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The international source of the best available evidence for effective health care

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Dear Colleague:

UnitedHealth Foundation is pleased to provide you with a complimentary copy of *Clinical Evidence,* Issue 4, an international resource that provides easy access to the most up-to-date information on what works in medicine. *Clinical Evidence* was developed by the BMJ Publishing Group, publisher of the 160-year old *British Medical Journal*, in conjunction with internationally recognized medical experts.

Today, the sheer volume of information on medical care that is available through the popular media and elsewhere is overwhelming — and much of it is biased, fragmentary and confusing. We recognize how difficult it can be for the practicing physician to discern what information is based on the latest scientific evidence. UnitedHealth Foundation is committed to helping physicians access objective, evidence-based information they can use to improve health care delivery.

This past summer, UnitedHealth Foundation distributed copies of *Clinical Evidence,* Issue 3 to approximately 400,000 physicians throughout the United States. The response to this initial distribution was so overwhelmingly positive that the Foundation now is distributing *Clinical Evidence,* Issue 4 and has expanded the recipients to include many academic teaching programs. This book has proven particularly timely given the increasing attention to, and support for, evidence-based decision-making as a standard for medical care.

Given the clear value and importance of this volume, coupled with the universally positive response to its distribution, UnitedHealth Foundation already has committed to provide complimentary copies of the next issue of *Clinical Evidence* to physicians and academic teaching programs. If you would like to receive a copy of ***Clinical Evidence,*** Issue 5, please e-mail us at uhfce@uhc.com, phone us at **1-877-485-8074**, or mail us at the address above with your name, specialty and the address where you would like the book sent.

The BMJ Publishing Group is solely responsible for the content of all issues of *Clinical Evidence* and is continually revising *Clinical Evidence* based on feedback from physicians. I encourage you to provide them with comments via CEfeedback@bmjgroup.com.

We hope that you continue to find *Clinical Evidence* a resource that can assist you and your patients in making the best decisions possible, and thus advance optimum medical care to all people.

Sincerely,

Bill McGuire

William W. McGuire, M.D.
Chairman
UnitedHealth Foundation

Team and advisors

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Burnett, Chris Henshall, and Tom Mann; the British National Formulary, and especially Dinesh Mehta; the Health Information Research Unit at McMaster University and especially Brian Haynes and Ann McKibbon; the Sowerby Centre for Health Informatics at Newcastle especially Nick Booth, Peter Johnson and Neill Jones; and the clinicians, epidemiologists, and members of patient support groups who have acted as peer reviewers. We also thank the following people for their help as freelance advisors and editors during our early development: Martin Duerden, José García, Richard Hardern, Harry Hemingway, Per Hjortdahl, Denise Kendrick, Tim Lancaster, Richard LeBlond, Helen Manson, Linda McIntyre, Edward Merrens, Sarah Purdy, Liam Smeeth, Nick Summerton, and Kieran Sweeney. Finally, we are grateful to the clinicians and patients who spare time to take part in focus groups, which are crucial to the development of *Clinical Evidence*.

Welcome to Issue 4

Welcome to Issue 4 of *Clinical Evidence*. *Clinical Evidence* is a six monthly, updated compendium of evidence on the effects of clinical interventions. It summarises the current state of knowledge, ignorance, and uncertainty about the prevention and treatment of clinical conditions, based on thorough searches and appraisal of the literature. It is not a textbook of medicine nor a book of guidelines. It describes the best available evidence, and where there is no good evidence, it says so.

RESPONSE TO ISSUE 3

Since the publication of Issue 3, around 400,000 people, mainly in the UK and USA, have received a printed copy of *Clinical Evidence*. Each month, a thousand more people register online and, in September 2000, a German translation of *Clinical Evidence* was published.[1]

We are delighted with the huge amount of feedback from physicians, pharmacists, nurses, and members of the general public. It is overwhelmingly positive, and we are encouraged that straight evidence about important clinical questions is useful in so many areas of clinical practice, policy formulation, education and life.

