Clinical academic medicine: a Socratic dialogue

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See editorial by Chaudhry and p 612

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Summary points

HIPPOCRATES: Never has the potential of medical research to discover the molecular causes of disease and design effective new treatments been so great

SOCRATES: So why so down in the mouth?

HIPPOCRATES: It is becoming impossible to perform as a competent clinician and promote really original research with full understanding of the molecular sciences

SOCRATES: Cannot clinical academics and basic biological scientists work side by side, each contributing their complementary skills?

HIPPOCRATES: Indeed, but our universities do not seem ready to meet this challenge

SOCRATES: How do the young see it?

HIPPOCRATES: Their hero is the busy clinician with his keyholes and imaging machines, not the scientific Colossi of yesteryear. There is a problem with the relative charismas of service and academic medicine

As in all walks of life, clinical academic medicine has many vested interests, some acting for the greater good, some not. Socrates has a penchant for sniffing out pretension and sectional interest. Hippocrates is a thoughtful, gentlemanly physician unaccustomed to ensnarement by Socratic wiles, and when he and Socrates meet one day in the marketplace in Athens the following conversation about the state of clinical academic medicine ensues. It is not a dialogue for the timid.

SOCRATES: Hippocrates, you are looking rather down in the mouth. What's up?

HIPPOCRATES: I am having a sabbatical from my clinical labours to spend time thinking about medical academic and scientific matters.

SOCRATES: How interesting. I had always thought of you as a proper doctor, not an academic one.

HIPPOCRATES: Sometimes, Socrates, you can be so wounding. How can I explain to you the difference between an everyday hardworking physician in service and one who, while active in clinical work, also has an obligation to teach and by original research to forward his subject?

SOCRATES: Are not research and practice compatible?

HIPPOCRATES: To some extent they are. Indeed, those who are not labelled "clinical academics," if they are enthusiastic clinicians with a love of order, can and do study their patients and make important and useful contributions to practice.

SOCRATES: How does that differ from the sort of research you do?

HIPPOCRATES: I have always been interested in the molecular causes of disease.

SOCRATES: What use is that?

HIPPOCRATES: Without such understanding, there can be no rational progress towards treatments and cures as yet undiscovered.

SOCRATES: Do you use the word molecular in the same way as the disciples of Watson and Crick?

Prepared minds seeking innovation

HIPPOCRATES: Not entirely. Although their special science of molecular biology is justifiably all pervading in medical research at present, there are other studies of a reductionist nature which are very important for putting that science into the context of disease, and these studies will come into their own when the functional role of obscure genes needs to be defined.

SOCRATES: So where does all this directed science leave serendipity, which I have been led to believe is one of the most important methods of advance in therapeutics? Were not digitalis, penicillin, and lithium discovered in this way?

HIPPOCRATES: Take care Socrates, not to join the chattering classes in their glibness. Most unlike you. You know very well that those treatments were discovered by prepared minds seeking innovation and developed by imaginative and painstaking clinical experiments. To dismiss this activity as pure serendipity is a travesty.

SOCRATES: All right, don't get upset. You know my method. Tell me how your reductionist probing of the molecular causes of disease can lead to effective new treatments, and how this differs from previous empirical methods.

HIPPOCRATES: I would give as important broad examples of the benefits of the reductionist approach levodopa in Parkinson's disease, many antiviral drugs, H_2 blockers and proton pump inhibitors in peptic ulceration, angiotensin converting enzyme inhibitors in hypertension, and allopurinol in gout, and these are

important advances made before the advent of the new molecular medicine.

SOCRATES: Very impressive, so why so down in the mouth?

HIPPOCRATES: Well, never in my lifetime has the potential of medical research to discover the molecular causes of disease and design new effective treatments been so great. However, I am worried about the serious problems which face clinical academic medicine as it attempts to realise that potential. Molecular medical science is burgeoning at such a pace that it has become impossible to perform as a fully competent physician and promote really original research with full understanding of the molecular sciences. The sheer volume of scientific research is overwhelming, and the proper practice of clinical medicine now so demanding that he who purports to be both a proper doctor and a proper scientist is deluded.

SOCRATES: Wow! Is that why the senate was so reluctant to pay clinical academics the same as their health service colleagues? Just a joke Hippocrates! Is it not possible to organise a system for medical scientific research in which clinical academics and basic biological scientists work side by side, each of them contributing their complementary skills.

HIPPOCRATES: Indeed that is possible and there are a few medical research institutes where this happens, but our universities do not as a matter of policy seem ready to meet this particular challenge of medical science.

SOCRATES: Why is that do you think?

