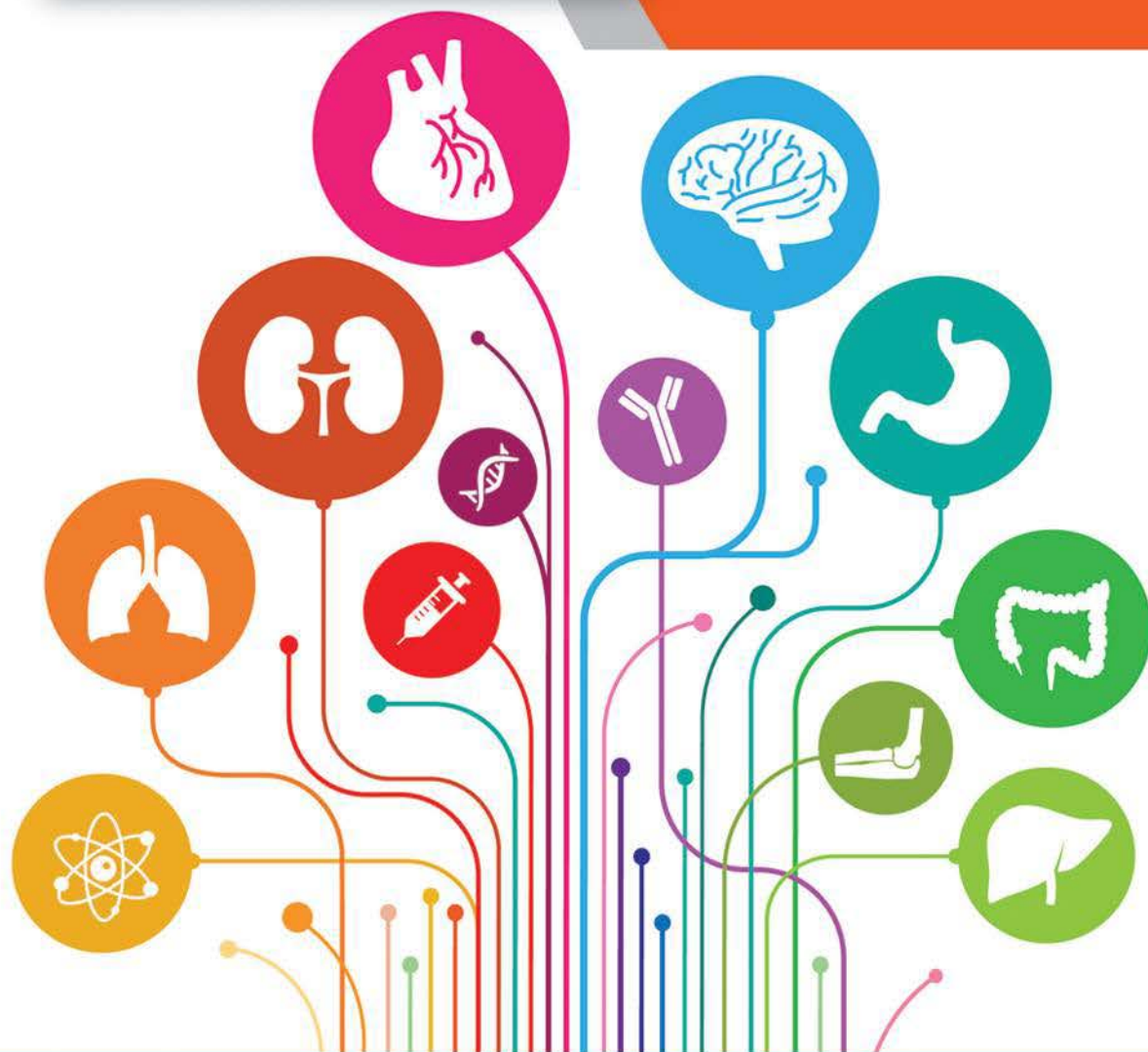


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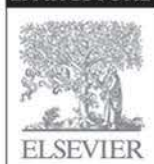
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ESSENTIALS OF INTERNAL MEDICINE

Nicholas J Talley, Brad Frankum
& David Currow

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3rd Edition

ESSENTIALS OF
INTERNAL MEDICINE

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Nicholas J. Talley

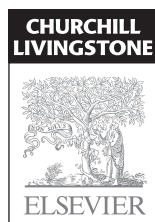
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FOREWORD BY KENNETH DEVAULT

