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Answering medical questions at the point of care: A study comparing rapid decisions based on MEDLINE and Epistemonikos searches with evidence-based recommendations developed with the GRADE approach.

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ABSTRACT

Introduction

Using the best current evidence to inform clinical decisions remains as a challenge for clinicians. Given the scarcity of trustworthy clinical practice guidelines providing recommendations to answer clinicians' daily questions, clinical decision support systems emerge as an attractive alternative. The trustworthiness of the recommendations achieved by such systems is unknown.

Objective

To evaluate the trustworthiness of a question identification and answering system to deliver timely recommendations.

Design

Cross-Sectional study

Methods

We compared the recommendations in response to 100 clinical questions related to inpatient management provided by two rapid response methods, one based on MEDLINE and the other based on the Epistemonikos database, with "Gold Standard" recommendations (trustworthy published evidence based recommendations or, when not available, recommendations developed locally by a panel of 6 clinicians following the GRADE approach). Based on this comparison, recommendations provided by the rapid strategies were classified as potentially misleading or reasonable. We also analyzed if the potentially misleading recommendations could have been avoided with the appropriate implementation of searching and summary of evidence tools.

Results

We were able to answer all the 100 questions with both rapid methods. Of the 200 recommendations obtained, 6.5% were classified as potentially misleading (3.5% inappropriate and 3% overconfident) and 93.5% as reasonable (62.5% concordant and 31% reasonable disagreement). Six of the 13 potentially misleading recommendations could have been avoided by the appropriate usage of the Epistemonikos matrix tool or by constructing summary of findings tables.

Conclusion

A question answering service based on the GRADE approach was feasible to implement and provided appropriate guidance for most identified questions. Our approach could help stakeholders in charge of managing resources and defining policies for patient care to access the best available evidence in an efficient and feasible way.

ARTICLE SUMMARY

Strengths and limitations

- The study was carried out in a real-world scenario (questions related to patients being treated in a clinical ward)
- Three different clinicians were randomly assigned to apply the different answering strategies
- Trustworthy published evidence based recommendations or, when not available, recommendations developed locally by a panel of six clinicians were assumed as “Gold Standard”
- We developed a transparent framework to categorize the recommendations obtained by the rapid strategies
- All the question answering strategies were based on the GRADE approach

INTRODUCTION

Using the best current evidence to inform clinical decisions remains as a challenge for clinicians.[1,2,3] Limited time, lack of training in critical appraisal and low expectations for finding relevant answers are among the most common obstacles.[4,5]

One of the potential solutions for binging evidence to bedside decisions is the use of trustworthy and transparent clinical practice guidelines. Although the last decade has seen significant advances in guideline methodology (http://www.gradeworkinggroup.org/), important limitations still remain: 1) only a small number of guidelines have been tailored to clinicians needs;[6] 2) Finding relevant guidelines can be laborious and time consuming; 3) Typically, only a few guidelines are kept up to date.[7]

Another alternative for bridging the gap between evidence and clinical practice are clinical decision support systems, which can help clinicians to formulate a clinical question, find the answer for them and present the information in a user-friendly way.[8-10] However the trustworthiness of the recommendations achieved by such systems is unknown.

The objective of this study is to evaluate the trustworthiness of a question identification and answering system to deliver timely recommendations. Additionally, we provide guidance on how to replicate the process.

METHODS

We conducted the study on the Internal Medicine Service of a German Hospital in Buenos Aires, Argentina, from March 2014 to March 2016.

We compared two rapid response methods, one based on MEDLINE and the other based in the Epistemonikos database, with trustworthy published evidence based recommendations or, when not available, recommendations developed locally by a panel of six clinicians. For the purpose of this study, we considered those recommendations as our “Gold Standard”.

Three clinicians trained in evidence based decision making (informationists) attempted to answer all the identified questions following three different strategies. The question answering strategy assignment to the three strategies described below was defined by randomization separately for every individual question using a computer pre-generated random number list. We describe the question identification process and strategies to address the questions in the following sections.

Identification and selection of clinical questions

One of the informationists (AI) identified questions relevant to the staff and residents of the Internal Medicine Service. Either the staff or residents explicitly formulated the questions, or the responsible physician inferred the question from the discussion of the clinical cases. We collected the relevant clinical question using the PICO (Population/Problem, Intervention, Comparison, Outcome) framework.

In order to focus on questions that could potentially impact clinicians' course of action, we excluded questions that: (1) were appropriately answered immediately by someone who was present in the session, typically, using electronic resources such as UpToDate, (2) were not related to therapeutic or diagnostic interventions, or (3) addressed interventions already implemented in the patient's care.

Rapid strategy based on MEDLINE (Strategy 1)

The informationist assigned to this strategy performed a literature search on MEDLINE using the PubMed clinical queries feature (supplementary figure 1). First he tried to identify relevant systematic reviews; when unavailable or when considered that additional relevant information could be available, he searched for primary studies. Once the informationist identified the most

relevant systematic review or primary study/s, he made a clinical decision following the GRADE evidence to decision framework,[11,12] simulating what a clinicians could do in the optimal scenario. To capture the decision, the informationist formulated a recommendation that included the direction (in favor or against the intervention) and the strength (strong or weak). The process took no more than two hours.

Rapid strategy based on Epistemonikos (Strategy 2)

The informationist assigned to this strategy searched on the Epistemonikos database (supplementary figure 2) and followed the same process described for the strategy 1.

Strategy based on guidelines recommendations ("Gold Standard") (Strategy 3)

The informationist assigned to this strategy searched for recommendations developed with the GRADE approach, on the following databases: Tripdatabase (http://www.tripdatabase.com); National guideline Cleringhouse (http://www.guidelines.gov); Canadian Medical Asociation (http://www.cma.ca/clinicalresources/practiceguidelines); NICE (http://www.nice.org.uk/); SIGN (http://www.sign.ac.uk); GuíaSalud (http://portal.guiasalud.es/web/guest/buscar-gpc); Australia (http://www.clinicalguidelines.gov.au); New Zeland (http://www.nzgg.org.nz/); US preventive Task Force (http://www.uspreventiveservicestaskforce.org/); eguidelines (https://www.guidelines.co.uk/), GIN (http://www.g-i-n.net/about-g-i-n/introduction).

He critically assessed the recommendations identified using the criteria proposed for evaluate GRADE recommendations[13] and qualitatively categorized recommendations' trustworthiness as High, Moderate or Low based on the answers to the following questions: Was the question clearly formulated? Were all the critical outcomes considered? Was the recommendation based on the best current evidence? The evidence was clearly presented? Was the recommendation coherent with the supporting evidence? Were the values and preferences considered?

Additionally, the same informationist, searched for systematic reviews, randomized controlled trials and observational studies on the following databases without time restriction: Medline, Epistemonikos and the Cochrane database of systematic review. He used the information of the relevant systematic review or primary studies to develop a Summary of Finding Table (SoF) following the GRADE principles.[14,15] The tables were then sent via email to six clinicians with experience with the GRADE approach. Each clinician provided a recommendation using the information included in the SoF table and following the evidence to decision framework. When more than 66% of the clinicians who answered agreed on the strength and direction of the recommendation, we considered the recommendation final. Disagreement in the direction or the strength of the recommendation were recorded and resolved by seventh clinician (IN) with experience in developing GRADE recommendations.

We considered as "Gold Standard" GRADE recommendations developed by guideline panels that were rated with "high trustworthiness", or in absence of those, the recommendations developed locally following the process described before (figure 1).

Outcomes:

Inappropriate recommendations: When the "Gold Standard" was a strong recommendation and the rapid strategies yielded a decision in the opposite direction of any strength; or when the "Gold Standard" was a weak recommendation and the rapid strategies yielded a strong recommendation in the opposite direction.

Overconfident recommendations: When the "Gold Standard" was a weak recommendation and the rapid strategies yielded a decision concordant with a strong recommendation on the same direction

Potentially misleading recommendations: Composite of inappropriate or overconfident recommendations

Concordant recommendations: When the "Gold Standard" and the rapid strategies yielded a recommendation of the same direction and strength

Reasonable disagreement: When the "Gold Standard" was a weak recommendation in favor and the rapid strategies yielded a weak recommendation against or vice versa, or when the "Gold Standard" was a strong recommendation and the rapid strategies yielded a decision concordant with a weak recommendation on the same direction

Reasonable recommendations: Composite of concordant recommendations and reasonable disagreement

Table 1. describes the framework for rapid recommendation categorization based on their comparison with "Gold Standard" recommendations.

Table 1. Framework to categorize recommendations

		GOLD STANDARD			
		Strong Against	Weak Against	Weak in Favor	Strong in Favor
RAPID STRATEGIES	Strong Against	Concordant	Overconfident	Inappropriate	Inappropriate
	Weak Against	Reasonable	Concordant	Reasonable	Inappropriate
	Weak in Favor	Inappropriate	Reasonable	Concordant	Reasonable
	Strong in	Inappropriate	Inappropriate	Overconfident	Concordant

	Favor				

Inappropriate quality of evidence judgment: Proportion of recommendations in which the quality of evidence: 1) was judged as Low or Very Low by the rapid strategies and High or Moderate by the "Gold Standard" or; 2) Was judged as High or Moderate by the rapid strategies and Low or Very low by the "Gold Standard"

Coincidence in information usage: Proportion of recommendations in which the publications used by the rapid methods was the same to the ones used by the "Gold Standard"

Additional analyses

We also performed a post-hoc qualitative analysis of the recommendations classified as potentially misleading. We analyzed the reasons for the disagreement between the rapid strategies and the gold standard and we considered potential solutions. For this purpose, in cases in which the potentially misleading recommendations were judged to be a consequence of inadequate evidence selection, we determined if the appropriate use of the epistemonikos matrixes tool could have prevented that problem (i.e identification of a SR containing primary studies that were not considered in the development of the original recommendation), and in cases in which potentially misleading recommendations were judged to be a consequence of inappropriate evidence interpretation we determined if the correct presentation of the evidence could have prevented the problem by sending the SoF table constructed in response to the same question for the "Gold Standard" strategy (strategy 3) to the investigator who originally constructed the potentially misleading recommendation, and asked him to provide a new recommendation based in the SoF. We judged that the correct usage of the Sof could have

prevented the problem when the investigator provided a reasonable recommendation in response (in comparison to the GS recommendation).

Statistical analysis

For the comparisons between the rapid strategies and the "Gold Standard" we calculated proportions and 95%CI for all the outcomes. We also calculated interrater agreement with Kappa statistic using VassarStats calculator (http://vassarstats.net/kappa.html). For the kappa calculation related to recommendation agreement (strong in favor, weak in favor, weak against or strong against) we imputed the double of distance between strong in favor - weak in favor and strong against - weak against than weak in favor - weak against. For the kappa calculation related to quality of evidence agreement (high, moderate, low or very low) we imputed the double of distance between moderate - low than very low - low and moderate - high. For the comparison between strategies 1 and 2 we calculated relative risks and 95%CI when possible.

RESULTS

During the study period we identified 100 questions all of which were successfully answered with strategies 1 and 2 (200 recommendations). With strategy 3 we were able to find recommendations in CPG for 80 of the 100 questions and all could be answered with the local panel strategy. Table 2 presents the characteristics of the recommendations delivered by each strategy. A list of the PICOs is available in the supplementary table 1.

Table 2. Recommendations according to the strategy implemented

	Strategy 1 (n=100)	Strategy 2 (n=100)	Strategy 3 (CPG) (n=80)(%)	Strategy 3 (local panel) ((n=100)
Recommendations				
Strong	14	12	21 (26.2)	21
In favor of the intervention	55	62	55 (68.7)	63
Quality of evidence				
High	8	5	-	12
Moderate	22	25	-	28
Low	34	26	-	44
Very Low	36	44	-	16
Confidence in the CPG recommendation				
High (%)	-	-	16 (20)	-

Following the process described in figure 3 we obtained 100 “Gold standard” recommendations. These recommendations were composed by 16 High confidence CPG recommendations, 55 panel recommendations and 29 expert recommendations. The results of the comparison between the rapid strategies and the “Gold standard” are described in table 3.

Table 3. Rapid strategies recommendations analysis

	Rapid strategies versus “Gold Standard” (n=200)	Kappa
Potentially misleading recommendations	6.5% (3 - 9.9%)	-
Inappropriate	3.5% (0.95 - 6%)	-
Overconfident	3% (0.64 - 5.3%)	-
Reasonable recommendations	93.5% (90 – 96.9%)	0.86 (0.79 – 0.93)

Concordant	62.5% (55.7 - 69.2%)	0.59 (0.36 - 0.82)
Reasonable disagreement	31% (24.5 – 37.4%)	-
Potentially misleading quality of evidence judgment	20% (14.4 - 25.5%)	-
Inappropriate Moderate or High	5% (1.9 - 8%)	-
Inappropriate Low or Very Low	15% (10 - 19.9%)	-
Quality of evidence agreement	55.5% (48.6 - 62.3%)	0.59 (0.46 - 0.72)
Coincidence in information use*	60% (50.4 - 69.6)	-

* The same publication/s were used to answer the question

The comparison between strategies 1 and 2 is described in supplementary table 2.

There were 13 recommendations that were judged as potentially misleading, the causes and possible solutions are summarized in supplementary table 3.

DISCUSSION

The results of the present study suggested that a rapid question answering system based on the GRADE approach provided appropriate guidance in response to most questions. Only 13 of the 200 recommendations were judged as potentially misleading and approximately half of these could possibly have been avoided with an appropriate use of the available tools (Epistemonikos matrix of evidence, SoF tables). The comparison between the different rapid answering strategies (Pubmed vs Epistemonikos) showed that although the proportion of potentially misleading recommendations was small in both strategies, there was a small (3%) absolute difference in favor of Pubmed strategy. One possible explanation for the difference is that the investigators involved in the study were less familiarized with Epistemonikos database and search engine than Pubmed's.

The main limitation of our study is that it is not possible define a “Gold Standard” recommendation for a medical question. We sought to provide trustworthy “Gold Standard” recommendations by performing rigorous evidence searches, constructing detailed evidence summaries and including multiple clinicians trained in evidence based decision making; the approach nevertheless does not guarantee optimal recommendations

Although investigators have previously undertaken evaluation of the implementation of question answering services,[16-21] these studies focused on clinicians’ attitudes and decisions in response to the answers provided. Without knowing that the answers the services provides are based on the best available evidence, and that clinicians interpret and use the provided information appropriately to make coherent decisions, the benefit of the service to improve patient outcomes remains uncertain.[22]

We found only one study that considered the trustworthiness of the answers provided.[23] In that study, the investigators inserted study evidence statements related to the management of clinical conditions for which high-quality randomised controlled trials, or metaanalyses had unequivocally established benefits greater than risks, costs and inconvenience into hospital discharge letters. The study results showed a significant increase in general practitioner adherence to discharge medications demonstrating that in optimal conditions (no time restrictions to perform evidence searches, high quality of evidence available) providing information to clinicians improve patient care. However, that optimal scenario is probably the exception: for most clinical questions high quality evidence remains unavailable, and clinicians usually need very prompt answers to their questions. Hence, ours is the first study to use a structured and objective approach to measure the quality of the information provided in a timely way to clinician-generates questions.

To achieve a medical practice consistent with what Ubbink et al. described as evidence-based practice,[24] clinicians need to be able to quickly obtain and accurately assess the best available evidence to answer their questions. Clinical practice guidelines endeavor to provide these answers at the point of care and when rigorously developed and up to date constitute optimal guidance. However most of the available guidelines have methodological flaws and do not provide trustworthy recommendations.[7] In the present study 80% of the identified questions could be answered with recommendations included in CPG but only 20% of them were judged to be trustworthy.

Given current guideline limitations, if feasible and properly implemented, a question answering system could provide a solution. This study adds to our previous study in which we evaluated the impact of implementing a response system similar to the one evaluated in the preset trial, on clinician's decisions.[9] The results of that trial suggested that response systems could influence clinician's courses of actions and therefore patient care.

The study was developed in a real life scenario with limited amount of resources, which suggest that the proposed intervention can possibly be implemented in variety of settings, including a busy clinical ward. We were able to efficiently implement the proposed system with: 1) one clinician trained in evidence based decision making exclusively dedicated to this task for at least 2 hours a day; 2) a computer with internet connection. We used systematic a transparent methods to arrive at decisions. Finally, we have developed a framework to compare different recommendations developed with the GRADE approach acknowledging that not any discrepancy should be considered inappropriate. Different values and preferences may lead to reasonable disagreement between recommendations.

Implication for practice

Those interested in improving evidence utilization in health care decision-making should consider the implementation of systems as the one proposed in the present study. Figure 2 presents an algorithm to provide guidance in the implementation of such a system but we think that the cornerstone to successfully incorporate these to clinical practice is practitioners training in evidence search, critical appraisal, summary and evidence to decision translation.

Implication for research

Investigators who addressed the clinical questions using the proposed strategies in the present study were highly trained in evidence-based decision-making and could possibly be classified as experts. Whether similar results could be obtained when those responsible for solving the identified questions are not experts remains uncertain.

CONCLUSION

A question answering service based on the GRADE approach was feasible to implement and provided appropriate guidance for most identified questions. Our approach could help stakeholders in charge of managing resources and defining policies for patient care to access the best available evidence in an efficient and feasible way.

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The corresponding author and manuscript's guarantor certifies that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Data sharing: no additional data available

Individual author contributions

Izcovich A. significantly contributed to the conception and design of the work, and the acquisition, analysis and interpretation of data.

Criniti J.M. significantly contributed to the design of the work, and the acquisition, analysis and interpretation of data.

Popoff F. significantly contributed to the design of the work, and the acquisition, analysis and interpretation of data.

Ragusa M.A. significantly contributed to the the acquisition and interpretation and of the data.

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Manzotti M. significantly contributed to the acquisition and interpretation and of the data.

Díaz M. significantly contributed to the acquisition and interpretation and of the data.

Catalano H.N. significantly contributed to the acquisition and interpretation and of the data.

Neumann I. significantly contributed to the design of the work, and the acquisition, analysis and interpretation of data.

Guyatt G. significantly contributed to the design of the work, and the acquisition, analysis and interpretation of data.