Venality in academe

HIPPOCRATES: This is difficult. Universities are egalitarian places, praise the Gods, and as such regard the department of byzantine studies to have equality with medicine. University medical schools are "cuckoos in the nest"—large, arrogant, loud, vocationally successful, clearly practical, and well regarded professionally and culturally by the populace. But they are very expensive. Senior clinical academic staff are paid more than anyone else in the university, medical research is well funded compared with many other subjects, and, although the universities are fortresses of liberty, all this sometimes grates with the rest of academe.

SOCRATES: I had no idea that such venality existed in the glades of academe. But tell me, the future is in the hands of the young. How do they see it?

HIPPOCRATES: Difficult to give a global answer. Their views are various: some enthusiastic, some not so.[1] No one ever really asks them in an ordered way, so I can give only anecdote. Every head of a clinical academic department is uneasy about the small number of applicants for the clinical academic jobs that are advertised.

SOCRATES: Why is that?

HIPPOCRATES: The future of top class medical research in this country is uncertain. It is a very expensive enterprise and the outcome is unpredictable if the research is very innovative and creative. Others have bemoaned the straitjacket which is placed on innovation and creativity in research when funding is very restricted, and they fear that the quality of our reductionist research in medicine is becoming prosaic. I have to say I agree. My recent investigations into the effects of drugs on gene expression in tissues shows that the vast majority of studies on this subject come from Gaul or the New World.

SOCRATES: Does that matter? Is not science a universal activity? Is it necessary to adopt scientific chauvinism?

HIPPOCRATES: My sentiment is not chauvinistic in the way you imply. I believe it is a serious matter, educationally and culturally, when young people cannot get caught up in the enthusiasm of new, creative science. If you fail to maintain an involvement with the cutting edge of science, your application of it at a later stage will be uninformed and unskilled and if the concepts are not well sown it will take a long time to catch up.

SOCRATES: I do see that. Is then the difficulty in getting support for what you would call creative, innovative, research into the molecular sciences in medicine the main barrier to recruitment of the young into that fold?

Corinthianism is out

HIPPOCRATES: No there are others. You will remember when we were young, Socrates, how we admired the way the academics of Corinth disported themselves. They wore their learning lightly; they were gentlemen rather than players, and their style was one a young man could aspire to. Times have changed. The world is for players, not gentlemen. Where now does the hero worship lie? Not with the Sherringtons, the Watsons or the Cricks, the Flemings, the Blacks, the Vanes, or the Eccleses, the cultural scientific Colossi of yesteryear. The medical students' hero is the busy clinician, the more specialised the better, with his tubes and his optic fibres, his keyholes and his needles and his machines of great imaging intensity.

MARK HUDSON

SOCRATES: Golly, your disillusionment is deep. You are implying that the type of medical research which interests you is no longer respected by your clinical peers.
HIPPOCRATES: Oddly enough, that is not so. The problem is that the art of my type of research is now so divorced from the bedside that it is difficult for devoted clinicians to relate to it, and this I believe is the same for the medical student, who will soon be the young doctor, who once upon a time might have been looking for a career in clinical academia.
SOCRATES: Beside this cultural division, what else is there to discourage the youngster from going into a clinical academic career?
HIPPOCRATES: If such a career is to continue as it has in the past the clinical academic has to be fully trained not only in his clinical speciality but also in those aspects of science necessary for his research. Even if he or she works all hours of the day and night at both of these disciplines, it plainly is going to take a very long while to reach that level of proficiency in both, which equally clever people, working equally hard in only one, acheive. You and I remember how quickly one's youth is past and how rapidly the energy for adventurous creativity dissipates. Many young people reject this situation and decide to get on with the job of curing people. So you see there is a problem with the comparative charismas of service and academic medicine today. However strapped for cash service medicine may be, the youngsters perceive it as being immensely effective, while, except for a few centres, dust threatens academe. Did you know that in our city state there are as many clinical professorships vacant in the various fields of medicine as there are varieties of Heinz?
SOCRATES: Heavens, as bad as that. What are we going to do?
HIPPOCRATES: The city fathers have initiated a number of committees to look into the problem and present their findings to the senate, but whether the senate will do anything about it, or whether it will instruct the universities and the medical profession to sort out their own problems, one cannot tell. It has to be said that within the resources available medical practice is surviving, despite all the grumbles, and keeping up by and large technically, and it is arguable whether putting more money into university medical schools is really going to improve the quality of health care delivered to the populace.
SOCRATES: Well Hippocrates, why not do away with medical schools in the universities and let the health service run them as sort of medical technical colleges producing "semi-shod" doctors practising medicine based on the discoveries made by medical scientists in other countries and honed here for our own purposes? Do you think patients would be any worse off? And another point while we are about it. Why does every medical school have separate departments of anatomy, physiology, biochemistry, and pharmacology, teaching mainly medical students those basic scientific disciplines? Are not the preclinical departments staffed by the very basic scientists that we would like to have working with clinicians in research? Why not amalgamate preclinical and clinical departments, combine the talents of clinical and basic scientists, and save money on plant and resources? Some basic scientists might gain new inspiration for both teaching and research if they were in a clinical milieu.