Here are some examples of feedback from readers that have led to changes in *Clinical Evidence:*

- **Evidence relevant to hospitals and to community**
  Many readers have commented that we should provide more evidence that is relevant to clinical care outside hospitals. They have argued strongly that clinical problems in community settings are often less defined because they present early in their natural history before diagnostic features are apparent. Also, for conditions that usually resolve spontaneously, routine diagnostic testing may add few benefits to justify their risks and costs. Some topics in *Clinical Evidence* already address undifferentiated problems (e.g. low back pain and sciatica, p 614). Others, mainly from within hospitals, feel that these topics would be improved by focusing on specific conditions established by modern advanced diagnostic methods. Neither view is right or wrong — the evidence of benefits and harms will vary from setting to setting. This dilemma spurs us on to do better by considering questions in a variety of settings (as in the topic on croup, p 206), and to ask the question whether evidence is available about comparisons of care in different settings (as in the topic on stroke management, p 114).

- **Discarding old issues of Clinical Evidence**
  If you want to be sure that you are using the latest available evidence, then discard old issues of *Clinical Evidence* as soon as the new issue arrives. From now, we will use a distinct colour on the cover to help you to identify the latest issue at a glance.

- **New topics**
  Many of you have suggested topics for future coverage. A list of suggested and commissioned topics and questions can be found on our web site www.clinicalevidence.org. Soon you will be able to indicate your preferences on the web site so that we can prioritise the commissioning of topics.

- **Evaluation of Clinical Evidence**
  We have embarked on a number of simple evaluations of *Clinical Evidence*. So far these have been simple qualitative studies of existing users, but we hope to commission more studies of the impact of *Clinical Evidence* as part of a specified intervention. If you are interested in the organisation of such an evaluation, then please contact us.

WHAT'S NEW IN ISSUE 4?

The content has been updated and expanded. Firstly, there is one new section on Poisoning and 17 new topics, including Paracetamol poisoning, Obesity, Hip fracture, Wax in ear, Chronic tension-type headache, and Opportunistic infections in HIV. All the new topics are labelled on the contents page. Secondly, several topics have been expanded, including Changing behaviour, Alzheimer's disease, Depressive disorders, and Schizophrenia. The newly included interventions are labelled on the summary page for each topic. Thirdly, 99 of the 103 topics from Issue 3 have been updated and re-edited. This has involved performing a *Clinical Evidence* search from the date of the previous search, appraising any new studies that were identified, and incorporating the new evidence into the *Clinical Evidence* review (e.g. one new systematic review found that progesterone is likely to be inneffective or harmful for premenstrual syndrome — causing no improvement of symptoms but numerous minor adverse effects). The topics have also been re-edited to make them, we hope, even clearer, and to make good any instances where we felt that we had misrepresented the evidence in Issue 3. In some cases this has meant promoting or demoting an intervention from one summary category to another.

QUALITY ASSURANCE

We have appointed a Quality Assurance editor to help guarantee that we present the best available evidence. We will make all the results of our quality processes available on our web site. Our existing quality assurance methods include overt search, critical appraisal, peer review, and editing processes. As a result of quality considerations, we have made two small adjustments to the way we produce *Clinical Evidence*.

- **Categorising interventions**
  We have refined the criteria for categorising interventions to make interpretation easier. It is impossible to avoid a subjective element in the categorisations because different issues need to be combined within the interventions table. Opinions differ from person to person on the relative importance of each issue. For example, it is difficult to weigh a frequent but small benefit versus a rare but severe harm. Another difficulty arises from strong evidence of a small benefit versus weaker evidence of a much larger benefit). Now interventions categorised as "beneficial" have (a) evidence of significant benefits derived from RCTs and (b) expectation of harms that is small compared with the benefits. These changes do not remove the subjective element, and we recognise the importance of applying the value judgements of those involved in medical decisions to the evidence. In a few instances, where RCTs would be regarded as unethical or impractical, we have categorised interventions as beneficial if there is sufficient evidence from non-RCT sources (e.g. oxygen versus no oxygen in severe acute asthma; treatment of generalised epilepsy). These exceptions have been clearly identified within the tables. Preliminary tests to assess the agreement in categorisation between raters have found encouarging agreement at least among our editors; more about this in future issues.