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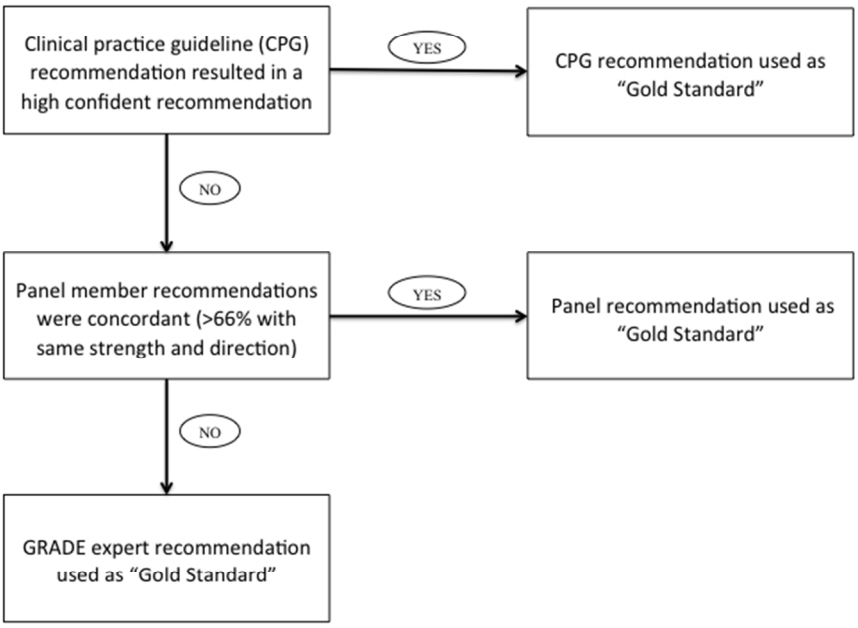
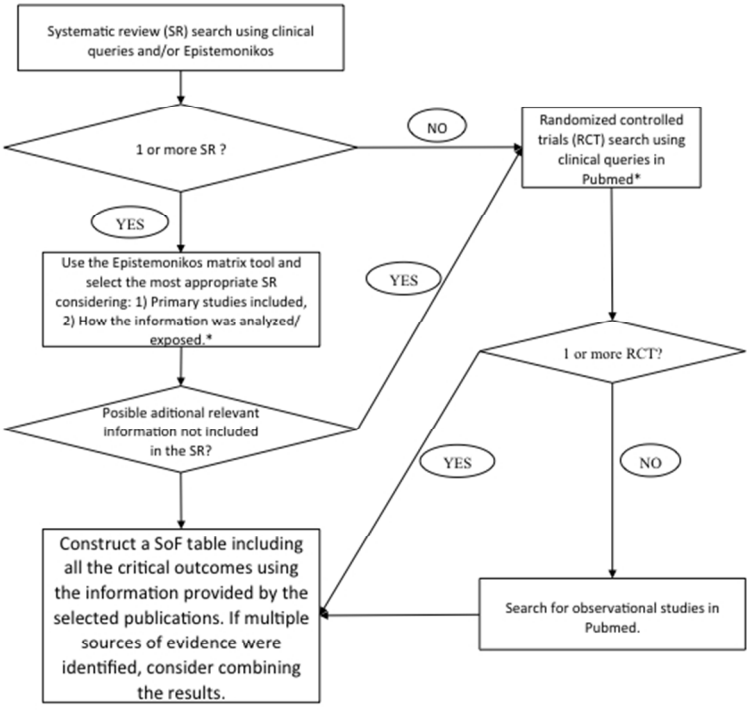
Figure 1. “Gold Standard” recommendation development

Figure 2. Rapid answering system proposal



"Gold Standard" recommendation development
Figure 1
254x190mm (72 x 72 DPI)



* Murad MH, Montori VM, Ioannidis JP, et al. How to read a systematic review and meta-analysis and apply the results to patient care: users' guides to the medical literature. *JAMA* 2014;312:171–9

Rapid answering system proposal
Figure 2
254x190mm (72 x 72 DPI)

Supplementary table 1. PICO questions

Nr.	Population	Intervention	Comparison	Outcomes
1	Patient with acute asthma and upper airway infection	Antibiotics	No antibiotics	Mortality
2	Renal transplant patient with pleural TB	Steroids	No steroids	Resolution time, complications and mortality
3	Patient with atrial fib on anticoagulants undergoing a breast biopsy	Stopping anticoagulant	Not stopping anticoagulant	Bleeding risk, thromboembolic event risk, mortality
4	Patient with severe hypokalemia (< 2.5 meq/l)	Intravenous potassium	Oral potassium	Arrythmia, morbidity and mortality
5	Patient with prosthetic valve endocarditis by MSSA	Cephalosporin+rifampicyin+gentamicin	Cephalosporin+rifampicyin	Complications, mortality
6	Patient with pericardial TB	Steroids	Placebo	Death, symptomatic improvement, sequel
7	Transplant patient with CMV resistant systemic infection	IV gamaglobulin	No IV Gamaglobulin	All cause mortality, CMV related mortality, time to viral load negativization, adverse events
8	Patient with congestive heart failure	IV furosemide bolus	IV furosemide continuous infusion	Mortality, adverse events, arrythmia
9	Patient with upper gastrointestinal bleeding, forrest III peptic ulcer and pulmonary embolism	Anticoagulants	Vena cava filter and prophylaxis	Major bleeding, upper gastrointestinal bleeding, PE mortality, all-cause mortality
10	Patient with atrial fibrillation and CHADS score > 1	Watchman plus antiplatelet therapy	Anticoagulation	Thromboembolic events, major bleeding, all cause mortality
11	Patient with acute ischemic stroke	Statins	Placebo	Recurrent stroke, all cause mortality
12	Patient undergoing neurosurgery for malignant disease	Early thromboprophylaxis with enoxaparin	Late thromboprophylaxis with enoxaparin	Surgical bleeding, major bleeding, thromboembolic events, mortality
13	Patient with acute diarrhea	Fecal leucocyte to guide therapy	No fecal leucocyte analysis	Morbidity, mortality
14	Inpatient with	Antibiotics AND	Antibiotics	Mortality, hospital

	pneumonia	steroids		stay, mechanical ventilation requirement, ICU stay
15	Patient with catheter related deep venous thrombosis	Anticoagulation and extraction	Wait and watch	Pulmonary embolism, stroke, death
16	Patient with distal inferior limb deep vein thromboses	Anticoaguation	No anticoagulation	Pulmonary embolism, mortality
17	Patient with traumatic splenic laceration	Splenectomy	Wait and watch	Mortality,hemoperitoneum
18	Adult with asymptomatic celiac disease	Gluten free diet	No treatment	Quality of life, cancer
19	Pacient with stable COPD	Non invasive mechanical ventilation	Standard treatment	Mortality, quality of life
20	Adult with facial cellulitis	Antibiotics and steroids	Antibiotics only	Symptomatic improvement
21	Patient with skin-soft tissue infection by MRSA	Linezolid	Vancomicin, clindamicin, TMS	Death, sepsis, cure
22	Patient with obstructive renal failure	Ureteral stent	Nephrostomy	Long term improvement of renal function
23	Patient with hypogammaglobulinemia AND acute infection	Immunoglobulin	No immunoglobulin	Symptomatic improvement, death, complications
24	Patient with supratentorial brain tumor	Antiepileptic drugs, primary prevention	No primary prevention	Seizures, death, adverse events
25	Patient undergoing knee arthroplasty	Extended thromboprophylaxis wih new oral anticoagulants.	Extended thromboprophylaxis wih low weight heparin	DVT,PE, death, bleeding
26	Patient with recurrent cellulitis	prophylactic antibiotic	No prophylactic antibiotic	New cellulitis, adverse events
27	Patient with hepatic encephalopathy	Rifaximin AND lactulose	Lactulose	Death, symptomatic improvement, adverse events
28	Patient with incidental brain aneurysm	Coil	No coil	Bleeding, mortality, adverse events
29	Patient with traumatic subarachnoid hemorrhage	Nimodipin	No nimodipin	Vasospasm, death, adverse effects
30	Patient with renal failure by wegener´s	Rituximab	Standard treatment	Death, end stage renal failure,

	granulomatosis		(Cyclophosphamide)	adverse event
31	Patient with acute pancreatitis	Early enteral feeding	Late feeding	Muerte, morbilidad, días de internación. death, morbidity, hospital stay
32	Patient with dyspnea and heart failure vs acute COPD	pro-BNP to guide managment	No pro-BNP	Symptomatic improvement, death
33	Patient with acute asthma	IV magnessium	No IV magnessium	Symptomatic improvement, hospital stay, death
34	Patient with liver abscess greater than 10 cm	Percutaneous drainage	Surgery	Death, abscess resolution
35	Tracheal stenosis by prolonged endotracheal intubation	Endoscopic treatment	Surgical treatment	Death, sympomatic improvment
36	Patient with uncomplicated abdominal aortic aneurysm	Endovascular treatment	Surgical treatment	Death, complications
37	Patient with chlamydia post-infective reactive arthritis	Systemic steroids	Placebo	Symptomatic improvement
38	Patient with splenic abscess	Percutaneous drainage	Splenectomy	Death, complications
39	Patient with venous sinus thrombosis on anticoagulants	Thrombophilia screeninig	No thrombophilia screening	Recurrence, bleeding, death
40	Patient with systemic sclerosis AND pulmonary hypertension	Heart-Lung Transplantation	No Heart-Lung transplantation	Death
41	Pregnant women	Screening and treatment of cmv infection with intrauterine gammaglobulin	No screening	Congenital infection
42	Patient with spontaneous Intracerebral Hemorrhage and suspected malformation-cavernoma	CTA	Angio MRI	Death, malformation diagnosis
43	Patient with ischemic heart disease	Discontinue aspirin	Continue aspirin	Death, vascular events

	undergoing non cardiovascular surgery			
44	Asymptomatic old patient	Hepres Zoster vaccine	No vaccine	Zoster
45	Atrial fibrillation of indeterminate duration	Rythm control	Frecuency control	Mortality, cardiac output
46	Inpatient with acute COPD	Antibiotic therapy based on procalcitonin level	Antibiotic therapy based on clinical criteria	Death, complications
47	Patient with acute ischemic stroke	Aspirin 325mg	Aspirin 100mg	New stroke, death, bleeding
48	Patient with acute ischemic stroke and occlusion of arterial large vessels	Trombectomy	Pharmacotherapy	Disability, death
49	Patient with Lyme disease and central nervous system compromise	Ceftriaxone	Doxycycline	Death, sequel
50	Patient with chronic heart failure	Pro-bnp guided treatment	No pro-bnp guided treatment	Death
51	Patient in early post neurosurgical period with acute PE	Anticoagulation	Vena cava filter	Death, bleeding
52	Patient with Spontaneous Intracerebral Hemorrhage	Antiepileptic drugs, primary prevention	No antiepileptic drugs-primary prevention	Seizures, death, disability
53	Patient with subarachnoid bleeding and without seizures	Antiepileptic drugs, primary prevention	No antiepileptic drugs-primary prevention	Seizures, death, disability
54	Patient with severe traumatic brain injury	Antiepileptic drugs, primary prevention	No antiepileptic drugs-primary prevention	Seizures, death, disability
55	Patient with ACS taking sildenafil in the last 6 hs	Nitroglycerin	No nitroglycerin	Death, shock
56	Patient undergoing renal transplant	Perioperative pharmacologycal thromboprophylaxis	No thromboprophylaxis	Death, deep vein thromboses, oulmonary embolism, bleeding
57	Patient with active cancer undergoing surgery	Extended thromboprophylaxis	Thromboprophylaxis during hospitalization	Deep vein thromboses or pulmonary embolism, bleeding, death
58	Patient with subarachnoid bleeding	Vasospasm screening with transcranial	No doppler	Death, complications

		doppler		
59	Patient with subarachnoid bleeding	Nimodipin	Placebo	Death, complications
60	Patient with chronic leg ulcer and peripheral artery disease	Hyperbaric oxigen therapy	No hyperbaric oxygen therapy	Healing, death
61	Patient undergoing chemotherapy	Erythropoiesis stimulating factors	Placebo	HRQL, death, adverse events, anemia
62	Patient with renal infarction	Anticoagulation	Aspirin	Recurrent thrombotic event, bleeding
63	Patient with post lumbar puncture headache	Caffeine	Placebo	Pain improvement, adverse events
64	Patient with TRALI	steroids	Placebo	death
65	Cancer patient with deep vein thrombosis/pulmonary embolism	Low weight heparin	VKA	Recurrent thrombotic event, death
66	Patient with unprovoked deep vein thromboses who finish 3-6 month therapy of anticoagulant treatment	Aspirin	Placebo	Recurrent deep vein thromboses, death
67	Diabetic patient who takes metformin undergoing IV contrast CT	Discontinue metformin	Continue metformin	Lactic acidosis
68	Patient with evolved ischemic stroke and intracranial stenosis	STENT	Medical therapy	Recurrent stroke, death, bleeding
69	Patient with cardiovascular risk factors who needs NSAIDs	Naproxen	Other NSAIDs	Major vascular events
70	Patient with dvt	Early deambulation	Bed rest	Pulmonary embolism, bleeding, death
71	Patient with giant meningioma	Pre-surgical embolization	NO Pre-surgical embolization	Bleeding, death, disability
72	Patient with cancer and deep vein thromboses	Enoxaparin 1 daily dose	Enoxaparin 2 daily doses	New thrombotic event, bleeding
73	Immunocompromised patient with pulmonary infiltrates	Determination of galactomannans in bronchoalveolar lavage	No Determination of galactomannans in bronchoalveolar	Death, adverse events

			lavage	
74	Metastatic renal cancer	Nefrectomy	No nefrectomy	Survival, adverse events
75	Patient with recent diagnosis of hiv and recent diagnosis of tb	Immediate start of HAART	Delay start of haart	Death, complications
76	Patient with dizziness	Ginkgo Biloba	Betahistin	symptomatic improvement, adverse events
77	patient with superior vena cava syndrome	Stent	medical treatment	symptomatic improvement, complications
78	Patient with HIV related immune reconstitution inflammatory syndrome	steroids	Placebo	Death, symptomatic improvement
79	Steroids-refractory Immune Thrombocytopenic Purpura	Rituximab	Steroids	bleeding, platelet count
80	Patient who had undergone endarterectomy	Aspirin	Aspirin and clopidogrel	Stroke, death, bleeding
81	Patient with ureteral lithiasis	Alpha adrenergic blockers	Placebo	Pain, stone removal, adverse events
82	Patient with recurrent reflex syncope	Midorine	Placebo	Symptomatic improvement, syncope recurrence, adverse events
83	Patient with hyponatremia	Urinary sodium measure	Physical examination	Symptomatic improvement
84	Patient with pre-diabetes	Metformin	No pharmacological treatment	Microvascular complications (events), macrovascular complications (events)
85	Patient with mild or moderate idiopathic pulmonary fibrosis	Pirfenidone	Placebo	Death, progresion, adverse events
86	Patient with systolic heart failure	Angiotensin-neprilysin inhibition	Enalapril	Death, vascular events, adverse events
87	Patient with acute pharyngitis and severe Odynophagia	Steroids	Placebo	Symptomatic improvement, adverse events
88	Patient with aneurysmatic	Surgical treatment	Endovascular treatment	Rebleeding, death, complications,

	subarachnoid hemorrhage			disability
89	Inpatient with pneumonia	Betalactams	Betalactams + macrolides	Death, mechanical ventilation, adverse events
90	Patient with moderate or severe dementia	Memantine	Placebo	Cognitive status, functional status, adverse events
91	Patient with acute asthma	Inhaled steroids	Placebo	Death, mechanical ventilation, hospitalization
92	Patient on anticoagulants undergoing central venous catheter insertion	Femoral	Yugular	Death, hematoma, other complications, successful insertion
93	Patient with acute asthma	Non invasive ventilation AND standard treatment	Standard treatment	Death, mechanical ventilation, hospitalization
94	Patient with non-convulsive epileptic status	Levetiracetam load dose	Phenytoin load dose	Symptomatic improvement, death
95	Women with osteoporosis and NO previous fracture	Vitamin K	Placebo	Hip fracture, vertebral fracture
96	Ratient with vertigo	Betahistin	Placebo	Symptomatic improvement, adverse events
97	Patient with severe clostridium dificille infection	Metronidazol	Vancomycin	cure, recurrence, adverse events
98	Patient undergoing knee or hip fracture surgery	Thromboprofilaxis with new oral anticoagulants	heparin	thromboembolic events, bleeding, death
99	Patient with acute ischemic stroke and low NIHSS score	Ticagrelor	ASA	Recurrent stroke, bleeding, death
100	Patient with asymptomatic cholelithiasis	Cholecystectomy	Observation	Cholelitiasis related complications, surgery related complications

Nr: Question number

Supplementary table 2. Comparison between rapid strategies

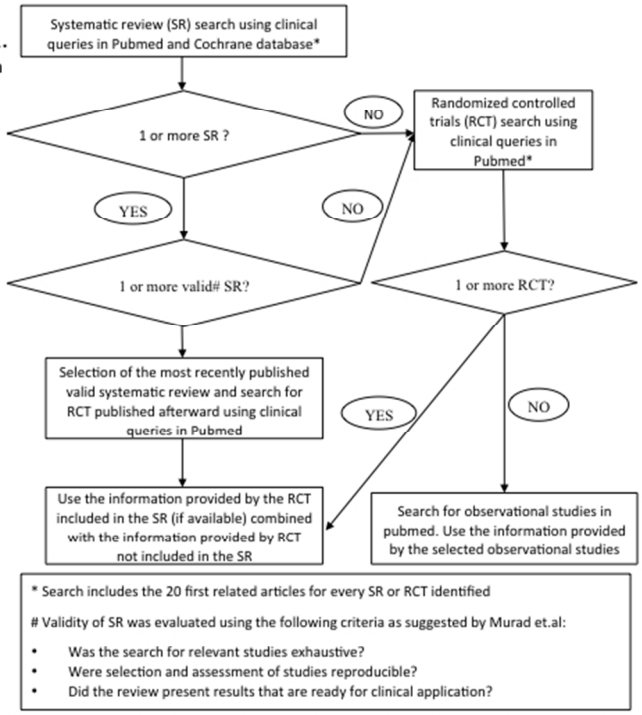
	Strategy 1 (n=100)	Strategy 2 (n=100)	RR (CI95%)
Potentially misleading recommendations	5% (0.7 - 9.2%)	8% (2.6 - 13.3)	0.62 (0.18 - 2)
Inappropriate	1% (0 - 2.9%)	6% (1.3 - 10.6%)	-
Overconfident	4% (0.1 - 7.8%)	2% (0 - 4.7%)	-
Reasonable recommendations	95% (90.7 – 99.2%)	92% (86.5 – 97.3%)	1 (0.95 – 1.1)
Concordant	64% (54.5 – 73.4%)	62% (52.4 – 71.5%)	-
Reasonable disagreement	31% (21.9 – 40%)	30% (21 – 38.9)%	-
Potentially misleading quality of evidence judgment	16% (8.8 - 23.1%)	24% (15.6 - 32.3%)	0.52 (0.24 - 1.13)
Inappropriate Moderate or High	3% (0 - 6.3%)	7% (2 - 12%)	0.41 (0.08 - 1.8)
Inappropriate Low or Very Low	13% (6.4 - 19.5%)	17% (9.6 - 24.3%)	-
Quality of evidence agreement	63% (54.4 - 72.4%)	48% (38.2 - 57.7%)	1.3 (1 – 1.7)
Coincidence in information usage	65% (55.6 - 74.3)	56% (46.2 - 65.7)	1.16 (0.91 - 1.47)