Conjuring up the synapse in outpatients

HIPPOCRATES: Such a reorganisation would be very unpopular with my preclinical colleagues, even though it might improve the competitiveness of our national medical research base. The universities might also argue that such an amalgamation may be contrary to the premise that universities exist to pursue knowledge for its own sake. Can you imagine Sherrington conjuring up the concept of the synapse while doing a neurological outpatient clinic?
SOCRATES: Never forget, Hippocrates, that Albert Einstein conceived the special theory of relativity while working in the Swiss patent office, an environment, one would have thought, almost as uncongenial to creative intellectual activity as a neurological outpatient clinic. However, Einstein himself observed that: "A practical profession is a salvation for a man of my type; an academic career compels a young man to scientific production and only strong characters can resist the temptation of superficial analysis." Think on that Hippocrates.

1 Independent Task Force. *Clinical academic careers*. London: Committee of Vice-Chancellors and Principals, 1997.
7 Antman EM, Lau J, Kupelnick B, Mosteller F, Chalmers TC. A comparison of results of meta-analyses of randomised controlled trials and recommendations of clinical experts. *JAMA* 1992;268:240-8.
8 Koudstaal P. Secondary prevention following stroke or TIA in patients with non-rheumatic atrial fibrillation: anticoagulant therapy versus control. *Cochrane Database of Systematic Reviews*. Oxford: Cochrane Collaboration, 1995. (Updated 14 February 1995.)
9 Greenhalgh T. Searching the literature. In: *How to read a paper*. London: BMJ Publishing Group, 1997:13-33.
10 Knipschild P. Some examples of systematic reviews. In: Chalmers I, Altman DG. *Systematic reviews*. London: BMJ Publishing Group, 1995:9-16.
11 Knipschild P. Searching for alternatives: loser pays. Lancet 1993; 341: 1135-6.
12 Oxman A, ed. Preparing and maintaining systematic reviews. In: *Cochrane Collaboration handbook, section VI*. Oxford: Cochrane Collaboration, 1995. (Updated 14 July 1995.)
13 Emerson JD, Burdick E, Hoaglin DC, Mosteller F, Chalmers TC. An empirical study of the possible relation of treatment differences to quality scores in controlled randomized clinical trials. *Controlled Clin Trials* 1990;11:339-52.
14 Moher D, Jadad AR, Tugwell P. Assessing the quality of randomized controlled trials: current issues and future directions. *Int J Health Technol Assess* 1996;12:195-208.
15 Garner P, Hetherington J. Establishing and supporting collaborative review groups. In: *Cochrane Collaboration handbook, section II*. Oxford: Cochrane Collaboration, 1995 (Updated 14 July 1995.)
16 Counsell CE, Clarke MJ, Slattery J, Sandercock PAG. The miracle of DICE therapy for acute stroke: fact or fictional product of subgroup analysis? *BMJ* 1994;309:1677-81.
17 Pocock SJ, Henderson RA, Rickards AF, Hampton JR, Sing SB III, Hamm CW, et al. Meta-analysis of randomised trials comparing coronary angioplasty with bypass surgery. *Lancet* 1995;346:1184-9.
18 Thompson SG. Why sources of heterogeneity in meta-analysis should be investigated. In: Chalmers I, Altman DG. *Systematic reviews*. London, BMJ Publishing Group, 1995:48-63.
19 Eysenck HJ. Problems with meta-analysis. In: Chalmers I, Altman DG. *Systematic reviews*. London: BMJ Publishing Group, 1995:64-74.
20 Magnesium, myocardial infarction, meta-analysis and mega-trials. *Drug Ther Bull* 1995;33:25-7.
21 Egger M, Davey Smith G. Misleading meta-analysis: lessons from "an effective, safe, simple" intervention that wasn't. *BMJ* 1995;310:752-4.

Endpiece

Dr Johnson on information retrieval

Knowledge is of two kinds. We know a subject ourselves, or we know where we can find information upon it.

James Boswell, *The Life of Samuel Johnson*

How to read a paper

Papers that tell you what things cost (economic analyses)

Trisha Greenhalgh

This is the eighth in a series of 10 articles introducing non-experts to finding medical articles and assessing their value

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What is economic analysis?