- **Systematic reviews**
  We now use a tighter definition of systematic reviews to mean those reviews which provide operationally explicit descriptions of their search and selection criteria so that the systematic review could be replicated by others. When we count how many systematic reviews found for a clinical question, then recent systematic reviews replace earlier reviews that used the same analytical methods.

UPDATING

The biggest challenge facing *Clinical Evidence* is that of producing high quality updates for a large number of topics at regular intervals. From early 2001, we will post new updates immediately to our web site, and an e-mail alert system will be developed to inform subscribers of updates in selected areas. We aim to update all topics on a regular cycle. The paper version will continue to be published every six months, and will contain all the updates available at that time.

THE FUTURE

We will expand *Clinical Evidence* as fast as we reasonably can (currently around 40 new topics per year). However, many people have written asking for a book that fits in a pocket. One way to achieve both of these objectives is to produce a summary version that can be used in conjunction with a larger book, CD-ROM, or online version of *Clinical Evidence*.

We are piloting an option for subscribers to address particular "snippets" of information within *Clinical Evidence*, so that they can be electronically linked to guidelines and other documents owned by the subscriber. The web version of *Clinical Evidence* is itself already linked to the National Library of Medicine's PubMed database. These links lead to abstracts of references and, where possible, to full text versions.[3] We aim to provide additional links from each reference to critical appraisal information and extracts of results from that reference.

We have started projects aimed at developing specialty versions of *Clinical Evidence* (for paediatrics, cardiology and mental health), and aimed at creating topics about questions on diagnostic strategies.

Today, most of our subscribers and authors are from Western countries. We hope that before long *Clinical Evidence* becomes a global resource with international contributors and readers. We are keen to work with agencies around the world to overcome the technical, financial, language, and other barriers which impede access.[4]

We look forward to hearing your views on what we are doing, how we could do it better, and what we should include in future issues.

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About Clinical Evidence

The inspiration for *Clinical Evidence* came in a phone call in 1995. Tom Mann and his colleagues at the NHS Executive asked the BMJ Publishing Group to explore the possibility of developing an evidence "formulary" along the lines of the *British National Formulary*. They recognised that clinicians were under increasing pressure to keep up to date and to base their practice more firmly on evidence, but that few had the necessary time or skills to do this. Their idea was to provide a pocket book containing concise and regularly updated summaries of the best available evidence on clinical interventions. However, they didn't think that the NHS could develop such a formulary itself. "It would be marvellous," said Tom Mann, "if somebody would just do it." A small team at the BMJ set to work to produce a pilot version of what was then called the *Clinical Effectiveness Directory*.

Since that pilot, a great deal has changed. In collaboration with the American College of Physicians–American Society of Internal Medicine, we convened an international advisory board, held focus groups of clinicians, talked to patient support groups, and adopted countless good ideas from early drafts by our contributors. Throughout we have kept in mind an equation set out by Slawson et al.[1] This states that the usefulness of any source of information is equal to its relevance, multiplied by its validity, divided by the work required to extract the information. In order to be as useful as possible, we aimed for high relevance, high validity, and low work in terms of the reader's time and effort. We also kept in mind principles of transparency and explicitness. Readers needed to understand where our information came from and how it was assembled.

A UNIQUE RESOURCE

Clinical Evidence joins a growing number of sources of evidence based information for clinicians. But it has several features that, we think, make it unique.