Supplementary table 3. Potentially misleading recommendations description

Strategy	Population	Intervention	Information used	Information analysis	Possible solution
Epistemonikos	Patient with cardiac dyspnea in the emergency department	Pro-BNP guided treatment	Adequate. A SR that included all the relevant information was used	Inappropriate judgment of the quality of evidence.	No solution
Epistemonikos	Patient with asthma reagudization	Intravenous magnesium	Inappropriate. A recent systematic review was not identified	-	Appropriate use of the Epistemonikos matrix of evidence tool solved the problem
Epistemonikos	Patient with acute minor stroke	Mechanical thrombectomy	Inappropriate. A recent systematic review was not identified	-	Appropriate use of the Epistemonikos matrix of evidence tool solved identified the missed SR
Epistemonikos	Patient with acute pancreatitis	Early enteral nutrition	Adequate	Inappropriate judgment of the quality of evidence. Probable inappropriate summary of the evidence.	The recommendation was coherent with the GS when the same SoF was used
Epistemonikos	Patient with tracheal stenosis	Mechanical dilatation	Adequate	Differences in the benefit risk balance judgment	No Solution
Epistemonikos	Patient with recent TB/HIV coinfection diagnoses	Early atiretroviral treatment initiation	Adequate	Differences in the benefit risk balance judgment. Probable inappropriate summary of the evidence.	The recommendation was coherent with the GS when the same SoF was used
Epistemonikos	Patient with	Vitamin K	Adequate	Differences	No solution

	osteoporosis			in the benefit risk balance judgment	
Epistemonikos	Patient with asymptomatic cholelitiasis	No surgical treatment	Inappropriate. One relevant publication not identified	-	No solution
Pubmed	Patient with acute aneurysmal rupture with SAH	Endovascular treatment	Inappropriate. Two relevant publications not identified	-	No solution
Pubmed	Patient with traumatic SHA	Nimodipine	Appropriate	Inappropriate judgment of the quality of evidence. Probable inappropriate summary of the evidence.	The recommendation was coherent with the GS when the same SoF was used
Pubmed	Patient with systemic sclerosis and severe lung compromise	Lung transplantation	Appropriate	Differences in the benefit risk balance judgment	No solution
Pubmed	Patient with chronic heart failure	BNP guided therapy	Inappropriate. A recent systematic review was not identified	-	Appropriate use of the Epistemonikos matrix of evidence tool identified the missed SR
Pubmed	Patient with severe Clostridium Difficile infection	Vancomicin	Inappropriate. A recent systematic review was not identified	-	No Solution

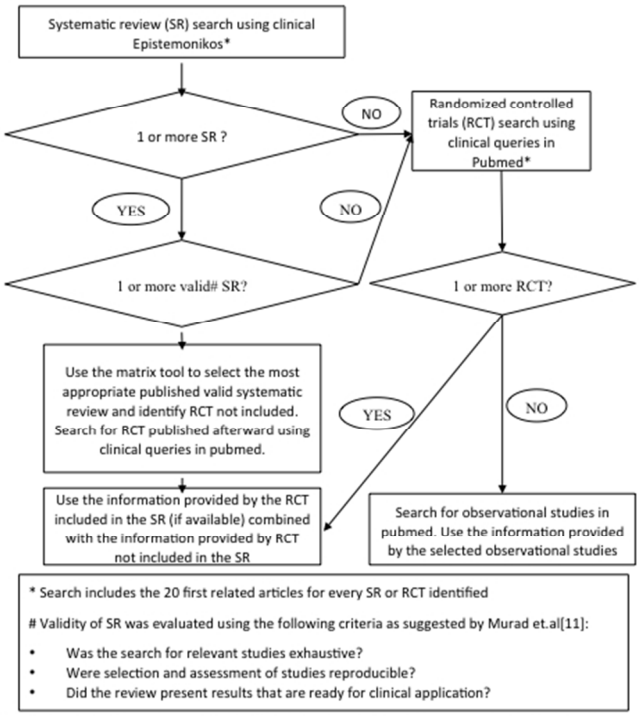
Supplementary Figure 1.
Rapid strategy based on MEDLINE



Murad MH, Montori VM, Ioannidis JP, et al. How to read a systematic review and meta-analysis and apply the results to patient care: users' guides to the medical literature. *JAMA* 2014;312:171–9

254x190mm (72 x 72 DPI)

Supplementary Figure 2.
Rapid strategy based on EPISTEMONIKOS



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Answering medical questions at the point of care: A cross-sectional study comparing rapid decisions based on PubMed and Epistemonikos searches with evidence-based recommendations developed with the GRADE approach.

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Answering medical questions at the point of care: A cross-sectional study comparing rapid decisions based on PubMed and Epistemonikos searches with evidence-based recommendations developed with the GRADE approach.

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ABSTRACT

Introduction

Using the best current evidence to inform clinical decisions remains as a challenge for clinicians. Given the scarcity of trustworthy clinical practice guidelines providing recommendations to answer clinicians' daily questions, clinical decision support systems (i.e. assistance in question identification and answering) emerge as an attractive alternative. The trustworthiness of the recommendations achieved by such systems is unknown.

Objective

To evaluate the trustworthiness of a question identification and answering system that delivers timely recommendations.

Design

Cross-Sectional study

Methods

We compared the recommendations in response to 100 clinical questions related to inpatient management provided by two rapid response methods, one based on PubMed and the other based on the Epistemonikos database, with "Gold Standard" recommendations (trustworthy published evidence based recommendations or, when not available, recommendations developed locally by a panel of 6 clinicians following the GRADE approach). Based on this comparison, recommendations provided by the rapid strategies were classified as potentially misleading or reasonable. We also determined if the potentially misleading recommendations could have been avoided with the appropriate implementation of searching and summary of evidence tools.

Results

We were able to answer all the 100 questions with both rapid methods. Of the 200 recommendations obtained, 6.5% (CI95% 3 – 9.9%) were classified as potentially misleading and 93.5% (CI95% 90 – 96.9%) as reasonable. Six of the 13 potentially misleading recommendations could have been avoided by the appropriate usage of the Epistemonikos matrix tool or by constructing summary of findings tables. No significant differences were observed between the evaluated rapid response methods.

Conclusion

A question answering service based on the GRADE approach proved feasible to implement and provided appropriate guidance for most identified questions. Our approach could help stakeholders in charge of managing resources and defining policies for patient care to improve evidence based decision making in an efficient and feasible manner.

ARTICLE SUMMARY

Strengths and limitations

- The study was carried out in a real-world scenario (questions related to patients being treated in a clinical ward)
- Three different clinicians were randomly assigned to apply the different answering strategies
- We developed a transparent framework to categorize the recommendations obtained by the rapid strategies
- We sought to provide trustworthy “Gold Standard” recommendations nevertheless it is not possible to guarantee that they were optimal
- It is unclear if the observed results can be replicated in other contexts, for example with participants less trained in evidence based decision-making

INTRODUCTION

Research consistently shows that there is an important gap between evidence and practice,[1,2] and clinicians seldom use the best available evidence to guide their decisions.[3,4,5] Limited time, lack of training in critical appraisal and low expectations for finding relevant answers are among the most common identified obstacles.[6,7] These practices are potentially problematic, as the benefits of using the best current evidence to inform clinical decisions are widely accepted to such extent that evidence based decision making is frequently considered a measure of healthcare quality.[8] In particular, hospital executive boards, insurance companies and consumers recognize that evidence based practice may help prevent unsafe or inefficient practices. [9-11]

One of the potential solutions for bringing evidence to bedside decisions is the use of trustworthy and transparent clinical practice guidelines. Although the last decade has seen significant advances in guideline methodology (http://www.gradeworkinggroup.org/), important limitations still remain: 1) only a small number of guidelines have been tailored to clinicians needs;[12] 2) Finding relevant guidelines can be laborious and time consuming; 3) Typically, only a few guidelines are kept up to date.[13]

Another alternative for bridging the gap between evidence and clinical practice are clinical decision support systems designed to provide assistance to clinicians in the question identification and resolution process by finding the answer for them and presenting the information in a user-friendly way.[14-18] Unlike products that passively provide pre-apprised evidence at the point of care (e.g. UpToDate) this systems involve trained practitioners that search and deliver tailored answers to identified questions. However the trustworthiness of the recommendations achieved by such systems is unknown.

The objective of this study was to evaluate the trustworthiness of a question identification and answering system that delivers timely recommendations to clinicians providing care to inpatients

by comparing the imparted guidance with “Gold Standard” recommendations. Additionally, we come up with a proposal on how to replicate the process.

METHODS

We conducted the study on the Internal Medicine Service of the German Hospital of Buenos Aires, Argentina, from March 2014 to March 2016. The context in which this study was carried out has been described in another publication.[17]

We compared two rapid response methods, one based on PubMed using clinical queries, which are a series of filters designed to improve the retrieval of scientifically strong and clinically relevant articles from PubMed database.[19] The other method was based on Epistemonikos, which is a relational, collaborative, multilingual database of health evidence that includes systematic reviews from multiple sources (Cochrane database of systematic reviews and PubMed, among others)[20], with trustworthy published evidence based recommendations or, when not available, recommendations developed locally by a panel of six clinicians. For the purpose of this study, we considered those recommendations as our “Gold Standard”.

Three clinicians trained in evidence based decision-making (informationists) attempted to answer all the identified questions following three different strategies. The informationists differ from clinical librarians in that they are trained in clinical epidemiology methods rather than simply information acquisition, and have clinical expertise relevant to the questions that allows contextual interpretation of research findings. Each question had its own randomization schedule drawn from a computer pre-generated random number list in which each informationist was assigned to one of the three strategies described below. We describe the question identification process and the strategies to address the questions in the following sections.

Identification and selection of clinical questions

One of the informationists (AI), otherwise uninvolved in the patients' care, identified questions relevant to the staff and residents of the Internal Medicine Service. Either the staff or residents explicitly formulated the questions, or AI inferred the question from the discussion of the clinical cases. We collected the relevant clinical question using the PICO (Population/Problem, Intervention, Comparison, Outcome) framework.

In order to focus on questions that could potentially impact clinicians' course of action, we excluded questions that: (1) were answered immediately by someone who was present in the session, other than the informationists, typically, using electronic resources such as UpToDate, (2) were not related to therapeutic or diagnostic interventions, or (3) addressed interventions already implemented in the patient's care.

All the identified questions that did not fulfilled one of the exclusion criteria were included and registered. The described question identification process was repeated until the study was finished.

Rapid strategy based on PUBMED (Strategy 1)

The informationist assigned to this strategy performed a literature search on MEDLINE using the PubMed clinical queries feature (supplementary figure 1). First he tried to identify relevant systematic reviews[21]; when unavailable or when considered that additional relevant information could be available, he searched for primary studies. Once the informationist identified the most relevant systematic review or primary study/s, he followed the GRADE approach to interpret the results and judge the certainty on the evidence (for a detailed description see GRADE handbook available at: gdt.guidelinedevelopment.org/app/handbook/handbook.html). Following the GRADE guidance the informationist also considered additional relevant information related to patients values and preferences, costs, applicability and feasibility,[22,23] and made a clinical decision simulating what clinicians could do in the optimal scenario. To capture the decision, the informationist

formulated a recommendation that included the direction (in favor or against the intervention) and the strength (strong or weak). The process took no more than two hours.

Rapid strategy based on Epistemonikos (Strategy 2)

The informationist assigned to this strategy searched on the Epistemonikos database using the "matrices of evidence" tool, which is a is a tabular way of displaying the cluster of systematic reviews that share at least one included study,[24] (supplementary figure 2) and followed the same process described for the strategy 1. He also searched PubMed for RCT in cases were systematic reviews were not available or when he considered that additional relevant information could be available (supplementary figure 2).

Strategy based on trustworthy recommendations ("Gold Standard") (Strategy 3)

The informationist assigned to this strategy searched for recommendations developed with the GRADE approach, on the following databases: Tripdatabase (http://www.tripdatabase.com); National guideline Cleringhouse (http://www.guidelines.gov); Canadian Medical Association (http://www.cma.ca/clinicalresources/practiceguidelines); NICE (http://www.nice.org.uk/); SIGN (http://www.sign.ac.uk); GuíaSalud (http://portal.guiasalud.es/web/guest/buscar-gpc); Australian clinical practice guidelines (http://www.clinicalguidelines.gov.au); New Zealand Guidelines Group (http://www.nzgg.org.nz/); US preventive Task Force (http://www.uspreventiveservicestaskforce.org/); eguidelines (https://www.guidelines.co.uk/), GIN (http://www.g-i-n.net/about-g-i-n/introduction).

He critically assessed the identified recommendations using the criteria proposed for evaluating GRADE recommendations[25] and qualitatively categorized their trustworthiness as High, Moderate or Low based on the answers to the following questions: Was the question clearly formulated? Were all the critical outcomes considered? Was the recommendation based on the

best current evidence? The evidence was clearly presented? Was the recommendation coherent with the supporting evidence? Were the values and preferences considered?

Additionally, for every question, the same informationist, searched for systematic reviews, randomized controlled trials and observational studies on the following databases without time restriction: PubMed, Epistemonikos and the Cochrane database of systematic review. He used the information of the relevant systematic review and/or primary studies to construct a Summary of Finding Table (SoF) following the GRADE principles (SoF example available in supplementary table 1).[26,27] The tables were then sent via email to six clinicians ("local panel") with experience with the GRADE approach. Each clinician provided a recommendation using the information included in the SoF tables and also considering additional relevant information related to patients values and preferences, costs, applicability and feasibility.[22,23] When more than 66% of the clinicians who answered agreed on the strength and direction of the recommendation, we considered that recommendation final. Disagreement in the direction or the strength of the recommendation were recorded and resolved by seventh clinician (IN) with experience in developing GRADE recommendations. Although we intended to answer every question with the described, "local panel", approach we only used the resultant recommendations when published GRADE recommendations developed by guideline panels that were rated with "high trustworthiness" were unavailable. We defined "Gold standard" recommendations using the available information as described in figure 1.

Outcomes:

We compared the recommendations, quality of evidence judgments and information used by rapid strategies and the "Gold standard" strategy to define the following outcomes:

Inappropriate recommendations: When the “Gold Standard” was a strong recommendation and the rapid strategies yielded a decision in the opposite direction of any strength; or when the “Gold Standard” was a weak recommendation and the rapid strategies yielded a strong recommendation in the opposite direction.

Overconfident recommendations: When the “Gold Standard” was a weak recommendation and the rapid strategies yielded a decision concordant with a strong recommendation on the same direction

Potentially misleading recommendations: Composite of inappropriate or overconfident recommendations

Concordant recommendations: When the “Gold Standard” and the rapid strategies yielded a recommendation of the same direction and strength

Reasonable disagreement: When the “Gold Standard” was a weak recommendation in favor and the rapid strategies yielded a weak recommendation against or vice versa, or when the “Gold Standard” was a strong recommendation and the rapid strategies yielded a weak recommendation on the same direction

Reasonable recommendations: Composite of concordant recommendations and reasonable disagreement

Table 1. describes the framework for rapid recommendation categorization based on their comparison with “Gold Standard” recommendations.

Table 1. Framework to categorize recommendations

		GOLD STANDARD			
		Strong Against	Weak Against	Weak in Favor	Strong in Favor
RAPID STRATEGIES	Strong Against	Concordant	Overconfident	Inappropriate	Inappropriate
	Weak Against	Reasonable	Concordant	Reasonable	Inappropriate
	Weak in Favor	Inappropriate	Reasonable	Concordant	Reasonable
	Strong in Favor	Inappropriate	Inappropriate	Overconfident	Concordant

Same direction recommendations: When the "Gold Standard" and the rapid strategies yielded a recommendation of the same direction regardless of its strength

Inappropriate quality of evidence judgment: Proportion of recommendations in which the quality of evidence: 1) was judged as Low or Very Low by the rapid strategies and High or Moderate by the "Gold Standard" or; 2) Was judged as High or Moderate by the rapid strategies and Low or Very low by the "Gold Standard"

Coincidence in information usage: Proportion of recommendations in which the publications used by the rapid methods was the same to the ones used by the "Gold Standard"

Additional analyses

We also performed a post-hoc qualitative analysis of the recommendations classified as potentially misleading. We analyzed the reasons for the disagreement between the rapid

strategies and the gold standard and we considered potential solutions. For this purpose, in cases in which the potentially misleading recommendations were judged to be a consequence of inadequate evidence selection, we determined if the appropriate use of the epistemonikos matrixes tool could have prevented that problem (i.e identification of a SR containing primary studies that were not considered for the development of the original recommendation). In cases in which potentially misleading recommendations were judged to be a consequence of inappropriate evidence interpretation, we determined if the correct presentation of the evidence could have prevented the problem. To assess this, we sent the SoF table constructed in response to the same question for the "Gold Standard" strategy (strategy 3) to the investigator who originally constructed the potentially misleading recommendation. We asked the investigator to provide a new recommendation based in the SoF. We judged that the correct use of the Sof could have prevented the problem when the investigator provided a reasonable recommendation in response (in comparison to the GS recommendation).

Statistical analysis

For the comparisons between the rapid strategies and the "Gold Standard" we calculated proportions and 95%CI for all the outcomes. We also calculated interrater agreement with Kappa statistic using VassarStats calculator (http://vassarstats.net/kappa.html). For the kappa calculation related to recommendation concordance (strong in favor, weak in favor, weak against or strong against) we imputed the double of distance between strong in favor - weak in favor and strong against - weak against than weak in favor - weak against. For the kappa calculation related to quality of evidence agreement (high, moderate, low or very low) we imputed the double of distance between moderate - low than very low - low and moderate - high. For the comparison between strategies 1 and 2 we calculated relative risks and 95%CI when possible.

RESULTS

During the study period we identified 100 questions all of which were answered with strategies 1 and 2 (200 recommendations). With strategy 3 we found recommendations in CPG for 80 of the 100 questions all of which could be answered by the "local panel" approach. The process of answering each question with strategy 3 ("Gold Standard, local panel" approach) took, on average, 1 week per question. Table 2 presents the characteristics of the recommendations delivered by each strategy. A list of the PICOs is available in the supplementary table 2.

Table 2. Recommendations according to the strategy implemented

	Strategy 1 (n=100)	Strategy 2 (n=100)	Strategy 3 (CPG) (n=80)(%)	Strategy 3 ("local panel") ((n=100)
Recommendations				
Strong	14	12	21 (26.2)	21
In favor of the intervention	55	62	55 (68.7)	63
Quality of evidence				
High	8	5	-	12
Moderate	22	25	-	28
Low	34	26	-	44
Very Low	36	44	-	16
Confidence in the CPG recommendation				
High (%)	-	-	16 (20)	-

Following the process described in figure 1 we obtained 100 "Gold standard" recommendations. These recommendations were composed by 16 High confidence CPG recommendations, 55

panel recommendations and 29 expert recommendations. The results of the comparison between the rapid strategies and the "Gold standard" are described in table 3.