Internal medicine is the broadest of fields, and a textbook to cover the breadth of the specialty is a daunting task. There are many attempts and few successes. The fact that this effort is now in its third edition speaks to its quality and popularity. This outstanding text has many highlights, including unique opening chapters on evaluating the literature, ethics, pharmacology, genetics and imaging. They are followed by specific, subspecialty-oriented discussions of all of the major aspects of internal medicine. There are well-written chapters on specialties outside of medicine but where patients often present to internists, including musculoskeletal disease, neurology, psychiatry, dermatology, ophthalmology and obstetrics. These chapters will be of great benefit not only to trainees but also to practicing internists who need a

quick and approachable reference when faced with problems outside their comfort zone. I am a practicing gastroenterologist who has to address general topics with my patients, and will keep this volume handy for rapid reference. The judicious use of tables and color figures make the reading particularly attractive. The editors and their impressive cadre of expert authors are to be congratulated on this outstanding edition which will compete for a prominent place on the desks of practicing health care providers, trainees and students, particularly those preparing for board examinations.

Kenneth R DeVault, MD, FACC, FACP
Professor and Chair, Department of Medicine, Mayo Clinic Florida

FOREWORD BY NICHOLAS SAUNDERS

Both physician trainees studying for their college and board examinations and senior medical students will welcome this new edition of *Essentials of Internal Medicine*. This third edition is enhanced by the inclusion of chapter authors who are experts in their field while maintaining the features of the book that have made earlier editions so popular among those preparing for examinations: conciseness; consistency; graphics, tables and images that clearly capture essential information; and reinforcement of important points through the use of 'clinical pearls' and self-assessment tasks.

In the main, chapters are organized by body system but there are very useful additional chapters at the beginning and end of the book that cover important basic concepts (such as clinical pharmacology and genetics), contexts (such as pregnancy and older age) and approaches (such as evidence-based practice and medical imaging) that are relevant to internist practice. Throughout the book the focus is on clinical features, pathogenesis and pathophysiology, investigation and management of patients with common disorders.

The editors comprise a very talented group, each recognized internationally for his expertise in internal medicine and, importantly, clinical education. At the time of publication of this edition, Talley, a gastroenterologist, is one of the 40 most highly cited living biomedical scientists in the world; Frankum, a clinical immunologist and allergist, is celebrated for his expert contributions to undergraduate and

postgraduate education; and Currow, a specialist in oncology and palliative care, is making important, novel contributions to the organization and delivery of cancer services and research.

The editors are also recognized for their professional leadership, with Talley currently President of the Royal Australasian College of Physicians, Frankum currently Vice President of the Australian Medical Association (New South Wales), and Currow a former President of both the Clinical Oncological Society of Australia and Palliative Care Australia.

It is fitting that each of the three editors is an alumnus of the University of Newcastle, Australia, whose medical school places clinical education at the centre of its mission and which has long been recognized for its educational innovation and excellence. The third edition of *Essentials of Internal Medicine* upholds and extends this reputation.

This book fills an important niche in the vast array of medical publications and will be a valuable addition to the bookshelves of students, physician trainees and generalists who are already established in practice. It is sure to be consulted frequently.

Nicholas Saunders AO, MD, Hon LLD
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‘The definition of a specialist as one who “knows more and more about less and less” is good and true. Its truth makes essential that the specialist, to do efficient work, must have some association with others who, taken altogether, represent the whole of which the specialty is only a part.’

—*Dr Charlie Mayo*

The American Board of Internal Medicine describes an internist as ‘a personal physician who provides long-term, comprehensive care in the office and in the hospital, managing both common and complex illnesses of adolescents, adults and the elderly’. Accurate diagnosis is the key to successful long-term management; the internist must be an expert diagnostician who applies their skill and knowledge like a detective to solve an often difficult problem, craft a sensible plan and make a positive difference. In order to practice safely and provide the best possible outcomes, the specialist physician must master multiple competencies that include a broad and deep knowledge of diseases in body systems and disease prevention.

The first edition of *Internal medicine: the essential facts* was written by a single author (the senior editor) while a consultant at Mayo Clinic, as a guide to mastering the core knowledge and clinical facts in internal medicine. The popularity of the first edition with those sitting the American Board in Internal Medicine, Membership of the Royal College of Physicians, Fellowship of the Royal Australasian College of Physicians (Part One) and similar examinations led to a successful second edition by the three of us. This new third edition has been completely revised and updated. All chapters have been written by experts in the field, followed by careful editing to ensure that the material is set at the correct standard. Every chapter has then undergone detailed peer

review and been subsequently revised and edited for consistency and clarity.

