Chapter 1
The Research Question and the Hypothesis

Peter R. Nelson

The Research Question

Getting Started

When first contemplating a clinical trial idea, one should start with a brainstorming session. This is your chance to have fun and simply assemble an inclusive list of ideas that come to mind. These ideas have likely developed from thoughts and experiences over time and may be on note cards or files that have accumulated on your desk or computer in need of some organization. Or, they may be the result of setting aside time dedicated to coming up with an idea either alone or with your research team. For most, it is probably a combination of both. Either way, they may all focus on one disease process with slight variations in concept, or they might cover a wide array of problems within your specialty and likely come from many different sources. Ideas often result from a recent patient, case, or series of cases. They may be the response to a single recent difficult case in which you might have contemplated the need for a new device or a novel application of an existing device. They may arise from hearing a recent presentation at a local grand rounds or at a regional/national scientific meeting or from a recent publication. They may arise from your very own translational research activity. Ideas may also simply arise from idle conversation with a partner or colleague in which you feel there might be a better, safer, or more efficient way to manage a particular clinical problem. And, finally, in this technological and social media age, you might even ask the voice inside your smartphone "What is a good research question?". Try it.

Examples of research ideas that are represented in the referenced clinical trials may have started with simple questions like:

P.R. Nelson (✉)
Surgical Service, James A. Haley VA Medical Center, 13000 Bruce B. Downs Boulevard, Tampa, FL 33612, USA
e-mail: peter.nelson@va.gov

K.M.F. Itani and D.J. Reda (eds.), *Clinical Trials Design in Operative and Non Operative Invasive Procedures*, DOI 10.1007/978-3-319-53877-8_1

- Is total mastectomy necessary? [1]
- Is arthroscopy any good? [2]
- Should we give up on open hernia repair? [3]
- Is surgery necessary for gastroesophageal reflux? [4]
- Can we do endovascular aortic aneurysm repair (EVAR) without incisions? [5]

These ideas start out unrefined, but represent the real thought or feeling you have in reaction to a vexing problem.

Does Your Idea Show Promise?

Before you get too far into thinking about your idea, make an early assessment as to whether or not it is a "good one." This means you need to ask yourself questions like "Is the idea timely and relevant?", "Is the question answerable?", "If so, will the answer change clinical practice?"…meaning "Will it have significant IMPACT?", and "Would it be feasible financially to embark on the study?". These checks and balances begin to address whether or not there is biological rationale for your question if needed; if there is clinical relevance of your question and if so, is there sufficient equipoise within the clinical community surrounding the idea; if the results will be generalizable; and if there is sufficient novelty to the idea to promise the delivery of new knowledge from your efforts? Table 1.1 offers a basic ten-point checklist you can run through to quickly test the merits of your idea.

Refining Your Thoughts

If your idea passes this ten-point evaluation, then it's time to really focus in and start formulating it into a formal "research" question. An essential foundation of clinical trial design is the premise that every clinical trial must center around a

Table 1.1 Ten-point checklist to test a research question

· Do I know the field?
· Do I know the literature?
· What areas need further exploration?
· Has sufficient research already been completed in this area?
· Could my work fill a gap in the current understanding?
· If a similar study has been done before, is there room for improvement?
· Is the timing right for this question to be answered?
· Would funding sources be interested?
· Would the target community (i.e., patients, practitioners, health policy makers, etc.) be interested?
· Will my study have a significant impact on the field?

primary question. The primary question, as well as any related secondary questions of interest (see below), should be carefully vetted, clearly defined, and stated a priori. The primary question should address the key who?, what?, by whom?, when?, how long?, and what result? type questions clearly and succinctly. Therefore, this primary question is the main interest of the trial, whether comparing effectiveness or determining equivalence of two treatments, determining safety and efficacy of a new treatment or procedure, applying existing treatment to a novel cohort of patients or a different disease process, or exploring functional or quality of life impacts of intervention. Logistically this translates into the question being the one that the trial is designed to be capable of answering, the one that the trial is powered to test statistically, and the one that will have the greatest impact following the conduct of a successful trial.

