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HOW TO REVIEW A CLINICAL PAPER

- **Evidence-based medicine involves the use of current best evidence in the clinical management of individual patients**
- **Clinical guidelines incorporate best available evidence and are developed to inform both the physician and patient about appropriate healthcare choices**
- **A structured approach should be used when reading clinical research papers and guidelines to assess the clinical applicability of the evidence for individual patients**
- **Statistical significance does not always equate to clinical relevance for individual patients**

INTRODUCTION

Evidence-based medicine may be defined as the "conscientious, explicit and judicious use of current best evidence in making clinical decisions about the care of individual patients".[1] Ideally, clinical decisions should be based on the totality of current best evidence, gathered from the results of individual clinical studies.[2] **Clinical effectiveness** describes a quality improvement approach which promotes evidence-based, cost-effective healthcare, in order to improve clinical decision making and clinical outcomes.[3] Clinical effectiveness has been identified as a key component of patient safety and quality in Ireland; in 2010, the Minister for Health established the **National Clinical Effectiveness Committee**, to provide strategic leadership in the promotion of patient safety and efficacy.[4] The committee, in conjunction with the Clinical Effectiveness Unit in the Department of Health, has been involved in the development of national clinical guidelines; to date several guidelines have been published and are available on the unit's website: http://health.gov.ie/patient-safety/ncec/.[5]

Clinical guidelines are systematically developed statements, based on a thorough evaluation of the available clinical evidence, to inform both the physician and patient about appropriate healthcare choices for specific individual clinical circumstances.[6] However, while guidelines frequently describe the evidence for single conditions, patients often have several comorbidities.[7] Therefore **an understanding of the processes used to evaluate the clinical evidence is important to enable healthcare professionals to determine the relevance of any clinical guidance for their own individual patients**.

This bulletin will outline the basic elements of clinical research and identify the key points in the critical review ("critical appraisal") of published clinical research papers.

TYPES OF CLINICAL STUDIES

Clinical research may be subdivided into **primary** (which involves "original" or new clinical studies) or **secondary** (which involves the use of existing data i.e. a review of a number of primary studies fulfilling certain eligibility criteria).[8] Most of the published clinical research is **"quantitative"** which implies a narrow focus of research (e.g. evaluating outcomes). There are two broad types of quantitative study in clinical research: experimental (or interventional) and observational (or epidemiological) - see Table 1.[9,10] The study type and design are determined by the clinical question under investigation.

Table 1: Types of Primary Clinical Research[9,10]

INTERVENTION ASSIGNED	
YES ↓	NO ↓
Experimental / Interventional study ↓	Observational study ↓
Randomised Controlled Trial (RCT)	Cohort study
Non-randomised /(open) controlled trial	Case-control study
Single arm trial	Cross-sectional study
	Case reports / case series

EXPERIMENTAL RESEARCH

Experimental research involves the researcher intervening in some way and evaluating the outcome of that intervention.[8] The most definitive evidence for the safety and effectiveness of a therapeutic intervention is provided by a **randomised controlled trial** (RCT), which is recognised as the gold standard in experimental research, especially for treatment regimens.[11] In a therapeutic RCT, subjects are **randomly assigned** to either treatment arm (i.e. allocation is by means of a method that is independent of the subject and investigator); subjects in each arm are then managed (**controlled**) in an identical manner with the exception of the treatment received, and their responses are compared.[11] This removes the potential for selection bias by the investigator and means that any difference between the study arms identified in the trial is likely to represent a true difference between the treatments. Many RCTs also involve masking ("blinding") of the assignment of subjects: in a **double-blind study** neither the subject nor the investigator are aware of the treatment allocation, which reduces the risk of evaluation bias.[9] The control group in a RCT may be allocated to no active treatment (a **placebo-controlled trial**) or to an existing treatment (an **active comparator trial**).[12] Placebo-controlled trials help to establish the true efficacy of a treatment regimen while active comparator trials help to determine the efficacy of the

test treatment, relative to an existing established treatment. In clinical research it may not always be ethically possible to undertake a placebo-controlled trial (e.g. in the management of serious conditions for which an existing therapy exists and which should not be withheld); neither may it always be possible to undertake a randomised trial.[9] **Non-randomised clinical trials** may be subject to selection and/or evaluation bias and therefore the information they provide is regarded as supplementary to RCTs.[9]

