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ASKING THE RIGHT QUESTIONS

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Learning Objectives

- Appreciate the importance of a clear and focused research question
- To be able to use criteria such as PICO (Population, Intervention, Comparison, Outcome) to frame an answerable question
- Understand the need for primary and secondary questions and the process of refinement
- To understand what a hypothesis is and how it differs from the aims and objectives of a study
- Be aware of over-interpreting the findings, post-hoc assumptions and spurious associations
- Understand the answer and appreciate negative results

Introduction

In health services research, asking the right question is important because everything else hinges upon it, such as your choice of study design, the interpretation of your results and their impact on clinical practice. Often when a researcher is having difficulty with designing the research, it is either because the methodology is inappropriate for answering the question, or the question itself is inappropriate. The focus and nature of these questions vary according to the perspective of the individual asking them. Patients and carers focus on issues often of immediate personal relevance such as the relief of symptoms or where to get treatment; clinicians bear in mind the broader issues, taking into account, for instance, the range of interventions available and the wider implications of choosing different treatments such as costs; whilst funders and researchers seek justification for an intervention and whether clinical care can be improved and/or money saved with it. For example, if a child had a sore throat, their question may be: 'When will I feel better so that I can play out?' The parent may ask: 'Should I take him to the doctor's?' The doctor may ask: 'Is it a bacterial or viral infection? Are antibiotics needed?' The funder of the health care may ask: 'Can we afford to routinely analyse throat swabs?' The researcher may then ask: 'Can we formulate an algorithm from signs and symptoms of illness to predict hospitalisation from bacterial infection?' Given the different perspectives, all of these questions are equally valid.

Questions do not just vary depending on the perspective from which they are being asked; they can often be multi-layered and interdependent. Breaking the overarching question down into what is known and unknown will help, but this is partly reliant on one's own knowledge already and the lengths one is prepared to go to read and critically appraise the peer-reviewed published literature on that topic (please see Chapter 3: 'Critical Appraisal'). With the exponential growth in the number of medical journals in recent years (Smith, 2006), online literature searching is now an important element of the clinician's armoury and it has become relatively easy to find out if a particular question has already been asked in full, or in part, and whether the methodology was robust enough to inform clinical practice (please see Chapter 2: 'Finding the Evidence to Support your Research Question'). Although this step seems initially a lot of effort, several purposes are served by it; it increases your knowledge of the field in general, starts to delineate the frontiers of what is known and not known at the present time and thus helps develop or refine your research question. Your literature search will also provide references for when you start to write up your protocol, grant or ethics applications, or findings, and can provide you with templates of good-quality research design. It is important to distinguish between when there is no evidence because a study has posed the question and come up with a negative result and no evidence because no study has actually asked the question yet. However not every question requires evidence. There has never been a single randomised controlled trial proving that parachutes are a safe intervention when you jump out of a plane at a great height (Smith and Pell, 2003) for example, but that does not mean we should not use them!

The culture of enquiry and collecting evidence in clinical practice has moved through a series of stages from early descriptive pioneering work on individual patients, such as the work of Edward Jenner who tested the smallpox vaccine initially on one person in 1796, through to more population-based evaluative studies in recent times (please see Chapter 10: 'Epidemiology'). The importance of evidence-based medicine has slowly gained momentum, challenging the idea that health care professionals, by the simple virtue of reading medical texts and their own anecdotal experience, have some sort of unique insight or unquestionable 'clinical judgement' into the social causes of disease (*The Lancet*, 1995). In 1747, the Scottish physician James Lind conducted the first clinical experiment, in which he researched treatments for scurvy. The results clearly showed that including citrus fruits in the diet produced the best recovery, but the medical establishment and Lind himself was wedded to the idea that scurvy was a disease of putrefaction, curable by the administration of elixir of vitriol (sulphuric acid) and other remedies designed to 'ginger up' the system such as mustard, or horseradish. It was another 50 years before the British Admiralty accepted the evidence of the first trial and recommended that lemon juice should be issued routinely to the whole fleet (Vale, 2008).

