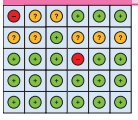
14 Evidence-based orthodontics



A fundamental goal of any healthcare intervention is to provide the best possible outcome for the patient. Orthodontic treatment is no different and should always be undertaken within the context of evidence-based medicine, which has been defined as:

- Integration of the best research evidence with clinical expertise, patient values and patient circumstances (Straus et al, 2011).

There are a number of steps involved in the routine practice of evidence-based medicine (Box 14.1), but a key component is accumulation of the highest quality evidence. Unfortunately, all research designs (and indeed, research studies with the same design) are not equal, and in many areas of orthodontics the contemporary evidence base is weak. It is important for the orthodontic practitioner to be able to assimilate the available evidence and provide the best treatment for their patients.

The hierarchy of evidence

A number of different research designs are available to evaluate the effectiveness of a particular healthcare intervention. The hierarchy of evidence provides a universally accepted framework for ranking this evidence on the basis of study design. Amongst the different types of evidence that can be obtained, the following are generally included in the hierarchy and are listed here in ascending order of merit (Fig. 14.1):

- A systematic review is a comprehensive review of the medical literature usually relating to a particular treatment or intervention. It uses specific and reproducible methods to perform a definitive literature search and critically appraise individual studies. Meta-analysis is a particular type of systematic review that combines and summarizes quantitative data from multiple studies using appropriate statistical methods to provide a conclusion about the overall effect of an intervention;
- A randomized controlled trial (RCT) is a prospective investigation involving participants being allocated randomly into experimental or control groups and followed over time for an outcome or outcomes of interest;
- A cohort study is an observational investigation that involves the identification of two groups (cohorts) of patients. One cohort receives a particular intervention and one does not. The outcome of interest is then followed amongst the two samples. Cohort studies can be retrospective or prospective;
- A case-control study is an observational, retrospective study that identifies cases with and without an outcome of interest and compares them to identify associations between the outcome and exposure to certain risk factors;
- A case series is simply a descriptive report of a particular outcome on a series of patients. There is no control group;
- A case report is a description of a particular outcome on a single patient; and
- Clinical opinion is the opinion of a single clinician based upon personal experience, expertise and judgement ('in my hands….').

Box 14.1 The five steps to practising evidence-based medicine

1. Formulating the right clinical question
2. Finding the best evidence
3. Critically appraising the evidence
4. Integrating critical appraisal with clinical practice and the patient
5. Evaluating effectiveness

(Adapted from Straus et al, 2011)

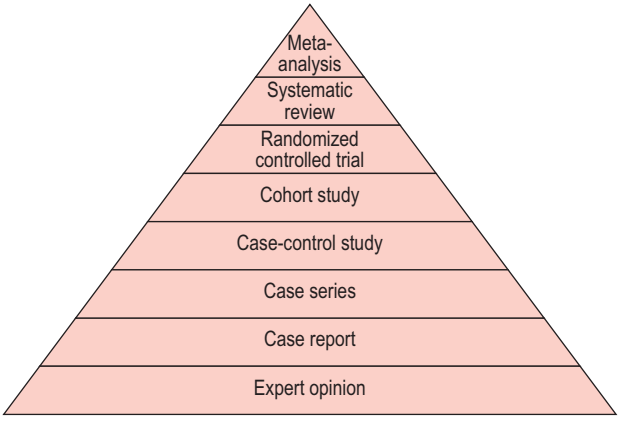


Figure 14.1 The hierarchy of evidence. The pyramid represents a decreasing level of bias associated with evidence obtained from ascending studies. The blocks up to randomized controlled trial represent primary research, whilst systematic review and meta-analysis represent secondary research.

It is clear from this list that properly conducted RCTs, either in isolation or collectively as part of a systematic review, provide the best available evidence for evaluating the outcome of particular treatment interventions. However, observational studies can be useful for developing prognostic and diagnostic models for large populations, and can also be used when an RCT is not feasible. Moreover, case series and case reports can introduce the clinician to unusual and rare conditions or outcomes, or new techniques or procedures. This can then form the basis for future research using more robust study designs.

- STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) is an international, collaborative initiative of epidemiologists, methodologists, statisticians, researchers and journal editors that aims to improve the conduct and dissemination of observational studies (von Elm et al, 2007).

Randomized controlled trials

RCTs are a form of prospective study that involve the random assignment of two or more interventions to a group of individuals. They are regarded as the gold standard for

investigating the effectiveness or efficiency of different treatment interventions, providing a consistent and unbiased estimate of effect. By randomly allocating a population to different interventions and following them up in an identical manner, pre-treatment equivalence is achieved amongst the sample and selection bias is minimized. Importantly, because of this pre-treatment equivalence, any differences in outcome will be attributable to the intervention.

- A CONSORT (CONsolidated Standards Of Reporting Trials) Statement has been produced to help improve the reporting of two-parallel design RCTs (Schulz et al, 2010).

The statement provides a CONSORT checklist and flow diagram that facilitates an understanding of the design, conduct and analysis of a RCT, allowing an assessment of the validity of the results (Fig. 14.2).

The number of RCTs that have been carried out in orthodontics has steadily increased over the last decade, which is a good thing. However, it should be remembered that RCTs are not beyond criticism as a research tool (Box 14.2). They are certainly difficult to organize properly and expensive to run when fully funded; they can also be impractical in some circumstances and can be associated with ethical problems. Interestingly, many orthodontic RCTs have often failed to identify any difference between different interventions and, in some circumstances, have simply confirmed the results of previous retrospective studies (Meikle, 2005).

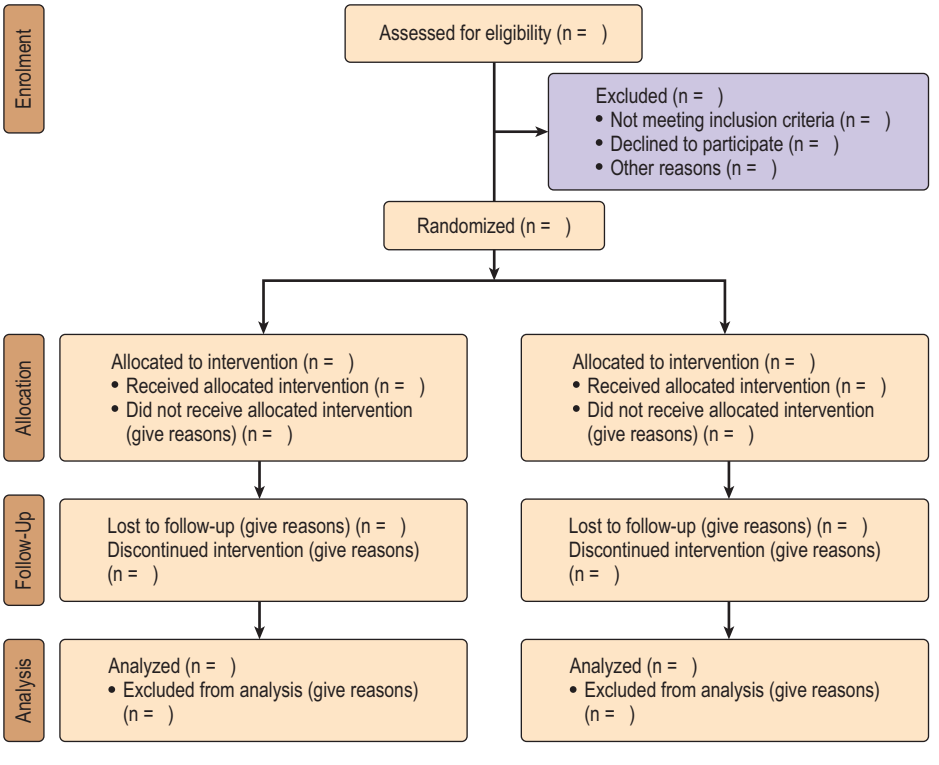


Figure 14.2 CONSORT flow diagram of the progress through the phases of a parallel RCT of two groups (enrolment, allocation, follow-up and data analysis).

