De Testimonio: on the evidence for decisions about the use of therapeutic interventions

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ABSTRACT – Decisions about the use of therapeutic interventions, whether for individuals or entire healthcare systems, should be based on the totality of the available evidence. The notion that evidence can be reliably or usefully placed in 'hierarchies' is illusory. Rather, decision makers need to exercise judgement about whether (and when) evidence gathered from experimental or observational sources is fit for purpose.

KEY WORDS: case-control studies, hierarchies of evidence, historical controlled trials, randomised controlled trials

William Harvey (1578–1657) was one of a group of 17th century natural philosophers who were no longer prepared to accept the authority of Aristotle, Plato and Galen as a reliable basis for understanding the natural world. As Harvey, himself, remarked:

> *It is base to receive instructions from others' comments without examination of the objects themselves, especially as the book of nature lies so open and is so easy of consultation.*[1]

Although united in their quest to examine 'the book of nature' for themselves, natural philosophers of the period were bitterly divided about how it should be done. Three hundred and fifty years later this dispute about the nature of science, and scientific method, still persists particularly in relation to the inductive and deductive approaches to the establishment of scientific knowledge.[2]

Nowhere though is this more hotly, and sometimes bitterly, argued than in the nature of the evidence that should support the use of therapeutic interventions. This has become particularly apparent with the emergence, over the past 30 years, of what are known variously as 'rules', 'levels' or 'hierarchies' of evidence. A typical example is shown in Table 1.[3]

Evidence, in the present context, has only one purpose. It forms the basis for informing decision makers about the appropriate use of therapeutic interventions in routine clinical practice. Such decisions have to be made at various levels but, invariably, with critical consequences for patients, families and society. Decision makers, for example, determine the appropriateness of treatments that are offered to individual patients; decide on the range of products to include in a local hospital's formulary; and may be charged with assessing whether particular interventions are sufficiently safe and effective – as well as cost effective – to be made available to entire healthcare systems. Mistakes in decision making may have dramatic repercussions.

Hierarchies place randomised controlled trials (RCTs) at their summit with various forms of observational studies nestling in the foothills. They are used – as a form of shorthand – to provide some intimation of the 'strength' of the underlying evidence; and, particularly by guideline developers, to then

Table 1. A hierarchy of evidence. Reproduced with permission from the BMJ Publishing Group.[3]

Level	Criteria
1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias.
1+	Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias.
1–	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias.
2++	High-quality systematic reviews of case-control studies or cohort studies; or high-quality case-control or cohort studies with a very low risk of confounding, bias, or chance
2+	Well conducted case-control or cohort studies with a low risk of confounding, bias, or chance.
2–	Case-control or cohort studies with a high risk of confounding, bias, or chance.
3	Non-analytic studies (eg case report, case studies)
4	Expert opinion

RCTs = randomised controlled trials.

The Harveian Oration is delivered annually at the Royal College of Physicians of London under an indenture of William Harvey in 1656. This article is based on the 2008 oration delivered on 16 October 2008 by **Sir Michael Rawlins** MD FRCP FFPM FMedSci, Chairman, National Institute for Health and Clinical Excellence, London; Emeritus Professor, University of Newcastle, Newcastle upon Tyne

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'grade' therapeutic recommendations on the basis of this perceived strength.

The notion that evidence can be reliably placed in hierarchies is illusory. Hierarchies place RCTs on an uncomfortable pedestal for while the technique has advantages it also has disadvantages.[4] Observational studies have defects but they also have merit. Decision makers need to assess and appraise all the available evidence irrespective as to whether it has been derived from RCTs or observational studies; and the strengths and weaknesses of each need to be understood if reasonable and reliable conclusions are to be drawn. Nor, in reaching these conclusions, is there any shame in accepting that judgements are required about the 'fitness for purpose' of the components of the evidence base. On the contrary, judgements are an essential ingredient of most aspects of the decision-making process.[5]

Randomised controlled trials

The introduction of the RCTs, in the middle of the 20th century, has had a profound impact on the practice of medicine and its essential features are well described.[4,6,7] It involves comparing the effects of two (or more) interventions that have been allocated randomly to groups of contemporaneously treated patients.

Double blind RCTs, when properly conducted and analysed, unquestionably provide confidence in the internal validity of the results in so far as the benefits of the intervention are concerned[6,8]; and the more so if replicated by subsequent studies. Consequently, RCTs are often called the 'gold standard' for demonstrating (or refuting) the benefits of a particular intervention. Yet the technique has important limitations of which four are particularly troublesome: the null hypothesis, probability, generalisability and resource implications.