An economic analysis can be defined as an analysis that uses analytical techniques to define choices in resource allocation. This article is based largely on a short booklet by Professor Michael Drummond[1] and two of the forerunners to the "Users' Guides to the Medical Literature" series.[2 3] A recent book, *Elementary Economic Evaluation in Health Care*, is also useful.[4]

Measuring costs and benefits of health interventions

Not long ago, I was taken to hospital to have my appendix removed. From the hospital's point of view, the cost of my care included my board and lodging for five days, a proportion of doctors' and nurses' time, drugs and dressings, and investigations (blood tests and a scan). Other direct costs (see box) included my general practitioner's time for attending me in the middle of the night and the cost of the petrol my husband used when visiting me (not to mention the grapes and flowers).

In addition to this, there were the indirect costs of my loss in productivity. I was off work for three weeks, and my domestic duties were temporarily carried out by various friends, neighbours, and a hired nanny. Also, from my point of view, there were several intangible costs, such as discomfort, loss of independence, and a cosmetically unsightly scar. As the box shows, these direct, indirect, and intangible costs constitute one side of the cost-benefit equation. On the benefit side, the operation greatly increased my chances of staying alive and I had a nice rest from work.

In this example, few patients (and even fewer purchasers) would perceive much freedom of choice in deciding to opt for the operation. But most health interventions do not concern definitive procedures for surgical emergencies. At some stage, almost all of us will be forced to decide whether having a routine operation, taking a particular drug, or compromising our lifestyle to treat a chronic but not immediately life threatening condition is "worth it."

It is fine for informed individuals to make choices about their own care by gut reaction ("I'd rather live with my hernia than be cut open," or "I know about the risk of thrombosis but I want to continue to smoke and stay on the pill"). But when the choices are about other people's care, subjective judgments are the last thing that should enter the equation. Most of us would want the planners and policymakers to use objective, explicit, and defensible criteria when making decisions such as "No, this patient may not have a kidney transplant."

One important way of addressing the "what's it worth?" question for a given health state (such as having poorly controlled diabetes or a flare up of rheumatoid arthritis) is to ask someone in that state how they feel. A number of questionnaires have been developed which attempt to measure overall health status, such as the Nottingham health profile, the SF-36 general health questionnaire, and the McMaster health utilities index questionnaire.[5]

In some circumstances, disease specific measures of wellbeing are more valid than general measures.[6] For example, answering "yes" to the question, "Do you get very concerned about the food you are eating?" might indicate anxiety in someone without diabetes but normal self care attitudes in someone with diabetes. There has also been an upsurge of interest in patient specific measures of quality of life, to allow different patients to place different values on particular aspects of their health and wellbeing.[7] Of course, when quality of life is being analysed from the point of view of the patient, this is a sensible and humane approach. However, the health economist tends to make decisions about groups of patients or populations, in which case patient specific, and even disease specific, measures of quality of life have limited relevance.[8]

The authors of standard instruments (such as the SF-36) for measuring quality of life have often spent years ensuring they are valid (that they measure what we think they are measuring), reliable (they do so every time), and responsive to change (if an intervention improves or worsens the patient's health, the scale will reflect that). For this reason, you should be highly suspicious of a paper that abandons these standard instruments in favour of the authors' own rough and ready scale (for example, "functional ability was classified as good, moderate, or poor according to the clinician's overall impression"). Note also that even instruments which have apparently been well validated often do not stand up to rigorous evaluation of their psychometric validity.[9]

Another way of addressing the "what's it worth?" of particular health states is through health state preference values—that is, the value which, in a hypothetical situation, a healthy person would place on a particular deterioration in their health, or which a

Summary points

An economic analysis should be based on a primary study or meta-analysis that is scientifically valid, reliable, and relevant

When deciding whether an economic analysis has been done correctly, you should not simply check the arithmetic but consider whether all direct, indirect, and intangible costs and benefits have been included

In the allocation of limited resources, the comparison of different health states is unavoidable, but instruments for measuring health related quality of life are not as objective as they seem

Examples of costs and benefits of health interventions

Costs	Benefits
Direct:	*Economic:*
"Board and lodging"	Prevention of illness that is expensive to treat
Drugs, dressings, etc	Avoidance of admission to hospital
Investigations	Return to paid work
Staff salaries	
Indirect:	*Clinical:*
Work days lost	Postponement of death or disability
Value of "unpaid" work	Relief of pain, nausea, breathlessness, etc
Intangible:	Improved vision, hearing, muscular strength, etc
Pain and suffering	
Social stigma	*Quality of life:*
	Increased mobility and independence
	Improved wellbeing
	Release from sick role

sick person would place on a return to health. There are three main methods of assigning such values:

- Rating scale measurements—the respondent is asked to make a mark on a fixed line, labelled, for example, "perfect health" at one end and "death" at the other, to indicate where he or she would place the state in question (for example, being confined to a wheelchair by arthritis of the hip);
- Time tradeoff measurements—the respondent is asked to consider a particular health state (for example, infertility) and estimate how many of their remaining years in full health they would sacrifice to be "cured" of the condition;
- Standard gamble measurements—the respondent is asked to consider the choice between living for the rest of their life in a particular health state and taking a "gamble" (such as having an operation) with a given odds of success which would return them to full health if it succeeded but kill them if it failed. The odds are then varied to see at what point the respondent decides the gamble is not worth taking.[10]