Box 14.2 Disadvantages of randomized controlled trials (RCTs)

- RCTs are expensive and time consuming to run;
- Random allocation of an intervention can be unethical in some circumstances and not suitable for investigation with a RCT;
- Clinicians within a trial can be forced to undertake interventions that they may not wish to do (use a particular functional appliance, for example);
- Heterogeneity amongst subjects is not always accounted for by a RCT;
- Subjects who are most likely to benefit from an intervention are not necessarily identified within a RCT; and
- Subjects within a RCT may not necessarily be representative of other populations.

Systematic review

A systematic review provides healthcare professionals with the best available summarized evidence from the world literature for any particular topic or intervention. Systematic reviews are different from the more traditional narrative reviews that are often available because they use defined, specific and reproducible methodology to search, critically appraise and evaluate the available literature. Narrative reviews do not do this, being reliant upon methodology that is often not stated and more vulnerable to influence from the personal opinions of the author or authors; and therefore, being at a higher risk of bias.

- PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines are available to help authors improve the reporting of systematic reviews and meta-analyses (Moher et al, 2009).

The PRISMA guidelines include a 27-item checklist and a four-phase flow diagram to clearly state the methodology that has been used to generate the review (Fig. 14.3).

Risk of bias

Bias represents a systematic error in the results derived from a clinical trial, which can lead to under- or overestimation of the true intervention effect. Different risks of bias between studies can help explain variation in the results, or heterogeneity; and an important component of a systematic review is to include a risk of bias assessment for studies that are included. In Cochrane systematic reviews, this forms a specific part of the appraisal process and is described as the risk of bias tool, which is usually summarized in a simple diagram (Fig. 14.4). This tool reflects the number of potential sources of bias in clinical trials:

- Selection bias refers to systematic differences in the fundamental characteristics of the groups that have been compared in a study. The method of allocating interventions must be specified and based on a random process (sequence generation). In addition, there should be no prior knowledge of these random allocations (allocation concealment);
- Performance bias refers to systematic differences in the care that has been provided to the groups, or variation in the exposure to factors other than the intervention being investigated in a study. Ideally, blinding (or masking) of study participants and