The null hypothesis

The analysis of an RCT has traditionally been based on the null hypothesis which presumes there is no difference between treatments and is tested by estimating the probability (the frequency) of obtaining a result as extreme, or more extreme, as the one observed were the null hypothesis to be true. If the probability is less than some arbitrary value – usually less than 1 in 20 (ie $p<0.05$) – then the null hypothesis is rejected. This is the 'frequentist' approach to the design and analysis of RCTs and has undoubted attractions: the statistical calculations are relatively simple; the methodology has become widely accepted; and the criteria for 'significance' are well established.

The null hypothesis may be irrelevant, though, if there have been previous studies demonstrating that a particular treatment has some benefits. This can occur during the development of a new drug when preliminary evidence of proof of principle, from phase II studies, is investigated in larger groups of patients during phase III. At that point, basing the analysis of the results of subsequent phase III studies on the null hypothesis becomes counterintuitive. Equally, the null hypothesis is inappropriate when previously published studies have already shown benefit. Yet surveys over the past 10 years show that 73% of RCTs, published in major journals, persistently fail to make any systematic attempt to set their results in the context of previous investigations.[9]

The null hypothesis is even more awkward for trials seeking to show whether there is no difference (equivalence), no less benefit (non-inferiority), or a pre-specific difference (futility) between treatment groups.[10] All require prior assumptions to be made about the extent to which the differences between treatments might be relevant or important. The null hypothesis may, indeed, be methodologically consistent with the deductive approach to science but, as Rothman observed: 'To entertain the universal null hypothesis is, in effect, to suspend belief in the real world and thereby to question the premises of empiricism'.[11]

Probability

The p value. In the frequentist approach, if the p value is sufficiently small either the null hypothesis is false or a very rare event has occurred. By convention, a probability of less than 5% (ie $p<0.05$) is generally used to distinguish between these two possibilities. However, a p value of greater or less than 0.05 neither disproves or proves (respectively) the null hypothesis. Some, though not all, of the problems associated with p values can avoided by expressing results as confidence intervals which indicates the degree of uncertainty, or lack of precision, of the estimate of interest. Nevertheless, p values and confidence interval are closely related.

Multiplicity. The difficulties in interpreting frequentist p values become convoluted when seeking to decide, during a clinical trial, whether a study should be terminated prematurely; or how (and whether) to assess outcomes in subgroups of patients once the trial has been completed. A similar problem occurs during the safety analysis of RCTs. In all of these instances, repeated tests of statistical significance – adopting the conventional p value (<0.05) – are increasingly likely to produce one or more 'significant' results. If, for example, 10 separate assumptions are tested, the probability of one being apparently significant (at $p<0.05$) is 40%. This is known as the 'problem of multiplicity'. There are, though, very divergent views among statisticians as to how to deal with this difficulty in devising stopping rules and in subgroup analyses.[12]

There is a natural desire for investigators, during the course of an RCT, to undertake interim analyses of the accruing data in order to decide whether the trial should continue or be prematurely stopped. Premature termination may be justified on the grounds that the study has already achieved its predefined beneficial endpoint(s); or because of safety concerns in one of the groups. There are, however, serious pitfalls in deciding whether and when to terminate a trial early. If an interim analysis shows an unexpected benefit, it may be difficult to distinguish a true effect from chance (a so-called 'random high').[13]

Various statistical approaches have been developed to resolve this form of multiplicity.[12] Many depend on changing the level of statistical significance (ie the p value) as each interim analysis is performed, so that for earlier examinations of the data a lower

p value is required to reject the null hypothesis. There is, however, no consensus among statisticians about stopping rules.[12,14] A resolution to the problem has, though, become urgent. Because stopping trials early, for benefit, may systematically overestimate treatment effects there is a real danger that some claims for efficacy – especially in oncology – may be unwarranted.[12,15]

Analyses of the effects of an intervention, in subgroups of patients, can be important in order to establish whether different types of people respond differently.[16] The most common solution to multiplicity in subgroup analyses is to accept, as reliable, only a limited number of clinically or biologically plausible ones that have been pre-specified during the planning stage.[12,17] A definition of what might be regarded as 'limited' is not generally offered. Opinions vary in the assessment of subgroups identified after a trial has been completed. Some eschew post hoc analyses altogether while others suggest cautious statistical adjustment of the p value.[17]

The Bayesian approach. A growing number of statisticians[18] believe that the solution to many of the difficulties inherent in the frequentist approach to the design, analysis and interpretation of RCTs is the greater use of Bayesian statistics. The Bayesian approach to probability is named after Thomas Bayes (1701–61) who was a non-conformist minister in Tunbridge Wells. This notion of probability – subjective or inverse probability – is the likelihood of a hypothesis given some data. Thus, while the frequentist approach is about the probability of some data conditional on a specific hypothesis (usually the null hypothesis), the Bayesian approach is the reverse (ie the probability of a hypothesis conditional on the data).