- Its contents are driven by questions rather than by the availability of research evidence. Rather than start with the evidence and summarise what is there, we have tried to identify important clinical questions, and then to search for and summarise the best available evidence to answer them.
- It identifies but does not try to fill important gaps in the evidence. In a phrase used by Jerry Osheroff, who has led much of the recent research on clinicians' information needs,[2] *Clinical Evidence* presents the dark as well as the light side of the moon. We feel that it will be helpful for clinicians to know when their uncertainty stems from gaps in the evidence rather than gaps in their own knowledge.
- It is updated every six months. This means that you can rely on it to keep you up to date in the areas that are covered.
- It specifically aims not to make recommendations. This is because we feel that simply summarising the evidence will make it more widely useful. The experience of the clinical practice guideline movement has shown that it is nearly impossible to make recommendations that are appropriate in every situation. Differences in individual patients' baseline risks and preferences, and in the local availability of interventions, will always mean that the evidence must be individually interpreted rather than applied across the board. *Clinical Evidence* provides the raw material for developing locally applicable clinical practice guidelines, and for clinicians and patients to make up their own minds on the best course of action. We supply the evidence, you make the decisions.

COMPLEMENTARY BUT DIFFERENT

We are often asked how *Clinical Evidence* differs from two other high quality sources of evidence based information: the Cochrane Library; and the evidence based journals *ACP Journal Club, Evidence Based Medicine, Evidence Based Mental Health,* and *Evidence Based Nursing*.

Clinical Evidence is complementary to but different from the work of the Cochrane Collaboration, which produces and publishes high quality systematic reviews of controlled trials.[3] *Clinical Evidence* has been called the friendly front end of the Cochrane Library, since it takes this, and other, high quality information and pulls it together in one place in a concise format. Many of our advisors and contributors are active members of the Cochrane Collaboration, and we are exploring closer ties between Clinical Evidence and the Collaboration in the way the evidence is searched for, summarised, and accessed by users.

Clinical Evidence is also complementary to but different from the evidence based journals, which select and abstract the best and most clinically relevant articles as they appear in the world's medical literature. Together these journals form a growing archive of high quality abstracts of individual articles, many of which are now pooled on the *Best Evidence* CD. *Clinical Evidence* takes a different approach. It begins not with the journals but with clinical questions. It is able to answer some. For others it simply reports that no good evidence was found.

A WORK IN PROGRESS

Clinical Evidence is an evolving project. We knew before we started that we were undertaking an enormous task, but the more we worked the more we realised its enormity. We recognise that there is some mismatch between what we aim eventually to achieve and what we have achieved so far. While we have made every effort to ensure that the searches were thorough and that the appraisals of studies were objective (see p xv), we will inevitably have missed some important studies. In order not to make unjustified claims about the accuracy of the information, we use phrases such as "we found no systematic review" rather than "there is no systematic review". In addition, some contributors helped us out by performing their own searches and appraisals in line with our guidance notes. In order to be as explicit as possible about the methods used for each contribution, we have asked each set of contributors to provide a brief methods section, describing the searches that were performed and how individual studies were selected.

UPDATING AND EXPANDING CLINICAL EVIDENCE

Our expectation is that *Clinical Evidence* will evolve rapidly in its early years. Indeed, it may well become a family of products, appearing in different formats and languages for different audiences: German, French, Italian, and Japanese language versions are already in development. In particular, *Clinical Evidence* will evolve in response to the needs of clinicians. We have tried hard to anticipate those needs (not least by involving clinicians at every stage), but it is only when people begin to use *Clinical Evidence* in daily practice that we can know how best to develop it. That's why your feedback is so important to us, and we are arranging for various ways to evaluate the product.

Clinical Evidence is updated every six months, and expanded to include summaries of the evidence on additional diseases, syndromes, and clinical questions. We also intend to develop versions of *Clinical Evidence* to cover questions about screening, diagnosis, and prognosis.

CLINICAL EVIDENCE ONLINE

Clinical Evidence Online is available to all individual subscribers as part of their annual subscription www.clinicalevidence.org. This provides full text of the current issue plus updates and new topics as they are finalised. *Clinical Evidence* is also available via Ovid www.ovid.com and we are developing versions for intranets and handheld computers.