The quality adjusted life year (QALY) can be calculated by multiplying the preference value for that state with the time the patient is likely to spend in that state. The results of cost-benefit analyses are usually expressed in terms of "cost per QALY," some examples of which are shown in the second box.[11]

The use of QALYs is controversial. Any measure of health state preference values is, at best, a reflection of the preferences and prejudices of the individuals who contributed to its development. Indeed, it is possible to come up with different values for QALYs, depending on how the questions from which the health state preference values are derived were posed.[12] Furthermore, it is virtually impossible to combine different QALYs to measure the effect of more than one serious or disabling condition on a patient.[13] As medical ethicist John Harris has pointed out, QALYs are, like the society that produces them, inherently agist, sexist, racist, and loaded against those with permanent disabilities (since even a complete cure of an unrelated condition would not restore the individual to "perfect health"). Furthermore, QALYs distort our ethical instincts by focusing our minds on years of life rather than people's lives. A disabled premature infant in need of an intensive care cot will, argues Harris, be allocated more resources than it deserves in comparison with a 50 year old woman with cancer, since the infant, were it to survive, would have so many more life years to quality adjust.[14]

Other authors have come up with the HYE (healthy years equivalent) measure, which incorporates the individual's likely improvement or deterioration in health status in the future and is said to avoid some, but not all, of the disadvantages of the QALY.[15] Given that the critics of QALYs and HYEs have offered no alternative, all encompassing measure of health status, these utility based units are set to remain in the health economist's toolkit for the forseeable future. For a more detailed discussion of these issues by a multidisciplinary panel, see Anthony Hopkins's booklet *Measures of the Quality of Life*.[16]

There is, however, another form of analysis which, although it does not abolish the need to place arbitrary numerical values on life and limb, avoids the buck stopping at the unfortunate health economist. This approach, known as cost-consequences analysis, presents the results of the economic analysis in a disaggregated form. In other words, it expresses different outcomes in terms of their different natural units (something real such as months of survival, legs amputated, or babies taken home), so that individuals can assign their own values to particular health states before calculating whether the intervention is "worth it."

Ten questions to ask about an economic analysis

The checklist which follows is based on the sources mentioned earlier,[1 2] as well as suggestions made by a working party set up by the *BMJ* to produce guidelines for journal editors on appraising economic evaluations (M Drummond, personal communication).

Question 1: Is the analysis based on a study that answers a clearly defined clinical question about an economically important issue?

Before pursuing any of the economic arguments, make sure that the trial being analysed is scientifically relevant and capable of giving unbiased and unambiguous answers to the clinical question posed in its introduction.

Results of cost-benefit analysis for some medical procedures

Procedure	Cost per QALY (£)
Cholesterol testing and diet therapy	220
Advice to stop smoking from patient's own doctor	270
Hip replacement for arthritis	1 180
Kidney transplant	4 710
Breast cancer screening	5 780
Cholesterol testing and drug therapy if indicated (ages 25-39)	14 150
Neurosurgery for malignant brain tumours	107 780


PETER BROWN

Question 2: Whose viewpoint are costs and benefits being considered from?

From the Treasury's point of view, the most cost effective health intervention is one which returns all citizens promptly to taxpayer status and, when this status is no longer tenable, causes immediate sudden death. From the drug company's point of view, it would be difficult to imagine a cost-benefit equation which did not contain one of the company's products, and from a physiotherapist's point of view, the removal of a physiotherapy service would never be cost effective. Almost all economic analyses have some funding, and all have been inspired by someone with a vested interest; the paper should say which.

Question 3: Have the interventions being compared been shown to be clinically effective?

In general, the intervention that "works out cheaper" should not be substantially less effective in clinical terms than the one which stands to be rejected on the grounds of cost.

Question 4: Are the interventions sensible and workable in the settings where they are likely to be applied?

Too many research trials look at intervention packages which would be impossible to implement in the non-research setting (they assume, for example, that general practitioners will own a state of the art computer and agree to follow a protocol, that infinite nurse time is available for the taking of blood tests, or that patients will make their personal treatment choices solely on the basis of the trial's conclusions). Remember that standard current practice, which may be to do nothing, should almost certainly be one of the alternatives compared.

Question 5: Which method of analysis was used, and was this appropriate?