With the emerging disciplines of statistical techniques in the early part of the 20th century and computing technology in the latter, evidence-based medicine has thrived and become more sophisticated in terms of research designs and methodologies, together with an increased understanding of the complexity of the different issues involved in the research process, for example, sources of potential bias, missing values, etc.; However in essence, evidence-based medicine is founded on a simple bottom-up approach that integrates the best external evidence with individual clinical expertise and patient choice (Sackett et al., 1996), and which begins with a clinical question. It might be a new treatment that needs testing, a particular problem that needs solving or a more general desire to improve the patient's well-being.

What is a good question?

A good question in health services research is one that is important and which will give a meaningful answer. For example, there would be no importance in researching a superseded medication or technique, or researching something when the definitive answer for it already exists from previous research. For people new to research, many of their initial questions are aimed at solving the problems of the world, which by their very nature are largely unanswerable. Although this enthusiasm is commendable, there needs to be a degree of 'funnelling' whereby a large topic is broken down into smaller more manageable ones, to generate an answerable clinical research question. By breaking the topic down to answer individual key questions elegantly and robustly, your results will remove the uncertainty about those parts, and so the knowledge about the larger topic slowly moves forward. An answerable question in research terms is one which seeks specific knowledge, is framed to facilitate literature searching and therefore follows a semi-standard

structure (Bragge, 2010). This process is critical because if a methodological approach is used to address a question that is too broad, lacks rigour, would be difficult to rerun or refine, and would create inefficiencies once the research process is under way, it would fail to answer the research question. Conversely a question that is too narrow may generate more questions than answers, findings would be less generalisable and therefore not worth the time of the researchers or the money of the funders.

It seldom happens that a researcher gets the question right first time. Indeed, most research questions undergo a series of iterations before the team are certain that the question they have framed is appropriate and timely. After reviewing the literature or discussions with colleagues and patients, aspects of your research question may change, such as the population, intervention or comparison. This sort of refinement and transformation of the question is common but does not happen quickly. Discussions are often frequent and lengthy before the whole team is agreed that they have an important and answerable question. Do not underestimate the importance of involvement of patients and public in this step, as your research needs to be meaningful and acceptable to those whom it will affect (please see the case study and Chapter 16: 'Patient and Public Involvement').

Case study

A study is being conducted regarding the effectiveness of steroids in children with asthma. The research team identified 'coughing at night' and 'days lost at school' as important outcomes to be measured. However, after discussing the study with parents of these children at the planning stage, it was revealed the most serious concern of the parents was the effects of long-term steroid use. Thus, research about the effectiveness of steroids would be redundant as, regardless of their efficacy, the intervention would not be acceptable to the parents of the children. The research team therefore refocused their question, to ascertain the minimum dose regimen of steroids and its relationship to efficacy. Due to their involvement strategy, they know that this information would be welcomed by the patients and their parents, and therefore more likely to influence clinical practice.

Research question criteria

There have been several criteria formulated to ease the process of drafting a good research question, such as the FINER criteria (Hulley et al., 2007):

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| Feasible | Adequate number of participants available and adequate skill mix in the research team. Also is the project manageable within the specified time frame, and budget? |
| Interesting | The answer will be interesting to other researchers in the field, health professionals and patients. |

Novel	Confirms, refutes or extends previous findings (whether yours or published).
Ethical	No reason why ethical approval could not be obtained.
Relevant	To current scientific knowledge, policy, future research and patients.

Whereas the FINER criteria outlines the important aspects to consider in general, the PICO criteria; Population, Intervention or Indicator, Comparison (if relevant) and Outcome (Richardson, 1995) is useful for the development of a specific research question. A clear, answerable research question has three or four of these PICO components. The general format of a PICO question is: 'In [Population], what is the effect of [Intervention] on [Outcome], compared with [Comparison]?'

- P:** Population/Patient/Problem
I: Intervention or indicator
C: Comparison/control (if relevant)
O: Outcome of interest

Your population is who your research will affect. Be precise, because if you put your sample as 'asthmatics', for example, this is a huge and variable population. However you may particularly be interested in asthmatics who smoke. This therefore is your population. The intervention is whatever treatment it is you will be studying, whereas an indicator is whatever risk factor you are interested in, such as smoking as the indicator in your study of asthma (for more discussion on risk factors please see Chapter 10: 'Epidemiology'). A comparator or control depends upon what type of study you are conducting, is there an alternative to your intervention/indicator? For example, you could compare asthmatics who smoke with those who do not, or from the previous example, you could compare outcomes from different steroid regimens. The outcome is what you hope to accomplish with this research, such as asthma control. In general, the more precise you are in defining the components, the more focused the study.

