PCFM Vol 5 No. 4 Oct-Dec 2022:251-258.

บทความปริทัศน์

การตั้งคำถามวิจัยที่ดี: แก่นสำคัญในการออกแบบและดำเนินการวิจัย

กรภัทร มยุระสาคร,[1] พบ. วว.เวชศาสตร์ครอบครัว, ธันยาภรณ์ พงษ์คุณากร,[1] วท.ม., กมล อุดล,[2] พบ., Sara Schwanke Khilji,[3] MD., MPH, ธมลวรรณ มะโนสาร[1] วท.บ.

[1]กลุ่มวิจัยสุขภาพประชากรและโภชนาการ ศูนย์วิจัยการแพทย์ศิริราช คณะแพทยศาสตร์ศิริราชพยาบาล; [2]สาขาวิชาเวชศาสตร์ป้องกันโรคหัวใจ หลอดเลือดและเมตะบอลิสม ภาควิชาเวชศาสตร์ป้องกันและสังคม คณะแพทยศาสตร์ศิริราชพยาบาล มหาวิทยาลัยมหิดล กรุงเทพมหานคร; [3]Division of Hospital Medicine, Department of Medicine, Oregon Health & Science University, United States

ผู้รับผิดชอบบทความ:
กรภัทร มยุระสาคร, พบ., กลุ่มวิจัยสุขภาพประชากรและโภชนาการ, ศูนย์วิจัยการแพทย์ศิริราช, คณะแพทยศาสตร์ศิริราชพยาบาล, มหาวิทยาลัยมหิดล
Email: korapat.may@mahidol.edu

Received: May 9, 2022;
Revised: June 29, 2022;
Accepted: July 11, 2022

บทคัดย่อ

หลายทศวรรษที่ผ่านมาข้อมูลขนาดใหญ่เป็นที่สนใจของนักวิชาการอย่างกว้างขวาง เพื่อใช้ในการขับเคลื่อนเทคโนโลยีทั้งเชิงวิทยาศาสตร์และไม่ใช่วิทยาศาสตร์ สำหรับการแพทย์เวชปฏิบัตินิยมใช้เป็นข้อมูลอ้างอิงประกอบการตัดสินใจขั้นเบื้องต้น อย่างไรก็ตามในทางปฏิบัติรูปแบบการรักษาโรคต้องปรับเปลี่ยนให้เหมาะสมกับผู้ป่วยแต่ละราย เนื่องจากมีความเฉพาะตัวของภาวะโรค ความซับซ้อน และผลแทรกซ้อนอื่น ๆ รวมถึงปัจจัยส่วนบุคคล เช่น เพศ วิถีชีวิต พันธุกรรม และการเข้าถึงบริการรักษา ซึ่งเป็นตัวแปรสำคัญที่ต้องพิจารณาประกอบในการตัดสินใจในเวชปฏิบัติ นอกจากนี้การผสมผสานองค์ความรู้จากผลงานวิจัยร่วมกับข้อมูลสนับสนุนการรักษาทางการแพทย์เป็นอีกปัจจัยที่สำคัญ ที่จะนำไปสู่รักษาแบบเฉพาะเจาะจง การแพทย์แม่นยำ การตัดสินใจถึงความเหมาะสมของรูปแบบการรักษา ชนิดและปริมาณยาที่ใช้ แนวทางการติดตามผลลัพธ์ให้บริการ การรักษาแบบทางเลือก และหลักฐานเชิงวิชาการ ดังนั้นผู้เขียนจึงมีวัตถุประสงค์เพื่อขยายความการตั้งคำถามวิจัยที่ดีด้วยแก่นสำคัญในการออกแบบ 2 ข้อ คือ การมองหาสิ่งที่ขาดหายในองค์ความรู้และการวิเคราะห์คำถามแบบแยกส่วน ซึ่งพบว่าสามารถช่วยผู้วิจัยลดทอนข้อมูลที่ไม่จำเป็น ใช้ระยะเวลาในการทำวิจัยให้เกิดประโยชน์สูงสุด ช่วยเชื่อมโยงข้อสงสัยกับหลักฐานสนับสนุนทางการแพทย์/เวชปฏิบัติคลินิก/และแนวทางคลินิกแบบเฉพาะบุคคลอย่างเหมาะสม จากบทความนี้แสดงให้เห็นว่า การได้มาซึ่งคำถามวิจัยที่ดีมีความจำเป็นและเป็นพื้นฐานการได้มาซึ่งการกำหนดเป้าหมายการวิจัยที่ชัดเจนและรูปแบบงานวิจัยที่ประสบความสำเร็จ

คำสำคัญ: คำถามงานวิจัย สมมุติฐาน จุดประสงค์ ระเบียบวิธีวิจัย

PCFM Vol 5 No. 4 Oct-Dec 2022:251-258.