OBSERVATIONAL RESEARCH

Observational research involves the researcher observing certain aspects of an existing situation (e.g. a therapeutic regimen) without intervention; this means the investigator has no role in assigning therapy.[10] The **main observational study types** are as follows:

Cohort study: subjects are followed up over time (often many years) to observe the effect of an exposure (e.g. to tobacco), or the natural history of ageing, or of disease aetiology in a specific cohort of subjects.[13] Examples include the national longitudinal study of children, "Growing up in Ireland", and TILDA (The Irish LongituDinal study on Ageing).[14,15]

Case-control study: this type of study works backward from an outcome (e.g. disease) in order to identify a *possible association* between the outcome and a particular exposure. Patients with the disease are matched (usually by age and gender) with a group of "controls" without the disease and the level of exposure to the suspected agent is identified for each group of subjects.[10,13] Case-control studies are useful in assessing disease aetiology; they have been used to evaluate potential drug safety issues e.g. risk of venous thromboembolism (VTE) with use of combined hormonal contraceptives (CHC).[16]

Cross-sectional studies are descriptive studies which provide a snapshot in time of the issue under investigation.[13] Examples include screening for the prevalence of cardiovascular (CV) disease / risk factors (e.g. EUROASPIRE IV study)[17] and lifestyle and attitudes surveys (e.g. Healthy Ireland survey).[18]

Case reports / series are uncontrolled observations of a single subject / group of subjects with a shared condition; these may be useful in identifying early potential drug safety signals.[10] Examples include the reports of teratogenicity with use of thalidomide, and hepatotoxicity with use of nimesulide.[19,20]

Limitations: Observational studies are susceptible to **potential biases**[10,13] which may interfere with the validity of the results. These include: (1) selection bias (such as inappropriate choice of controls), (2) recall bias (subjects may forget or underestimate prior exposure; records may be incomplete), (3) loss to follow-up / non-responder bias (any potential differences between responders and non-responders cannot be captured) and (4) the "healthy-volunteer" effect – e.g. the apparent beneficial CV effects noted with use of hormone replacement therapy (HRT) in observational studies which were refuted by the Women's Health Initiative (WHI) RCT which showed an increased risk of CV disease with certain types of HRT.[21] **Confounding** (also described as confounding bias) which may be defined as any factor which distorts the association between exposure and outcome[10,13] may also interfere with the validity of results (e.g. a high BMI and VTE risk in women taking CHC).[22] In the case of drug safety issues, it may be **difficult to confirm a causal association** between use of a medicine and a noxious outcome, based on observational studies. Therefore healthcare professionals should give consideration to all sources of potential bias and their impact on the results when reviewing observational research.[23]

SECONDARY RESEARCH

Secondary research focuses on reviewing primary research.[24] It involves defining a specific research question and performing a **systematic review** of a group of primary research studies, in order to look for consistency in the findings from the individual studies.[25,26] A **meta-analysis** involves statistical analysis of pooled results from these primary studies.[8,26] A systematic review of all available evidence is always more reliable than any single study, provided the review is properly conducted. Table 2 outlines the essential elements of a systematic review.