Bayes' theorem relates the probabilities from what is known before (*a priori*) an experiment, such as an RCT, to the probabilities re-calculated after the experiment (*a posteriori*). The link between the 'prior' and 'posterior' probabilities is the result of the experiment itself. The 'posterior' probability provides an estimate of the probability of a hypothesis conditional on the observed data but taking account of what was already known (the 'prior') before the experiment was performed.[19,20]

An application of a Bayesian approach, to the analysis of an RCT, is shown in Fig 1. The GREAT trial was designed to test the hypothesis that early domiciliary thrombolytic therapy for acute myocardial infarction (MI) would be better than later treatment in hospital.[21] The investigators therefore undertook an RCT comparing the effectiveness of thrombolysis given by general practitioners in the patients' own homes with later treatment once they had reached their local hospital. At three months, the relative reduction in all cause mortality was 49% (p=0.04), for patients treated at home compared to those treated only when they had reached hospital. Although early thrombolysis might well have had survival advantages, a reduction of almost 50% seemed implausible given that hospital thrombolytic therapy, itself, reduces mortality by about 25%.

Pocock and Spiegelhalter therefore undertook a Bayesian re-analysis (Fig 1).[22] They derived a prior distribution (Fig 1a), based on the results of previous RCTs of hospital treatment with thrombolytics, but expressing their belief that a 15 to 20% reduction in mortality was highly plausible but that extremes of no benefit and a 40% reduction were both unlikely. Figure 1b shows the probability distribution of the results of the GREAT trial. Figure 1c represents the posterior distribution obtained by multiplying the prior and the likelihood. This figure shows that the likelihood derived from the original analysis of the GREAT study has been 'pulled back' to provide a formal representation of the belief that the original results were 'too good to be true'.[22]

As well avoiding the indiscriminate use of the null hypothesis, Bayesian approaches are claimed to overcome problems in the design and analysis of RCTs as well as issues relating to multiplicity.[19,20] Why then are Bayesian methods not more commonly used? There appear to be five main reasons.

Firstly, although the subjective approach to probability dates back to the 18th century, some (especially those of a frequentist mindset) regard this interpretation of probability – as a personal belief or judgement – with distaste.[20] They prefer the apparent (but illusory) security of a clear definition of what constitutes an

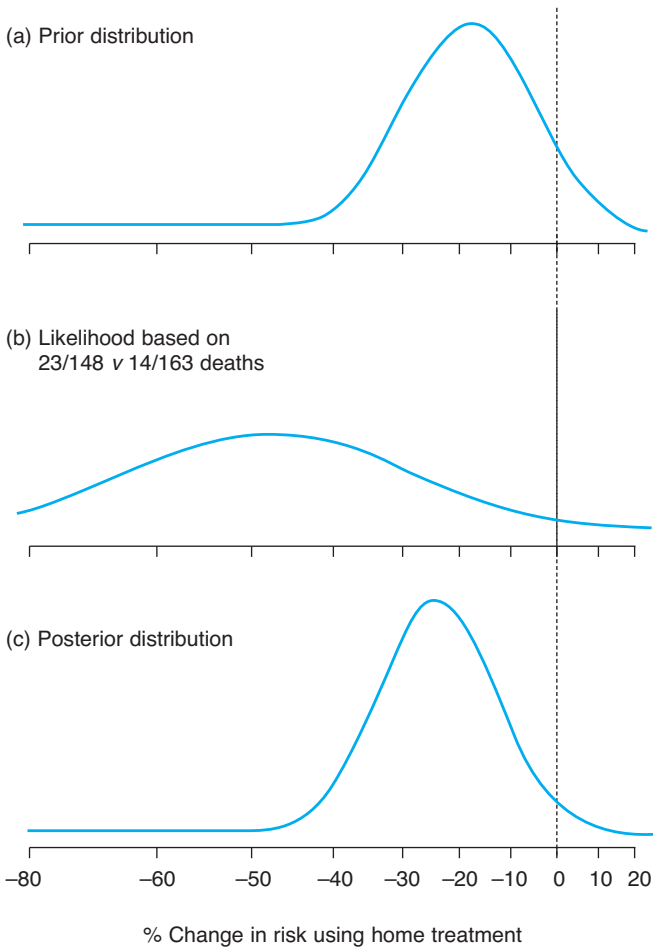

Fig 1. Bayesian re-analysis of the GREAT trial showing change (reduction) in mortality, from home thrombolytic therapy, compared with treatment in hospital (a) prior probability distribution of home treatment; (b) likelihood probability distribution from the GREAT trial; (c) posterior probability distribution of home treatment using Bayes' theorem. Reproduced with permission from the BMJ Publishing Group.[22]

'extreme' result when tested against the null hypothesis; and they are reluctant to accept that personal belief or judgement should come into play in decision making.