Therefore, the revised versions of the original questions above might start look something like this:

- Can similar results be obtained with breast conservation compared to mastectomy? [1]
- How does arthroscopic surgery impact knee pain and function in patients with osteoarthritis? [2]
- Which is better—open or laparoscopic hernia repair with respect to 2-year recurrence rates? [3]
- How does early laparoscopic anti-reflux surgery compare with optimized medical management for GERD? [4]
- Is percutaneous femoral access comparable to open femoral exposure with respect to overall treatment success following EVAR? [5]

These refined questions now demonstrate clarity in what the researcher is thinking, what will be tested in each of the clinical trials and sheds light on aspects of subject eligibility, what will become the key trial design features, and even what are the critical statistical considerations. Your trial is starting to take shape. Table 1.2 summarizes the key features of the primary research question.

Table 1.2 Primary research question

Key features
· Main interest of trial
· Capable of being answered by trial
· Trial powered to answer this question
· May focus on differences between or equivalence of comparison groups
· States the hypothesis
· Dictates the research design
· Defines the sample
· Identifies the intervention to be studied and the comparison treatment
· Specifies the endpoints/outcomes
· Suggests statistical analytic strategy

Secondary Research Questions

Secondary questions can oftentimes be very important, but at the very least often represent the subtle things that "we really want to know" regarding the treatment of a particular disease process "but were afraid to ask." However, in order to be effective, these questions need to be clearly defined and stated in advance to avoid any question or criticism of post hoc data mining. Secondary questions often dive into more detail within the data generated from a trial and may be aimed at addressing important subgroup analyses, focusing on a single risk factor's association to an outcome, or addressing an alternative, more focused, or less prevalent response variable. However, since these questions are more narrowly focused, the trial is likely not powered to definitively answer them due to the potentially large enrollment that would be required and the statistical challenges that they would present. Therefore, the trialist should avoid the expectation of finding definitive answers to these questions, but should potentially take advantage of the information gained to form the basis for interesting, important future direction for study.

The Hypothesis

The primary research question, once defined, then sets the foundation for subsequent trial design and conduct. First, the primary question must be restated as the primary hypothesis to be tested by the trial. For the researcher, it is more than just simply restating or rewording the question to a statement, but this is where you need to commit to what you think the trial is going to show once it is completed. You need to "pick sides" and define this in advance in a clear statement. The null hypothesis has critical meaning statistically and will be discussed elsewhere, but at this point you need to recognize that it defines that there will be no difference between comparison groups in your trial. Therefore, you need to define whether you agree with this assumption or whether you feel your trial will result in a detectable, meaningful difference for the intervention studied. Importantly, this is another fun part of the process because you eventually get to see if you're "right" once the trial is complete.

For the referenced trial examples, the hypotheses look like this:

- Segmental mastectomy (with or without radiation) provides comparable results to total mastectomy in patients with Stage I and II breast tumors ≤ 4 cm in size [1].
- Arthroscopic knee surgery (i.e., debridement, lavage) will significantly reduce pain and improve functionality in patients with osteoarthritis compared to sham [2].
- Open tension-free hernia repair and laparoscopic tension-free hernia repair are equivalent with respect to 2-year hernia recurrence rates [3].

- Laparoscopic fundoplication can significantly improve outcomes compared to long-term drug treatment for chronic GERD [4].
- Percutaneous femoral arterial access using large bore closure with a preclose technique will provide the same or better results than surgical femoral exposure with respect to vascular complications and overall treatment success following EVAR [5].

Once you've stated your hypothesis, it needs to be testable. This seems implied, but there needs to be clearly defined endpoints and validated measurement tools available to pursue the answer. More on this later.

In addition to the hypothesis, the research question begins to define the other structural components of your trial design. It indicates the type of trial planned whether single- or multi-arm, single- or multicenter, randomized or non-randomized, or explanatory or pragmatic in design, etc. It also begins to define the patient population to be studied and the sample to be enrolled including some direction as to how subjects will be identified, what the control group might look like, and what the initial inclusion/exclusion criteria might look like. It will indicate the intervention to be offered to the subjects and if/how it will be tested for safety, effectiveness, and/or economics. And finally it will define the endpoints and analyses to be used to test the hypothesis and answer the question. These relationships will be developed in the following chapters.

"Practical Exercise"

As a practical exercise, you can use the guidelines put forth in this chapter to identify a research question you are interested in developing. You can then carry this through the entire text and in the end you will have your clinical trial established. One brief example from a vascular surgery perspective could be the treatment of intermittent claudication. Claudication results from the progression of mild to moderate peripheral arterial disease. At this early stage, medical management along with smoking cessation and structured exercise have proved to be effective for upwards of 80% of patients. The Achilles heal of this strategy is the lack of formal programs and the resulting poor compliance with the noninvasive methods in patients without supervision. This unfortunately results in early adoption of invasive intervention with angioplasty/atherectomy/stenting and ultimately the risk of premature acceleration of disease with intervention failure and critical limb ischemia. If one were to develop a research question in this area, he/she might start with:

- Does exercise really help with claudication?