Case study

A cardiologist proposes the initial simple question: whether placing antibiotic sponges into the chest cavity at the end of heart surgery will prevent infections?

After discussion with various groups, amendments to the question are made:

- 'heart surgery' is too broad and it might be sensible to pick a specific procedure;
- different types of sponges are on the market so it is decided to stick to one type;

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- the sponges are not free, so cost and cost-effectiveness need to be considered;
- getting out of hospital and home as soon as possible is seen as a priority by patients.

Thus the question became: in patients undergoing coronary artery bypass grafting, what is the effectiveness and cost-effectiveness of inserting a gentamicin-impregnated collagen sponge into the chest cavity at closure on wound infection rates and length of stay?

Thus the PICO format for this question would be:

- P: Patients who are undergoing coronary artery bypass grafting
- I: Gentamicin-impregnated collagen sponge
- C: No gentamicin-impregnated collagen sponge
- O: Wound infection rates and length of stay

Clarity in articulating the question not only helps you in designing the research, but helps the reader to understand what the research is about and what to expect upon further reading about the project. Different question types can follow similar formats, but the key principle in the criteria approach is that important components of the question are identified and defined (please see Chapter 2: 'Finding the Evidence', for examples of criteria for other research designs). Using a strategy such as this to break down the question determines the question type and thus determines the most appropriate study design to answer it.

Mnemonics like PICO are used in an evidence-based literature search, and in the conduct of a systematic review (please see Chapter 14: 'Systematic Reviews'), where the components of the systematic review question will set the criteria for selecting studies to appraise. The PICO components of the question may directly translate into medical subject headings or key words guiding the literature searches. Thus, well-formulated questions are directly linked to the data collection process which will not only help you design your literature search strategy, but also improve the citation rate associated with any ensuing publications stemming from your research.

There is also a wider element to 'framing' a question that goes beyond the particular format used. Often in health services research there is a flux of particular issues that need to be addressed which are sometimes highlighted in the media or manifest themselves in theme-specific calls from funding bodies. The general area of a themed call, for example, obesity, smoking, etc., may be clear to a funder, but by using a framework such as PICO, it allows you to crystallise what you are actually looking at, and how your question relates to those issues/themes and, if appropriate, is framed in order to meet the needs of resolving them.

Primary and secondary questions

The primary question serves as the main focus of a particular study, although it is rarely that only one question is being answered. So, although there are often several questions driving an investigation, there is a need, especially with intervention trials, for one primary question to be resolved. This achieves the required focus in order to design an investigation that will provide a definitive answer for at least one particular question. It also means the primary question can be used to calculate the number of people we might require in some study designs. For instance, a sample size calculation is required in a randomised controlled trial (RCT) in order to obtain sufficient power to test the intervention without oversampling patients and wasting resources and the patient's time (see Chapter 17: 'Sampling'). This calculation is conducted by using an estimate obtained from previously published results which have used the same/similar outcome measure as the one you propose using in your primary question. Alternatively you may have previously gathered the data to inform your sample size calculation from a pilot study, i.e. a small-scale preliminary study to test if the chosen design works. Having several questions, all requiring sample size calculations and then choosing the largest sample calculated to cover all the questions can often be an inefficient approach to use.

In studies, not only is a primary question answered, but often ancillary data are collected and studied to answer secondary questions. The study design is centred on the primary question, and any causal claims of the study are specifically in regards to this primary question, as the main outcome measure will be chosen in order to answer this primary question, and the sample size will be based on this also. Therefore the power of the study is to detect a change in that one main outcome. Secondary questions are generally instrumental in defining future research projects, as they may be based on underpowered samples, due to the fact that the sample size calculation was conducted on another measure. There is an argument, however, that in some intervention studies, especially the more complex ones, the role of secondary questions should be more prominent, especially if the study is powered to adequately test these questions. In observational studies such as case-control or cohort studies (please see Chapter 6: 'Quantitative Methodology') these rules can be slightly more relaxed and the intention is often to test a set of primary and secondary hypotheses.