Secondly, there have been substantial controversies about the derivation of the prior probability. Where there is evidence from previous studies a so-called 'clinical prior' is readily available. Where there is no clinical prior use is made of 'default' priors.[20] Too much has been made of the alleged difficulties in using these and Bayesians, anyway, tend to use a number of default priors in the absence, and even, sometimes, in the presence, of clinical priors as part of their sensitivity analyses.

Thirdly, Bayesian analyses are computationally complex and are more demanding than the methods used in most frequentist analyses.

Fourthly, some statisticians – albeit a dwindling number – are unfamiliar with the techniques of Bayesian analysis and are unwilling (or unable) to adapt. Some attribute this variation in skill-mix to a statistician's original choice of university.[23] Others, less kindly, believe it to be generational. As one Bayesian explained to me: 'Statisticians who were taught how to use log books and slide rules can't usually do Bayesian statistics'.

Finally, regulatory authorities have sometimes been hesitant to concede that Bayesian approaches may have advantages.[24] There are, though, signs of rising interest particularly in the evaluation of devices.[25] And manufacturers, themselves, are increasingly adopting Bayesian approaches in phase II and III trials.[26,27]

Bayesian approaches to the design and analysis of RCTs are likely to play a much greater role in the future.[18] Eliminating the rigidity of the p value, and resolving some of the questions about multiplicity, are prizes worth securing. Above all, Bayesian approaches might help decision makers draw more appropriate conclusions.

Generalisability

RCTs are generally undertaken in selected patient populations for a finite, usually relatively brief, period of time. In clinical practice the intervention is likely be used in a more heterogeneous population of patients – often with co-morbid illnesses – and frequently for much longer periods. The extent to which the findings from RCTs have external validity and can be extrapolated or generalised to wider patient populations has become an increasingly important issue.[28,29] The most significant problems are outlined in Table 2.

That there are real concerns over the issue of generalisability is discussed in greater detail elsewhere.[10] Bartlett and colleagues, for example, reviewed the exclusion criteria adopted in RCTs of both statins (27 trials) and non-steroidal anti-inflammatory agents (NSAIDs) (25 trials).[30] They noted under-representation of women, older people and ethnic minorities, compared with use in the general population. Similar under-representation has been observed in RCTs of other cardiovascular interventions.[31]

Assessment of benefit. There is therefore uncertainty as to whether the benefits achieved by 'average' patients in RCTs can be extrapolated to 'average' patients undergoing routine clinical care. Does, for example, the under-representation of certain groups in RCTs really matter? There is a presumption, by some, that the results of RCTs in discrete patient populations can, other things being equal, be reliably extrapolated to the care of patients in general.[7,32] It is argued that, if the pathogenesis of a disease is the same in all subgroups, similar benefits can be expected in wider patient populations.

The problem with this claim is that there is little systematic evidence to support it and some that refutes it.[29,32] There are, unquestionably, individual studies demonstrating concordance between the beneficial effects seen in RCTs with those observed during conventional medical care. The benefits of anticoagulation in patients with non-valvular atrial fibrillation (AF) are a case in point.[33] But the extent to which the differing characteristics of patients treated in RCTs, compared to those undergoing routine clinical care, really matters, in relation to the claimed benefits, remains uncertain. Indeed, as the authors of the CONSORT group themselves admit, 'External validity is a matter of judgement'.[7]

Assessment of harms. Although there is optimism, albeit with a fair degree of uncertainty about the generalisability of the results of RCTs in relation to efficacy, experience shows that in the assessment of harms RCTs are weak at providing relevant

Table 2. Adverse influences on the generalisability of the results of randomised controlled trials (RCTs).

Factors	Issues	Potential problems
Patients	Age	Effectiveness in younger or older patients
	Gender	Effectiveness generally
	Severity of the disease	Effectiveness in milder or severer forms of the condition
	Risk factors	Effectiveness in patients with risk factors for the condition (eg smokers)
	Co-morbidities	Influence of other conditions on effectiveness
	Ethnicity	Effectiveness in other ethnic groups
	Socioeconomic status	Effectiveness in disadvantaged patients
Treatment	Dose	Too high a dose used in RCTs
	Timing of administration	Influence on adherence (compliance) to treatment regimens
	Duration of therapy	Effectiveness during long-term use
	Co-medication	Adverse interactions
	Comparative effectiveness	Effectiveness in comparison with other products used for the same indication
Setting	Quality of care	Prescription and monitoring by less specialist (expert) healthcare providers

evidence. RCTs may detect 'dramatic' safety issues; but they are an unreliable approach.