Table 3. Rapid strategies recommendations analysis

	Rapid strategies versus "Gold Standard" (n=200)	Kappa
Potentially misleading recommendations	6.5% (3 - 9.9%)	-
Inappropriate	3.5% (0.95 - 6%)	-
Overconfident	3% (0.64 - 5.3%)	-
Reasonable recommendations	93.5% (90 – 96.9%)	-
Concordant	62.5% (55.7 - 69.2%)	0.59 (0.36 - 0.82)
Reasonable disagreement	31% (24.5 – 37.4%)	-
Same direction recommendations	74% (67.5 – 79.5%)	-
Strong (rapid strategies) (n=26)	96.1% (82.2 – 99.3%)	-
Weak (rapid strategies) (n=174)	70.6% (64.5 – 76.9%)	-
Potentially misleading quality of evidence judgment	20% (14.4 - 25.5%)	-
Inappropriate Moderate or High	5% (1.9 - 8%)	-
Inappropriate Low or Very Low	15% (10 - 19.9%)	-
Quality of evidence agreement	55.5% (48.6 - 62.3%)	0.59 (0.46 - 0.72)
Coincidence in information use*	60% (50.4 - 69.6)	-

* The same publication/s were used to answer the question

The comparison between strategies 1 and 2 is described in supplementary table 3.

There were 13 recommendations that were judged as potentially misleading, the causes and possible solutions are summarized in supplementary table 4.

DISCUSSION

The results of the present study suggest that a rapid question answering system based on the GRADE approach provided appropriate guidance in response to most questions. Although the proportion of concordant recommendations (same strength and direction between rapid strategies and GS) was 62.5%, most of the remainder (31% of the total), were classified as "reasonable disagreements". Only 13 of the 200 recommendations were judged as potentially misleading and approximately half of these could possibly have been avoided with an appropriate use of the available tools (Epistemonikos matrix of evidence, SoF tables). We also analyzed the results considering exclusively the direction of the recommendations. The results showed that almost all strong recommendations constructed with the rapid strategies shared the same "Gold Standard's" direction while 70% of the weak recommendations did. This finding is not surprising given that weak recommendation's are frequently based on low or very low quality of evidence, or are warranted in situations were benefits and risks are closely balanced, hence their direction is subjectively defined by weighting those aspects (e.g. in a situation in which benefits and harms are balanced, some guideline panel members can interpret the results as favoring the intervention while others as favoring the comparison).[22,23,25] Although 30% of weak recommendations had a different direction from the "Gold Standard's", we consider that it is unlikely that they would have resulted in misleading guidance, as those willing to use them should carefully analyze the fundamentals of the recommendation before deciding their course of action.[22,23,24] An exception would be the situation in which the "Gold Standard" recommendations were strong in the opposite direction but this was captured in the primary analysis as those recommendations were classified as inappropriate.

The comparison between the different rapid answering strategies (Pubmed vs Epistemonikos) showed that although the proportion of potentially misleading recommendations was small in both strategies, there was a slight (3%) absolute difference in favor of PubMed strategy. One possible explanation for the difference is that the investigators involved in the study were less familiarized with Epistemonikos database and search engine than PubMed's.

The main limitation of our study is that it is not possible define a “Gold Standard” recommendation for a medical question. We sought to provide trustworthy “Gold Standard” recommendations by performing rigorous evidence searches, constructing detailed evidence summaries and including multiple clinicians trained in evidence based decision making; the approach nevertheless does not guarantee optimal recommendations. In addition, the system was applied to a specific subgroup of questions (intervention related questions that were not immediately answered). We consider that addressing questions that do not meet these criteria are less likely to change clinicians’ behavior.

Although investigators have previously undertaken evaluation of the implementation of question answering services, [28-33] these studies focused on clinicians’ attitudes and decisions in response to the answers provided. Without knowing that the answers the services provides are based on the best available evidence, and that clinicians interpret and use the provided information appropriately to make coherent decisions, the benefit of the service to improve patient outcomes remains uncertain.[34] Another approach would be to directly measure the impact of this kind of services on clinical important outcomes (i.e. mortality or length of hospital stay). However demonstrating such an effect of interventions intended to improve quality of care through affecting physician’s behavior could be very difficult (huge sample sizes needed, low signal-to-noise ratio).[35-37] Attempts have been made in this direction and the results suggest possible benefits with the implementation of the evaluated interventions but the quality of evidence provided was low, either because of imprecision (underpowered studies)[16-18] or because of risk of bias (non-randomized comparisons).[38-40]

We found only one study that considered the trustworthiness of the answers provided.[41] In that study, the investigators inserted study evidence statements related to the management of

clinical conditions for which high-quality randomised controlled trials, or metaanalyses had unequivocally established benefits greater than risks, costs and inconvenience into hospital discharge letters. The study results showed a significant increase in general practitioner adherence to discharge medications demonstrating that in optimal conditions (no time restrictions to perform evidence searches, high quality of evidence available) providing information to clinicians improve patient care. However, that optimal scenario is probably the exception as for most clinical questions high quality evidence remains unavailable, [16,42,43] and clinicians usually need very prompt answers to their questions. Hence, ours is the first study to use a structured and objective approach to measure the quality of the information provided in a timely way to clinician-generated questions.

To achieve a medical practice consistent with what Ubbink et al. described as evidence-based practice,[44] clinicians need to be able to quickly obtain and accurately assess the best available evidence to answer their questions. Clinical practice guidelines endeavor to provide these answers at the point of care and when rigorously developed and up to date constitute optimal guidance. However most of the available guidelines have methodological flaws and do not provide trustworthy recommendations.[12,13] In the present study 80% of the identified questions could be answered with recommendations included in CPG but only 20% of them were judged to be trustworthy.

Given current guideline limitations, if feasible and properly implemented, a question answering system could provide a solution. This study adds to our previous study in which we evaluated the impact of implementing a response system similar to the one evaluated in the preset trial, on clinician's decisions.[16] The results of that trial suggested that response systems could influence clinician's courses of actions and therefore patient care.

The study was developed in a real life scenario with limited amount of resources, which suggest that the proposed intervention can possibly be implemented in variety of settings, including a

busy clinical ward. We were able to efficiently implement the proposed system with: 1) one clinician trained in evidence based decision making exclusively dedicated to this task for at least 2 hours a day and; 2) a computer with internet connection. We used a systematic and transparent method to arrive at decisions. Finally, we have developed a framework to compare different recommendations developed with the GRADE approach acknowledging that not any discrepancy should be considered inappropriate as different values and preferences may lead to reasonable disagreement between recommendations.

Implication for practice

Those interested in improving evidence utilization in health care decision-making should consider the implementation of systems as the one proposed in the present study. This would require, at least, one trained health care provider (informationist) who would: 1) Search for trustworthy published recommendations or, when not available, systematic reviews in Epistemonikos and/or PubMed; 2) Use the Epistemonikos matrices of evidence tool and/or Pubmed to identify additional information (not included in the selected systematic review); 3) Construct a summary of findings table including all critical outcomes; 4) Define a recommendation based on identified trustworthy recommendations or constructed summary of findings tables (Figure 2). We think that the cornerstone to successfully replicate the described process is practitioners training in evidence search, critical appraisal, summary and evidence to decision translation.

Implication for research

Investigators who addressed the clinical questions using the proposed strategies in the present study were highly trained in evidence-based decision-making and could possibly be classified as experts. Whether similar results could be obtained when those responsible for solving the identified questions are not experts remains uncertain.

CONCLUSION

A question answering service based on the GRADE approach proved feasible to implement and provided appropriate guidance for most identified questions. Our approach could help stakeholders in charge of managing resources and defining policies for patient care to improve evidence based decision-making in an efficient and feasible manner.

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The corresponding author and manuscript's guarantor certifies that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Data sharing: no additional data available

Individual author contributions

Izcovich A. significantly contributed to the conception and design of the work, and the acquisition, analysis and interpretation of data.

Criniti J.M. significantly contributed to the design of the work, and the acquisition, analysis and interpretation of data.

Popoff F. significantly contributed to the design of the work, and the acquisition, analysis and interpretation of data.

Ragusa M.A. significantly contributed to the the acquisition and interpretation and of the data.

Gigler C. significantly contributed to the acquisition and interpretation and of the data.

Gonzalez Malla C. significantly contributed to the acquisition and interpretation and of the data.

Clavijo M. significantly contributed to the acquisition and interpretation and of the data.

Manzotti M. significantly contributed to the acquisition and interpretation and of the data.

Díaz M. significantly contributed to the acquisition and interpretation and of the data.

Catalano H.N. significantly contributed to the acquisition and interpretation and of the data.

Neumann I. significantly contributed to the design of the work, and the acquisition, analysis and interpretation of data.

Guyatt G. significantly contributed to the design of the work, and the acquisition, analysis and interpretation of data.

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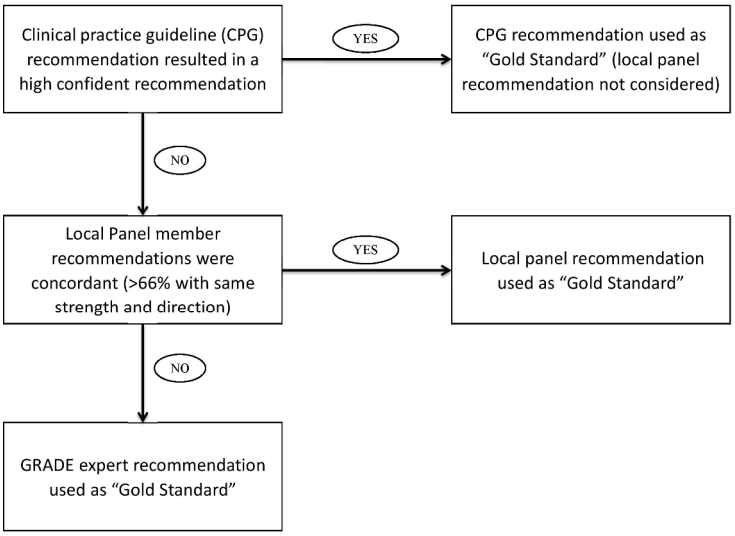
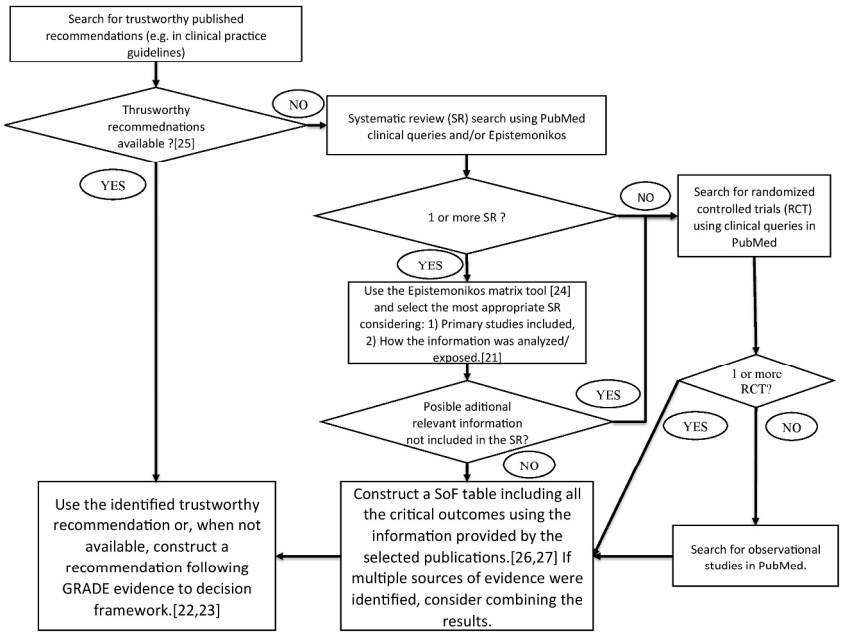
Figure 1. “Gold Standard” recommendation development

Figure 2. Rapid answering system proposal



"Gold Standard" recommendation development

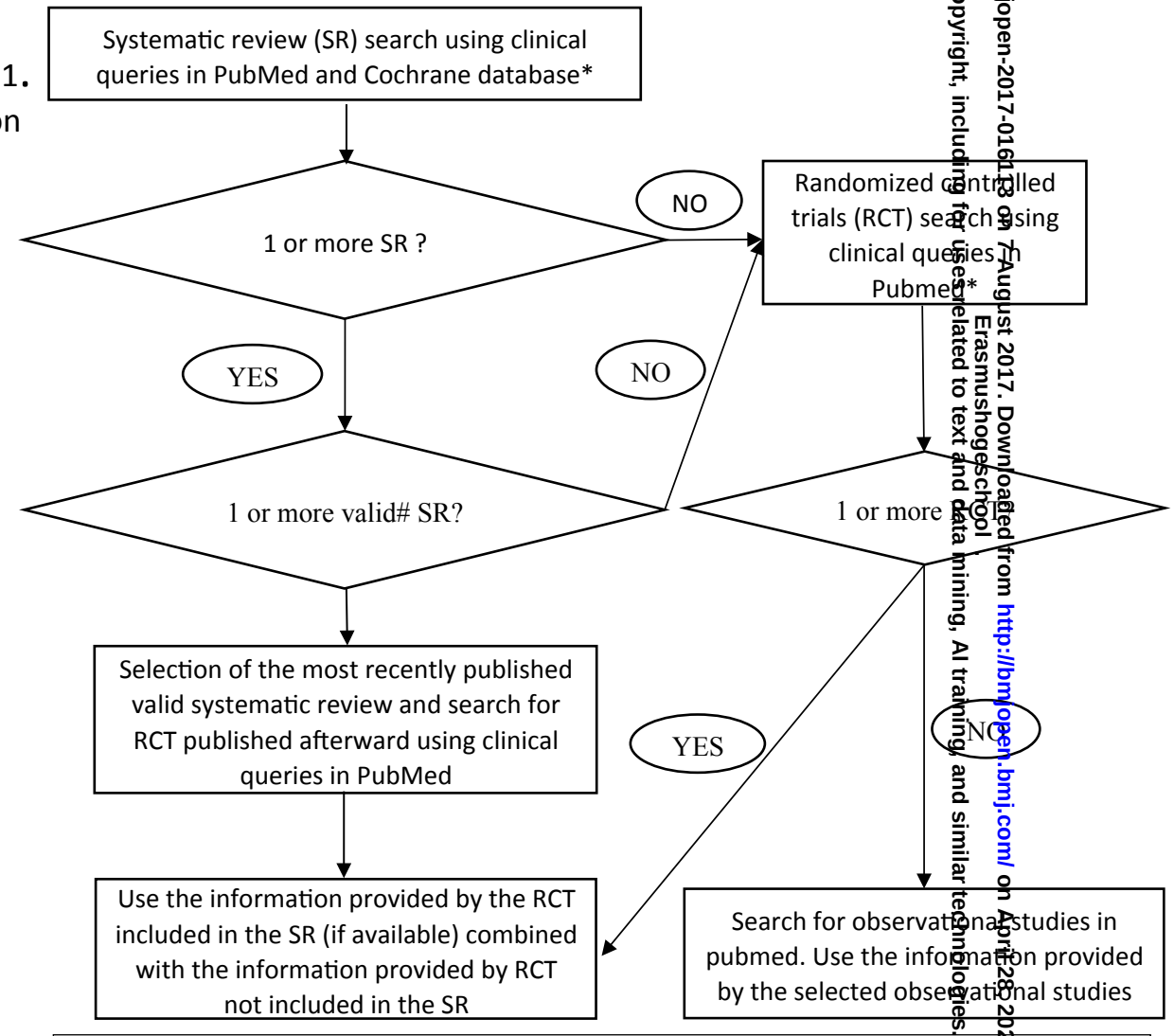
297x209mm (300 x 300 DPI)



Rapid answering system proposal

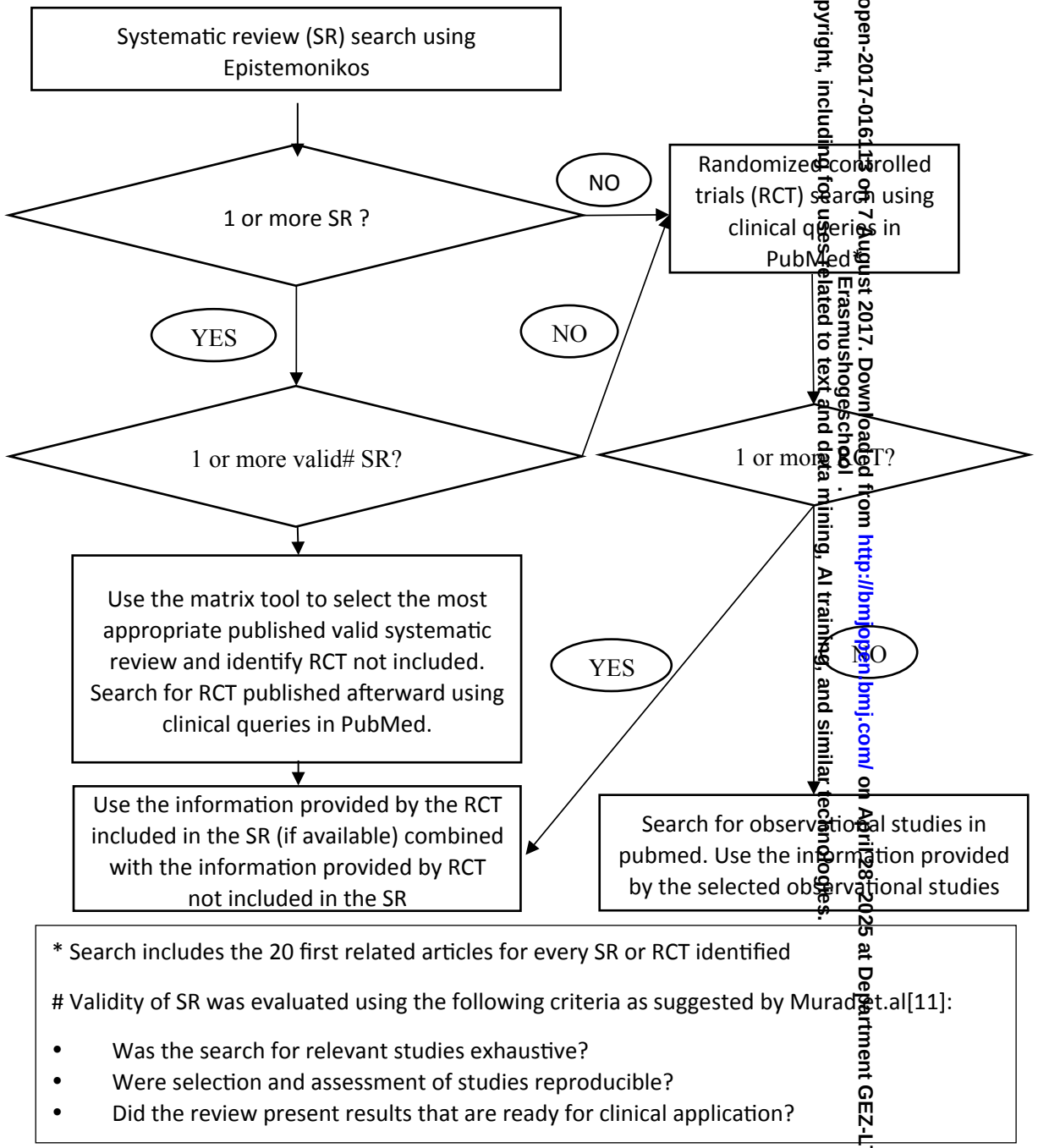
297x209mm (300 x 300 DPI)