Table 2: Steps involved in a systematic review [2,8,26]

- Formulate clear objective(s) of the review (e.g. PICO* format)
- Undertake a search of the literature, using clearly defined criteria (e.g. types of studies to be included, sources to be searched)
- Apply clearly defined inclusion / exclusion criteria for all identified studies
- Seek additional information from primary researchers if possible (especially important for meta-analysis)
- Undertake the review of each study using explicit criteria (to evaluate the quality (e.g. risk of bias) of research)
- Analyse the pooled data using validated methods: either systematic critical appraisal or meta-analysis
- Publish the findings, using a similar format to that used for primary research papers

*PICO=**P**opulation of interest; **I**ntervention; **C**omparator; **O**utcome

The Cochrane Collaboration is an independent organisation, consisting of global experts, which undertakes systematic reviews of the effects of various healthcare interventions; these reviews are valuable sources of information for decision makers and researchers, as well as patients.[27] **Access to the online Cochrane Library of systematic reviews is available free of charge in Ireland**, via **www.hrb.ie**.

PRACTICAL CONSIDERATIONS WHEN REVIEWING CLINICAL PAPERS

Most clinical papers are presented in a standard [IMRAD] format: *Introduction* (why the research was done), *Methodology* (how the study was done and what statistical analysis was used), *Results* (what was found) and *Discussion* (what the results mean).[28]

The **Introduction section** of a paper should provide the background to the research and highlight the aim(s) of the study, including details on the study population of interest; intervention carried out; comparator used (if appropriate); outcome(s) evaluated (**PICO**).[28]

Study Design Issues

The **study design** is determined by the question being investigated. Table 3 summarises the preferred study design appropriate to the research question under evaluation.

Table 3: Preferred study design according to the research question[28]

Research question	Preferred study design
Therapy	Randomised controlled trial / systematic review
Diagnosis / Screening	Cross-sectional study
Prognosis	Cohort study
Association / Causation	Case-control study / case series

Normally the aim of a comparative clinical trial is to "reject" the **null hypothesis** and the study sample size is calculated to achieve this aim.[29] This calculation takes into account several issues including the study design, and the level of departure from the null hypothesis (i.e. **Minimal Clinically Important Difference** (MCID) in effect between treatments).[30] It is important to check that the MCID used in a trial is *clinically relevant* for the condition under evaluation (e.g. blood pressure drop of 10mmHg between antihypertensive agents) since the **power** of a study to find a difference if one truly exists relates to the chosen MCID as well as sample size.[31] **Statistical significance** does not always equate to **clinical relevance**.[29,32]

RCTs can be designed to show (1) **superiority** (i.e. a significant difference in one treatment arm over another, in terms of the chosen MCID), (2) **equivalence** between treatment arms (i.e. "no better or no worse", in terms of the MCID) or (3) to show that any difference is not clinically inferior, in terms of the MCID (**non-inferiority** trial).[33,34] Many of the pivotal studies in new drug development use a non-inferiority design; examples include the clinical trials which formed the basis of approval for the new oral anticoagulant agents (with warfarin, the standard therapy used as the active comparator agent).[35-37] Finally, an important aspect of the study design is the **choice of study population**, since this will determine the applicability of the study results for the larger population of patients.[11,38]

Statistical considerations

The **methodology** section should contain detailed information about how the study was conducted (how all subjects were managed, evaluated and followed up) and how the results were analysed. Table 4 summarises frequently encountered statistical terms when reading a clinical paper. Justification for the sample size calculation should usually be presented in the methodology section of a clinical paper. Clinical trial findings should be analysed on the basis of the ITT (**intention-to-treat**) principle, where study subjects are analysed as members of the intervention arm to which they were randomised, irrespective of whether they received or adhered to that intervention (e.g. treatment regimen) during the study. They may also be analysed according to the treatment regimen that they actually received (**per protocol analysis**, PPA).[11,39] ITT is said to reflect "real-life" usage of medicines, where effectiveness of therapy is not just related to biological benefit but is also influenced by other issues such as the patient's adherence (problems with dosing regimen, adverse effects etc.); PPA is said to reflect the innate efficacy of the intervention.[39]

Table 4: Commonly used statistical terms[33,40-42]