In clinical trials, it is now customary to collect and record all the adverse events occurring after randomisation. This reduces the chance of investigator bias in interpreting the causal nature of any intercurrent illnesses that some patients will inevitably develop during the course of a study. Adverse events include abnormal symptoms and signs, abnormalities detected by routine clinical biochemical tests (full blood counts, urea and electrolytes, liver function tests, urinalysis etc), and the results of special monitoring (eg electrocardiography, echocardiography). Those adverse events causally related to the intervention can (in theory) be identified by simple group comparisons. Although this approach has superficial attractions, there are several problems.

RCTs are designed to ensure that the statistical power will be sufficient to demonstrate clinical benefit. Such power calculations do not, however, usually take harms into account.[34] As a consequence, although RCTs can identify the more common adverse reactions, they singularly fail to recognise less common ones or those with a long latency (such as malignancies). Most RCTs, even for interventions that are likely to be used by patients for many years, are only of six- to 24-months duration. And, if adverse events are detected at a statistically significant level, it is easy to dismiss them as being due to chance rather than a real difference between the groups.

The analysis of RCTs, for harms, poses yet another unresolved multiplicity problem.[34] In large-scale, long-term studies it will be almost inevitable that some statistically significant effects will be observed. Distinguishing those that are iatrogenic, from those that are intercurrent and non-causal, or just random error, is as much an art as a science. Where the events are typically iatrogenic (eg anaphylaxis, morbilliform rashes, toxic epidermal necrolysis) a causal relationship can be inferred. Similarly, if the adverse events are biologically plausible (eg breast cancer with hormone replacement therapy (HRT)), a causal relationship might also be inferred. Where these factors do not apply, difficulties in interpretation may arise. Properly conducted and analysed RCTs can, certainly, provide important information about adverse effects. Examples include RCTs of prophylactic antiarrhythmic therapy, with class 1 agents, after MI[35]; and of HRT in postmenopausal women.[36] These, though, are exceptions.

Resources

The costs of RCTs are substantial in money, time and energy. Figure 2 shows the range of costs of 153 RCTs that were completed in 2005 and 2006. This data combines the costs of trials that were funded by the National Institute for Health Research and the Medical Research Council as well as those incurred by three major pharmaceutical companies in their phase 2 and 3 studies. The median cost was £3,202,000 with an interquartile range of £1,929,000 to £6,568,000. These data are neither comprehensive nor, necessarily, representative of RCTs generally but they demonstrate that trials can be very expensive undertakings. Costs, too, appear to be rising. One manufacturer estimates that the average cost per patient, included in trials, has increased from £6,300 (in 2005), to £7,300 (in 2006) and to £9,900 (in 2007).

Much of the rise in costs is due to the increasing regulatory (and other) requirements imposed on privately and publicly funded trials over the past few years.[37] Each measure was introduced with the best of intentions. These included the desire to protect patients from unscrupulous investigators and sponsors; to ensure the collection and timely reporting of adverse event data during trials; to audit individual case report forms thus avoiding the consequences of untruthful behaviour by investigators; and so on. But even simple studies, with products that have been available for many years, now place a massive bureaucratic challenge on potential sponsors and investigators irrespective of whether they are based in universities or in the private sector.

Recent proposals by academic clinical investigators, themselves, indicate that clinical trial costs could be decreased by between 40% and 60% without detriment to their quality.[38] Simple measures to reduce the bureaucratic burden such as electronic data capture, reduction in the length of case management forms, and modified site management practices would substantially reduce costs.

Observational studies

The nomenclature describing observational (non-randomised) studies is confused. I eschew a distinction between 'controlled' and 'uncontrolled' studies because all observational studies involve some form of implicit (informal) or explicit (formal) comparisons. Nor do I consider the terms 'cohort studies' or 'quasi-experimental studies' particularly illuminating. The former combines studies that are, in reality, distinct entities. The latter is a term that I have never found to be adequately (or even consistently) defined. The varieties of observational studies that have been, and continue to be, used in deriving evidence about the benefits and harms of therapeutic interventions are shown in Table 3.

