THE RESEARCH QUESTION

From the Therapy chapter for the 3rd edition of Clinical Epidemiology, by DL Sackett
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Research Question Check List:

1 ❍	Involve every potential collaborator (plus some critics and consumers) in hammering out your trial question. Don't rush it.
2 ❍	Decide where to site your question along the explanatory – management continuum.
3 ❍	Make sure that your question includes the relevant Persons, the Intervention, the Comparison intervention, the key Outcomes, and the Target of the trial = "PICOT"
4 ❍	Consider the impact of your question in each subsequent step in the trial design and execution.

Although the RRPCE question never appeared in the "PICOT" form in 1969, it can be stated as follows: "Among highly compliant out-patients with TIAs (or minor completed strokes), can aspirin (325 mg. qid) or sulfinpyrazone (200 mg. qid), singly or in combination, when administered by expert neurologists, reduce the risk of subsequent stroke or death better than placebos (and with an acceptably low rate of adverse drug effects)?"

However, this was the first RCT designed by our team and submitted to the Canadian Medical Research Council. To convince them that we could pull off this first-ever multicentre Canadian trial, we proposed a two-stage trial. The first stage added a more frequent but less serious outcome, continuing TIAs, so that our PICOT question ended: "….. can these drugs reduce subsequent TIA, stroke, or death?"

Once we convinced the MRC that we were capable of running the trial, we shifted to the second stage and restricted our question to the outcomes to stroke or death. In one of life's ironies, we graciously shared our protocol with a Texan who used it to test just aspirin and published [before us!] a positive result for TIAs but an indeterminate one for stroke or death.

As it happened, the first draft of our PICOT question confined the intervention to a single drug, sulfinpyrazone. But, Mike Gent and I argued that a factorial design could test two drugs in the same trial. When the other PIs and participating neurologists finally accepted our argument, we added aspirin to the trial. (Imagine our disappointment if we'd stuck with our initial, single-drug RCT of sulfinpyrazone, which turned out not to benefit our patients.)

This is the most important section in this chapter.

That's because the question drives the entire trial. As you will see throughout this chapter, it is the question that specifies which sorts of individuals will receive which sorts of interventions (and ancillary care) at which sorts of sites (primary or tertiary care) from which sorts of clinicians (average ones or experts) with what sort, length and intensity of follow-up, and with what sorts of mechanisms for identifying which sorts of events (both good and bad).

As you may already have recognized, the RRPCE question describes an explanatory trial: "When given by experts to highly compliant patients, CAN these drugs do more good than harm?" (NOTE: if the terms "explanatory" and "management" are new to you, take a side-trip right now to page xx.) As you'll see throughout the rest of this chapter, the fact that we were posing an explanatory question dictated our decisions at every subsequent stage of the trial's design, planning, execution, analysis, and interpretation.

To help you focus on the tactics of designing and executing an RCT, I'll open each section with a "check-list" of issues you'll need to consider and resolve.

1. Involve every potential collaborator (plus some critics and consumers) in hammering out your trial question. Don't rush it.

In hammering out your PICOT question, you need to involve every potential collaborator (methodologists, relevant bench scientists, and clinicians, plus potential collaborators in every study center), plus some critics who disagree with your question, plus some of the patients and policy-makers who will have to implement and pay for your results. By not rushing prematurely to your question's final wording, you will reap at least two benefits before you start. First, as you saw in the RRPCE scenario, you can avoid the indeterminate result that would occur if you studied the wrong treatment, or just one of several promising treatments. Second, when potential collaborators join the process of hammering out the study question, the study becomes "theirs" rather than "yours," and they are much more likely to expend the time and energy necessary for recruiting, caring for, and following sufficient numbers of study patients.

Third, it's wise to discuss your question with those who think you're asking the wrong one, or one that's already been answered. They may be right, in which case you need to revise your question. Ideally, your revisions will convert your critics to your supporters. But if your critics are wrong, you can build the refutation of their criticisms into the way you conduct and report your trial.

Fourth, you should discuss your question with some of the patients who would be offered your experimental treatment if it proved efficacious. They can give you a good idea of the acceptability of your experimental regimen. Even more important, they may suggest some outcome measures – especially around function and quality of life – that will add greatly to the power and persuasiveness of your results.

Finally, especially a positive trial would call for changes in facilities, staff, drug budgets, or clinical organizations, you'd do well to discuss your question and seek ideas from the relevant managers.

2. Decide where to site your question along the explanatory – management continuum.

As I've already said, and as I'll show you on pages xx-xx, whether you ask your question in an explanatory mode ("Can the intervention do more good than harm under ideal circumstances?" = efficacy) or a pragmatic one ("Does the intervention do more good than harm under the usual circumstances?" = effectiveness) determines every subsequent step in the design, execution, analysis, and interpretation of your trial. It determines not only your approach to the recruitment of both patients and clinicians. It also determines your choice of regimens, events, analyses, and interpretations.

Our question in the RRPCE scenario resided toward the explanatory end of the continuum. As a result, we not only anticipated readers' reactions to our final report, but also were ready to respond to them. For example, we weren't surprised when readers wondered whether aspirin could also be effective when applied by non-specialists in primary care settings. Our response proposed that most first trials of a health care intervention will, and ought to be, towards the explanatory pole[1], for two good reasons. First, although the cost per patient is usually higher in explanatory trials, their smaller sample sizes usually make them less expensive to run and quicker to produce results than management trials. Second, when an explanatory trial result rules out any humanly important benefit, you can close the books on that intervention.