Null hypothesis: A test of significance, which is based on the premise that there is no association between 2 variables in a study (i.e. the reverse of what the study is designed to show). The aim is to reject this null hypothesis, thereby showing statistical significance

Power of a Test: The probability that a test will produce a significant difference at a given significance level, e.g. many studies use a power of 80% and a significance level of 5%

Sample size: This refers to the desired number of subjects in a study. It is calculated with reference to the power of the study, the significance level chosen for the study and the departure from the null hypothesis (the so-called minimal effect size/clinically important difference in outcome between the two treatments) and the study design

Statistical significance: The observed result is unlikely to have occurred by chance

Intention to treat (ITT) analysis: Analysis of results of an interventional study based on allocation at randomisation i.e. the way it was intended to treat subjects, not the way in which they were actually treated. Therefore dropouts etc. are still included in order to maintain comparability between groups (may result in reducing actual difference, if present, between groups)

Per Protocol Analysis: Analysis of results of an interventional study based on the subset of subjects who complied with the protocol sufficiently to ensure that these data would be likely to exhibit the (scientific) effects of the treatment

***P*-value:** The probability of getting the observed result (or one more extreme) if the null hypothesis were true. $P<0.05$ means less than 5% (1 in 20) probability, which is the conventional level of statistical significance

Confidence Interval: A range of values around a study result within which, at a given level of confidence, the true population value is likely to be found (e.g. 95% CI means 95% confidence that the true population value lies within the range of the confidence interval presented)

Relative risk (RR): The risk of an outcome in subjects with a particular characteristic (e.g. treatment) compared with the risk of that outcome in subjects who don't have that characteristic. A RR of 1 indicates no association between treatment and outcome; RR >1 indicates a positive association between treatment and outcome; RR <1 indicates a negative association between treatment and outcome

Risk (Absolute Risk): Chances of something happening in a specific population, i.e. number of events in a population in a time period, divided by the total population at the start of the time period

Odds Ratio (OR): Ratio of odds of outcome (e.g. disease) occurring in a group exposed to a possible risk factor compared to the odds for a non-exposed group. An OR of 1 indicates no association between exposure and outcome

Hazard ratio (HR): Ratio of the chance of an event occurring in one study arm of a comparative study, compared to the chance of that event occurring in the other study arm. A HR of 1 indicates no difference between study arms

Number needed to treat [or harm]: Number of people needed to be treated in order to achieve benefit [or develop an adverse outcome] in one person

Statistical tests: The presentation and interpretation of results depend on the study design and the statistical tests used to analyse the data. Although there are many statistical tests available, **many studies use a small number of statistical tests**; in most cases the *p*-value and confidence intervals are used (see Table 4). If unfamiliar statistics have been used in the analysis, the validity of such usage should be questioned. In addition, it is important to know if the statistical tests used in the study were part of the original statistical analysis plan (***a priori*** analysis), or were adopted after the study protocol was finalised (***post-hoc*** analysis); the latter analysis lessens scientific validity of results.[41]

The ***p*-value** relates to the probability that any particular outcome would have arisen by chance. Standard scientific practice usually deems a *p*-value of less than one in 20 (written as $p<0.05$) to be statistically significant.[42]

Confidence intervals (CI; usually 95% CI is reported) can be calculated for most statistical tests and provide information about the *magnitude* of the result, which is useful in evaluating the *clinical relevance* of the results.[32] The **larger the sample size the narrower the CI,** which increases the **precision** (i.e. accuracy) of the result. Statistical significance can also be inferred from CI as follows: if the 95% CI for a clinical trial comparing two different treatments lies either side of zero (which reflects the null value or no difference between the two treatments), statistical significance is implied and a *p*-value<0.05 is assumed; if 95% CI includes zero, this result is taken as non-significant i.e. no difference between the treatments (*p*-value≥0.05).[42]