The new edition retains the most successful elements of previous editions, including an emphasis on the facts that all specialist physicians should know (or need to remember for their examinations). In particular, we have striven to ensure that essential areas that may be overlooked when one is reading a major textbook or a review are highlighted, and irrelevant facts or waffle are avoided. Traditionally difficult-to-master topics such as medical genetics, poisonings, acid-base disturbances, medical epidemiology, medical dermatology and interpreting cross-sectional images are included. Color illustrations to enhance recognition and learning, clinical pearls, and lists and tables that must be memorized are integrated into the text. Multiple-choice questions with answers and explanations are included for revision purposes.

This book aims to provide a framework of knowledge and the core facts that those sitting postgraduate examinations in internal medicine must know. For those wishing to further enhance their clinical skills, a complimentary textbook *Talley and O’Connor’s Clinical examination: a systematic guide to physical diagnosis* (seventh edition) should be consulted. *Essentials of Internal Medicine* should also prove useful for senior medical students and those studying for other examinations where core knowledge in internal medicine is a requirement. We sincerely hope that this concise guide to internal medicine will serve those striving for excellence.

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INTERNAL MEDICINE IN THE 21st CENTURY—BEST PRACTICE, BEST OUTCOMES

Brad Frankum, David Currow and Nicholas J Talley

The technological tools available to the modern internist allow us to understand and investigate disease in our patients in great depth. In the 21st century, targeted therapy offers enormous capacity to alleviate suffering, but challenges us to be absolutely precise with diagnosis, and with the use of evidence in decision-making. Deciding when and how to employ resources that are limited and expensive raises questions of ethics, equity, and where the balance lies between the science of human biology and the art of caring for sick people.

Computer technology (including sophisticated approaches to dredging big data to rapidly identify the likely diagnosis), ready access to information (for physicians, their patients and families), and increasing use of molecular and genetic diagnostic techniques are rapidly changing the practice of modern internal medicine. Physicians need to be able to use these tools, and we need to be flexible in the way we learn. Perhaps surprisingly in this internet-driven world the textbook, with its synthesis of information and perspective on what is clinically important, retains its relevance as a cornerstone of medical education. We must also, however, recognize that the experience and expertise of our colleagues remains absolutely crucial to guide our ongoing learning and development.

GENERAL VERSUS SUB-SPECIALTY MEDICINE

There is a dichotomy in the practice of internal medicine. On the one hand is the lure of specialization, of becoming

expert and authoritative in very narrow fields. On the other hand is the need to retain the ability to treat patients in a holistic manner.

Many patients present with undifferentiated illness, often accompanied by multiple comorbidities. These people require a physician with the skills to sort out multiple problems in the context of their overall health, both physical and psychological, while taking into account their social and cultural background. Too often the sub-specialist has lost the will or confidence to manage a patient's problems when they fall outside a particular organ system. Patients with multiple medical problems can become the victims of an unseemly conflict between medical teams as to who should take responsibility for their overall care, while each specialty is absolute about how their body system should be treated. For best outcomes, care must be highly coordinated; fragmented care puts patients at risk. Physicians as medical experts must take a leadership role here; it is not the responsibility of someone else.

As life expectancy increases in populations globally, as a result of both improved living conditions and longer survival due to the course of much chronic disease being ameliorated, physicians need to maintain the skills to manage the elderly. There is no doubt that the elderly experience unique physiological and pathological changes, but too often physicians fail to factor this into their decision-making. As an example, there is good evidence that polypharmacy is detrimental to the prognosis of elderly patients regardless of which drug combinations are being prescribed, yet most physicians are more comfortable adding medications to a patient's

treatment than removing them. Similarly, the care provided must be appropriate for each individual, and toward the end of life withholding potential treatment may be a much better choice than attempting heroic but clinically futile measures.

Arguments are made that there should be a renaissance of generalism, particularly in the hospital setting, to allow for more holistic and rational treatment of patients. Perhaps a better alternative would be for all of us in the field of internal medicine to strive to practice as internist first and sub-specialist second. We also help patients more effectively when we work as part of a healthcare team, recognizing and employing the unique skills of colleagues as well as nursing and allied health staff.

Most importantly, the care of patients should be conducted in a partnership with the patient, and often also with their family. No amount of technical knowledge and procedural expertise on the part of the physician can treat patients effectively in the absence of trust and empathy. Communication skills need to be increasingly sophisticated as people's health literacy increases. Poor outcomes for patients occur much more frequently through failures of communication than due to a lack of scientific knowledge on the part of physicians.