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A guide to the text

SUMMARY PAGE

The summary page for each topic presents the questions addressed, some key messages, and a list of the interventions covered, categorised according to whether they have been found to be effective or not. We have borrowed the categories of effectiveness from one of the Cochrane Collaboration's first and most popular products, *A guide to effective care in pregnancy and childbirth*.[1] These categories are:

Beneficial: Interventions whose effectiveness has been demonstrated by clear evidence from randomised controlled trials, and expectation of harms that is small compared with the benefits.

Likely to be beneficial: Interventions for which effectiveness is less well established than for those listed under "beneficial".

Trade off between benefits and harms: Interventions for which clinicians and patients should weigh up the beneficial and harmful effects according to individual circumstances and priorities.

Unknown effectiveness: Interventions for which there are currently insufficient data or data of inadequate quality (includes interventions that are widely accepted as beneficial but have never been formally tested in RCTs, often because RCTs would be considered unethical).

Unlikely to be beneficial: Interventions for which lack of effectiveness is less well established than for those listed under "likely to be ineffective or harmful".

Likely to be ineffective or harmful: Interventions whose ineffectiveness or harmfulness has been demonstrated by clear evidence.

Fitting interventions into these categories is not always straightforward. For one thing, the categories represent a mix of several hierarchies: the level of benefit (or harm), the level of evidence (RCT or observational data), and the level of certainty around the finding (represented by the confidence interval). Another problem is that much of the evidence that is most relevant to clinical decisions relates to comparisons between different interventions rather than to comparison with placebo or no intervention. Where necessary, we have indicated the comparisons in brackets. A third problem is that interventions may have been tested, or found to be effective, in only one group of people, such as those at high risk of an outcome. Again, we have indicated this where possible. But perhaps most difficult of all has been to trying to maintain consistency across different topics. We are working on refining the criteria for putting interventions under each category.

NEGATIVE FINDINGS

A surprisingly hard aspect to get right has been the reporting of negative findings. As we have had to keep reminding ourselves, saying that there is no good evidence that a treatment works is not the same as saying that the treatment doesn't work. In trying to get this right, we may have erred too much on the side of caution; when in doubt we have changed summary phrases from, for example, "the review found no difference," to "the review found no evidence of a difference." We recognise that to get this right, we need a better handle on the power of individual systematic reviews and trials to demonstrate statistically significant differences between groups, and better information on what constitute clinically important differences in

the major outcomes for each intervention. In the meantime, we hope that the text makes a clear distinction between lack of benefit and lack of evidence of benefit.

OUTCOMES

Clinical Evidence focuses on outcomes that matter to patients, meaning those that patients themselves are aware of, such as symptom severity, quality of life, survival, disability, walking distance, and live birth rate. We are less interested in proxy outcomes such as blood lipid concentrations, blood pressure, or ovulation rates. Each topic includes a list of the main patient oriented outcomes, and where possible describes how these are measured. We have for the moment decided not to address the vexed question of what constitutes a clinically important change in an outcome, but we would welcome any suggestions.

EFFECTS, NOT EFFECTIVENESS

A key aim of *Clinical Evidence* is to emphasise the important trade offs between the benefits and harms, advantages and disadvantages, of different treatment options. We therefore talk about the effects of interventions, both positive and negative, rather than the effectiveness, and for each question or intervention option we present data on benefits and harms under separate headings.

HARMS

"Harms" include adverse effects of treatment and inconvenience to the patient. Finding good data on harms of treatments is not easy. Ideally these would come from RCTs, but many trials are not sufficiently large or long term to capture rarer or more distant evnts, and many do not adequately report adverse effects. We have asked contributors to keep the negative effects of interventions in mind at all times. Where possible, from good data, we indicate the frequency of adverse effects, and to highlight which adverse effects have not been adequately studied or reported.

DRUG INFORMATION

We make no attempt to provide information on drug dosages, formulations, indications, and contraindications. For this information, we refer readers to their national drug formularies. Drug dosages are included when a question explores the relative effects of different doses.

