

## Evidence-based medicine and clinical practice

Mirjana Huić

Clinical pharmacologist  
Institute for Clinical Medical Research  
University Hospital "Sestre milosrdnice"  
Zagreb, Croatia

Corresponding author:  
Mirjana Huić, MD, MSc  
Clinical pharmacologist  
Institute for Clinical Medical Research  
University Hospital "Sestre milosrdnice"  
Vinogradska cesta 29, 10000 Zagreb, Croatia  
[mhuic@mef.hr](mailto:mhuic@mef.hr)

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Evidence-based medicine (EBM) is the conscientious, explicit, and judicious use of current best evidence in making decision about the care of individual patients. The practice of evidence-based medicine integrates physician's individual clinical expertise, best available research evidence, and patient unique values in the process of decision-making about the health-care. It should be accompanied by evidence-based patient choice. Evidence-based patient information, patient decision aids, have been developed to assist patients with difficult health-related decisions. The rationale of evidence-based practice is to improve the quality of care through the identification and promotion of effective practice and elimination of practices that are ineffective or harmful. The practice of EBM involves five essential steps: converting information needs into an answerable question (PICO format); finding the best evidence to answer the question; critical appraisal of the evidence for its validity and usefulness; application of the results into clinical practice; and evaluating performance. The practice of EBM should be a part of patients' daily care.

**Key words:** Evidence-based medicine, Evidence-based practice, Evidence-based patient choice, Evidence-based physician-patient relationship, Patient decision aids.

### Introduction

Evidence-based medicine (EBM) is the conscientious, explicit, and judicious use of current best evidence (about therapy, prevention, etiology, harm, prognosis, diagnosis and economic analysis) in making decision about the care of individual patients (1).

The practice of evidence-based medicine is a systematic approach to clinical problem solving, which allows the integration of the best available research evidence with clinical expertise (defined as the proficiency and judgment that individual clinicians acquire through clinical practice) and patient values (defined as the unique preferences, concerns

and expectations, such as cultural and religious). It should be accompanied by the evidence-based patient choice. Evidence-based medicine is applied to improve quality of care through the identification and promotion of effective practice and the elimination of practices that are ineffective or harmful. Good physicians use both their own individual clinical expertise and the best available external evidence, because neither alone is enough (1-3). To make the right decision about patient's health care, physicians combine their individual knowledge, clinical experience, close cooperation with colleagues, and evidence-based tools, such as standard operating procedures, protocols, guidelines, algorithms, and current best evidence on the Internet. In addition to clinical expertise, a clinician must have compassion and good listening skills, to understand patients' illnesses in the context of their experience, personalities, and cultures. However, the experience relates to the past, and fast-developing science of medicine requires our orientation towards future, the last, newest, and most useful refinements of physicians' knowledge and practice. Keeping up-to-date with current best evidence is challenging, and requires a habit of looking for current best evidence as efficiently as possible (5).

### Evidence-based clinical practice

The practice of evidence-based medicine requires the integration of individual clinical expertise and patient values with the best available clinical evidence from systematic research. Evidence-based health care means the application of the principles of evidence-based medicine to all professions associated with health care, including purchasing and management. Evidence-based health care should be accompanied by evidence-based patient choice, offering patients information about treatment alternatives, the ben-

efits and harms, and empowering them in decision making (6). The practice of EBM involves five essential steps (Box 1).

#### **Box 1 Five essential steps of EBM practice:**

- Step 1 converting information needs into an answerable question
- Step 2 finding the best evidence to answer the question
- Step 3 critically appraising the evidence for its validity and usefulness
- Step 4 applying the results of the appraisal into clinical practice
- Step 5 evaluating clinical performance

Physicians can incorporate best evidence into their evidence-based practice through two main modes: 1) the "doing" mode and 2) the "using" mode (2). In the "doing" mode physicians use at least the first four steps of evidence-based practice. In this mode, searches are restricted to freely available Internet resources that have not already undergone critical appraisal. So, physicians must invest time and effort for critical appraisal of articles for their validity and usefulness. After that, they can create an individual structured written summary of these first 3 steps - a "Critically Appraised Topics" or CAT. The aims of CATs are to summarize and consolidate physicians learning, make it cumulative, share it with others in the team, and refine physicians EBM skills. CATs have a number of limitations: they are based on quick searches for at least one useful article, therefore they are not a systematic review and practice guideline; might contain errors of calculation or appraisal judgments, and they become obsolete as soon as newer, better evidence becomes available. In the "using" mode, searches use evidence resources that have already undergone critical appraisal (eg, evidence summaries such as ACP Journal Club), thus skipping step 3. Unfortunately, most of pre-appraised resources are not freely available (2).

**A. Step 1 of EBM practice: formulating an answerable clinical question**

A clinician starts his or her search for the best and newest data needed to solve individual patient’s problem by formulating an answerable clinical question. Good clinical question must be clear, directly focused on the problem, and answerable by searching the medical literature (1-4).

*1 PICO format*

A good clinical question should have **four** essential components structured in the **PICO** format (**P**atient or problem, **I**ntervention, **C**omparison, **O**utcome) (Box 2).

**Box 2 PICO format:**

- the **p**atient or problem – who are the relevant patients, what kind of problem we try to solve?
- the **i**ntervention – what is the management strategy, diagnostic test or exposure (drugs, diagnostic test, foods or surgical procedure)?
- **c**omparison of interventions – what is the control or alternative management strategy, test or exposure that we will compare?
- the **o**utcome – what are the patient-relevant consequences of the exposure in which we are interested?

*2 Type of clinical question*

The most common type of clinical question is about how to treat a disease or condition. Such questions are questions about intervention. The other types are: questions about intervention, questions about etiology and risk factors, questions about frequency and rate, questions about diagnosis, questions about prognosis and prediction, question about cost-effectiveness, and question about phenomena (4).

**B. Step 2 of evidence-based medicine practice: finding the evidence**

After formulating the clinical question, which stems from a concrete patient, the next step is to search for relevant evidence that will provide the answer to the question. Some research designs are more powerful than others in their ability to answer research questions. For each type of questions a systematic review of all the available studies is better than any individual study.

Important sources of evidence include *online electronic resources*. Physicians should use websites and texts that are revised at least once a year, select and appraise evidence in

Table 1 Levels of evidence and grade of recommendation for ranking the validity of studies about *therapy, prevention, etiology and harm*, Oxford Centre for Evidence-based Medicine\*

Grade†	Level	Therapy/prevention, etiology/harm
A	1a	Systematic review (SR) (with homogeneity) of randomized controlled trials (RCTs)
	1b	Individual randomized controlled trial (RCT) (with narrow confidence interval)
	1c	All-or-none study‡
B	2a	SR (with homogeneity) of cohort studies
	2b	Individual cohort study or low quality RCT(<80% follow-up)
	2c	“Outcomes” research; ecological studies
	3a	SR (with homogeneity) of case-control studies
	3b	Individual case-control study
C	4	Case-series (and poor quality cohort and case-control studies)
D	5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or “first principles”

\* Produced by Phillips B, Ball C, Sackett D, Badenoch D, Straus S, Haynes B, Dawes M; www.cebm.net.

† Grades of recommendation: **A** consistent level 1 studies; **B** consistent level 2 or 3 studies or extrapolations from level 1 studies; **C** level 4 studies or extrapolations from level 2 or 3 studies; **D** level 5 evidence or troublingly inconsistent or inconclusive studies of any level.

‡ All-or-none study: when all patients died before the intervention became available, but some now survive on it; or when some patients died before the intervention became available, but none now die on it.

Table 2 Levels of evidence and grade of recommendation for ranking the validity of studies about *prognosis*, Oxford Centre for Evidence-based Medicine\*

Grade†	Level	Prognosis
A	1a	SR (with homogeneity) of inception cohort studies; or a clinical rule validated on a test set
	1b	Individual inception cohort study with $\geq 80\%$ follow-up; or a clinical rule validated in a single population
	1c	All-or-none case-series
B	2a	SR (with homogeneity) of either retrospective cohort studies or untreated control groups in RCTs
	2b	Retrospective cohort study or follow-up of untreated control patients in an RCT; or clinical rule non validated on a test set
	2c	"Outcomes" research
	3a	
	3b	
C	4	Case-series (and a poor quality prognostic cohort studies)
D	5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

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†Grades of recommendation: **A** consistent level 1 studies; **B** consistent level 2 or 3 studies or extrapolations from level 1 studies; **C** level 4 studies or extrapolations from level 2 or 3 studies; **D** level 5 evidence or troublingly inconsistent or inconclusive studies of any level.

Table 3 Levels of evidence and grade of recommendation for ranking the validity of studies about *diagnosis*, Oxford Centre for Evidence-based Medicine\*

Grade†	Level	Diagnosis
A	1a	SR (with homogeneity) of level 1 diagnostic studies; or a clinical rule validated on a test set
	1b	Validating cohort study with good reference standards; or a clinical decision rule not validated on a second set of patients
	1c	Absolute SpPins and SnNouts‡
B	2a	SR (with homogeneity) of level >2 diagnostic studies
	2b	Any of independent blind or objective comparison; study performed in a set of non-consecutive patients or confined to a narrow spectrum of study individuals (or both) all of whom have undergone both the diagnostic test and the reference standard; a diagnostic clinical rule not validated in a test set
	2c	
	3a	SR (with homogeneity) of 3b and better studies
	3b	Non-consecutive study; or without consistently applied reference standards
C	4	Case-control study, poor or non-independent reference standard
D	5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

\*Produced by Phillips B, Ball C, Sackett D, Badenoch D, Straus S, Haynes B, Dawes M; www.cebm.net.

†Grades of recommendation: **A** consistent level 1 studies; **B** consistent level 2 or 3 studies or extrapolations from level 1 studies; **C** level 4 studies or extrapolations from level 2 or 3 studies; **D** level 5 evidence or troublingly inconsistent or inconclusive studies of any level.

‡ An "Absolute SpPin" is a diagnostic finding whose Specificity is so high that a Positive result rules-in the diagnosis. An "Absolute SnNout" is a diagnostic finding whose Sensitivity is so high that a Negative result rules-out the diagnosis.

explicit way, and cite evidence in support of statements about clinical care (1-5).

### 1 Levels of evidence and grades of recommendation

The Oxford Centre for Evidence-based Medicine (www.cebm.net) recommended the

levels of evidence for ranking the validity of studies about therapy, prevention, etiology, harm, prognosis, diagnosis and economic analyses and grades of recommendation for clinical guidelines (Tables 1-4). Recommendations based on this approach are made for an average patient and may need to be

Table 4 Levels of evidence and grade of recommendation for ranking the validity of studies about *economic and decision analyses*, Oxford Centre for Evidence-based Medicine\*

Grade†	Level	<i>Economic and decision analyses</i>
A	1a	SR (with homogeneity) of level 1 economic studies
	1b	Analysis based on clinically sensible costs or alternatives; SR of evidence; and including multi-way sensitivity analyses
	1c	Absolute better-value or worse-value analyses
B	2a	SR (with homogeneity) of level >2 economic studies
	2b	Analyses based on clinically sensible costs or alternatives; limited review(s) of the evidence, or single studies; and including multi-way sensitivity analyses
	2c	Audit or outcomes research
	3a	SR (with homogeneity) of 3b and better studies
	3b	Analysis based on limited alternatives or costs, poor quality estimates of data, but including sensitivity analyses incorporating clinically sensible variations
C	4	Analysis with no sensitivity analysis
D	5	Expert opinion without explicit critical appraisal, or based on economic theory or first principles

\*Produced by Phillips B, Ball C, Sackett D, Badenoch D, Straus S, Haynes B, Dawes M; www.cebm.net.

†Grades of recommendation: **A** consistent level 1 studies; **B** consistent level 2 or 3 studies or extrapolations from level 1 studies; **C** level 4 studies or extrapolations from level 2 or 3 studies; **D** level 5 evidence or troublingly inconsistent or inconclusive studies of any level.

modified in light of an individual patient's unique biology and preferences.

## 2 Sources of evidence

There are different web sources of evidence. The search for best evidence should begin by looking at the highest-level source available for the problem in question.

*Evidence-based journals of secondary publication like ACP Journal Club; <http://www.acpjc.org>, Evidence-Based Medicine; <http://ebm.bmjournals.com>, Evidence-Based Mental Health; <http://ebmh.bmjournals.com>, Evidence-based Obstetrics and Gynecology; <http://www.harcourt-international.com/journals/ebog>, Evidence-Based Nursing; <http://ebn.bmj.com>, select from the biomedical literature original and review articles, summarize them, and present comments by clinical experts (2, 4, 5).*

There are several *online evidence-based databases* (Box 3).

The other databases are MEDLINE with version PubMed and *PubMed Clinical Queries* (National Library of Medicine free In-

ternet MEDLINE database), TRIP database, and SUMSearch (Box 4).

### Box 3 Evidence-based databases:

The Cochrane Library (through the Cochrane Collaboration, <http://www.cochrane.org>)

- The Cochrane database of systematic reviews: a collection of full text systematic reviews of the effects of health care, presents the best evidence, abstracts of reviews are freely available; <http://www.cochrane.org/reviews/index.htm>
- The DARE: includes systematic reviews that have been published outside of the Cochrane collaboration, all quality-assesses and with structured summaries, freely available on the Web outside the Cochrane library through Centre for reviews and dissemination databases; <http://www.crd.york.ac.uk/crdweb>
- The Cochrane Controlled Trials Register (CENTRAL): a bibliography of some 200,000 controlled trials, not freely available

Clinical Evidence; <http://www.clinicalevidence.com>; not freely available

CRD database; <http://www.crd.york.ac.uk/crdweb>; freely available

Internet sources of *evidence-based clinical practice guidelines* are The National Guideline Clearinghouse (NGC) ([33](http://www.guide-</a></p>
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**Box 4 Other evidence-based databases (free access):**

- PubMed Clinical Queries (<http://www.ncbi.nlm.nih.gov/entrez/query/static/clinical.shtml>): question-focused interface with filters for identifying most appropriate studies for the question about therapy, diagnosis, etiology, and prognosis
- SUMSearch (<http://sumsearch.uthscsa.edu/>): a meta-searching service
- TRIP Database (<http://www.tripdatabase.com/>): filters results by evidence-based synopses, clinical question, systematic reviews, guidelines, core primary research, e-textbooks, medical images, and patient information leaflet

line.gov) and Primary Care Clinical Practice Guidelines (<http://medicine.ucsf.edu/resources/guidelines/index.html>).

**3 The search strategy**

The starting point in the search for answers depends on the type of question we have asked. For *questions about intervention*, the best evidence comes from a systematic review of RCTs. The best first choice is the Cochrane database of systematic reviews. If there is not a Cochrane systematic review, the DARE review is the next best evidence. If there is not a DARE review, the next choice is PubMed Clinical Queries. PubMed Clinical Queries are the choice for *questions other than questions about intervention*, as well as TRIP Database and SUMSearch. The basic principles of search strategy includes: 1) defining of appropriate keywords from the clinical question, 2) choosing a bibliographic database, and 3) combining keywords with Boolean operators (AND/OR/NOT) (4).

**C. Step 3 of evidence-based medicine practice: appraising the evidence**

The next step is to appraise the evidence for its validity and clinical usefulness. Critical appraisal is a process developed by biostatisticians and clinical epidemiologists for assessing trials. Research evidence may be ap-

praised with regard to the three main areas: validity (Are the results of the study valid?), importance (What are the results?), and applicability to the patients (How can we apply these results to patient care?) (2-4).

There are several tools for appraising a research article. One of them was developed by the *Critical Appraisal Skills Programme (CASP)*, Oxford, UK. CASP aims to help individuals to develop the skills to find and make sense of research evidence, helping them to put knowledge into the practice. CASP provides appraisal tools in the form of questions to help in critical appraising of systematic reviews, randomized controlled trials, qualitative research studies, economic evaluation studies, cohort studies, case control studies, and diagnostic test studies. The CASP tools are simple, easy to use, and freely available on the Internet ([http://www.phru.nhs.uk/casp/critical\\_appraisal\\_tools.htm](http://www.phru.nhs.uk/casp/critical_appraisal_tools.htm)).

**D. Step 4 of evidence-based medicine model: applying the evidence**

After we decide that the evidence is valid and important, we have to decide whether the evidence can be applied to our individual patient. The evidence should be fully discussed with the patient. The decision also should take into account the potential side effects of the drug (does side effect outweigh its potential benefits in a particular patient), the cost and availability of that particular treatment in the hospital or practice. The questions that we should ask before the decision to apply the results of the study are (2-5):

**1 Are the participants in the study similar enough to my patient?**

Factors affecting this decision include the age, different risk profile (as many drugs have increasing adverse effects in the ageing population), co-morbidity that could affect drug interaction and adverse effects (eg, renal insufficiency), and compliance with treatment dosage and duration. An example

is a patient with myocardial infarction and bronchial asthma, who should receive a beta-blocker for the secondary prevention of myocardial infarction, but which is contraindicated in bronchial asthma.

*2 Is the treatment available and is health care system prepared to fund it?*

Some interventions may be unavailable (an example is the diagnostic procedure involving positron emission tomography/computed tomography). Some intervention may be expensive, and require approval from the Hospital Drug Committee (eg, therapy with rituximab for lymphoma or infliximab for resistant Crohn's disease).

*3 What alternatives are available?*

If there are alternative treatments or procedures that we could use, we need to decide which one is most suitable for our patient, balancing the potential benefits and harms. An example is drug therapy for arterial hypertension (there are different groups of drugs for the treatment of this condition, with the same effect).

*4 Do the potential side effects of the drug or procedure outweigh the benefits?*

Some of the adverse effects may not be mentioned in trials, but may be very relevant to our patient (eg, mood disturbances, impotence). The invasiveness of a test or procedure may affect patient's willingness to participate.

*5 Are the outcomes appropriate to the patient? Does the treatment conflict with the patient's values and expectations?*

We must take account of what the patient thinks, once we have explained the risk and benefits of different treatment options. The outcomes that are important to us may not be of same importance to the patient, particularly where quality of life is concerned. An example is a terminal cancer patient, who

rejects all therapy except palliative therapy, with pneumococcal pneumonia. Despite the fact that antibiotics may reduce symptoms and prolong his life, his values are such that he would prefer a rapid natural death.

To help in clinical decision making, there are practical clinical guidelines, protocols, and algorithms. The ultimate judgment regarding the care of a particular patient must be made by the healthcare provider and the patient in light of all circumstances presented by the patient. The responsible physician's judgment is paramount in managing patients. There are circumstances in which deviations from guidelines are appropriate.

***E. Step 5 of evidence-based medicine model: evaluating clinical performance***

It is important to keep records of our clinical questions, search results, and critical appraisal of evidence, to follow up patients, and to record (and publish) outcomes. Also, we need to ask whether we formulate answerable questions, find best evidence quickly, effectively appraise the evidence, and integrate clinical expertise and patient preferences and values with the evidence in a way that leads to a rational, acceptable management strategy. We need to evaluate our approach at frequent intervals and decide whether we need to improve any of the four steps discussed above. After a process of self-evaluating, we must look whether our clinical practice becomes better. Do we need new protocols or algorithms, better access to Internet sources, and new changes in organizational processes? After implementation of those changes, we must look if they have actually occurred (4). The practice of EBM involves a process of life-long, self-directed learning in which caring for patients creates the need for important information about clinical and other health care issues. The practice and teaching of EBM should be part of the daily care of patients.

## Evidence-based physician-patient relationship

During the examination of a patient (eg, in general practice or in a hospital) we use our individual knowledge, clinical experience, team work, and evidence-based tools (protocols, guidelines and algorithms) to complete evidence-based information and solve the problem. When the problem is new and have not been answered in the guidelines, we must look for current best evidence in available Internet resources, using the first four (the “*doing*” mode) or three steps (the “*using*” mode) of evidence-based practice (2).

In the process of decision-making, physicians must incorporate patient values (preferences, concerns and expectations). The physician should discuss with the patient the harms and benefits of all available options, patient’s treatment goals and risk tolerance, and than decide *together* about a course of action. For some of the patients and problems, discussion should involve the patient’s family. Patients who wish to delegate decision-making to a doctor or family member would still be given the information that they want. Evidence-based health care should be accompanied by evidence-based patient choice. Because of that, physicians should explain to patients the possibility of finding evidence-based patient information and patient guidelines on the Internet. But not all patients have the skills or access to the computer resources, so that downloadable version of information or materials are needed. Examples of such evidence-based patient information are patient decision aids, which have been developed to assist patients with difficult health-related decisions. Available trials indicate that decision aids improve knowledge and realistic expectations, enhance active participation in decision making, lower decisional conflict, decrease the proportion of patients remaining undecided, and improve agreement between

values and choice. These decision support tools help patients become more engaged in their healthcare, but do not provide medical advice or replace physicians care (7, 8).

Databases of patient decision aids have been made available to the public by several academic institutions (Box 5.)

### Box 5 Online patient decision aids:

- Canadian Cochrane Collaboration Systematic Review team created two databases of patient decision aids;
  - 1 *Decision Aid* contains more than 500 patient decision aids at various stages of development (<http://decisionaid.ohri.ca/cochinvent.php>)
  - 2 *A-Z Global Inventory* of available and evaluated patient decision aids with links to their authors (<http://decisionaid.ohri.ca/AZinvent.php>).
- The *BMJ online Evidence-Based Rheumatology* textbook, containing downloadable patient decision aids and consumer summaries (<http://www.blackwellpublishing.com/medicine/bmj/rheumatology/decids.asp>).

## Treats to the evidence-based medicine, recent activities and solutions

Study publication bias and outcome reporting bias are two major factors already known that negatively influence on evidence-based medicine by overestimation the effect of the experimental treatment (9, 10). The International Committee of Medical Journals’ (ICMJE) policy on mandatory registration of clinical trials and the most recent US legislation on mandatory registration of trial summative results, which came in effect on September 27, 2007, have made an important contribution to the transparency of clinical research (10-15). Also they will decrease publication and outcome reporting bias, and will speed the dissemination of trial information. Finally, the revised Declaration of Helsinki (<http://www.wma.net/e/policy/b3.htm>) in two items elaborate registration in publicly available database and ethical obligation on publication of negative and inconclusive as well as positive results; item

19: „Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.“, and item 30: „Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.“

All those activities are promising for a good future of evidence-based medicine and clinical practice.

## References

1. Sackett DL, Rosenberg WM, Gray JA, Richardson WS. Evidence based medicine: what it is and what it isn't. *BMJ*. 1996;312:71-2.
2. Straus SE, Richardson WS, Glaziov P, Haynes RB, editors. Evidence-based medicine. How to practice and teach EBM. Edinburgh: Elsevier Churchill Livingstone; 2005.
3. Akobeng AK. Evidence based child health. Principles of evidence based medicine. *Arch Dis Child*. 2005;90:837-40.
4. Glasziou P, Del Mar C, Salisbury J, editors. Evidence-based medicine workbook. London: BMJ publishing group; 2003.
5. Guyatt G, Rennie D, editors. Users guides to the medical literature. Chicago: American Medical Association; 2002.
6. Holmes-Rovner M, Liewellyn-Thomas H, Entwistle V, Coulter A, O'Connor A, Rovner DR. Patient choice modules for summaries of clinical effectiveness: a proposal. *BMJ*. 2001;322:664-67.
7. O'Connor AM, et al. Decision aids for people facing health treatment or screening decisions. *The Cochrane Database of Systematic Reviews*, 2004, Issue 1.
8. O'Donnell S, Cranney A, Jacobsen MJ, Graham ID, O'Connor AM, Tugwell P. Understanding and overcoming the barriers of implementing patient decision aids in clinical practice. *J Eval Clin Pract*. 2006;12:174-81.
9. Dwan K, Altman DG, Arnaiz JA, Bloom J, Chan A-W, Cronin E, et al. Systematic Review of the Empirical Evidence of Study Publication Bias and Outcome Reporting Bias. *PLoS ONE* 2008;3:e3081.
10. Lee K, Bacchetti P, Sim I. Publication of clinical trials supporting successful new drug applications: A literature analysis. *PLoS Med*. 2008;5:e191.
11. De Angelis C, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R, et al. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. *Croat Med J*. 2004;45:531-2.
12. De Angelis CD, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R, et al. Is this clinical trial fully registered? A statement from the International Committee of Medical Journal Editors. *Croat Med J*. 2005;46:499-501.
13. Laine C, Horton R, DeAngelis CD, Drazen JM, Frizelle FA, Godlee F, et al. Clinical trial registration: looking back and moving ahead. *Croat Med J*. 2007;48:289-91.
14. Krleža-Jerić K. International dialogue on the public reporting of clinical trial outcome and results – PROCTOR meeting. *Croat Med J*. 2008;49:267-8.
15. Marušić A, Huić M. Registration of Clinical Trials Still Moving Ahead – Update to Uniform Requirements for Manuscripts Submitted to Biomedical Journals. *Croat Med J*. 2008;49:582-5.