The great strength of RCTs is that the allocation of treatments is random so that the groups being compared are similar for baseline factors. This may not be so in controlled observational

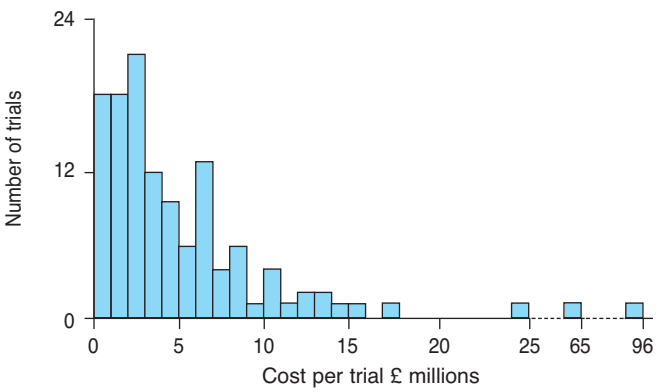

Fig 2. Range of study costs of individual randomised controlled trials (pharmaceuticals).

trials where there is the real danger of selection bias and confounding.[39] There is, indeed, an extensive and sometimes disputatious, literature comparing the merits and demerits of randomised and observational studies of the effectiveness of therapeutic interventions.[10]

Attempts at systematic reviews of published comparisons between the two approaches, however, have been bedevilled by two problems. Firstly, there is the difficulty in identifying relevant studies. Because many observational studies have not been consistently 'tagged' in electronic bibliographic databases, it is difficult to ensure that conventional search strategies have identified them in an unbiased manner. Many reviewers have therefore relied on personal collections of papers, their own (or others') memories, or studies identified in previous systematic reviews. The possibility of 'reviewer bias' is therefore not inconsiderable. The second difficulty is that very few of these reviews have distinguished between the various types of observational designs.[40]

There is general agreement that 'dramatic' effects can be discerned without the need for RCTs.[41-43] There is, though, much less of a consensus about the role of observational studies in defining benefit when the effect size is more modest.[31] There may well be a tendency for observational studies to provide larger treatment effects than RCTs. This has not, though, been an invariable finding. Indeed, in some instances underestimates as well as overestimates have been reported. The magnitude of differences between RCTs and observational data may also vary with the specific type of design used in the observational studies.[40] Analytical strategies to reduce the effects of selection bias and confounding, in observational studies, are discussed elsewhere.[44]

Two varieties of observational study are considered in detail, here, because they have been especially significant in providing evidence on the benefits and harms of therapeutic interventions. A fuller discussion of the others, which have also made extremely important contributions, can be found elsewhere.[10]

Table 3. Varieties of observational studies.

Historical controlled trials
A study of the effects of an intervention among a group of patients treated with an intervention compared, retrospectively with a group who had previously received standard therapy (including best supportive care).

Non-randomised contemporaneously controlled trials
A comparison of the outcome(s) of patients receiving one treatment compared to another group of patients (untreated, or treated with an alternative intervention) during the same time period.

Case-control study
A comparison of the use of an intervention in groups of patients with, and without a particular disease or condition.

Before-and-after designs
Observations among groups of patients before, and after, treatment with an intervention. Patients therefore act as their own controls. This technique has often been used in implicit historical controlled trials where the natural history of the disease or condition is well-established and predictable.

Case-series
The outcomes of a group (series) of patients treated with an intervention during routine clinical practice. Although there is no formal control group, implicit or explicit comparisons are invariably made.

Case reports
Case reports (anecdotes) of harms to individual patients either reported in the literature or to a central agency (eg the Medicines Healthcare products Regulatory Agency in the UK, or the Food and Drugs Administration in the USA).

Historical controlled trials

Examples of interventions of unquestioned benefit, as demonstrated by historical controlled trials where comparisons are made between a new intervention and past experience with the condition, are shown in Table 4.

In the past, the use of historical controls has been the subject of considerable criticism.[6] During the late 1980s, however, clinical trialists became less hostile to the concept. Prompted by the emerging AIDS epidemic they accepted that 'some of the traditional approaches to clinical trial design were unnecessarily rigid'.[45] The authors proposed that historical controlled trials, in support of claims of efficacy for a new drug to treat AIDS, should meet the following specific requirements: 1) there must be no other treatment appropriate to use as a control; 2) there must be sufficient experience to ensure that the patients not receiving treatment will have a uniformly poor prognosis; 3) the therapy must not be expected to have substantial side effects that would compromise the potential benefit to the patient; 4) there must be a justifiable expectation that the potential benefit to the patient will be sufficiently large to make interpretation of the results of a non-randomised trial unambiguous; 5) the scientific

Table 4. Some interventions with established effectiveness based on historical controlled trials. Abridged from Reference 10.