INFORMATION ON COST

We have decided not to include information on the cost or cost effectiveness of interventions, for the first few issues of *Clinical Evidence* at least. This is not because we believe cost to be unimportant, but because the question of what constitutes good evidence on cost is much disputed and because costs vary greatly both within and between countries. However, we believe that it will become increasingly untenable for clinicians to act without paying attention to resources, and future issues of *Clinical Evidence* may provide relevant information on costs.

NUMERICAL DATA

Whenever possible, data are presented in the same form as in the original studies. However, sometimes we have changed the units or type of information used to allow comparison with results from other studies. This has mainly involved converting odds ratios into relative risks. For many situations (when the absolute risk of an outcome is low and the 95% confidence interval is not too wide) the relative risk and odds ratio are comparable. Where this was not the case, relative risks and their confidence intervals have been calculated from baseline event rates and odds ratios cited in studies or, where appropriate, from pooled results.[2, 3]

AN INTERNATIONAL APPROACH TO THE EVIDENCE

Clinical Evidence takes an international approach to the evidence. This means including drugs despite the fact that they are not licensed in some countries. It also means keeping in mind the practicalities of treating patients in rich as well as poorer countries, by covering

interventions even if they have been superceded (for example, single drug treatment for HIV infection as opposed to three drug treatment).

COMPETING INTERESTS

In line with the *BMJ*'s policy,[4] our aim is not to try to eliminate conflicts of interest but to make them explicit, so that readers can judge for themselves what influence if any these may have had on the contributors' interpretation of the evidence. We therefore ask all contributors to let us know about any potential conflicts or, as we now call them, competing interests, and we append any that are declared to the end of the contribution. Where the contributor gives no competing interests, we record "none declared".

CHANGES SINCE THE LAST ISSUE

The text has been edited and updated. Substantive changes since the last issue are listed at the end of each topic. These are defined as:

- Presentation of additional evidence that either confirms or alters the conclusions
- Re-evaluation of the evidence
- Correction of an important error

HOW TO USE THE INFORMATION IN CLINICAL EVIDENCE

The type of information contained in *Clinical Evidence* is necessary but not sufficient for the provision of effective, high quality health care. It is intended as an aid to clinical decision making, to be used in conjunction with other important sources of information. These other sources include estimates of patients' baseline risk of a condition or outcome based on history, physical examination, and clinical investigations; patients' preferences; economic arguments; availability of treatments; and local expertise.

Some guidance on how to apply research evidence in practice is available on our website www.clinicalevidence.org and in appendix 3 in this issue.

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How Clinical Evidence is put together

The summaries in *Clinical Evidence* result from a rigorous process aimed at ensuring that the information they contain is both reliable and relevant to clinical practice.

SELECTING TOPICS

Clinical Evidence aims to cover common or important clinical conditions seen in primary and hospital care. To decide which conditions to cover in the first few issues, we reviewed national data on consultation rates, morbidity, and mortality, and took advice from generalist clinicians and patient groups. See our website www.clinicalevidence.org for a list of conditions that we are planning to cover in future issues. Further suggestions are welcome.

SELECTING THE QUESTIONS

The questions in *Clinical Evidence* concern the benefits and harms of preventative and therapeutic interventions, with emphasis on outcomes that matter to patients. Questions are selected for their relevance to clinical practice by section advisors and contributors, in collaboration with primary care clinicians and patient groups. Each new issue of *Clinical Evidence* will include new questions as well as updates of existing questions. Readers can suggest new clinical questions using the feedback slips to be found at the back of the book and on the *Clinical Evidence* website www.clinicalevidence.org, or by writing directly to *Clinical Evidence*.