Number of questions

A common error is overloading a study with too many questions and too much data collection. Life is a fairly complex thing and trying to replicate the many variants by collecting lots of data to answer a battery of questions often leads to simplistic assumptions and an over-reliance on modelling techniques that are not sensitive enough for the task. Given a certain number of observations in a data set, there is an upper limit to the complexity of the model that can be derived with any acceptable degree of uncertainty (Babyak, 2004). Therefore the more questions you are

answering, the more there is likely to be the introduction of error. You also need to be sensitive to the work load of your participants, which in turn can have an effect on your recruitment and retention. For example, if your research regarded post-operative care, not many patients recovering from an operation would like to complete a huge stack of questionnaires for the purpose of your project. In instances like these, obtaining as much data as you can from notes or staff would be preferable to burdening the patient.

Using the study design to simplify comparisons by choosing a particular group of patients or matching on certain factors should reduce the many potential variants, and therefore remove the need to ask questions about that variant, for example, for a case control study investigating cot death you may restrict the age limit from birth to 12 months, as few cot deaths occur after this age, and also age-match the controls so that questions on infant care practices such as breastfeeding take into account the age-related variability of the practice you wish to measure. Modelling the remaining variants will bring further clarity but only up to a point. Sometimes a programme of work is needed which may require more than one study, often building on what is learnt, to provide a more definitive answer. Therefore, if it becomes apparent that you have many research questions, it would be wiser to dissect the work into separate work packages or projects. As a rule of thumb, in qualitative work, you may have one primary, but no more than seven secondary questions (Cresswell, 2009).

Hypothesis, aims and objectives

Qualitative research is often regarded as hypothesis generating, whilst quantitative is regarded as hypothesis answering. Therefore in qualitative work research questions (rather than hypothesis) are posed. However in reality the contrast is not as stark as this. Quantitative studies can often generate many hypotheses whilst qualitative studies can often provide complex answers to questions that are difficult to measure.

Whereas a research question is just that: 'What', 'Why', 'When', 'How', 'Where' and 'Who', a hypothesis is a statement of prediction of what you believe will happen in your study. A simple hypothesis contains one predictor and one outcome, for example, 'patients with Crohn's disease who take the new medication X, will have less abdominal pain than those on usual care'. You could design a complex hypothesis with more than one predictor or outcome variable, for example, 'patients with Crohn's disease who take the new medication X, *and do not have a stressful life*, will have less abdominal pain than those on usual care'. Here there are two predictors, i.e. medication and stress, with one outcome, less abdominal pain. However, complex hypothesis cannot be easily tested, so ideally you would split these hypotheses into two: (i) Those who take the new medication X will have less abdominal pain than those on usual care; and (ii) those who do not have a stressful life will have less abdominal pain.

As you can see, hypotheses can describe the direction of the difference, for example, you are not only expecting there to be a difference in abdominal pain between those who are on the new medication X when compared to those on usual care, but you are predicting a direction, that those on the new medication X will have *less* abdominal pain. This therefore is a one-tailed hypothesis (as you are specifying the direction of the association). If your research question was however, 'Those who take the new medication X, will have a *different* level of abdominal pain compared to those on usual care', this is a two-tailed hypothesis, as you are not predicting the direction of the association, just that there will be one, either negative or positive. A null hypothesis is the statement that there will be no association between the intervention and the outcome, for example, 'Those who take the new medication X will not have a different level of abdominal pain compared to those on usual care.' The null hypothesis is usually the default position when analysing quantitative data, i.e. you set out to disprove the null hypothesis (thereby proving an association).