Supplementary Figure 1. Rapid strategy based on PubMed



Murad MH, Montori VM, Ioannidis JP, et al. How to read a systematic review and meta-analysis and apply the results to patient care: users' guides to the medical literature. *JAMA* 2014;312:171-9

Supplementary Figure 2.
Rapid strategy based on EPISTEMONIKOS



Murad MH, Montori VM, Ioannidis JP, et al. How to read a systematic review and meta-analysis and apply the results to patient care: users' guides to the medical literature. *JAMA* 2014;312:171-9

Supplementary table 1. Summary of findings table example

P: Patient with acute ischemic stroke

I: Ticagrelor

C: Aspirin

O: Death, recurrent stroke, bleeding

Ticagrelor compared to Aspirin for patients with acute ischemic stroke

Results № of participants (Studies)	Relative effects (95% CI)	Anticipated absolute effects (95% CI)			Quality of the evidence	What
		Without Ticagrelor	With Ticagrelor	Difference		
Recurrent stroke Follow up: 90 days № de participants: 13199 (1 RCT)	**HR 0.87** (0.76 a 1.00)	6.7%	**5.8%** (5.1 a 6.7)	**0.8% Less** (1.6 Less to 0 Less)	⨁⨁⨁◯ MODERATE [1]	Ticagrelor probably marginally reduces stroke recurrence risk.
AMI Follow up: 90 days № de participants: 13199 (1 RCT)	**HR 1.20** (0.67 a 2.14)	0.3%	**0.4%** (0.2 a 0.7)	**0.1% more** (0.1 less to 0.4 more)	⨁⨁⨁◯ MODERADO [1]	Ticagrelor probably does not increases nor reduces AMI risk
Death Follow up: 90 days № de participants: 13199 (1 RCT)	**HR 1.18** (0.83 a 1.67)	0.9%	**1.0%** (0.7 a 1.5)	**0.2% more** (0.1 less to 0.6 more)	⨁⨁⨁◯ MODERADO [1]	Ticagrelor probably does not increases nor reduces mortality
Major bleeding Follow up: 90 days № de participants: 13199 (1 RCT)	**HR 0.83** (0.47 a 1.46)	0.4%	**0.3%** (0.2 a 0.6)	**0.1% Less** (0.2 Less to 0.2 more)	⨁⨁⨁⨁ ALTA	Ticagrelor probably does not increases nor reduces major bleeding risk
Burden of treatment	Ticagrelor requires two doses a day. Aspirin requires one dose a day				⨁⨁⨁⨁ ALTA	

1. 95%CI included both significant benefits and harms

- Johnston SC, Amarenco P, Albers GW, Denison H, Easton JD, Evans SR, Held P, Jonasson J, Minematsu K, Molina CA, Wang Y, Wong KS; SOCRATES Steering Committee and Investigators.. Ticagrelor versus Aspirin in Acute Stroke or Transient Ischemic Attack. N Engl J Med. 2016 Jul 7;375(1):35-43. doi: 10.1056/NEJMoa1603060. Epub 2016 May 10.

Supplementary table 2. PICO questions

Nr.	Population	Intervention	Comparison	Outcomes
1	Patient with acute asthma and upper airway infection	Antibiotics	No antibiotics	Mortality
2	Renal transplant patient with pleural TB	Steroids	No steroids	Resolution time, complications and mortality
3	Patient with atrial fib on anticoagulants undergoing a breast biopsy	Stopping anticoagulant	Not stopping anticoagulant	Bleeding risk, thromboembolic event risk, mortality
4	Patient with severe hypokalemia (< 2.5 meq/l)	Intravenous potassium	Oral potassium	Arrythmia, morbidity and mortality
5	Patient with prosthetic valve endocarditis by MSSA	Cephalosporin+rifampicyin+gentamicin	Cephalosporin+rifampicyin	Complications, mortality
6	Patient with pericardial TB	Steroids	Placebo	Death, symptomatic improvement, sequel
7	Transplant patient with CMV resistant systemic infection	IV gamaglobulin	No IV Gamaglobulin	All cause mortality, CMV related mortality, time to viral load negativization, adverse events
8	Patient with congestive heart failure	IV furosemide bolus	IV furosemide continuous infusion	Mortality, adverse events, arrythmia
9	Patient with upper gastrointestinal bleeding, forrest III peptic ulcer and pulmonary embolism	Anticoagulants	Vena cava filter and prophylaxis	Major bleeding, upper gastrointestinal bleeding, PE mortality, all-cause mortality
10	Patient with atrial fibrillation and CHADS score > 1	Watchman plus antiplatelet therapy	Anticoagulation	Thromboembolic events, major bleeding, all cause mortality
11	Patient with acute ischemic stroke	Statins	Placebo	Recurrent stroke, all cause mortality
12	Patient undergoing neurosurgery for malignant disease	Early thromboprophylaxis with enoxaparin	Late thromboprophylaxis with enoxaparin	Surgical bleeding, major bleeding, thromboembolic events, mortality
13	Patient with acute diarrhea	Fecal leucocyte to guide therapy	No fecal leucocyte analysis	Morbidity, mortality
14	Inpatient with	Antibiotics AND	Antibiotics	Mortality, hospital

	pneumonia	steroids		stay, mechanical ventilation requirement, ICU stay
15	Patient with catheter related deep venous thrombosis	Anticoagulation and extraction	Wait and watch	Pulmonary embolism, stroke, death
16	Patient with distal inferior limb deep vein thromboses	Anticoaguation	No anticoagulation	Pulmonary embolism, mortality
17	Patient with traumatic splenic laceration	Splenectomy	Wait and watch	Mortality,hemoperitoneum
18	Adult with asymptomatic celiac disease	Gluten free diet	No treatment	Quality of life, cancer
19	Pacient with stable COPD	Non invasive mechanical ventilation	Standard treatment	Mortality, quality of life
20	Adult with facial cellulitis	Antibiotics and steroids	Antibiotics only	Symptomatic improvement
21	Patient with skin-soft tissue infection by MRSA	Linezolid	Vancomicin, clindamicin, TMS	Death, sepsis, cure
22	Patient with obstructive renal failure	Ureteral stent	Nephrostomy	Long term improvement of renal function
23	Patient with hypogammaglobulinemia AND acute infection	Immunoglobulin	No immunoglobulin	Symptomatic improvement, death, complications
24	Patient with supratentorial brain tumor	Antiepileptic drugs, primary prevention	No primary prevention	Seizures, death, adverse events
25	Patient undergoing knee arthroplasty	Extended thromboprophylaxis wih new oral anticoagulants.	Extended thromboprophylaxis wih low weight heparin	DVT,PE, death, bleeding
26	Patient with recurrent cellulitis	prophylactic antibiotic	No prophylactic antibiotic	New cellulitis, adverse events
27	Patient with hepatic encephalopathy	Rifaximin AND lactulose	Lactulose	Death, symptomatic improvement, adverse events
28	Patient with incidental brain aneurysm	Coil	No coil	Bleeding, mortality, adverse events
29	Patient with traumatic subarachnoid hemorrhage	Nimodipin	No nimodipin	Vasospasm, death, adverse effects
30	Patient with renal failure by Wegener´s	Rituximab	Standard treatment	Death, end stage renal failure,

	granulomatosis		(Cyclophosphamide)	adverse event
31	Patient with acute pancreatitis	Early enteral feeding	Late feeding	Muerte, morbilidad, días de internación. death, morbidity, hospital stay
32	Patient with dyspnea and heart failure vs acute COPD	pro-BNP to guide managment	No pro-BNP	Symptomatic improvement, death
33	Patient with acute asthma	IV magnessium	No IV magnessium	Symptomatic improvement, hospital stay, death
34	Patient with liver abscess greater than 10 cm	Percutaneous drainage	Surgery	Death, abscess resolution
35	Tracheal stenosis by prolonged endotracheal intubation	Endoscopic treatment	Surgical treatment	Death, sympomatic improvment
36	Patient with uncomplicated abdominal aortic aneurysm	Endovascular treatment	Surgical treatment	Death, complications
37	Patient with chlamydia post-infective reactive arthritis	Systemic steroids	Placebo	Symptomatic improvement
38	Patient with splenic abscess	Percutaneous drainage	Splenectomy	Death, complications
39	Patient with venous sinus thrombosis on anticoagulants	Thrombophilia screeninig	No thrombophilia screening	Recurrence, bleeding, death
40	Patient with systemic sclerosis AND pulmonary hypertension	Heart-Lung Transplantation	No Heart-Lung transplantation	Death
41	Pregnant women	Screening and treatment of cmv infection with intrauterine gammaglobulin	No screening	Congenital infection
42	Patient with spontaneous Intracerebral Hemorrhage and suspected malformation-cavernoma	CTA	Angio MRI	Death, malformation diagnosis
43	Patient with ischemic heart disease	Discontinue aspirin	Continue aspirin	Death, vascular events

	undergoing non cardiovascular surgery			
44	Asymptomatic old patient	Hepres Zoster vaccine	No vaccine	Zoster
45	Atrial fibrillation of indeterminate duration	Rythm control	Frecuency control	Mortality, cardiac output
46	Inpatient with acute COPD	Antibiotic therapy based on procalcitonin level	Antibiotic therapy based on clinical criteria	Death, complications
47	Patient with acute ischemic stroke	Aspirin 325mg	Aspirin 100mg	New stroke, death, bleeding
48	Patient with acute ischemic stroke and occlusion of arterial large vessels	Trombectomy	Pharmacotherapy	Disability, death
49	Patient with Lyme disease and central nervous system compromise	Ceftriaxone	Doxycycline	Death, sequel
50	Patient with chronic heart failure	Pro-bnp guided treatment	No pro-BNP guided treatment	Death
51	Patient in early post neurosurgical period with acute PE	Anticoagulation	Vena cava filter	Death, bleeding
52	Patient with Spontaneous Intracerebral Hemorrhage	Antiepileptic drugs, primary prevention	No antiepileptic drugs-primary prevention	Seizures, death, disability
53	Patient with subarachnoid bleeding and without seizures	Antiepileptic drugs, primary prevention	No antiepileptic drugs-primary prevention	Seizures, death, disability
54	Patient with severe traumatic brain injury	Antiepileptic drugs, primary prevention	No antiepileptic drugs-primary prevention	Seizures, death, disability
55	Patient with ACS taking sildenafil in the last 6 hs	Nitroglycerin	No nitroglycerin	Death, shock
56	Patient undergoing renal transplant	Perioperative pharmacologycal thromboprophylaxis	No thromboprophylaxis	Death, deep vein thromboses, oulmonary embolism, bleeding
57	Patient with active cancer undergoing surgery	Extended thromboprophylaxis	Thromboprophylaxis during hospitalization	Deep vein thromboses or pulmonary embolism, bleeding, death
58	Patient with subarachnoid bleeding	Vasospasm screening with transcranial	No doppler	Death, complications

		doppler		
59	Patient with subarachnoid bleeding	Nimodipin	Placebo	Death, complications
60	Patient with chronic leg ulcer and peripheral artery disease	Hyperbaric oxigen therapy	No hyperbaric oxygen therapy	Healing, death
61	Patient undergoing chemotherapy	Erythropoiesis stimulating factors	Placebo	HRQL, death, adverse events, anemia
62	Patient with renal infarction	Anticoagulation	Aspirin	Recurrent thrombotic event, bleeding
63	Patient with post lumbar puncture headache	Caffeine	Placebo	Pain improvement, adverse events
64	Patient with TRALI	steroids	Placebo	death
65	Cancer patient with deep vein thrombosis/pulmonary embolism	Low weight heparin	VKA	Recurrent thrombotic event, death
66	Patient with unprovoked deep vein thromboses who finish 3-6 month therapy of anticoagulant treatment	Aspirin	Placebo	Recurrent deep vein thromboses, death
67	Diabetic patient who takes metformin undergoing IV contrast CT	Discontinue metformin	Continue metformin	Lactic acidosis
68	Patient with evolved ischemic stroke and intracranial stenosis	STENT	Medical therapy	Recurrent stroke, death, bleeding
69	Patient with cardiovascular risk factors who needs NSAIDs	Naproxen	Other NSAIDs	Major vascular events
70	Patient with dvt	Early deambulation	Bed rest	Pulmonary embolism, bleeding, death
71	Patient with giant meningioma	Pre-surgical embolization	NO Pre-surgical embolization	Bleeding, death, disability
72	Patient with cancer and deep vein thromboses	Enoxaparin 1 daily dose	Enoxaparin 2 daily doses	New thrombotic event, bleeding
73	Immunocompromised patient with pulmonary infiltrates	Determination of galactomannans in bronchoalveolar lavage	No Determination of galactomannans in bronchoalveolar	Death, adverse events

			lavage	
74	Metastatic renal cancer	Nefrectomy	No nefrectomy	Survival, adverse events
75	Patient with recent diagnosis of HIV and recent diagnosis of tb	Immediate start of HAART	Delay start of haart	Death, complications
76	Patient with dizziness	Ginkgo Biloba	Betahistin	symptomatic improvement, adverse events
77	patient with superior vena cava syndrome	Stent	medical treatment	symptomatic improvement, complications
78	Patient with HIV related immune reconstitution inflammatory syndrome	steroids	Placebo	Death, symptomatic improvement
79	Steroids-refractory Immune Thrombocytopenic Purpura	Rituximab	Steroids	bleeding, platelet count
80	Patient who had undergone endarterectomy	Aspirin	Aspirin and clopidogrel	Stroke, death, bleeding
81	Patient with ureteral lithiasis	Alpha adrenergic blockers	Placebo	Pain, stone removal, adverse events
82	Patient with recurrent reflex syncope	Midorine	Placebo	Symptomatic improvement, syncope recurrence, adverse events
83	Patient with hyponatremia	Urinary sodium measure	Physical examination	Symptomatic improvement
84	Patient with pre-diabetes	Metformin	No pharmacological treatment	Microvascular complications (events), macrovascular complications (events)
85	Patient with mild or moderate idiopathic pulmonary fibrosis	Pirfenidone	Placebo	Death, progresion, adverse events
86	Patient with systolic heart failure	Angiotensin-neprilysin inhibition	Enalapril	Death, vascular events, adverse events
87	Patient with acute pharyngitis and severe Odynophagia	Steroids	Placebo	Symptomatic improvement, adverse events
88	Patient with aneurysmatic	Surgical treatment	Endovascular treatment	Rebleeding, death, complications,

	subarachnoid hemorrhage			disability
89	Inpatient with pneumonia	Betalactams	Betalactams + macrolides	Death, mechanical ventilation, adverse events
90	Patient with moderate or severe dementia	Memantine	Placebo	Cognitive status, functional status, adverse events
91	Patient with acute asthma	Inhaled steroids	Placebo	Death, mechanical ventilation, hospitalization
92	Patient on anticoagulants undergoing central venous catheter insertion	Femoral	Yugular	Death, hematoma, other complications, successful insertion
93	Patient with acute asthma	Non invasive ventilation AND standard treatment	Standard treatment	Death, mechanical ventilation, hospitalization
94	Patient with non-convulsive epileptic status	Levetiracetam load dose	Phenytoin load dose	Symptomatic improvement, death
95	Women with osteoporosis and NO previous fracture	Vitamin K	Placebo	Hip fracture, vertebral fracture
96	Ratient with vertigo	Betahistin	Placebo	Symptomatic improvement, adverse events
97	Patient with severe clostridium dificille infection	Metronidazol	Vancomycin	cure, recurrence, adverse events
98	Patient undergoing knee or hip fracture surgery	Thromboprofilaxis with new oral anticoagulants	heparin	thromboembolic events, bleeding, death
99	Patient with acute ischemic stroke and low NIHSS score	Ticagrelor	ASA	Recurrent stroke, bleeding, death
100	Patient with asymptomatic cholelithiasis	Cholecystectomy	Observation	Cholelitiasis related complications, surgery related complications

Nr: Question number

Supplementary table 3. Comparison between rapid strategies

	Strategy 1 (n=100)	Strategy 2 (n=100)	RR (CI95%)
Potentially misleading recommendations	5% (0.7 - 9.2%)	8% (2.6 - 13.3)	0.62 (0.18 - 2)
Inappropriate	1% (0 - 2.9%)	6% (1.3 - 10.6%)	-
Overconfident	4% (0.1 - 7.8%)	2% (0 - 4.7%)	-
Reasonable recommendations	95% (90.7 – 99.2%)	92% (86.5 – 97.3%)	1 (0.95 – 1.1)
Concordant	64% (54.5 – 73.4%)	62% (52.4 – 71.5%)	-
Reasonable disagreement	31% (21.9 – 40%)	30% (21 – 38.9)%	-
Potentially misleading quality of evidence judgment	16% (8.8 - 23.1%)	24% (15.6 - 32.3%)	0.52 (0.24 - 1.13)
Inappropriate Moderate or High	3% (0 - 6.3%)	7% (2 - 12%)	0.41 (0.08 - 1.8)
Inappropriate Low or Very Low	13% (6.4 - 19.5%)	17% (9.6 - 24.3%)	-
Quality of evidence agreement	63% (54.4 - 72.4%)	48% (38.2 - 57.7%)	1.3 (1 – 1.7)
Coincidence in information usage	65% (55.6 - 74.3)	56% (46.2 - 65.7)	1.16 (0.91 - 1.47)

Supplementary table 4. Potentially misleading recommendations description

Strategy	Population	Intervention	Information used	Information analysis	Possible solution
Epistemonikos	Patient with cardiac dyspnea in the emergency department	Pro-BNP guided treatment	Adequate. A SR that included all the relevant information was used	Inappropriate judgment of the quality of evidence.	No solution
Epistemonikos	Patient with asthma reagudization	Intravenous magnesium	Inappropriate. A recent systematic review was not identified	-	Appropriate use of the Epistemonikos matrix of evidence tool identified the missed SR
Epistemonikos	Patient with acute minor stroke	Mechanical thrombectomy	Inappropriate. A recent systematic review was not identified	-	Appropriate use of the Epistemonikos matrix of evidence tool identified the missed SR
Epistemonikos	Patient with acute pancreatitis	Early enteral nutrition	Adequate	Inappropriate judgment of the quality of evidence. Probable inappropriate summary of the evidence.	The recommendation was coherent with the GS when the same SoF was used
Epistemonikos	Patient with tracheal stenosis	Mechanical dilatation	Adequate	Differences in the benefit risk balance judgment	No Solution
Epistemonikos	Patient with recent TB/HIV co-infection diagnoses	Early antiretroviral treatment initiation	Adequate	Differences in the benefit risk balance judgment. Probable inappropriate summary of the evidence.	The recommendation was coherent with the GS when the same SoF was used

Epistemonikos	Patient with osteoporosis	Vitamin K	Adequate	Differences in the benefit risk balance judgment	No solution
Epistemonikos	Patient with asymptomatic cholelitiasis	No surgical treatment	Inappropriate. One relevant publication not identified	-	No solution
PubMed	Patient with acute aneurysmal rupture with SAH	Endovascular treatment	Inappropriate. Two relevant publications not identified	-	No solution
PubMed	Patient with traumatic SHA	Nimodipine	Appropriate	Inappropriate judgment of the quality of evidence. Probable inappropriate summary of the evidence.	The recommendation was coherent with the GS when the same SoF was used
PubMed	Patient with systemic sclerosis and severe lung compromise	Lung transplantation	Appropriate	Differences in the benefit risk balance judgment	No solution
PubMed	Patient with chronic heart failure	BNP guided therapy	Inappropriate. A recent systematic review was not identified	-	Appropriate use of the Epistemonikos matrix of evidence tool identified the missed SR
PubMed	Patient with severe Clostridium Difficile infection	Vancomicin	Inappropriate. A recent systematic review was not identified	-	No Solution

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Answering medical questions at the point of care: A cross-sectional study comparing rapid decisions based on PubMed and Epistemonikos searches with evidence-based recommendations developed with the GRADE approach.