THE IMPORTANCE OF DIAGNOSIS

Rational treatment of patients can only occur after rational diagnosis. When diagnosis proves elusive, a sensible differential diagnosis can allow for the formulation of an appropriate plan of investigation and management. "Non-cardiac chest pain", "dyspnea", or "abdominal pain for investigation" are not diagnoses—they are symptoms. The internist needs to do better than allocating broad symptomatic labels to patients. Internal medicine is the branch of medicine for the expert diagnostician, and the discipline of committing to a refined provisional and differential diagnosis identifies the path forward for both clinician and patient.

Too often in modern medicine, physicians make cursory attempts to form a diagnosis based on limited history and physical examination, and then rely on investigations to refine the diagnosis. A defensive approach often results in excessive numbers of tests and more mistakes; this trap should be avoided. An investigation is only helpful diagnostically if there is a reasonable pre-test probability that it will be positive.

As an example, an "autoimmune screen" is often performed for a patient with fatigue as a presenting problem but no other features of a systemic autoimmune disease. What, then, to do when the antinuclear antibody (ANA) comes back detectable in a titer of 1:160? Is this within the range of normal? How many asymptomatic patients will have a detectable ANA in low titer? How many extra tests should now be performed to ensure that the ANA is not of significance? How do we deal with the inevitable anxiety of our patient who consults the internet to find that ANA is found in systemic lupus erythematosus, as indeed is the symptom of fatigue? How will we look in the eyes of the patient when we say to them that the "positive" test was really negative and unimportant? If so, why was it ordered in the first place?

Furthermore, the larger the number of investigations performed, the higher the likelihood that a result will fall outside the reference range as a matter of chance. This is the statistical nature of a normal distribution curve. An abnormal result may be of no clinical significance, but still needs to be explained to a patient. As diagnostic techniques become more sensitive, especially imaging modalities, increasing numbers of incidental findings result. The physician needs to be able to discern when this needs further investigation and when it can be dismissed. Most investigations are not innocuous and run the risk of potential harm. Physicians have a societal responsibility to be cost-conscious and all investigations should be ordered judiciously.

THE PHYSICIAN'S ROLE IN PUBLIC HEALTH

In the era of personalized medicine, there remains a critical role for the physician as an advocate for, and guardian of, public health.

The greatest impact on health that we can make as physicians remains in the area of global preventative medicine. The world population's health will only continue to improve with concentrated, ongoing efforts to implement vital measures such as large-scale vaccination against infection; tobacco, alcohol, and recreational drug control; screening for pre-cancerous lesions, and earlier-stage cancers that can be cured; obesity and diabetes mellitus prevention; protection from war, violence, and road trauma; reduction in the spread of HIV, malaria, and tuberculosis; and minimalization of climate change. Even at a local level, it is essential for physicians to argue the case for these measures, especially in the face of ever-pressured health budgets, anti-scientific misinformation from vested interests, and governments intent on spending vastly more money on military defenses than on preventative health.

As physicians we generally treat patients on a one-on-one basis. Most feel, quite appropriately, duty-bound to facilitate the best possible care for each individual patient. There is, however, an opportunity cost for every dollar spent on healthcare. It is an obligation for each of us to spend this money appropriately and not waste valuable resources. Appropriate care is not necessarily the same as the most expensive care. Sometimes, simplifying investigations and treatments serves patients' interests far better.

THE PHYSICIAN AS SCHOLAR

Scholarly activity continues to define the essence of internal medicine. Scientific analysis of material, education of others, and ongoing research into basic and clinical mechanisms of health and disease are the cornerstones of practice for the internist.

The sources of information available to the physician continue to expand. The temptation to be influenced by vested interests is ever-present, whether that be from pharmaceutical companies trying to market drugs, researchers

trying to maintain grant funding, colleagues trying to boost referrals, or even textbook authors trying to sell their books! Critical analysis of information through understanding the many factors influencing and biasing the production and presentation of data is the only way to guard against poor decision-making. All physicians need to exercise the intellectual discipline of critical appraisal in these settings.

Most medical graduates understand the importance of teaching and role-modeling provided by their senior colleagues. There is no more powerful lesson than seeing an expert in action in a clinical setting, or having a complex concept explained in an insightful and succinct fashion. As learning becomes increasingly blended between the classroom, the internet, and the clinical setting, the physician remains the central reference point for students and junior doctors to comprehend what is really important to

understand and master. Physicians must take this responsibility as educators seriously. They must strive for excellence as teachers just as they do as clinicians.