Your hypotheses should always be drafted prior to the research commencing as this will help prevent too much *post-hoc* (from the Latin 'after this') analysis being conducted, which is the looking at the data after the investigation has concluded for patterns that were not specified *a priori* (from the Latin 'what comes before'). Sometimes described as data dredging, in that the more one looks, the more likely something will be found, i.e. the more comparisons are made, the more likely you will get a type I error, which is the incorrect rejection of a true null hypothesis and instead reporting a false positive finding. For example, if there was a 5% chance of incorrectly rejecting a true null hypothesis per test, if you did 100 tests where the null hypothesis is true for them all, the expected number of incorrect rejections would be 5, with a probability of 99.4% for at least one incorrect rejection! Post-hoc analyses should always be explicitly labelled in any publication or report, the idea being to strike a balance between limiting the chance of obtaining false positives and the use of post-hoc analyses to inform and generate hypotheses that may be worth investigating in the future.

Your research objectives and aims should be linked to your hypothesis or research question. Aims are broad statements about what you hope your research will achieve, for example, to evaluate the efficacy of the new medication X in patients with Crohn's disease. Objectives on the other hand are the steps you need to take in order to meet your aims and so are usually more specific and are usually numbered in sequence, for example, your first objective may be to assess effectiveness of new medication X in lowering abdominal pain in patients with Crohn's disease, as measured with the McGill Pain scale (Melzack, 1975). Objectives should be 'SMART':

- Specific** clear about what will be achieved
- Measurable** you have a measure of when objectives have been achieved
- Achievable** are the objectives feasible?
- Realistic** they can be achieved using the resources available
- Timed** they can be achieved within the timescales specified.

Obtaining a good answer

When you are determining the most appropriate research question/s for your project, you must bear in mind what the answer may be, as this will ensure that you understand what it means to evidence-based medicine, and also help you in the formulation of your hypothesis if you are conducting quantitative work. Moreover, if you anticipate presenting your work at a peer-reviewed conference or publishing in a scientific journal, you may have to defend your work, therefore you do not merely have to know what the answer is, you have to *understand* it and be confident that your project was conducted as robustly as possible.

When writing up the findings of an investigation after a sustained period of often laborious work, there can always be a temptation to overinterpret what has been found. This can be driven by a need to justify the effort, to increase the chances of publication, to argue a particular point for which you are a keen proponent, or simply just from enthusiasm. It should be remembered that publications are peer-reviewed and, if published, the findings will be further scrutinised by a discerning audience. It is far better to interpret your findings with a critical eye and ask 'why might my findings be wrong' and proactively seek alternative interpretations and limiting factors to your findings. In qualitative studies, any derived themes should be substantiated with quotes which will enable your reader to ascertain whether your conclusion is warranted or whether there could be an alternative explanation. In quantitative studies, we rely on statistical inference to determine whether an association or an effect is really 'true', i.e. that our observed association or effect is not due to chance (please see Chapter 19: 'Quantitative Analysis'). If we can say chance is very unlikely, our results are positive, if chance is a distinct possibility, then we report a negative result, like the case study shows.

Case study

Faced with an association between dental flossing and obesity (lack of daily flossing is associated with being morbidly obese), the authors of a cross-sectional survey in the US (Hujoel et al., 2006) adjusted for potential confounding variables (other factors that may be responsible for the association) as they thought the association was spurious. However, even after adjustment for socio-demographic variables, age, sex, smoking status, and diabetes, they still found a dose-dependent relationship between dental flossing and obesity. They explained this as good oral health being an indicator of general health awareness, which is why the participants who floss more are also more likely to have a normal weight.

It is therefore important to not just report the associations or themes found, but also report any suspected error by investigating how robust your results are in terms of the strength of the association, and the consistency with other findings in

the literature. A good answer is not necessarily a positive answer, as long as the study is robust and valid. There are many instances when a failure to demonstrate that a new treatment works can be a benefit to both patients and health care providers. In the case of a new and more expensive treatment, there is a temptation to assume it must be better for the patient. However, if rigorous research demonstrates that the new treatment is no better than the presently used, cheaper one; this will save the health care provider money that can be diverted to more useful treatments. There are numerous examples of interventions that have been routinely performed in clinical practice until rigorous research evidence has demonstrated that they are entirely useless or even harmful. For example, for many years women in labour who were about to deliver would routinely have their pubic hair shaved off in the belief that this would lessen the chances of infection, in particular if there was any tearing during delivery. It was only the negative results from well-designed trials that provided evidence that the practice was completely unnecessary. Even when there was perineal damage, the practice appeared to increase the rate of infection rather than prevent it (Basevi and Lavender, 2001)!