This decision can be summarised as follows:

- Cost minimisation analysis would be most appropriate if the interventions produced identical outcomes;
- Cost effectiveness analysis would be most appropriate if the important outcome is unidimensional;
- Cost utility analysis would be most appropriate if the important outcome is multidimensional;
- Cost benefit analysis would be most appropriate if the cost benefit equation for this condition needs to be compared with cost benefit equations for different conditions;
- Cost consequences analysis would be most appropriate if a cost benefit analysis would otherwise be appropriate but the preference values given to different health states are disputed or likely to change.

Question 6: How were costs and benefits measured?

Consider an economic evaluation of a trial comparing the rehabilitation of stroke patients into their own homes, including attendance at a day centre, with a standard alternative intervention (rehabilitation in a long stay hospital). The economic analysis must take into account not just the time of the various professionals involved, the time of the secretaries and administrators who help run the service, "overheads" (such as heating and lighting), and the cost of the food and drugs consumed by the stroke patients, but also a fraction of the capital cost of building the day centre and maintaining a transport service to and from it.

In a cost effectiveness analysis, changes in health status will be expressed in natural units. But just because the units are natural does not automatically make them appropriate. For example, the economic analysis of the treatment of peptic ulcer by two different drugs might measure outcome as "proportion of ulcers healed after a six week course." Treatments could be compared according to the cost per ulcer healed. However, if the relapse rates on the two drugs were very different, drug A might be falsely deemed "more cost effective" than drug B. A better outcome measure here might be "ulcers that remained healed at one year."

Question 7: Were incremental, rather than absolute, benefits considered?

This question is best illustrated by a simple example. Let's say drug X, at £100 per course, cures 10 out of every 20 patients. Its new competitor, drug Y, costs £120 per course and cures 11 out of 20 patients. The cost per case cured with drug X is £200 (since you spent £2000 curing 10 people), and the cost per case cured with drug Y is £218 (since you spent £2400 curing 11 people).

The incremental cost of drug Y—the extra cost of curing the extra patient—is not £18, but £400, since this is the total amount extra that you have had to pay to achieve an outcome over and above what you would have achieved by giving all patients the cheaper drug. This striking example should be borne in mind the next time a pharmaceutical representative tries to persuade you that his or her product is "more effective and only marginally more expensive."

Question 8: Was the "here and now" given precedence over the distant future?

A bird in the hand is worth two in the bush: in health as well as money terms, we value a benefit today more highly than we value a promise of the same benefit in five years' time. When the costs or benefits of an intervention (or lack of the intervention) will occur some time in the future, their value should be discounted to reflect this. The actual amount of discount that should be allowed for future, as opposed to immediate, health benefit is fairly arbitrary, but most analyses use a figure of around 5% per year.

Question 9: Was a sensitivity analysis performed?
Let's say a cost-benefit analysis comes out as saying that hernia repair by day case surgery costs £1150 per QALY whereas traditional open repair, with its associated hospital stay, costs £1800 per QALY. But, when you look at how the calculations were done, you are surprised at how cheaply the laparoscopic equipment has been costed. If you raise the price of this equipment by 25%, does day case surgery still come out dramatically cheaper? It may, or it may not.

Sensitivity analysis, or exploration of "what ifs," was described earlier in this series in relation to meta-analysis.[17] Exactly the same principles apply here: if adjusting the figures to account for the full range of possible influences gives you a totally different answer, you should not place too much reliance on the analysis. For a good example of a sensitivity analysis on a topic of both scientific and political importance, see Pharoah and Hollingworth's paper on the cost effectiveness of lowering cholesterol (which addresses the difficult issue of who should receive, and who should be denied, effective but expensive drugs to lower cholesterol).[18]

Question 10: Were "bottom line" aggregate scores overused?
The notion of cost-consequences analysis, in which the reader of the paper can attach his or her own values to different utilities, was introduced earlier. In practice, this is an unusual way of presenting an economic analysis, and, more commonly, the reader is faced with a cost-utility or cost-benefit analysis which gives a composite score in unfamiliar units which do not translate readily into exactly what gains and losses the patient can expect. The situation is analogous to the father who is told "your child's IQ is 115" when he would feel far better informed if he were presented with the disaggregated data: "Johnny can read, write, count, and draw pretty well for his age."

Thanks to Professor Mike Drummond and Dr Alison Tonks for advice on this chapter.

1 Drummond M. *Economic analysis alongside controlled trials.* Leeds: Department of Health, 1994. (R&D Directorate, document F51/066 2515 5k.)

The articles in this series are excerpts from *How to read a paper: the basics of evidence based medicine.* The book includes chapters on searching the literature and implementing evidence based findings. It can be ordered from the BMJ Publishing Group: tel 0171 383 6185/6245; fax 0171 383 6662. Price £13.95 UK members, £14.95 non-members.