To research is to improve. If we do not strive for new knowledge and understanding, our patients will not be able to look forward to better healthcare in the future. Research may involve an audit of an individual's current practice, or may involve participation in a multi-national trial of a new therapy. Whatever form it takes, it underpins the practice of internal medicine. Our participation in research such as a clinical trial is likely to improve our practice, no matter what the outcome of the clinical trial.

As physicians, we must remain curious, vigilant, and sceptical. If we remain inspired by the scholarship of medicine, we can no doubt be an inspiration to our patients and colleagues.

EVIDENCE-BASED MEDICINE AND CRITICAL APPRAISAL OF THE LITERATURE

Jane Young and David Currow

CHAPTER OUTLINE

- INTRODUCTION
- ASSESSING THE EVIDENCE
 - Sources of error
 - Assessing potential biases in different study designs
- CRITICAL APPRAISAL OF THE LITERATURE
- INTERPRETING A STUDY'S FINDINGS
- INTERPRETING STATISTICAL ANALYSIS
- INTERPRETING TEST RESULTS
- SCREENING
- CONCLUSION

INTRODUCTION

In order for patients to benefit from gains in knowledge achieved by medical science, the findings of research must be integrated into routine clinical practice. Evidence-based medicine is an approach to clinical practice in which there is an explicit undertaking to incorporate the best available scientific evidence into the process of clinical decision-making. Achievement of this requires skills in the identification, critical appraisal and interpretation of relevant research studies in order to assess the strengths, limitations and relevance of the evidence for the care of an individual patient.

ASSESSING THE EVIDENCE

When assessing the findings of scientific research, one of the first considerations is whether the results of a study are **accurate**. The accuracy of a study is also referred to as

its 'internal validity'. To assess internal validity, potential sources of error or bias in the study must be considered.

Sources of error

There are two major sources of error that affect research studies. **Random error** arises due to chance variations in study samples and can be thought of as adding 'noise' to the data. It reduces the precision of the findings but can be minimized by increasing the sample size of the study.

In contrast, **systematic error** is due to the way in which the study was designed or conducted and will always deviate a research finding away from the truth in a particular direction, resulting in an under- or over-estimate of the true value. Systematic error may arise from the way in which study participants were selected into the study ('selection bias'), the accuracy of study measures ('information bias') or the concomitant effect of other factors on the outcome in question ('confounding') (Box 2-1, overleaf). It should be recognized that different sources of

Box 2-1**Types of systematic error****Selection bias**

Error in the study's findings which arises from the methods used to select and recruit study participants.

- If the relationship between the study factor and the outcome is different for participants and non-participants (those excluded, omitted or who declined to participate), the study's results will be inaccurate.
- Recruitment of random, population-based samples with high consent rates minimizes potential selection bias in a study.
- Be alert to potential selection bias in studies which:
 - » recruit volunteers
 - » recruit other non-representative groups
 - » have low participation or consent rates
 - » have high losses to follow-up.

Information bias

Errors in the study's findings due to inaccurate collection of information.

- Accuracy is how well the measure represents the true value.
- Reliability is the ability of a measure to provide consistent results when repeated.
- Measures that rely on the judgment of an individual can be influenced subconsciously by knowledge of the research question.
- In clinical trials, blinding of outcome assessors, clinicians and patients to treatment allocation reduces the potential for awareness of group allocation to influence study measures.

- In case-control studies, cases may have heightened awareness of possible causes of their disease and so have different recall of exposure to factors of interest than controls ('recall bias').

Confounding

Error in the study's findings owing to mixing up of effects due to the study factor with those due to other factors.

- Occurs when there is an uneven distribution of prognostic factors between the groups being compared.
- In clinical trials, randomization aims to produce groups which are equally balanced for both known and unknown prognostic factors.
- Randomization will usually control for confounding if the sample size of the trial is large enough for the comparison groups to have similar distributions of prognostic factors.
- Potential confounding is a major issue in non-randomized studies that can be minimized by:
 - » restricting study participation to exclude potential confounding factors
 - » matching participants in different study groups for prognostic factors
 - » stratifying participants by the prognostic factor and analyzing each stratum separately
 - » statistical modeling to adjust for the effect of confounding.

systematic error within the same study may work in the same or opposing directions. However, as the true value of interest is generally not known, the size of any error cannot be measured directly. Unlike random error, systematic error cannot be reduced by increasing the size of the study but must be minimized by good study design. Assessment of the potential for systematic error requires consideration of the potential for selection bias, information bias and confounding within each study.