Risk and benefit can be assessed using **relative risk** (RR) when dealing with a full study "population" as in a cohort study, or **odds ratio** (OR) when the full "population" is unknown as in a case-control study (see Table 4).[32] Statistical significance can be inferred from CI if the 95% CI for RR or OR lies either side of one (as one represents no difference in risk between groups).[42] **The RR result should always be presented with the Absolute Risk (AR) estimate**, because if the AR is very small, then even a high RR (>2-fold increased RR between the groups) may not be clinically significant.[32]

Hazard Ratio (HR) is the ratio of the chance of an event occurring in one study arm of a comparative study, compared to the chance of that event occurring in the other study arm.[40] HR may be used to present results involving survival or time-to-event data (e.g. mortality, acute myocardial infarction) and is frequently reported alongside a measure of time; e.g. after a mean follow-up of 5.2 years, the WHI study showed a significantly increased risk of coronary heart disease in the combined HRT group compared with the placebo group, which was reported as a HR of 1.29 (95% CI 1.02, 1.63).[21]

Points to note in the Results and Discussion sections

The presentation and interpretation of study results vary according to the study design. Usually, they will be presented in a series of graphs / tables and explanatory text which should enable the reader to understand the results and their potential relevance to clinical practice.[28] In a RCT, it is important to review the **baseline characteristics of subjects** in each arm as any difference might impact on the interpretation of the findings; similarly, it is important to check that all study subjects were followed up and accounted for in the study.[11,32] In addition to the statistical results, the **number needed to treat** (Table 4) may also be presented; this is an important calculation as it provides a comprehensible measure of the absolute benefit of the intervention for the target population.[7,32] Another important aspect of any paper is the discussion of **potential limitations of the study;** limitations include problems with inclusion / exclusion criteria, insufficient numbers recruited and loss to follow up of patients.[26] Any of these issues may impact on the (**internal**) **validity** of the study findings (i.e. whether the results are true or may be affected by bias).

How to check the applicability of a study

Protocols for research studies, especially clinical trials, normally contain strict inclusion / exclusion criteria to ensure a homogeneous study population for each arm (i.e. the only difference between the two arms is the intervention) and in this way increase the scientific validity of the results.[11,32] However, this may adversely affect the relevance of the study (known as **external validity**) for specific patient groups.[26] In addition, a single scientific paper rarely leads to change in clinical practice. Therefore each healthcare provider needs to check the applicability of published research for his/her clinical practice. Table 5 proposes a checklist for assessing the clinical relevance of published scientific papers.

Table 5: Checklist for assessing the relevance of research findings for local practice[7,32]

- Does the study population differ from the "local" population (in terms of age, gender, genetic composition, health status, "beliefs and attitudes" towards treatment)?
- Are the results in keeping with other available evidence on the subject?
- Does the local healthcare service have the potential to provide the service(s) described in the study (in terms of trained personnel, finances, infrastructure)?

SUMMARY

When reviewing the medical literature, it is important that healthcare professionals check that (1) the study design is the most appropriate to answer the specific question being investigated, (2) the study is methodologically correct and (3) the results are relevant to the individual patients under their care.[32] Table 6 provides a summary checklist of relevant questions in the review of a clinical paper.

Table 6: Summary checklist of questions to address when reading a clinical paper[12,28,43]

General	Validity	Results	Applicability
Clear question (information on PICO* provided)?	Randomisation	Presentation	Study population
Appropriate study design?	Sample size	Statistics	Results
	Study conduct	Results clinically relevant?	
	correct?	correct?	relevant to your practice?

*PICO=Population of interest; Intervention; Comparator; Outcome

USEFUL SOURCES OF INFORMATION

www.casp-uk.net CASP (Critical Appraisal Skills Programme) which provides checklists and other tools to assist critical appraisal
www.bmj.com Series of articles entitled "How to Read a Paper" – search under Trisha Greenhalgh as author
www.consort-statement.org This comprises a checklist and a flow diagram outlining the minimum recommendations for reporting RCTs

List of references available on request. Date of preparation: August 2016

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