2 Drummond MF, Richardson WS, O'Brien BJ, Levine M, Heyland D. Users' guides to the medical literature XIII. How to use an article on economic analysis of clinical practice. A. Are the results of the study valid? *JAMA* 1997;277:1552-7.
3 O'Brien BJ, Heyland D, Richardson WS, Levine M, Drummond MF. Users' guides to the medical literature XIII. How to use an article on economic analysis of clinical practice. B. What are the results and will they help me in caring for my patients? *JAMA* 1997;277:1802-6.
4 Jefferson T, Demicheli V, Mugford M. *Elementary economic evaluation in health care.* London: BMJ Publishing Group, 1996.
5 Patrick DL, Erikson P. *Health status and health policy.* New York: Oxford University Press, 1993.
6 Fallowfield LJ. Assessment of quality of life in breast cancer. *Acta Oncol* 1995;34:689-94.
7 Hickey AM, Bury G, O'Boyle CA, Bradley F, O'Kelley FD, Shannon W. A new short-form individual quality of life measure (SEIQoL-DW). Application in a cohort of individuals with HIV/AIDS. *BMJ* 1996;313:29-33.
8 Cairns J. Measuring health outcomes. *BMJ* 1996;313:6.
9 Gill TM, Feinstein AR. A critical appraisal of the quality of quality of life measurements. *JAMA* 1994;272:619-26.
10 Krabbe PFM, Essink-Bot M-L, Bonsel GK. On the equivalence of collectively and individually collected responses: standard-gamble and time-tradeoff judgements of health status. *Med Decis Making* 1996;16:120-32.
11 Ham C. Priority setting in the NHS. *Br J Health Care Manage* 1995;1:27-9.
12 Weinberger M, Oddone EZ, Samsa G, Landsman P. Are health-related quality of life measures affected by the mode of administration? *J Clin Epidemiol* 1996;49:135-40.
13 Richardson J, Hall J, Salkeld G. The measurement of utility in multiphase health states. *Int J Technol Assess Health Care* 1996;12:151-62.
14 Harris J. QALYfying the value of life. *J Med Ethics* 1987;13:117-23.
15 Mehrez A, Gafni A. Quality-adjusted life years, utility theory and healthy year equivalents. *Med Decis Making* 1989;9:142-9.
16 Hopkins A, ed. *Measures of the quality of life.* London: Royal College of General Practitioners, 1992.
17 Greenhalgh T. Papers that summarise other papers (systematic reviews and meta-analyses). *BMJ* 1997 (in press).
18 Pharoah PDP, Hollingworth W. Cost-effectiveness of lowering cholesterol concentration with statins in patients with and without pre-existing coronary heart disease: life table method applied to health authority population. *BMJ* 1996;312:1443-8.

When I use a word...
Sausages

I recently learnt about a rare type of neuropathy called hereditary neuropathy with liability to pressure palsies (abbreviated to HNPP) or hereditary pressure sensitive neuropathy (HPSN), also known as tomaculous neuropathy. In many cases it is associated with a deletion in chromosome 17p11.2. However, the term is not exclusive, and tomaculous changes have been described in other neuropathies, such as type 1B Charcot–Marie–Tooth syndrome and hereditary neuralgic amyotrophy.

Tomaculous refers to the sausage shaped swellings of myelin that occur along the affected nerves—Latin: tomaculum, a sausage. Latin had several other words for a sausage: hillae, which also meant the intestines; farcimen, meaning something that was stuffed (intestines again); and botulus, a word for the stomach. The bacterium *Clostridium botulinum* is so called because it looks sausage shaped, not because it gets into sausages or affects the stomach. And intestinal sausages feature in other languages too: drisheen, for instance, is an Irish type of sausage, made with sheep's blood and intestines (Irish: drisín, intestine).

Some modern sausages are named after the place from which they originally came: boloney from Bologna, polony from Bologna or Poland, frankfurter from Frankfurt, viennas from Vienna.

Sometimes the name of a sausage prosaically describes its contents. For instance, a chipolata was originally made with onions (Italian: cipolla). One such sausage to avoid is the saveloy, also called cervelat, which was originally made with brains, from the Latin word cerebellum, the diminutive of cerebrum. Not a wise choice these days.

Spices are another important ingredient. The currently popular pepperoni, not surprisingly, contains peppers. The word sausage itself (originally salsicia) comes from the Latin: sal, meaning salt, as does salami. Because you slice a salami thinly, the word has been used for metaphorical slicing: salami tactics, the gradual whittling away of the members of an organisation; salami technique, a fraud involving the deduction of tiny amounts of money from innumerable sources (like Richard Pryor's scam in *Superman III*); and salami publication, when you get several papers out of a single piece of work, slicing it up as finely as you can.

Which brings us back to tomaculous neuropathy. The tomaculum was a sausage that could be served sliced, from the Greek word τομή (tome) meaning a cut.