Intervention	Indication
Thyroxine (1891)	Myxoedema
Insulin (1922)	Diabetic ketoacidosis
Vitamin B_{12} (1926)	Pernicious anaemia
Sulfonamides (1937)	Puerperal sepsis
Penicillin (1941)	Lobar pneumonia
Defibrillation (1948)	Ventricular fibrillation
Streptomycin (1948)	Tuberculous meningitis
Ganglion blockers (1959)	Malignant hypertension
Heimlich manoeuvre (1975)	Laryngeal obstruction by a foreign body
Cisplatin plus vinblastine and bleomycin (1977)	Disseminated testicular cancer
N-acetylcysteine (1979)	Paracetamol poisoning
Ganciclovir (1986)	Cytomegalovirus retinitis
Laser treatment (2000)	Removal of port wine stains
Imatinib (2002)	Chronic myeloid leukaemia

rationale for the treatment must be sufficiently strong that a positive result would be widely accepted.[45]

My own adaptation of these requirements to historical controlled trials more generally are unashamedly influenced by the considerations outlined by Bradford Hill in distinguishing causal from non-causal associations in epidemiological studies.[46] I therefore consider historical controlled trials should generally be accepted as evidence for effectiveness provided they meet all of the following conditions:

1 The treatment should have a biologically plausible basis. This is met by all the treatments shown in Table 4.
2 There should be no appropriate treatment that could be reasonably used as a control. The term 'appropriate' would exclude, for example, the use of bone marrow transplantation as a control for enzyme replacement therapy in the treatment of Gaucher's disease.
3 The condition should have an established and predictable natural history. I prefer this phraseology to 'poor prognosis'. Conditions such as port wine stains may significantly impair patients' quality of life without threatening life expectancy.
4 The treatment should not be expected to have adverse effects that would compromise its potential benefits. This has to be a sine qua non.
5 There should be a reasonable expectation that the magnitude of the treatment will be large enough to make the interpretation of the benefits unambiguous. A 'signal-to-noise' ratio of 10 or more appears to be strongly suggestive of a genuine therapeutic effect.[41,43] The magnitude of the 'signal-to-noise' ratio representing a 'dramatic' (ie 10-fold) effect, however, is based on impression and is not (at present) supported by any substantive empirical evidence.

In the future, there will be circumstances when we must continue to be prepared to accept evidence of benefits from historical controlled trials. Interventions falling into this category might, for example, include treatments that completely arrest the progressive neurodegeneration seen in Creutzfeldt-Jakob disease or Huntington's disease. In both these conditions objective, as well as subjective, measures are available to confirm (or refute) claims that progression has been arrested. The fact that clinical investigators in the UK, Europe and North America are currently accumulating cohorts of patients with these diseases – specifically for the purpose of providing historical controls for future studies – gives me optimism.[10]

Case-control studies

Case-control studies compare the use of an intervention in groups with, and without, a particular disease or condition. Like other observational designs they provide information about an *association* between exposure to a particular intervention but not necessarily whether the relationship is *causal*. The problems of selection bias and confounding are no less relevant to the interpretation of case-control studies than they are with other controlled observational designs. They can, however, be minimised by care in their design and analysis.[34]

Assessment of benefit. Case-control studies have been used, though with mixed results, to provide support for demonstrating the benefits of interventions.

During the 1980s a number of observational (mainly case-control) studies suggested that the long-term use of HRT was associated with a substantial reduction in ischaemic heart disease. Quantitative overviews in the early 1990s indicated that the relative risk in users, compared to non-users, might be associated with a reduction of as much as 50%.[47,48] In the light of this, HRTs became the most widely prescribed drugs in the USA.[49]

It is now known from the results of several large, well-conducted RCTs that HRTs have no beneficial effect on ischaemic heart disease and that they increase the risk of stroke.[36] The discrepancies between the results of observational studies and RCTs, in the perceived benefits of HRT, were largely due to selection bias. If the observational studies had taken account of age, socioeconomic status, smoking habits and duration of use most (though not all) of the claimed advantages would have disappeared.[50] Some women, though, have paid a high price for this error.

There have, however, been circumstances where case-control studies have provided significant indications of the benefits of interventions. These include the protective effects of aspirin against acute MI,[51] the prevention of neural tube defects by folate,[52] the relationship between sleeping posture and sudden infant death syndrome,[53] and the protective effects of NSAIDs and colorectal cancer.[54] For the future we need to develop approaches that allow us to be confident that the results of observational studies generally, and case-control studies in particular, can provide information that permits reasonable assumptions about internal validity.[55] Newer techniques, such as Mendelian randomisation, may well assist.[56] More resources, time and energy to undertake methodological research are needed if causality is to be more securely based on observational evidence.

