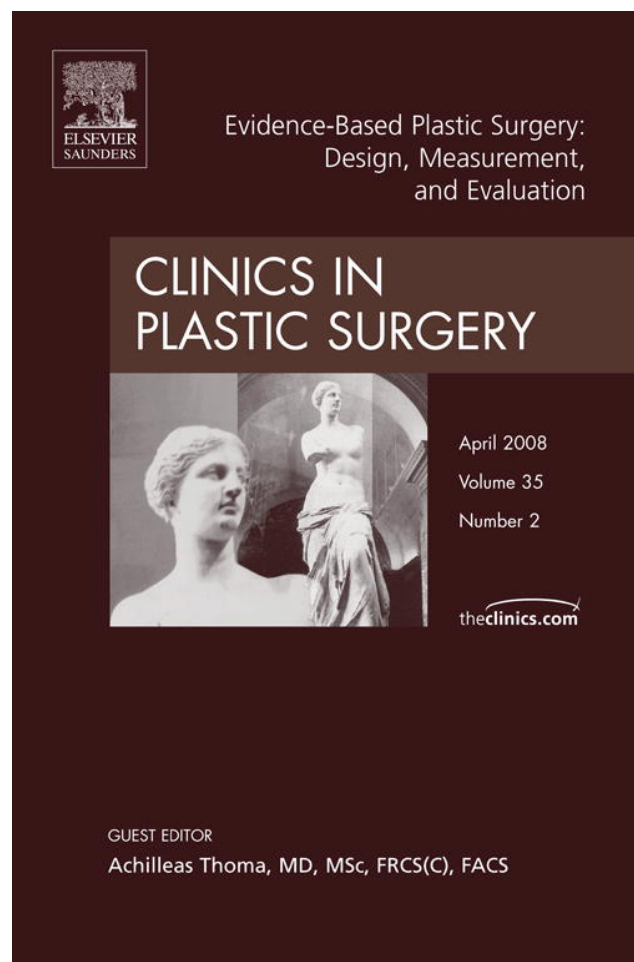


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# Forming the Research Question

Achilleas Thoma, MD, MSc, FRCS(C), FACS<sup>a,b,c,\*</sup>, Leslie McKnight, MSc<sup>b</sup>,  
Paula McKay, BSc<sup>d</sup>, Ted Haines, MD, MSc, FRCPC<sup>a</sup>

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In clinical practice, when doing rounds with residents, or in academic rounds, journal clubs, or clinical conferences, questions are frequently raised for which clinicians don't know the answer. If a literature search of various electronic databases does not provide the answer, and the question is believed to be clinically important, this may be the impetus for a research project. Some of you who are working in academic centers may encourage your resident or fellow to pursue a research project and find the answer to this question. However, the support provided to the resident or fellow may be variable, depending on your own circumstances. It can vary from minimal to exemplary support from a well-defined, organized research team that provides biostatistical and methodologic support. If the support is minimal, it is highly unlikely this research will lead to meaningful results. On the other hand, support within "a well greased research group" makes it more likely that the effort will lead to meaningful findings and culminate in one or more publications.

(See the article by Thoma, Haines, Duku, McKnight, and Goldsmith in this issue.)

The most important precondition for performing a clinical research project in plastic surgery (or any other surgical subspecialty) is the need to ask the "right question." Although this might seem to be an easy task, in truth it requires a lot of effort and hard work. It may take up to a year or more before a clear research question emerges. However, when the question is finally formulated, much of the work entailed in the project has already been done.

## Identifying clinically relevant questions

Before beginning a research project, it is important to consider what types of questions are worth addressing. Investigators undertake a research question because they are not happy with the outcomes of a particular surgical intervention or approach to a clinical problem. The intervention question should be of importance to the patients

<sup>a</sup> Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton Health Sciences Centre, 1200 Main Street West, Hamilton, ON L8N 3Z5, Canada

<sup>b</sup> Department of Surgery, Division of Plastic Surgery, McMaster University, St. Joseph's Healthcare, 50 Charlton Avenue East, Hamilton, ON L8N 4A6, Canada

<sup>c</sup> Surgical Outcomes Research Centre (SOURCE), McMaster University, St. Joseph's Healthcare, 50 Charlton Avenue East, Hamilton, ON L8N 4A6, Canada

<sup>d</sup> Department of Surgery, McMaster University, 293 Wellington Street North, Suite 110, Hamilton, ON L8L 8E7, Canada

\* Corresponding author. 206 James Street South, Suite 101, Hamilton, ON L8P 3A9, Canada.