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Answering medical questions at the point of care: A cross-sectional study comparing rapid decisions based on PubMed and Epistemonikos searches with evidence-based recommendations developed with the GRADE approach.

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ABSTRACT

Introduction: Using the best current evidence to inform clinical decisions remains a challenge for clinicians. Given the scarcity of trustworthy clinical practice guidelines providing recommendations to answer clinicians' daily questions, clinical decision support systems (i.e. assistance in question identification and answering) emerge as an attractive alternative. The trustworthiness of the recommendations achieved by such systems is unknown.

Objective: To evaluate the trustworthiness of a question identification and answering system that delivers timely recommendations.

Design: Cross-Sectional study

Methods: We compared the responses to 100 clinical questions related to inpatient management provided by two rapid response methods with "Gold Standard" recommendations. One of the rapid methods was based on PubMed and the other on Epistemonikos database. We defined our "Gold Standard" as trustworthy published evidence-based recommendations or, when unavailable, recommendations developed locally by a panel of 6 clinicians following the GRADE approach. Recommendations provided by the rapid strategies were classified as potentially misleading or reasonable. We also determined if the potentially misleading recommendations could have been avoided with the appropriate implementation of searching and evidence summary tools.

Results: We were able to answer all of the 100 questions with both rapid methods. Of the 200 recommendations obtained, 6.5% (CI95% 3 – 9.9%) were classified as potentially misleading and 93.5% (CI95% 90 – 96.9%) as reasonable. Six of the 13 potentially misleading recommendations could have been avoided by the appropriate usage of the Epistemonikos matrix tool or by constructing summary of findings tables. No significant differences were observed between the evaluated rapid response methods.

Conclusion: A question answering service based on the GRADE approach proved feasible to implement and provided appropriate guidance for most identified questions. Our approach could help stakeholders in charge of managing resources and defining policies for patient care to improve evidence-based decision making in an efficient and feasible manner.

ARTICLE SUMMARY

Strengths and limitations

- The study was carried out in a real-world scenario (questions related to patients being treated in a clinical ward)
- Three different clinicians were randomly assigned to apply the different answering strategies
- We developed a transparent framework to categorize the recommendations obtained by the rapid strategies
- We sought to provide trustworthy “Gold Standard” recommendations nevertheless it is not possible to guarantee that they were optimal
- It is unclear if the observed results can be replicated in other settings, for example with participants less trained in evidence-based decision-making

INTRODUCTION

Research consistently shows that there is an important gap between evidence and practice,[1,2] and clinicians seldom use the best available evidence to guide their decisions.[3,4,5] Limited time, lack of training in critical appraisal and low expectations for finding relevant answers are among the most common identified obstacles.[6,7] These practices are problematic, as the

benefits of using the best current evidence to inform clinical decisions are widely accepted to such extent that evidence-based decision making is frequently considered a measure of healthcare quality.[8] In particular, hospital executive boards, insurance companies and consumers recognize that evidence-based practice may help prevent unsafe or inefficient practices. [9-11]

One of the potential solutions for bringing evidence to bedside decisions is the use of trustworthy and transparent clinical practice guidelines. Although the last decade has seen significant advances in guideline methodology (http://www.gradeworkinggroup.org/), important limitations still remain: 1) only a small number of guidelines have been tailored to clinicians' needs;[12] 2) Finding relevant guidelines can be laborious and time consuming; 3) Typically, only a few guidelines are kept up to date.[13]

Another alternative for bridging the gap between evidence and clinical practice are clinical decision support systems designed to provide assistance to clinicians in the question identification and resolution process by finding the answer for them and presenting the information in a user-friendly way.[14-18] Unlike products that passively provide pre-apprised evidence at the point of care (e.g. UpToDate) this systems involve trained practitioners that search and deliver tailored answers to identified questions. However the trustworthiness of the recommendations achieved by such systems is unknown.

The objective of this study was to evaluate the trustworthiness of a question identification and answering system that delivers timely recommendations to clinicians providing care to inpatients by comparing the imparted guidance with "Gold Standard" recommendations. Additionally, we come up with a proposal on how to replicate the process.

METHODS

We conducted the study on the Internal Medicine Service of the German Hospital of Buenos Aires, Argentina, from March 2014 to March 2016. The context in which this study was carried out has been described in another publication.[17]

We compared two rapid response methods with trustworthy published evidence-based recommendations or, when not available, recommendations developed locally by a panel of six clinicians which, for the purpose of this study, we considered as our "Gold Standard". One of the rapid response methods was based on PubMed using clinical queries, which are a series of filters designed to improve the retrieval of scientifically strong and clinically relevant articles from PubMed database.[19] The other was based on Epistemonikos, which is a relational, collaborative, multilingual database of health evidence that includes systematic reviews from multiple sources (Cochrane database of systematic reviews and PubMed, among others).[20]

Three clinicians trained in evidence-based decision-making (informationists) attempted to answer all the identified questions following three different strategies. The informationists differ from clinical librarians in that they are trained in clinical epidemiology methods rather than simply information acquisition, and have clinical expertise relevant to the questions that allows contextual interpretation of research findings. Each question had its own randomization schedule drawn from a computer pre-generated random number list in which each informationist was assigned to one of the three strategies defined below. We describe the question identification process and the strategies to address the questions in the following sections.

Identification and selection of clinical questions

One of the informationists (AI), otherwise uninvolved in the patients' care, identified questions relevant to the staff and residents of the Internal Medicine Service. Either the staff or residents explicitly formulated the questions, or AI inferred them from the discussion of the clinical cases.

He collected the relevant clinical question using the PICO (Population/Problem, Intervention, Comparison, Outcome) framework.

In order to focus on questions that could potentially impact clinicians' course of action, we excluded questions that: 1) were answered immediately by someone who was present in the session, other than the informationists, typically using electronic resources such as UpToDate; 2) were not related to therapeutic or diagnostic interventions; 3) addressed interventions already implemented in the patient's care.

All the identified questions that did not fulfilled one of the exclusion criteria were included and registered. The described question identification process was repeated until the study was finished.

Rapid strategy based on PUBMED (Strategy 1)

The informationist assigned to this strategy performed a literature search on MEDLINE using the PubMed clinical queries feature (supplementary figure 1). First he tried to identify relevant systematic reviews;[21] when unavailable or when considered that additional relevant information could exist, he also searched for primary studies. Once the informationist identified the most relevant systematic review and/or primary study/s, he followed the GRADE approach to interpret the results and judge the certainty on the evidence (for a detailed description see GRADE handbook available at: gdt.guidelinedevelopment.org/app/handbook/handbook.html). Following the GRADE guidance the informationist also considered additional relevant information related to patients' values and preferences, costs, applicability and feasibility,[22,23] and made a clinical decision simulating what clinicians could do in the optimal scenario. To capture the decision, the informationist formulated a recommendation that included the direction (in favor or against the intervention) and the strength (strong or weak). The process took no more than two hours.

Rapid strategy based on Epistemonikos (Strategy 2)

The informationist assigned to this strategy searched on the Epistemonikos database using the "matrices of evidence" tool, which is a is a tabular way of displaying the cluster of systematic reviews that share at least one included study,[24] and followed the same process described for the strategy 1 (supplementary figure 2). He also searched PubMed for RCT in cases were systematic reviews were not available or when he considered that additional relevant information could exist (supplementary figure 2).

Strategy based on trustworthy recommendations ("Gold Standard") (Strategy 3)

The informationist assigned to this strategy searched for recommendations developed with the GRADE approach, on the following databases: Tripdatabase (http://www.tripdatabase.com); National guideline Cleringhouse (http://www.guidelines.gov); Canadian Medical Association (http://www.cma.ca/clinicalresources/practiceguidelines); NICE (http://www.nice.org.uk/); SIGN (http://www.sign.ac.uk); GuíaSalud (http://portal.guiasalud.es/web/guest/buscar-gpc); Australian clinical practice guidelines (http://www.clinicalguidelines.gov.au); New Zealand Guidelines Group (http://www.nzgg.org.nz/); US preventive Task Force (http://www.uspreventiveservicestaskforce.org/); eGuidelines (https://www.guidelines.co.uk/), GIN (http://www.g-i-n.net/about-g-i-n/introduction).

He critically assessed the identified recommendations, using the criteria proposed for evaluating GRADE recommendations,[25] and qualitatively categorized their trustworthiness as High, Moderate or Low based on the answers to the following questions: Was the question clearly formulated? Were all the critical outcomes considered? Was the recommendation based on the best current evidence? The evidence was clearly presented? Was the recommendation coherent with the supporting evidence? Were the values and preferences considered?

Additionally, for every question, the same informationist, searched for systematic reviews, randomized controlled trials and observational studies on the following databases without time restriction: PubMed, Epistemonikos and the Cochrane database of systematic review. He used the information extracted from the relevant systematic reviews and/or primary studies to construct a Summary of Finding Table (SoF) following the GRADE principles (SoF example available in supplementary table 1).[26,27] The tables were then sent via email to six clinicians ("local panel") with experience in applying the GRADE approach. Each clinician used the information included in the SoF tables and considered issues related to patients' values and preferences, costs, applicability and feasibility to individually construct a recommendation.[22,23] When more than 66% of the clinicians who answered agreed on the strength and direction of the recommendation, we considered that recommendation final. Disagreement in the direction or the strength of the recommendation were recorded and resolved by seventh clinician (IN) with experience in developing GRADE recommendations. Although we intended to answer every question with the described "local panel" approach, we only used the resultant recommendations when published GRADE recommendations developed by guideline panels rated as "high" for trustworthiness were unavailable. Figure 1 provides a description of the "Gold Standard" recommendation construction process.

Outcomes:

We compared the recommendations, quality of evidence judgments and information used by rapid strategies and the "Gold standard" strategy to define the following outcomes:

Inappropriate recommendations: when the "Gold Standard" was a strong recommendation and the rapid strategies yielded a decision in the opposite direction of any strength; or when the "Gold Standard" was a weak recommendation and the rapid strategies yielded a strong recommendation in the opposite direction.

Overconfident recommendations: when the “Gold Standard” was a weak recommendation and the rapid strategies yielded a decision concordant with a strong recommendation on the same direction

Potentially misleading recommendations: composite of inappropriate or overconfident recommendations

Concordant recommendations: when the “Gold Standard” and the rapid strategies yielded a recommendation of the same direction and strength

Reasonable disagreement: when the “Gold Standard” was a weak recommendation in favor and the rapid strategies yielded a weak recommendation against or vice versa, or when the “Gold Standard” was a strong recommendation and the rapid strategies yielded a weak recommendation on the same direction

Reasonable recommendations: composite of concordant recommendations and reasonable disagreement

Table 1. describes the framework for rapid recommendation categorization based on their comparison with “Gold Standard” recommendations.

Table 1. Framework to categorize recommendations

		GOLD STANDARD			
		Strong Against	Weak Against	Weak in Favor	Strong in Favor

RAPID STRATEGIES	Strong Against	Concordant	Overconfident	Inappropriate	Inappropriate
	Weak Against	Reasonable	Concordant	Reasonable	Inappropriate
	Weak in Favor	Inappropriate	Reasonable	Concordant	Reasonable
	Strong in Favor	Inappropriate	Inappropriate	Overconfident	Concordant

Same direction recommendations: when the “Gold Standard” and the rapid strategies yielded a recommendation of the same direction regardless of its strength

Inappropriate quality of evidence judgment: proportion of recommendations in which the quality of evidence: 1) was judged as Low or Very Low by the rapid strategies and High or Moderate by the “Gold Standard” or; 2) Was judged as High or Moderate by the rapid strategies and Low or Very low by the “Gold Standard”

Coincidence in information usage: proportion of recommendations in which the publications used by the rapid methods were the same as the ones used by the “Gold Standard”

Additional analyses

We also performed a post-hoc qualitative analysis of the recommendations classified as potentially misleading. We analyzed the reasons for the disagreement between the rapid strategies and the gold standard and we considered potential solutions. For this purpose, in cases in which the potentially misleading recommendations were judged to be a consequence of inadequate evidence selection, we determined if the appropriate use of the Epistemonikos matrices tool could have prevented that problem (i.e identification of a SR containing primary

studies that were not considered for the development of the original recommendation). In cases in which potentially misleading recommendations were judged to be a consequence of inappropriate evidence interpretation, we determined if the correct presentation of the evidence could have prevented the problem. To assess this, we sent the SoF table constructed in response to the same question for the "Gold Standard" strategy (strategy 3) to the investigator who originally constructed the potentially misleading recommendation. We asked the investigator to provide a new recommendation based in the SoF. We judged that the correct use of the Sof could have prevented the problem when the investigator provided a reasonable recommendation in response (compared to the GS recommendation).

Statistical analysis

For the comparisons between the rapid strategies and the "Gold Standard" we calculated proportions and 95%CI for all the outcomes. We also calculated interrater agreement with Kappa statistic using VassarStats calculator (http://vassarstats.net/kappa.html). For the kappa calculation related to recommendation concordance (strong in favor, weak in favor, weak against or strong against) we imputed the double of distance between strong in favor - weak in favor and strong against - weak against than weak in favor - weak against. For the kappa calculation related to quality of evidence agreement (high, moderate, low or very low) we imputed the double of distance between moderate - low than very low - low and moderate - high. For the comparison between strategies 1 and 2 we calculated relative risks and 95%CI when possible.

RESULTS

During the study period we identified 100 questions all of which were answered with strategies 1 and 2 (200 recommendations). With strategy 3 we found recommendations in CPG for 80 of the 100 questions all of which could be answered by the "local panel" approach. The process of

answering each question with strategy 3 (“Gold Standard, local panel” approach) took, on average, 1 week per question. Table 2 presents the characteristics of the recommendations delivered by each strategy. A list of the PICOs is available in the supplementary table 2.

Table 2. Recommendations according to the strategy implemented

	Strategy 1 (n=100)	Strategy 2 (n=100)	Strategy 3 (CPG) (n=80)(%)	Strategy 3 (“local panel”) ((n=100)
Recommendations				
Strong	14	12	21 (26.2)	21
In favor of the intervention	55	62	55 (68.7)	63
Quality of evidence				
High	8	5	-	12
Moderate	22	25	-	28
Low	34	26	-	44
Very Low	36	44	-	16
Confidence in the CPG recommendation				
High (%)	-	-	16 (20)	-

Following the process described in figure 1 we obtained 100 “Gold standard” recommendations. These recommendations were composed by 16 High confidence CPG recommendations, 55 panel recommendations and 29 expert recommendations. The results of the comparison between the rapid strategies and the “Gold standard” are described in table 3.

Table 3. Rapid strategies recommendations analysis

	Rapid strategies versus “Gold Standard” (n=200)	Kappa

Potentially misleading recommendations	6.5% (3 - 9.9%)	-
Inappropriate	3.5% (0.95 - 6%)	-
Overconfident	3% (0.64 - 5.3%)	-
Reasonable recommendations	93.5% (90 – 96.9%)	-
Concordant	62.5% (55.7 - 69.2%)	0.59 (0.36 - 0.82)
Reasonable disagreement	31% (24.5 – 37.4%)	-
Same direction recommendations	74% (67.5 – 79.5%)	-
Strong (rapid strategies) (n=26)	96.1% (82.2 – 99.3%)	-
Weak (rapid strategies) (n=174)	70.6% (64.5 – 76.9%)	-
Potentially misleading quality of evidence judgment	20% (14.4 - 25.5%)	-
Inappropriate Moderate or High	5% (1.9 - 8%)	-
Inappropriate Low or Very Low	15% (10 - 19.9%)	-
Quality of evidence agreement	55.5% (48.6 - 62.3%)	0.59 (0.46 - 0.72)
Coincidence in information use*	60% (50.4 - 69.6)	-

* The same publication/s were used to answer the question

The comparison between strategies 1 and 2 is described in supplementary table 3.

There were 13 recommendations that were judged as potentially misleading, the causes and possible solutions are summarized in supplementary table 4.

DISCUSSION

The results of the present study suggest that a rapid question answering system based on the GRADE approach provided appropriate guidance in response to most questions. Although the proportion of concordant recommendations (same strength and direction between rapid strategies and GS) was 62.5%, most of the remainder (31% of the total), were classified as “reasonable disagreements”. Only 13 of the 200 recommendations were judged as potentially

misleading and approximately half of those could possibly have been avoided with an appropriate use of the available tools (Epistemonikos matrix of evidence or SoF tables). We also analyzed the results considering exclusively the direction of the recommendations. The results showed that almost all strong recommendations constructed with the rapid strategies shared the same “Gold Standard’s” direction while 70% of the weak recommendations did. This finding is not surprising given that weak recommendations are frequently based on low or very low quality of evidence, or are warranted in situations where benefits and risks are closely balanced, hence their direction is subjectively defined by weighting those aspects (e.g. in a setting in which benefits and harms are balanced, some guideline panel members can interpret the results as favoring the intervention while others as favoring the comparison).[22,23,25] Although 30% of weak recommendations had a different direction from the “Gold Standard’s”, we consider that it is unlikely that they would have resulted in misleading guidance, as those willing to use them should carefully analyze the fundamentals of the recommendation before deciding their course of action.[22,23,24] An exception would be the situation in which the “Gold Standard” recommendations were strong in the opposite direction but this was captured in the primary analysis as those recommendations were classified as inappropriate. A third analysis in which we calculated rapid strategies’ and “Gold Standard’s” recommendation strength and direction agreement beyond chance using weighted Kappa informed moderate to substantial agreement.[28] As described for the former analysis (considering only the direction of recommendations) this approach also does not acknowledge the possibility of reasonable disagreement. Hence it only reflects the capability of the rapid strategies to provide concordant recommendations (same direction and strength) with the “Gold Standard’s” which we believe is an over-demanding approach that underestimates the ability of the rapid strategies to provide adequate guidance.

The comparison between the different rapid answering strategies (Pubmed vs Epistemonikos) showed that although the proportion of potentially misleading recommendations was small in

both strategies, there was a slight (3%) absolute difference in favor of PubMed strategy. One possible explanation for the difference is that the investigators involved in the study were less familiarized with Epistemonikos database and search engine than PubMed's.

The main limitation of our study is that it is not possible define a "Gold Standard" recommendation for a medical question. We sought to provide trustworthy "Gold Standard" recommendations by performing rigorous evidence searches, constructing detailed evidence summaries and including multiple clinicians trained in evidence-based decision making; nevertheless this approach does not guarantee optimal recommendations. In addition, the system was applied to a specific subgroup of questions (intervention related questions that were not immediately answered). We consider that addressing questions that do not meet these criteria are less likely to change clinicians' behavior. Also this study was carried out in a singular context (clinicians trained in evidence-based decision making with advanced understanding of the GRADE system). It is unknown to what extent the observed results can be replicated in different situations were clinicians are less familiarized with evidence-based medicine concepts.

Although investigators have previously undertaken evaluation of the implementation of question answering services, [29-34] these studies focused on clinicians' attitudes and decisions in response to the answers provided. As long as it remains uncertain that the answers the services provide are based on the best available evidence, and that clinicians interpret and use the provided information appropriately to make coherent decisions, the benefits of the implementation of these services to improve patient outcomes cannot be assumed.[35] Another approach would be to directly measure the impact of answering clinicians' questions on patients' clinical important outcomes (i.e. mortality or length of hospital stay). However, for these kind of interventions that are designed to improve quality of care through affecting physician's behavior, demonstrating such an effect could be very difficult (huge sample sizes needed, low signal-to-

noise ratio).[36-38] Attempts have been made in this direction and the results suggest possible benefits with the implementation of the evaluated interventions but the quality of evidence provided was low, either because of imprecision (underpowered studies)[16-18] or because of risk of bias (non-randomized comparisons).[39-41]

We found only one study that considered the trustworthiness of the answers provided.[42] In that study, the investigators inserted study evidence statements related to the management of clinical conditions for which high-quality randomized controlled trials, or metaanalyses had unequivocally established benefits greater than risks, costs and inconvenience into hospital discharge letters. The study results showed a significant increase in general practitioner adherence to discharge medications demonstrating that, in optimal conditions (no time restrictions to perform evidence searches, high quality of evidence available), providing information to clinicians improve patient care. However, that optimal scenario is probably the exception as for most clinical questions high quality evidence remains unavailable, [16,43,44] and clinicians usually need very prompt answers to their questions. Hence, ours is the first study to use a structured and objective approach to measure the quality of the information provided in a timely way to clinician-generated questions.

To achieve a medical practice consistent with what Ubbink et al. described as evidence-based practice,[45] clinicians need to be able to quickly obtain and accurately assess the best available evidence to answer their questions. Clinical practice guidelines endeavor to provide these answers at the point of care and, when rigorously developed and up to date, constitute optimal guidance. However most of the available guidelines have methodological flaws and do not provide trustworthy recommendations.[12,13] In the present study 80% of the identified questions could be answered with recommendations included in CPG but only 20% of them were judged to be trustworthy.

Given current guideline limitations, if feasible and properly implemented, a question answering system could provide a solution. This study adds to our previous study in which we evaluated the impact of implementing a response system, similar to the one evaluated in the preset trial, on clinician's decisions.[16] The results of that trial suggested these kind of interventions can influence clinician's courses of actions and therefore patient care.

The present study was developed in a real life scenario with limited amount of resources, which suggest that the proposed intervention can possibly be implemented in variety of settings, including a busy clinical ward. We were able to efficiently implement the proposed system with: 1) one clinician trained in evidence-based decision making exclusively dedicated to this task for at least 2 hours a day and; 2) a computer with internet connection. We used a systematic and transparent method to arrive at decisions. Finally, we have developed a framework to compare different recommendations developed with the GRADE approach acknowledging that not every discrepancy should be considered inappropriate as different values and preferences may lead to reasonable disagreement between recommendations.

Implication for practice

Those interested in improving evidence utilization in health care decision-making should consider the implementation of systems as the one proposed in the present study. This would require, at least, one trained health care provider (informationist) who would: 1) Search for trustworthy published recommendations or, when not available, systematic reviews in Epistemonikos and/or PubMed; 2) Use the Epistemonikos matrices of evidence tool and/or PubMed to identify additional information (not included in the selected systematic review); 3) Construct a summary of findings table including all critical outcomes; 4) Define a recommendation based on the identified trustworthy recommendations or the summary of findings tables (Figure 2). We think that the cornerstone to successfully replicate the described

process is practitioners training in evidence search, critical appraisal, summary and evidence to decision translation.

Implication for research

Investigators who addressed the clinical questions using the proposed strategies in the present study were highly trained in evidence-based decision-making and could possibly be classified as experts. Whether similar results could be obtained when those responsible for solving the identified questions are not experts remains uncertain.

CONCLUSION

A question answering service based on the GRADE approach proved feasible to implement and provided appropriate guidance for most identified questions. Our approach could help stakeholders in charge of managing resources and defining policies for patient care to improve evidence-based decision-making in an efficient and feasible manner.

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The corresponding author and manuscript's guarantor certifies that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive licence (or non exclusive for government employees) on a

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Data sharing: no additional data available

Individual author contributions

Izcovich A. significantly contributed to the conception and design of the work, and the acquisition, analysis and interpretation of data.

Criniti J.M. significantly contributed to the design of the work, and the acquisition, analysis and interpretation of data.

Popoff F. significantly contributed to the design of the work, and the acquisition, analysis and interpretation of data.

Ragusa M.A. significantly contributed to the the acquisition and interpretation and of the data.

Gigler C. significantly contributed to the acquisition and interpretation and of the data.

Gonzalez Malla C. significantly contributed to the acquisition and interpretation and of the data.

Clavijo M. significantly contributed to the acquisition and interpretation and of the data.

Manzotti M. significantly contributed to the acquisition and interpretation and of the data.

Díaz M. significantly contributed to the acquisition and interpretation and of the data.

Catalano H.N. significantly contributed to the acquisition and interpretation and of the data.

Neumann I. significantly contributed to the design of the work, and the acquisition, analysis and interpretation of data.

Guyatt G. significantly contributed to the design of the work, and the acquisition, analysis and interpretation of data.

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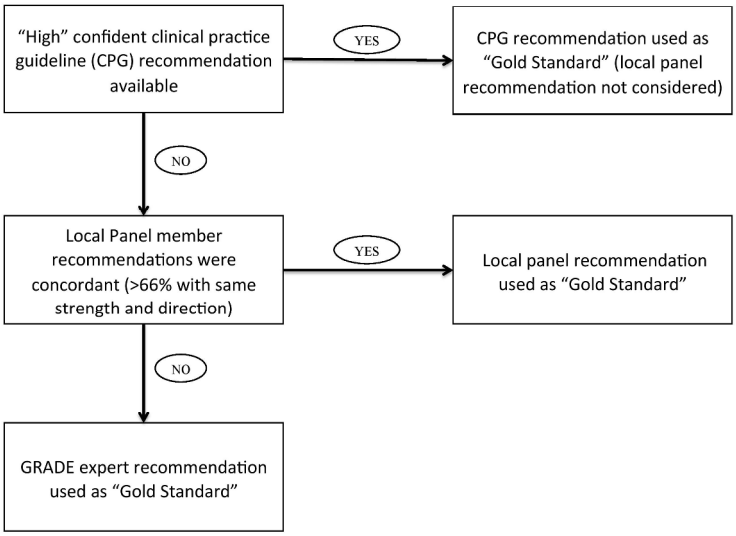
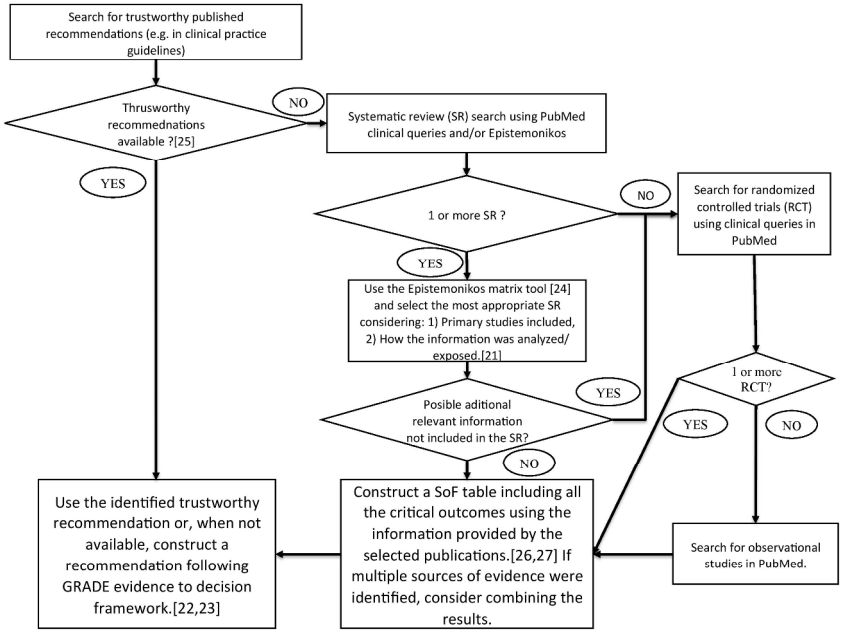
Figure 1. “Gold Standard” recommendation development

Figure 2. Rapid answering system proposal



"Gold Standard" recommendation development

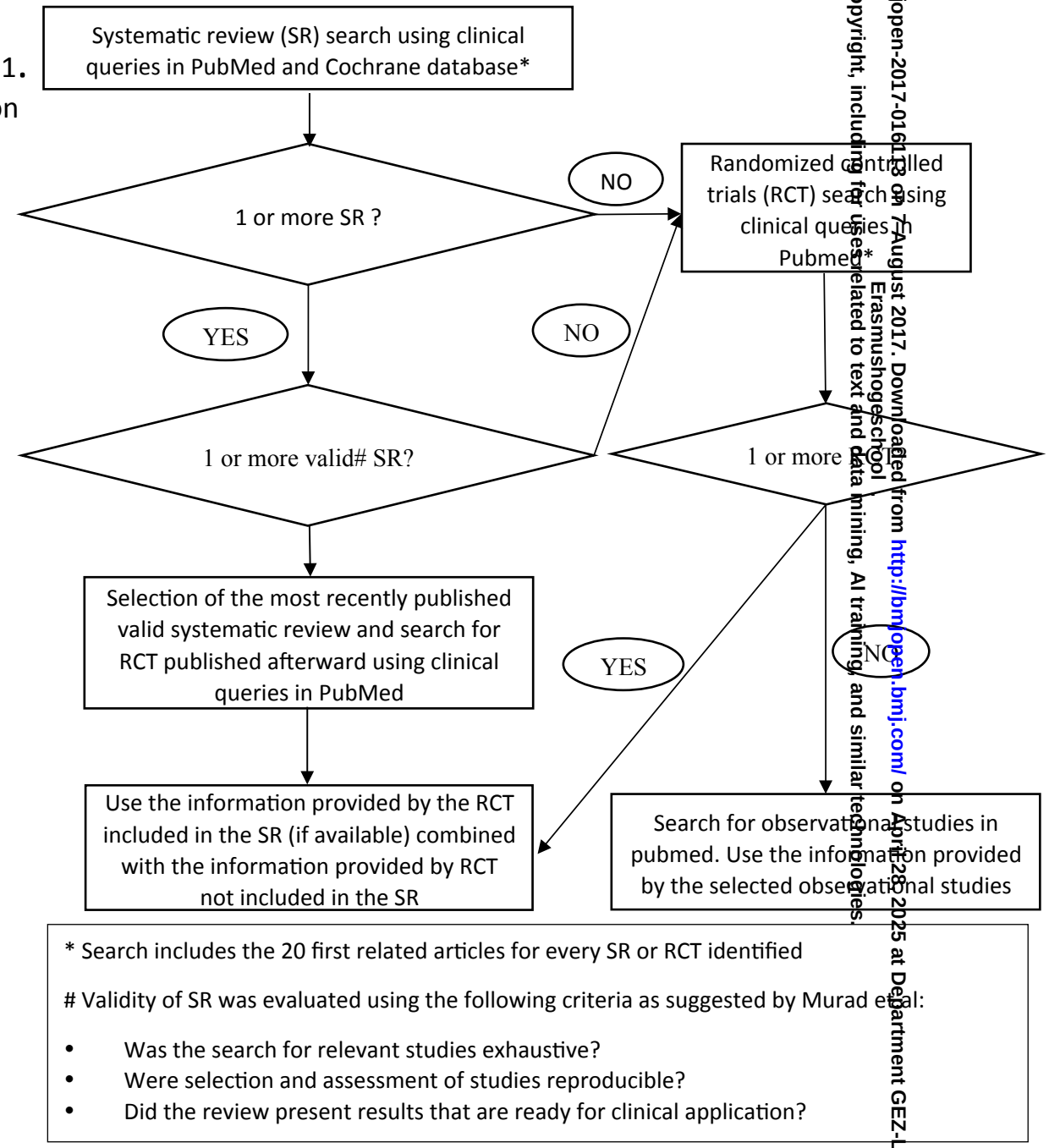
297x209mm (300 x 300 DPI)



Rapid answering system proposal

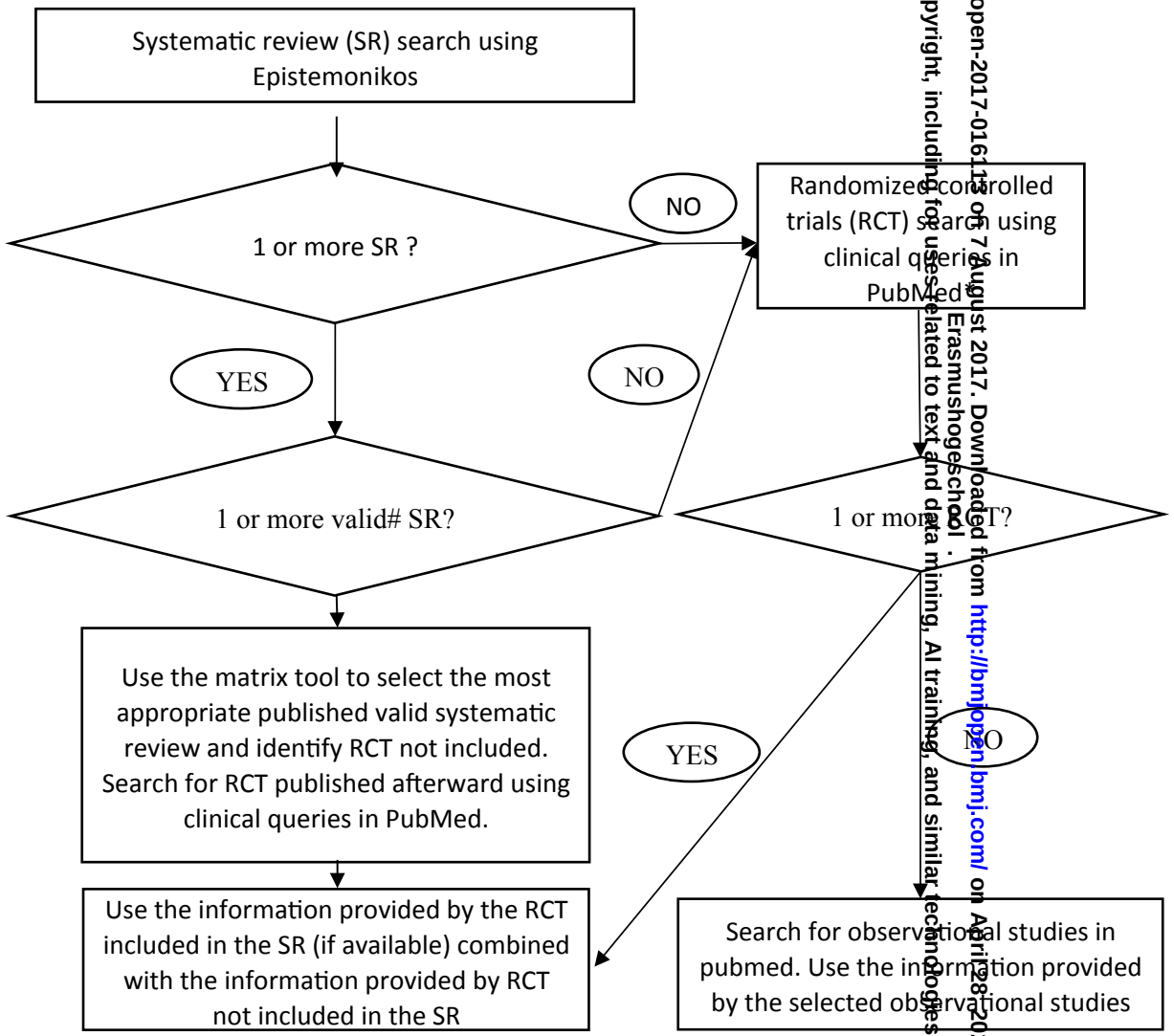
297x209mm (300 x 300 DPI)

Supplementary Figure 1. Rapid strategy based on PubMed



Murad MH, Montori VM, Ioannidis JP, et al. How to read a systematic review and meta-analysis and apply the results to patient care: users' guides to the medical literature. *JAMA* 2014;312:171-9

Supplementary Figure 2.
Rapid strategy based on EPISTEMONIKOS



Murad MH, Montori VM, Ioannidis JP, et al. How to read a systematic review and meta-analysis and apply the results to patient care: users' guides to the medical literature. *JAMA* 2014;312:171-9

Supplementary table 1. Summary of findings table example

P: Patient with acute ischemic stroke

I: Ticagrelor

C: Aspirin

O: Death, recurrent stroke, bleeding

Ticagrelor compared to Aspirin for patients with acute ischemic stroke

Results № of participants (Studies)	Relative effects (95% CI)	Anticipated absolute effects (95% CI)			Quality of the evidence	What
		Without Ticagrelor	With Ticagrelor	Difference		
Recurrent stroke Follow up: 90 days № de participants: 13199 (1 RCT)	**HR 0.87** (0.76 a 1.00)	6.7%	**5.8%** (5.1 a 6.7)	**0.8% Less** (1.6 Less to 0 Less)	⨁⨁⨁◯ MODERATE [1]	Ticagrelor probably marginally reduces stroke recurrence risk.
AMI Follow up: 90 days № de participants: 13199 (1 RCT)	**HR 1.20** (0.67 a 2.14)	0.3%	**0.4%** (0.2 a 0.7)	**0.1% more** (0.1 less to 0.4 more)	⨁⨁⨁◯ MODERADO [1]	Ticagrelor probably does not increases nor reduces AMI risk
Death Follow up: 90 days № de participants: 13199 (1 RCT)	**HR 1.18** (0.83 a 1.67)	0.9%	**1.0%** (0.7 a 1.5)	**0.2% more** (0.1 less to 0.6 more)	⨁⨁⨁◯ MODERADO [1]	Ticagrelor probably does not increases nor reduces mortality
Major bleeding Follow up: 90 days № de participants: 13199 (1 RCT)	**HR 0.83** (0.47 a 1.46)	0.4%	**0.3%** (0.2 a 0.6)	**0.1% Less** (0.2 Less to 0.2 more)	⨁⨁⨁⨁ ALTA	Ticagrelor probably does not increases nor reduces major bleeding risk
Burden of treatment	Ticagrelor requires two doses a day. Aspirin requires one dose a day				⨁⨁⨁⨁ ALTA	

1. 95%CI included both significant benefits and harms

- Johnston SC, Amarenco P, Albers GW, Denison H, Easton JD, Evans SR, Held P, Jonasson J, Minematsu K, Molina CA, Wang Y, Wong KS; SOCRATES Steering Committee and Investigators.. Ticagrelor versus Aspirin in Acute Stroke or Transient Ischemic Attack. N Engl J Med. 2016 Jul 7;375(1):35-43. doi: 10.1056/NEJMoa1603060. Epub 2016 May 10.