Assessment of harms. In contrast to the difficulties in assessing the benefits of interventions using case-control designs, this method has been extremely important in identifying causal relationships between specific interventions and their adverse effects. Some examples are shown in Table 5. Case-control studies have also been useful in providing reassurance that putative adverse effects 'signalled' by spontaneous reporting schemes do not appear to be problematic. Examples of this include suspected associations between bisphosphonates and AF[57]; and sympathomimetic bronchodilators with excess asthma deaths.[58]

Although selection bias and confounding by indication may still occur in case-control studies designed to investigate harms. For example, in 1974 three case-control studies published simultaneously suggested an association between the use of reserpine, for the treatment of hypertension, and the subsequent development of breast cancer.[59–61] Other studies, published later, failed to confirm the original association which now

appears to have resulted from excluding, as controls, those patients with cardiovascular disease.[62,63] Here, a subtle form of selection bias (exclusion bias) was probably responsible for the erroneous conclusions that were originally drawn.

Hierarchies of evidence

The first hierarchy of evidence was published in the late 1970s.[64] Since then many similar hierarchies, of increasing elaboration and complexity, have appeared in the literature. A survey in 2002 identified 40 such grading systems and a more recent (2006) study identified 20 more.[65,66]

The hierarchy in Table 1, like others, places RCTs at the highest level with a lesser place for those based on observational studies. This hierarchical approach to evidence has not only been adopted by many in the evidence-based medicine and health technology assessment movements, but it has come to dominate the development of clinical guidelines. Giving such prominence to the results of RCTs, however, is unreasonable. As Bradford Hill, the architect of the RCT, stated so cogently: 'Any belief that the controlled trial is the only way would mean not that the pendulum had swung too far but that it had come right off the hook'. [67]

As discussed, RCTs are particularly weak in relationship to generalisability and most especially in the assessment of harms. Although RCTs can, indeed, identify those adverse effects that occur relatively commonly, and which appear within the short timescales of their duration, there remain significant limitations. Contrary to a recent claim, only observational studies can offer the evidence required for assessing less common, or long-latency, harms.[68]

Hierarchies cannot, moreover, accommodate evidence that relies on combining the results from RCTs and observational studies. Combining evidence derived from a range of study designs is a feature of decision-analytic modelling as well as in the emerging fields of teleoanalysis and patient preference trials.[68,69,70,71]

Apart from their sheer number, the inconsistencies between hierarchies demonstrate their unsatisfactory nature. These include the variable prominence given to meta-analyses with some positioning them above large, high-quality RCTs while others ignore them. There are also inconsistencies between hierarchies in their grading of observational studies: some give a higher rating to cohort studies than case-control; some consider them to be all equal; and others reverse the order.

Hierarchies attempt to replace judgement with an oversimplistic, pseudo-quantitative, assessment of the quality of the available evidence. Decision makers have to incorporate judgements, as part of their appraisal of the evidence, in reaching their conclusion.[5] Such judgements relate to the extent to which each of the components of the evidence base is 'fit for purpose'. Is it reliable? Is it generalisable? Do the intervention's benefits outweigh its harms? And so on.

Concluding thoughts

Experiment, observation and mathematics – individually and collectively – have a crucial role to play in providing the evidential basis for modern therapeutics. Arguments about the relative importance of each are an unnecessary distraction. Hierarchies of evidence should be replaced by accepting – indeed embracing – a diversity of approaches. This is not a plea to abandon RCTs and replace them with observational studies. Nor is it a claim that the Bayesian approaches to the design and analysis of experimental and non-experimental data should supplant all other statistical methods. Rather, it is a plea to investigators to continue to develop and improve their methodologies; to decision makers to avoid adopting entrenched positions about the nature of evidence; and for both to accept that the interpretation of evidence requires judgement.

Table 5. Some adverse effects confirmed by case-control studies. Abridged from Reference 10.

Intervention (year of publication)	Adverse effect
Oral contraceptive agents (1967)	Venous thromboembolism
Stilboestrol during pregnancy (1972)	Genital tract carcinoma (in young females)
Aspirin in children (1985)	Reye's syndrome
L-tryptophan (1990)	Eosinophilia-myalgia syndrome
Non-steroidal anti-inflammatory drugs (1994)	Upper gastrointestinal bleeding
Hormone replacement therapy (1996)	Venous thromboembolism
Hormone replacement therapy (1997)	Breast cancer
Selective serotonin reuptake inhibitors (1999)	Upper gastrointestinal bleeding
Anticonvulsants (1999)	Stevens-Johnson syndrome and toxic epidermal necrolysis
Olanzepine (2002)	Diabetes
Fluoroquinolones (2002)	Achilles tendon disorders

For those with lingering doubts about the nature of evidence, itself, I remind them that while Gregor Mendel (1822–84) developed the monogenic theory of inheritance on the basis of experimentation, Charles Darwin (1809–82) conceived the theory of evolution as a result of close observation, and Albert Einstein's (1879–1955) special theory of relativity was a mathematical description of certain aspects of the world around us. William Harvey's discovery of the circulation of the blood – as he described in *De Motu Cordis* – was based on an elegant synthesis of all three forms of evidence.

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