E-mail address: athoma@mcmaster.ca (A. Thoma).

because it may improve pain or ability to return to gainful employment, or improve their quality of life overall. Questions that need to be addressed are ones that are clinically relevant (**Box 1**).

Research questions may lead to solutions to clinically important problems because, from the societal perspective, current surgical interventions consume significant health care resources. Even if they do not consume significant resources singly, if they are very common, cumulatively they may do so. For example, a hand transplant may consume large health care resources, but if it is performed infrequently, then it will be of no great consequence to the society. On the other hand, hand transplantation costs at the societal level may be dwarfed by a procedure that is less expensive at the level of the individual case, such as an endoscopic carpal tunnel release (ECTR), which because of its frequency cumulatively may cost more to the society. Therefore, a research question on the effectiveness of ECTR, rather than hand transplantation, may be more appropriate in terms of societal impact. Questions that do not address a significant burden in terms of cost, prevalence, or severity should not be considered as the motivation for clinical research activity, as they consume time, energy, and resources which could be expended more efficiently in worthwhile projects. This decision, however, requires judgment and may even require expert consensus. In other words, the difference between a clinically important question and a trivial one may not be apparent to a novice investigator. The pursuit of scholarship, a mentorship period, or an attachment to a research group will enable a young investigator to learn how to ask the important questions.

To formulate a proper clinical research question, the investigator (who may be a surgical resident, fellow, or surgeon) must have extensive knowledge of the subject matter he or she is investigating. In other words, he or she “must know the boundary between current knowledge and ignorance” [1]. The researchable question comes from finding the “cutting edge” of knowledge for a health problem you are familiar with [1]. Before embarking on the

#### **Box 1: Reasons to pursue a clinical research question**

- The intervention is novel
- The intervention consumes large health care resources
- There is a controversy on the effectiveness of the novel procedure (as compared with the existing procedure)
- There is a large cost difference between two prevailing interventions

research project, it is important to summarize this “cutting edge evidence” in the form of a systematic review (see the article by Haines, McKnight, Duku, Perry, and Thoma in this issue).

For example, one clinical question that arose in the authors’ surgical group was whether ECTR was more effective than open carpal tunnel release (OCTR) for the treatment of carpal tunnel syndrome. Although the authors were performing both techniques in our clinical practice, we were uncertain that ECTR was more effective than OCTR. To formulate the research question, we performed an extensive literature search on the subject and familiarized ourselves with the current evidence. Only when we thought we had found the “cutting edge” of knowledge on the subject did we then feel comfortable developing our research question [2]. This scholarship allowed us to carry out a research project, in this case a meta-analysis, designed to determine whether ECTR was more effective than OCTR [3]. The findings from one research project may lead to other questions as well, providing the basis for further research. In the case of ECTR, we wanted to know if this novel technique was a cost-effective procedure, leading us to an economic evaluation of ECTR versus OCTR [4].

#### **Initial groundwork for research question formulation**

Before beginning the process of explicit formulation of the research question, it is important to consider several factors, bearing on whether the project will be practicable [5]. These include: (1) the plausibility of the question (whether or not it is answerable); (2) the feasibility of the proposed design to answer the question; (3) the support you expect to obtain from your surgical colleagues; and (4) the resources available to you.

#### **Plausibility**

When evaluating the plausibility of a research question, it is important to consider whether or not the question is answerable. To determine plausibility, one must have a thorough understanding of the anatomy, biology, physiology, and prevalence of the problem. In short, the question being asked should be within the realm of the plastic surgeon’s expertise. For example, it would not be plausible for a clinical investigator to examine the outcomes of reconstruction of the congenitally absent ear in a parallel randomized controlled trial (RCT) comparing the Nagata technique [6,7] with the genetic engineering method, because the genetic engineering methods are not advanced enough at this point in time to regenerate an acceptable ear.

### **Feasibility of the research design**

Evaluating the feasibility of a question involves determining whether the study design chosen is one that can potentially answer the research question. There is no such thing as one best study design; the best study design will depend on what the question is. For example, it would be fruitless to attempt to answer the question of whether smoking affects the short-term survival of replanted digits with an RCT design. The main barrier to using this design is that smoking is a harmful activity. Ethically, investigators cannot randomize patients to either Group A: continue smoking, or Group B: non-smoking after replantation of digits. For questions of harm, appropriate study designs include case-controlled studies and cohort studies (see the article by Sprague, McKay, and Thoma in this issue).