Summary

- The bedrock of good research is in asking the right questions and then designing a study that will provide meaningful answers to these questions.
- The larger and often unanswerable questions can often be broken down into smaller ones and should go through a refinement process involving the different perspectives of a multi-disciplined team including patients.
- The question should be structured using criteria such as PICO which breaks down an individual question into components which may directly translate into keywords that inform the design and literature search of any study. Using a criterion also ensures that any publications resulting from your project will be found during a literature search on the same subject.
- The primary question serves as the main focus of a particular study. Secondary questions can be used to define future studies or can be answered in the current study (if quantitative these need to be suitably powered).
- In general, a qualitative project will have a research question and is hypothesis generating. A quantitative project will have a hypothesis, including the expected direction of the association. Projects should detail the aims and objectives of the research.
- Any answers to a question should be interpreted with a critical eye; associations, whether part of the analytical plan or spurious, should be robustly tested and viewed in a wider context, and in qualitative work, themes should be assessed for alternative explanations.
- Negative findings are usually just as useful as positive ones and can be of equal benefit to the patients and health care providers.

Questions for Discussion

1. A themed call has come out to address the growing pandemic of obesity in children. Researchers have found a strong association between obesity in children and lack of sleep.
 - i. How could the primary question be framed to provide a meaningful answer?
 - ii. Would you need any secondary questions?
2. What are the differences between 'research question', 'hypotheses', 'aims' and 'objectives'?

Further Reading

- Cross, N.B., Craig, J.C. and Webster, A.C. (2010) 'Asking the right question and finding the right answers', *Nephrology*, 15: 8–11.
- Bragge, P. (2010) 'Asking good clinical research questions and choosing the right study design', *Injury, International Journal of Care of the Injured*, S3–S6.
- Lees, J., Manning N. and Rawlings, B. (2004) 'A culture of enquiry: research evidence and the therapeutic community', *Psychology Quarterly*, 75 (3): 279–93.

References

- Babayak, M.A. (2004) 'What you see may not be what you get: a brief, nontechnical introduction to over-fitting in regression-type models', *Psychosom Med*, 66(3):411–421.
- Basevi, V., Lavender, T. (2001) 'Routine perineal shaving on admission in labour', *Cochrane Database Syst Rev*. 2001;(1):CD001236. Review.
- Bragge, P. (2010) 'Asking good clinical research questions and choosing the right study design', *Injury, International Journal of Care of the Injured*, S3–S6.
- Cresswell, J. (2009) *Research Design: Qualitative, Quantitative and Mixed Methods Approaches*. London: SAGE.
- Hujoel, P.P., Cunha-Cruz, J. and Kressin, N.R. (2006) 'Spurious associations in oral epidemiological research: the case of dental flossing and obesity', *Journal of Clinical Periodontology*, 33 (8): 520–3.
- Hulley, S.B., Cummings, S.R., Browner, W.S., Grady, D.G. and Newman, T.B. (2007) *Designing Clinical Research* (3rd edn). Philadelphia, PA: Lippincott, Williams & Wilkins.
- Melzack, R. (1975) 'The McGill Pain Questionnaire: major properties and scoring methods', *Pain*, 1: 277–99.
- Richardson, W.S., Wilson, M.C., Nishikawa, J. and Hayward, R.S. (1995) 'The well-built clinical question: a key to evidence-based decisions', *ACP Journal Club*, 123 (3) A12–13.
- Sackett, D.L., Rosenberg, W.M.C., Gray, J.A.M. et al. (1996) 'Evidence based medicine: what it is and what it isn't', *British Medical Journal*, 312: 71.
- Smith, G.C. and Pell, J.P. (2003) 'Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials', *British Medical Journal*, 20: 327 (7429): 1459–61.

- Smith, R. (2006) 'The trouble with medical journals', *Journal of the Royal Society of Medicine*, 99: 115–19.
- The Lancet* (1995) Editorial: 'Evidence-based medicine, in its place', 346: 785.
- Vale, B. (2008) 'The conquest of scurvy in the Royal Navy 1793–1800: a challenge to current orthodoxy', *The Mariners' Mirror*, 94 (2): 160–75.