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Statistics notes

Trials randomised in clusters

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In most randomised trials each subject is individually assigned at random to an intervention group. The intervention is applied directly to the subject and observations are made on each individual to determine the outcome of the intervention. Sometimes subjects cannot be allocated independently, or they may interact with one another during the treatment period.

In trials of population screening, for example, screening centres may be set up in some districts and not in others. This may be necessary because widespread publicity is needed to encourage subjects to come for screening, or because members of the screening group might pass on information to neighbours who have been allocated to the control arm (no screening), leading them to demand screening.

In the Swedish two county trial of breast cancer screening the county of Kopparberg was divided into seven geographical areas.[1 2] Each was then subdivided into three units, either parishes or municipalities, two of which were randomly allocated to screening and the other to control. The county of Östergötland was divided into 12 areas, each of which was subdivided into two experimental units, one allocated to screening and the other to control. The subjects within a unit are called a cluster, and the trial used cluster randomisation. Cluster randomisation is used especially in public health and general practice research.

A price must be paid

There is a price to be paid for this design at the analysis stage. We cannot think of our trial subjects as independent individuals but must do the analysis at the level of the experimental unit.[3] In the two county trial women within a parish will be more alike than a random sample of women from the two counties. We have two sources of variation: that between people in a parish and that between parishes. The variability between parishes must be taken into account in the analysis.

The effect of cluster randomisation is to increase the size of standard errors and hence widen confidence intervals and increase P values compared with a study of the same size using simple randomisation. The effective sample size is reduced and power is lost. The larger and fewer the clusters are, the more important and greater the effect becomes.

Many cluster randomised trials ignore this design effect in the analysis. Early reports of the two county trial[1 2] did this, although more recent analyses have taken it into account.[4] In a review of 16 non-therapeutic intervention trials employing cluster randomisation only eight allowed for the clusters in the analysis.[5] Ignoring the correct unit of analysis in this way may lead to spurious positive findings.[3]

Health promotion is another area where cluster randomised designs are common. For example, in the evaluation of a health education programme schools may be randomly allocated to receive the education programme or to act as control. The subsequent behaviour and knowledge of the children can be compared. As children may influence each other children within a school cannot be regarded as independent of one another and the school should be the unit of analysis.

Use the right unit

Patients are often allocated so that all the patients of one general practitioner receive the same treatment. In a trial of terminal care coordination, for example, general practices were allocated into two groups and the patients of doctors in one group were offered the extra intervention.[6] All the patients needing terminal care in a practice formed a single cluster. In this example the treatment was applied directly to the patient, who received visits from the care coordinators. Sometimes the treatment is applied to the provider of care rather than to the patient directly; and here the effect of the clustering may be much larger. For example, to improve the treatment of asthma in general practice general practitioners were allocated randomly to three groups.[7] The first group was given an intensive programme of small group education, the second a lesser intervention, and the third no intervention at all. A sample of each general practitioner's asthmatic patients was selected. These patients received questionnaires about their symptoms, and the prevalence was compared between the groups. The experimental unit was the general practitioner, not the patient. The proportion of patients who reported symptoms was used as a measure of the general practitioner's effectiveness and the three groups of doctors compared by analysis of variance.[8]

We shall discuss the design and analysis of cluster randomised trials in future statistics notes.

1 Tabar L, Gad A. Screening for breast cancer: the Swedish trial. *Radiology* 1981;138:219-22.
2 Tabar L, Gad A, Holmberg LH, Ljunquist U, Fagerberg CJG, Baldetorp L, et al. Reduction in mortality from breast cancer after mass screening with mammography. *Lancet* 1985;i:829-3.
3 Altman DG, Bland JM. Statistics notes. Units of analysis. *BMJ* 1997;314:1874.
4 Tabar L, Fagerberg CJG, Chen HH, Duffy SW, Smart CR, Gad A, et al. Efficacy of breast cancer screening by age. New results from the Swedish two-county trial. *Cancer* 1995;75:2507-17.
5 Donner A, Brown KS, Brasher P. A methodological review of non-therapeutic intervention trials employing cluster randomisation 1979-1989. *Int J Epidemiol* 1990;19:795-800.
6 Addington-Hall JM, Macdonald LD, Anderson HR, Chamberlain J, Freeling P, Bland JM, et al. A randomised controlled trial of the effects of co-ordinating care for terminally ill cancer patients. *BMJ* 1992;305:1317-22.
7 White PT, Pharaoh CA, Anderson HR, Freeling P. Improving the outcome of chronic asthma in general practice: a randomised controlled trial of small group education. *J R Coll Gen Pract* 1987;39:182-6.
8 Altman DG, Bland JM. Statistics notes. Comparing several groups using analysis of variance. *BMJ* 1995;312:1472-3.