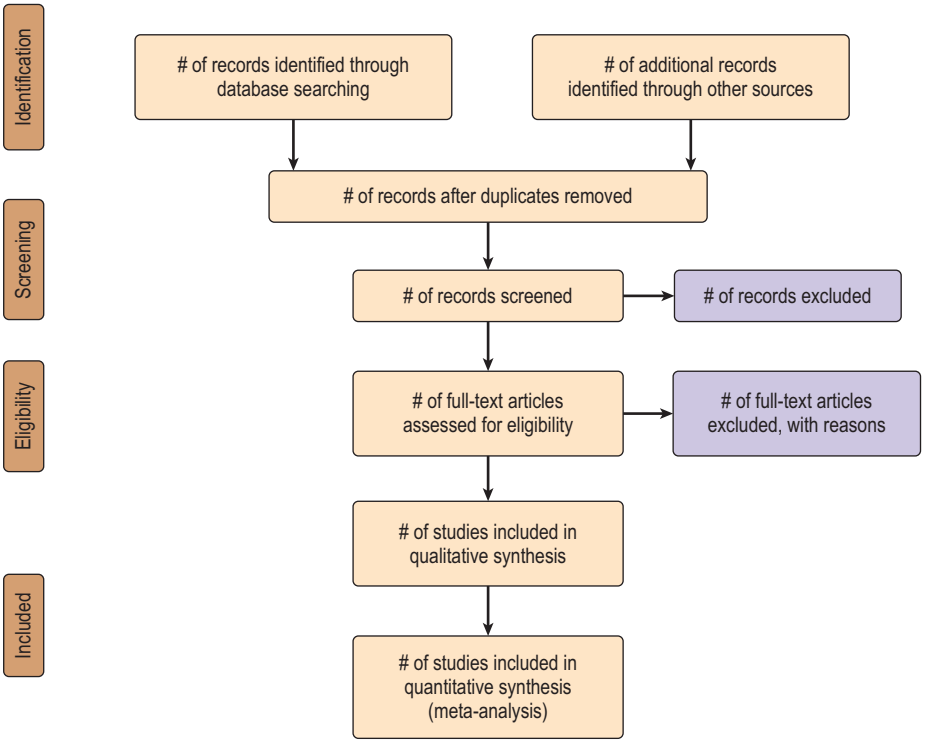


Figure 14.3 PRISMA flow of information through the different phases of a systematic review (identification, screening, eligibility, inclusion).

personnel should take place (although this is not always practical) to reduce the risk that knowledge of the intervention that was received, rather than the intervention itself, might affect the outcome. The presence of blinding also ensures that groups receive similar attention, ancillary treatment and diagnostic investigations during a study;

- Detection bias refers to systematic differences in how outcomes are recorded between groups in a study. Blinding (or masking) of outcome assessors may reduce the risk that knowledge of the intervention that was received, rather than the intervention itself, might affect the outcome measurement. Blinding of outcome assessors can be especially important for assessment of subjective outcomes, such as degree of post-operative pain;
- Attrition bias refers to systematic differences in withdrawals between groups in a study. Withdrawals from a study lead to incomplete outcome data and excluding lost subjects from data analysis may produce groups that demonstrate a different response to the intervention. An intention-to-treat analysis is recommended, which includes all trial participants, regardless of loss, in the final analysis;
- Reporting or publication bias refers to systematic differences between reported and unreported findings from a study. Within a published report, analyses with statistically

Figure 14.4 Risk-of-bias summary for five (fictional) studies (listed on the left). The green (+), yellow (?) and red (–) circles describe whether the particular risk of bias (listed vertically) was absent, whether it was not possible to discern from the information included within the study or whether it was present, respectively (green (+), yellow (?) and red (–)).

significant differences are more likely to be reported than non-significant differences and benefits are more likely to be reported than harms. This can lead to treatment effects being overestimated, which can be compounded when data is pooled in systematic reviews; and

- Other sources of bias can also exist, which are related to particular trial designs or clinical settings.

Meta-analysis

The process of meta-analysis involves the pooling of data from studies identified within a systematic review and then undertaking a formal statistical analysis. It is based upon the results of multiple studies that have been judged systematically to be of high quality and at a low risk of bias.

If we are going to use a particular orthodontic intervention to influence an outcome measure (also known as an effect measure), we need to know the relative benefit or

harm of this intervention in relation to the outcome, which is represented by a measurement of treatment effect (also known as the effect size or effect estimate).

- In meta-analysis, a treatment effect size is calculated for each individual study and then an overall treatment effect is calculated as a weighted average of these individual summary statistics.

Each study included in the meta-analysis contributes to this weighted average in a proportionate manner, based upon the strength of its conclusions. The results of a meta-analysis are usually represented in a forest plot, which is a graphical representation of the overall effect size and its confidence interval, plotted on a common scale. The forest plot provides a graphical summary of the salient meta-analysis results, which:

- Conveniently allows patterns within the results to be identified;
- Highlights areas of agreement and disagreement, and
- Provides a contemporaneous synthesis of the results from multiple studies.

Effect sizes

An investigation reporting that the outcome measure for a particular orthodontic intervention is 'statistically significant' means that this effect is unlikely to have occurred by chance. However, when dealing with multiple studies that have investigated a particular intervention, effect size is more important. Unlike statistical significance, effect size calculations take into account sample size and are 'weighted' accordingly.

- Assuming similar levels of bias, a study reporting a large effect size that contained a small number of individuals would carry less weight than one reporting a smaller effect size but containing a larger sample. This is because the precision of an effect size is inversely proportional to the sample size and imprecise studies have less weight than precise ones. This would be reflected in the overall effect size in the forest plot.