REVIEW ARTICLE

Asking an important Question: A Crucial Step in Research Design and Conduct

Korapat Mayurasakorn,[1] MD. FRCFPT, Tanyaporn Pongkunakorn,[1] MS.,
Kamol Udol,[2] MD., Sara Schwanke Khilji,[3] MD. MPH, Thamonwan Manosan[1] BS.

[1]Population Health and Nutrition Research Group, Siriraj Medicial Research Center, [2]Division of Cardiovascular and Metabolic Disease Prevention, Department of Preventive and Social Medicine; Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand; [3]Division of Hospital Medicine, Department of Medicine, Oregon Health & Science University, United States

Corresponding author :
Korapt Mayurasakorn, MD., Population Health and Nutrition Research Group, Siriraj Medicial Research Center, Faculty of Medicine Siriraj Hospital, Mahidol University
Email: korapat.may@mahidol.edu

Received: May 9, 2022;
Revised: June 29, 2022;
Accepted: July 11, 2022

ABSTRACT

In the era of big data, considerable attention has been focused on data-driven technologies in both scientific and non-scientific communities over the past decade. In medicine, evidence-based medicine (EBM) is used as a well-accepted model to aid clinical decision-making. Although EBM has been appropriately applied in general, the specific characteristics of each patient must be considered in clinical decision-making, due to the complexity and frequency of comorbid conditions in the management of modern disease. Individual-level factors such as gender, lifestyle, genetic differences, and accessibility of care are important considerations for the actual implementation of EBM. In addition, incorporating state-of-the-art medical research into clinical management is increasingly vital as medical management moves forward into the era of precision medicine. Decisions regarding whom to treat, which medication to use, what outcomes to monitor and which alternatives to consider require not only common sense and clinical experience, but also research evidence. Therefore, we aim to elaborate a well-articulated research question by two crucial steps including an identified the gap in knowledge and the question components. It can help to eliminate extraneous information and minimize time spent in conducting research, bridging the gap between EBM, clinical practice guidelines (CPGs), and individualized clinical care. This review demonstrates that a precisely formulated research question is an essential foundation for articulating the ultimate goal and a successful research activity.

Keywords: research question, hypothesis, objective, research methods

Introduction

Recent development in biomedical sciences, including high-throughput technologies, are likely to prompt a new paradigm for understanding human health. The concept of "big data" has triggered multiple national initiatives focused on developing precision care mechanisms for individual patients. Patient care has also shifted conceptually from physician-centered to patient-centered approaches. The "one size fits all" approach to treatment may offer an imperfect solution for individuals. According to the evidence-based care model, it is imperative that medical providers define specific clinical questions and select relevant evidence from high quality research to answer a given clinical dilemma and provide appropriate individualized medical care. To conduct high quality research, one must start by asking a sound research question.

To begin with, developing a good question is a vital yet challenging task a researcher faces when establishing a research project, in order to ascertain the truth in a defined situation. Yusuf and colleagues suggest criteria for sound research.[1] First, "ask an important question" and, second, "answer it reliably" according to this formulation, research that generates unreliable and invalid answers is useless or, worse, misleading, regardless of the importance of the question it attempts to answer. However, research yielding reliable and valid answers may still not be useful to guide clinical practice if the driving question is not important. Therefore, the importance of the problem leading to the research to be undertaken must be regarded as a major determinant of a good research question.

In a clinical context, questions are formulated based on problems faced on a day-to-day basis in practice, and research-supported solutions are needed to address such challenges within a specific patient population. Such research ideas often begin broadly and ambiguously in nature. Iterative processes of refinement and modification are required to achieve a specific and, ultimately, researchable question. These iterative processes include literature reviews, gathering information from existing evidence, and discussion with colleagues and experts, until saturation is achieved.

Objectives

In this article, we elaborate crucial steps for developing both good and researchable questions. We employ a step-by-step case presentation to illustrate the discrete elements required to develop a concrete research question, defining a corresponding research method for each. The article introduces the Participants/Problem, Intervention, Control/Comparator, Outcome(s) and Time (PICO(T)) framework for outlining a research question. Lastly, we describe and assess common categories of clinical research questions in the context of establishing a researchable project.