Another example of a hypothetical research question that may not be feasible to answer is whether the supramicrosurgical reconstruction with a periumbilical abdominal flap is superior to the deep inferior epigastric perforator flap in breast reconstruction [8]. Possible barriers to answering this research question could be: the investigators don't know how to transfer a flap with a 0.8-mm luminal diameter of the vascular pedicle; the investigators don't have the required delicate instruments to perform the supramicrosurgery; and the quality-of-life scales that are available may not be sensitive enough to capture the differential effect of the competing interventions.

Another example raising issues of feasibility would be a project in which a clinical investigator intends to perform an RCT comparing the use of intermittent lower extremity pump versus low molecular heparin in preventing fatal pulmonary embolism in cosmetic abdominoplasty. Fatal pulmonary embolism in cosmetic abdominoplasty is a very rare event. As the frequency of the "end points" is a critical factor in the sample size calculation, the rarity of the target event means that the investigator will require a sample size measured in thousands of patients, making it unlikely that he or she will be able to answer the proposed question.

Most clinical research is incremental in nature. The more research that has been done previously, the more investigators can do presently. If there are big gaps in knowledge, it may be prudent to start with a simpler and less expensive study design, such as a case series or cohort study (lower level of evidence), and advance from there. The appropriate time to perform an RCT (higher level of evidence) comparing two surgical interventions is when a novel surgical intervention has entered the main stream of surgery and challenges a prevailing one

(see the article by Thoma, Sprague, Temple, and Archibald in this issue).

### **Support**

The support we expect from our colleagues is another important consideration when evaluating a proposed research question. Because most plastic surgeons are unlikely to have a sufficient number of patients with the condition of interest to meet the sample size requirements, investigators frequently rely on their colleagues to contribute cases. We may tempt them by making them collaborators in research design and interpretation and coauthors in future publication. Unfortunately, many plastic surgeons are entrenched into their beliefs that their preferred technique is the only one that works. For example, in the authors' division, we encountered resistance in persuading some of our colleagues to participate in an RCT comparing intramuscular versus submuscular transposition of the ulnar nerve at the level of the elbow after electromyography-proven clinical entrapment neuropathy of the ulnar nerve. While initially enthusiastic about participating in the study, some of them were subsequently unwilling to submit their patients to randomization.

### **Resources**

The financial resources available for the project are also crucial to the ultimate completion of the study. It is important that a realistic budget be considered, and that the study commence only after funding from local or peer-reviewed grant competitions has been secured. It would be a mistake to commence the project without the funds required to meet its ongoing needs, such as support for a study coordinator.

### **Formulating the final research question**

When formulating the final research question, the investigator should, in general, aim to ask a "foreground" question as compared with a "background" question. Background questions have three essential components: a question root (who, what, where, when, how, why) together with a verb and a disorder, or an aspect of a disorder of interest [9]. For example, a background question would be: "what complications can occur with the free transverse rectus abdominis musculocutaneous (TRAM) flap?" or "why does the TRAM sometimes suffer necrosis?" These types of questions seek to increase basic or background understanding about the disorder of interest.

Foreground questions, on the other hand, are more directly applicable to practice, because they ask specifically how to manage patients. To

formulate the final, well-constructed clinical question, five elements, often captured by the acronym PICOT, need to be incorporated [10].

- P: Describe the Population or Patients relevant to the question
- I: Define the surgical Intervention
- C: Define the Comparative intervention
- O: Describe the Outcomes of interest, and
- T: Define the Time horizon for measurement of the outcome.

When defining these elements of PICOT, it is important to be specific. The population should briefly and precisely describe a specific group of patients. Basically, the investigator is asking, "How can I describe a group of patients similar to mine?" For example, in a research project on carpal tunnel release, an investigator may consider excluding only patients with handwork exposure, or may decide to allocate them to a subgroup of the study.

When defining the intervention, the investigator must determine the main intervention, prognostic factor, or exposure he or she is interested in. For example, the investigator may be interested in the effectiveness of the ECTR versus OCTR. As there are many variations of the ECTR release, the investigator needs to be specific about which one he intends to use. For example he may decide to consider the Agee and colleagues [11] endoscopic carpal tunnel release and not the Chow technique [12]. The comparison is then defined as the main alternative to the intervention. In the case of a surgical intervention, this may be an alternative surgical technique or perhaps conservative management.

The comparative intervention to the ECTR may be the OCTR. Here there are various techniques, such as the classical approach, with a long incision from the wrist crease to the proximal palmar crease or very small incisions over the carpal tunnel area (1 cm–2 cm). Again, the investigator needs to specify which of these variations he or she is using.