Assessing potential biases in different study designs

A number of different types of study are used in clinical research and each is susceptible to varying sources of systematic bias. An understanding of the key features of each study design, and the most important sources of bias, provides the basis for critical appraisal of the scientific literature. Furthermore, once the design of the study has been identified, there are design-specific critical appraisal checklists, such as those developed by the Critical Appraisal Skills Programme (CASP) in the United Kingdom, that are readily available

on-line to provide a step-by-step guide to the assessment of the methodological quality of research studies.

Randomized controlled trials

In randomized trials, participants are randomly allocated to treatment groups, for example to new treatment or placebo. The randomization process should achieve treatment groups in which patients are similar for both known and unknown prognostic factors (confounders) so that any differences in outcome can be attributed to differences in treatment.

Well-designed randomized trials use a method to allocate patients to treatment groups that is truly random and that ensures that the sequence cannot be known or guessed in advance by patients or those recruiting them ('allocation concealment'). Random number tables or computer-generated sequences are the best methods to obtain a truly random sequence. Inappropriate methods of 'randomization' are those in which the group allocation is not truly random, such as alternating patients between treatment groups or selecting the treatment group based on a patient characteristic (such as date of birth) or day of clinic attendance. In addition to generating

a truly random sequence, the trial methods need to ensure allocation concealment so that a clinician's decision to recruit a particular patient to a trial and the patient's decision whether or not to participate cannot be influenced by knowledge of the treatment group to which they will be allocated. Trial methods must ensure that the randomization schedule is not freely available to those involved in the actual recruitment of patients. This can be achieved by use of a central randomization service in which clinicians contact the service by phone, fax or e-mail to register a patient who has already consented to be in the study, and to find out which treatment the patient has been randomly allocated to receive.

Intention-to-treat (ITT) analysis is a method used to preserve the randomization of participants at the analysis stage of a clinical trial. In ITT analysis, patients are analyzed in the groups to which they were originally allocated, regardless of what may have happened in practice. So any patients who decline the treatment to which they were randomized, those who cross over to another group for any reason, and those who drop out are analyzed as part of their original allocated group. As all patients who were randomized must be accounted for at final follow-up, the trial methods should attempt to minimize any drop-outs or losses to follow-up. Furthermore, the statistical methods should describe how any losses to follow-up were dealt with in the statistical analysis.

The use of **blinding** is a method to guard against information bias in randomized trials that also can be used in non-randomized studies. 'Blinding' or concealment of a study participant's treatment group ensures that preconceived attitudes or expectations of the relative effectiveness of the treatments being compared cannot influence the study data. Blinding of patients can guard against a placebo effect, in which patients report better outcomes due to the psychological effect of receiving a treatment that they perceive as being more effective than a control treatment. Blinding of clinicians reduces the potential for overt or subconscious differences in patient management that could arise from knowledge of the treatment that has been received. Blinding of other study staff such as outcome assessors, data collectors and biostatisticians can minimize the risk that measurement or analysis decisions are influenced by awareness of treatment group. As blinding addresses any information bias that results from participants' attitudes and expectations of the likely benefits of the treatment being tested, blinding is particularly important for study outcome measures that are subjective, such as pain, quality of life or satisfaction. Blinding is less important for objective measures such as mortality.

Key points to consider in the assessment of a randomized trial are summarized in Box 2-2.

Pseudo-randomized or quasi-experimental trials

In these trials, the method of developing the treatment allocation sequence is not truly random. For example, alternate patients could be allocated to different treatment groups, or treatments could be offered according to days of the week or last digit of a medical record number. A major concern is whether there is any relationship between the method of allocation and specific types of patient. For example, it may

Box 2-2

Key points for appraisal of a randomized controlled trial

- How was the randomization schedule developed?
- Was this a truly random process?
- Could patients, or those recruiting them, have been able to know or deduce the next treatment allocation?
- Were patients concealed to their treatment allocations?
- Were clinicians concealed to the patients' treatment allocations?
- Were those responsible for measurement of study outcomes blinded to the patients' treatment allocations, or were objective measures used?
- Were all patients who were randomized accounted for in the final analysis in the groups to which they were allocated (regardless of whether they actually received this treatment)?
- Were there any other factors that could have influenced the results of the study (e.g. poor compliance with allocated treatment, large numbers of patients crossing over to a non-allocated treatment group, contamination between treatment groups, co-interventions or changes in healthcare delivery during the trial that may have influenced outcomes)?