SEARCHING AND APPRAISING THE LITERATURE

For each question, the literature is searched using the Cochrane Library, Medline, Embase and, occasionally, other electronic databases, looking first for good systematic reviews of RCTs; then for good RCTs published since the search date of the review. Where we find no good recent systematic reviews, we search for individual RCTs. The date of the search is recorded in the methods section for each topic. Of the studies that are identified in the search, we select and summarise only a small proportion. The selection is done by critically appraising the abstracts of the studies identified in the search, a task performed independently by two information scientists using validated criteria similar to those of Sackett, et al[5] and Jadad.[6,7] Where the search identifies more than one or two good reviews or trials, we select those we judge to be the most robust or relevant, using the full text of the article. Where we identify few or no good reviews or trials, we include other studies but highlight their limitations. Contributors, who are chosen for their expertise in the field and their skills in epidemiology, are asked to review our selection of studies, and to justify any additions or exclusions they wish to make.

Our search strategy and critical appraisal criteria are available on our web site www.clinicalevidence.org.

SUMMARISING THE EVIDENCE, PEER REVIEW, AND EDITING

The contributors summarise the evidence relating to each question. Each topic is then peer reviewed by the section advisors, and by at least three external expert clinicians. The revised text is then extensively edited by editors with clinical and epidemiological training, and data are checked against the original study reports.

Feedback

Despite the extensive peer review and quality checks described above, we expect that the text will contain some errors and inconsistencies. Please let us know of any you find, either by using the response form at the back of the book or at www.evidence.org/response.htm, or by contacting *Clinical Evidence* directly (by post, via our web site, or by e-mail to CEfeedback@bmjgroup.com.

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Clinical Evidence Glossary

Absolute risk (AR) This is the probability that an individual will experience the specified outcome during a specified period. It lies in the range 0 to 1. In contrast to common usage, the word 'risk' may refer to adverse events (such as myocardial infarction), or desirable events (such as cure).

Absolute risk reduction (ARR) The absolute difference in risk between the experimental and control groups in a trial. It is used when the risk in the control group exceeds the risk in the experimental group, and is calculated by subtracting the AR in the experimental group from the AR in the control group. This figure does not give any idea of the proportional reduction between the two groups; for this, relative risk reduction (RRR) is needed — see below.

Absolute risk increase (ARI) The absolute difference in risk between the experimental and control groups in a trial. It is used when the risk in the experimental group exceeds the risk in the control group, and is calculated by subtracting the AR in the control group from the AR in the experimental group. This figure does not give any idea of the proportional increase between the two groups; for this, relative risk increase (RRI) is needed (see below).

Bias Systematic deviation of study results from the true results, due to the way(s) in which the study is conducted.

Case control study A study design that examines a group of people who have experienced an event (usually an adverse event) and a group of people who have not experienced the same event, and looks at how exposure to suspect (usually noxious) agents differed between the two groups. This type of study design is most useful for trying to ascertain the cause of rare events, such as rare cancers.

Clinically significant A finding that is clinically important. Here, 'significant' takes its everyday meaning of 'important' (compare with statistically significant, see below). Where the word 'significant' or 'significance' is used without qualification in the text, it is being used in its statistical sense.

Cohort study A non-experimental study design that follows a group of people (a cohort), and then looks at how events differ among people within the group. A study that examines two cohorts, one that has been exposed to a suspect agent or treatment, and one that has not been exposed, is useful for trying to ascertain whether exposure is likely to cause specified events (often adverse).
Prospective cohort studies (which track participants forward in time) are more reliable than retrospective cohort studies (which look back in time to ascertain whether or not participants were exposed to the agent in question).

Completer analysis Analysis of data from only those participants who remained at the end of the study. Compare with intention to treat analysis, which uses data from all participants who enrolled (see below).

Confidence interval (CI) The 95% confidence interval (or 95% confidence limits) would include 95% of results from studies of the same size and design. This is close but not identical to saying that the true size of the effect (never exactly known) has a 95% chance of falling within the confidence interval. If the 95% CI for a relative risk or an odds ratio crosses 1, the effect size is likely to lie in a range where risk is either increased or decreased.

Controls in a randomised controlled trial refer to the participants in its comparison group. They are allocated either to placebo, to no treatment, or to the standard treatment.

Cross sectional study A study design that involves surveying a population about an exposure, or condition, or both, at one point