When defining "outcomes," investigators are asking, "What can I hope to accomplish, measure, improve, or affect?" For any given plastic surgery problem, there are numerous clinically relevant outcomes. Therefore, it is important to be specific when selecting which outcomes are relevant to the question. For example, when considering the outcomes of carpal tunnel release, the investigator may be interested in return to work of specific ergonomic characteristics, return to activities of daily living, pain control, or adjusted quality-of-life years. The choice of outcome measures should consider the relevant perspectives of, for example, surgeon, patient, society, hospital, or primary payer. The surgeon may consider a successful flap as the primary outcome measure, whereas the patient

would consider improvement in quality of life an important outcome. It is important to consider all outcomes relevant to the intervention, from as many perspectives as feasible (see the article by Thoma, Strumas, Rockwell, and McKnight in this issue).

Time horizon refers to the most appropriate time to measure the outcome of interest. The outcomes may be associated with different time horizons, and the time horizons require consideration of whether the investigator is interested in short, intermediate, or long-term follow-ups. For example, a digital replant may be a success at the short follow-up of 3 weeks in terms of survival, but at the long-term follow-up, it may be considered a failure if the digit becomes nonsensate and stiff, and hinders the patient from returning to work at a year's time. There should be consensus among the research team as to when a particular outcome should be measured.

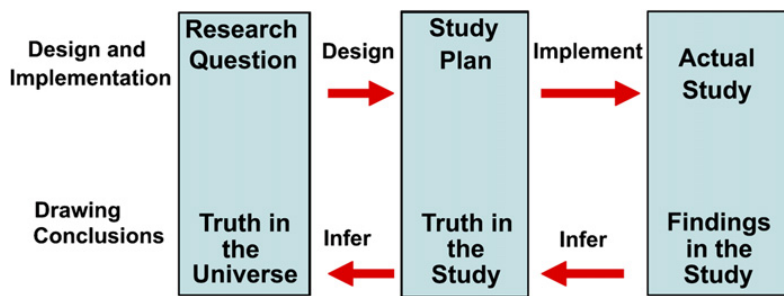
Recently, the authors' research group wanted to determine whether the superficial inferior epigastric artery flap was more cost-effective than the deep inferior epigastric perforator flap in postmastectomy reconstruction. For this investigation, the essential elements of the question were as follows:

- P: The population of interest was all patients who underwent postmastectomy reconstruction
- I: The surgical intervention being studied was the superficial inferior epigastric artery flap
- C: The comparative surgical intervention was the deep inferior epigastric perforator flap
- O: The outcomes of interest were cost-effectiveness and health-related quality of life
- T: The time horizon was the patient's remaining life

This yielded the following research question: *In postmastectomy patients undergoing reconstruction, is the superficial inferior epigastric artery flap more cost-effective than the deep inferior epigastric perforator flap?*

The research question guides the literature search, protocol development, and conduct of the study. Thus, a well-defined question will serve as a reference point throughout the study. However, the research question is but one aspect of a larger iterative process. This iterative process is shown in Fig. 1 [13].

There is a tendency among clinical investigators to ask multiple questions in a clinical study. It is important to understand that all the primary and secondary questions need to be asked up front. This ensures that the questions are hypothesis driven (ie, based on predictions of what will happen) rather than data driven (ie, made up after the study results are in, especially to explain findings that may well be simply the play of chance) [1].



**Fig. 1.** The iterative research process. (From Hulley SB, Cummings SR, Browner WS, et al. *Designing Clinical Research*, 2nd Edition. Philadelphia: Lippincott Williams & Wilkins, 2001; with permission.)

The crucial distinction between the primary and the secondary questions is that only the primary question will be able to provide a definitive answer. This is because the sample size of the study will be based only on the primary questions. Any answers obtained from the secondary questions need to be considered as tenuous or hypothesis generating. They may need to be addressed in another study, in which they become the primary questions. The authors' recommendation is to simplify the surgical research project and consider relying on only one well-developed primary question.

### Summary

The key points to remember when formulating the research question are:

1. Focus on a single primary research question; this will determine the calculation of the sample size of the study (see the article by Thoma, Sprague, Temple, and Archibald in this issue).
2. Develop the primary research question in a structured manner (PICOT formulation).
3. Perform a systematic review to reach the "boundary of knowledge" on the subject you are investigating (see the article by Haines, McKnight, Duku, Perry, and Thoma in this issue).
4. Gain an understanding of clinical research methodology, find a mentor, and preferably work within a research group (see the article by Thoma, Haines, Duku, McKnight, and Goldsmith in this issue).
5. Ensure that a biostatistician is involved early on in the formulation of the question and the execution of the study.

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