There are different types of outcome measure used in clinical research, for example continuous data (these measures can be an infinite range of values along a specific continuum, e.g. mandibular unit length before and after treatment with a functional appliance) or binary (dichotomous) data (these measures have just two values, e.g. incidence of incisor trauma in two groups either treated early with a functional appliance or not: they either experienced incisor trauma or they did not). To calculate the effect size, we need to take into account whether the outcome measure is continuous or binary:

- For continuous outcomes, data is usually represented by mean values (with their standard deviations) and the effect size is represented by the mean difference between groups (a mean difference of zero meaning no difference between groups); and
- For binary outcomes, data is usually represented as risk or odds ratios, which are essentially two slightly different methods of calculating the risk or probability of an event (the outcome) occurring in the intervention group rather than the control group.

Interpreting the forest plot

The forest plot is usually composed of five main columns situated from left to right (Fig. 14.5). In column 1, each study that has been included in the meta-analysis is listed chronologically. Column 2 provides data relating to the outcome measure recorded for each study and for the included studies overall. Column 3 contains the actual forest plot itself. The vertical line in column 3 represents the line-of-no-effect, meaning no difference between the intervention and control (or the null hypothesis). Values to the left of this line favour the intervention, whilst those on the right favour the control. Ideally, all the studies should show the same fundamental effect (i.e. all should be situated on the same

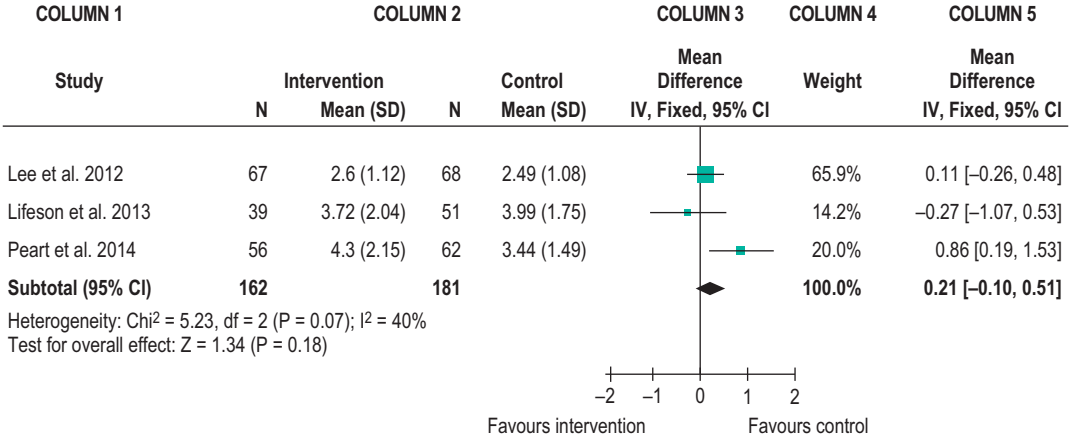


Figure 14.5 A forest plot illustrating the effect of a particular intervention versus a control. In this case, three (fictional) studies have been included, which are listed in column 1. The outcome data is continuous and therefore represented by mean values (with their standard deviations) in column 2 (note that for binary outcomes, data is usually represented as risk or odds ratios and plotted on a logarithmic scale: with the line-of-no-effect represented by 1 and values of <1 to 0.01 favouring the intervention and >1 to 100 favouring the control). The actual forest plot can be seen in column 3. The percentage weight allocated to each study is shown in column 4 and the summary effect size data (with the 95% confidence intervals) is seen in column 5. Measures of heterogeneity are also included (Chi^2 and I^2) with an I^2 of 40% indicating relatively low heterogeneity (and therefore a fixed-effect analysis). For this particular intervention, there is no statistically significant difference when compared to the control (the diamond crosses the line-of-no-effect).

side of the line-of-no-effect) even if they differ in size (efficiency). It is also important to look at the confidence interval of a study, because if it overlaps the vertical line, this means that the results are not significant. The plot itself consists of a square with a horizontal line running through it. The mid-point of the square represents the effect size for each study and the area of the square represents the weight (the larger the area, the larger the effect). The horizontal line shows the 95% confidence interval of the effect size (which means that there is a 95% chance that the true effect in the population lies within this range). The black diamond at the bottom represents the overall effect size for the intervention, with the width of the diamond showing the confidence interval. This overall effect size is the best guess of the true effect of the intervention in the population, certainly for a fixed-effect model. Column 4 contains the percentage weight data for each study. Column 5 contains the summary effect size data (with the 95% confidence intervals) for each study and overall.