If, on the other hand, one or more explanatory trials have already shown your treatment to be beneficial under ideal conditions, you can move along the spectrum toward its management pole. Indeed, you may even create one of the "large, simple trials" that are described on pages xx-xx.

3. Make sure that your question includes the relevant Persons, the Intervention, the Comparison intervention, the key Outcomes, and the Target of the trial = "PICOT"

Forcing yourself and your collaborators to specify each of the PICOT elements refines the process of translating an initial idea into a viable study:
Persons: what sort of patients or other persons, from which sources, with what qualifying features, and undergoing which pre-admission determinations of things like compliance with health recommendations?
Interventions: of what sorts, at what doses, administered by whom, where, and with what sorts of monitoring for compliance and side-effects?
Comparison intervention: again, of what sort (placebo or active), at what doses, administered by whom, where, and with what sorts of monitoring for compliance and side-effects?
Outcomes: both good and bad, of what sort, when, defined how, and ascertained and adjudicated by whom?
Target of your trial: are you asking whether the experimental intervention is "superior" to the control intervention, or "non-inferior" to it but preferable for some other reason such as safety or cost? (If these terms are new to you, you might want to make a side-trip to page xx.)

Almost all collaborators in our RCTs start out disagreeing with us and each other about at least one of these PICOT elements. The earlier you expose these differing opinions, the sooner you will achieve a thoughtful "buy-in" and consensus about "our" trial. This process both deserves and requires a great deal of time. Although my co-authors claim I'm exaggerating, I hold that 1/3 of all the effort in an RCT should go to hammering out the question it is supposed to answer. Along the way, a useful way to tell whether your question remains sensible is to confirm that it (still) can be answered "yes," "no," or with a specific number.

Most of the elements of "PICOT" are self-explanatory, but the "T," the Target of your trial, might not be familiar to you. I'll discuss it in some detail in the second "Principles" offering that follows this section on tactics (page xx). At issue is the direction in which you want to compare your experimental and control interventions, and I'll describe the different targets briefly here[A].

Introducing superiority and non-inferiority trials

Consider the question we posed in the RRPCE study: "….can aspirin or sulfinpyrazone reduce the risk of subsequent stroke or death better than placebos?" We asked whether either or both drugs were superior to placebos, and the direction posed by this sort of question gives it its name: a superiority trial. After our positive RRPCE trial, other investigators conducted a superiority trial to see whether a newer drug (ticlopidine) was superior to placebo.[2]. Again, the answer was yes, but ticlopidine displayed some worrisome side-effects (it wasn't until later that an arguably more appropriate "head-to-head" superiority trial found that ticlopidine was superior to aspirin[3]).

But the target of other trials may be to find out whether a new, experimental treatment is as good as (equivalent), or at least not inferior to some established therapy already validated in a prior RCT.

Finally, some RCTs ask both questions in the same trial. First, is the new experimental treatment superior to established treatment? If not: second, can it at least be shown to "no worse" (non-inferior) than established treatment? For example, some cardiologists thought that a combination of anti-thrombotics might be better, or at least no worse but preferable for other reasons, to a single anti-thrombotic[4]. Sure enough, you needed to treat about 333 patients with the

[A] There's another reason why we use the term PICOT rather than PICO, and it has to do with our Spanish colleagues and the Spanish translation of this book. It seems that "PICO" is what a small Spanish-speaking boy calls his penis.

combination to save one more life at 30-days (the combination wasn't superior to the single drug), but it satisfied their criteria for non-inferiority (and provided some other advantages).

Unless this brief superiority/non-inferiority discussion has told you all that (or more than) you wanted to know about these ideas, you can find more about them, including a graphical way of thinking about them, starting on page xx.

4. Consider the impact of your question in each subsequent step in the trial design and execution.

It is at this stage that methodological purity begins to confront reality. "Ideal" patients are highly compliant, have only the disease of interest and no other[B], and usually can be found in primary care settings. One the other hand, they may be so scarce, so atypical, or so difficult and expensive to identify that it doesn't make sense to plan an RCT just around them. Furthermore, you don't want to attempt a pragmatic, primary care trial of an intervention that is so complex and tricky that generalists can't or won't apply it. Will the outcomes you've chosen require rare or expensive investigations that are not available to most patients? These sorts of confrontations have arisen in the planning stages of every RCT we've ever done. Once again, their discussion and resolution are central to hammering out the study question.

Checklists should be read in both directions

Finally, remember that the Research Question Checklist reads in both directions. Not only does the question determine the methodology at later steps in a trial. So too, the conclusions at each of these later steps should cause you to reverse course and revisit the question you posed at the outset. When there is a mismatch between your question and your methods, then you'll have to revise one (or both) of them. At the end of the day, you will succeed only if you couple the question that you really want to answer to a set of methods that will really answer it.

REFERENCES

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[B] However, patients with no comorbid conditions are relatively healthy, and their low event rates may come back to haunt you. See page xx.