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be that older or sicker patients attend a clinic on a particular day for reasons relating to clinical, administrative, access or transport issues. In addition to careful consideration of potential pitfalls of the group allocation method, other points to consider in the assessment of a pseudo-randomized study are the same as for randomized trials.

Cohort studies

Cohort studies involve the longitudinal follow-up of groups of individuals to identify those who develop the outcome of interest.

- In a prospective cohort study, the individuals are identified at the start of the study and data are collected about the study factors or exposures of interest as well as all potential confounding factors. The cohort is then followed, usually for several years, with regular assessment of study outcomes over this period.
- In a retrospective cohort study, individuals are usually identified from existing databases or records, and information about study factors, potential confounders and outcomes is also obtained from existing data sources.

Retrospective cohort studies are usually much quicker to complete than prospective studies, but a major disadvantage is that information about potential confounders may not have been collected at the time the original data were obtained. Box 2-3 (overleaf) summarizes key points to consider in the assessment of a cohort study.

Box 2-3**Key points for appraisal of a cohort study**

- Is the study prospective or retrospective?
- Is the cohort well-defined in terms of person, time and place?
- Is the cohort population-based?
- Were data collected on all important confounding factors?
- Were study outcomes and potential confounders measured in the same way for all members of the cohort?
- Was the length of follow-up sufficient to identify the outcomes of interest?
- Were there large losses to follow-up?
- Were those lost to follow-up likely to have different outcomes to those who continued in the study?

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Box 2-4**Ten questions to ask about a research article**

- 1 Is the study question relevant?
- 2 Does the study add anything new?
- 3 What type of research question is being asked?
- 4 Was the study design appropriate for the research question?
- 5 Did the study methods address the most important potential sources of bias?
- 6 Was the study performed according to the original protocol?
- 7 Does the study test a stated hypothesis?
- 8 Were the statistical analyses performed correctly?
- 9 Are the conclusions justified from the data?
- 10 Are there any conflicts of interest?

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Case-control studies

In case-control studies, cases are selected because they have already developed the outcome of interest, for example a disease, and their history of exposure, risk factors or treatment are compared with similar people who have not developed the outcome of interest ('controls'). Case-control studies are particularly useful to investigate risk factors when the clinical condition of interest is rare, as it would take too long to recruit and follow up a prospective cohort of patients. Selection of appropriate controls and the possibility of recall bias are major concerns with case-control studies.

Cross-sectional studies

In cross-sectional studies, information about the study factors and outcomes of interest are collected at one point in time. The purpose of this type of study is to investigate associations between these factors, but it is not possible to draw conclusions about causation as a sequence of events cannot be established. A survey is an example of a cross-sectional study.

CRITICAL APPRAISAL OF THE LITERATURE

While a focus of the critical appraisal of a research study is an assessment of the potential for bias in the design and conduct of the research, there are a number of other important factors that should be considered (Box 2-4).

Two important considerations are whether the specific research question addressed in the study is relevant to the clinical question of interest, and whether the appropriate study design was used to answer this question. While it is widely recognized that well-designed randomized

controlled trials provide the best quality evidence about the effectiveness of medical therapies, other study designs are optimal for different types of research question. For example, an evaluation of the accuracy of a new diagnostic test would be best investigated using a cross-sectional study design in which a consecutive sample of patients received both the new test and an existing 'gold standard' test simultaneously. The accuracy of the new test could then be established by comparing the results with the 'gold standard' test. Questions about prognosis are best answered using prospective cohort studies.

Many studies are conducted that are not the optimal design for the research question being addressed. This can be because the optimal design is not acceptable or is not feasible with the time and resources available. For example, it can be very difficult to conduct randomized trials to test new surgical procedures, particularly when there is a large difference in the extent of surgery between the experimental and standard approaches. Patients are likely to refuse to have a non-reversible treatment option decided essentially on the basis of the toss of a coin. Another circumstance where randomized trials are difficult is when the condition of interest is very rare so that it would be impossible to achieve the required sample size within a reasonable timeframe. Many organizations, such as those involved in the development of evidence-based clinical practice guidelines, have developed hierarchies of evidence that rank study designs from strongest to weakest for questions relating to therapeutic effectiveness, prognosis or diagnostic test accuracy. For therapeutic effectiveness, for example, one hierarchy from strongest to weakest would be: randomized trial; a comparative study with concurrent controls (pseudo-randomized trial, prospective cohort study, case-control study, controlled time series); comparative study with historical controls;

uncontrolled (single-arm) studies such as uncontrolled time series or uncontrolled case series.