What this question doesn't clearly define are critical concepts like the following. Help? Help how? Help whom? With what degree of claudication? What type of exercise? Within the context of what medical therapy? How frequently?

How intense? How are we going to implement and assess the compliance with exercise? And, how will we determine if exercise actually helps? Therefore, we might refine our question to:

- Do structured walking, stationary bicycle, weight-based resistance, or aquatic exercise offer superior benefit over unsupervised standard care in terms of pain relief, walking distance, and walking duration in patients with peripheral arterial disease compliant with the best medical therapy but suffering from disabling claudication?

Even this question is a little complex since it is potentially asking three questions as to whether the intervention will benefit (1) pain relief, (2) walking distance, and/or (3) walking duration. Therefore, you'd have two options to simplify this issue. First, you could consider a composite endpoint of all three outcome measures together (see Chap. 2). Or, perhaps better, you could determine which of these outcomes you view as having the most critical impact. Let's say you decide that from a patient perspective, pain relief would be considered most important. This would lead to the following primary hypothesis:

- Any structured exercise methodology, when tailored to a specific patient's needs to optimize compliance, will result in overall improvement in pain-free walking ability, when combined with the best medical therapy compared to unsupervised current standard medical practice.

Using this question and hypothesis as a guide, one could begin to envision a randomized prospective clinical trial comparing standard medical treatment consisting of general recommendations for smoking cessation and increased exercise to a structured program with optimized medical therapy, assisted smoking cessation, and structured supervised exercise specifically tailored to an individual patient's comorbidities and physical condition aimed primarily at a pain-free walking goal. Then, the effects of the intervention on walking duration and distance might then be considered the most important secondary questions to ask. Finally, you might then complete the process by considering other secondary questions such as: (1) Will establishment of community-based outreach with long-term monitoring improve compliance and durability of the intervention? and (2) Will patient-specific molecular biomarkers or gene profiles improve traditional clinical prediction models to identify a cohort of subjects in the population that might truly benefit from early intervention? These questions might be more exploratory, but important to pursue as part of this trial at least for proof-of-principle confirmation leading to more detailed subsequent validation trials.

Summary

A clear, thoughtfully designed research question is a critical start to your journey toward a successful clinical trial. You can't answer every question so choose one that can be answered. Once you've defined your primary question, it needs to be

relevant, feasible, and generalizable. Your subsequent trial design depends on this primary question as the one you hope to answer, your hypothesis should then translate directly from the question, and your endpoint(s), patient selection, intervention, and analyses will all follow as the process progresses. It is an iterative process, however, and you should continuously reflect back to the original question as the study evolves to maintain focus. Also keep in mind that the results of clinical trials generally have greater relevance when the design is pragmatic, but don't always answer mechanistic questions, and are often a compromise between the ideal and the practical. In any case, dedicated effort spent at this beginning stage often sets your clinical trial up for success.

References

1. Fisher B, Bauer M, Margolese R, et al. Five-year results of a randomized clinical trial comparing total mastectomy and segmental mastectomy with or without radiation in the treatment of breast cancer. N Engl J Med. 1985;31:665–73.
2. Moseley JB, O'Malley K, Peterson N, et al. A controlled trial of arthroscopic surgery for osteoarthritis of the knee. N Engl J Med. 2002;347:81–8.
3. Neumayer L, Gobbie-Hurder A, Jonasson O, et al. Open mesh versus laparoscopic mesh repair of inguinal hernia. N Engl J Med. 2004;350:1819–27.
4. Grant AM, Wileman SM, Ramsay CR, et al. Minimal access surgery compared with medical management for chronic gastrooesophageal reflux disease: UK collaborative randomized trial. Br Med J. 2008;337:a2664.
5. Nelson PR, Kracjer Z, Kansal N, Rao V, Bianchi C, Hashemi H, Jones P, Bacharach JM. Multicenter, randomized, controlled trial outcomes of totally percutaneous aortic aneurysm repair (The PEVAR Trial). J Vasc Surg. 2014;59:1181–94.