A forest plot will also contain a measure of heterogeneity for the included studies, which gives a statistical estimation of whether there are genuine differences underlying the results or whether the variation is simply due to chance. Chi-squared (Chi^2 or X^2) is the test statistic for heterogeneity resulting from the statistical test used to derive the *P* value; degrees of freedom (df) equals the number of trials minus 1 and these values are used to calculate the *P* value. The Higgins I^2 statistic is a further measure of heterogeneity (the percentage of variation between sample estimates that is due to heterogeneity).

Heterogeneity

Some variability between individual studies that have been included in a meta-analysis almost always occurs. Variation in the true effect of an intervention is called heterogeneity and it can be caused by a number of factors:

- Variation in sample sizes and participants;
- Differences in the precise intervention being investigated; and
- Different methods of studying the outcome in different investigations.

Unless all the studies included in the meta-analysis have been conducted in an identical manner, some heterogeneity is likely to be present and a brief examination of the forest plot can provide some clues:

- The individual effect estimates should ideally be all on the same side as the pooled effect estimate; and
- The confidence intervals should all overlap.

When undertaking a systematic review it is important to ensure that heterogeneity is kept to a minimum. Strategies to achieve this include making sure that data extraction from individual investigations is correct, studies thought to be of low quality or fundamentally different are not pooled and, indeed, not undertaking meta-analysis if it is felt that the available investigations are simply too heterogeneous.

A number of more formal statistical tests can be carried out to investigate heterogeneity and these are also normally included in the forest plot, situated below the list of investigations. These tests will use the null hypothesis that homogeneity is present between studies. A commonly used test is the Higgins I^2 statistic, which is a measure of how heterogeneity impacts on a meta-analysis and represents the percentage total variation across studies that is due to heterogeneity rather than chance:

- The higher the value of I^2, the greater the likelihood that variability across the studies is due to heterogeneity, rather than chance; and
- Values of $I^2 = 25\%$, 50% and 75% are categorized as low, moderate and high heterogeneity, respectively (Higgins et al, 2003).

Fixed-effect and random-effects analysis

The presence of heterogeneity has an impact on the type of model that should be used in the statistical meta-analysis. In the presence of low heterogeneity ($I^2 < 50\%$), a fixed-effect statistical analysis is appropriate, whereas for high heterogeneity ($I^2 \geq 50\%$) a random-effects analysis should be used:

- Fixed-effect analysis assumes that each study is estimating the same true effect size and that any differences between them are due to chance. In this model, larger studies are given more weight. The overall total effect size is generally, more precise; and
- Random-effects analysis assumes that each study has a different true effect and that some of these differences are due to heterogeneity and not chance alone. In this model, differences are expected and more weight is given to smaller studies. A random-effects analysis produces a wider confidence interval for total overall effect, which means a less accurate overall total effect size.

The type of analysis that is carried out will affect the results and interpretation of the meta-analysis. In the presence of heterogeneity, the confidence interval associated with the pooled estimate is wider in a random-effects than a fixed-effect model (Fig. 14.6).

2007

Analysis I. I. Comparison I Early treatment at the end of Phase I: functional versus control, Outcome I Final overjet.

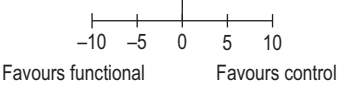
Review: Orthodontic treatment for prominent upper front teeth in children

Comparison: I Early treatment at the end of Phase I: functional versus control

Outcome: I Final overjet

Study or subgroup	Functional (N)	Mean (SD)	Control (N)	Mean (SD)	Mean Difference IV, Random, 95% CI	Weight	Mean Difference IV, Random, 95% CI
UK (Mixed)	89	3.7 (2.27)	84	10.7 (2.4)		33.5%	–7.00 [–7.70, –6.30]
Florida	85	3.88 (1.9)	79	5.42 (2.67)		33.5%	–1.54 [–2.25, –0.83]
North Carolina	41	5.38 (2.67)	54	8.94 (1.84)		33.1%	–3.56 [–4.51, –2.61]
Total (95% CI)	**215**		**217**			**100.0%**	**–4.04 [–7.47, –0.60]**

Heterogeneity: $Tau^2 = 9.06$; $Chi^2 = 117.02$, df = 2 (P<0.00001); $I^2 = 98\%$
Test for overall effect: Z = 2.30 (P = 0.021)



2013

Analysis I. I. Comparison I Early orthodontic treatment: 2-phase versus adolescent treatment, Outcome I Outcomes at the end of phase I: functional versus observation.

Review: Orthodontic treatment for prominent upper front teeth (Class II malocclusion) in children

Comparison: I Early orthodontic treatment: 2-phase versus adolescent treatment

Outcome: I Outcomes at the end of phase I: functional versus observation

Study or subgroup	Functional (N)	Mean (SD)	Observation (N)	Mean (SD)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
I Final overjet							
UK (Mixed) 2009	89	3.7 (2.27)	84	10.7 (2.4)		40.2%	–7.00 [–7.70, –6.30]
Florida 1998	85	3.88 (1.9)	79	5.42 (2.67)		38.3%	–1.54 [–2.25, –0.83]
North Carolina 2004	41	5.38 (2.67)	54	8.94 (1.84)		21.5%	–3.56 [–4.51, –2.61]
Subtotal (95% CI)	**215**		**217**			**100.0%**	**–4.17 [–4.61, –3.73]**

Heterogeneity: $Chi^2 = 117.02$, df = 2 (P<0.00001); $I^2 = 98\%$
Test for overall effect: Z = 18.49 (P<0.00001)

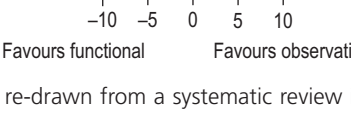


Figure 14.6 Forest plots that have been re-drawn from a systematic review investigating the effects of early versus late treatment with a functional appliance; in this case, showing the meta-analysis in relation to overjet reduction (Harrison et al, 2007; Thiruvenkatachari et al, 2013). The upper panel shows the forest plot from the original 2007 analysis, whilst the lower panel shows the plot from the updated meta-analysis carried out 6 years later in 2013. The plots actually relate to the same three RCTs and contain identical data, but in the 2007 plot (upper panel) a random-effects analysis was carried out, whilst in the 2013 plot (lower panel) a fixed-effect analysis was performed. Whilst the overall result is the same (not surprisingly, early treatment with a functional appliance does favour overjet reduction when compared with no treatment), the confidence interval for the overall effect estimate (the black diamond) is much narrower with the fixed-effect analysis. The heterogeneity between the included studies is certainly high: the I^2 value is 98% and there is a complete lack of overlap between the confidence intervals of the three individual studies (Schroll et al, 2011).

The Cochrane collaboration

The Cochrane collaboration is an international network concerned with the dissemination of high-quality evidence across all areas of healthcare. The collaboration takes its name from Archie Cochrane, a prominent Scottish epidemiologist who strongly advocated the use of RCTs and systematic review for informing decision-making in healthcare (Cochrane, 1972).

One of the main roles of the collaboration is facilitating the preparation and dissemination of Cochrane systematic reviews, which are maintained within the Cochrane Database of Systematic Reviews, part of the Cochrane Library. Review topics are

Table 14.1 Cochrane systematic reviews in orthodontics published 2011–15

Borrie FR, Bearn DR, Innes NP, Iheozor-Ejiofor Z (2015). Interventions for the cessation of non-nutritive sucking habits in children. Cochrane Database Syst. Rev. 3: CD008694.
Agostino P, Ugolini A, Signori A, Silvestrini-Biavati A, Harrison JE, Riley P (2014). Orthodontic treatment for posterior crossbites. Cochrane Database Syst. Rev. 8: CD000979.
Jambi S, Walsh T, Sandler J, Benson PE, Skeggs RM, O'Brien KD (2014). Reinforcement of anchorage during orthodontic brace treatment with implants or other surgical methods. Cochrane Database Syst. Rev. 8: CD005098.
Benson PE, Parkin N, Dyer F, Millett DT, Furness S, Germain P (2013). Fluorides for the prevention of early tooth decay (demineralised white lesions) during fixed brace treatment. Cochrane Database Syst. Rev. 12: CD003809.
Hu H, Li C, Li F, Chen J, Sun J, Zou S, Sandham A, Xu Q, Riley P, Ye Q (2013). Enamel etching for bonding fixed orthodontic braces. Cochrane Database Syst. Rev. 11: CD005516.
Jambi S, Thiruvenkatachari B, O'Brien KD, Walsh T (2013). Orthodontic treatment for distalising upper first molars in children and adolescents. Cochrane Database Syst. Rev. 10: CD008375.
Jian F, Lai W, Furness S, McIntyre GT, Millett DT, Hickman J, Wang Y (2013). Initial arch wires for tooth alignment during orthodontic treatment with fixed appliances. Cochrane Database Syst. Rev. 4: CD007859.
Thiruvenkatachari B, Harrison JE, Worthington HV, O'Brien KD (2013). Orthodontic treatment for prominent upper front teeth (Class II malocclusion) in children. Cochrane Database Syst. Rev. 11: CD003452.
Watkinson S, Harrison JE, Furness S and Worthington HV (2013). Orthodontic treatment for prominent lower front teeth (Class III malocclusion) in children. Cochrane Database Syst. Rev. 9: CD003451.
Yu Y, Sun J, Lai W, Wu T, Koshy S, Shi Z (2013). Interventions for managing relapse of the lower front teeth after orthodontic treatment. Cochrane Database Syst. Rev. 9: CD008734.
Minami-Sugaya H, Lentini-Oliveira DA, Carvalho FR, Machado MA, Marzola C, Saconato H, Prado GF (2012). Treatments for adults with prominent lower front teeth. Cochrane Database Syst. Rev. 5: CD006963.
Guo J, Li C, Zhang Q, Wu G, Deacon SA, Chen J, Hu H, Zou S, Ye Q (2011). Secondary bone grafting for alveolar cleft in children with cleft lip or cleft lip and palate. Cochrane Database Syst. Rev. 6: CD008050.
Millett DT, Mandall NA, Mattick RC, Hickman J, Glenny AM (2011). Adhesives for bonded molar tubes during fixed brace treatment. Cochrane Database Syst. Rev. 6: CD008236.

suggested and prepared by relevant healthcare workers and have to address clearly formulated questions. Cochrane maintain strict criteria for the collation and assessment of evidence for these reviews, and they have to be updated regularly. There are now over 5000 of these reviews within the database, which are all freely available and allow clinicians to make healthcare decisions based on the most up-to-date and reliable evidence.

Orthodontics is now a well-represented specialty within the Cochrane database of systematic reviews, having a significant number of review protocols, completed reviews and, increasingly, updated reviews – which are all freely available online. Indeed, since the first edition of this textbook was published, thirteen new or updated systematic reviews in orthodontics have been published, on subjects ranging from strategies to help stop digit sucking to adhesives for bonded molar tubes (Table 14.1). However, a recurring theme amongst many of these reviews is the lack of high-quality evidence that is available to properly inform clinical orthodontic practice. Much work remains to be done.

In this textbook, we have attempted to synthesize the theoretical basis of contemporary orthodontic practice within the context of the best available current evidence, although in many cases this is still lacking.

Further reading

Akobeng, A.K., 2005. Evidence in practice. Arch. