 40 kb)

Competing interests

Laura Martínez García, Andrea Juliana Sanabria, David Rigau, Leticia Barajas-Nava, Ivan Solà and Pablo Alonso-Coello have received research grants from Instituto de Salud Carlos III (FIS PI10/00346). R. Brian Haynes and Jennifer Lawson have received research grants from the Canadian Institutes of Health Research. R. Brian Haynes and Jennifer Lawson have been involved in developing the McMaster PLUS Project and RBH originated the development of Clinical Queries, so did not participate in identifying key references or potential update recommendations. No other competing interests were declared.

Authors' contributions

LMG, AJS, IA, PAC, DR and IS conceived the idea of the study. IA, JL, IS, RWMV and DL designed and/or ran searches strategies. EGA, MMTM, IEI, AK, DR, ALG, LBN, PDC and MDE screened the references. LMG and AJS performed the statistical analysis. LMG and PAC drafted the manuscript. All of the authors revised the manuscript critically for important intellectual content and approved the final version submitted for publication.

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Laura Martínez García is a doctoral candidate at the Pediatrics, Obstetrics and Gynecology, and Preventive Medicine Department, Universitat Aunònoma de Barcelona, Barcelona, Spain.

Data sharing

The dataset is available from the corresponding author at laura.martinez.garcia@cochrane.es.

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Discusión

6. Discusión

6.1. Principales resultados

Las instituciones que elaboran GPC actualizan sus guías, aunque reconocen que el método que utilizan no está estandarizado y puede ser más riguroso (publicación I) [100]. Esto se debe, quizá en parte, a la escasa investigación metodológica sobre la actualización de las GPC, que se limita, principalmente, a las estrategias para identificar la nueva evidencia (publicación II) [101].

Las recomendaciones de las GPC se desactualizan más rápidamente de lo que se asumía hasta la fecha. En el análisis de supervivencia hemos observado que la vigencia de las recomendaciones se reduce gradualmente después de uno (92,0 %), dos (85,7 %), tres (81,3 %) y cuatro años (77,8 %) de su elaboración (publicación III) [102].

En la evaluación de recomendaciones actualizadas hemos observado una gran heterogeneidad en la presentación de los cambios respecto a las recomendaciones originales, así como una falta de justificación de los mismos (publicación IV) [103].

Finalmente, en la evaluación sobre estrategias pragmáticas de búsqueda de la literatura hemos observado que la búsqueda restrictiva recupera menos referencias que la búsqueda exhaustiva e identifica la mayor parte de las referencias clave. La búsqueda en la base de datos McMaster PLUS también recupera menos referencias que la búsqueda exhaustiva, aunque identifica pocas referencias clave (publicación V) [104].

6.2. Resultados en el contexto del conocimiento actual

Los resultados de la investigación expuestos en la presente tesis amplían el conocimiento sobre el marco conceptual del proceso de actualización de GPC (tiempo, método, unidad, herramientas y recursos) (figura 3). En su conjunto, informan sobre el tiempo de vigencia de las recomendaciones (principalmente las

publicaciones II y III) [101, 102], sobre las etapas del proceso de actualización de GPC (publicaciones II-V) [101-104], sobre su periodicidad (publicación II) [101], sobre la unidad de actualización (publicaciones II-V) [101-104] y sobre las herramientas y recursos disponibles para llevarlo a cabo (publicación III) [102].

6.2.1. Tiempo de vigencia de las guías de práctica clínica

Tiempo de vigencia

Diferentes estudios han evaluado el tiempo de vigencia de las GPC utilizando diferentes unidades de actualización (p.ej., las GPC o las recomendaciones); diferentes métodos para identificar la nueva evidencia y evaluar su impacto, o diferentes desenlaces de interés (p.ej., el porcentaje de recomendaciones vigentes en un tiempo concreto o el tiempo medio de vigencia) [102, 117, 126-128]. En consecuencia, los resultados de los diferentes estudios son difícilmente comparables.

Dos estudios han evaluado el tiempo de vigencia de las GPC [117, 126]. Shekelle *et al*. 2001 evaluaron 17 GPC de la AHRQ aplicando una estrategia basada en una búsqueda limitada de la literatura, la opinión de expertos y una evaluación cualitativa del impacto de la nueva evidencia [117]. Los autores observaron que el 90 % de las GPC siguen estando vigentes a los 3,6 años de su elaboración (IC 95 %: 2,6 a 4,6) [117]. Alderson *et al*. 2014 evaluaron 134 GPC de NICE aplicando estrategias diferentes según el manual metodológico vigente [126]. Los autores observaron que el 86 % de las GPC siguen estando vigentes a los tres años de su publicación (IC 95 %: 79 a 92) [126].

Dos estudios han evaluado el tiempo de vigencia de las recomendaciones [102, 127]. Lyratzopoulos *et al*. 2012 evaluaron 11 recomendaciones sobre nuevas intervenciones aplicando una estrategia basada en una búsqueda exhaustiva de la literatura, la opinión de expertos y una evaluación cualitativa del impacto de la nueva evidencia [127]. Los autores observaron un tiempo medio de supervivencia de las recomendaciones de 5,3 años (rango: 3,3 a 6,5) [127]. Nuestro grupo de

trabajo ha evaluado 113 recomendaciones de las guías del Programa de GPC del SNS aplicando una estrategia basada en una búsqueda exhaustiva de la literatura, la opinión de expertos y una evaluación cualitativa del impacto de la nueva evidencia (publicación III) [102]. Se ha observado que el 81,3 % de las recomendaciones siguen estando vigentes a los tres años de su publicación (IC 95 %: 74,0 a 88,5) (publicación III) [102].

La información más precisa (a nivel de recomendación y en base a una búsqueda exhaustiva de la literatura) muestra que un 20 % de las recomendaciones de las GPC necesitan ser revisadas antes de que transcurran tres años de su elaboración (publicación III) [102]. Estos resultados deberían modificar la política actual, que siguen manteniendo algunas instituciones que elaboran GPC, de revisar y actualizar las GPC cada tres o más años (publicaciones I y VII) [100, 106].

En el campo de las RS, también se ha evaluado, de forma heterogénea, el tiempo de vigencia de sus conclusiones (diferentes estudios con diferentes métodos y diferentes desenlaces de interés) [60, 62, 76, 85].

Shojania *et al*. 2007 analizaron 100 RS y observaron un tiempo medio libre de señales de actualización de 5,5 años (IC 95 %: 4,6 a 7,6), aunque el 23 % de las RS presentaron una señal de actualización a los dos años de su publicación [76]. De forma parecida, Peterson *et al*. 2011 evaluaron 41 CER y observaron un tiempo medio hasta la actualización de, aproximadamente, dos años [85]. Sin embargo, French *et al*. 2005 y Jaidee *et al*. 2010 observaron pocos cambios en las conclusiones de las RS actualizadas después de dos o más años de su elaboración [60, 62]. En base a estos resultados, las instituciones que elaboran RS como, por ejemplo, la Colaboración Cochrane [19], aconsejan una política de actualización conservadora, con la revisión y la actualización de las RS cada dos años.

El tiempo de vigencia de las recomendaciones de las GPC (menor o igual a tres años) [102] es parecido al tiempo de vigencia de las RS (menor o igual a dos años) [76]. Teniendo en cuenta que las GPC se basan en RS, es razonable que el tiempo de vigencia de las RS esté íntimamente relacionado con el tiempo de

vigencia de las GPC. Sin embargo, este aspecto aún no ha sido evaluado de manera sistemática.

Factores asociados a una mayor probabilidad de actualización

En los estudios sobre la vigencia de las GPC se han identificado algunos factores asociados a una mayor probabilidad de actualización como, por ejemplo, recomendaciones con mayor volumen de estudios nuevos publicados (publicación III) [102], recomendaciones basadas en estudios que incluyen más pacientes [127] o recomendaciones que no se basan en múltiples ECA [128].

Paralelamente, en el campo de las RS se han identificado aspectos similares asociados a una mayor probabilidad de actualización, como el tema abordado (p.ej. tópicos cardiovasculares o psiquiátricos) [76, 85], un mayor volumen de estudios nuevos relevantes [85], la presencia de heterogeneidad en la RS original [76] o la identificación de un nuevo fármaco [85].

El estudio de los factores asociados a una mayor probabilidad de actualización se puede enfocar, al menos, desde dos perspectivas: 1) a través del análisis retrospectivo de la vigencia de las recomendaciones (publicación III) [102] o 2) mediante un registro sistemático de las recomendaciones actualizadas (publicación IV) [103]. La identificación de estos factores permitiría priorizar la revisión (vigilancia o monitorización) de las GPC o las recomendaciones más sensibles de ser actualizadas. Una estrategia de este tipo (en base a la priorización de recomendaciones, preguntas clínicas o GPC más sensibles a ser actualizadas) constituiría una aproximación más eficiente que la estrategia actualmente utilizada (en base a un tiempo de vigencia predeterminado para todas las GPC).

6.2.2. Etapas en la actualización de las guías de práctica clínica

Identificación de la nueva evidencia: estrategias de búsqueda de la literatura

Shekelle *et al*. 2001 diseñaron e implementaron una estrategia de búsqueda limitada de la literatura basada en la recuperación de revisiones, editoriales y

comentarios en cinco revistas biomédicas generales y en revistas biomédicas especializadas [117]. Posteriormente, Gartlhner *et al*. 2004 compararon la estrategia desarrollada por Shekelle *et al*. 2001 con una estrategia de búsqueda exhaustiva de la literatura [115]. La estrategia limitada recuperó menos referencias e identificó todas las señales de actualización [115].

Nuestro grupo de trabajo ha comparado una estrategia de búsqueda exhaustiva de la literatura con dos alternativas más pragmáticas: 1) la estrategia restrictiva (basada en la búsqueda exhaustiva original de la literatura [mínimo número de términos MeSH y términos en texto libre requeridos], la búsqueda en una sola base de datos bibliográfica [MEDLINE a través de PubMed] y la aplicación de filtros validados para recuperar determinados diseños de estudios [ECA y RS]) y 2) la estrategia PLUS (búsqueda en la base de datos McMaster PLUS). La búsqueda restrictiva ha sido eficiente en la identificación de las señales de actualización, en cambio, la búsqueda en la base de datos McMaster PLUS no ha mostrado un rendimiento óptimo (publicación V) [104].

Tanto la búsqueda limitada de la literatura, propuesta por Shekelle *et al.* 2001 [117], como la búsqueda restrictiva, propuesta por nuestro grupo de trabajo (publicación V) [104], tienen el objetivo común de identificar la señal de actualización, priorizar la precisión y disminuir el volumen de referencias recuperadas en el proceso de actualización.

En el campo de las RS y de las CER también se han propuesto diferentes estrategias pragmáticas de búsqueda de la literatura para disminuir el volumen de referencias recuperadas en el proceso de actualización [61, 64, 72, 75, 86-88]. Ninguna estrategia ha mostrado, por el momento, un rendimiento excelente para identificar toda la nueva evidencia, aunque se ha observado que los estudios que no identifican estas estrategias no modifican las conclusiones de las RS [61, 64].

Shekelle *et al*., en varias de sus publicaciones, adaptaron la estrategia limitada de búsqueda de la literatura para identificar señales de actualización en GPC y la utilizaron en el campo de las RS [72, 75, 87, 88, 117]. Aunque no han realizado una comparación formal de los resultados, parece que la estrategia es útil tanto en el campo de las GPC como en el de las RS. Nuestro grupo de trabajo, en base

a las estrategias pragmáticas de búsqueda de la literatura propuestas por Hemens *et al.* 2012 para actualizar RS [61], ha diseñado y evaluado estrategias pragmáticas en el campo de las GPC (publicación V) [104]. La utilización de los filtros *Clinical Queries* de PubMed ha mostrado un rendimiento similar entre GPC y RS, sin embargo, la utilización de la base de datos McMaster PLUS no ha mostrado un rendimiento adecuado en el campo de las GPC.

Identificación de la nueva evidencia: fuentes de información

Existen diferentes fuentes de información que se pueden utilizar de forma complementaria durante la identificación de nueva evidencia como, por ejemplo, la búsqueda en bases de datos bibliográficas, la consulta a elaboradores y expertos, la búsqueda de GPC recientes, o la búsqueda de alertas de medicamentos.

La mayoría de estrategias pragmáticas de búsqueda de la literatura se basan en la búsqueda en bases de datos bibliográficas y se complementan con la consulta a los expertos clínicos en el área de la GPC. El número de participantes y la tasa de respuesta varían según los estudios (Shekelle *et al*. 2001: 146 participantes, tasa de respuesta del 71 %; Gartlhner *et al*. 2004: 13 participantes, tasa de respuesta del 28 %; Martínez García *et al*. 2014: 24 participantes, tasa de respuesta del 70,8 %) (publicaciones II y III) [101, 102]. Sin embargo, ninguno de los estudios ha valorado la eficiencia del proceso (tiempo invertido en diseñar, rellenar y analizar la encuesta frente a la relevancia de la información aportada por los participantes).

Hasta el momento, no se ha valorado el rendimiento de identificar GPC recientes como fuente de estudios clave para la actualización. Una aproximación a esta estrategia la sugirieron Nunes *et al.* 2009, que identificaron y revisaron GPC recientes para valorar si las GPC de su institución necesitaban ser actualizadas [116]. Una estrategia basada en la identificación y adaptación de GPC recientes podría ser útil para instituciones que elaboran GPC y cuentan con pocos recursos para su actualización.

La búsqueda de alertas de medicamentos de las agencias reguladoras de medicamentos u otros tipos de tecnologías sanitarias (p.ej., la Agencia Europea de Medicamentos [129] o, en nuestro entorno, la Agencia Española de Medicamentos y Productos Sanitarios [130]) se contempla en los manuales metodológicos, sin embargo, son pocos los que abordan cómo sistematizar el proceso [6, 131].

Identificación de la nueva evidencia: tipos de evidencia

La estrategia limitada de búsqueda de la literatura propuesta por Shekelle *et al.* 2001 se basó en la recuperación de revisiones, editoriales y comentarios [117]. En cambio, las estrategias pragmáticas de nuestro grupo de trabajo se basaron en la identificación de ECA y RS, para: 1) disminuir el riesgo de no identificar una referencia clave y 2) utilizar con posterioridad los resultados para la revisión y, si fuese necesario, la modificación de las recomendaciones (publicación V) [104].

Hasta el momento, solo se había considerado, fundamentalmente, la información sobre eficacia como una posible señal de actualización de las GPC o de sus recomendaciones. Actualmente, nuestro grupo de trabajo está implementando un proceso de actualización continuo (estrategia: búsqueda restrictiva de la literatura, evaluación cualitativa del impacto de la nueva evidencia, revisión y modificación de las recomendaciones; periodicidad: cada seis meses) en la «Guía de práctica clínica de atención en el embarazo y puerperio» [132], que incluye otros tipos de evidencia como posibles señales de actualización (p.ej., evidencia sobre los valores y preferencias o los costes y el uso de recursos). Aunque los resultados son preliminares, en el primer ciclo de actualización (desde enero de 2012 hasta agosto de 2014 [periodo de 32 meses]) se han recuperado 9710 referencias y se han identificado 318 referencias pertinentes, 289 referencias relevantes y 55 posibles referencias clave. El 18,2 % (10/55) de las referencias clave son referencias relacionadas con los valores y preferencias y el 12,7 % (7/55) son referencias relacionadas con los costes y el uso de recursos. Será necesario esperar a los resultados de la actualización de las recomendaciones para valorar las implicaciones de estas referencias.

Evaluación del impacto de nueva evidencia

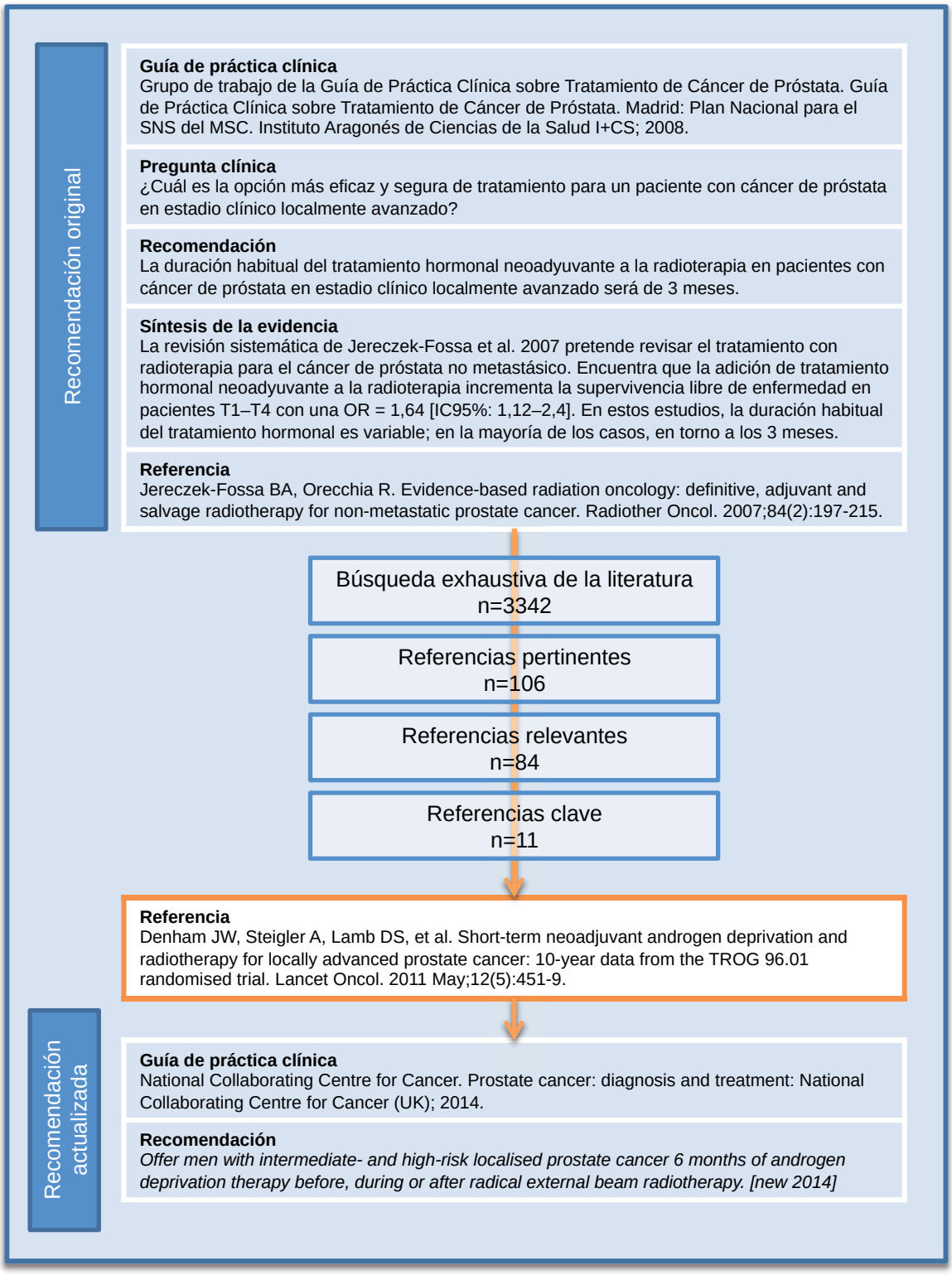
Shekelle *et al*. 2001 propusieron una evaluación cualitativa de la evidencia identificada para decidir su impacto en las GPC: 1) actualización mayor (la evidencia identificada sugiere la necesidad de nuevas recomendaciones), 2) actualización menor (la nueva evidencia identificada sugiere cambios en las recomendaciones) o 3) la GPC aún está vigente [117].

Nuestro grupo de trabajo también ha propuesto una aproximación cualitativa, aunque con un método más sistemático y explícito que el de Shekelle *et al*. 2001 (publicación III) [102]. Nuestra aproximación propone una clasificación de las referencias (pertinentes, relevantes y claves), una clasificación de las recomendaciones (recomendaciones vigentes o recomendaciones a revisar) y aspectos que pueden ser sensibles al cambio (la población, la intervención, la comparación, los desenlaces, la calidad de la evidencia, la dirección y la fuerza de la recomendación) (publicación III) [102]. Además, se ha evaluado la incorporación de expertos clínicos como evaluadores de las referencias para identificar las señales de actualización.

Así, por ejemplo, en la «Guía de práctica clínica sobre el tratamiento de cáncer de próstata» [123] (publicada en el año 2008) se recomendaba en pacientes con cáncer de próstata en estadio clínico localmente avanzado el tratamiento hormonal neoadyuvante a la radioterapia durante tres meses (esta recomendación se basaba en una RS de 2007) (figura 6). En el proceso de revisión de la nueva evidencia se identificó la referencia de Denham *et al.* 2011 (ECA, que comparaba el tratamiento durante tres o seis meses y presentaba resultados tras diez años de seguimiento) y se clasificó como clave [133]. Posteriormente, en la GPC de NICE «*Prostate cancer: diagnosis and treatment*» [134] (publicada en el año 2014)[4] se recomienda en pacientes con cáncer de próstata localizado, de intermedio o alto riesgo, el tratamiento hormonal antes, durante o después de la radioterapia durante seis meses.

[4] Se ha revisado la GPC «*Prostate cancer: diagnosis and treatment*» de NICE debido a que la «Guía de práctica clínica sobre el tratamiento de cáncer de próstata» del Programa de GPC en el SNS aún no ha sido actualizada.

Figura 6. Identificación y evaluación del impacto de una referencia



Nuestro grupo de trabajo, en base a la investigación previa desarrollada por Shekelle *et al*. 2001 [117], ha intentado desarrollar un método más sistemático y

explícito para evaluar el impacto de la nueva evidencia identificada. Sin embargo, no hemos podido estandarizar un método para establecer qué tipo de evidencia desencadena potencialmente una actualización, quién debe evaluar la nueva evidencia, qué factores se deben considerar o cómo ponderarlos. Evaluar el impacto de la nueva evidencia sobre las recomendaciones originales es un proceso complejo que, necesariamente, requiere un juicio subjetivo de los evaluadores y un consenso con el grupo de trabajo. Seguramente, será necesario desarrollar un marco conceptual y metodológico para hacer este proceso más sistemático y explícito.

En el campo de las RS se ha desarrollado e implantado un método cualitativo (método RAND), un método cuantitativo (método Ottawa) o una combinación de ambos [72, 75, 76, 88]. La implementación de estos métodos en el área de las GPC aún no se ha contemplado.

Revisión y modificación de las guías de práctica clínica

Se ha prestado poca atención al proceso de revisión y modificación de las GPC o de sus recomendaciones, al asumirse que es similar al proceso de elaboración de las mismas (publicación II) [101]. En principio, la actualización de las GPC debe realizarse con el mismo enfoque sistemático y explícito que la elaboración *de novo*. Sin embargo, asumir que la calidad de una GPC actualizada es igual o mejor que la GPC original es un riesgo. Por ejemplo, Hasenfeld *et al.* 2003 observaron que las GPC actualizadas eran de peor calidad metodológica que las GPC originales [135].

Asimismo, durante el proceso de revisión y modificación de las recomendaciones también deberían introducirse, en caso necesario, mejoras metodológicas (p.ej., adaptar una GPC del sistema SIGN [56] al sistema GRADE [26]), así como mejoras de edición (p.ej., corregir erratas o mejorar la redacción del texto).

La revisión y modificación parcial de las GPC puede dar como resultado GPC «parcheadas» (con una mezcla de secciones originales y secciones actualizadas en diferentes momentos del tiempo) (publicación IV) [103]. Por ello, se debería

considerar revisar todas las GPC de manera global después de varios ciclos de actualización.

Edición de las guías de práctica clínica actualizadas

La edición de las GPC actualizadas es un área poco desarrollada, se observa una gran variabilidad en los formatos de presentación de las recomendaciones actualizadas y una falta de justificación de los cambios (publicación IV) [103]. El proyecto europeo DECIDE (*Developing and Evaluating Communication Strategies to Support Informed Decisions and Practice Based on Evidence*), iniciativa del grupo GRADE, ha desarrollado formatos óptimos de presentación de las recomendaciones en salud para diferentes grupos de interés, pero no ha abordado la presentación de GPC o recomendaciones actualizadas [136].

Hasta el momento, solo en el campo de las RS se ha evaluado el formato de presentación de los resultados de una actualización, y se ha observado que diferentes grupos de interés tienen diferentes necesidades de información [73]. Así, por ejemplo, los gestores sanitarios necesitan tener acceso a todos los datos y análisis de una RS (los originales y los actualizados), en cambio, los usuarios se benefician de una síntesis que muestre claramente qué es lo que ha cambiado [73].

Actualmente, nuestro grupo de trabajo está elaborando un lista de verificación con el objetivo de desarrollar una herramienta para establecer qué información y cómo debe ser presentada en las GPC actualizadas [131, 137].

6.2.3. Proceso de actualización continuo o puntual

Solo Johnston *et al*. 2003 han evaluado un proceso de actualización continuo de 20 GPC (estrategia: búsqueda exhaustiva continua de la literatura, evaluación cualitativa del impacto de la nueva evidencia, revisión y modificación de recomendaciones y difusión de la actualización; periodicidad: mensual) [121]. Después de implementar la estrategia durante un año, los autores propusieron

optimizarla realizando búsquedas limitadas de la literatura en MEDLINE, *The Cochrane Library* y actas de reuniones y aplicándola de forma trimestral [121].

Eccles *et al*. 2002 y Parmelli *et al*. 2011 evaluaron un proceso de actualización puntual de GPC (estrategia: búsqueda exhaustiva de la literatura, evaluación cualitativa del impacto de la nueva evidencia, revisión y modificación de recomendaciones; periodicidad: tres o más años de la elaboración) [118, 120]. Ambos concluyeron que la inversión de recursos en el proceso de actualización era parecida a la de la elaboración de las GPC [118, 120].

Como ya se ha expuesto anteriormente, nuestro grupo de trabajo está implementando un proceso de actualización continuo (estrategia: búsqueda restrictiva de la literatura, evaluación cualitativa del impacto de la nueva evidencia, revisión y modificación de las recomendaciones; periodicidad: cada seis meses) en la «Guía de práctica clínica de atención en el embarazo y puerperio» [132]. En el primer ciclo de actualización (desde enero de 2012 hasta agosto de 2014 [periodo de 32 meses]) se han recuperado 9710 referencias y se han identificado 318 referencias pertinentes, 289 referencias relevantes y 55 posibles referencias clave. En el segundo (desde septiembre de 2014 hasta febrero de 2015 [periodo de seis meses]) y en el tercer ciclo de actualización (desde marzo de 2015 hasta agosto de 2015 [periodo de seis meses]) se han recuperado 2160 referencias y 2010 referencias, respectivamente. Aunque los resultados son preliminares, en nuestro entorno, parece recomendable optar por un proceso de actualización continuo ya que supone un volumen de información más manejable y una inversión de recursos, en principio, similar a largo plazo (tabla 5).

Tabla 5. Características del proceso de actualización continuo o puntual

	Proceso de actualización continuo (GPC vivas o dinámicas)	**Proceso de actualización puntual**
Periodicidad	Cada 6-12 meses.	Cada 2-3 años.
Búsqueda de la literatura	Búsqueda restrictiva de la literatura.	Búsqueda exhaustiva de la literatura.
Volumen de información	Menor volumen de información de forma continua*.	Mayor volumen de información de forma puntual.

Recursos	Menos personal contratado, aunque de forma continua. P.ej., el coste aproximado para la actualización continua de una GPC a los tres años de su elaboración sería de 84000 € (1 contrato media jornada * 56 pagas (48 meses) * 1500 € / mes).	Más personal contratado, aunque de forma puntual. P.ej., el coste aproximado para la actualización puntual de una GPC a los tres años de su elaboración sería de 84000 € (2 contratos jornada completa * 14 pagas (12 meses) * 3000 € / mes).
Riesgos	Actualizaciones muy frecuentes: - Consumo de recursos si la actualización no aporta cambios. - Introducción de sesgos [138].	Actualizaciones poco frecuentes: - Práctica clínica y asistencial inadecuada. - Pérdida de credibilidad de las instituciones que elaboran GPC.

*Es recomendable programar, durante la elaboración de la GPC, un proceso de identificación y evaluación continua de la nueva evidencia. La acumulación exponencial de nueva evidencia tras la elaboración de la GPC (*backlog*) limita la factibilidad del proceso en el primer ciclo de actualización. Abreviatura: GPC: guía de práctica clínica.

En el campo de las RS, dos estudios han implementado una estrategia de revisión (vigilancia o monitorización) cada seis meses para identificar señales de actualización (en base a la estrategia propuesta por Shekelle *et al*. 2009) [71, 74]. En ambos estudios, los autores observaron que pocas RS necesitaban ser actualizadas rápidamente y propusieron aplicar la estrategia de forma anual. A pesar de que se ha contemplado el proceso de actualización continuo para las RS (RS vivas), la investigación metodológica en el área es incipiente [139, 140].

6.2.4. Unidad de actualización

Hasta el momento, la mayor parte de la investigación metodológica desarrollada ha tomado como unidad de actualización las GPC (publicación II) [101]; aunque recientemente algunos estudios se han basado en un análisis de las recomendaciones [101, 102, 120, 128, 141].

Nuestro grupo de trabajo ha basado sus estudios iniciales en el análisis de las recomendaciones, considerando: 1) que las recomendaciones son los elementos esenciales de las GPC, 2) que el objetivo final del proceso de actualización es la revisión y modificación de las recomendaciones, y 3) que la información individual

por recomendación es más precisa que la información agrupada por GPC (publicaciones III-V) [102-104]. No obstante, por otro lado, el análisis por recomendación ha supuesto cierta rigidez durante el proceso (p.ej., en la publicación III, las referencias no relacionadas con alguna de las recomendaciones originales no se evaluaron) y un aumento del volumen de información (p.ej., en la publicación III, las referencias relacionadas con dos o más de las recomendaciones originales se evaluaron por duplicado) [102].

Para optimizar el proceso de actualización de GPC se debería reconsiderar la unidad de actualización y encontrar un equilibrio entre la precisión de los resultados (análisis por recomendación más preciso que el análisis por GPC) y la factibilidad del proceso (análisis por recomendación menos viable que el análisis por GPC). Llegados a este punto, considerar la pregunta clínica o las secciones como la unidad de actualización parece el camino natural en la evolución del proceso de actualización de GPC [131].

6.2.5. Herramientas y recursos en la actualización

Proceso normalizado de trabajo

Nuestro grupo de trabajo ha diseñado un método sistemático y explícito para identificar la señal de actualización (publicación III) [102]. Esto ha supuesto el desarrollo de diferentes herramientas *ad hoc* para llevar a cabo el proceso:

- **Mapa de las GPC:** El mapeo de las GPC es un esquema que relaciona las preguntas clínicas con sus recomendaciones y con las referencias correspondientes. La elaboración de esta herramienta facilita la consulta rápida de la información original y su enlace con la nueva evidencia [131]. No obstante, la falta de transparencia en el proceso de elaboración de algunas GPC limita el desarrollo del mapa de las GPC [102].
- **Cuestionario para la recogida de la evidencia de los expertos clínicos** [131].
- **Cuestionario para la evaluación de las referencias** [131].

Asimismo, se han adaptado los softwares de gestión de referencias (Reference Manager [142] o EndNote [143]) para la identificación y clasificación de las referencias en pertinentes, relevantes y claves.

Manuales metodológicos

Hasta el momento, los manuales metodológicos no aportaban suficiente información para realizar el proceso de actualización de forma óptima; muy pocos describían cómo identificar la nueva evidencia, cómo evaluar el impacto de la nueva evidencia o cómo revisar y modificar las recomendaciones (publicación VII) [106]. Recientemente, se han actualizado los manuales metodológicos de algunas de las instituciones que elaboran GPC como por ejemplo, NICE, SIGN o el Programa de GPC en el SNS - GuíaSalud.

- **NICE 2014:** En la nueva versión del manual metodológico de NICE se propone un nuevo enfoque para identificar la nueva evidencia [6, 144, 145]. Se distingue entre una búsqueda más limitada de la literatura a los dos, seis y diez años de la publicación de la GPC original y una búsqueda más exhaustiva de la literatura a los cuatro y ocho años [6].

  Indistintamente del tiempo evaluado, se valora la información cualitativamente y se clasifican las GPC en: actualización completa con el mismo alcance; actualización completa con un alcance modificado; actualización parcial con el mismo alcance; actualización parcial con un alcance modificado; no actualización; refrescar la GPC (revisión editorial); transferencia a una lista estática, y retirada de algunas recomendaciones o de toda la GPC [6].

  La nueva propuesta de NICE sigue manteniendo como unidad de actualización las GPC, seguramente por la magnitud de su catálogo [43].

  Finalmente, cabe destacar que, seguramente en base a nuestro trabajo sobre la evaluación de GPC actualizadas (publicación IV) [103], se ha incluido una lista de criterios a considerar para presentar una GPC parcialmente actualizada [6].

- **SIGN 2014:** Aunque el manual de SIGN del año 2011 fue actualizado en 2014, no se ha incorporado ningún cambio en la sección de actualización de las GPC [7, 56].
- **Programa de guías de práctica clínica en el Sistema Nacional de Salud - GuíaSalud (pendiente de publicación):** Actualmente, se está finalizando la actualización del manual metodológico para la elaboración de GPC, en él se ha incluido un capítulo sobre el proceso de actualización de GPC [131]. En el manual se propone, en base a las experiencias de nuestro grupo de trabajo, una nueva estrategia para actualizar las guías del Programa de GPC en el SNS [101-104, 131]. Los elementos innovadores propuestos consisten en priorizar preguntas clínicas para su actualización y utilizar una estrategia de búsqueda restrictiva y continua de la literatura.

Sinergias entre las guías de práctica clínica y las revisiones sistemáticas en el campo de la actualización

Como se ha comentado anteriormente, las RS y las GPC están íntimamente relacionadas: 1) ambas son herramientas útiles para la toma de decisiones clínicas de los usuarios, de los profesionales y de los gestores sanitarios, 2) las RS son la base para la elaboración de las GPC [2], 3) la metodología utilizada para actualizar las RS podría ser adaptada para actualizar las GPC y 4) las RS actualizadas (que presenten cambios en sus conclusiones) podrían ser utilizadas para actualizar las GPC.

Sin embargo, el proceso de actualización de GPC es más complejo que el de las RS por varias razones: 1) hay más agentes implicados, 2) son documentos más extensos, 3) se incluye más información de diferentes contextos y 4) el proceso comprende también la actualización de las RS incluidas (tabla 6).

Tabla 6. Características del proceso de actualización de guías de práctica clínica y de revisiones sistemáticas

	Proceso de actualización de guías de práctica clínica	Proceso de actualización de revisiones sistemáticas
Responsabilidad	- Instituciones que elaboran GPC	- Autores

Grupo de trabajo	- Expertos clínicos - Expertos en metodología - Otros grupos de interés - Revisores externos	- Autores
Unidad de actualización	- Recomendaciones (basadas en RS) - Preguntas clínicas - GPC	- Conclusiones de las RS
Tipos de evidencia	- Balance entre beneficios y riesgos - Calidad de la evidencia - Valores y preferencias - Uso de recursos y costes - Otros (equidad, aceptabilidad o factibilidad)	- Según el objetivo de la RS (p.ej. terapéuticas, de diagnóstico, metodológicas, cualitativas o de pronóstico)
Volumen de información	+++	+
Investigación metodológica desarrollada	+	++

Abreviatura: GPC: guía de práctica clínica, RS: revisión sistemática.

A pesar de las diferencias comentadas, existe cierto paralelismo en la investigación metodológica llevada a cabo en el proceso de actualización de GPC y de las RS (tabla 7). Así, por ejemplo, se ha analizado paralelamente el tiempo de vigencia de las GPC y de las RS [60, 62, 76, 85, 102, 117, 126, 127]. No obstante, hay algunas áreas desarrolladas en el proceso de actualización de RS que aún no se han considerado en profundidad en el proceso de actualización de GPC, como, por ejemplo, la presentación de las recomendaciones actualizadas o el uso de las nuevas tecnologías (tabla 2) [73, 95, 96].

Tabla 7. Investigación metodológica en el proceso de actualización de guías de práctica clínica y de revisiones sistemáticas

Clasificación[#]	Guías de práctica clínica Primer autor y año *(orden cronológico)*	Revisiones sistemáticas Primer autor y año *(orden cronológico)*
Publicaciones relacionadas con el análisis del contexto		
Encuesta sobre actualización	- Alonso-Coello 2011 [100]	- Garritty 2010 [78]
Revisión de los métodos de actualización	- Martínez García 2012 [127] - Vernooij 2014 [106]	- Moher 2008* [79], Moher 2007 [80]

	- Becker 2014 [146]	- Tsertsvadze 2011a* [77], Tsertsvadze 2011b [81]
Publicaciones relacionadas con el tiempo		
Tiempo de vigencia	- Shekelle 2001a* [117], Shekelle 2001b [147], Eccles 2002b [148] - Lyratzopoulos 2012 [127] - Alderson 2014 [126] - Martínez García 2014a [102]	- French 2005 [60] - Shojania 2007a* [76], Shojania 2007b [84] - Jaidee 2010 [62] - Peterson 2011 [85]
Factores asociados a la actualización	- Lyratzopoulos 2012 [127] - Martínez García 2014a [102] - Martínez García 2014b [103] - Neuman 2014 [128]	- Shojania 2007a* [76], Shojania 2007b [84] - Peterson 2011 [85]
Proceso de revisión y/o actualización continuo o puntual	- Eccles 2002a [118] - Johnston 2003* [121], Brouwers 2001 [149] - Parmelli 2011 [120]	- Ahmadzai 2013 [71] - Newberry 2013b [74]
Publicaciones relacionadas con la metodología		
Identificación de la nueva evidencia	- Gartlhner 2004* [115], Gartlhner 2007 [97], Voisin 2008 [150] - Martínez García 2015 [104]	- Sampson 2008a [86] - Hemens 2012 [61] - Sagliocca 2013 [64]
Identificación de la nueva evidencia y evaluación del impacto de nueva evidencia	- Shekelle 2001a* [117], Shekelle 2001b [147], Eccles 2002b [148] - Bosquet 2003 [114] - Nunes 2009 [116] - Martínez García 2014a [102]	- Shojania 2007a* [76], Shojania 2007b [84] - Shekelle 2009 [75] - Pattanittum 2012 [63] - Chung 2012* [72], Shekelle 2011 [87] - Shekelle 2014a* [88], Shekelle 2014b [89]
Calidad de las actualizaciones	- Hasenfeld 2003 [135]	- Shea 2006 [65]
Edición de la actualización	- Martínez García 2014b [103]	- Newberry 2013a [73]

[#]Una misma publicación se puede clasificar en diferentes apartados. *Publicación principal.

Seguramente, la optimización del proceso de actualización de RS aumentará la disponibilidad de RS revisadas y actualizadas. Esto tendrá un impacto positivo en la actualización de las GPC: 1) el mayor número de RS actualizadas facilitará la identificación, evaluación y síntesis de la evidencia y 2) la metodología y las herramientas utilizadas en el proceso de actualización de RS se podrán adaptar al campo de las GPC (adoptando, probablemente, una aproximación más pragmática dadas las diferencias apuntadas en la tabla 6).

Nuevas tecnologías e innovaciones

Actualmente la actualización de las GPC se realiza de forma manual y consume mucho tiempo. Una mejor utilización de las nuevas tecnologías podría mejorar la eficiencia del proceso, tanto en la elaboración como en la posterior actualización de las GPC. Así, por ejemplo, el uso de *softwares online*, como el GDT *(Guideline Development Tool)* [151] o el MAGIC (*making GRADE the irresistible choice*) [57, 152], permitirán elaborar y actualizar GPC más fácilmente.

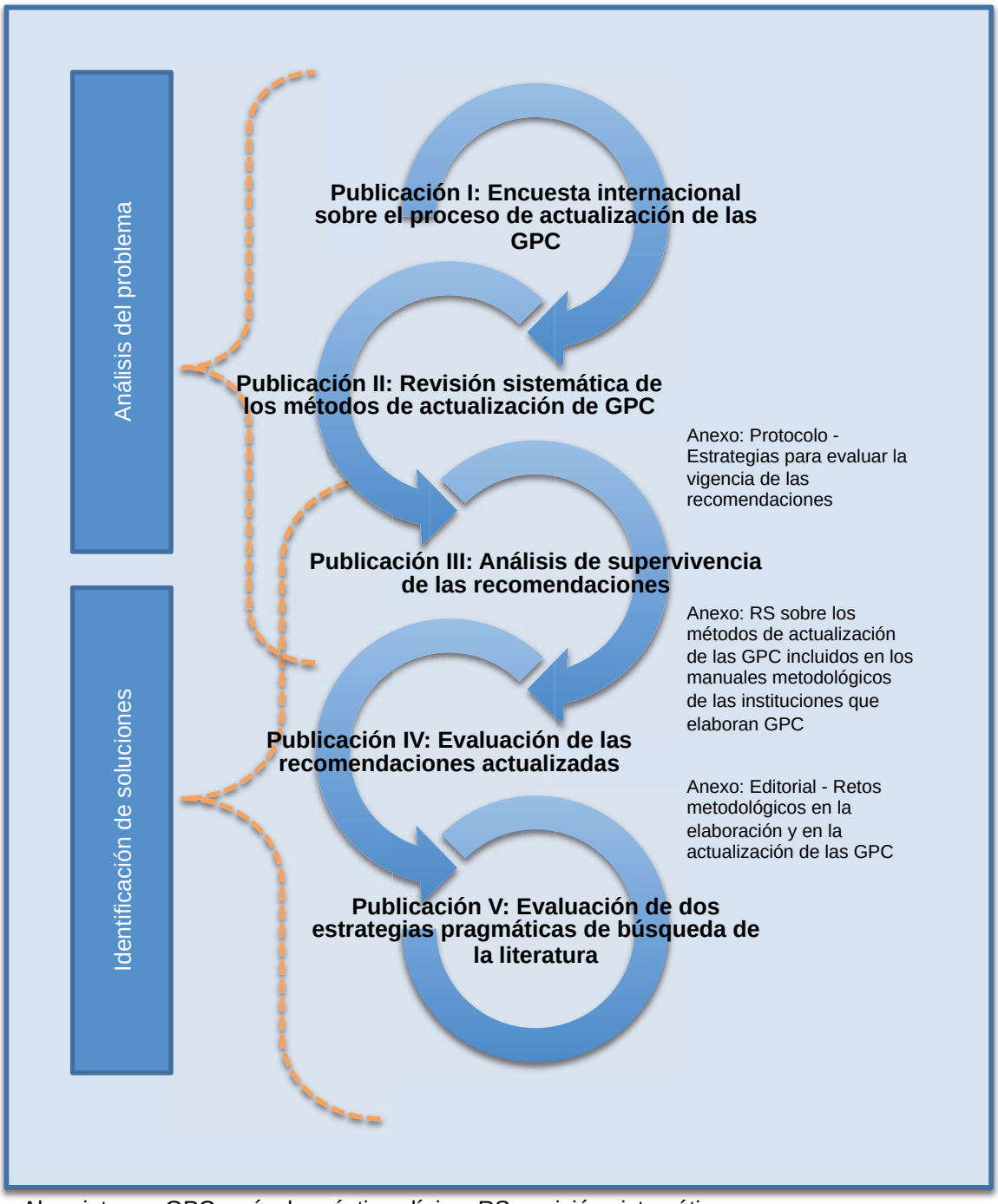
En el campo de las RS se están considerando otras innovaciones, como los sistemas de aprendizaje automáticos para identificar las referencias relevantes [95, 96], la colaboración abierta (*crowdsourcing*) para ayudar a los autores de las RS con pequeñas tareas [153], o el enlace entre referencias [153].

6.3. Fortalezas y limitaciones

6.3.1. Fortalezas

La tesis presentada incluye cinco publicaciones con un objetivo final común: mejorar el proceso de actualización de GPC. El proceso de investigación que hemos desarrollado se basa en: 1) el análisis de un problema concreto y la identificación de soluciones y 2) la identificación de las limitaciones de los proyectos previos y la implantación de alternativas en los proyectos sucesivos (proceso de retroalimentación del conocimiento) (figura 7).

Figura 7. Cronología del proceso de investigación



Abreviaturas: GPC: guía de práctica clínica; RS: revisión sistemática.

El proceso de investigación se ha desarrollado de forma estructurada y transparente, con la elaboración y, en algunos casos la publicación, de los correspondientes protocolos de investigación (publicación VI) [105].

Todas las publicaciones presentadas en la tesis han pasado por un proceso de revisión por pares de las revistas biomédicas a las que se han sometido, lo que garantiza su calidad y originalidad. Además, el factor de impacto (rango: 2,270 a 5,959) y el cuartil (la mayoría en el Q1) de estas revistas implica un alto impacto y difusión de la investigación metodológica en el área de las GPC.

Asimismo, algunas de las publicaciones desarrolladas en la tesis han sido ya incluidas en los manuales metodológicos de las instituciones que elaboran GPC o en herramientas para la elaboración de GPC [7, 11, 131]. En nuestro entorno, como se ha comentado anteriormente, los resultados de la tesis se han utilizado en el diseño de una nueva estrategia para actualizar las guías del Programa de GPC en el SNS [131].

Las diferentes publicaciones que constituyen la tesis son el resultado de la colaboración de un grupo multidisciplinario de investigadores nacionales e internacionales con un interés específico en este campo. Actualmente, en base a la actualización continua de la RS sobre los métodos de actualización de GPC (publicación II) [101], este grupo es autor del mayor número de publicaciones relevantes sobre el proceso de actualización de GPC (24,2 %; 8/33 [57, 97, 99-107, 114-121, 126-128, 135, 141, 146-150, 154-157]). La red de investigadores que ha impulsado el desarrollo de estas publicaciones se ha formalizado recientemente con la creación de un grupo de trabajo en G-I-N (*Updating Guidelines Working Group*) [158].

La mayoría de las publicaciones incluidas en la presente tesis son el resultado final de un proyecto financiado por una convocatoria competitiva del Instituto de Salud Carlos III (número de expediente PI10/00346) [101, 102, 104, 105]. El proyecto ha sido seleccionado en esta convocatoria por su relevancia, interés, aplicabilidad y capacidad de transferencia del conocimiento.

6.3.2. Limitaciones

Cada publicación presenta limitaciones inherentes a su diseño de estudio. Durante la elaboración de los protocolos de investigación, se identificaron las principales limitaciones y se consideraron estrategias para minimizar su impacto en los resultados (tabla 8).

Tabla 8. Principales limitaciones de las publicaciones incluidas en la tesis

Publicación	Identificación de las limitaciones	Estrategias para minimizar el impacto de las limitaciones
Publicación I: Encuesta internacional sobre el proceso de actualización de guías de práctica clínica	Sesgo de información (cuestionario autoadministrado *online)*	- Se pilotó y mejoró el cuestionario. - Se contactó con informadores clave de las instituciones que elaboran GPC.
	Baja tasa de respuesta (validez externa)	- Se enviaron tres correos electrónicos de recordatorio.
Publicación II: Revisión sistemática de los métodos de actualización de guías de práctica clínica	Sesgo de publicación	- Se realizó una búsqueda exhaustiva de la literatura donde se incluyeron diferentes fuentes de información.
	Elevada variabilidad entre estudios	- Se realizó una descripción narrativa y exhaustiva de los estudios incluidos.
Publicación III: Análisis de supervivencia de las recomendaciones	Limitada generalización de los resultados (validez externa)	- Se incluyeron cuatro GPC que abarcaban cuatro áreas amplias de salud (cáncer, enfermedades cardiovasculares, salud mental y estilos de vida).
Publicación IV: Evaluación de las recomendaciones actualizadas	Sesgo de selección	- Dos evaluadores identificaron y emparejaron los casos y los controles.
	Tamaño de la muestra limitado	- Se incluyeron todas las GPC NICE parcialmente actualizadas.
Publicación V: Evaluación de dos estrategias pragmáticas de búsqueda de la literatura	Adecuación del diseño de estudio (estudio descriptivo frente a estudio diagnóstico)	- Se evaluaron todas las referencias recuperadas en la búsqueda exhaustiva (patrón oro) pero no se evaluaron todas las referencias recuperadas con las búsquedas pragmáticas. - Se consideró que las estrategias pragmáticas no aportarían referencias clave adicionales.

Abreviaturas: GPC: guía de práctica clínica; NICE: *National Institute for Health and Care Excellence.*

La principal limitación del conjunto de publicaciones presentadas en la tesis es que se contextualiza el problema (publicaciones I, II y IV) [101, 103, 105] y se desarrolla investigación metodológica sobre el proceso (publicaciones III y V) [102, 104]; sin embargo, los resultados de la investigación no se han implementado ni evaluado en los programas de GPC.

Un paso intermedio significativo para implementar y evaluar los resultados de esta tesis ha sido su utilización en el diseño de una nueva estrategia para actualizar las guías del Programa de GPC en el SNS [131].

6.4. Implicaciones

6.4.1. Implicaciones para las instituciones que elaboran guías de práctica clínica

- Las instituciones que elaboran GPC deberían revisar las GPC de sus catálogos al menos cada tres años.
- El proceso de actualización de GPC debería ser más sistemático y explícito. Aunque por el momento se desconoce el método óptimo, las instituciones que elaboran GPC deberían detallar un proceso que incluya: 1) la identificación de nueva evidencia (estrategias de búsqueda de la literatura, fuentes de información o tipos de evidencia), 2) la evaluación del impacto de nueva evidencia, y 3) la revisión y, en caso necesario, la modificación de las recomendaciones. En la actualización del manual metodológico para la elaboración de GPC en el SNS se propone una nueva estrategia para actualizar las guías del Programa de GPC en el SNS [131]. Será necesario implementar y evaluar los resultados de la estrategia en el Programa de GPC en el SNS y revisar y actualizar la estrategia a medida que se disponga de más investigación metodológica y más experiencias empíricas.
- Las instituciones que elaboran GPC deberían mantener un equilibrio entre la elaboración de nuevas GPC y la actualización de las ya publicadas. Los

recursos se deberían redistribuir para conseguir mantener un catálogo de GPC actualizadas, desincentivando la inclusión de nuevos temas de salud que no puedan ser actualizados con garantías.

- Las instituciones que elaboran GPC deberían trabajar en colaboración para compartir conocimientos, experiencias, tareas y recursos relacionados con el proceso de actualización de GPC.

6.4.2. Implicaciones para la investigación

Algunas de las líneas prioritarias identificadas hasta el momento son:

- **Identificación de las señales de actualización:** Aunque nuestro grupo de trabajo ha conseguido importantes avances en este campo (sobre todo relacionados con la sistematización y transparencia del proceso) aún hay aspectos a mejorar relacionados con la identificación de nueva evidencia (estrategia de búsqueda, fuentes de información y tipo de evidencia) y la evaluación de su impacto.
- **Priorización en la actualización:** La priorización en las GPC tiene como objetivo asegurar que los recursos se destinan a problemas de salud relevantes para la población. En la elaboración de GPC tienen lugar, implícita o explícitamente, diferentes procesos de priorización, tanto en la selección del tema de la GPC, en la selección de las preguntas clínicas que abordará la GPC, como en la selección de las preguntas clínicas de la GPC que se actualizarán [11]. Hasta el momento, se han desarrollado algunos instrumentos para priorizar y actualizar GPC o RS; aunque la experiencia es limitada [68, 154]. En breve, nuestro grupo de trabajo iniciará un proyecto de investigación, financiado por el Fondo de Investigación Sanitaria - Instituto de Salud Carlos III (número de expediente PI15/00325), con el objetivo de elaborar y evaluar una herramienta de priorización para actualizar las preguntas clínicas de las guías del Programa de GPC en el SNS.
- **Actualizaciones rápidas:** Las revisiones rápidas son revisiones de la literatura que utilizan métodos para acelerar o simplificar el proceso de las

RS tradicionales [159]. Su metodología y utilidad aún es controvertida [160-163]. En el año 2013, NICE inició un programa piloto de actualizaciones rápidas de secciones de las GPC, aunque su impacto aún no ha sido evaluado [145].

- **Edición en la actualización:** La edición en el proceso de actualización de GPC tiene como objetivo mejorar la difusión de las recomendaciones actualizadas; para ello es necesario desarrollar formatos óptimos de presentación dirigidos a los diferentes grupos de interés (p.ej., usuarios, profesionales o gestores sanitarios). La experiencia de nuestro grupo de trabajo en el proyecto europeo DECIDE es un buen punto de partida para abordar este aspecto [136].
- **Sinergias entre las GPC y las RS en el campo de la actualización:** Por definición, las GPC se basan en RS de la información disponible, por lo tanto, todos los aspectos que se consideren en la actualización de las RS podrían ser adaptados potencialmente en la actualización de las GPC (p.ej., los métodos de actualización o la utilización de las RS actualizadas en la actualización de las GPC). Explorar cómo la actualización de RS puede alimentar la actualización de las GPC es un reto que hemos iniciado ya al comparar la investigación metodológica en ambas áreas (tabla 7).
- **Nuevas tecnologías e innovaciones en la actualización de las GPC:** Actualmente se están desarrollando *softwares online* para la elaboración de GPC, como por ejemplo el GDT [151] o el MAGIC [152]. Cómo estos *softwares online* mejorarán la actualización de las GPC constituye un campo de enorme potencialidad para evaluar.
- **Implementación de las actualizaciones:** El objetivo de la implementación de GPC actualizadas no difiere del de la implementación de las GPC originales, que consiste en producir cambios en la práctica orientados a mejorar los resultados asistenciales. La influencia de la actualización, frecuente o no, de las GPC en la implementación de las mismas será un aspecto a evaluar en el futuro, sobre todo cuando la actualización continua de las GPC sea una realidad.

Conclusiones

7. Conclusiones

- Las instituciones que elaboran GPC no tienen un proceso estandarizado para actualizar sus GPC (publicación I) [100].
- La investigación metodológica sobre el proceso de actualización de GPC es limitada y está focalizada en la identificación de las señales de actualización (publicación II) [101].
- Las recomendaciones de las GPC se desactualizan rápidamente, un 20% de las recomendaciones ya no están vigentes después de tres años de su elaboración (publicación III) [102].
- Para identificar señales de actualización se sugiere utilizar una estrategia de búsqueda restrictiva y continua de la literatura (cada 6 o 12 meses) y priorizar preguntas clínicas con una rápida velocidad de producción científica (publicaciones III y V) [102, 104].
- Para comunicar recomendaciones actualizadas se recomienda desarrollar un formato explícito y común para todas las guías de una institución que elabora GPC (publicación IV) [103].
- Es necesario continuar la investigación metodológica para optimizar y estandarizar el proceso de actualización de GPC, así como implementar y evaluar los resultados de dicha investigación en los programas de GPC.

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8. Bibliografía

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Anexos

9. Anexos

Anexo 1. Abreviaturas

AGREE	*Appraisal of Guidelines for Research and Evaluation*
AHRQ	*Agency for Healthcare Research and Quality's*
CER	*Comparative Effectiveness Reviews*
DECIDE	*Developing and Evaluating Communication Strategies to Support Informed Decisions and Practice Based on Evidence*
ECA	Ensayos clínicos aleatorizados
FI	Factor de impacto
G-I-N	*Guidelines International Network*
GPC	Guía de práctica clínica
GRADE	*Grading of Recommendations Assessment, Development and Evaluation*
IC	Intervalo de confianza
IOM	*Institute of Medicine*
MeSH	*Medical Subject Headings*
NICE	*National Institute for Health and Care Excellence*
OMS	Organización Mundial de la Salud
p.ej.	Por ejemplo
PICO	Paciente, intervención, comparador, desenlace (*outcome*)
PLUS	*Premium Literature Service*
Q1	Primer cuartil
Q2	Segundo cuartil
RS	Revisión sistemática
SIGN	*Scottish Intercollegiate Guidelines Netwok*
SNS	Sistema Nacional de Salud

Anexo 2. Publicaciones complementarias

Publicación VI: Martínez García L, Sanabria AJ, Araya I, Lawson J, Haynes RB, Rigau D, *et al*. Strategies to assess the validity of recommendations: a study protocol. Implement Sci. 2013;8:94.

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IMPLEMENTATION SCIENCE

STUDY PROTOCOL Open Access

Strategies to assess the validity of recommendations: a study protocol

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Abstract

Background: Clinical practice guidelines (CPGs) become quickly outdated and require a periodic reassessment of evidence research to maintain their validity. However, there is little research about this topic. Our project will provide evidence for some of the most pressing questions in this field: 1) what is the average time for recommendations to become out of date?; 2) what is the comparative performance of two restricted search strategies to evaluate the need to update recommendations?; and 3) what is the feasibility of a more regular monitoring and updating strategy compared to usual practice?. In this protocol we will focus on questions one and two.

Methods: The CPG Development Programme of the Spanish Ministry of Health developed 14 CPGs between 2008 and 2009. We will stratify guidelines by topic and by publication year, and include one CPG by strata.
We will develop a strategy to assess the validity of CPG recommendations, which includes a baseline survey of clinical experts, an update of the original exhaustive literature searches, the identification of key references (reference that trigger a potential recommendation update), and the assessment of the potential changes in each recommendation.
We will run two alternative search strategies to efficiently identify important new evidence: 1) PLUS search based in McMaster Premium LiteratUre Service (PLUS) database; and 2) a Restrictive Search (ReSe) based on the least number of MeSH terms and free text words needed to locate all the references of each original recommendation.
We will perform a survival analysis of recommendations using the Kaplan-Meier method and we will use the log-rank test to analyse differences between survival curves according to the topic, the purpose, the strength of recommendations and the turnover. We will retrieve key references from the exhaustive search and evaluate their presence in the PLUS and ReSe search results.

Discussion: Our project, using a highly structured and transparent methodology, will provide guidance of when recommendations are likely to be at risk of being out of date. We will also assess two novel restrictive search strategies which could reduce the workload without compromising rigour when CPGs developers check for the need of updating.

Keyword: Clinical practice guidelines, Diffusion of innovation, Dissemination and implementation, Evidence-based medicine, Information storage and retrieval, Knowledge translation, Methodology, Updating

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Background

Clinical practice guidelines (CPGs) are "statements that include recommendations intended to optimize patient care that are informed by systematic reviews (SRs) of evidence and an assessment of the benefits and harms of alternative care options" [1]. CPGs, just like SRs, become outdated as new evidence is published and require a periodic reassessment of research evidence to remain valid.

Guideline development institutions are concerned about the growing number of CPGs that are not regularly updated [2]. However, methodological handbooks include very little guidance about how to update guidelines other than to do so periodically [3-5]. In general, despite scant research [6], guideline programs endorse three years as a reasonable time period to update their guidelines [7].

Frequently, research in this area focuses on how to identify new evidence. However updating a GCP is a far more complex process and includes three main stages: 1) identifying important new evidence; 2) assess if the new evidence implies the updating of recommendations; and 3) the actual updating.

The identification of important new evidence that justifies an update is a challenge. Usually the original exhaustive search strategy that has been used to identify new evidence to update CPGs is used [8,9]. However, this strategy is very resource intensive, and a barrier to timely updates. Consequently, some studies have evaluated more restricted searches strategies to assess the need to update CPGs [10,11]. These strategies are likely to be sufficient to monitor new evidence and assess the need to update; however, more information is needed about the timing and type of search.

Nowadays, other resources could be used to make the process more efficient [12]. One is the McMaster Premium Literature Service (PLUS) database, from the McMaster Health Knowledge Refinery, which contains a searchable subset of pre-appraised primary studies and SRs from more than 120 journals and since 2003 [13,14]. The PLUS database includes substantially fewer articles than common databases, potentially increasing precision, with a small loss of sensitivity when updating. Recently, PLUS has been shown to be capable of identifying key articles that would be needed to update SRs [15]. These results would suggest that PLUS could prove an efficient method to update CPGs.

The updating guidelines working group

The Updating Guidelines Working Group goal is to draw on existing work and knowledge in the area of CPGs updating and to provide guidance for both guideline developers and users. Our group has run several studies about CPG updating. We conducted an international survey to identify current practices in CPG updating across guideline development institutions that showed high variability and a lack of standardization of the updating processes [3]. Additionally we conducted a SR that confirmed that there is very limited evidence about what is the optimal strategy or strategies for keeping CPGs up to date [6].

At present we are running several projects to fill this research gap. Our broader project "Assessing the validity and update strategies for CPG: analysis of the GPC National Program for National Health System in Spain" includes three studies addressing three pressing questions in this field: 1) what is the average time for recommendations to become out of date?; 2) what is the comparative performance of two restricted search strategies to evaluate the need to update recommendations?; and 3) what is the feasibility of a more regular monitoring and updating strategy compared to usual practice?.

Objectives

- Primary objectives:
  - ○Estimate average time for recommendations to become out of date.
  - ○Evaluate two alternative search strategies to assess the validity of CPGs recommendations.
- Secondary objectives:
  - ○Design a strategy to assess the validity of CPGs recommendations.
  - ○Evaluate resources used to perform each strategy.
  - ○Assess the agreement between study participants in identifying references that potentially could update CPGs recommendations.

Methods

Design

Intervention study in a cohort of CPGs recommendations.

Population and eligibility criteria

We will include CPGs developed in the CPG Development Programme of the Spanish Ministry of Health between 2008 and 2009 that are available in English (Additional file 1). We will select a sample of four CPGs. We will stratify guidelines by topic (cancer and palliative care, cardiovascular disease, mental health and metabolic disease) and then by publication year (2008 and 2009). We will select one guide for each topic and two guidelines published in 2008 and two guidelines published in 2009. We will choose the guidelines at random if there is more than one guideline by strata.

Strategies

We will develop a strategy to assess the validity of recommendations based on the identification (by collating evidence from clinical experts and by exhaustive literature searches) and evaluation of new evidence (Table 1).

Table 1 Strategy to assess the validity of recommendations

Stages	What	How	Who
Stage 1	Identification of clinical questions and recommendations	Review original CPG	Guideline methodologist from research group
Stage 2	Baseline survey	Recommendation basal survey (http://www.surveymonkey.com)	Clinical experts
Stage 3	Update exhaustive literature search	- Recover original exhaustive literature search	- Guideline methodologist from original CPG
		- Define the filters that will be used: 1) study design; 2) publication date	- Information specialist
Stage 4	References database by clinical questions	Reference management software	Information specialist
Stage 5	First references screening	Reference management software	Guideline methodologist from research group
	- Topic		
	- Study design		
	- Publication type		
Stage 6	References matching	Reference management software	Guideline methodologist from research group
Stage 7	Recommendations database	Statistic program	Guideline methodologist from research group
Stage 8	Second references screening	**Stage 8a** Reference survey to assess the updating effect: feasibility test	- Guideline methodologist from original CPG- Guideline methodologist from research group
	- Identification of relevant references		
	- Identification of key references	**Stage 8b** Sample size calculation	Statistician
	- Assess the potential changes in the recommendation	**Stage 8c** Reference survey to assess the updating effect (pdf forms)	- Guideline methodologist from original CPG
			- Guideline methodologist from research group
			- Clinical experts
Stage 9	Final report	Final report with study results	Guideline methodologist from research group
	- Recommendations still valid		
	- Recommendation needed update		

Abbreviations: CPG Clinical practice guideline.

A PLUS search strategy for the PLUS database (Table 2), and a restrictive search strategy (ReSe) for MEDLINE database (Table 3) will be developed.

Strategy to assess the validity of recommendations

- **Stage 1: Identification of clinical questions and recommendations.** We will extract the clinical questions, the recommendations (identified in the "Summary of recommendations" section) and their strength (SIGN [16] or GRADE [17] system) for each original CPG. Recommendations will be numbered and classified (prevention, screening, diagnosis or treatment).
- **Stage 2: Baseline survey.** Using a similar approach as Shekelle et al. [10] we will conduct a survey by e-mail (www.surveymonkey.com) with clinical experts for each CPG. They will evaluate whether they consider that recommendations are up to date and if they know any new studies that might change the recommendations (Additional file 2).

Table 2 PLUS search strategy

Stages	What	How	Who
Stage 1	Identification contents	Review original CPG	Guideline methodologist from research group
Stage 2	PLUS search	- Choose existing MeSH and SNOMED in PLUS database related with original CPG contents	PLUS information specialist
		- Define the filters that will be used: 1) population; 2) study purpose categories; 3) publication date	
Stage 3	Reference databases by CPGs	Reference management software	PLUS information specialist

Abbreviations: CPG Clinical practice guideline, *MeSH* Medical Subject Headings, *PLUS* Premium LiteratUre Service, *SNOMED* Systematized Nomenclature of Medicine.

Table 3 Restrictive search strategy

Stages	What	How	Who
Stage 1	Identification clinical questions	Review original CPG	Guideline methodologist from research group
Stage 2	Clinical questions eligibility	Include clinical questions with ≥ two explicitly PICO components	Guideline methodologist from research group
Stage 3	ReSe	**Stage 3a** Development ReSe serches	Guideline methodologist from research group
		Stage 3b Evaluation ReSe serches	
		Stage 3c Refinement ReSe serches	
		Stage 3d Define the filters that will be used: 1) study design; 2) publication date	
Stage 4	References database by clinical questions	Reference management software	Guideline methodologist from research group

Abbreviations: CPG Clinical practice guideline, *PICO* population, intervention, comparator and outcome, ReSe restrictive search.

We will perform the survey in a convenience sample of six clinical experts who participated in the CPG development. Original guideline methodologists will identify the survey participants: 1) four clinical experts representing the different areas covered by the guideline; and 2) two external clinical experts.

- **Stage 3: Update literature search.** We will recover the original exhaustive literature searches per clinical questions.
  Information specialists, preferably from the original guideline, will run the searches in the databases and apply the corresponding study design filters (randomised controlled trials [RCTs] or SRs) used in the original searches. Date filters will be established from the complete year in which the original search was completed onwards.
- **Step 4: References database by clinical question.** We will cluster the references obtained from the baseline survey and from the search. We will identify and eliminate duplicates and build a database by clinical questions with the references identified.
- **Step 5: First reference screening.** We will evaluate whether references are pertinent to the topic of interest, the study design (RCTs or SRs) and the publication type (we will include original articles or abstracts from conferences about original studies) (Additional file 3).
- **Step 6: Reference matching.** We will match pertinent references with one or more related recommendations.
- **Step 7: Recommendations database.** We will analyse the references databases to obtain recommendations: 1) without references; 2) with low turnover (≤ median number of references per recommendation); or 3) with high turnover (> median number of references per recommendation).
- **Step 8: Second reference screening.** We will design a recommendation form to sort out the pertinent references identified (Additional file 4). The form will contain: 1) relative to each recommendation: clinical question, recommendation, evidence quality and strength of recommendation; 2) relative to the related references : citation, ± PubMed Unique Identifier (PMID), abstract and study design; and 3) relative to the assessed references: a question to identify relevant references (references that could be use when considering the update of a recommendation but not necessarily trigger a potential update), a question to identify key references (references that could potentially trigger a recommendation update) and a question to assess the potential changes in the recommendation (in relation with population, intervention, comparison, outcome, quality of evidence, direction and/or strength of the recommendation [18]).
  We will send the recommendations forms to clinical experts and guidelines methodologist by e-mail (we will schedule three remainders every two weeks). Each form will be assessed by two clinical experts and one guideline methodologist. The disagreements will be resolved by consensus.
- **Step 9: Final report.** We will prepare a final report with recommendations that may need updating, in relation to the new evidence identified. The final report will be sent the corresponding institutions that developed these guidelines and the clinicians who will collaborate in the study.

PLUS search strategy

- **Stage 1: Identification topics.** We will extract the topics for each original CPG (identified in "table of contents").
- **Stage 2: PLUS search.** PLUS information specialists will develop the corresponding search strategies by matching existing Medical Subject Headings (MeSH) and Systematized Nomenclature of Medicine (SNOMED) with the CPGs topics. They will perform the searches applying PLUS population,

study purpose categories (therapy/prevention; diagnosis; prognosis; etiology; economics; clinical predication guide; differential diagnosis) and publication date filters. No filter will be applied to select for either original or review articles.

- **Stage 3: References database by CPGs.** PLUS information specialists will obtain a database of references by CPG.

Restrictive search strategy

- **Stage 1: Identification of clinical questions.** We will extract the clinical questions for each CPG.
- **Stage 2: Clinical questions eligibility.** Restrictive searches will be structured taking into account the PICO (population, intervention, comparator and outcome) structure of each clinical question. To develop each strategy we will include at least two PICO components from each question and their corresponding most representative keywords. The questions that do not explicitly include PICO components will be excluded.
  E.g. an explicit clinical question from the CPG for Prostate Cancer Treatment is "In patients with prostate specific antigen (PSA) relapse after radical prostatectomy, what kind of salvage intervention is safer and more effective?". A non explicit clinical question would be "What is the safest treatment and most effective option for a patient with prostate cancer at the locally advanced clinical stage?". In this question treatment alternatives are not clearly defined and make it a very broad question to be answered by the ReSe strategy [19].
- **Stage 3: ReSe.** To develop ReSe, based on original exhaustive search strategy, we will: 1) Select MeSH terms: If available, for each keyword we will find the most specific MeSH term (e.g. "Prostate-Specific Antigen" MeSH term for the population of the question "In patients with PSA relapse after radical prostatectomy, what kind of salvage intervention is safer and more effective?" [19]); 2) Select free text words [Tw]: for each keyword we will select the most relevant specifics free text words and search them in title (e.g. we would select "prostate[ti] AND specific[ti] AND antigen[ti]" free text words for the question "In patients with PSA relapse after radical prostatectomy, what kind of salvage intervention is safer and more effective?" [19]).
  We will evaluate if the ReSe retrieves all original references considered in the recommendations of the original CPGs. We will evaluate this by calculation the proportion of original references which are retrieved (sensitivity). If a ReSe search does not find all the original references (sensitivity <100%) we will refine it until it retrieves them all.
  For the refinement, if needed, we will be using one or both of the following options: 1) use of less specific MeSH terms; and/or 2) free text words to search in title or abstract. We will limit each ReSe by type of design. For each ReSe we will apply the filter Therapy of the Clinical Study Categories of Clinical Queries, using both narrow and broad scope, and we will apply the SR filter developed at the Health Information Research Unit, McMaster University [20]. Finally, we will perform the searches applying publication date filters.
- **Step 4: References databases by clinical questions.** For each clinical question we will obtain three databases, one using the therapy filter plus narrow scope, one using the therapy filter plus broad scope, and one using the SR filter.

Outcomes

Primary outcomes

- Average time for recommendations to become out of date.
- Proportion references that trigger a potential recommendation update (key references) identified by the alternative search strategies.

Secondary outcomes

- Resources used by strategy (time and participants).
- Agreement between clinical experts and guideline methodologists across references screening.

Analysis

Baseline characteristics

We will perform a descriptive analysis of CPGs recommendations included using mean and the standard deviation (for normal distribution), median and range (for abnormal distribution) or absolute and relative frequencies (and the associated 95% CI [confidence interval]), as appropriate.

Strategy performance

We will calculate the proportion and 95% CI of pertinent, relevant and key references identified by the exhaustive strategy. We will determine the number of key references from the exhaustive strategy (gold standard) retrieved by PLUS and ReSe strategies. We will estimate the mean time spent on each strategy and the proportion of researchers involved. We will evaluate the agreement between clinical experts and guideline methodologists about the assessment of key references from the exhaustive strategy (step 8). We will calculate the kappa coefficient and the 95% CI, and interpret it

according these criteria: poor (0.00-0.20); fair (0.21–0.40); moderate (0.41–0.60); substantial (0.61–0.80); and almost perfect (0.81–1.00) [21].

Survival analysis

We will perform a survival analysis of recommendations. We will define the event as the identification of a key reference related to a recommendation. We will consider: 1) recommendation inception date when the original search of each CPG started; 2) recommendation obsolescence date when first key reference is published for potential updated recommendations; and 3) last observation date when the update search of each CPG started for recommendations is still valid. Finally, we will calculate the survival time for the potential updated recommendations (obsolescence date - inception date) and for recommendations still valid (last observation date - inception date).

The estimated rate of survival of recommendations will be calculated using the Kaplan-Meier method and we will use the log-rank test to analyse differences between survival curves according to the topic (cancer, cardiovascular disease, mental health or metabolic disease), the purpose (prevention, screening, diagnosis or treatment), the strength of recommendations and the turnover (number of references linked per recommendation).

Sample size

In a feasibility test, we sampled 20.9% (52/249) of recommendations from selected CPGs and identified 17 key references; these warranted an update of eight recommendations (15.4% of recommendations from sample).

Accepting an alpha risk of 0.95 for a precision of ± 0.05 units in a two-sided test for an estimated proportion of 0.154, 112 recommendations randomly selected from the whole recommendations are required assuming that such population corresponds to 249 recommendations. It has been anticipated a replacement rate of 1%.

We will accept p value ≤ 0.05 as significant in all calculations. We will do the analysis with SPSS 18.0 (SPSS Inc., Chicago, Illinois, United States).

Discussion

In this protocol we are outlining a research project that will address two important questions about the updating of guidelines. Our project will provide evidence both: 1) the assessment of the validity of a cohort of CPGs and; 2) the evaluation of alternative search strategies to update CPGs recommendations.

Using a sample of four CPGs developed in the CPG Development Programme of the Spanish Ministry of Health we will evaluate two potentially more efficient search strategies for the updating of guidelines, and compare them to an exhaustive search strategy (our gold standard). We will include the McMaster Premium LiteratUre Service (PLUS), evaluated for the first time in this context, and an innovative restrictive search strategy. Finally, we will perform a survival analysis of recommendations providing additional evidence about this important topic.

Our work in the light of previous research

We recently systematically reviewed the research available about strategies for monitoring and updating CPGs [6]. We observed that there is limited evidence about what are the most optimal strategies for this. A restricted search is likely to be sufficient to monitor new evidence and assess the need to update; however, more information is needed about the timing and type of search with only the exhaustive search strategy having been assessed for the actual update of CPGs [6]. The development and evaluation of more efficient strategies is hence needed to improve the timeliness and reduce the burden of maintaining the validity of CPGs.

Only one previous study by Shekelle et al. [10] analysed the survival time of CPGs and suggested that these should be reassessed every three years. We built on the methodology proposed in this study addressing some of its shortcomings. First we will use an exhaustive search strategy, as opposed to the restrictive used by Shekelle et al. [10], that will likely provide a more reliable estimate. We will analyse our results in terms of recommendations out of date, instead of CPGs out of date. Finally, we will also publish a more detailed and explicit approach that will allow developers to be able to implement it in their institutions.

One previous study evaluated the McMaster Premium LiteratUre Service (PLUS) for the updating of SRs with promising results. We therefore decided to include this free of access service as a potential resource that could prove to be highly efficient.

Given all of the above, our research project is timely and fits well with the needs from the guideline community.

Strengths and limitations

Our study has several strengths. We will use a rigorous and transparent methodology, both to assess the validity of recommendations as well as the performance of the search strategies. We are building on previous research in this area improving its deficiencies [10] and implementing innovative solutions (e.g. standardized reporting) [6]. We will compare three search strategies, head to head, something that only one study, by Gartlehner 2004 et al. [11], has done so far. That study found that the restrictive search (review approach) identified fewer studies but included all-important references rated by their task force. Nevertheless they only evaluated their final strategy in two topics, the results being inconsistent. Finally our group has important expertise in guideline updating [3,6,22] and guideline methodology in general [23,24].

Our study has also some limitations. We will limit our searches by type of study including only SRs and RCTs, however, we think it is unlikely that we will miss important studies that will compromise the generalisability of our findings. Our study will not include the actual updating of the guidelines identified to be out of date and, hence, we will not evaluate whether our strategies are optimal for the final updating. Nevertheless, we believe that our outcome is a reliable surrogate of actual updating.

Implications of this study

We expect that our work will produce one or more efficient strategies to assess the validity of recommendations, and provide detailed guidance to replicate the process. Furthermore, our results will inform guideline developers about the expected validity of their recommendations in a representative sample of guidelines from a typical cohort of a National Guideline program. If the evaluated search strategies perform optimally, our work could be highly influential for evidence surveillance. Our results could therefore have important implications for a more efficient use of resources in the CPG arena.

Additional files

Additional file 1: Clinical practice guidelines developed within the framework of the CPG Development Programme of the Spanish Ministry of Health between 2008 and 2009.

Additional file 2: Recommendation baseline survey to clinical experts. Example on clinical practice guideline for secondary prevention of stroke (2009) [25].

Additional file 3: Reference screening by pertinence.

Additional file 4: Reference survey to assess the updating effect. Example on clinical practice guideline for secondary prevention of stroke (2009) [25].

Abbreviations

CI: Confidence interval; CPG: Clinical practice guideline; E.g.: *Exempli gratia*; MeSH: Medical subject headings; PICO: Population, intervention, comparator and outcome; PLUS: Premium literatUre service; PMID: PubMed unique identifier; PSA: Prostate specific antigen; RCT: Randomised controlled trial; ReSe: REstrictive SEarch; SNOMED: Systematized nomenclature of Medicine; SR: Systematic review.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

LMG, PAC, DR and IS participated in the conception of the study. All authors participated in the design. LMG and PAC drafted a first version of the protocol. All authors participated revising it critically for important intellectual content and have given final approval of the version to be published.

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IMPLEMENTATION SCIENCE

SYSTEMATIC REVIEW Open Access

Guidance for updating clinical practice guidelines: a systematic review of methodological handbooks

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Abstract

Background: Updating clinical practice guidelines (CPGs) is a crucial process for maintaining the validity of recommendations. Methodological handbooks should provide guidance on both developing and updating CPGs. However, little is known about the updating guidance provided by these handbooks.

Methods: We conducted a systematic review to identify and describe the updating guidance provided by CPG methodological handbooks and included handbooks that provide updating guidance for CPGs. We searched in the Guidelines International Network library, US National Guidelines Clearinghouse and MEDLINE (PubMed) from 1966 to September 2013. Two authors independently selected the handbooks and extracted the data. We used descriptive statistics to analyze the extracted data and conducted a narrative synthesis.

Results: We included 35 handbooks. Most handbooks (97.1%) focus mainly on developing CPGs, including variable degrees of information about updating. Guidance on identifying new evidence and the methodology of assessing the need for an update is described in 11 (31.4%) and eight handbooks (22.8%), respectively. The period of time between two updates is described in 25 handbooks (71.4%), two to three years being the most frequent (40.0%). The majority of handbooks do not provide guidance for the literature search, evidence selection, assessment, synthesis, and external review of the updating process.

Conclusions: Guidance for updating CPGs is poorly described in methodological handbooks. This guidance should be more rigorous and explicit. This could lead to a more optimal updating process, and, ultimately to valid trustworthy guidelines.

Keywords: Clinical practice guidelines, Evidence-based medicine, Handbooks, Methodology, Systematic review

Background

Clinical practice guidelines (CPGs) intend to patient care by providing recommendations about the benefits and downsides of best practice in healthcare [1]. If adequately implemented, CPGs have the potential of reducing variability and translating scientific research into clinical practice and consequently improve the quality and safety of healthcare [2-4].

However, scientific knowledge is in constant change; therefore CPGs need to be updated regularly to maintain validity [5]. The obsolescence of a CPG might occur because of new scientific research, including the development of new technologies in treatment and diagnosis alternatives, economic differences, or changes in values and preferences [6,7]. Generally, an updating process consists of three components: the identification of new evidence, the assessment of the need to update, and the formulation of new or modified recommendations [5,8-11]. Some authors suggest that an update is generally required after three to five years; however, little research has been undertaken so far [8,12,13].

Several institutions responsible for developing CPGs drafted their own methodological handbooks including methodology for developing and updating their CPGs. Some of these handbooks are very influential and often used in smaller organizations [6,14]. Even though the methodology developed greatly over the last years, the quality of CPGs is lagging behind [1,15,16]. A lack of compliance with state of the art methodology for developing CPGs has been found, and hence the methodological quality of CPGs remained very similar over the

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last two decades [17,18]. Little is known about the guidance for updating CPGs included in these handbooks [19,20]. Therefore, we systematically reviewed CPGs methodological handbooks to identify and describe the methodological guidance about updating.

Methods

Search strategy

We conducted a systematic search in September 2013 in MEDLINE (via PubMed, from 1966 onwards), using a combination of free text terms (Clinical Practice Guidelines, Clinical Guidelines, Guidelines, Methodolog*, Handbook*). The search strategy is available as supplementary data (Additional file 1). In addition, we searched: the database of the Guidelines International Network (http://www.g-i-n.net); the US National Guidelines Clearinghouse database (http://www.guidelines.gov); and the website of institutions that reported to use a methodological handbook in a previous international survey conducted by our group [12]. If necessary, we contacted organizations to obtain the handbooks.

Eligibility criteria

We included methodological handbooks that provide guidance on the updating process of CPGs. Handbooks that exclusively report methodologies for developing *de novo* guidelines were excluded. We included handbooks regardless of their language or publication status. When necessary, the handbook was translated.

Study selection

Two authors (RV, AJS) independently selected potential handbooks by reviewing titles and abstracts, and finally full text for a more detailed evaluation. Disagreements were initially resolved by consensus, and if necessary, with the help of a third author (PA-C).

Data extraction

Based on our previous experiences concerning updating, including an international survey [12] a systematic review [8] and additional relevant literature [5,6,9-11,14] we developed, reviewed, and piloted iteratively a case report form (CRF). After consensus, the following items are included in the CRF: characteristics of the handbook and institution, group responsible for updating CPGs, strategy for identifying new evidence, methodology for assessing the need for an update, methods for the literature search, evidence selection, evidence assessment, evidence synthesis, external review, and for the edition and dissemination of the updated CPG. The CRF can be made available upon request.

Two authors (RV, AJS) extracted independently the data of the handbooks accepted for inclusion. Disagreements were initially resolved by consensus, and if necessary, with the help of a third author (PA-C). While extracting the data, we considered a strategy to be specific if the handbook included a detailed methodology, enabling the reader to conduct the suggested strategy. We considered a non-specific strategy if not enough methodological guidance is provided to facilitate an adequate approach.

Data analysis

We used descriptive statistics to analyze the extracted data. We calculated absolute frequencies and proportions for all items. In addition, we conducted a narrative synthesis. Data analysis was performed using SPSS statistical software, version 18.0 (SPSS INC., Chicago, IL, USA). By consensus of two authors (RV, AJS), we collected relevant quotations within the themes included in the handbooks and provide these in the free text area.

Results

Handbooks selection

We screened the titles and abstracts of 1,992 references (Figure 1). We selected 94 articles for full-text review. Thirty-eight articles were excluded because they were not methodological handbooks. Additionally, ten handbooks were excluded because they exclusively focused on developing *de novo* CPGs. We could not locate eight articles and one article was a summary of an included handbook. Two handbooks were excluded because a more recent version was included. Additional file 2 provides an overview of the excluded documents. Finally, we included thirty-five handbooks (Additional file 3) [5,6,14,21-52].

Handbooks characteristics

In total, 48.6% of the included handbooks are developed by institutions based in Europe [5,6,14,21-34] mostly being public institutions (57.1%) (Table 1) [5,6,14,22-26,28,31,35-43]. One handbook (2.9%) addresses specifically the methodology of updating CPGs [5]; the others (97.1%) focus mainly on developing *de novo* CPGs, and include variable degrees of information about updating [6,14,21-52]. Fourteen handbooks (40.0%) are published between 2005 and 2010 [5,21,23,26,30,32,34,39,40,43,44,46,48,50].

Updating group

The persons responsible for updating the CPG are specified in twelve handbooks (34.3%). Seven handbooks (20.0%) state that the updating group should have a similar structure to the group that contributed to developing the CPG [6,14,23,30,37,44,45]. Four handbooks (11.4%) state that the group, responsible for updating the CPG, should be tailored to the new scope of the guideline [5,38,39,41].

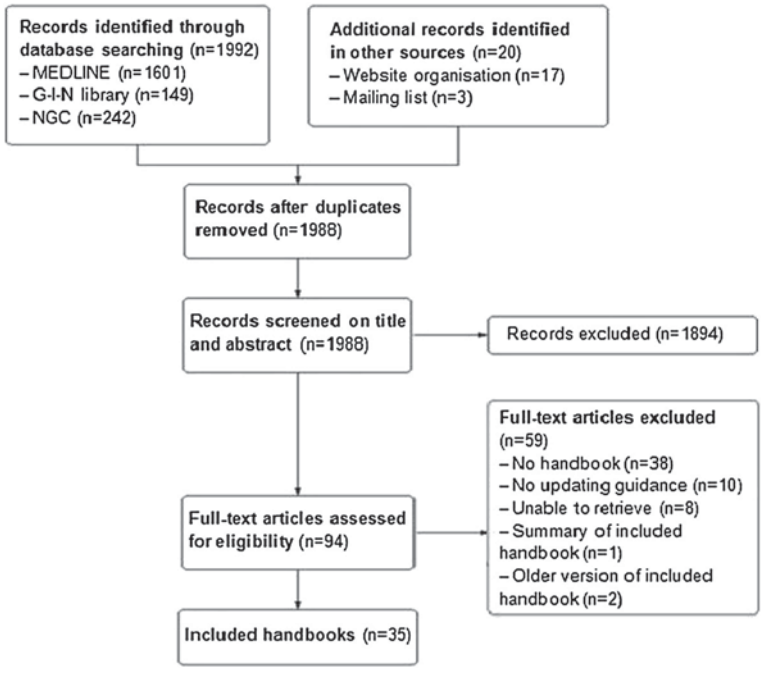

Figure 1 Flow chart of the screening literature process.

Time between updates

Twenty-five (71.4%) of the included handbooks recommend a time frame between publishing a CPG and commencing an updating process (Table 2), with two to three years being the most frequently recommended (40.0%) [5,6,14,22,27,28,30-32,37,39,41,45,46]. Furthermore, three handbooks (8.6%) suggest a time frame of less than one year [33,34,44], and eight handbooks (22.9%) include a four to five year time frame [24,36,38,42,43,47-49].

Identification of new relevant evidence

Eleven handbooks (31.4%) provide guidance on how to identify new relevant evidence. Of these eleven handbooks, six (17.1%) suggest using opinions or experiences from experts, users, or members of the original development group for identifying new relevant evidence [5,14,23,37,43,46]. Five handbooks (14.3%) provide guidance on conducting limited searches to identify new relevant evidence [5,37-39,47]. Furthermore, two handbooks (5.7%) propose the editorial board to have periodic meetings to discuss topics with experts [32,33]. One handbook (2.9%) suggests collecting alerts to identify newly published articles [5]. Externally reviewing the CPG by experts, who were not involved in developing the CPGs, is recommended by one handbook (2.9%) [47]. Two other handbooks (5.7%) provide a 'non-specific strategy' and only emphasize the importance of identifying new relevant evidence (Table 2) [23,28]. Figure 2 shows examples of relevant passages included in the handbooks.

Assessment of the need for an update

The methodology of assessing the need for an update is described in eight handbooks (22.8%). Six of them (17.1%) give guidance on how to assess the importance and relevance of the new evidence, the disagreement between the new evidence and current recommendations, and whether the new knowledge is not yet included [5,6,23,38,43,49]. Two handbooks (5.7%) recommend expert judgment to assess the need for an update [38,40]. Producing and regularly updating evidence summaries and assessing the need for an update with these summaries are described in one handbook (2.9%) (Figure 2) [32].

Updating recommendations

Eight handbooks (22.9%) provide guidance on what type of update is required in specific situations, by making a distinction between partial or full updates (Table 2) [5,6,14, 33,37,38,43,44].

Guidance for conducting a literature search strategy is included in seventeen handbooks (48.6%). Eight of them (22.8%) include guidance to adjust the original search strategy [5,6,14,24,26,27,37,43]. Four handbooks (11.4%) provide guidance on what kind of evidence to search for, including evidence based guidelines, health technology assessments, systematic reviews, and randomized controlled trials [14,27,38,41]. Two handbooks (5.7%) recommend to include a medical librarian or research officer in the team to conduct the literature searches [41,48]. Using multiple databases, *e.g.*, MEDLINE and Cochrane Library, in the search strategy is recommended by two handbooks

Table 1 Characteristics of institutions and handbooks

Institution characteristics	n	(%)
Continent		
Europe	17	48.6
North America	12	34.3
Oceania	4	11.4
International	2	5.7
Type of organization		
Public institution	20	57.1
Scientific society	9	25.7
Private organism	3	8.6
Other (Federal institute, NGO)	3	8.6
Number of years developing guidelines		
≤10 years	10	28.6
10 – 20 years	19	54.3
>20 years	6	17.1
Number of guidelines published		
≤5 per year	22	62.9
>5 per year	8	22.9
Unknown	5	14.3
Handbook characteristics		
Type of handbook		
Development CPG handbook	34	97.1
Update CPG handbook	1	2.9
Publication date		
Before the year 2004	8	22.9
Between 2005 – 2010	14	40.0
Between 2011 – 2013	8	22.9
Unknown	5	14.3

Table 2 Guidance reported in the included handbooks

Group responsible for updating CPG	n	(%)
Are the participants in the updating group specified?		
Yes	12	34.3
No	23	65.7
What members do the updating group consist of?		
Similar to the development team	7	20.0
Updating group specifically defined	4	11.4
Not defined	24	68.6
Identification of new evidence		
Time frame for updating		
≤1 year	3	8.6
2-3 years	14	40.0
4-5 years	8	22.9
No specific time frame indicated	10	28.6
Identification of new evidence		
Specific strategy	9	25.7
Non specific strategy	2	5.7
Not defined	24	68.6
Assessment of the need for an update		
Assessment of the need for an update		
Specific strategy	8	22.8
Not defined	27	77.1
Updating strategy		
Distinction between different updates (partial / full)		
Yes	8	22.9
No	27	77.1
Literature search		
Specific strategy	11	31.4
Similar to the development process	6	17.1
No strategy defined	18	51.4
Evidence selection		
Specific strategy	3	8.6
Similar to the development process	8	22.9
Not defined	24	68.6
Evidence assessment		
Specific strategy	5	14.3
Similar to the development process	8	22.9
Not defined	22	62.9
Evidence synthesis		
Specific strategy	3	8.6
Similar to the development process	5	14.3
Not defined	27	77.1

(5.7%) [41,43]. Furthermore, six handbooks (17.1%) suggest using the original strategy used for the development of the original guideline (Table 2, Figure 2) [23,28,34,40,44,50].

Eleven handbooks (31.4%) provide guidance for selecting adequate evidence in the updating process. Three handbooks (8.6%) provide specific guidance on how to discard irrelevant information [5,14,44]. Eight handbooks (22.9%) refer the reader to the development process for guidance on evidence selection [6,27,28,34,37,38,48,50].

Guidance for evidence assessment is provided in thirteen handbooks (37.1%). The assessment of the available evidence on the consistency, directness, validity or reliability is described in four handbooks (11.4%) [14,37,43,48]. Using critical appraisal frameworks, like OstFLCritica, is recommended in one handbook (2.9%) (Figure 2) [5]. Eight handbooks (22.9%) recommend the same original development strategy [6,23,27,28,34,38,44,50].

Table 2 Guidance reported in the included handbooks *(Continued)*

External review		
Specific strategy	5	14.3
Similar to development process	6	17.1
Non specific strategy	2	5.7
Not defined	22	62.9
Edition and dissemination		
Indication of changes		
Specific strategy	5	14.3
Not defined	30	85.7
Dissemination of the updated CPG		
Specific strategy	3	8.6
Not defined	32	91.4

Similarly, guidance for the evidence synthesis is described in eight handbooks (22.9%). Three handbooks (8.6%) recommend producing evidence tables including the characteristics of included studies, quality of randomized trials, results for continuous outcomes, and results for dichotomous outcomes [14,43,48]. Moreover, five handbooks (14.3%) direct the reader to the section with guidance for evidence synthesis used for developing *de novo* CPGs [5,6,34,44,50].

Guidance for an external review of the updated CPG is described in thirteen handbooks (37.1%). Five handbooks (14.3%) describe the process of external reviewing the updated CPG by multiple external reviewers [37,43,45,47,48]. Furthermore, two handbooks (5.7%) provides 'non-specific guidance' for conducting an external review of the updated CPG [28,38]. Six handbooks (17.1%) refer to the guidance described in the section of developing *de novo* CPGs [5,6,27,34,44,50].

Edition and dissemination

Two handbooks (5.7%) suggest to post a notification on the website of the institution whenever the need for an update is confirmed [28,29]. Five handbooks (14.3%) include a specific strategy for indicating the changes made in the update (Table 2, Figure 2). These handbooks recommended actions to identify the main changes in the update without any difficulty, including a table of updated evidence, summary reports, or highlight the updated parts in the text with a red font [5,32,33,37,47].

Three handbooks (8.6%) provide guidance on how to publish and disseminate the updated CPG. All three of them include methods to disseminate the updated CPG as widely as possible by publishing in relevant indexed journals [5], disseminate within the patient organization of the specific disease [48], or working together with

Identification of relevant new evidence:

- *"¨All comments received on published SIGN guidelines, or information on important new evidence in the field, or evidence of impacts on equality groups are fed back to the guideline development group, either for immediate response or for more detailed consideration on review of the guideline."*[14]
- *¨The editorial board meets once a month, and at every meeting, one speciality or a group of topics are discussed with 1-3 top experts on the field invited to attend.¨*[32]

Assessment of the need for an update:

- *¨The editorial team produces and updates evidence summaries continuously, and whenever the evidence summaries give rise to updates to the guidelines, the guidelines are updated.¨*[32]
- *¨At this point, the group should determine the extent of the update required. In addition, the composition of the group should be reassessed based on the planned extent of the update.¨*[38]

Updating process:

- *¨An update search is carried out looking for evidence based guidelines, HTAs, and systematic reviews produced since publication of the last version of a guideline. These searches are based on the key questions and search strategies used in the original guidelines.¨*[14]
- *¨Use of critical appraisal files like: OstFLCrítica, the free-access critical appraisal files IT application of Osteba.¨*[5]

Edition and dissemination:

- *"In EBM Guidelines, updated content appears in red font for 6 months after the update was made."*[32]
- "*Publish the changes using different methods: publishing in relevant indexed journals and/or the journals of the societies involved, indexing in their own website or in other international sources like the National Guideline Clearinghouse (NGC)."*[5]

Figure 2 Box of relevant comments.

public and private partners to reach specific groups and individuals [43].

Discussion

We systematically reviewed 35 methodological handbooks that provide some type of guidance on the updating process of CPGs. Our results show that overall the updating guidance is poorly described. Crucial elements in identifying new evidence, the assessment for the need for an update and the updating strategy itself, are generally lacking or include solely a reference to the development process. Our findings resonate with previous findings that suggest that there is a need for rigorous international guidance for updating CPGs [8,14].

Figure 3 summarizes an updating process framework for CPGs based on a previous systematic review from our group and the results of the present study [8]. The process of updating a CPG starts with assembling a group responsible for updating the CPG. However, we found that the majority of the institutions (65.7%) do not include any information about this first step. There is no clear consensus on who should participate in an updating process and, consequently different organizations use different strategies, depending on the characteristics of the organization and type of update. An updating working group, should consist of individuals with a background in methodology and experts in the field of interest, just as the original guideline group [5]. New developments in the clinical area, such as new technologies, might require including additional members with different expertise.

The actual updating process starts with identifying new relevant evidence. Currently, the period between the last publication of the CPG and starting the updating process (time frame) is frequently determined at the time of publication. The majority of the handbooks (62.9%) include a fixed time frame from two to five years, consistent with the results of previous research by Shekelle et al. [13]. This study including a sample of 17 guidelines, estimated that approximately one-half of the CPGs will be outdated after 5.8 years (95% CI: 5.0 – 6.6), and 10% are obsolete after 3.6 years (95% CI: 2.6 – 4.6) [13]. However, these average estimates can be misleading as CPG deteriorating speed is highly topic-specific, with some fields with rapid developments requiring more frequent surveillance for new evidence than others. Suboptimal time frames are likely to result in guidelines becoming obsolete or inefficient use of resources.

After identifying new relevant evidence, an assessment of the effect of this new evidence should be conducted, determining the need for an update [5,9-11]. We believe that this process is best conceptualized as a two-stage process because these are two independent stages with identifying possible new relevant evidence as first step, and, subsequently, deciding whether the identified evidence this evidence alters the validity of the current

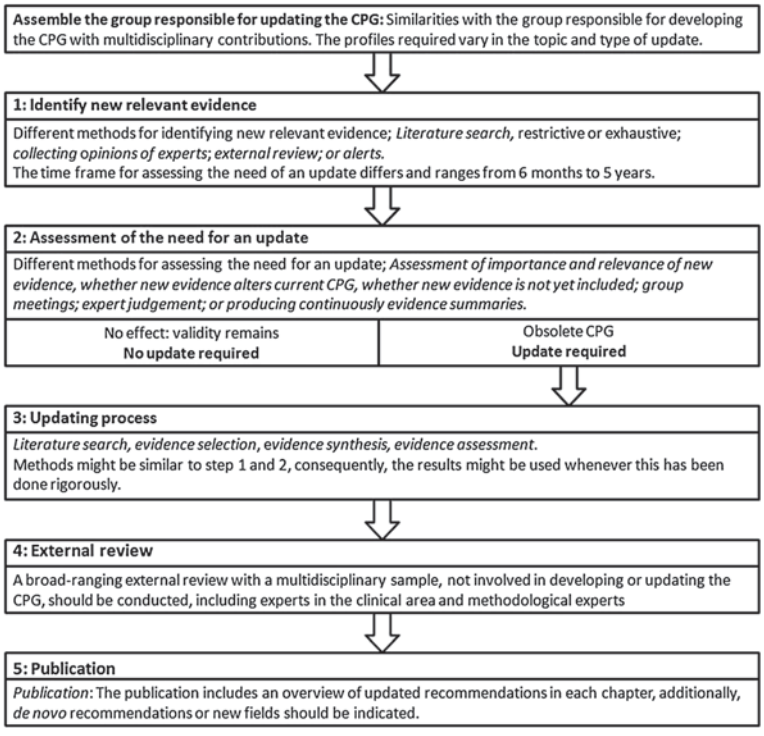

Figure 3 The updating process of CPGs.

recommendations as second step. However, at the moment, formal explicit procedures for assessing the need for an update are not available, with most of the included handbooks (77.1%) not providing explicit methods for assessing the need for an update.

When the need for an update is confirmed, the new evidence has to be incorporated in the current recommendations. However, less than one-half of the included handbooks state specific methods for this process. Previous studies suggest a model of assessing the need for an update using expert opinion, focused literature reviews, and consensus meeting [11,13]. A reference to the development process, often included in the evaluated handbooks, is not enough because the aim of any update should be to incorporate new evidence in the context of previous recommendations. More specific methods should be included in the handbooks.

A further problem is that several institutions use different terminology and consequently bring further confusion. Some institutions use the term 'monitoring' for the identification of new evidence and assessment of the need for an update, often within an abridged time frame [5,14,32,33,37,43,44,52]. In addition, the term 'dynamic updating' and 'living guideline' is used indistinctively, suggesting that CPGs are updated promptly and are always up-to-date [14,40,46]. Nevertheless, none of these handbooks provide guidance for conducting these processes and there is no consensus on when a guideline starts being dynamic or can be considered as a living guideline (Figure 3). We suggest avoiding these terms because it solely reflects the aspect of time between two versions. In Figure 3, we include a proposal regarding consistent terminology. Further research and consensus is needed in the international community about coherent terminology.

Our study is, as far as we know, the first study to examine the guidance about the updating process provided by CPG methodological handbooks. Our work has several strengths. We conducted a systematic and exhaustive search that included main databases, clearinghouses, and several institutions identified by a previous survey [12]. In addition, we contacted several organizations to retrieve non-published handbooks; therefore we believe that we included most of the existing handbooks. We independently performed eligibility and data extraction with a CRF developed and piloted by a group with extensive experience in the field.

Our study, however, might be subject to some limitations. It is possible that, after our extensive literature search, we did not identify all available handbooks because some are not indexed nor published, and only used for in-house purposes. However, unpublished handbooks are likely to be of lower quality. If this is the case, it would imply that we overestimated the quality of the updating guidance, further strengthening our conclusions. Finally, the reported methods in handbooks might not reflect the actual updating in CPGs. However, we believe that this is unlikely given previous results of our international survey with CPG developers [12].

Conclusion

Our work shows that updating guidance included in CPGs methodological handbooks is overall of poor quality. CPGs developers should provide more explicit and rigorous guidance and standardize the terminology used. This could, consequently, lead to a more optimal updating process of CPGs, and ultimately, to valid trustworthy guidelines.

Additional files

Additional file 1: Search strategy (September 16, 2013).

Additional file 2: List of excluded studies after full-text evaluation [in alphabetic order].

Additional file 3: Included handbooks [ordered by organisation].

Abbreviations

CPGs: Clinical practice guidelines; CRF: Case report form.

Competing interests

PA-C is an author of one of the included handbooks. For this reason, other authors completed data extraction for this handbook.

Authors' contribution

Conceiving the review: PA-C, LM. Design of the study: PA-C, LM, RV, AJS. Undertaking searches: IS, RV. Screening and extracting data: RV, AJS. Writing the review: RV, AJS, PA-C. Comment and editing of review drafts: all authors. All authors read and approved the final manuscript.

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MEDICINA CLINICA

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Editorial

Guías de práctica clínica: viejos y nuevos retos

Clinical guidelines: Old and new challenges

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La popularidad de las guías de práctica clínica (GPC) es actualmente innegable. Se ha pasado de haber 70 guías indexadas en PubMed en 1990, a ser hoy en día más de 2.000. La definición actual las presenta como «documentos que incluyen recomendaciones destinadas a optimizar la atención al paciente, formuladas en base a revisiones sistemáticas de la evidencia científica y a una evaluación de los riesgos y beneficios de las diferentes opciones de manejo[1]. A lo largo de las últimas 2 décadas, la definición, al igual que la metodología, de las GPC ha evolucionado incorporando un mayor énfasis en la necesidad de dotar de mayor rigor y transparencia a su elaboración.

Este énfasis en los métodos refleja la necesidad que siempre ha existido por mejorar la elaboración de las GPC, dados los potenciales problemas y limitaciones que pueden presentar. Afortunadamente diversas iniciativas se pusieron en marcha para paliar esta situación. Por un lado, instituciones pioneras en el campo de la elaboración de las GPC, como el *National Institute for Health and Care Excellence* (NICE) en el ámbito internacional o, en nuestro entorno, el Programa de GPC en el SNS del Ministerio de Sanidad (coordinado por GuíaSalud: http://www.guiasalud.es/web/guest/gpc-sns), publicaron manuales metodológicos[2,3]. Por otro lado, se elaboró el instrumento *Appraisal of Guidelines for Research and Evaluation (AGREE II)*,, estableciendo las bases para la evaluación de la calidad de las GPC[4]. Por último, la iniciativa *Grading of Recommendations Assessment, Development and Evaluation* (GRADE) ha sistematizado y estandarizado la evaluación de la calidad de la evidencia y la graduación de las recomendaciones[5,6].

Los clínicos han respondido positivamente a estos esfuerzos, y en general tienen una actitud positiva hacia las guías, siendo su recurso de consulta más frecuente. Los profesionales confían en las GPC y esta confianza está íntimamente ligada al rigor de sus métodos y a la confianza en sus autores[7,8]. No obstante, a pesar de este esfuerzo por mejorar la calidad de las GPC, aún hay importantes retos por superar. Revisiones sobre la calidad de las GPC muestran cómo hay un amplio margen de mejora, sin un avance sustancial en las 2 últimas décadas[9,10]. Esta falta de rigor metodológico en la elaboración de GPC conduce a que diferentes instituciones difieran en sus recomendaciones, siendo más intervencionistas cuanto menor es su rigor[11].

Esta variabilidad en la calidad es probablemente debida, en parte, a que para elaborar guías con rigor son necesarios muchos recursos y un alto grado de especialización. Dentro de la actual proliferación de las GPC, muchas organizaciones no disponen habitualmente de la capacidad para realizarlas adecuadamente. La complejidad alcanzada ha llevado a que algunos autores aboguen por estudiar el impacto real de este refinamiento metodológico, así como a la necesidad de buscar un equilibrio para que esta sofisticación no llegue a ser contraproducente.

Entre las asignaturas pendientes, una crucial y que ha sido relegada a un segundo plano es el proceso de revisión y actualización de las GPC. Si no existen garantías de que una GPC puede ser actualizada adecuadamente no es posible asegurar la validez de las recomendaciones[12]. Por otro lado, desde el punto de vista metodológico existen todavía retos en la elaboración de GPC que deben resolverse. Entre ellos, destacaríamos el abordaje de los conflictos de interés de los autores[13], la consideración de los valores y preferencias de los pacientes en la formulación de recomendaciones[14], la incorporación del uso de recursos y los costes o la consideración de la pluripatología y comorbilidad[15].

Hasta hace muy poco la mayoría de las instituciones elaboradoras han dado la espalda a la actualización, menos atractiva cara a la galería, enfocándose fundamentalmente en la elaboración. Probablemente debido a este motivo, la mayoría no disponen de un proceso formal para la evaluación y actualización de sus GPC[16,17]. No obstante, una guía desactualizada es poco útil porque sus recomendaciones pierden vigencia.

Para mantener una guía actualizada se requiere una revisión periódica de la nueva literatura científica que pueda identificar cambios significativos en la GPC. Se deben valorar no solo los aspectos relacionados con el alcance de las preguntas clínicas incluidas (pacientes, intervención, comparadores, o desenlaces de interés), sino también con los factores que influyen en la formulación de las recomendaciones (calidad de la evidencia, balance entre beneficios y daños, preferencias y valores de los pacientes y en el uso de recursos y costes)[14]. La revisión y actualización de una GPC es un proceso cíclico que requiere de una inversión importante de recursos.

Asimismo, la investigación sobre esta crucial etapa de la vida de las GPC es muy escasa todavía[12]. Proyectos recientemente impulsados en

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nuestro entorno muestran que la vigencia de las recomendaciones es a menudo limitada y variable. Afortunadamente, estas investigaciones han permitido la formulación de estrategias potencialmente más eficientes para la actualización de GPC[18,19].

En estas circunstancias, los grupos elaboradores sufren, impotentes, la imposibilidad de mantener sus documentos actualizados. En nuestro entorno, el Programa de GPC en el SNS también se debate entre la necesidad de abordar nuevos temas y la necesidad de actualizar los existentes, necesidad de actualizar los existentes.

Los conflictos de interés de los autores pueden influir sobre el sentido en el que se formulan las recomendaciones de una GPC[20], sin embargo, muchas GPC no indican los conflictos de sus autores[21]. Existe una necesidad de mejorar la metodología de evaluación de los conflictos de interés en las GPC. Actualmente, se han desarrollado propuestas que incluyen estrategias como la de excluir parcial o totalmente a los autores con conflictos importantes[13]. En este sentido, en nuestro entorno, el Programa de Elaboración ha mejorado su metodología y ha incorporado un procedimiento explícito que permite una mejor evaluación de los conflictos de interés y que será próximamente implantado.

Cuando se formulan recomendaciones o cuando se toman decisiones en la práctica clínica se ponderan los beneficios y riesgos/carga de la enfermedad (por ejemplo, aumento de supervivencia frente a toxicidad del tratamiento en mujeres con cáncer de mama localizado) de las alternativas consideradas. Al realizar esta ponderación se asigna una importancia relativa diferente para cada uno de los desenlaces de interés. Es necesario reflejar de manera explícita la importancia relativa de los desenlaces de interés en la formulación de recomendaciones, puesto que a menudo los pacientes asignan valores diferentes (los pacientes más jóvenes con cáncer suelen priorizar la supervivencia sobre la toxicidad, mientras los más mayores puede haber variabilidad) y, por otro lado, no es infrecuente que el punto de vista de los profesionales sea también diferente[22].

Hasta ahora los grupos elaboradores de GPC no son explícitos en este tipo de decisiones, ni en sus implicaciones. Habitualmente el proceso de realizar el balance entre beneficios y riesgos/carga de la enfermedad se realiza de manera implícita casi exclusivamente, considerando los valores del grupo elaborador. Solo recientemente, gracias a la iniciativa GRADE, se está comenzando a considerar este aspecto de manera más explícita, aunque todavía muy tímidamente y de manera muy variable.

El valor o importancia que se asigna a los desenlaces de interés debería estar basado, al igual que muchos otros aspectos (por ejemplo, costes o aceptabilidad), en la mejor evidencia disponible, y reflejar de la manera más fehaciente los valores y preferencias de los pacientes. Existen diversas formas de considerar la importancia relativa de los desenlaces de interés. Estos pueden ser obtenidos, entre otras maneras, a partir de una revisión de la literatura científica disponible[23], incorporando pacientes en los grupos elaboradores, y/o mediante la explicitación por parte de los grupos elaboradores de qué importancia han concedido a los diferentes desenlaces de interés. En este último caso, esta valoración debe ser el resultado de un proceso de reflexión de los profesionales clínicos, que tomen decisiones compartidas con pacientes similares a las de la situación clínica de interés, en el cual se intenten reflejar los valores de este tipo de pacientes.

Este auténtico reto es parte del desafío, aún mayor, de la incorporación de la perspectiva de los pacientes de manera amplia (por ejemplo, incluyendo aspectos como la aceptabilidad o factibilidad), incorporándola potencialmente a las distintas fases del proceso de elaboración de las GPC. Si bien existen algunas experiencias, la evaluación de la participación de los pacientes y su impacto es muy escasa en la literatura médica, y no se conoce la forma óptima de llevarla a cabo[24].

Dado que los recursos económicos son limitados, la toma de decisiones debe basarse no solo en aspectos relacionados con la efectividad de las intervenciones evaluadas, sino también en las diferencias en cuanto al consumo de recursos derivados de la adopción de las diferentes alternativas y sus costes. Es por ello que el uso de recursos y costes (URC) es uno de los factores determinantes en la formulación de recomendaciones para la práctica clínica. La importancia y complejidad de todos los aspectos relacionados con el proceso de incorporación del URC merecen ser tenidas en cuenta desde las etapas iniciales del proceso de elaboración de las GPC. Es necesario explicitar desde un inicio la perspectiva que la GPC adoptará (por ejemplo, del sistema sanitario/poblacional o del paciente individual). La adopción de una u otra perspectiva determinará cómo se tienen en cuenta el URC y otros factores[25]. Por ejemplo, en el caso de las GPC del Programa de GPC en el SNS, el marco es necesariamente el del SNS, y se deberían tener en cuenta el URC, así como otros factores como la equidad, la factibilidad y la aceptabilidad.

Aunque es necesario contar con un proceso explícito para incorporar el URC a las GPC, pocas instituciones describen en sus manuales metodológicos de desarrollo de GPC este proceso con un mínimo de detalle. El NICE es una de las excepciones[2]. En nuestro entorno, la valoración de este aspecto en las GPC es testimonial. En el manual metodológico de elaboración de GPC para Programa de GPC en el SNS, se mencionan los costes como uno de los aspectos a tener en cuenta en el desarrollo de recomendaciones, si bien esta temática no fue abordada en dicho manual[3].

Las evaluaciones económicas son el mejor diseño para tomar decisiones sobre el URC porque permiten el análisis comparativo entre las diferentes alternativas evaluadas[26]. No obstante, dada la limitación existente en cuanto a tiempo, recursos y conocimientos, en la mayoría de los grupos elaboradores de GPC es difícil poder realizar, en caso de necesitarse, evaluaciones económicas formales para cada una de las preguntas de una guía.

Muy pocas instituciones, todas fuera de nuestro entorno, cuentan con economistas de la salud que participan dando apoyo en las reuniones iniciales de los grupos elaboradores[2]. Una de las primeras aproximaciones que proponen es realizar una búsqueda en la literatura médica de estudios económicos relevantes, evaluando su calidad y realizando una síntesis de los resultados encontrados[2,25]. Sin embargo, dada la limitada disponibilidad y el carácter específico de contexto de las evaluaciones económicas, la aplicabilidad de sus resultados a contextos diferentes (por ejemplo, con otra perspectiva, otro sistema sanitario, otro año, etc.) sigue siendo un reto. Por otro lado, se ha observado que, a pesar de la disponibilidad de estudios económicos rigurosos y directamente aplicables al contexto en el cual se desarrollan las GPC, su incorporación sigue siendo escasa[27]. En el caso de ausencia de estudios que sean directamente aplicables, la realización de nuevas evaluaciones económicas puede ser necesaria, aunque poco realista en la mayoría de las instituciones. Es por ello que sería necesario desarrollar métodos para la incorporación del URC en instituciones o países que no dispongan de los recursos necesarios.

Habitualmente las GPC se dirigen a un único problema de salud, sobre todo a los más prevalentes (HTA, diabetes, EPOC, etc.), sin tener en cuenta que la comorbilidad es una norma en estas afecciones, sobre todo en los pacientes de mayor edad[28]. Aplicar las GPC «monotemáticas» en vigor a un paciente de estas características conduce de manera habitual a la polimedicación, y a una acumulación de recomendaciones de difícil cumplimiento para el paciente y su familia[29]. Para que las GPC sean realmente útiles en la atención sanitaria deben resolver este nuevo desafío metodológico[15].

Elaborar GPC con rigor y mantenerlas actualizadas es una tarea compleja. Como hemos visto, requiere de muchos recursos y competencias avanzadas en múltiples campos, desde la documentación bibliográfica, a la epidemiología clínica o la economía de la salud. Una vez elaboradas, requieren estrategias concretas para

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mantenerlas actualizadas. Por todo ello, cada vez se hace más acuciante la colaboración entre organizaciones elaboradoras, en especial entre las sociedades científicas, para no duplicar esfuerzos[30].

El Programa de GPC en el SNS es un marco para conseguir sinergias. Así, ha comenzado ya la actualización de algunas guías y del manual metodológico de elaboración, que incorporará la consideración de los recursos y costes, el abordaje de GPC dirigidas a pacientes con pluripatología, y una propuesta de monitorización y actualización. No obstante, para seguir avanzando se requiere una inversión más ambiciosa por parte del Ministerio de Sanidad, para acercarnos a una situación remotamente parecida a la del NICE. Es necesaria una apuesta centralizada de más calado que permita la planificación a largo plazo. Aunque las circunstancias actuales no son las mejores, esperamos que nuestros gobernantes tengan la visión y audacia necesarias para llevarla a cabo.

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Anexo 3. Anexos de las publicaciones

Publicación I: Encuesta internacional sobre el proceso de actualización de guías de práctica clínica

Documento adicional 1: Encuesta sobre el proceso de actualización de guías de práctica clínica

A. Organization characteristics

A1. What is the name of your organization?

A2. Which kind of organization is your institution?

☐ Public institution
☐ Private organism
☐ Scientific society
☐ Other

If other, please specify……..……..……..

A3. How many years have you been developing guidelines?

☐ Less than 3 years
☐ 3-5 years
☐ 6-10 years
☐ More than 10 years

A4. How many guidelines do you publish per year?

☐ Less than 3 per year
☐ 3-5 per year
☐ 6-10 per year
☐ More than 10 per year

A5. Does your organization update its guidelines?

☐ Yes
☐ No

B. The updating process

B1. How many guidelines per year do you check to asses the need of updating?

☐ Less than 3
☐ 3-5 per year
☐ 6-10 per year
☐ More than 10 per year
☐ Varies.

If varies, please specify……..

B2. How many do you actually update (partially or globally)?

☐ None
☐ Less than 3
☐ 3-5 per year
☐ 6-10 per year
☐ More than 10

☐ Varies

If you know the actual percentage of Guidelines do you update, please specify……...

B3. Does your organization have a formal procedure to update your guidelines or recommendations?

☐ No

☐ Yes

If YES please specify if it is published somewhere and if available on-line provide the link..

B4. Do you have a specific time frame to decide when to check for the need of updating a guideline?

☐ No, it varies

☐ Less than 3 years

☐ 3 years

☐ 4-5 years

☐ More than 5 years

B5. Who decides the need for updating? (More than one option possible)

Guideline coordinator	☐ No	☐ Yes
Guideline group	☐ No	☐ Yes
Expert committee	☐ No	☐ Yes
Standing Editorial staff	☐ No	☐ Yes
Other	☐ No	☐ Yes

If guideline group please specify if the original group or just a few. If other please specify….

B6. Which parts of the guideline do you check?

Key recommendations	☐ No	☐ Yes	☐ Partially
All recommendations	☐ No	☐ Yes	☐ Partially
Key questions	☐ No	☐ Yes	☐ Partially
Full text	☐ No	☐ Yes	☐ Partially
Patient information	☐ No	☐ Yes	☐ Partially
Annexes	☐ No	☐ Yes	☐ Partially

B7. Do you have a formal process to decide when a guideline becomes out of date (e.g. if new evidence available)?

☐ No

☐ Yes

If yes, please specify……

B8. Do you have a formal method to reach a consensus or to decide whether to update just a section or the full guideline?

☐ No

☐ Yes

If yes please specify (Delphi, voting, etc.)……

B9. Who participates in the updating process?

Original guideline authors	☐ No	☐ Yes	☐ Sometimes
Original information managers/specialist	☐ No	☐ Yes	☐ Sometimes
Original external-reviewers	☐ No	☐ Yes	☐ Sometimes

New group of experts	☐ No	☐ Yes	☐ Sometimes
Patients	☐ No	☐ Yes	☐ Sometimes
Staff of organization	☐ No	☐ Yes	☐ Sometimes
Others	☐ No	☐ Yes	☐ Sometimes

If others or sometimes please specify……..……

B10. What kind of searches do you run when updating?

Original search strategies	☐ No	☐ Yes
Original searches strategies modified to be specific rather than sensitive	☐ No	☐ Yes
Original search strategies plus some horizon scaning (eg. new treatments or technology)	☐ No	☐ Yes
Other	☐ No	☐ Yes

Please, comment your answer……..……

B11. Has the updating process used in your organization been piloted?

☐ No
☐ Yes

If yes, please specify……

B12. How rigorous do you think is the updating process that you use?

☐ Unreliable
☐ Not very reliable
☐ Could certainly be more rigorous
☐ Moderately rigorous
☐ Very rigorous

B13. Do you check for other guidelines about the same topic of interest when developing a guideline?[a]

☐ No
☐ Yes

B14. In case you do, do you trust their evidence synthesis and update only from the search date of this guideline? [a]

☐ Yes
☐ No, we only use them to check if we miss relevant references
☐ No, never
☐ Others

If others, please specify……..……

B15. Does your organization adapt CPG when developing your own? [a]

☐ No
☐ Yes

B16. In case you do, does your organization take part in the ADAPTE Collaboration? [a]

☐ No
☐ Yes

C. Updating and users

C1. Do you alert guideline users on your website when a guideline is older than a certain number of years or when there is a risk of being outdated?

☐ No

☐ Yes

If yes please specify how you do it……

C2. How do you alert guideline users when a modification has taken place?

D. Updating CPG in the future

D1. Do you think is it worth having living guidelines? Considering "living" as guidelines that are continuously being monitored and updated.

☐ No

☐ Yes

☐ Not sure

Regardless of your answer please comment pros and cons……

D2. Do you have plans in your organization to set up a protocol to improve the updating of your guidelines?

☐ No

☐ Yes

☐ Maybe

If yes, please specify……

D3. Would your organization be willing to share resources to optimize guideline updating and/or developing process internationally?

☐ No

☐ Yes

☐ Not sure

If not sure please tell us why or what would it depend on……..……

D4. Which resources would you be willing to share with other organizations?

Key questions	☐ No	☐ Yes	☐ Not sure	☐ Not worth it
Search strategies	☐ No	☐ Yes	☐ Not sure	☐ Not worth it
References	☐ No	☐ Yes	☐ Not sure	☐ Not worth it
Evidence tables	☐ No	☐ Yes	☐ Not sure	☐ Not worth it
Evidence synthesis	☐ No	☐ Yes	☐ Not sure	☐ Not worth it
Considered judgement forms (document that explicitly includes the factors taken into account when grading recommendations)	☐ No	☐ Yes	☐ Not sure	☐ Not worth it

E. Please comment about any issues you find relevant, and you want to mention, regarding updating clinical guidelines that might be of use for our survey. Thank you for your help!

[a]Exluded item

Documento adicional 2: Instituciones incluidas en el estudio

	Name of organizations (alphabetical classification by name organization)	Countries	Source of contact
1	Agency for Quality in Medicine	Germany	G-I-N
2	American College of Physicians	USA	G-I-N
3	American Urological Association	USA	G-I-N
4	American Academy of Otolaryngology	USA	G-I-N
5	American Academy of Paediatrics	USA	NGC
6	American College of Cardiology	USA	Expert Committee
7	American College of Chest Physicians	USA	G-I-N
8	American College of Obstetricians and Gynaecologists	USA	NGC
9	American College of Radiology	USA	NGC
10	Basque Office for Health Technology Assessment	Spain	G-I-N
11	Belgian Health Care Knowledge Centre	Belgium	Expert Committee
12	Brazilian Medical Association	Brazil	G-I-N
13	British Columbia Council on Clinical Practice Guidelines	Canada	NGC
14	CARI Guidelines	Australia	G-I-N
15	Catalan Agency for Health Technology Assessment and Research	Spain	G-I-N
16	Current Care / Duodecim - Finnish Medical Society	Finland	G-I-N
17	Domus Medica vzw; Flemish College of General Practitioners	Belgium	G-I-N
18	Duodecim Medical Publications Ltd	Finland	G-I-N
19	Dutch Association of Comprehensive Cancer Centres	Netherlands	G-I-N
20	Dutch Institute for Healthcare Improvement	Netherlands	G-I-N
21	German Cancer Society	Germany	G-I-N
22	Guidelines Advisory Committee	Canada	NGC
23	Health Austria, Federal Institute for Quality in Health Care	Austria	G-I-N
24	HTA Unit, Ministry of Health, Malaysia	Malaysia	G-I-N
25	Hungarian Ministry of Health	Hungary	Expert Committee
26	Infectious Diseases Society of America	USA	G-I-N
27	Italian National Institute of Health	Italy	G-I-N
28	Joanna Briggs Institute	Australia	G-I-N

29	Kidney Disease Improving Global Outcomes	USA	NGC
30	Michigan Quality Improvement Consortium	USA	NGC
31	National Heart Foundation of Australia	Australia	G-I-N
32	National Institute for Clinical Excellence	United Kingdom	G-I-N
33	New Zealand Accident Compensation Corporation	New Zealand	G-I-N
34	New Zealand Guidelines Group	New Zealand	G-I-N
35	Registered Nurses Association of Ontario	Canada	NGC
36	Royal Dutch Society for Physical Therapy	Netherlands	G-I-N
37	Scottish Intercollegiate Guidelines Network	United Kingdom	G-I-N
38	Trimbos Institute Netherlands Institute of Mental Health & Addiction	Netherlands	G-I-N
39	United States Preventive Services Task Force	USA	NGC

Abbreviations: G-I-N: Guidelines International Network; NGC: National Guideline Clearinghouse

Publicación II: Revisión sistemática de los métodos de actualización de guías de práctica clínica

Documento adicional 1: Estrategia de búsqueda de la literatura para identificar métodos de actualización de guías de práctica clínica

MEDLINE (PubMed) - June 15th 2012

#1	Clinical Practice Guideline*[tw]	5830
#2	Clinical guideline*[tiab]	5509
#3	Guideline*[ti]	42590
#4	Updat*[tw]	69510
#5	Up to date[tw]	9969
#6	(#1 OR #2) OR #3	48302
#7	#4 OR #5	78504
#8	#6 AND #7	2781

The Cochrane Methodology Register (*The Cochrane Library*) - June 15th 2012

#1	clinical practice guideline*	7963
#2	clinical guideline*	11911
#3	guideline*:ti	1568
#4	(#1 OR #2 OR #3)	12425
#5	updat*	374634
#6	up to date	105931
#7	(#5 OR #6)	404782
#8	(#4 AND #7)	10503

There are **126** results out of 15388 records for: "(#4 AND #7) in Cochrane Methodology Register"

Tags used in PubMed search syntax

- **[ti]:** Words and numbers included in the title of a citation.
- **[tiab]:** Words and numbers included in the title, abstract, and other abstract of a citation.
- **[tw]:** Includes all words and numbers in the title, abstract, other abstract, MeSH terms, MeSH Subheadings, Publication Types, Substance Names, Personal Name as Subject, Corporate Author, Secondary Source, and Other Terms (see Other Term [OT] above) typically non-MeSH subject terms (keywords), including NASA Space Flight Mission, assigned by an organization other than NLM.

Documento adicional 2: Publicaciones excluidas del estudio

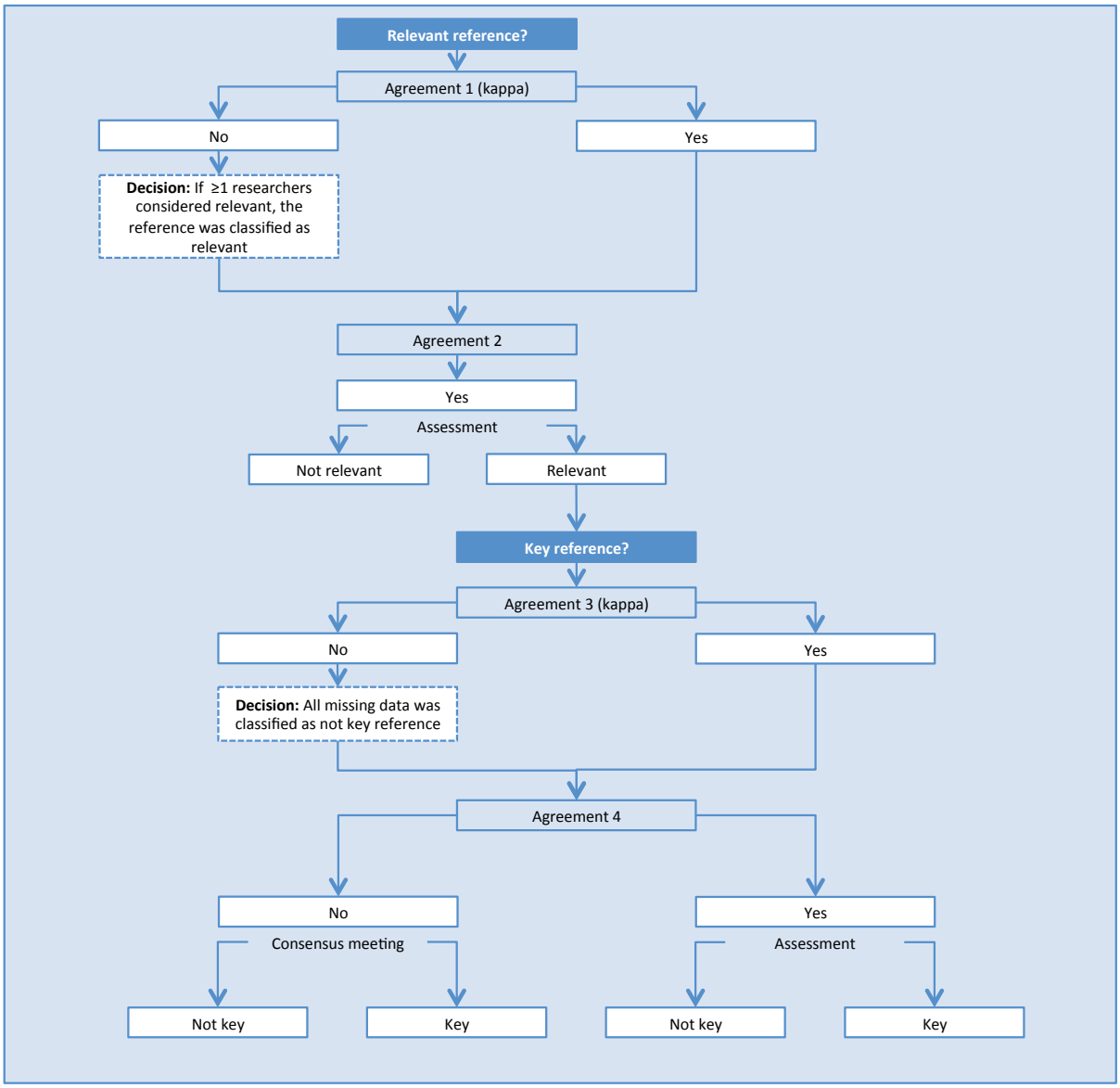
	Reference (ordered by first autor)	Reason for exclusion
1	Process for determining need for updates of clinical practice guidelines--AHCPR. Fed Regist. 1994;59(79 Pt 1):19723-5.	Methodological handbook or report
2	Clinical guidelines are not immortal: when do clinical guidelines become outdated? How can you know when an update is necessary? Prescrire Int. 2003;12(68):233-4.	Narrative review
3	Boer MM, Kersten S. Fast track guideline update successful. Proceedings of the 8th Guidelines International Network Conference; 2011 Aug 28-31; Seoul, Korea. p. 106-7.	Describes update method or tool
4	Bosch M, Tavender E, Bragge P, Gruen R, Green S. How to define 'best practice' for use in Knowledge Translation research: a practical, stepped and interactive process. J Eval Clin Pract. 2012 Apr 9.	Methodological handbook or report
5	Bouaud J, Seroussi B. Characterizing the dimensions of clinical practice guideline evolution. Stud Health Technol Inform. 2008;136:139-44.	Computer support
6	Brouwers MC, Rawski E, Spithoff K, Oliver TK. Inventory of Cancer Guidelines: a tool to advance the guideline enterprise and improve the uptake of evidence. Expert Rev Pharmacoecon Outcomes Res. 2011;11(2):151-61.	Describes update method or tool
7	Clark E, Donovan EF, Schoettker P. From outdated to updated, keeping clinical guidelines valid. Int J Qual Health Care. 2006;18(3):165-6.	Narrative review
8	De Palma R, Liberati A, Ciccone G, Bandieri E, Belfiglio M, Ceccarelli M,et al. Developing clinical recommendations for breast, colorectal, and lung cancer adjuvant treatments using the GRADE system: a study from the Programma Ricerca e Innovazione Emilia Romagna Oncology Research Group. J Clin Oncol. 2008;26(7):1033-9.	Describes development method
9	Fishman L, Weinbrenner S, Ollenschläger G. Analysis of chronic respiratory disease guideline updates of the past 10 years. Proceedings of the 7th Guidelines International Network Conference; 2010 Aug 25-28; Chicago, Illinois USA. p. 53.	Comparison updated guidelines
10	Gillis AM, Skanes AC. Canadian Cardiovascular Society Atrial Fibrillation Guidelines 2010: Implementing GRADE and Achieving Consensus. Can J Cardiol 2011; 27(1):27-30.	Describes update method or tool
11	Glover S. Guidance review: Issues, methods, and the role of the Information Specialist. Proceedings of the 7th Guidelines International Network Conference; 2010 Aug 25-28; Chicago, Illinois USA. p. 101.	Narrative review
12	Guirguis-Blake J, Calonge N, Miller T, Siu A, Teutsch S, Whitlock E; U.S. Preventive Services Task Force.Current processes of the U.S. Preventive Services Task Force: refining evidence-based recommendation development.Ann Intern Med. 2007;147(2):117-22.	Methodological handbook or report
13	Honkanen M, Sipilä R, Komulainen J, Ketola E. Improving the updating process of current care guidelines. Proceedings of the 7th Guidelines International Network Conference; 2010 Aug 25-28; Chicago, Illinois USA. p. 101-2.	Describes update method or tool
14	Kaiser K, Miksch S. Versioning computer-interpretable guidelines: semi-automatic modeling of 'Living Guidelines' using an information	Computer support

	extraction method. Artif Intell Med. 2009;46(1):55-66.	
15	Kumar A, Quaglini S, Stefanelli M, Ciccarese P, Caffi E. Modular representation of the guideline text: an approach for maintaining and updating the content of medical education. Med Inform Internet Med. 2003;28(2):99-115.	Computer support
16	Latchem S, Alderson P. The process and outcomes of reviews of the need to update NICE guidelines. Proceedings of the 7th Guidelines International Network Conference; 2010 Aug 25-28; Chicago, Illinois USA. p. 53-4.	Describes update method or tool
17	Latoszek-Berendsen A, Tange H, van den Herik HJ, Hasman A. From clinical practice guidelines to computer-interpretable guidelines. A literature overview. Methods Inf Med 2010; 49(6):550-70.	Computer support
18	MacDougall C , Percival J, McGregor C. Integrating health information technology into clinical guidelines. Conf Proc IEEE Eng Med Biol Soc. 2009:4646-9.	Evaluates health information technology
19	Moher D, Tsertsvadze A, Tricco AC et al. A systematic review identified few methods and strategies describing when and how to update systematic reviews. J Clin Epidemiol. 2007;60(11):1095-104.	Systematic review update
20	National Institute for Clinical Excellence (February 2004, updated 2005) Guideline Development Methods: Information for National Collaborating Centres and Guideline Developers. London: National Institute for Clinical Excellence. Available from: www.nice.org	Methodological handbook or report
21	Olver I, von Dincklage J. Use of wiki technology to develop and update cancer care guidelines. Proceedings of the 8th Guidelines International Network Conference; 2011 Aug 28-31; Seoul, Korea. p. 61.	Describes update method or tool
22	Oxman AD, Schunemann HJ, Fretheim A. Improving the use of research evidence in guideline development: 16. Evaluation . Health Res Policy Syst. 2006;4:28.	Narrative review
23	Parkhill A, Hill K. Identifying the effective evidence sources to use in developing Clinical Guidelines for Acute Stroke Management: lived experiences of the search specialist and project manager. Health Info Libr J. 2009;26(1):47-55.	Evaluates evidence sources
24	Pau AK, Dutcher G, Cadden C, Nochetto F. Electronic dissemination of US HIV Treatment Guideline as a living document: Free access for a global audience. Proceedings of the 7th Guidelines International Network Conference; 2010 Aug 25-28; Chicago, Illinois USA. p. 56.	Describes update method or tool
25	Peleg M, Kantor R. Approaches for guideline versioning using GLIF. AMIA Annu Symp Proc. 2003;509-13.	Computer support
27	Qaseem A, Snow V, Owens DK, Shekelle P; Clinical Guidelines Committee of the American College of Physicians.The development of clinical practice guidelines and guidance statements of the American College of Physicians: summary of methods. Ann Intern Med. 2010;153(3):194-9.	Methodological handbook or report
26	Qaseem A, Forland F, Macbeth F, Ollenschläger G, Phillips S, van der Wees P; Board of Trustees of the Guidelines International Network. Guidelines International Network: toward international standards for clinical practice guidelines. Ann Intern Med. 2012 Apr 3;156(7):525-31.	Methodological handbook or report
28	Rios M, Desandes E, Bresson B et al. [Clinical practice guidelines in cancerology: comparative study of three decision support-systems for	Computer support

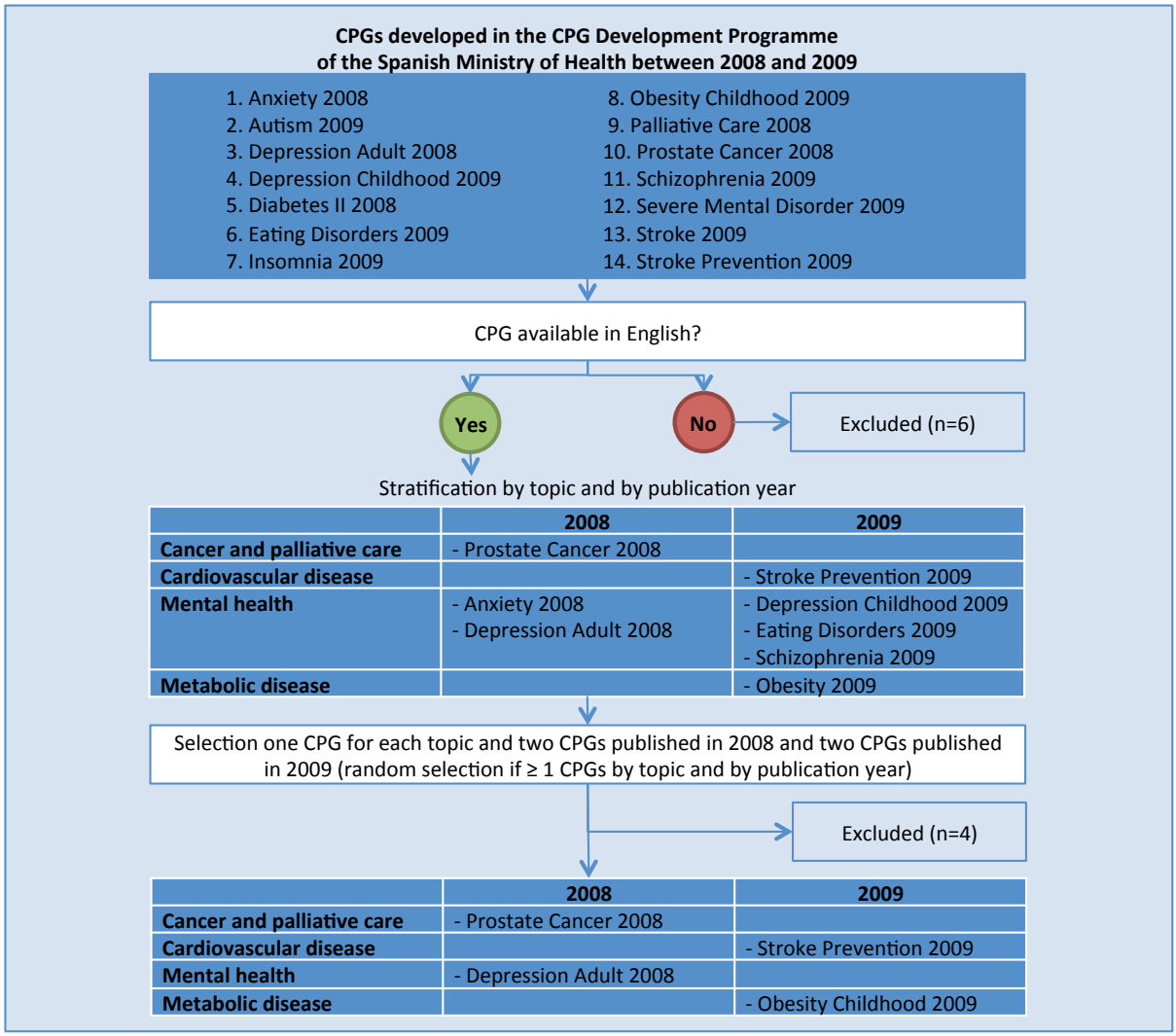
	breast and prostate cancer in Lorraine french region]. Bull Cancer. 2003;90(4):363-70.	
29	Scott A, Moga C, Taenzer P, Findlay T, Harstall C. Updating adapted guidelines: How to streamline the process without losing rigour. Proceedings of the 8th Guidelines International Network Conference; 2011 Aug 28-31; Seoul, Korea. p. 33.	Describes update method or tool
30	Scott-Wright AO, Fischer RP, Denekamp Y, Boxwala AA. A methodology for modular representation of guidelines. Stud Health Technol Inform. 2004;107(Pt 1):149-53.	Computer support
31	Serban R, ten Teije A, van Harmelen F, Marcos M, Polo-Conde C. Extraction and use of linguistic patterns for modelling medical guidelines. Artif Intell Med. 2007;39(2):137-49.	Computer support
32	Seyfang A, Martinez-Salvador B, Serban R, Wittenberg J, Miksch S, Marcos M. Maintaining formal models of living guidelines efficiently. In: Bellazzi R, Abu-Hanna A, Hunter J editors. Proceedings of the 11th conference on Artificial Intelligence in Medicine (AIME'07), LNAI 4594; 2007; Amsterdam, NL: Springer Verlag; p. 441-5.	Computer support
33	Shekelle P, Eccles MP, Grimshaw JM, Woolf SH. When should clinical guidelines be updated? BMJ. 2001;323(7305):155-7.	Describes update method or tool
34	Sparrow K, Lavibond K, Rabar S. A rapid update to a guideline: when new evidence questions the safety of a recommendation. Proceedings of the 8th Guidelines International Network Conference; 2011 Aug 28-31; Seoul, Korea. p. 32.	Describes update method or tool
35	Theobald S, Blanc-Vincent MP, Farsi F et al. The identification of questions in the updating process of clinical practice guidelines for oncology [abstract]. 15th Annual Meeting of the International Society of Technology Assessment in Health Care; 1999 Jun 20-23; Edinburgh, UK 1999; 90.	Describes update method or tool
36	Washington DL, Bernstein SJ, Kahan JP, Leape LL, Kamberg CJ, Shekelle PG. Reliability of clinical guideline development using mail-only versus in-person expert panels. Med Care. 2003;41(12):1374-81.	Describes update method or tool
37	Weissbach L. [Which components should living guidelines contain?]. Urologe A. 2012;51(1):57-9.	Describes update method or tool
38	Zarnke KB, Campbell NR, McAlister FA, Levine M; Canadian Hypertension Recommendations Working Group.A novel process for updating recommendations for managing hypertension: rationale and methods.Can J Cardiol. 2000;16(9):1094-102.	Describes update method or tool
39	Zelman Lewis S. Sustainable Living Guidelines: A Model for the Future. Proceedings of the 8th Guidelines International Network Conference; 2011 Aug 28-31; Seoul, Korea. p. 30.	Describes update method or tool

Publicación III: Análisis de supervivencia de las recomendaciones

Documento adicional 1: Algoritmo de decisión para identificar las referencias relevantes y las referencias clave



Documento adicional 2: Selección de las guías de práctica clínica incluidas en el estudio



Abbreviations: CPG: Clinical practice guideline.

Documento adicional 3: Tablas complementarias

Tabla complementaria 1: Características de las guías de práctica clínica incluidas en el estudio

	Major Depression in Adults 2008		Obesity in Childhood and Adolescence 2009		Prostate Cancer Treatment 2008		Secondary Prevention of Stroke 2009		Total	
Clinical questions, n	14		25		26		22		87	
Recommendations, n	58		64		78		49		249	
Topic	Mental health		Metabolic disease		Cancer and palliative care		Cardiovascular disease			
Search dates										
. Start	1/2/07		01/08/2008b		1/11/07		1/9/07			
Publication date	30/9/08		15/12/09		24/11/08		22/4/09			
Strength of recommendations (SIGN system), n %										
. A	8	13,8	1	1,6	13	16,7	14	28,6	36	14,5
. B	18	31,0	12	18,8	14	17,9	15	30,6	59	23,7
. C	4	6,9	7	10,9	3	3,8	5	10,2	19	7,6
. D	2	3,4	7	10,9	25	32,1	2	4,1	36	14,5
. Good Practice Point	26	44,8	37	57,8	23	29,5	13	26,5	99	39,8
Clinical purpose, n %										
. Prevention	0	0,0	56	87,5	0	0,0	49	100,0	105	42,2
. Screening	7	12,1	0	0,0	0	0,0	0	0,0	7	2,8
. Treatment	51	87,9	0	0,0	78	100,0	0	0,0	129	51,8
. Others	0	0,0	8	12,5	0	0,0	0	0,0	8	3,2

Tabla complementaria 2: Resultados del cuestionario inicial a expertos clínicos

	Major Depression in Adults 2008		Obesity in Childhood and Adolescence 2009		Prostate Cancer Treatment 2008		Secondary Prevention of Stroke 2009		Total	
Clinical questions, n	14		25		26		22		87	
Recommendations, n	58		64		78		49		249	
Dates										
. Start	1/6/11		1/6/11		1/6/11		1/6/11			
. Finish	1/8/11		1/8/11		1/8/11		1/8/11			
Population, n %										
. Clinical experts contacted	6		6		6		6		24	
. Included questionnaires	6	100,0	4	66,7	5	83,3	2	33,3	17	70,8
Question 1 - Recommendations with releva	49	84,5	42	65,6	39	50,0	10	20,4	140	56,2
Question 2 - Recommendations with key re	29	50,0	5	7,8	24	30,8	10	20,4	68	27,3
Question 3 - Key references, n (3)	91		9		79		10		189	
Question 4 - New topics, n (4)	11		1		7		0		19	
First screening – Pertinent references, n %										
. Duplicate	3	3,3	1	11,1	5	6,3	0	0,0	9	4,8
. Excluded	59	64,8	7	77,8	43	54,4	5	50,0	114	60,3
. Included	12	13,2	1	11,1	31	39,2	5	50,0	49	25,9
. New	17	18,7	0	0,0	0	0,0	0	0,0	17	9,0
Pertinent references, n (%)										
. Identified in exhaustive search	3	25,0	0	0,0	22	71,0	3	60,0	28	57,1
. Not identified in exhaustive search	9	75,0	1	100,0	9	29,0	2	40,0	21	42,9
(1) Question 1: Are you aware of new studies in the field relevant to this guideline recommendation?										
(2) Question 2: If you are aware of this new evidence, are the new studies of sufficient importance to change the guideline recommendation?										
(3) Question 3: If you are aware of these new published studies, please specify in each frame the citation of a study										
(4) Question 4: Do you know new topics that the guideline did not address and should be included?										

Tabla complementaria 3: Resultados de la actualización de la búsqueda de la literatura

	Major Depression in Adults 2008	Obesity in Childhood and Adolescence 2009	Prostate Cancer Treatment 2008	Secondary Prevention of Stroke 2009	Total
Clinical questions, n	14	25	26	22	87
Recommendations, n	58	64	78	49	249
Original search strategy, n	1	0	1	1	3
Original information specialist, n	0	0	0	1	1
Search dates					
. Lower limit	1/1/07	01/01/2008	01/01/2007	01/01/2007	
. [Start]	17/6/11	28/11/2011	31/05/2011	28/06/2011	
. Upper limit [Finish]	26/10/11	14/12/2011	31/07/2011	24/02/2012	
Time search					
. Lower - upper limit, years	4,8	3,9	4,5	5,1	
. Start - finish, months	4,3	0,5	2,0	7,9	
References, n	11243	9763	3343	14787	39136

Tabla complementaria 4: Resultados del primer cribado de referencias

	Major Depression in Adults 2008		Obesity in Childhood and Adolescence 2009		Prostate Cancer Treatment 2008		Secondary Prevention of Stroke 2009		Total	
Clinical questions, n	14		25		26		22		87	
Recommendations, n	58		64		78		49		249	
References, n	11243		9763		3343		14787		39136	
First references screening [pertinent], n %										
. Duplicate	3846	34,2	2445	25,0	286	8,6	1582	10,7	8159	20,8
. Excluded	6976	62,0	6981	71,5	2901	86,8	12940	87,5	29798	76,1
. Included	260	2,3	334	3,4	102	3,1	255	1,7	951	2,4
. New references (1)	161	1,4	3	0,0	54	1,6	10	0,1	228	0,6
References matching with recommendations, n %										
. Recommendations witout references	10	17,2	14	21,9	24	30,8	14	28,6	62	24,9
. Recommendations with references	48	82,8	50	78,1	54	69,2	35	71,4	187	75,1
References/recomomendation, median (rar	5	1_55	7	1_61	2	1_17	7	1_61		
Recommendations turnover, n %										
. Without references	10	17,2	14	21,9	24	30,8	14	28,6	62	24,9
. With low turnover (2)	26	44,8	25	39,1	28	35,9	18	36,7	97	39,0
. With high turnover (3)	22	37,9	25	39,1	26	33,3	17	34,7	90	36,1
(1) Studies may be related to new recommendations										
(2) ≤ median of references linked										
(3) > median of references linked										

Tabla complementaria 5: Resultados del grado de acuerdo en el segundo cribado de referencias

	Major Depression in Adults 2008		Obesity in Childhood and Adolescence 2009		Prostate Cancer Treatment 2008		Secondary Prevention of Stroke 2009		Total	
Clinical questions, n	14		25		26		22		87	
Recommendations, n	58		64		78		49		249	
Agreement 1 (relevant references)										
. No	108	56,3	210	71,9	71	67,0	43	55,1	432	64,7
. Yes	84	43,8	82	28,1	35	33,0	35	44,9	236	35,3
Total	192		292		106		78		668	
Kappa	0,2	0.1_0.3	0,0	0.0_0.1	0,1	0.0_0.2	0,2	0.1_0.4		
Agreement 2 (relevant references - post sintaxis)										
. No	0		0		0		0	0,0	0	0,0
. Yes	192	100,0	292	100,0	106	100,0	78	100,0	668	100,0
Total	192		292		106		78		668	
Agreement 3 (key references)										
. No	37	31,1	55	27,6	16	19,0	37	56,1	145	31,0
. Yes	82	68,9	144	72,4	68	81,0	29	43,9	323	69,0
Total	119		199		84		66		468	
Kappa, range	0,1	0.0_0.2	0,2	0.1_0.3	0,2	(-)0.1_0.6	0,1	(-)0.1_0.3		
Agreement 4 (key references - post sintaxis)										
. No	34	28,6	52	26,1	16	19,0	35	53,0	137	29,3
. Yes	85	71,4	147	73,9	68	81,0	31	47,0	331	70,7
Total	119		199		84		66		468	

Tabla complementaria 6: Resultados del análisis de supervivencia de las recomendaciones

Time	% of probability to still valid (95% CI)
1 year	92,0 (86,9 – 97,0)
2 years	85,7 (79,2 – 92,2)
3 years	81,3 (74,0 – 88,5)
4 years	77,8 (69,8 – 85,7)
Abbreviations: CI: coefficient interval.	

Tabla complementaria 7: Resultados relacionados con la utilización de recursos para realizar el estudio

	Major Depression in Adults 2008			Obesity in Childhood and Adolescence 2009			Prostate Cancer Treatment 2008			Secondary Prevention of Stroke 2009			Total			
	Person, n	Ref, n	Time, hours	Person, n	Ref, n	Time, hours	Person, n	Ref, n	Time, hours	Person, n	Ref, n	Time, hours	Person, n	Ref, n	Time, hours	Ref/ hour
Baseline survey(1)																
. Expert clinicians	6	-	-	6	-	-	6	-	-	6	-	-	24	-	-	-
Update exhaustive search																
. Information specialist	1	-	180	1	-	30	1	-	51	1	-	18	4	-	279	
First screening – Pertinent references + References matched with recommendations																
. Guideline methodologists	4	7608	142,4	5	7656	111,5	1	3217	160	6	13379	152,6	16	31860	566,5	70,4 (20,1-848,0)
Feasibility Test(1)																
. Guideline methodologists	3	160	-	3	120	-	3	61	-	3	187	-	12	528	-	-
Second screening – Relevant and key references(2)																
. Guideline methodologists	2	87	14,5	2	174	23,2	1	61	4,0	2	35	7,2	7	357	48,9	6,0 (4,0-15,3)
. Expert clinicians	6	192	93,0	4	292	67,2	6	112	69,3	5	78	47,0	21	674	276,5	4,8 (1,5-15,2)
Abbreviations: Ref: References.																
(1)Time not recorded.																
(2)Reported n=17 (60.7%); Not reported n=9 (39.3%) impute 1 reference/10 minutes.																

Documento adicional 4: Listado de referencias clave identificadas en el estudio

IdRef(1)	Clinical practice guideline	IdRec(2)	Recommendation	PMID(3)	Key reference
1	Major Depression in Adults 2008	1485	If the patient does not improve at the third or fourth week, any of the following strategies could be followed: 1)Switching from an antidepressant to any family, including another serotonergic. 2)Combining antidepressants. 3)Augmenting the initiated treatment with lithium or triiodothyronine.	17288688	Dorée JP, Des Rosiers J, Lew V, Gendron A, Elie R, Stip E, et al. Quetiapine augmentation of treatment-resistant depression: a comparison with lithium. Curr Med Res Opin. 2007;23(2):333-41.
2	Major Depression in Adults 2008	1485	If the patient does not improve at the third or fourth week, any of the following strategies could be followed: 1)Switching from an antidepressant to any family, including another serotonergic. 2)Combining antidepressants. 3)Augmenting the initiated treatment with lithium or triiodothyronine.	18047754	Cooper-Kazaz R, Lerer B. Efficacy and safety of triiodothyronine supplementation in patients with major depressive disorder treated with specific serotonin reuptake inhibitors. Int J Neuropsychopharmacol. 2008;11(5):685-99.
3	Major Depression in Adults 2008	1490	There is insufficient data for recommending augmentation with valproate, carbamazepine, lamotrigine, gabapentin or topiramate, pindolol, benzodiazepines, buspirone, methylphenidate or atypical antipsychotics.	17592905	Papakostas GI, Shelton RC, Smith J, Fava M. Augmentation of antidepressants with atypical antipsychotic medications for treatment-resistant major depressive disorder: a meta-analysis. J Clin Psychiatry. 2007;68(6):826-31.
4	Major Depression in Adults 2008	1490	There is insufficient data for recommending augmentation with valproate, carbamazepine, lamotrigine, gabapentin or topiramate, pindolol, benzodiazepines, buspirone, methylphenidate or atypical antipsychotics.	17592907	Berman RM, Marcus RN, Swanink R, McQuade RD, Carson WH, Corey-Lisle PK, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled study. J Clin Psychiatry. 2007;68(6):843-53.
5	Major Depression in Adults 2008	1490	There is insufficient data for recommending augmentation with valproate, carbamazepine, lamotrigine, gabapentin or topiramate, pindolol, benzodiazepines, buspirone, methylphenidate or atypical antipsychotics.	17975181	Mahmoud RA, Pandina GJ, Turkoz I, Kosik-Gonzalez C, Canuso CM, Kujawa MJ, et al. Risperidone for treatment-refractory major depressive disorder: a randomized trial. Ann Intern Med. 2007;147(9):593-602.

6	Major Depression in Adults 2008	1490	There is insufficient data for recommending augmentation with valproate, carbamazepine, lamotrigine, gabapentin or topiramate, pindolol, benzodiazepines, buspirone, methylphenidate or atypical antipsychotics.	18344725	Marcus RN, McQuade RD, Carson WH, Hennicken D, Fava M, Simon JS, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a second multicenter, randomized, double-blind, placebo-controlled study. J Clin Psychopharmacol. 2008;28(2):156-65.
7	Major Depression in Adults 2008	1490	There is insufficient data for recommending augmentation with valproate, carbamazepine, lamotrigine, gabapentin or topiramate, pindolol, benzodiazepines, buspirone, methylphenidate or atypical antipsychotics.	18586273	Keitner GI, Garlow SJ, Ryan CE, Ninan PT, Solomon DA, Nemeroff CB, et al. A randomized, placebo-controlled trial of risperidone augmentation for patients with difficult-to-treat unipolar, non-psychotic major depression. J Psychiatr Res. 2009;43(3):205-14.
8	Major Depression in Adults 2008	1490	There is insufficient data for recommending augmentation with valproate, carbamazepine, lamotrigine, gabapentin or topiramate, pindolol, benzodiazepines, buspirone, methylphenidate or atypical antipsychotics.	EL KHALILI	El Khalili, N., Bauer, M., Datto, C., Earley, W., Astrom, M., and Eriksson, H. Pooled analysis of adjunctive extended release quetiapine fumarate (Quetiapine XR) in patients with major depressive disorder (MDD). European Psychiatry Conference: 17th European Psychiatric Association, EPA Congress. Lisbon, Portugal. 2009. 24(pp S637).
9	Major Depression in Adults 2008	1490	There is insufficient data for recommending augmentation with valproate, carbamazepine, lamotrigine, gabapentin or topiramate, pindolol, benzodiazepines, buspirone, methylphenidate or atypical antipsychotics.	19358791	Bauer M, Pretorius HW, Constant EL, Earley WR, Szamosi J, Brecher M. Extended-release quetiapine as adjunct to an antidepressant in patients with major depressive disorder: results of a randomized, placebo-controlled, double-blind study. J Clin Psychiatry. 2009;70(4):540-9.
10	Major Depression in Adults 2008	1490	There is insufficient data for recommending augmentation with valproate, carbamazepine, lamotrigine, gabapentin or topiramate, pindolol, benzodiazepines, buspirone, methylphenidate or atypical antipsychotics.	19687129	Nelson JC, Papakostas GI. Atypical antipsychotic augmentation in major depressive disorder: a meta-analysis of placebo-controlled randomized trials. Am J Psychiatry. 2009;166(9):980-91.
11	Major Depression in Adults 2008	1490	There is insufficient data for recommending augmentation with valproate, carbamazepine, lamotrigine, gabapentin or topiramate, pindolol, benzodiazepines, buspirone, methylphenidate or atypical antipsychotics.	20433324	Thomas SP, Nandhra HS, Jayaraman A. Systematic review of lamotrigine augmentation of treatment resistant unipolar depression (TRD). J Ment Health. 2010;19(2):168-75.

12	Major Depression in Adults 2008	1490	There is insufficient data for recommending augmentation with valproate, carbamazepine, lamotrigine, gabapentin or topiramate, pindolol, benzodiazepines, buspirone, methylphenidate or atypical antipsychotics.	20175941	El-Khalili N, Joyce M, Atkinson S, Buynak RJ, Datto C, Lindgren P, et al. Extended-release quetiapine fumarate (quetiapine XR) as adjunctive therapy in major depressive disorder (MDD) in patients with an inadequate response to ongoing antidepressant treatment: a multicentre, randomized, double-blind, placebo-controlled study. Int J Neuropsychopharmacol. 2010;13(7):917-32.
13	Major Depression in Adults 2008	1511	The use of St John's Wort is not recommended as a treatment option for patients with major depression.	18843608	Linde K, Berner MM, Kriston L. St John's wort for major depression. Cochrane Database Syst Rev. 2008;(4):CD000448.
14	Obesity in Childhood and Adolescence 2009	1050	Schools should include educational programmes which aim to improve diet, increase physical activity levels and reduce sedentary lifestyles. These should include families and teaching staff	21679476	Bjelland M, Bergh IH, Grydeland M, Klepp KI, Andersen LF, Anderssen SA, et al. Changes in adolescents' intake of sugar-sweetened beverages and sedentary behaviour: results at 8 month mid-way assessment of the HEIA study--a comprehensive, multi-component school-based randomized trial. Int J Behav Nutr Phys Act. 2011;8:63.
15	Obesity in Childhood and Adolescence 2009	1053	Multidisciplinary interventions should be implemented in schools to encourage children and adolescents to eat fruit and vegetables.	18719006	de Sa J, Lock K. Will European agricultural policy for school fruit and vegetables improve public health? A review of school fruit and vegetable programmes. Eur J Public Health. 2008;18(6):558-68.
16	Obesity in Childhood and Adolescence 2009	1053	Multidisciplinary interventions should be implemented in schools to encourage children and adolescents to eat fruit and vegetables.	21371499	Hoffman JA, Thompson DR, Franko DL, Power TJ, Leff SS, Stallings VA. Decaying behavioral effects in a randomized, multi-year fruit and vegetable intake intervention. Prev Med. 2011;52(5):370-5.
17	Obesity in Childhood and Adolescence 2009	1095	Physical activity programmes outside school hours are recommended for children and adolescents. These must be suited to their ages and preferences.	21852659	de Heer HD, Koehly L, Pederson R, Morera O. Effectiveness and spillover of an after-school health promotion program for Hispanic elementary school children. Am J Public Health. 2011;101(10):1907-13.
18	Obesity in Childhood and Adolescence 2009	1101	Educational programmes that target the family so as to encourage a healthy lifestyle are needed. These must cover healthy eating, education to understand nutritional information on food labels and the promotion of active leisure activities.	18180410	Paineau DL, Beaufils F, Boulier A, Cassuto DA, Chwalow J, Combris P, et al. Family dietary coaching to improve nutritional intakes and body weight control: a randomized controlled trial. Arch Pediatr Adolesc Med. 2008;162(1):34-43.

19	Obesity in Childhood and Adolescence 2009	1101	Educational programmes that target the family so as to encourage a healthy lifestyle are needed. These must cover healthy eating, education to understand nutritional information on food labels and the promotion of active leisure activities.	20107454	Olvera N, Bush JA, Sharma SV, Knox BB, Scherer RL, Butte NF. BOUNCE: a community-based mother-daughter healthy lifestyle intervention for low-income Latino families. Obesity (Silver Spring). 2010;18 Suppl 1:S102-4.
20	Obesity in Childhood and Adolescence 2009	1101	Educational programmes that target the family so as to encourage a healthy lifestyle are needed. These must cover healthy eating, education to understand nutritional information on food labels and the promotion of active leisure activities.	20107464	Fulkerson JA, Rydell S, Kubik MY, Lytle L, Boutelle K, Story M, et al. Healthy Home Offerings via the Mealtime Environment (HOME): feasibility, acceptability, and outcomes of a pilot study. Obesity (Silver Spring). 2010;18 Suppl 1:S69-74.
21	Obesity in Childhood and Adolescence 2009	1101	Educational programmes that target the family so as to encourage a healthy lifestyle are needed. These must cover healthy eating, education to understand nutritional information on food labels and the promotion of active leisure activities.	19933120	Chen JL, Weiss S, Heyman MB, Lustig RH. Efficacy of a child-centred and family-based program in promoting healthy weight and healthy behaviors in Chinese American children: a randomized controlled study. J Public Health (Oxf). 2010;32(2):219-29.
22	Obesity in Childhood and Adolescence 2009	1101	Educational programmes that target the family so as to encourage a healthy lifestyle are needed. These must cover healthy eating, education to understand nutritional information on food labels and the promotion of active leisure activities.	21041592	Robinson TN, Matheson DM, Kraemer HC, Wilson DM, Obarzanek E, Thompson NS, et al. A randomized controlled trial of culturally tailored dance and reducing screen time to prevent weight gain in low-income African American girls: Stanford GEMS. Arch Pediatr Adolesc Med. 2010;164(11):995-1004.
23	Obesity in Childhood and Adolescence 2009	1101	Educational programmes that target the family so as to encourage a healthy lifestyle are needed. These must cover healthy eating, education to understand nutritional information on food labels and the promotion of active leisure activities.	20508978	Karanja N, Lutz T, Ritenbaugh C, Maupome G, Jones J, Becker T, et al. The TOTS community intervention to prevent overweight in American Indian toddlers beginning at birth: a feasibility and efficacy study. J Community Health. 2010;35(6):667-75.
24	Obesity in Childhood and Adolescence 2009	1101	Educational programmes that target the family so as to encourage a healthy lifestyle are needed. These must cover healthy eating, education to understand nutritional information on food labels and the promotion of active leisure activities.	20576004	Monasta L, Batty GD, Macaluso A, Ronfani L, Lutje V, Bavcar A, et al. Interventions for the prevention of overweight and obesity in preschool children: a systematic review of randomized controlled trials. Obes Rev. 2011;12(5):e107-18.
25	Obesity in Childhood and Adolescence 2009	1119	Televisions, video consoles and computers should be removed from the bedrooms of children and adolescents who are overweight or obese.	21708797	Maniccia DM, Davison KK, Marshall SJ, Manganello JA, Dennison BA. A meta-analysis of interventions that target children's screen time for reduction. Pediatrics. 2011;128(1):e193-210.

26	Obesity in Childhood and Adolescence 2009	1125	Combined interventions including diet, physical exercise and changes to behaviour, with family involvement, are recommended for weight loss in children and adolescents aged 6-16 who are overweight or obese.	19160202	Oude Luttikhuis H, Baur L, Jansen H, Shrewsbury VA, O'Malley C, Stolk RP, et al. Interventions for treating obesity in children. Cochrane Database Syst Rev. 2009;(1):CD001872.
27	Obesity in Childhood and Adolescence 2009	1125	Combined interventions including diet, physical exercise and changes to behaviour, with family involvement, are recommended for weight loss in children and adolescents aged 6-16 who are overweight or obese.	19628106	Yackobovitch-Gavan M, Nagelberg N, Phillip M, Ashkenazi-Hoffnung L, Hershkovitz E, Shalitin S. The influence of diet and/or exercise and parental compliance on health-related quality of life in obese children. Nutr Res. 2009;29(6):397-404.
28	Obesity in Childhood and Adolescence 2009	1125	Combined interventions including diet, physical exercise and changes to behaviour, with family involvement, are recommended for weight loss in children and adolescents aged 6-16 who are overweight or obese.	Reinehr	Reinehr T, Schaefer A, Winkel K, Finne E, Kolip P. An effective lifestyle intervention in overweight children ('Obeldicks light'): Long-term findings from a randomized controlled trial. Obesity Reviews. 2010.
29	Obesity in Childhood and Adolescence 2009	1125	Combined interventions including diet, physical exercise and changes to behaviour, with family involvement, are recommended for weight loss in children and adolescents aged 6-16 who are overweight or obese.	20107463	Sacher PM, Kolotourou M, Chadwick PM, Cole TJ, Lawson MS, Lucas A, et al. Randomized controlled trial of the MEND program: a family-based community intervention for childhood obesity. Obesity (Silver Spring). 2010;18 Suppl 1:S62-8.
30	Obesity in Childhood and Adolescence 2009	1125	Combined interventions including diet, physical exercise and changes to behaviour, with family involvement, are recommended for weight loss in children and adolescents aged 6-16 who are overweight or obese.	20447648	Okely AD, Collins CE, Morgan PJ, Jones RA, Warren JM, Cliff DP, et al. Multi-site randomized controlled trial of a child-centered physical activity program, a parent-centered dietary-modification program, or both in overweight children: the HIKCUPS study. J Pediatr. 2010;157(3):388-94, 394.e1.
31	Obesity in Childhood and Adolescence 2009	1125	Combined interventions including diet, physical exercise and changes to behaviour, with family involvement, are recommended for weight loss in children and adolescents aged 6-16 who are overweight or obese.	20655544	Jelalian E, Lloyd-Richardson EE, Mehlenbeck RS, Hart CN, Flynn-O'Brien K, Kaplan J, et al. Behavioral weight control treatment with supervised exercise or peer-enhanced adventure for overweight adolescents. J Pediatr. 2010;157(6):923-928.e1.

32	Obesity in Childhood and Adolescence 2009	1125	Combined interventions including diet, physical exercise and changes to behaviour, with family involvement, are recommended for weight loss in children and adolescents aged 6-16 who are overweight or obese.	21135337	Ciampa PJ, Kumar D, Barkin SL, Sanders LM, Yin HS, Perrin EM, et al. Interventions aimed at decreasing obesity in children younger than 2 years: a systematic review. Arch Pediatr Adolesc Med. 2010;164(12):1098-104.
33	Obesity in Childhood and Adolescence 2009	1125	Combined interventions including diet, physical exercise and changes to behaviour, with family involvement, are recommended for weight loss in children and adolescents aged 6-16 who are overweight or obese.	20070541	Kelly KP, Kirschenbaum DS. Immersion treatment of childhood and adolescent obesity: the first review of a promising intervention. Obes Rev. 2011;12(1):37-49.
34	Obesity in Childhood and Adolescence 2009	1125	Combined interventions including diet, physical exercise and changes to behaviour, with family involvement, are recommended for weight loss in children and adolescents aged 6-16 who are overweight or obese.	21300674	Savoye M, Nowicka P, Shaw M, Yu S, Dziura J, Chavent G, et al. Long-term results of an obesity program in an ethnically diverse pediatric population. Pediatrics. 2011;127(3):402-10.
35	Obesity in Childhood and Adolescence 2009	1125	Combined interventions including diet, physical exercise and changes to behaviour, with family involvement, are recommended for weight loss in children and adolescents aged 6-16 who are overweight or obese.	21444600	Collins CE, Okely AD, Morgan PJ, Jones RA, Burrows TL, Cliff DP, et al. Parent diet modification, child activity, or both in obese children: an RCT. Pediatrics. 2011;127(4):619-27.
36	Obesity in Childhood and Adolescence 2009	1125	Combined interventions including diet, physical exercise and changes to behaviour, with family involvement, are recommended for weight loss in children and adolescents aged 6-16 who are overweight or obese.	21487425	Coppins DF, Margetts BM, Fa JL, Brown M, Garrett F, Huelin S. Effectiveness of a multi-disciplinary family-based programme for treating childhood obesity (the Family Project). Eur J Clin Nutr. 2011;65(8):903-9.
37	Obesity in Childhood and Adolescence 2009	1125	Combined interventions including diet, physical exercise and changes to behaviour, with family involvement, are recommended for weight loss in children and adolescents aged 6-16 who are overweight or obese.	21514017	Schaefer A, Winkel K, Finne E, Kolip P, Reinehr T. An effective lifestyle intervention in overweight children: one-year follow-up after the randomized controlled trial on "Obeldicks light". Clin Nutr. 2011;30(5):629-33.
38	Obesity in Childhood and Adolescence 2009	1126	The clinical and family environments are the most appropriate settings for combined interventions for weight loss in children and adolescents who are overweight or obese.	20102858	Díaz RG, Esparza-Romero J, Moya-Camarena SY, Robles-Sardín AE, Valencia ME. Lifestyle intervention in primary care settings improves obesity parameters among Mexican youth. J Am Diet Assoc. 2010;110(2):285-90.

39	Obesity in Childhood and Adolescence 2009	1126	The clinical and family environments are the most appropriate settings for combined interventions for weight loss in children and adolescents who are overweight or obese.	20585269	Ellis DA, Janisse H, Naar-King S, Kolmodin K, Jen KL, Cunningham P, et al. The effects of multisystemic therapy on family support for weight loss among obese African-American adolescents: findings from a randomized controlled trial. J Dev Behav Pediatr. 2010;31(6):461-8.
40	Obesity in Childhood and Adolescence 2009	1126	The clinical and family environments are the most appropriate settings for combined interventions for weight loss in children and adolescents who are overweight or obese.	21262890	Magarey AM, Perry RA, Baur LA, Steinbeck KS, Sawyer M, Hills AP, et al. A parent-led family-focused treatment program for overweight children aged 5 to 9 years: the PEACH RCT. Pediatrics. 2011;127(2):214-22.
41	Obesity in Childhood and Adolescence 2009	1126	The clinical and family environments are the most appropriate settings for combined interventions for weight loss in children and adolescents who are overweight or obese.	21487425	Coppins DF, Margetts BM, Fa JL, Brown M, Garrett F, Huelin S. Effectiveness of a multi-disciplinary family-based programme for treating childhood obesity (the Family Project). Eur J Clin Nutr. 2011;65(8):903-9.
42	Obesity in Childhood and Adolescence 2009	1129	For adolescents (aged 12-18) suffering from obesity and severe comorbidities who have not responded to dietary and lifestyle treatment, orlistat* treatment (120 mg with breakfast, lunch and dinner) may be considered as part of a programme of changes to lifestyle. This must be supervised by specialists in endocrinology and nutrition, family medicine or paediatrics who have been trained to treat obesity. * Sibutramine and orlistat are not funded by Spanish Social Security.	19160202	Oude Luttikhuis H, Baur L, Jansen H, Shrewsbury VA, O'Malley C, Stolk RP, et al. Interventions for treating obesity in children. Cochrane Database Syst Rev. 2009;(1):CD001872.
43	Obesity in Childhood and Adolescence 2009	1129	For adolescents (aged 12-18) suffering from obesity and severe comorbidities who have not responded to dietary and lifestyle treatment, orlistat* treatment (120 mg with breakfast, lunch and dinner) may be considered as part of a programme of changes to lifestyle. This must be supervised by specialists in endocrinology and nutrition, family medicine or paediatrics who have been trained to treat obesity. * Sibutramine and orlistat are not funded by Spanish Social Security.	20083531	Whitlock EP, O'Connor EA, Williams SB, Beil TL, Lutz KW. Effectiveness of weight management interventions in children: a targeted systematic review for the USPSTF. Pediatrics. 2010;125(2):e396-418.

44	Obesity in Childhood and Adolescence 2009	1129	For adolescents (aged 12-18) suffering from obesity and severe comorbidities who have not responded to dietary and lifestyle treatment, orlistat* treatment (120 mg with breakfast, lunch and dinner) may be considered as part of a programme of changes to lifestyle. This must be supervised by specialists in endocrinology and nutrition, family medicine or paediatrics who have been trained to treat obesity. * Sibutramine and orlistat are not funded by Spanish Social Security.	19922432	Viner RM, Hsia Y, Tomsic T, Wong IC. Efficacy and safety of anti-obesity drugs in children and adolescents: systematic review and meta-analysis. Obes Rev. 2010;11(8):593-602.
45	Obesity in Childhood and Adolescence 2009	1129	For adolescents (aged 12-18) suffering from obesity and severe comorbidities who have not responded to dietary and lifestyle treatment, orlistat* treatment (120 mg with breakfast, lunch and dinner) may be considered as part of a programme of changes to lifestyle. This must be supervised by specialists in endocrinology and nutrition, family medicine or paediatrics who have been trained to treat obesity. * Sibutramine and orlistat are not funded by Spanish Social Security.	20858149	Chanoine JP, Richard M. Early weight loss and outcome at one year in obese adolescents treated with orlistat or placebo. Int J Pediatr Obes. 2011;6(2):95-101.
46	Prostate Cancer Treatment 2008	1204	In patients with prostate cancer at a locally advanced stage with a life expectancy less than 10 years, watching and waiting or hormone therapy may be therapeutic alternatives.	18349064	Shahani S, Braga-Basaria M, Basaria S. Androgen deprivation therapy in prostate cancer and metabolic risk for atherosclerosis. J Clin Endocrinol Metab. 2008;93(6):2042-9.
47	Prostate Cancer Treatment 2008	1206	The normal duration of neoadjuvant hormonal treatment with radiotherapy in patients with prostate cancer at a locally advanced stage is 3 months.	21440505	Denham JW, Steigler A, Lamb DS, Joseph D, Turner S, Matthews J, et al. Short-term neoadjuvant androgen deprivation and radiotherapy for locally advanced prostate cancer: 10-year data from the TROG 96.01 randomised trial. Lancet Oncol. 2011;12(5):451-9.
48	Prostate Cancer Treatment 2008	1208	The normal duration of neoadjuvant hormonal treatment after radiotherapy in patients with prostate cancer at a locally advanced stage is 2-3 years.	17102802	Wirth M, Tyrrell C, Delaere K, Sánchez-Chapado M, Ramon J, Wallace DM, et al. Bicalutamide (Casodex) 150 mg plus standard care in early non-metastatic prostate cancer: results from Early Prostate Cancer Trial 24 at a median 7 years' follow-up. Prostate Cancer Prostatic Dis. 2007;10(1):87-93.

49	Prostate Cancer Treatment 2008	1208	The normal duration of neoadjuvant hormonal treatment after radiotherapy in patients with prostate cancer at a locally advanced stage is 2-3 years.	MARTINEZ-PINEIRO	Martinez-Pineiro L. Does neoadjuvant and adjuvant treatment improve outcome in localised prostatic cancer? European Urology Supplements. 2008;7(5):406-409.
50	Prostate Cancer Treatment 2008	1208	The normal duration of neoadjuvant hormonal treatment after radiotherapy in patients with prostate cancer at a locally advanced stage is 2-3 years.	COLLETTE	Collette L, Mauer M, Bolla M, Van Tienhoven G, De Reijke TM, Van Den Bergh ACM, et al. 745 health related quality of life and symptoms in an international phase iii trial of long term versus short-term androgen suppression and radiation therapy for locally advanced prostate cancer (eortc trial 22961). European Urology Supplements. 2009;8(4):307.
51	Prostate Cancer Treatment 2008	1208	The normal duration of neoadjuvant hormonal treatment after radiotherapy in patients with prostate cancer at a locally advanced stage is 2-3 years.	BOLLA	Bolla M, Collette L, Van Tienhoven G, Warde P, Dubois JB, Mirimanoff RO, et al. 7007 Three years of adjuvant androgen deprivation with goserelin in patients with locally advanced prostate cancer treated with radiotherapy: Results at 10 years of EORTC trial 22863. European Journal of Cancer Supplements. 2009;7(2):408.
52	Prostate Cancer Treatment 2008	1208	The normal duration of neoadjuvant hormonal treatment after radiotherapy in patients with prostate cancer at a locally advanced stage is 2-3 years.	22129214	Iversen P, McLeod DG, See WA, Morris T, Armstrong J, Wirth MP, et al. Antiandrogen monotherapy in patients with localized or locally advanced prostate cancer: final results from the bicalutamide Early Prostate Cancer programme at a median follow-up of 9.7 years. BJU Int. 2010;105(8):1074-81.
53	Prostate Cancer Treatment 2008	1230	In patients with disseminated prostate cancer for whom hormone therapy has been indicated, castration (surgical or chemical) is recommended as a first-line treatment.	18491137	Arai Y, Akaza H, Deguchi T, Fujisawa M, Hayashi M, Hirao Y, et al. Evaluation of quality of life in patients with previously untreated advanced prostate cancer receiving maximum androgen blockade therapy or LHRHa monotherapy: a multicenter, randomized, double-blind, comparative study. J Cancer Res Clin Oncol. 2008;134(12):1385-96.
54	Prostate Cancer Treatment 2008	1233	In patients with disseminated prostate cancer and low tumour load, intermittent androgen suppression may be assessed as an alternative to continuous androgen suppression if there is a good response to the initial hormone treatment.	19249153	Calais da Silva FE, Bono AV, Whelan P, Brausi M, Marques Queimadelos A, Martin JA, et al. Intermittent androgen deprivation for locally advanced and metastatic prostate cancer: results from a randomized phase 3 study of the South European Uroncological Group. Eur Urol. 2009;55(6):1269-77.

55	Prostate Cancer Treatment 2008	1234	To be able to indicate intermittent hormone therapy, the patient must have received androgen deprivation for at least 7 months and reached a PSA < 4 ng/ml (stable or in decline during the sixth and seventh months), or a 90% reduction from pre-treatment levels. Monitoring will be carried out every 6 months. Patients who have stopped androgen deprivation will receive another cycle on request, when the PSA increases or when clinical symptoms of disease progression appear. If the PSA returns to normal after the new round of androgen deprivation, hormone therapy can be stopped again.	19249153	Calais da Silva FE, Bono AV, Whelan P, Brausi M, Marques Queimadelos A, Martin JA, et al. Intermittent androgen deprivation for locally advanced and metastatic prostate cancer: results from a randomized phase 3 study of the South European Uroncological Group. Eur Urol. 2009;55(6):1269-77.
56	Prostate Cancer Treatment 2008	1243	The systematic use of bisphosphonates (zoledronic acid) as a preventive treatment in bone complications is not recommended. Zoledronic acid (4 mg every 3 weeks) can be offered in selected hormone-independent patients with demonstrated metastasis.	21353695	Fizazi K, Carducci M, Smith M, Damião R, Brown J, Karsh L, et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. Lancet. 2011;377(9768):813-22.
57	Secondary Prevention of Stroke 2009	1400	Patients who have suffered a stroke are encouraged to exercise regularly within their capabilities and reduce body weight or abdominal obesity to normal levels.	19821305	Saunders DH, Greig CA, Mead GE, Young A. Physical fitness training for stroke patients. Cochrane Database Syst Rev. 2009;(4):CD003316.
58	Secondary Prevention of Stroke 2009	1400	Patients who have suffered a stroke are encouraged to exercise regularly within their capabilities and reduce body weight or abdominal obesity to normal levels.	22071806	Brazzelli M, Saunders DH, Greig CA, Mead GE. Physical fitness training for stroke patients. Cochrane Database Syst Rev. 2011;(11):CD003316.
59	Secondary Prevention of Stroke 2009	1406	It is recommended to treat patients with ischemic stroke or prior transient ischemic attack of atherothrombotic etiology with atorvastatin (80 mg/d), regardless of their basal LDL-cholesterol levels.	19228842	Amarenco P, Benavente O, Goldstein LB, Callahan A 3rd, Sillesen H, Hennerici MG, et al. Results of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial by stroke subtypes. Stroke. 2009;40(4):1405-9.

60	Secondary Prevention of Stroke 2009	1406	It is recommended to treat patients with ischemic stroke or prior transient ischemic attack of atherothrombotic etiology with atorvastatin (80 mg/d), regardless of their basal LDL-cholesterol levels.	19588332	Manktelow BN, Potter JF. Interventions in the management of serum lipids for preventing stroke recurrence. Cochrane Database Syst Rev. 2009;(3):CD002091.
61	Secondary Prevention of Stroke 2009	1407	Treatment with other statins (simvastatin 40 mg) is also indicated in patients with ischemic stroke or prior transient ischemic attack of atherothrombotic etiology, regardless of their basal LDL-cholesterol levels.	17986516	Henyan NN, Riche DM, East HE, Gann PN. Impact of statins on risk of stroke: a meta-analysis. Ann Pharmacother. 2007;41(12):1937-45.
62	Secondary Prevention of Stroke 2009	1407	Treatment with other statins (simvastatin 40 mg) is also indicated in patients with ischemic stroke or prior transient ischemic attack of atherothrombotic etiology, regardless of their basal LDL-cholesterol levels.	19588332	Manktelow BN, Potter JF. Interventions in the management of serum lipids for preventing stroke recurrence. Cochrane Database Syst Rev. 2009;(3):CD002091.
63	Secondary Prevention of Stroke 2009	1410	The combination of statins with other hypolipemiant drugs to reach LDLcholesterol target values should be avoided.	19884623	Sharma M, Ansari MT, Abou-Setta AM, Soares-Weiser K, Ooi TC, Sears M, et al. Systematic review: comparative effectiveness and harms of combination therapy and monotherapy for dyslipidemia. Ann Intern Med. 2009;151(9):622-30.
64	Secondary Prevention of Stroke 2009	1417	In cases where anticoagulant treatment is contraindicated, treatment with aspirin (300 mg/d) is an appropriate alternative.	19336502	ACTIVE Investigators, Connolly SJ, Pogue J, Hart RG, Hohnloser SH, Pfeffer M, et al. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. N Engl J Med. 2009;360(20):2066-78.
65	Secondary Prevention of Stroke 2009	1417	In cases where anticoagulant treatment is contraindicated, treatment with aspirin (300 mg/d) is an appropriate alternative.	20388864	Ansara AJ, Nisly SA, Arif SA, Koehler JM, Nordmeyer ST. Aspirin dosing for the prevention and treatment of ischemic stroke: an indication-specific review of the literature. Ann Pharmacother. 2010;44(5):851-62.
66	Secondary Prevention of Stroke 2009	1417	In cases where anticoagulant treatment is contraindicated, treatment with aspirin (300 mg/d) is an appropriate alternative.	21309657	Connolly SJ, Eikelboom J, Joyner C, Diener HC, Hart R, Golitsyn S, et al. Apixaban in patients with atrial fibrillation. N Engl J Med. 2011;364(9):806-17.
67	Secondary Prevention of Stroke 2009	1417	In cases where anticoagulant treatment is contraindicated, treatment with aspirin (300 mg/d) is an appropriate alternative.	HART	Hart RG, Eikelboom J, Yusuf S, Gao P, Paolasso E, De Caterina R, et al. Efficacy and safety of the novel oral factor Xa inhibitor apixaban in atrial fibrillation (AF) patients with chronic kidney disease (CKD): The AVERROES trial. European Heart Journal. Conference: European Society of Cardiology, ESC Congress. 2011.

68	Secondary Prevention of Stroke 2009	1424	In patients with previous ischemic stroke or transient ischemic attack who present permeable foramen ovale, treatment with antiaggregants (100-300 mg/d of aspirin) is recommended.	-	Kent DM, Kitsios GD. Meta-analysis of observational studies for the risk of recurrent stroke with PFO closure or medical treatment and comparison to the results of the closure I trial. Cerebrovascular Diseases. Conference. 2011; Hamburg, Germany.
69	Secondary Prevention of Stroke 2009	1427	Carotid endarterectomy is recommended in patients with ischemic stroke of less than 6 months evolution and significant stenosis of the carotid artery (70% to 99%, NASCET values), if and when the surgical team confirms a perioperative morbimortality of less than 6%.	19769803	Patterson BO, Holt PJ, Hinchliffe RJ, Thompson MM, Loftus IM. Urgent carotid endarterectomy for patients with unstable symptoms: systematic review and meta-analysis of outcomes. Vascular. 2009;17(5):243-52.
(1) IdRef: identification number of reference					
(2) IdRec: identification number of recommendation					
(3) PMID: unique identifier for an article that is in PMC (PubMed Central)					

Publicación IV: Evaluación de las recomendaciones actualizadas

Documento adicional 1: Información sobre el proceso de recodificación de las recomendaciones actualizadas

Tabla complementaria 1: Recodificación sobre el propósito de las recomendaciones

Access to services - Referral and approach to care - Service organisation [Access]	Diagnostic	Monitoring - Follow up [Monitoring]	Prevention practices [Prevention]	Supporting patients and carers [Supporting]	Treatment	>1 procedure - Others [Others]
access to	analysis	follow	alcohol	advice	resp	
admission	assess	measured	catheter	agree	administration	
admission	CT	monitor	clean	aware	dosing	
available	define	observations	container	card	drug	
care	diagnos	reappraisal	contaminat	carer	effecti	
centre	EEG	review	drainage	communication	indicat	
clinician	examination	others	dressing	counselling	intervention	
consultant	exclude		exercise	discuss	manag	
discharg	identif		full-body fluid-repellent	educat	medication	
document	imaging		gloves	empower	pharma	
environment	investigation		hygiene	encourag	prescribe	
guideline	measure		infect	enquiry	prescription	
hospital	MRI		lifestyle	famil	programmes	
multidisciplinary	radiograph		needle	inform	surg	
network	scan		no-touch technique	instruction	surgery	
nurse	spirometry		plastic aprons	participate	therap	
protocol	stud		prevent	preference	treat	
refer	suspect		prophyla	relative	others	
service	test		protect	self		
setting	X-ray		ready-to-use feeds	share		
specialist	others		risk	support		
staff			screening	others		
team			septic			
transfer			sharp			
unit			single (use)			
others			smoke			
			sterile			
			vaccin			
			wash			
			others			

Tabla complementaria 2: Recodificación sobre la fuerza de la recomendación (método SIGN)

A	B	C	D	GPP	Others
A	B	C	D	GPP	>1
A (DS)	B (DS)	C (DS)	D (GPP)		HSC
A (NICE)			D H&S		NICE
					H&S
Abbreviations: DS: Diagnostic Studies; GPP: Good Practice Point; H&S: Health and Safety (H&S) requirement; HSC: Evidence from Health Service Circulars; NICE: Evidence from NICE guidelines or Health Technology					

Tabla complementaria 3: Recodificación sobre la fuerza de la recomendación (método GRADE)

Legal	Strong	Weak
Must	Should	Consider
Must and Should	Ensure	*[Without others]*
	Should and Consider	

Tabla complementaria 4: Recodificación sobre el estado de actualización de las recomendaciones

Amended	New	Not changed	Not reviewed
[2003, amended 2010]	[2007]	[2010]	-
[2003, amended 2010] KPI	[new 2010]	[2011]	[2003]
[2003, amended 2012]	[new 2010] KPI	[2012]	[2003] KPI
[2004, amended 2011]	[new 2011]	[2013]	[2004]
[2004, amended 2012]	[new 2012]	Not changing	[2005]
[2004, amended 2013]	[new 2013]		[without orange color]
[2006, amended 2011]	[NEW]		[without pink color]
[Amended]	New		
[partially highlighted in orange co	NEW 2010		
[partially highlighted in pink color]			

Documento adicional 2: Selección de las guías de práctica clínica incluidas en el estudio

Id	Ref	CGs	Date Issued	Review	Version	Selection	Exclusion reason
1	C	Electronic fetal monitoring (C) (replaced by CG55)	may-01		OriginalCG, replaced	Excluded	
2	D	Induction of labour (D) (replaced by CG70)	jun-01		OriginalCG, replaced	Excluded	
3	A	Myocardial infarction (A) (replaced by CG48) (withdrawn)	abr-01		OriginalCG, replaced	Excluded	
4	B	Pressure ulcers (see Pressure ulcer management, CG29) (B)	abr-01		OriginalCG, reviewed but not updated		
5	G	Type 2 diabetes - blood glucose (G) (replaced by CG66)	sept-02		OriginalCG, replaced	Excluded	
6	H	Type 2 diabetes - management of blood pressure and blood lipids (H) (replaced by CG66)	oct-02		OriginalCG, replaced	Excluded	
7	F	Type 2 diabetes - renal disease (F)(replaced by CG66)	feb-02		OriginalCG, replaced	Excluded	
8	E	Type 2 diabetes - retinopathy (E) (replaced by CG66)	feb-02		OriginalCG, replaced	Excluded	
9	CG1	Schizophrenia (CG1) (replaced by CG82)	dic-02		OriginalCG, replaced	Excluded	
10	CG2	Infection control (CG2) (replaced by CG139)	jun-03		OriginalCG, replaced	Included	
11	CG3	Preoperative tests (CG3)	jun-03		OriginalCG, not reviewed		
12	CG4	Head injury (CG4) (replaced by CG56) (withdrawn)	jun-03		OriginalCG, replaced	Included	
13	CG5	Chronic heart failure (CG5) (replaced by CG108)	jul-03		OriginalCG, replaced	Included	
14	CG6	Antenatal care (CG6) (replaced by CG62)	oct-03		OriginalCG, replaced	Excluded	
15	CG7	Pressure relieving devices (CG7)	oct-03	may-11	OriginalCG, reviewed but not updated		
16	CG8	Multiple sclerosis (CG8)	nov-03	jun-11	OriginalCG, reviewed but not updated		
17	CG9	Eating disorders (CG9)	ene-04		OriginalCG, not reviewed		
18	CG10	Type 2 diabetes - footcare (CG10)	ene-04	ago-11	OriginalCG, reviewed but not updated		
19	CG11	Fertility (CG11) (replaced by CG156)	feb-04		OriginalCG, replaced	Included	
20	CG12	Chronic obstructive pulmonary disease (CG12) (replaced by CG101)	feb-04		OriginalCG, replaced	Included	
21	CG13	Caesarean section (replaced by CG132) (CG13)	abr-04		OriginalCG, replaced	Included	
22	CG14	Familial breast cancer (CG14) (replaced by CG41) (withdrawn)	may-04		OriginalCG, replaced	Excluded	
23	CG15	Type 1 diabetes (CG15)	jul-04	ago-11	OriginalCG, reviewed but not updated		
24	CG16	Self-harm (CG16)	jul-04	feb-12	OriginalCG, reviewed but not updated		
25	CG17	Dyspepsia (CG17)	ago-04	jul-11	OriginalCG, reviewed but not updated		

26	CG18	Hypertension (CG18) (replaced by CG34) (withdrawn)	ago-04		OriginalCG, replaced	Excluded	
27	CG19	Dental recall (CG19)	oct-04	ago-12	OriginalCG, reviewed but not updated		
28	CG20	Epilepsy (CG20) (replaced by CG137)	oct-04		OriginalCG, replaced	Included	
29	CG21	Falls (CG21)	nov-04	jul-11	OriginalCG, reviewed but not updated		
30	CG22	Anxiety (CG22) (replaced by CG113)	dic-04		OriginalCG, replaced	Excluded	
31	CG23	Depression (CG23) (replaced by CG90)	dic-04		OriginalCG, replaced	Excluded	
32	CG24	Lung cancer (CG24) (replaced by CG121)	feb-05		OriginalCG, replaced	Included	
33	CG25	Violence (CG25)	feb-05	feb-12	OriginalCG, reviewed but not updated		
34	CG26	Post-traumatic stress disorder (PTSD) (CG26)	mar-05		OriginalCG, not reviewed		
35	CG27	Referral for suspected cancer (CG27)	jun-05		OriginalCG, not reviewed		
36	CG28	Depression in children and young people (CG28)	sept-05	feb-11	OriginalCG, reviewed but not updated		
37	CG29	Pressure ulcer management (CG29)	sept-05	may-11	OriginalCG, reviewed but not updated		
38	CG30	Long-acting reversible contraception (CG30)	oct-05	mar-11	OriginalCG, reviewed but not updated		
39	CG31	Obsessive compulsive disorder (OCD) and body dysmorphic disorder (BDD) (CG31)	nov-05		OriginalCG, not reviewed		
40	CG32	Nutrition support in adults (CG32)	feb-06	jun-11	OriginalCG, reviewed but not updated		
41	CG33	Tuberculosis (CG33) (replaced by CG117)	mar-06		OriginalCG, replaced	Excluded	
42	CG34	Hypertension (CG34) (replaced by CG127)	jun-06		UpdatedCG (first update)	Excluded	Not update status
43	CG35	Parkinson's disease (CG35)	jun-06	jul-11	OriginalCG, reviewed but not updated		
44	CG36	Atrial fibrillation (CG36)	jun-06	ago-11	OriginalCG, reviewed but not updated		
45	CG37	Postnatal care (CG37)	jul-06	feb-12	OriginalCG, reviewed but not updated		
46	CG38	Bipolar disorder (CG38)	jul-06	jul-11	OriginalCG, reviewed but not updated		
47	CG39	Anaemia management in chronic kidney disease (CG39) (replaced by CG114)	sept-06		OriginalCG, replaced	Included	
48	CG40	Urinary incontinence (CG40)	oct-06		OriginalCG, not reviewed		
49	CG41	Familial breast cancer (CG41)	oct-06		UpdatedCG (first update)	Excluded	Not partial update
50	CG42	Dementia (CG42)	nov-06	abr-12	OriginalCG, reviewed but not updated		
51	CG43	Obesity (CG43)	dic-06	dic-11	OriginalCG, reviewed but not updated		
52	CG44	Heavy menstrual bleeding (CG44)	ene-07	ene-12	OriginalCG, reviewed but not updated		
53	CG45	Antenatal and postnatal mental health (CG45)	feb-07	jul-11	OriginalCG, reviewed but not updated		
54	CG46	Venous thromboembolism (surgical) (CG46) (replaced by CG92) (withdrawn)	abr-07		OriginalCG, replaced	Excluded	
55	CG47	Feverish illness in children (CG47)	may-07	ene-11	OriginalCG, reviewed but not updated		

56	CG48	MI: secondary prevention (CG48)	may-07	feb-11	UpdatedCG (first update)	Excluded	Not partial update
57	CG49	Faecal incontinence (CG49)	jun-07	dic-10	OriginalCG, reviewed but not updated		
58	CG50	Acutely ill patients in hospital (CG50)	jul-07	dic-10	OriginalCG, reviewed but not updated		
59	CG51	Drug misuse: psychosocial interventions (CG51)	jul-07	mar-11	OriginalCG, reviewed but not updated		
60	CG52	Drug misuse: opioid detoxification (CG52)	jul-07	mar-11	OriginalCG, reviewed but not updated		
61	CG53	Chronic fatigue syndrome / Myalgic encephalomyelitis (CG53)	ago-07	mar-11	OriginalCG, reviewed but not updated		
62	CG54	Urinary tract infection in children (CG54)	ago-07	may-11	OriginalCG, reviewed but not updated		
63	CG55	Intrapartum care (CG55)	sept-07		UpdatedCG (first update)	Excluded	Not partial update
64	CG56	Head injury (CG56)	sept-07	mar-11	UpdatedCG (first update)	Included	
65	CG57	Atopic eczema in children (CG57)	dic-07		OriginalCG, not reviewed		
66	CG58	Prostate cancer (CG58)	feb-08	jul-11	OriginalCG, reviewed but not updated		
67	CG59	Osteoarthritis (CG59)	feb-08	jun-11	OriginalCG, reviewed but not updated		
68	CG60	Surgical management of OME (CG60)	feb-08		OriginalCG, not reviewed		
69	CG61	Irritable bowel syndrome (CG61)	feb-08		OriginalCG, not reviewed		
70	CG62	Antenatal care (CG62)	mar-08	may-11	UpdatedCG (first update)	Excluded	Not update status
71	CG63	Diabetes in pregnancy (CG63)	mar-08	may-11	OriginalCG, reviewed but not updated		
72	CG64	Prophylaxis against infective endocarditis (CG64)	mar-08		OriginalCG, not reviewed		
73	CG65	Perioperative hypothermia (inadvertent) (CG65)	abr-08	nov-11	OriginalCG, reviewed but not updated		
74	CG66	Type 2 diabetes (partially updated by CG87) (CG66)	may-08	ago-11	UpdatedCG (first update)	Excluded	Not partial update
75	CG67	Lipid modification (CG67)	may-08		OriginalCG, not reviewed		
76	CG68	Stroke (CG68)	jul-08	abr-12	OriginalCG, reviewed but not updated		
77	CG69	Respiratory tract infections (CG69)	jul-08	jun-12	OriginalCG, reviewed but not updated		
78	CG70	Induction of labour (CG70)	jul-08	ago-11	UpdatedCG (first update)	Excluded	Not partial update
79	CG71	Familial hypercholesterolaemia (CG71)	ago-08	ago-11	OriginalCG, reviewed but not updated		
80	CG72	Attention deficit hyperactivity disorder (ADHD) (CG72)	sept-08	nov-11	OriginalCG, reviewed but not updated		
81	CG73	Chronic kidney disease (CG73)	sept-08	dic-11	OriginalCG, reviewed but not updated		
82	CG74	Surgical site infection (CG74)	oct-08		OriginalCG, not reviewed		
83	CG75	Metastatic spinal cord compression (CG75)	nov-08	ago-12	OriginalCG, reviewed but not updated		
84	CG76	Medicines adherence (CG76)	ene-09		OriginalCG, not reviewed		
85	CG77	Antisocial personality disorder (CG77)	ene-09	ene-12	OriginalCG, reviewed but not updated		
86	CG78	Borderline personality disorder (BPD) (CG78)	ene-09	ene-12	OriginalCG, reviewed but not updated		
87	CG79	Rheumatoid arthritis (CG79)	feb-09	nov-11	OriginalCG, reviewed but not updated		

88	CG80	Breast cancer (early & locally advanced) (CG80)	feb-09	mar-12	OriginalCG, reviewed but not updated		
89	CG81	Breast cancer (advanced) (CG81)	feb-09	mar-12	OriginalCG, reviewed but not updated		
90	CG82	Schizophrenia (update) (CG82)	mar-09	ago-11	UpdatedCG (first update)	Excluded	Not partial update
91	CG83	Critical illness rehabilitation (CG83)	mar-09	jun-12	OriginalCG, reviewed but not updated		
92	CG84	Diarrhoea and vomiting in children under 5 (CG84)	abr-09	jul-12	OriginalCG, reviewed but not updated		
93	CG85	Glaucoma (CG85)	abr-09	ago-12	OriginalCG, reviewed but not updated		
94	CG86	Coeliac disease (CG86)	may-09	jul-12	OriginalCG, reviewed but not updated		
95	CG87	Type 2 Diabetes - newer agents (partial update of CG66) (CG87)	may-09	ago-11	UpdatedCG (second update)		
96	CG88	Low back pain (CG88)	may-09	jun-12	OriginalCG, reviewed but not updated		
97	CG89	When to suspect child maltreatment (CG89)	jul-09	ago-12	OriginalCG, reviewed but not updated		
98	CG90	Depression in adults (update) (CG90)	oct-09	oct-12	UpdatedCG (first update)	Excluded	Not partial update
99	CG91	Depression with a chronic physical health problem (CG91)	oct-09	oct-12	OriginalCG, reviewed but not updated		
100	CG92	Venous thromboembolism - reducing the risk (CG92)	ene-10	ene-13	UpdatedCG (first update)	Excluded	Not partial update
101	CG93	Donor breast milk banks (CG93)	feb-10	feb-13	OriginalCG, not reviewed		
102	CG94	Unstable angina and NSTEMI (CG94)	mar-10	mar-13	OriginalCG, not reviewed		
103	CG95	Chest pain of recent onset (CG95)	mar-10	mar-13	OriginalCG, not reviewed		
104	CG96	Neuropathic pain - pharmacological management (CG96)	mar-10		OriginalCG, not reviewed		
105	CG97	Lower urinary tract symptoms (CG97)	may-10	may-13	OriginalCG, not reviewed		
106	CG98	Neonatal jaundice (CG98)	may-10	may-13	OriginalCG, not reviewed		
107	CG99	Constipation in children and young people (CG99)	may-10	may-13	OriginalCG, not reviewed		
108	CG100	Alcohol-use disorders: physical complications (CG100)	jun-10	jun-13	OriginalCG, not reviewed		
109	CG101	Chronic obstructive pulmonary disease (updated) (CG101)	jun-10	jun-13	UpdatedCG (first update)	Included	
110	CG102	Bacterial meningitis and meningococcal septicaemia (CG102)	jun-10	jun-13	OriginalCG, not reviewed		
111	CG103	Delirium (CG103)	jul-10	jul-13	OriginalCG, not reviewed		
112	CG104	Metastatic malignant disease of unknown primary origin (CG104)	jul-10	jul-13	OriginalCG, not reviewed		
113	CG105	Motor neurone disease - non-invasive ventilation (CG105)	jul-10	jul-13	OriginalCG, not reviewed		

114	CG106	Barrett's oesophagus - ablative therapy (CG106)	ago-10	ago-13	OriginalCG, not reviewed		
115	CG107	Hypertension in pregnancy (CG107)	ago-10	ago-13	OriginalCG, not reviewed		
116	CG108	Chronic heart failure (CG108)	ago-10	ago-13	UpdatedCG (first update)	Included	
117	CG109	Transient loss of consciousness in adults and young people (CG109)	ago-10	ago-13	OriginalCG, not reviewed		
118	CG110	Pregnancy and complex social factors (CG110)	sept-10	sept-13	OriginalCG, not reviewed		
119	CG111	Nocturnal enuresis - the management of bedwetting in children and young people (CG111)	oct-10	oct-13	OriginalCG, not reviewed		
120	CG112	Sedation in children and young people (CG112)	dic-10		OriginalCG, not reviewed		
121	CG113	Anxiety (CG113)	ene-11		UpdatedCG (first update)	Excluded	Not update status
122	CG114	Anaemia management in people with chronic kidney disease (CG114)	feb-11	dic-11	UpdatedCG (first update)	Included	
123	CG115	Alcohol dependence and harmful alcohol use (CG115)	feb-11		OriginalCG, not reviewed		
124	CG116	Food allergy in children and young people (CG116)	feb-11		OriginalCG, not reviewed		
125	CG117	Tuberculosis (CG117)	mar-11		UpdatedCG (first update)	Excluded	Not update status
126	CG118	Colonoscopic surveillance for prevention of colorectal cancer in people with ulcerative colitis, Crohn's disease or adenomas (CG118)	mar-11		OriginalCG, not reviewed		
127	CG119	Diabetic foot problems - inpatient management (CG119)	mar-11		OriginalCG, not reviewed		
128	CG120	Psychosis with coexisting substance misuse (CG120)	mar-11		OriginalCG, not reviewed		
129	CG121	Lung cancer (CG121)	abr-11		UpdatedCG (first update)	Included	
130	CG122	Ovarian cancer (CG122)	abr-11		OriginalCG, not reviewed		
131	CG123	Common mental health disorders (CG123)	may-11		OriginalCG, not reviewed		
132	CG124	Hip fracture (CG124)	jun-11	TBC	OriginalCG, not reviewed		
133	CG125	Peritoneal dialysis (CG125)	jul-11		OriginalCG, not reviewed		
134	CG126	Stable angina (CG126)	jul-11		OriginalCG, not reviewed		
135	CG127	Hypertension (CG127)	ago-11		UpdatedCG (second update)		
136	CG128	Autism in children and young people (CG128)	sept-11		OriginalCG, not reviewed		
137	CG129	Multiple pregnancy (CG129)	sept-11		OriginalCG, not reviewed		
138	CG130	Hyperglycaemia in acute coronary syndromes (CG130)	oct-11		OriginalCG, not reviewed		
139	CG131	Colorectal cancer (CG131)	nov-11		OriginalCG, not reviewed		

140	CG132	Caesarean section (CG132)	nov-11		UpdatedCG (first update)	Included	
141	CG133	Self-harm (longer term management) (CG133)	nov-11		OriginalCG, not reviewed		
142	CG134	Anaphylaxis (CG134)	dic-11		OriginalCG, not reviewed		
143	CG135	Organ donation (CG135)	dic-11		OriginalCG, not reviewed		
144	CG136	Service user experience in adult mental health (CG136)	dic-11		OriginalCG, not reviewed		
145	CG137	Epilepsy (CG137)	ene-12		UpdatedCG (first update)	Included	
146	CG138	Patient experience in adult NHS services (CG138)	feb-12		OriginalCG, not reviewed		
147	CG139	Infection control (CG139)	mar-12		UpdatedCG (first update)	Included	
148	CG140	Opioids in palliative care (CG140)	may-12		OriginalCG, not reviewed		
149	CG141	Acute upper GI bleeding (CG141)	jun-12		OriginalCG, not reviewed		
150	CG142	Autism in adults (CG142)	jun-12		OriginalCG, not reviewed		
151	CG143	Sickle cell acute painful episode (CG143)	jun-12		OriginalCG, not reviewed		
152	CG144	Venous thromboembolic diseases (CG144)	jun-12		OriginalCG, not reviewed		
153	CG145	Spasticity in children and young people (CG145)	jul-12		OriginalCG, not reviewed		
154	CG146	Osteoporosis fragility fracture (CG146)	ago-12		OriginalCG, not reviewed		
155	CG147	Lower limb peripheral arterial disease (CG147)	ago-12		OriginalCG, not reviewed		
156	CG148	Urinary incontinence in neurological disease (CG148)	ago-12		OriginalCG, not reviewed		
157	CG149	Antibiotics for early-onset neonatal infection (CG149)	ago-12		OriginalCG, not reviewed		
158	CG150	Headaches (CG150)	sept-12		OriginalCG, not reviewed		
159	CG151	Neutropenic sepsis (CG151)	sept-12		OriginalCG, not reviewed		
160	CG152	Crohn's disease (CG152)	oct-12		OriginalCG, not reviewed		
161	CG153	Psoriasis (CG153)	oct-12		OriginalCG, not reviewed		
162	CG154	Ectopic pregnancy and miscarriage (CG154)	dic-12		OriginalCG, not reviewed		
163	CG155	Psychosis and schizophrenia in children and young people (CG155)	ene-13		OriginalCG, not reviewed		
164	CG156	Fertility (CG156)	feb-13		UpdatedCG (first update)	Included	
165	CG157	Hyperphosphataemia in chronic kidney disease (CG157)	mar-13		OriginalCG, not reviewed		
166	CG158	Conduct disorders in children and young people (CG158)	mar-13		OriginalCG, not reviewed		
Source: http://guidance.nice.org.uk/CG/Published (this page was last updated: 09 May 2013). **Accessed:** 15/05/2013.							

Documento adicional 3: Justificación de los cambios en las recomendaciones

	Amended recommendations (n=35)		Deleted recommendations (n=13)		New-replaced recommendations (n=33)	
Documented changes*	n	%	n	%	n	%
. Conflicted with others recommendations	-	-	2	15,4	-	-
. Drug licence	2	5,7	-	-	-	-
. New evidence	1	2,9	2	15,4	21	63,6
. New scope	3	8,6	-	-	-	-
. Recommendation not applicable	-	-	3	23,1	-	-
. Outside the scope	-	-	4	30,8	-	-
. Population	1	2,9	-	-	2	6,1
. Reference guideline updated	4	11,4	-	-	-	-
. Writing style (accuracy, clarity, consistency, terminology)	23	65,7	-	-	11	33,3
. Others	2	5,7	2	15,4	2	6,1
*More than one possible category						

Documento adicional 4: Formatos de presentación de las recomendaciones actualizadas

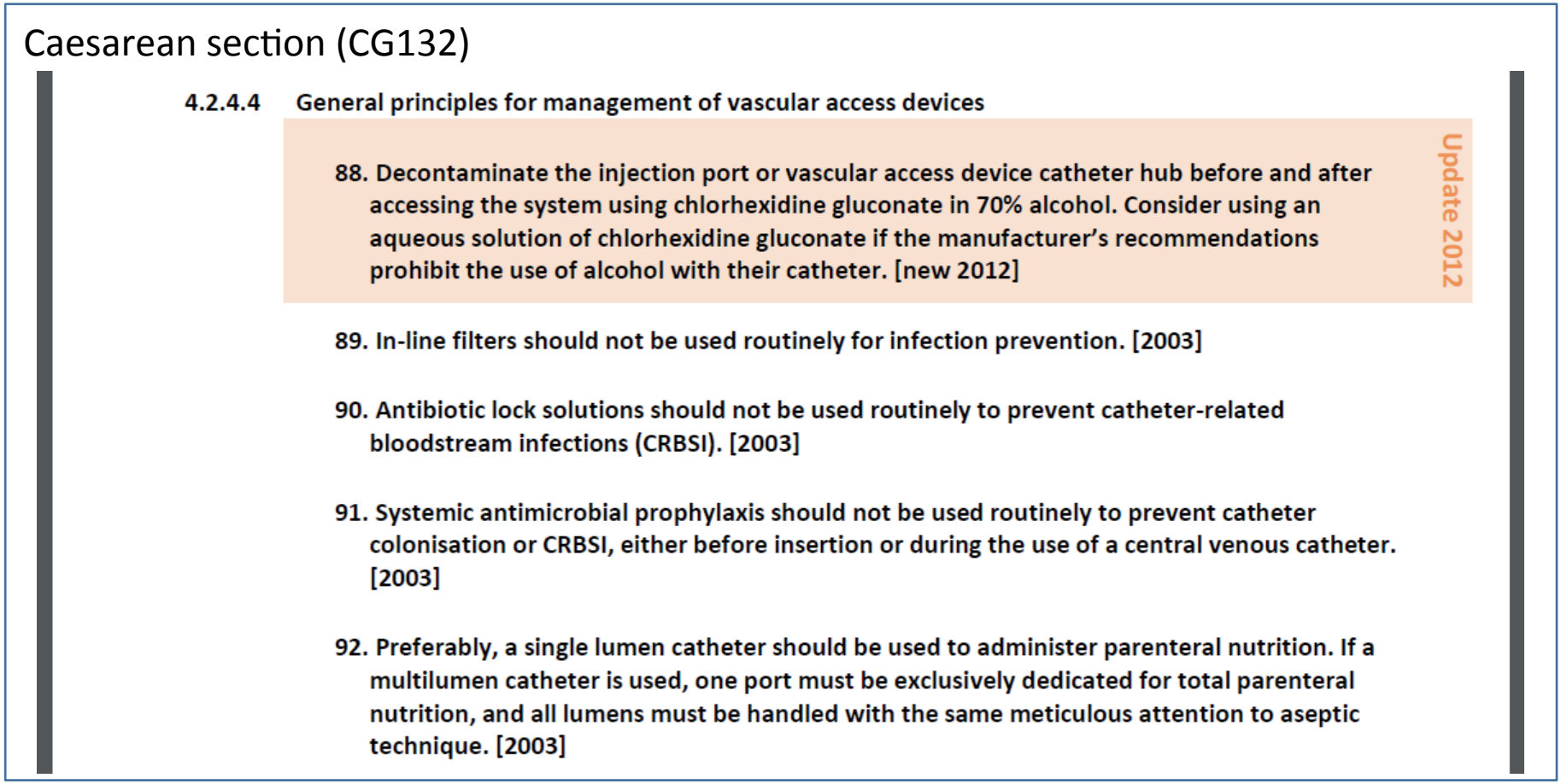
Id	Clinical guidelines	Update status labels?	Highlight colour?	Bar down the side of the page?	Update status definition	Change recorded and/or explained
1	Anaemia management in people with chronic kidney disease (CG114), 2011	Yes	Yes	No	Our assumption: • **without orange color** if the evidence has not been reviewed since the original guideline. • **partially highlighted in orange color or [2006, amended 2011]** if the evidence has not been reviewed, but an essential change has been made that affects the meaning of the recommendation. • **[2011]** if the evidence has been reviewed but no change has been made to the recommendation. • **[new 2011]** if the evidence has been reviewed and the recommendation has been updated or added.	• **Amended** recommendations partially highlighted in orange color and with footnotes • **Deleted** recommendations in "Appendix J: Deleted parts from the 2006 guideline (no longer relevant)" (pg. 544 full CG)
2	Caesarean section (CG132), 2011	Yes	No	Yes	Quote (pg. 2 full CG): *"Recommendations are marked to indicate the year of the last evidence review:* • ***[2004]** if the evidence has not been reviewed since the original guideline.* • ***[2004], amended [2011]** if the evidence has not been reviewed, but an essential change has been made that affects the meaning of the recommendation.* • ***[2011]** if the evidence has been reviewed but no change has been made to the recommendation.* • ***[new 2011]** if the evidence has been reviewed and the recommendation has been updated or added."*	• **Amended, new and deleted** recommendations in "Appendix J Changes to original recommendations"
3	Chronic heart failure (CG108), 2010	Yes	No	No	Quote (pg. 32 full CG): *"The status of each recommendation is indicated as follows:* • ***[2003]**: Recommendation from the 2003 guideline where the evidence has not been formally reviewed for the 2010 update.* • ***[2003, amended 2010]**: A small amendment has been made to the 2003 recommendation but the evidence has not been updated or reviewed.* • ***[2010]**: Recommendation from the 2003 guideline where evidence has been reviewed but the recommendation is not changed. (This includes recommendations which are reworded in a new direct style.)* • ***[new 2010]**: Recommendation from 2003 guideline which has been changed following review of evidence; or New recommendation following review of evidence"*	• **Deleted** recommendations in "Appendix N – 2003 deleted recommendations"
4	Chronic obstructive pulmonary disease (updated) (CG101), 2010	Yes	Yes	No	Our assumption: • **without pink color** Recommendation from the 2004 guideline where the evidence has not been formally reviewed for the 2010 update. • **partially highlighted in pink color** A small amendment has been made to the 2004 recommendation but the evidence has not been updated or reviewed. • **[new 2010]** Recommendation from 2004 guideline which has been changed following review of evidence; or New recommendation following review of evidence • **[Deleted]**	• **Amended** recommendations partially highlighted in pink color • **Deleted** recommendations in "Appendix K NEW 2010 deleted sections from original guideline" (pg. 531 full CG)

5	Epilepsy (CG137), 2012	Yes	Yes	No	Quote (pg. 28 full CG): *"Labelling of recommendations* *• New recommendations are defined as either an additional area for the guideline or changed because of an updated evidence review. New recommendations are labelled by adding **[NEW 2012]** to the end of the recommendation.* *• Unchanged recommendations where the evidence has been reviewed for the 2012 update are labelled as **[2012]**. These recommendations could be reworded to match new-style recommendations but the developers checked with the GDG that rewording hasn't changed the meaning.* *• Unchanged recommendations from 2004, where the evidence has not been formally reviewed for the 2011 update, are labelled as **[2004]**.* *• Where evidence has not been reviewed, but there have been minor changes in 2012 to the wording of a 2004 recommendation that do not affect the meaning, for specific reasons such as in terminology or availability of drugs, these are labelled as **[2004, amended 2012]**.* *Deleted recommendations from the 2004 guideline can be viewed in Appendix X"*	• **Amended** recommendations with footnotes • **Deleted** recommendations in "APPENDIX V Removed sections from original guideline"
6	Fertility (CG156), 2013	Yes	No	Yes	Quote (pg. 4 full CG): *"Recommendations are marked to indicate the year and type of review:* *• **[2004]** if the evidence has not been reviewed since the original guideline.* *• **[2004, amended 2013]** if the evidence has not been reviewed, but an essential change has been made that affects the meaning of the recommendation.* *• **[2013]** if the evidence has been reviewed but no change has been made to the recommendation.* *• **[new 2013]** if the evidence has been reviewed and the recommendation has been updated or added."*	• **Amended, new and deleted** recommendations in "Appendix L Proposed changes to original recommendations"
7	Head injury (CG56), 2007	Yes	Yes	No	Quote (pg. 30 full CG): *"In this update, there are new recommendations in the sections on prehospital management, emergency department assessment, investigations for clinically important brain injuries, investigation for non-accidental injury in children, and transfer from secondary settings. These are highlighted in the document as **'New'**. A number of amendments have been made to other recommendations from the initial guideline, and these are highlighted in the document as **'Amended'**."*	-
8	Infection control (CG139), 2012	Yes	Yes	No	Quote (pg. 4 full CG): *"Recommendations are marked to indicate the year of the last evidence review:* *• **[2003]** if the evidence has not been updated since the original guideline,* *• **[2003, amended 2012]** if the evidence has not been updated since the original guideline, but changes have been made that alter the meaning of the recommendation,* *• **[2012]** if the evidence has been reviewed but no change has been made to the recommendation and* *• **[new 2012]** if the evidence has been reviewed and the recommendation has been added or updated."*	• **Amended, new and deleted** recommendations in "Appendix D: D.10 Deleted and amended recommendations (2003)"

9	Lung cancer (CG121), 2011	Yes	No	Yes	Quote (pg. 1 full CG): *"Recommendations are marked as [2005], [2011] or [new 2011].* ***[2005]** indicates that the evidence has not been updated and reviewed since 2005.* ***[2011]** indicates that the evidence has been reviewed but no changes have been made to the recommendation.* ***[new 2011]** indicates that the evidence has been reviewed and the recommendation has been added or updated."*	-

Documento adicional 5: Ejemplos de formatos de presentación de las recomendaciones actualizadas

Presentation format example - recommendations update status labels plus highlight colour



Reference: National Institute for Clinical Excellence. CG132 - Caesarean section (update). http://guidance.nice.org.uk/CG132 (accessed 15 May, 2013).

Presentation format example - recommendations update status labels plus bar down the side of the page

Infection control (CG139)

Provision of information

1	Pregnant women should be offered evidence-based information and support to enable them to make informed decisions about childbirth. Addressing women's views and concerns should be recognised as being integral to the decision-making process. [C] **[2004]**	4.1
2	Give pregnant women evidence-based information about CS during the antenatal period, because about 1 in 4 women will have a CS. Include information about CS, such as: • indications for CS (such as presumed fetal compromise, 'failure to progress' in labour, breech presentation) • what the procedure involves • associated risks and benefits • implications for future pregnancies and birth after CS. [GPP] **[new 2011]**	4.1

2011 update

Reference: National Institute for Clinical Excellence. CG139 - Infection: prevention and control of healthcare-associated infections in primary and community care. http://guidance.nice.org.uk/CG139 (accessed 15 May, 2013).

Presentation format example - head to head comparison between original and updated recommendations

Fertility (CG156)

Recommendation	Replaced with	Reason for change/deletion
	response and less than 4 IU/l for a high response[6]. **[new 2013]**	
Women should be informed that the value of assessing ovarian reserve using inhibin B is uncertain and is therefore not recommended. [C]	Do not use any of the following tests individually to predict any outcome of fertility treatment: • ovarian volume • ovarian blood flow • inhibin B • oestradiol (E2). **[new 2013]**	New evidence on ovarian reserve was reviewed and and the recommendation has been updated accordingly.

Reference: National Institute for Clinical Excellence. CG156 - Fertility: assessment and treatment for people with fertility problems. http://guidance.nice.org.uk/CG156 (accessed 15 May, 2013).

Documento adicional 6: Resultados de la puntuación para valorar el registro de los cambios en las recomendaciones actualizadas

Id	CGs	Recommendation update status defined?	Amended - Changes recorded?	Amended - Changes explanation?	Deleted - Changes recorded?	Deleted - Changes explanation?	New (replaced) - Changes recorded?	New (replaced) - Changes explanation?	Points	Max possible points	10 Score
1	Anaemia management in people with chronic kidney disease (CG114), 2011	0	1	1	1	0	0	0	**3**	7	**4,3**
2	Caesarean section (CG132), 2011	1	1	1	1	1	1	1	**7**	7	**10,0**
3	Chronic heart failure (CG108), 2010	1	0	0	1	0	0	0	**2**	7	**2,9**
4	Chronic obstructive pulmonary disease (updated) (CG101), 2010	0	1	0	1	0	-	-	**2**	5	**4,0**
5	Epilepsy (CG137), 2012	1	1	1	1	1	0	0	**5**	7	**7,1**
6	Fertility (CG156), 2013	1	1	1	1	1	1	1	**7**	7	**10,0**
7	Head injury (CG56), 2007	1	0	0	0	0	0	0	**1**	7	**1,4**
8	Infection control (CG139), 2012	1	1	1	1	0	1	0	**5**	7	**7,1**
9	Lung cancer (CG121), 2011	1	-	-	0	0	-	-	**1**	3	**3,3**

Publicación V: Evaluación de dos estrategias pragmáticas de búsqueda de la literatura

Documento adicional 1: Ejemplo de las estrategias de búsqueda de la literatura diseñadas para una pregunta clínica

Clinical guideline Clinical Practice Guideline on the Management of Major Depression in Adults, 2008
Clinical question Is treatment with St John's Wort effective?

Exhaustive approach, randomized control trials, MEDLINE	
5	Search #3 AND #4
4	Search ("Clinical trials as Topic"[MH] OR "clinical trial"[PT] OR "controlled clinical trial"[PT] OR "single blind method"[MH] OR "double blind method"[MH] OR "cross over studies"[MH] OR "random allocation"[MH]) OR ((Trial*[TIAB] OR Random*[TIAB]) AND ("blind"[TIAB]))
3	Search #1 AND #2 Limits: English, French, Italian, Spanish, Catalan, Portuguese, All Adult: 19+ years, Publication Date from 2007 to 2011
2	("Depressive Disorder"[MH] OR "Depressive Disorder, Major"[MH] OR "Dysthymic Disorder"[MH] OR "Seasonal Affective Disorder"[MH] OR Depressi*[TI] OR Dysthym*[TI] OR Seasonal[TI] OR "Affective"[TI]) NOT ("Bipolar Disorder"[MH] OR "Depression, Postpartum"[MH] OR Mania*[TI] OR Bipolar*[TI] OR Puerper*[TI] OR Postpart*[TI] OR Pregnan*[TI] OR Post-Natal*[TI] OR Postnatal[TI]) Limits: English, French, Italian, Spanish, Catalan, Portuguese, All Adult: 19+ years, Publication Date from 2007 to 2011
1	"Hypericum"[MeSH] OR "Hypericum perforatum" [TW] OR "Saint John's Wort" [TW] OR "St. John's Wort" [TW] OR "St. Johns Wort" [TW]

Exhaustive approach, randomized control trials, EMBASE	
1	exp 'hypericum perforatum'/
2	("Hypericum" or "Hypericum perforatum" or "Saint John's Wort" or "St. John's Wort" or "St. Johns Wort").ti,sh,hw,ab,tn,dm,kw.
3	1 or 2
4	exp depression/ or exp recurrent brief depression/ or exp endogenous depression/ or exp reactive depression/ or exp major depression/ or exp involutional depression/
5	exp dysthymia/
6	exp seasonal affective disorder/
7	4 or 5 or 6

8	(depressi* or dysthym* or "Seasonal Affective" or Involutional*).ti.
9	exp manic psychosis/
10	exp bipolar disorder/
11	puerperal depression/
12	9 or 10 or 11
13	(Mania* or Bipolar* or Postpart* or Puerper* or Pregnant*).ti.
14	7 or 8
15	12 or 13
16	14 not 15
17	limit 16 to (embase and (basque or catalan or english or french or gallegan or italian or portuguese or spanish) and yr="2006 - 2011" and adult <18 to 64 years>)
18	exp clinical trial/
19	exp crossover procedure/
20	exp randomization/
21	exp randomized controlled trial/
22	exp double blind procedure/
23	exp single blind procedure/
24	exp triple blind procedure/
25	(single or double or triple).ti,ab.
26	(blind and method*).ti,ab.
27	25 and 26
28	"random*".ti,ab.
29	"trial*".ti,ab.
30	18 or 19 or 20 or 21 or 22 or 23 or 24 or 27 or 28 or 29
31	"systematic review".af,ti,ab.
32	30 not 31
33	17 and 32
34	3 and 33

Exhaustive approach, randomized control trials, Psychinfo	
1	exp hypericum perforatum/
2	("Hypericum" or "Hypericum perforatum" or "Saint John's Wort" or "St. John's Wort" or "St. Johns Wort").ab,hw,id,sh,ti.
3	1 or 2
4	clinical trials/
5	(randomized adj4 Trials).ab,ti.
6	(crossover adj5 design).ab,ti.

7	(random adj4 assignment).ab,ti.
8	(double adj1 blind).ab,ti.
9	(single adj1 blind).ab,ti.
10	(triple adj1 blind).ab,ti.
11	randomization.ab,ti.
12	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13	(systematic adj3 review).ab,sh,ti.
14	12 not 13
15	seasonal affective disorder/
16	"depression (emotion)"/
17	reactive depression/
18	recurrent depression/
19	endogenous depression/
20	anaclitic depression/
21	15 or 16 or 17 or 18 or 19 or 20
22	"depress*".ti.
23	seasonal affective disorder.ti.
24	22 or 23
25	21 or 24
26	bipolar disorder/
27	postpartum depression/
28	pregnancy/
29	(mania* or bipolar* or pregnan* or postpart* or puerper*).ti.
30	26 or 27 or 28 or 29
31	25 not 30
32	limit 31 to (adulthood <18+ years> and "300 adulthood " and (catalan or english or french or italian or portuguese or spanish) and yr="2007 - 2011")
33	14 and 32
34	3 and 33

Exhaustive approach, systematic reviews, MEDLINE	
5	Search #3 AND #4
4	((Systematic Review*[TIAB] OR systematic literature review*[TIAB] OR meta-analysis[PT] OR "meta analysis as topic"[MH] OR meta-analysis[TI] OR meta-analysis[TI] OR metaanalys*[TI] OR "evidence-based"[TI]) OR (("evidence-based" OR Review* OR Overview* OR Survey* OR recommendation* OR consensus development conference[PT] OR health planning guidelines OR guideline[PT]) AND (systematic[TIAB] OR systematically OR critical[TIAB] OR studie*[TIAB] OR study[TIAB] AND selection[TIAB] OR (inclusion criteri*) OR (exclusion criteri*) OR

	review*[TIAB] OR search* OR analysis[TIAB] OR critique*[TIAB] OR appraisal OR "mantel haenszel" OR peto OR dersimonian OR (der simonian) OR handsearch*[TIAB] OR bibliography*[TIAB] OR citation* OR database*[TIAB] OR "medline" OR "embase" OR "scisearch" OR "science citation" OR "isi web" OR "web of science" OR internet[TIAB] OR reference* OR trial*[TIAB]))) NOT ("Case report"[TI] OR "editorial"[TI] OR "editorial"[PT] OR "letter"[PT] OR "newspaper article"[PT] OR "Clinical Trial"[PT])
3	#1 AND #2 Limits: English, French, Italian, Spanish, Catalan, Portuguese, All Adult: 19+ years, Publication Date from 2007 to 2011
2	("Depressive Disorder"[MH] OR "Depressive Disorder, Major"[MH] OR "Dysthymic Disorder"[MH] OR "Seasonal Affective Disorder"[MH] OR Depressi*[TI] OR Dysthym*[TI] OR Seasonal[TI] OR "Affective"[TI]) NOT ("Bipolar Disorder"[MH] OR "Depression, Postpartum"[MH] OR Mania*[TI] OR Bipolar*[TI] OR Puerper*[TI] OR Postpart*[TI] OR Pregnan*[TI] OR Post-Natal*[TI] OR Postnatal[TI]) Limits: English, French, Italian, Spanish, Catalan, Portuguese, All Adult: 19+ years, Publication Date from 2007 to 2011
1	"Hypericum"[MeSH] OR "Hypericum perforatum" [TW] OR "Saint John's Wort" [TW] OR "St. John's Wort" [TW] OR "St. Johns Wort" [TW]

Exhaustive approach, systematic reviews, EMBASE	
1	exp 'hypericum perforatum'/
2	("Hypericum" or "Hypericum perforatum" or "Saint John's Wort" or "St. John's Wort" or "St. Johns Wort").ti,sh,hw,ab,tn,dm,kw.
3	1 or 2
4	exp meta analysis/ or exp evidence based medicine/ or exp statistical analysis/
5	exp "meta analysis (topic)"/
6	(meta analysis or metaanalysis or meta-analysis).ti.
7	(meta analysis or metaanalysis or meta-analysis).ab.
8	"systematic review"/ or "systematic review (topic)"/
9	((systematic or literature) and review).ti.
10	((systematic or literature) and review).ab.
11	9 or 10
12	(evidence* or review* or overview* or survey or surveis).ab.
13	(evidence* or review* or overview* or survey or surveis).ti.
14	12 or 13
15	4 or 5 or 6 or 7 or 8 or 11 or 14
16	databases.ti. or databases.ab.
17	medline.ti. or medline.ab. or Embase.ti. or Embase.ab. or pubmed.ti. or Pubmed.ab. or Cocrhane.ti. or Cocrhane.ab. or Scisearch.ti. or Scisearch.ab. or Isi web.ti.
18	16 and 17
19	((handsearch and literature) or bibliograph*).ab.
20	18 or 19
21	15 and 20

22	exp depression/ or exp recurrent brief depression/ or exp.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
23	exp dysthymia/
24	exp seasonal affective disorder/
25	22 or 23 or 24
26	(depressi* or dysthym* or "Seasonal Affective" or Involutional*).ti.
27	exp manic psychosis/
28	exp bipolar disorder/
29	puerperal depression/
30	(Mania* or Bipolar* or Postpart* or Puerper* or Pregnant*).ti.
31	25 or 26
32	27 or 28 or 29 or 30
33	31 not 32
34	21 and 33
35	limit 34 to (embase and (basque or catalan or english or french or gallegan or italian or portuguese or spanish) and adult <18 to 64 years>)
36	3 and 35

Exhaustive approach, systematic reviews, Psychinfo	
1	exp hypericum perforatum/
2	("Hypericum" or "Hypericum perforatum" or "Saint John's Wort" or "St. John's Wort" or "St. Johns Wort").ab,hw,id,sh,ti.
3	1 or 2
4	(metaanaly* or meta analy* or meta-analy*).tw.
5	(research or systematic or quantitative or methodologic*).af.
6	(overview* or review* or integration*).af.
7	5 and 6
8	databases.ti. or databases.ab.
9	medline.ti. or medline.ab. or Embase.ti. or Embase.ab. or pubmed.ti. or Pubmed.ab. or Cocrhane.ti. or Cocrhane.ab. or Scisearch.ti. or Scisearch.ab. or Isi web.ti.
10	((handsearch and literature) or bibliograph*).ab.
11	4 or 7
12	8 or 10
13	9 and 12
14	11 and 13
15	(case report or editorial).ti. or editorial.pt. or letter.ti. or letter.pt. or newspaper article.pt. or newspaper.ti.

16	14 not 15
17	exp seasonal affective disorder/
18	exp major depression/ or exp anaclitic depression/ or exp "depression (emotion)"/ or exp endogenous depression/ or exp reactive depression/ or exp recurrent depression/
19	depress*.ti.
20	seasonal affective disorder.ti.
21	17 or 18 or 19 or 20
22	exp postpartum depression/
23	exp pregnancy/
24	(mania* or bipolar* or pregnan* or postpart* or puerper*).ti.
25	exp bipolar disorder/
26	22 or 23 or 24 or 25
27	21 not 26
28	limit 27 to (adulthood <18+ years> and "300 adulthood " and (catalan or english or french or italian or portuguese or spanish) and yr="2007 - 2011")
29	16 and 28
30	3 and 29

Restrictive approach, randomized controlled trials, broad filter	
9	(#8) AND (((((English[lang] OR French[lang] OR Italian[lang] OR Spanish[lang] OR Catalan[lang] OR Portuguese[lang])) AND ("2007/01/01"[PDat] : "2011/06/20"[PDat]))))
8	(Therapy/Broad[filter]) AND (#7)
7	(#3) AND #6
6	(#4) OR #5
5	John’s Wort[ti]
4	"Hypericum"[Mesh]
3	(#1) OR #2
2	Depress*[ti]
1	"Depressive Disorder"[Mesh]

Restrictive approach, randomized controlled trials, narrow filter	
9	(#8) AND (((((English[lang] OR French[lang] OR Italian[lang] OR Spanish[lang] OR Catalan[lang] OR Portuguese[lang])) AND ("2007/01/01"[PDat] : "2011/06/20"[PDat]))))
8	(Therapy/Narrow[filter]) AND (#7)
7	(#3) AND #6
6	(#4) OR #5

5	John’s Wort[ti]
4	"Hypericum"[Mesh]
3	(#1) OR #2
2	Depress*[ti]
1	"Depressive Disorder"[Mesh]

Restrictive approach, systematic reviews	
9	(#8) AND (((((English[lang] OR French[lang] OR Italian[lang] OR Spanish[lang] OR Catalan[lang] OR Portuguese[lang])) AND ("2007/01/01"[PDat] : "2011/06/20"[PDat]))))
8	(#7) AND ((((((MEDLINE[Title/Abstract] OR (systematic[Title/Abstract] AND review[Title/Abstract]) OR meta analysis[Publication Type]))))))
7	(#3) AND #6
6	(#4) OR #5
5	John’s Wort[ti]
4	"Hypericum"[Mesh]
3	(#1) OR #2
2	Depress*[ti]
1	"Depressive Disorder"[Mesh]

PLUS approach
((Depression [MeSH] ORDepressive Disorder[MeSH] ORDepressive Disorder, Major[MeSH] ORDepressive Disorder, Treatment-Resistant[MeSH] ORSuicide[MeSH] ORSuicidal Ideation[MeSH] ORSuicide, Assisted[MeSH] ORSuicide, Attempted[MeSH] ORAntidepressive Agents [MeSH] ORAntidepressive Agents, Second-Generation[MeSH] ORAntidepressive Agents, Tricyclic[MeSH]) OR (depressive disorder (disorder) [SNOMED CT: 35489007] OR depressive disorder (disorder) x Physical agent therapy (regime/therapy) [SNOMED CT: 35489007x229553000] OR depressive disorder (disorder) x Drug therapy (procedure) [SNOMED CT: 35489007x416608005] OR Depression(disorder) x psychological therapies (procedure) [SNOMED CT: 35489007x390822007] OR Self-injurious behavior (finding) [SNOMED CT: 248062006]))

Documento adicional 2: Referencias clave identificadas según las diferentes estrategias de búsqueda de la literatura

IdRef	CPG	IdRecom	Recommendation	IdDatabase	Key reference	Restrictive approach* [0=No, 1=Yes]	PLUS approach [0=No, 1=Yes]
1	Major Depression in Adults 2008	1485	If the patient does not improve at the third or fourth week, any of the following strategies could be followed: 1)Switching from an antidepressant to any family, including another serotonergic. 2)Combining antidepressants. 3)Augmenting the initiated treatment with lithium or triiodothyronine.	17288688	Dorée JP, Des Rosiers J, Lew V, Gendron A, Elie R, Stip E, et al. Quetiapine augmentation of treatment-resistant depression: a comparison with lithium. Curr Med Res Opin. 2007;23(2):333-41.	1	0
2	Major Depression in Adults 2008	1485	If the patient does not improve at the third or fourth week, any of the following strategies could be followed: 1)Switching from an antidepressant to any family, including another serotonergic. 2)Combining antidepressants. 3)Augmenting the initiated treatment with lithium or triiodothyronine.	18047754	Cooper-Kazaz R, Lerer B. Efficacy and safety of triiodothyronine supplementation in patients with major depressive disorder treated with specific serotonin reuptake inhibitors. Int J Neuropsychopharmacol. 2008;11(5):685-99.	1	0
3	Major Depression in Adults 2008	1490	There is insufficient data for recommending augmentation with valproate, carbamazepine, lamotrigine, gabapentin or topiramate, pindolol, benzodiazepines, buspirone, methylphenidate or atypical antipsychotics.	17592905	Papakostas GI, Shelton RC, Smith J, Fava M. Augmentation of antidepressants with atypical antipsychotic medications for treatment-resistant major depressive disorder: a meta-analysis. J Clin Psychiatry. 2007;68(6):826-31.	1	0
4	Major Depression in Adults 2008	1490	There is insufficient data for recommending augmentation with valproate, carbamazepine, lamotrigine, gabapentin or topiramate, pindolol, benzodiazepines, buspirone, methylphenidate or atypical antipsychotics.	17592907	Berman RM, Marcus RN, Swanink R, McQuade RD, Carson WH, Corey-Lisle PK, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled study. J Clin Psychiatry. 2007;68(6):843-53.	1	0
5	Major Depression in Adults 2008	1490	There is insufficient data for recommending augmentation with valproate, carbamazepine, lamotrigine, gabapentin or topiramate, pindolol, benzodiazepines, buspirone, methylphenidate or atypical antipsychotics.	17975181	Mahmoud RA, Pandina GJ, Turkoz I, Kosik-Gonzalez C, Canuso CM, Kujawa MJ, et al. Risperidone for treatment-refractory major depressive disorder: a randomized trial. Ann Intern Med. 2007;147(9):593-602.	1	1
6	Major Depression in Adults 2008	1490	There is insufficient data for recommending augmentation with valproate, carbamazepine, lamotrigine, gabapentin or topiramate, pindolol, benzodiazepines, buspirone, methylphenidate or atypical antipsychotics.	18344725	Marcus RN, McQuade RD, Carson WH, Hennicken D, Fava M, Simon JS, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a second multicenter, randomized, double-blind, placebo-controlled study. J Clin Psychopharmacol. 2008;28(2):156-65.	1	1