Meta-analysis is a statistical technique in which the findings of several studies can be pooled together to provide a summary measure of effect. Meta-analysis should always follow a comprehensive systematic review of the literature to identify all relevant primary studies and to assess the quality and comparability of these studies. When conducted according to strict protocols, such as those developed by the Cochrane Collaboration to minimize bias, systematic review and meta-analysis can provide the strongest evidence on a topic as it incorporates all the relevant scientific evidence from individual studies. Hence, most evidence hierarchies have meta-analysis as the highest-ranked study design. In the case of questions of therapeutic effectiveness, meta-analysis of individual randomized controlled trials would be considered the strongest evidence on the topic. Key points to consider when assessing a systematic review or meta-analysis are summarized in Box 2-5.

Box 2-5

Key points for appraisal of a systematic review or meta-analysis

- Was the literature review sufficiently comprehensive to identify all the relevant literature?
- Were specific inclusion and exclusion criteria used to select articles to be included in the review?
- Were important types of article excluded (e.g. those in foreign languages, unpublished articles)?
- Was the quality of the included articles assessed using explicit criteria by two independent reviewers?
- Were numerical results and key findings extracted from the included articles by two independent reviewers?
- Was sufficient detail about the included studies provided to enable comparisons of patient characteristics, treatments and outcomes between studies?
- If a meta-analysis was conducted, was an assessment of heterogeneity and the appropriateness of calculating a summary measure assessed?

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INTERPRETING A STUDY'S FINDINGS

Clinical studies use a variety of measures to summarize their findings.

- A '**point estimate**' is the single value or result that is obtained from the study sample. It is the best estimate of the underlying true value that has been obtained from the study data. Different studies that address the same clinical question may yield slightly different point

estimates due to small differences between the study methods and samples and the play of chance.

- **Incidence** and **prevalence** are measures commonly used to describe the burden of disease in the community.
- A **rate** is the number of events occurring in a defined population over a specific time period, such as one year.

Incidence and prevalence are often mixed up, but shouldn't be! An **incidence rate** is the number of *new* cases per population in a given time period, and is a measure of the risk of developing the condition of interest. For example, cancer incidence rates are usually reported as the number of new cases per 100,000 people per year. In contrast, **prevalence** is the number of people in the population with the condition of interest during a specified time period and is a good measure of the impact of the disease in the community. Prevalence includes cases that were diagnosed prior to but continue to exist during the time period, as well as the new cases that occur for the first time during the time period. **Point prevalence** is the number of people in the population with the disease at a single point in time.

Rates can be **standardized** to allow valid comparisons to be made between two or more different populations. For example, the risk of most cancers increases with advancing age. A comparison of cancer incidence rates between two regions with different age structures would be misleading if age were not taken into account, as a higher cancer incidence rate would be expected in the region with the older population. The incidence rates for the different regions can be age-standardized by calculating what the rates would be if each region had the age structure of a standard population (direct standardization). In this way, the effect of age is removed as much as possible from the comparison of the cancer incidence rates.

Many clinical studies investigate the relationship between a study factor (e.g. risk factor or type of treatment) and an outcome. The results can be presented in a 2×2 contingency table, from which various measures of association or effect can be calculated (Figure 2-1, overleaf). These measures can be reported in *absolute* or *relative* terms.

- The **absolute** effect is simply the difference in means, medians, proportions or rates between groups. Imagine that in a hypothetical trial, 200 patients are randomly allocated to either a new treatment for cancer (intervention group) or standard treatment (control group) and the proportion who are disease-free at 12 months is the primary outcome measure (Figure 2-1). If 20 (10%) patients in the intervention group and 10 (5%) patients in the control group are disease-free at 12 months, the **absolute risk reduction** is $10 - 5 = 5\%$. The number needed to treat (NNT) is the number of people who need to be treated based on the trial to prevent 1 additional event over a specified period of time. The NNT is calculated by taking the inverse of the absolute risk reduction. In this example, the NNT is $1/(5/100) = 20$, showing that 20 people would need to be treated to prevent 1 additional recurrence at 12 months.
- These results can also be presented in terms of the outcome of the intervention group **relative** to the control group. The **relative risk** (sometimes called the risk