Supplementary table 2. PICO questions

Nr.	Population	Intervention	Comparison	Outcomes
1	Patient with acute asthma and upper airway infection	Antibiotics	No antibiotics	Mortality
2	Renal transplant patient with pleural TB	Steroids	No steroids	Resolution time, complications and mortality
3	Patient with atrial fib on anticoagulants undergoing a breast biopsy	Stopping anticoagulant	Not stopping anticoagulant	Bleeding risk, thromboembolic event risk, mortality
4	Patient with severe hypokalemia (< 2.5 meq/l)	Intravenous potassium	Oral potassium	Arrythmia, morbidity and mortality
5	Patient with prosthetic valve endocarditis by MSSA	Cephalosporin+rifampicyin+gentamicin	Cephalosporin+rifampicyin	Complications, mortality
6	Patient with pericardial TB	Steroids	Placebo	Death, symptomatic improvement, sequel
7	Transplant patient with CMV resistant systemic infection	IV gamaglobulin	No IV Gamaglobulin	All cause mortality, CMV related mortality, time to viral load negativization, adverse events
8	Patient with congestive heart failure	IV furosemide bolus	IV furosemide continuous infusion	Mortality, adverse events, arrythmia
9	Patient with upper gastrointestinal bleeding, forrest III peptic ulcer and pulmonary embolism	Anticoagulants	Vena cava filter and prophylaxis	Major bleeding, upper gastrointestinal bleeding, PE mortality, all-cause mortality
10	Patient with atrial fibrillation and CHADS score > 1	Watchman plus antiplatelet therapy	Anticoagulation	Thromboembolic events, major bleeding, all cause mortality
11	Patient with acute ischemic stroke	Statins	Placebo	Recurrent stroke, all cause mortality
12	Patient undergoing neurosurgery for malignant disease	Early thromboprophylaxis with enoxaparin	Late thromboprophylaxis with enoxaparin	Surgical bleeding, major bleeding, thromboembolic events, mortality
13	Patient with acute diarrhea	Fecal leucocyte to guide therapy	No fecal leucocyte analysis	Morbidity, mortality
14	Inpatient with	Antibiotics AND	Antibiotics	Mortality, hospital

	pneumonia	steroids		stay, mechanical ventilation requirement, ICU stay
15	Patient with catheter related deep venous thrombosis	Anticoagulation and extraction	Wait and watch	Pulmonary embolism, stroke, death
16	Patient with distal inferior limb deep vein thromboses	Anticoaguation	No anticoagulation	Pulmonary embolism, mortality
17	Patient with traumatic splenic laceration	Splenectomy	Wait and watch	Mortality,hemoperitoneum
18	Adult with asymptomatic celiac disease	Gluten free diet	No treatment	Quality of life, cancer
19	Pacient with stable COPD	Non invasive mechanical ventilation	Standard treatment	Mortality, quality of life
20	Adult with facial cellulitis	Antibiotics and steroids	Antibiotics only	Symptomatic improvement
21	Patient with skin-soft tissue infection by MRSA	Linezolid	Vancomicin, clindamicin, TMS	Death, sepsis, cure
22	Patient with obstructive renal failure	Ureteral stent	Nephrostomy	Long term improvement of renal function
23	Patient with hypogammaglobulinemia AND acute infection	Immunoglobulin	No immunoglobulin	Symptomatic improvement, death, complications
24	Patient with supratentorial brain tumor	Antiepileptic drugs, primary prevention	No primary prevention	Seizures, death, adverse events
25	Patient undergoing knee arthroplasty	Extended thromboprophylaxis wih new oral anticoagulants.	Extended thromboprophylaxis wih low weight heparin	DVT,PE, death, bleeding
26	Patient with recurrent cellulitis	prophylactic antibiotic	No prophylactic antibiotic	New cellulitis, adverse events
27	Patient with hepatic encephalopathy	Rifaximin AND lactulose	Lactulose	Death, symptomatic improvement, adverse events
28	Patient with incidental brain aneurysm	Coil	No coil	Bleeding, mortality, adverse events
29	Patient with traumatic subarachnoid hemorrhage	Nimodipin	No nimodipin	Vasospasm, death, adverse effects
30	Patient with renal failure by Wegener´s	Rituximab	Standard treatment	Death, end stage renal failure,

	granulomatosis		(Cyclophosphamide)	adverse event
31	Patient with acute pancreatitis	Early enteral feeding	Late feeding	Muerte, morbilidad, días de internación. death, morbidity, hospital stay
32	Patient with dyspnea and heart failure vs acute COPD	pro-BNP to guide managment	No pro-BNP	Symptomatic improvement, death
33	Patient with acute asthma	IV magnessium	No IV magnessium	Symptomatic improvement, hospital stay, death
34	Patient with liver abscess greater than 10 cm	Percutaneous drainage	Surgery	Death, abscess resolution
35	Tracheal stenosis by prolonged endotracheal intubation	Endoscopic treatment	Surgical treatment	Death, sympomatic improvment
36	Patient with uncomplicated abdominal aortic aneurysm	Endovascular treatment	Surgical treatment	Death, complications
37	Patient with chlamydia post-infective reactive arthritis	Systemic steroids	Placebo	Symptomatic improvement
38	Patient with splenic abscess	Percutaneous drainage	Splenectomy	Death, complications
39	Patient with venous sinus thrombosis on anticoagulants	Thrombophilia screeninig	No thrombophilia screening	Recurrence, bleeding, death
40	Patient with systemic sclerosis AND pulmonary hypertension	Heart-Lung Transplantation	No Heart-Lung transplantation	Death
41	Pregnant women	Screening and treatment of cmv infection with intrauterine gammaglobulin	No screening	Congenital infection
42	Patient with spontaneous Intracerebral Hemorrhage and suspected malformation-cavernoma	CTA	Angio MRI	Death, malformation diagnosis
43	Patient with ischemic heart disease	Discontinue aspirin	Continue aspirin	Death, vascular events

	undergoing non cardiovascular surgery			
44	Asymptomatic old patient	Hepres Zoster vaccine	No vaccine	Zoster
45	Atrial fibrillation of indeterminate duration	Rythm control	Frecuency control	Mortality, cardiac output
46	Inpatient with acute COPD	Antibiotic therapy based on procalcitonin level	Antibiotic therapy based on clinical criteria	Death, complications
47	Patient with acute ischemic stroke	Aspirin 325mg	Aspirin 100mg	New stroke, death, bleeding
48	Patient with acute ischemic stroke and occlusion of arterial large vessels	Trombectomy	Pharmacotherapy	Disability, death
49	Patient with Lyme disease and central nervous system compromise	Ceftriaxone	Doxycycline	Death, sequel
50	Patient with chronic heart failure	Pro-bnp guided treatment	No pro-BNP guided treatment	Death
51	Patient in early post neurosurgical period with acute PE	Anticoagulation	Vena cava filter	Death, bleeding
52	Patient with Spontaneous Intracerebral Hemorrhage	Antiepileptic drugs, primary prevention	No antiepileptic drugs-primary prevention	Seizures, death, disability
53	Patient with subarachnoid bleeding and without seizures	Antiepileptic drugs, primary prevention	No antiepileptic drugs-primary prevention	Seizures, death, disability
54	Patient with severe traumatic brain injury	Antiepileptic drugs, primary prevention	No antiepileptic drugs-primary prevention	Seizures, death, disability
55	Patient with ACS taking sildenafil in the last 6 hs	Nitroglycerin	No nitroglycerin	Death, shock
56	Patient undergoing renal transplant	Perioperative pharmacologycal thromboprophylaxis	No thromboprophylaxis	Death, deep vein thromboses, oulmonary embolism, bleeding
57	Patient with active cancer undergoing surgery	Extended thromboprophylaxis	Thromboprophylaxis during hospitalization	Deep vein thromboses or pulmonary embolism, bleeding, death
58	Patient with subarachnoid bleeding	Vasospasm screening with transcranial	No doppler	Death, complications

		doppler		
59	Patient with subarachnoid bleeding	Nimodipin	Placebo	Death, complications
60	Patient with chronic leg ulcer and peripheral artery disease	Hyperbaric oxigen therapy	No hyperbaric oxygen therapy	Healing, death
61	Patient undergoing chemotherapy	Erythropoiesis stimulating factors	Placebo	HRQL, death, adverse events, anemia
62	Patient with renal infarction	Anticoagulation	Aspirin	Recurrent thrombotic event, bleeding
63	Patient with post lumbar puncture headache	Caffeine	Placebo	Pain improvement, adverse events
64	Patient with TRALI	steroids	Placebo	death
65	Cancer patient with deep vein thrombosis/pulmonary embolism	Low weight heparin	VKA	Recurrent thrombotic event, death
66	Patient with unprovoked deep vein thromboses who finish 3-6 month therapy of anticoagulant treatment	Aspirin	Placebo	Recurrent deep vein thromboses, death
67	Diabetic patient who takes metformin undergoing IV contrast CT	Discontinue metformin	Continue metformin	Lactic acidosis
68	Patient with evolved ischemic stroke and intracranial stenosis	STENT	Medical therapy	Recurrent stroke, death, bleeding
69	Patient with cardiovascular risk factors who needs NSAIDs	Naproxen	Other NSAIDs	Major vascular events
70	Patient with dvt	Early deambulation	Bed rest	Pulmonary embolism, bleeding, death
71	Patient with giant meningioma	Pre-surgical embolization	NO Pre-surgical embolization	Bleeding, death, disability
72	Patient with cancer and deep vein thromboses	Enoxaparin 1 daily dose	Enoxaparin 2 daily doses	New thrombotic event, bleeding
73	Immunocompromised patient with pulmonary infiltrates	Determination of galactomannans in bronchoalveolar lavage	No Determination of galactomannans in bronchoalveolar	Death, adverse events

			lavage	
74	Metastatic renal cancer	Nefrectomy	No nefrectomy	Survival, adverse events
75	Patient with recent diagnosis of HIV and recent diagnosis of tb	Immediate start of HAART	Delay start of haart	Death, complications
76	Patient with dizziness	Ginkgo Biloba	Betahistin	symptomatic improvement, adverse events
77	patient with superior vena cava syndrome	Stent	medical treatment	symptomatic improvement, complications
78	Patient with HIV related immune reconstitution inflammatory syndrome	steroids	Placebo	Death, symptomatic improvement
79	Steroids-refractory Immune Thrombocytopenic Purpura	Rituximab	Steroids	bleeding, platelet count
80	Patient who had undergone endarterectomy	Aspirin	Aspirin and clopidogrel	Stroke, death, bleeding
81	Patient with ureteral lithiasis	Alpha adrenergic blockers	Placebo	Pain, stone removal, adverse events
82	Patient with recurrent reflex syncope	Midorine	Placebo	Symptomatic improvement, syncope recurrence, adverse events
83	Patient with hyponatremia	Urinary sodium measure	Physical examination	Symptomatic improvement
84	Patient with pre-diabetes	Metformin	No pharmacological treatment	Microvascular complications (events), macrovascular complications (events)
85	Patient with mild or moderate idiopathic pulmonary fibrosis	Pirfenidone	Placebo	Death, progresion, adverse events
86	Patient with systolic heart failure	Angiotensin-neprilysin inhibition	Enalapril	Death, vascular events, adverse events
87	Patient with acute pharyngitis and severe Odynophagia	Steroids	Placebo	Symptomatic improvement, adverse events
88	Patient with aneurysmatic	Surgical treatment	Endovascular treatment	Rebleeding, death, complications,

	subarachnoid hemorrhage			disability
89	Inpatient with pneumonia	Betalactams	Betalactams + macrolides	Death, mechanical ventilation, adverse events
90	Patient with moderate or severe dementia	Memantine	Placebo	Cognitive status, functional status, adverse events
91	Patient with acute asthma	Inhaled steroids	Placebo	Death, mechanical ventilation, hospitalization
92	Patient on anticoagulants undergoing central venous catheter insertion	Femoral	Yugular	Death, hematoma, other complications, successful insertion
93	Patient with acute asthma	Non invasive ventilation AND standard treatment	Standard treatment	Death, mechanical ventilation, hospitalization
94	Patient with non-convulsive epileptic status	Levetiracetam load dose	Phenytoin load dose	Symptomatic improvement, death
95	Women with osteoporosis and NO previous fracture	Vitamin K	Placebo	Hip fracture, vertebral fracture
96	Ratient with vertigo	Betahistin	Placebo	Symptomatic improvement, adverse events
97	Patient with severe clostridium dificille infection	Metronidazol	Vancomycin	cure, recurrence, adverse events
98	Patient undergoing knee or hip fracture surgery	Thromboprofilaxis with new oral anticoagulants	heparin	thromboembolic events, bleeding, death
99	Patient with acute ischemic stroke and low NIHSS score	Ticagrelor	ASA	Recurrent stroke, bleeding, death
100	Patient with asymptomatic cholelithiasis	Cholecystectomy	Observation	Cholelitiasis related complications, surgery related complications

Nr: Question number

Supplementary table 3. Comparison between rapid strategies

	Strategy 1 (n=100)	Strategy 2 (n=100)	RR (CI95%)
Potentially misleading recommendations	5% (0.7 - 9.2%)	8% (2.6 - 13.3)	0.62 (0.18 - 2)
Inappropriate	1% (0 - 2.9%)	6% (1.3 - 10.6%)	-
Overconfident	4% (0.1 - 7.8%)	2% (0 - 4.7%)	-
Reasonable recommendations	95% (90.7 – 99.2%)	92% (86.5 – 97.3%)	1 (0.95 – 1.1)
Concordant	64% (54.5 – 73.4%)	62% (52.4 – 71.5%)	-
Reasonable disagreement	31% (21.9 – 40%)	30% (21 – 38.9)%	-
Potentially misleading quality of evidence judgment	16% (8.8 - 23.1%)	24% (15.6 - 32.3%)	0.52 (0.24 - 1.13)
Inappropriate Moderate or High	3% (0 - 6.3%)	7% (2 - 12%)	0.41 (0.08 - 1.8)
Inappropriate Low or Very Low	13% (6.4 - 19.5%)	17% (9.6 - 24.3%)	-
Quality of evidence agreement	63% (54.4 - 72.4%)	48% (38.2 - 57.7%)	1.3 (1 – 1.7)
Coincidence in information usage	65% (55.6 - 74.3)	56% (46.2 - 65.7)	1.16 (0.91 - 1.47)

Supplementary table 4. Potentially misleading recommendations description

Strategy	Population	Intervention	Information used	Information analysis	Possible solution
Epistemonikos	Patient with cardiac dyspnea in the emergency department	Pro-BNP guided treatment	Adequate. A SR that included all the relevant information was used	Inappropriate judgment of the quality of evidence.	No solution
Epistemonikos	Patient with asthma reagudization	Intravenous magnesium	Inappropriate. A recent systematic review was not identified	-	Appropriate use of the Epistemonikos matrix of evidence tool identified the missed SR
Epistemonikos	Patient with acute minor stroke	Mechanical thrombectomy	Inappropriate. A recent systematic review was not identified	-	Appropriate use of the Epistemonikos matrix of evidence tool identified the missed SR
Epistemonikos	Patient with acute pancreatitis	Early enteral nutrition	Adequate	Inappropriate judgment of the quality of evidence. Probable inappropriate summary of the evidence.	The recommendation was coherent with the GS when the same SoF was used
Epistemonikos	Patient with tracheal stenosis	Mechanical dilatation	Adequate	Differences in the benefit risk balance judgment	No Solution
Epistemonikos	Patient with recent TB/HIV co-infection diagnoses	Early antiretroviral treatment initiation	Adequate	Differences in the benefit risk balance judgment. Probable inappropriate summary of the evidence.	The recommendation was coherent with the GS when the same SoF was used

Epistemonikos	Patient with osteoporosis	Vitamin K	Adequate	Differences in the benefit risk balance judgment	No solution
Epistemonikos	Patient with asymptomatic cholelitiasis	No surgical treatment	Inappropriate. One relevant publication not identified	-	No solution
PubMed	Patient with acute aneurysmal rupture with SAH	Endovascular treatment	Inappropriate. Two relevant publications not identified	-	No solution
PubMed	Patient with traumatic SHA	Nimodipine	Appropriate	Inappropriate judgment of the quality of evidence. Probable inappropriate summary of the evidence.	The recommendation was coherent with the GS when the same SoF was used
PubMed	Patient with systemic sclerosis and severe lung compromise	Lung transplantation	Appropriate	Differences in the benefit risk balance judgment	No solution
PubMed	Patient with chronic heart failure	BNP guided therapy	Inappropriate. A recent systematic review was not identified	-	Appropriate use of the Epistemonikos matrix of evidence tool identified the missed SR
PubMed	Patient with severe Clostridium Difficile infection	Vancomicin	Inappropriate. A recent systematic review was not identified	-	No Solution