7	Major Depression in Adults 2008	1490	There is insufficient data for recommending augmentation with valproate, carbamazepine, lamotrigine, gabapentin or topiramate, pindolol, benzodiazepines, buspirone, methylphenidate or atypical antipsychotics.	18586273	Keitner GI, Garlow SJ, Ryan CE, Ninan PT, Solomon DA, Nemeroff CB, et al. A randomized, placebo-controlled trial of risperidone augmentation for patients with difficult-to-treat unipolar, non-psychotic major depression. J Psychiatr Res. 2009;43(3):205-14.	1	0
8	Major Depression in Adults 2008	1490	There is insufficient data for recommending augmentation with valproate, carbamazepine, lamotrigine, gabapentin or topiramate, pindolol, benzodiazepines, buspirone, methylphenidate or atypical antipsychotics.	EL KHALILI	El Khalili, N., Bauer, M., Datto, C., Earley, W., Astrom, M., and Eriksson, H. Pooled analysis of adjunctive extended release quetiapine fumarate (Quetiapine XR) in patients with major depressive disorder (MDD). European Psychiatry Conference: 17th European Psychiatric Association, EPA Congress. Lisbon, Portugal. 2009. 24(pp S637).	0	0
9	Major Depression in Adults 2008	1490	There is insufficient data for recommending augmentation with valproate, carbamazepine, lamotrigine, gabapentin or topiramate, pindolol, benzodiazepines, buspirone, methylphenidate or atypical antipsychotics.	19358791	Bauer M, Pretorius HW, Constant EL, Earley WR, Szamosi J, Brecher M. Extended-release quetiapine as adjunct to an antidepressant in patients with major depressive disorder: results of a randomized, placebo-controlled, double-blind study. J Clin Psychiatry. 2009;70(4):540-9.	1	0
10	Major Depression in Adults 2008	1490	There is insufficient data for recommending augmentation with valproate, carbamazepine, lamotrigine, gabapentin or topiramate, pindolol, benzodiazepines, buspirone, methylphenidate or atypical antipsychotics.	19687129	Nelson JC, Papakostas GI. Atypical antipsychotic augmentation in major depressive disorder: a meta-analysis of placebo-controlled randomized trials. Am J Psychiatry. 2009;166(9):980-91.	0	1
11	Major Depression in Adults 2008	1490	There is insufficient data for recommending augmentation with valproate, carbamazepine, lamotrigine, gabapentin or topiramate, pindolol, benzodiazepines, buspirone, methylphenidate or atypical antipsychotics.	20433324	Thomas SP, Nandhra HS, Jayaraman A. Systematic review of lamotrigine augmentation of treatment resistant unipolar depression (TRD). J Ment Health. 2010;19(2):168-75.	1	0
12	Major Depression in Adults 2008	1490	There is insufficient data for recommending augmentation with valproate, carbamazepine, lamotrigine, gabapentin or topiramate, pindolol, benzodiazepines, buspirone, methylphenidate or atypical antipsychotics.	20175941	El-Khalili N, Joyce M, Atkinson S, Buynak RJ, Datto C, Lindgren P, et al. Extended-release quetiapine fumarate (quetiapine XR) as adjunctive therapy in major depressive disorder (MDD) in patients with an inadequate response to ongoing antidepressant treatment: a multicentre, randomized, double-blind, placebo-controlled study. Int J Neuropsychopharmacol. 2010;13(7):917-32.	1	0
13	Major Depression in Adults 2008	1511	The use of St John's Wort is not recommended as a treatment option for patients with major depression.	18843608	Linde K, Berner MM, Kriston L. St John's wort for major depression. Cochrane Database Syst Rev. 2008 Oct 8;(4):CD000448. doi: 0.1002/14651858.CD000448.pub3.	0	1
14	Obesity in Childhood and Adolescence 2009	1050	Schools should include educational programmes which aim to improve diet, increase physical activity levels and reduce sedentary lifestyles. These should include families and teaching staff	21679476	Bjelland M, Bergh IH, Grydeland M, Klepp KI, Andersen LF, Anderssen SA, et al. Changes in adolescents' intake of sugar-sweetened beverages and sedentary behaviour: results at 8 month mid-way assessment of the HEIA study--a comprehensive, multi-component school-based randomized trial. Int J Behav Nutr Phys Act. 2011;8:63.	1	0

15	Obesity in Childhood and Adolescence 2009	1053	Multidisciplinary interventions should be implemented in schools to encourage children and adolescents to eat fruit and vegetables.	18719006	de Sa J, Lock K. Will European agricultural policy for school fruit and vegetables improve public health? A review of school fruit and vegetable programmes. Eur J Public Health. 2008;18(6):558-68.	1	0
16	Obesity in Childhood and Adolescence 2009	1053	Multidisciplinary interventions should be implemented in schools to encourage children and adolescents to eat fruit and vegetables.	21371499	Hoffman JA, Thompson DR, Franko DL, Power TJ, Leff SS, Stallings VA. Decaying behavioral effects in a randomized, multi-year fruit and vegetable intake intervention. Prev Med. 2011;52(5):370-5.	1	0
17	Obesity in Childhood and Adolescence 2009	1095	Physical activity programmes outside school hours are recommended for children and adolescents. These must be suited to their ages and preferences.	21852659	de Heer HD, Koehly L, Pederson R, Morera O. Effectiveness and spillover of an after-school health promotion program for Hispanic elementary school children. Am J Public Health. 2011;101(10):1907-13.	1	0
18	Obesity in Childhood and Adolescence 2009	1101	Educational programmes that target the family so as to encourage a healthy lifestyle are needed. These must cover healthy eating, education to understand nutritional information on food labels and the promotion of active leisure activities.	18180410	Paineau DL, Beaufils F, Boulier A, Cassuto DA, Chwalow J, Combris P, et al. Family dietary coaching to improve nutritional intakes and body weight control: a randomized controlled trial. Arch Pediatr Adolesc Med. 2008;162(1):34-43.	1	1
19	Obesity in Childhood and Adolescence 2009	1101	Educational programmes that target the family so as to encourage a healthy lifestyle are needed. These must cover healthy eating, education to understand nutritional information on food labels and the promotion of active leisure activities.	20107454	Olvera N, Bush JA, Sharma SV, Knox BB, Scherer RL, Butte NF. BOUNCE: a community-based mother-daughter healthy lifestyle intervention for low-income Latino families. Obesity (Silver Spring). 2010;18 **Suppl** 1:S102-4.	1	0
20	Obesity in Childhood and Adolescence 2009	1101	Educational programmes that target the family so as to encourage a healthy lifestyle are needed. These must cover healthy eating, education to understand nutritional information on food labels and the promotion of active leisure activities.	20107464	Fulkerson JA, Rydell S, Kubik MY, Lytle L, Boutelle K, Story M, et al. Healthy Home Offerings via the Mealtime Environment (HOME): feasibility, acceptability, and outcomes of a pilot study. Obesity (Silver Spring). 2010;18 **Suppl** 1:S69-74.	1	0
21	Obesity in Childhood and Adolescence 2009	1101	Educational programmes that target the family so as to encourage a healthy lifestyle are needed. These must cover healthy eating, education to understand nutritional information on food labels and the promotion of active leisure activities.	19933120	Chen JL, Weiss S, Heyman MB, Lustig RH. Efficacy of a child-centred and family-based program in promoting healthy weight and healthy behaviors in Chinese American children: a randomized controlled study. J Public Health (Oxf). 2010;32(2):219-29.	1	0
22	Obesity in Childhood and Adolescence 2009	1101	Educational programmes that target the family so as to encourage a healthy lifestyle are needed. These must cover healthy eating, education to understand nutritional information on food labels and the promotion of active leisure activities.	21041592	Robinson TN, Matheson DM, Kraemer HC, Wilson DM, Obarzanek E, Thompson NS, et al. A randomized controlled trial of culturally tailored dance and reducing screen time to prevent weight gain in low-income African American girls: Stanford GEMS. Arch Pediatr Adolesc Med. 2010;164(11):995-1004.	1	1

23	Obesity in Childhood and Adolescence 2009	1101	Educational programmes that target the family so as to encourage a healthy lifestyle are needed. These must cover healthy eating, education to understand nutritional information on food labels and the promotion of active leisure activities.	20508978	Karanja N, Lutz T, Ritenbaugh C, Maupome G, Jones J, Becker T, et al. The TOTS community intervention to prevent overweight in American Indian toddlers beginning at birth: a feasibility and efficacy study. J Community Health. 2010;35(6):667-75.	1	0
24	Obesity in Childhood and Adolescence 2009	1101	Educational programmes that target the family so as to encourage a healthy lifestyle are needed. These must cover healthy eating, education to understand nutritional information on food labels and the promotion of active leisure activities.	20576004	Monasta L, Batty GD, Macaluso A, Ronfani L, Lutje V, Bavcar A, et al. Interventions for the prevention of overweight and obesity in preschool children: a systematic review of randomized controlled trials. Obes Rev. 2011;12(5):e107-18.	1	0
25	Obesity in Childhood and Adolescence 2009	1119	Televisions, video consoles and computers should be removed from the bedrooms of children and adolescents who are overweight or obese.	21708797	Maniccia DM, Davison KK, Marshall SJ, Manganello JA, Dennison BA. A meta-analysis of interventions that target children's screen time for reduction. Pediatrics. 2011;128(1):e193-210.	1	0
26	Obesity in Childhood and Adolescence 2009	1125	Combined interventions including diet, physical exercise and changes to behaviour, with family involvement, are recommended for weight loss in children and adolescents aged 6-16 who are overweight or obese.	19160202	Oude Luttikhuis H, Baur L, Jansen H, Shrewsbury VA, O'Malley C, Stolk RP, et al. Interventions for treating obesity in children. Cochrane Database Syst Rev. 2009 Jan 21;(1):CD001872. doi: 10.1002/14651858.CD001872.pub2.	NA	1
27	Obesity in Childhood and Adolescence 2009	1125	Combined interventions including diet, physical exercise and changes to behaviour, with family involvement, are recommended for weight loss in children and adolescents aged 6-16 who are overweight or obese.	19628106	Yackobovitch-Gavan M, Nagelberg N, Phillip M, Ashkenazi-Hoffnung L, Hershkovitz E, Shalitin S. The influence of diet and/or exercise and parental compliance on health-related quality of life in obese children. Nutr Res. 2009;29(6):397-404.	NA	0
28	Obesity in Childhood and Adolescence 2009	1125	Combined interventions including diet, physical exercise and changes to behaviour, with family involvement, are recommended for weight loss in children and adolescents aged 6-16 who are overweight or obese.	Reinehr	Reinehr T, Schaefer A, Winkel K, Finne E, Kolip P. An effective lifestyle intervention in overweight children ('Obeldicks light'): Long-term findings from a randomized controlled trial. Obesity Reviews. 2010.	NA	0
29	Obesity in Childhood and Adolescence 2009	1125	Combined interventions including diet, physical exercise and changes to behaviour, with family involvement, are recommended for weight loss in children and adolescents aged 6-16 who are overweight or obese.	20107463	Sacher PM, Kolotourou M, Chadwick PM, Cole TJ, Lawson MS, Lucas A, et al. Randomized controlled trial of the MEND program: a family-based community intervention for childhood obesity. Obesity (Silver Spring). 2010;18 **Suppl** 1:S62-8.	NA	0
30	Obesity in Childhood and Adolescence 2009	1125	Combined interventions including diet, physical exercise and changes to behaviour, with family involvement, are recommended for weight loss in children and adolescents aged 6-16 who are overweight or obese.	20447648	Okely AD, Collins CE, Morgan PJ, Jones RA, Warren JM, Cliff DP, et al. Multi-site randomized controlled trial of a child-centered physical activity program, a parent-centered dietary-modification program, or both in overweight children: the HIKCUPS study. J Pediatr. 2010;157(3):388-94, 394.e1.	NA	0

31	Obesity in Childhood and Adolescence 2009	1125	Combined interventions including diet, physical exercise and changes to behaviour, with family involvement, are recommended for weight loss in children and adolescents aged 6-16 who are overweight or obese.	20655544	Jelalian E, Lloyd-Richardson EE, Mehlenbeck RS, Hart CN, Flynn-O'Brien K, Kaplan J, et al. Behavioral weight control treatment with supervised exercise or peer-enhanced adventure for overweight adolescents. J Pediatr. 2010;157(6):923-928.e1.	NA	1
32	Obesity in Childhood and Adolescence 2009	1125	Combined interventions including diet, physical exercise and changes to behaviour, with family involvement, are recommended for weight loss in children and adolescents aged 6-16 who are overweight or obese.	21135337	Ciampa PJ, Kumar D, Barkin SL, Sanders LM, Yin HS, Perrin EM, et al. Interventions aimed at decreasing obesity in children younger than 2 years: a systematic review. Arch Pediatr Adolesc Med. 2010;164(12):1098-104.	NA	1
33	Obesity in Childhood and Adolescence 2009	1125	Combined interventions including diet, physical exercise and changes to behaviour, with family involvement, are recommended for weight loss in children and adolescents aged 6-16 who are overweight or obese.	20070541	Kelly KP, Kirschenbaum DS. Immersion treatment of childhood and adolescent obesity: the first review of a promising intervention. Obes Rev. 2011;12(1):37-49.	NA	0
34	Obesity in Childhood and Adolescence 2009	1125	Combined interventions including diet, physical exercise and changes to behaviour, with family involvement, are recommended for weight loss in children and adolescents aged 6-16 who are overweight or obese.	21300674	Savoye M, Nowicka P, Shaw M, Yu S, Dziura J, Chavent G, et al. Long-term results of an obesity program in an ethnically diverse pediatric population. Pediatrics. 2011;127(3):402-10.	NA	1
35	Obesity in Childhood and Adolescence 2009	1125	Combined interventions including diet, physical exercise and changes to behaviour, with family involvement, are recommended for weight loss in children and adolescents aged 6-16 who are overweight or obese.	21444600	Collins CE, Okely AD, Morgan PJ, Jones RA, Burrows TL, Cliff DP, et al. Parent diet modification, child activity, or both in obese children: an RCT. Pediatrics. 2011 ;127(4):619-27.	NA	0
36	Obesity in Childhood and Adolescence 2009	1125	Combined interventions including diet, physical exercise and changes to behaviour, with family involvement, are recommended for weight loss in children and adolescents aged 6-16 who are overweight or obese.	21487425	Coppins DF, Margetts BM, Fa JL, Brown M, Garrett F, Huelin S. Effectiveness of a multi-disciplinary family-based programme for treating childhood obesity (the Family Project). Eur J Clin Nutr. 2011;65(8):903-9.	NA	0
37	Obesity in Childhood and Adolescence 2009	1125	Combined interventions including diet, physical exercise and changes to behaviour, with family involvement, are recommended for weight loss in children and adolescents aged 6-16 who are overweight or obese.	21514017	Schaefer A, Winkel K, Finne E, Kolip P, Reinehr T. An effective lifestyle intervention in overweight children: one-year follow-up after the randomized controlled trial on "Obeldicks light". Clin Nutr. 2011;30(5):629-33.	NA	0
38	Obesity in Childhood and Adolescence 2009	1126	The clinical and family environments are the most appropriate settings for combined interventions for weight loss in children and adolescents who are overweight or obese.	20102858	Díaz RG, Esparza-Romero J, Moya-Camarena SY, Robles-Sardín AE, Valencia ME. Lifestyle intervention in primary care settings improves obesity parameters among Mexican youth. J Am Diet Assoc. 2010;110(2):285-90.	NA	0

39	Obesity in Childhood and Adolescence 2009	1126	The clinical and family environments are the most appropriate settings for combined interventions for weight loss in children and adolescents who are overweight or obese.	20585269	Ellis DA, Janisse H, Naar-King S, Kolmodin K, Jen KL, Cunningham P, et al. The effects of multisystemic therapy on family support for weight loss among obese African-American adolescents: findings from a randomized controlled trial. J Dev Behav Pediatr. 2010;31(6):461-8.	NA	0
40	Obesity in Childhood and Adolescence 2009	1126	The clinical and family environments are the most appropriate settings for combined interventions for weight loss in children and adolescents who are overweight or obese.	21262890	Magarey AM, Perry RA, Baur LA, Steinbeck KS, Sawyer M, Hills AP, et al. A parent-led family-focused treatment program for overweight children aged 5 to 9 years: the PEACH RCT. Pediatrics. 2011;127(2):214-22.	NA	1
41	Obesity in Childhood and Adolescence 2009	1126	The clinical and family environments are the most appropriate settings for combined interventions for weight loss in children and adolescents who are overweight or obese.	21487425	Coppins DF, Margetts BM, Fa JL, Brown M, Garrett F, Huelin S. Effectiveness of a multi-disciplinary family-based programme for treating childhood obesity (the Family Project). Eur J Clin Nutr. 2011;65(8):903-9.	NA	0
42	Obesity in Childhood and Adolescence 2009	1129	For adolescents (aged 12-18) suffering from obesity and severe comorbidities who have not responded to dietary and lifestyle treatment, orlistat* treatment (120 mg with breakfast, lunch and dinner) may be considered as part of a programme of changes to lifestyle. This must be supervised by specialists in endocrinology and nutrition, family medicine or paediatrics who have been trained to treat obesity. * Sibutramine and orlistat are not funded by Spanish Social Security.	19160202	Oude Luttikhuis H, Baur L, Jansen H, Shrewsbury VA, O'Malley C, Stolk RP, et al. Interventions for treating obesity in children. Cochrane Database Syst Rev. 2009 Jan 21;(1):CD001872. doi: 10.1002/14651858.CD001872.pub2.	1	1
43	Obesity in Childhood and Adolescence 2009	1129	For adolescents (aged 12-18) suffering from obesity and severe comorbidities who have not responded to dietary and lifestyle treatment, orlistat* treatment (120 mg with breakfast, lunch and dinner) may be considered as part of a programme of changes to lifestyle. This must be supervised by specialists in endocrinology and nutrition, family medicine or paediatrics who have been trained to treat obesity. * Sibutramine and orlistat are not funded by Spanish Social Security.	20083531	Whitlock EP, O'Connor EA, Williams SB, Beil TL, Lutz KW. Effectiveness of weight management interventions in children: a targeted systematic review for the USPSTF. Pediatrics. 2010;125(2):e396-418.	1	1
44	Obesity in Childhood and Adolescence 2009	1129	For adolescents (aged 12-18) suffering from obesity and severe comorbidities who have not responded to dietary and lifestyle treatment, orlistat* treatment (120 mg with breakfast, lunch and dinner) may be considered as part of a programme of changes to lifestyle. This must be supervised by specialists in endocrinology and nutrition, family medicine or paediatrics who have been trained to treat obesity. * Sibutramine and orlistat are not funded by Spanish Social Security.	19922432	Viner RM, Hsia Y, Tomsic T, Wong IC. Efficacy and safety of anti-obesity drugs in children and adolescents: systematic review and meta-analysis. Obes Rev. 2010;11(8):593-602.	1	0

45	Obesity in Childhood and Adolescence 2009	1129	For adolescents (aged 12-18) suffering from obesity and severe comorbidities who have not responded to dietary and lifestyle treatment, orlistat* treatment (120 mg with breakfast, lunch and dinner) may be considered as part of a programme of changes to lifestyle. This must be supervised by specialists in endocrinology and nutrition, family medicine or paediatrics who have been trained to treat obesity. * Sibutramine and orlistat are not funded by Spanish Social Security.	20858149	Chanoine JP, Richard M. Early weight loss and outcome at one year in obese adolescents treated with orlistat or placebo. Int J Pediatr Obes. 2011;6(2):95-101.	1	0
46	Prostate Cancer Treatment 2008	1204	In patients with prostate cancer at a locally advanced stage with a life expectancy less than 10 years, watching and waiting or hormone therapy may be therapeutic alternatives.	18349064	Shahani S, Braga-Basaria M, Basaria S. Androgen deprivation therapy in prostate cancer and metabolic risk for atherosclerosis. J Clin Endocrinol Metab. 2008;93(6):2042-9.	NA	0
47	Prostate Cancer Treatment 2008	1206	The normal duration of neoadjuvant hormonal treatment with radiotherapy in patients with prostate cancer at a locally advanced stage is 3 months.	21440505	Denham JW, Steigler A, Lamb DS, Joseph D, Turner S, Matthews J, et al. Short-term neoadjuvant androgen deprivation and radiotherapy for locally advanced prostate cancer: 10-year data from the TROG 96.01 randomised trial. Lancet Oncol. 2011;12(5):451-9.	NA	1
48	Prostate Cancer Treatment 2008	1208	The normal duration of neoadjuvant hormonal treatment after radiotherapy in patients with prostate cancer at a locally advanced stage is 2-3 years.	17102802	Wirth M, Tyrrell C, Delaere K, Sánchez-Chapado M, Ramon J, Wallace DM, et al. Bicalutamide (Casodex) 150 mg plus standard care in early non-metastatic prostate cancer: results from Early Prostate Cancer Trial 24 at a median 7 years' follow-up. Prostate Cancer Prostatic Dis. 2007;10(1):87-93.	NA	0
49	Prostate Cancer Treatment 2008	1208	The normal duration of neoadjuvant hormonal treatment after radiotherapy in patients with prostate cancer at a locally advanced stage is 2-3 years.	MARTINEZ-PINEIRO	Martinez-Pineiro L. Does neoadjuvant and adjuvant treatment improve outcome in localised prostatic cancer? European Urology Supplements. 2008;7(5):406-409.	NA	0
50	Prostate Cancer Treatment 2008	1208	The normal duration of neoadjuvant hormonal treatment after radiotherapy in patients with prostate cancer at a locally advanced stage is 2-3 years.	COLLETTE	Collette L, Mauer M, Bolla M, Van Tienhoven G, De Reijke TM, Van Den Bergh ACM, et al. 745 health related quality of life and symptoms in an international phase iii trial of long term versus short-term androgen suppression and radiation therapy for locally advanced prostate cancer (eortc trial 22961). European Urology Supplements. 2009;8(4):307.	NA	0
51	Prostate Cancer Treatment 2008	1208	The normal duration of neoadjuvant hormonal treatment after radiotherapy in patients with prostate cancer at a locally advanced stage is 2-3 years.	BOLLA	Bolla M, Collette L, Van Tienhoven G, Warde P, Dubois JB, Mirimanoff RO, et al. 7007 Three years of adjuvant androgen deprivation with goserelin in patients with locally advanced prostate cancer treated with radiotherapy: Results at 10 years of EORTC trial 22863. European Journal of Cancer Supplements. 2009;7(2):408.	NA	0

52	Prostate Cancer Treatment 2008	1208	The normal duration of neoadjuvant hormonal treatment after radiotherapy in patients with prostate cancer at a locally advanced stage is 2-3 years.	22129214	Iversen P, McLeod DG, See WA, Morris T, Armstrong J, Wirth MP, et al. Antiandrogen monotherapy in patients with localized or locally advanced prostate cancer: final results from the bicalutamide Early Prostate Cancer programme at a median follow-up of 9.7 years. BJU Int. 2010;105(8):1074-81.	NA	0
53	Prostate Cancer Treatment 2008	1230	In patients with disseminated prostate cancer for whom hormone therapy has been indicated, castration (surgical or chemical) is recommended as a first-line treatment.	18491137	Arai Y, Akaza H, Deguchi T, Fujisawa M, Hayashi M, Hirao Y, et al. Evaluation of quality of life in patients with previously untreated advanced prostate cancer receiving maximum androgen blockade therapy or LHRHa monotherapy: a multicenter, randomized, double-blind, comparative study. J Cancer Res Clin Oncol. 2008;134(12):1385-96.	1	0
54	Prostate Cancer Treatment 2008	1233	In patients with disseminated prostate cancer and low tumour load, intermittent androgen suppression may be assessed as an alternative to continuous androgen suppression if there is a good response to the initial hormone treatment.	19249153	Calais da Silva FE, Bono AV, Whelan P, Brausi M, Marques Queimadelos A, Martin JA, et al. Intermittent androgen deprivation for locally advanced and metastatic prostate cancer: results from a randomized phase 3 study of the South European Uroncological Group. Eur Urol. 2009;55(6):1269-77.	1	0
55	Prostate Cancer Treatment 2008	1234	To be able to indicate intermittent hormone therapy, the patient must have received androgen deprivation for at least 7 months and reached a PSA < 4 ng/ml (stable or in decline during the sixth and seventh months), or a 90% reduction from pre-treatment levels. Monitoring will be carried out every 6 months. Patients who have stopped androgen deprivation will receive another cycle on request, when the PSA increases or when clinical symptoms of disease progression appear. If the PSA returns to normal after the new round of androgen deprivation, hormone therapy can be stopped again.	19249153	Calais da Silva FE, Bono AV, Whelan P, Brausi M, Marques Queimadelos A, Martin JA, et al. Intermittent androgen deprivation for locally advanced and metastatic prostate cancer: results from a randomized phase 3 study of the South European Uroncological Group. Eur Urol. 2009;55(6):1269-77.	1	0
56	Prostate Cancer Treatment 2008	1243	The systematic use of bisphosphonates (zoledronic acid) as a preventive treatment in bone complications is not recommended. Zoledronic acid (4 mg every 3 weeks) can be offered in selected hormone-independent patients with demonstrated metastasis.	21353695	Fizazi K, Carducci M, Smith M, Damião R, Brown J, Karsh L, et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. Lancet. 2011;377(9768):813-22.	1	0
57	Secondary Prevention of Stroke 2009	1400	Patients who have suffered a stroke are encouraged to exercise regularly within their capabilities and reduce body weight or abdominal obesity to normal levels.	19821305	Saunders DH, Greig CA, Mead GE, Young A. Physical fitness training for stroke patients. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD003316. doi: 10.1002/14651858.CD003316.pub3.	0	0
58	Secondary Prevention of Stroke 2009	1400	Patients who have suffered a stroke are encouraged to exercise regularly within their capabilities and reduce body weight or abdominal obesity to normal levels.	22071806	Brazzelli M, Saunders DH, Greig CA, Mead GE. Physical fitness training for stroke patients. Cochrane Database Syst Rev. 2011 Nov 9;(11):CD003316. doi: 10.1002/14651858.CD003316.pub4.	0	0

59	Secondary Prevention of Stroke 2009	1406	It is recommended to treat patients with ischemic stroke or prior transient ischemic attack of atherothrombotic etiology with atorvastatin (80 mg/d), regardless of their basal LDL-cholesterol levels.	19228842	Amarenco P, Benavente O, Goldstein LB, Callahan A 3rd, Sillesen H, Hennerici MG, et al. Results of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial by stroke subtypes. Stroke. 2009;40(4):1405-9.	1	0
60	Secondary Prevention of Stroke 2009	1406	It is recommended to treat patients with ischemic stroke or prior transient ischemic attack of atherothrombotic etiology with atorvastatin (80 mg/d), regardless of their basal LDL-cholesterol levels.	19588332	Manktelow BN, Potter JF. Interventions in the management of serum lipids for preventing stroke recurrence. Cochrane Database Syst Rev. 2009 Jul 8;(3):CD002091. doi: 10.1002/14651858.CD002091.pub2.	1	1
61	Secondary Prevention of Stroke 2009	1407	Treatment with other statins (simvastatin 40 mg) is also indicated in patients with ischemic stroke or prior transient ischemic attack of atherothrombotic etiology, regardless of their basal LDL-cholesterol levels.	17986516	Henyan NN, Riche DM, East HE, Gann PN. Impact of statins on risk of stroke: a meta-analysis. Ann Pharmacother. 2007;41(12):1937-45.	1	0
62	Secondary Prevention of Stroke 2009	1407	Treatment with other statins (simvastatin 40 mg) is also indicated in patients with ischemic stroke or prior transient ischemic attack of atherothrombotic etiology, regardless of their basal LDL-cholesterol levels.	19588332	Manktelow BN, Potter JF. Interventions in the management of serum lipids for preventing stroke recurrence. Cochrane Database Syst Rev. 2009 Jul 8;(3):CD002091. doi: 10.1002/14651858.CD002091.pub2.	1	1
63	Secondary Prevention of Stroke 2009	1410	The combination of statins with other hypolipemiant drugs to reach LDLcholesterol target values should be avoided.	19884623	Sharma M, Ansari MT, Abou-Setta AM, Soares-Weiser K, Ooi TC, Sears M, et al. Systematic review: comparative effectiveness and harms of combination therapy and monotherapy for dyslipidemia. Ann Intern Med. 2009;151(9):622-30.	1	0
64	Secondary Prevention of Stroke 2009	1417	In cases where anticoagulant treatment is contraindicated, treatment with aspirin (300 mg/d) is an appropriate alternative.	19336502	ACTIVE Investigators, Connolly SJ, Pogue J, Hart RG, Hohnloser SH, Pfeffer M, et al. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. N Engl J Med. 2009;360(20):2066-78.	1	1
65	Secondary Prevention of Stroke 2009	1417	In cases where anticoagulant treatment is contraindicated, treatment with aspirin (300 mg/d) is an appropriate alternative.	20388864	Ansara AJ, Nisly SA, Arif SA, Koehler JM, Nordmeyer ST. Aspirin dosing for the prevention and treatment of ischemic stroke: an indication-specific review of the literature. Ann Pharmacother. 2010;44(5):851-62.	1	0
66	Secondary Prevention of Stroke 2009	1417	In cases where anticoagulant treatment is contraindicated, treatment with aspirin (300 mg/d) is an appropriate alternative.	21309657	Connolly SJ, Eikelboom J, Joyner C, Diener HC, Hart R, Golitsyn S, et al. Apixaban in patients with atrial fibrillation. N Engl J Med. 2011;364(9):806-17.	1	1
67	Secondary Prevention of Stroke 2009	1417	In cases where anticoagulant treatment is contraindicated, treatment with aspirin (300 mg/d) is an appropriate alternative.	HART	Hart RG, Eikelboom J, Yusuf S, Gao P, Paolasso E, De Caterina R, et al. Efficacy and safety of the novel oral factor Xa inhibitor apixaban in atrial fibrillation (AF) patients with chronic kidney disease (CKD): The AVERROES trial. European Heart Journal. Conference: European Society of Cardiology, ESC Congress. 2011.	0	0

68	Secondary Prevention of Stroke 2009	1424	In patients with previous ischemic stroke or transient ischemic attack who present permeable foramen ovale, treatment with antiaggregants (100-300 mg/d of aspirin) is recommended.	KENT	Kent DM, Kitsios GD. Meta-analysis of observational studies for the risk of recurrent stroke with PFO closure or medical treatment and comparison to the results of the closure I trial. Cerebrovascular Diseases. Conference. 2011; Hamburg, Germany.	0	0
69	Secondary Prevention of Stroke 2009	1427	Carotid endarterectomy is recommended in patients with ischemic stroke of less than 6 months evolution and significant stenosis of the carotid artery (70% to 99%, NASCET values), if and when the surgical team confirms a perioperative morbimortality of less than 6%.	19769803	Patterson BO, Holt PJ, Hinchliffe RJ, Thompson MM, Loftus IM. Urgent carotid endarterectomy for patients with unstable symptoms: systematic review and meta-analysis of outcomes. Vascular. 2009;17(5):243-52.	1	0
					Total key references identified	**39**	**18**
*Narrow filter and clustering all clinical questions. Abbreviations: NA: not applicable.							

Documento adicional 3: Tablas complementarias

Tabla complementaria 1: Identificación de recomendaciones a actualizar con la estrategia restrictiva

	Recommendations not identify by restrictive approach (n=3)		Recommendations identify by restrictive approach (n=17)		p*
CPGs topic, n (%)					
. Mental health	1	33,3	2	11,8	0,312
. Metabolic disease	0	0,0	6	35,3	
. Cancer and palliative care	0	0,0	4	23,5	
. Cardiovascular disease	2	66,7	5	29,4	
Strength of recommendations (SIGN system), n (%)					
. A	0	0,0	3	17,6	0,151
. B	3	100,0	5	29,4	
. C	0	0,0	2	11,8	
. D	-	-	-	-	
. GPP	0	0,0	7	41,2	
Section purpose, n (%)					
. Prevention	2	66,7	11	64,7	1,000
. Screening	-	-	-	-	
. Treatment	1	33,3	6	35,3	
. Others	-	-	-	-	
Recommendation turnover, n (%)					
. Without references	-	-	-	-	1,000
. With low references	1	33,3	5	29,4	
. With high references	2	66,7	12	70,6	
Total	3		17		
Abbreviations: CPG: Clinical practice guideline; GPP: Good practice point.					
*Pearson's chi-square test or Fisher's Exact Test, as appropiate.					

Tabla complementaria 2: Identificación de recomendaciones a actualizar con la estrategia PLUS

	Recommendations not identify by PLUS approach (n=15)		Recommendations identify by PLUS approach (n=10)		p*
CPGs topic, n (%)					
. Mental health	1	6,7	2	20,0	0,365
. Metabolic disease	4	26,7	4	40,0	
. Cancer and palliative care	6	40,0	1	10,0	
. Cardiovascular disease	4	26,7	3	30,0	
Strength of recommendations (SIGN system), n (%)					
. A	2	13,3	1	10,0	0,763
. B	6	40,0	3	30,0	
. C	1	6,7	2	20,0	
. D	1	6,7	0	0,0	
. GPP	5	33,3	4	40,0	
Section purpose, n (%)					
. Prevention	8	53,3	7	70,0	0,678
. Screening	-	-	-	-	
. Treatment	7	46,7	3	30,0	
. Others	-	-	-	-	
Recommendation turnover, n (%)					
. Without references	-	-	-	-	0,020
. With low references	7	46,7	0	0,0	
. With high references	8	53,3	10	100,0	
Total	15		10		
Abbreviations: CPG: Clinical practice guideline; GPP: Good practice point.					
*Pearson's chi-square test or Fisher's Exact Test, as appropiate.					

Actualización
de guías de
práctica clínica