The primary key step: define the gap the question seeks to address

The principal step in creating a sound research question is defining a problem and/or gap in knowledge. Dr. Ernest M. Allen (Chief of the Division of Research Grants, National Institutes of Health, US Department of Health & Human Services) long ago demonstrated that 58% of declined proposals focused on a research problem deemed to be "not of sufficient importance" or "unlikely to produce any new or useful information", and 30% used methodology that was inconsistent with the stated research objectives.[2]

Many researchers still question an existing theory but are hesitant to conduct a replication study. However, given recent medical advances, repeating previously published studies can help to assure that results are reproducible and strengthen the evidence of a previously documented finding.[3] Alternatively, a replication study might address and rectify limitations of a previous study. Importantly, results may contribute back to a researcher's own patient care practices.

Meticulously updated literature reviews relating to a topic of interest will help researchers articulate a research problem and select appropriate methodologies. Not only is a well-formulated research question the fundamental foundation for any type of research, it is integrally linked to all aspects of a project's methods, including study design, eligibility criteria, outcomes, statistical analyses and sample size estimation. Each of these methodologic considerations rests on the cornerstone of a well-developed research question, while also serving as the building blocks of research that will ultimately answer identified knowledge gaps in clinical practice.[4-6]

Developing the research question should begin with an initial review of previously published evidence, including peer-reviewed literature, expert opinion, case reports and/or data sets. These activities are likely to generate a number of potential research questions. It then becomes crucial to ask which one of these questions is the primary research question: that is, the most important question to be studied using available methods.[7]

Cummings et al. suggest that characteristics of a good research question be FINER: Feasible, Interesting, Novel, Ethical and Relevant.[8] Feasibility is based on the possibility of securing adequate numbers of subjects, tools, time, and budget; in short, the scope must be appropriate to available resources. The research question must be Interesting enough to capture the enthusiasm and focus of the research team, peers, funding agencies and scientific community at large. Good research provides Novel information that can elucidate unknown findings or expand on questions raised by a previous study. A good research question must be Ethical, avoiding, at a minimum, unacceptable mental or physical risks and invasion of privacy. Finally, and perhaps most importantly, good research must be practical and Relevant to serve the needs of target communities and to advance the bounds of scientific knowledge. Moreover, relevant research should influence practice not only in relation to the general population but also in the application to individuals. We also add that Scalability of the research should be considered. While studies may be well-structured and yield statistically significant outcomes, they may yet fail to be applicable in real world settings due to complex research design, strict research conditions, and/or lack of generalizability to heterogeneous populations. Take, for example, the research design of a diabetes prevention program targeting subjects at high risk of developing diabetes. Subjects in the intervention group were asked to follow activities according to a very strict protocol that included a controlled diet, frequent physical exercise, and other related activities. Although the study results might reveal significantly improved outcomes in the intervention group compared with control, the complex nature of the intervention poses a challenge to implementation in everyday life.[9]

The second key step: define the question components

Here we present a common clinical scenario and explore how clinical questions emerge in practice.

A case scenario

A 76-year-old woman presents at a primary care unit with poorly controlled blood sugar. She has a 20-year history of type-2 diabetes and has used multiple oral hypoglycemic agents, including glipizide, metformin, and a long-acting basal insulin analog. She finds it difficult to take the metformin as prescribed due to side effects such as an anorexia and stomach upset. Recently her estimated glomerular filtration rate (eGFR) and a random urine albumin-to-creatinine ratio (ACR) were 43 mL/min/1.73 m^2 and 450 mg/g, respectively. She is concerned about outcomes associated with angiotensin converting enzyme inhibitor agent (ACEI) use in renal insufficiency. Finally, she wants to know if she can still use metformin, or if it can be substituted with another hypoglycemic agent to avoid its side effects.

Several questions arise from this scenario. These can be cathegorized broadly as background and foreground questions.[6,10] On the one hand, a background question generally relates to a condition, a clinical problem, or knowledge about a specific disease. Background questions prompt a researcher to ask the "W5H" questions (who, what, when, where, why, how) as they apply to the relevant problem, pathology, or treatment. Background questions in this scenario could, for example, take the form of, "How does an ACEI work in diabetic kidney disease?" or "What are consequences of long-term metformin treatment?" Most background questions can be answered by information in standard textbooks and evidence-based resources. However, caution should be taken when unreliable sources of information are used.

Foreground questions, on the other hand, generally are very specific and involve choices of treatment, harm, diagnosis, prognosis, and/or outcomes, ultimately providing the evidentiary basis for decision making. This type of question can, at best, be partly answered with information contained in the published literature. An example would be "Does ACEI retard the deterioration of kidney function in diabetic elderly patients with

preexisting renal impairment?", or "Will the measurement of urine albumin be helpful in managing type-2 diabetes mellitus with renal insufficiency?"

The question framework

A useful format used in the development of a foreground research question is the PICO(T) framework (formerly well described as PICO).[6, 7, 11] The PICO(T) criteria include the Population/Patient of interest, the Intervention (treatment or diagnostic procedures being used), the Comparison/Control (the procedure/activity/drugs with which the intervention of interest will be compared), the expected Outcome of interest (measurable expected outcomes under given conditions), and an optional Time element.7 The PICOT framework helps generate a structured question leading to a tangible research methodology and, subsequently, to protocol development.

Population/Patient (P): Clearly describing a specific population of interest will help define appropriate inclusion and exclusion criteria. A restricted study population may help decrease confounding effects related to subjects' characteristics, particularly in a non-randomized study, at the expense of reduced availability of eligible subjects and diminished external validity of the study. A loosely defined population, on the contrary, may enable easier recruitment of subjects with diverse characteristics and may enhance external validity of the study. However, the risk of confounding effects may increase, especially in a non-randomized study. Thinking back to our clinical scenario, we can identify our "P" as "elderly diabetic patients with preexisting renal impairment". Note that this description needs further clarification in terms of age range, stage of diabetes, and definition of renal impairment.

Intervention (I): The intervention may be a lifestyle measure (such as diet control or exercise), a pharmacologic agent, a therapeutic procedure, a diagnostic test, or an exposure to a risk factor. It is important to recognize that, when utilizing a specific test to support an intervention or treatment, the use of a diagnostic test must be considered in conjunction with the associated treatment, such as using HbA1C to identify prediabetes in a population. In our case scenario, based on clinical observation and existing literature, we can venture that pioglitazone has fewer GI side effects as compared to metformin, or that administering an ACEI helps reduce proteinuria in the general population. Nevertheless, the clinician may remain uncertain about the efficacy of these medications in diabetic elderly patients with stage 3b chronic kidney disease, prompting a study to answer this question. The intervention would then be a new therapeutic approach, namely replacement of metformin with pioglitazone, or introduction of a specific ACEI. The details of the intervention must be clearly specified. These include the dose, route of administration, frequency and duration of pioglitazone or the ACEI.

Control/Comparator (C): When studying the effect of a new treatment or a risk factor, it must be compared to a control condition. For a new treatment, the control intervention may be the conventional treatment, a placebo, or no treatment, depending on the concurrent standard of care of the disease. For a risk factor or a prognostic factor, the control condition is usually absence of the factor, or the reference level of the factor. In the scenario, the comparator of pioglitazone would be metformin. For an ACEI, the comparator would be placebo. Again, the details of the control intervention need to be clearly specified.

Outcome (O): The outcome in the research question has to be viewed and defined as a variable expected to be related to or influenced by the intervention. For example, if we speculate that ACEI could help control proteinuria in diabetic elderly people, then the outcome would be "proteinuria", which requires a clear definition. Proteinuria can be measured as a continuous variable by quantifying the amount of protein in a 24-hour urine collection, or it may be measured as a dichotomous variable, such as progression of proteinuria (yes/no). The latter case demonstrates the use of single clinical event as the outcome. Sometimes, we might be interested in many related clinical events as the outcome of the research. We could then have multiple events combined together as the outcome, called the "composite outcome". For example, we may include "progression of proteinuria", "doubling of serum creatinine" and/or "development of end stage renal disease" as the outcome. Presence of any of these events in a subject would qualify that person as experiencing the outcome of interest.

Time (optional) (T): When will the expected outcome be measured? Sometimes researchers

specify the study duration in the research question or objectives. For example, "What is the efficacy of ACEI in controlling proteinuria after an exposure duration of 6 months?"

Common aspects of clinical research questions

Recognizing the level of inquiry that a clinical question represents is an important step in developing a successful research proposal and study design. Table 1 shows many aspects of clinical questions commonly encountered (modified from many authors).[6,11,12] Questions may relate to issues of clinical judgement in clinical medicine such as prevention, screening, diagnosis, treatment, risk and prognosis. Some questions, particularly in the field of epidemiology, may relate to magnitude of health problems, clinical characteristics, practice patterns, or patients' experiences.

Primary and secondary research questions

It is common for researchers to be interested in many related research questions, and to attempt to answer them simultaneously within a given research project, as conducting research requires considerable investment of resources and time. The researcher must then designate which question is the primary research question, and which are secondary. A primary research question is the most important question the researchers want to answer with validity and adequate precision. A secondary research question, on the other hand, is less important and may not be answered conclusively in the research. Specifying the primary research question is very important because the design and conduct of the research must aim to obtain a definite and conclusive answer to the primary research question. Answers to secondary research questions are viewed at best as hypothesis generating. It is not a common practice to have more than one primary research questions for a single research project, because having multiple primary research questions would increase the complexity of the research design and conduct, and may complicate data analyses. However, there are often several secondary research questions.

Questions, hypothesis and objectives

As mentioned earlier, researchers must invest considerable effort and time to formulate the best possible research question, in order to avoid invalid results that might hamper identifying information of clinical significance.

Once a research question has been selected, the research hypothesis should next be articulated. In fact, a research question, a research hypothesis and research objective(s) convey essentially the same information expressed in different forms. A hypothesis is an expected answer to a primary research question that summarizes the crucial parts of the study according to the PICO(T) framework, in a form that establishes a basis for statistical testing. Once a research question has been clearly established, the research hypothesis can be easily formulated by converting the research question into an affirmative sentence. For example, if the research question is: "In elderly patients with type 2 diabetes who have normal blood pressure, does administration of an ACEI retard the development or progression of albuminuria, compared to placebo?", then the research hypothesis would be "In elderly patients with type 2 diabetes who have normal blood pressure, administration of an ACEI retards the development or progression of albuminuria, compared to placebo." It is possible that some research questions may not directly translate into a research hypothesis. Consider the research question, "What is the prevalence of renal insufficiency in elderly diabetic patients in primary care settings?" You can see that no research hypothesis can be formulated for this research question. Indeed, for any research question that does not contain the "C" component, there will be no research hypothesis. These include research questions about the properties of a diagnostic test, prognosis, and magnitude of health problems/clinical characteristics. The presence or absence of a research hypothesis is crucial in determining the appropriate statistical approach in data analyses and sample size estimation.[13]

In addition to clear research questions and hypotheses, research objective(s) may be indicated. The research objective is closely related to the research question, insofar as it contains the same components of the research question PICO(T). For the research question "In elderly patients with type 2 diabetes who have normal blood pressure (P), does administration of an ACEI (I) retard the development or progression of albuminuria (O), compared to placebo (C)?", the

Table 1. Levels of enquiry for commonly encountered research question types

Level of enquiry	Type of research question	PICO Component	Examples
Magnitude of health problems or clinical characteristics	Questions about prevalence, incidence, clinical characteristics, practice pattern or patients' experiences	P-O	What is the prevalence of renal insufficiency in elderly diabetic patients in primary care settings? What is the status of diabetes control in elderly diabetic patients in primary care settings?
Prevention and treatment	Questions about the efficacy or effectiveness of an intervention or exposure in preventing disorders from developing or in improving outcomes in patients. Examples of a preventive or therapeutic intervention include a behavioral or lifestyle measure, an educational or counselling program, a pharmacological agent, a surgical procedure, a rehabilitation program, or a vaccine.	P-I-C-O	In elderly patients with Type 2 diabetes who have normal blood pressure (P, does administration of an ACEI (specify the regimen) (I) retard the development or progression of albuminuria (O), compared to placebo (C)?
Diagnosis and screening	Questions about the ability of a test or procedure to differentiate between those with and without a condition or disorder	P-I-(C)[a]-O	In asymptomatic individuals in a community (P), does capillary blood glucose (I) perform comparably to plasma glucose (C) in screening for diabetes mellitus (O)? In Type 2 diabetes mellitus patients (P), does spot urine microalbumin using a commercial strip (I) help diagnose microalbuminuria as defined by 24-hour urine albumin excretion (O)?
Prognosis	Questions about the probability of some events occurring, or changes in status or some parameters over time, in a specific group of patients	P-O	In elderly diabetic patients with persistent albuminuria (P), what is the probability of developing end stage renal disease (O) over time?
Risk factors, prognostic factors or predictors	Questions about the association between exposure to a factor and selected outcomes. The exposure may be called a risk factor, a prognostic factor or a predictor	P-I-C[b]-O	In elderly diabetic patients (P), is albuminuria (I) a risk factor for cardiovascular death (O)?

[a]C may be present or absent in this type of research question. If the aim of the research is to compare the performance of two or more tests, then C is present. If the research aims to study the performance of just one test, then C is absent. The gold standard test in this situation is not the C; it is merely the method of determining the outcome (O).
[b] C is always present in this type of research question, even though it is occasionally not mentioned explicitly. C is usually the absence of the factor of interest, or the "reference" level of the factor of interest.
[c] One factor is regarded as I/C and the other as O, even though they may not completely match the definitions in some situations. I and C are grouped together if the factor is analyzed as a continuous variable.

research objective would be "to study the effects of an ACEI, compared to placebo, on progression of albuminuria in elderly patients with type 2 diabetes who have normal blood pressure". Unlike research hypotheses, which may be absent in some aspects of research questions, research objectives can be articulated for all aspects of research questions.

Returning to our clinical scenario, here are a few examples to illustrate the construction of research hypothesis. A relatively simple hypothesis might be put forth as "A high fat diet is asso-

ciated with an increased risk of proteinuria in the elderly with diabetes." Or: "High blood pressure is associated with an increased risk of proteinuria in the elderly with diabetes". Having multiple hypotheses eventually will help the researcher decide which question is the primary research question.

Conclusion

Developing a high-quality research question is the most fundamental part of the entire research project. To generate a good research question, one needs to understand gaps in knowledge about the topic of interest, based on review of a broad variety of sources. A clear and specific research question can be formulated using the PICO(T) framework. Each component of the question must be defined in as much detail as possible. A research hypothesis is a theoretical answer to a research question that is measurable. Finally, primary research objectives must be generated to delineate what a study aims to accomplish. Developing "important", "relevant" and "researchable" questions with linked hypotheses and objectives is a difficult task, but it will definitely guide a successful research activity.

Acknowledgments

We would like to appreciate to all colleagues for their dedication to this article. Moreover, we thank Faculty of Medicine Siriraj Hospital, Mahidol University for all facilities.

References

1. Yusuf S, Collins R, Peto R. Why do we need some large, simple randomized trials? Stat Med. 1984;3:409-22.
2. Allen EM. Why are research grant applications disapproved? Science. 1960;132(3439):1532-4.
3. Aslam S, Emmanuel P. Formulating a researchable question: A critical step for facilitating good clinical research. Indian J Sex Transm Dis AIDS. 2010;31:47-50.
4. Bragge P. Asking good clinical research questions and choosing the right study design. Injury. 2010;41 Suppl 1:S3-6.
5. Naccarella L, Buchan J, Brooks P. Evidence-informed primary health care workforce policy: are we asking the right questions? Aust J Prim Health. 2010;16:25-8.
6. Price CP, Christenson RH. Ask the right question: a critical step for practicing evidence-based laboratory medicine. Ann Clin Biochem. 2013;50(Pt 4):306-14.
7. Brian Haynes R. Forming research questions. J Clin Epidemiol. 2006;59:881-6.
8. Cummings SR, Browner WS, Hulley SB. Conceiving the research question and developing the sutdy plan. In Hulley SB, Cummings SR, Browner WS, Grady DG, Newman TB, editors. Designing clinical research. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2013. p. 14-22.
9. Diabetes Prevention Program Research G. Long-term effects of lifestyle intervention or metformin on diabetes development and microvascular complications over 15-year follow-up: the Diabetes Prevention Program Outcomes Study. Lancet Diabetes Endocrinol. 2015;3:866-75.
10. Agoritsas T, Vandvik P, Neumann I, Rochwerg B, Jaeschke R, Hayward R, et al. Finding current best evidence. In: Guyatt G, Rennie D, Meade M, Cook D, editors. Users' guides to the medical literature: a manual for evidence-based clinical practice. 3rd ed. New York: McGraw-Hill; 2015.
11. Richardson WS, Wilson MC, Nishikawa J, Hayward RS. The well-built clinical question: a key to evidence-based decisions. ACP J Club. 1995;123:A12-3.
12. Fineout-Overholt E, Johnston L. Teaching EBP: asking searchable, answerable clinical questions. Worldviews Evid Based Nurs. 2005;2:157-60.
13. Browner WS, Newman TB, Hulley SB. Getting ready to estimate sample size: Hypotheses and underlying principles. In: Hulley SB, Cummings SR, Browner WS, Grady DG, Newman TB, editors. Designing clinical research. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2013. p. 43-53.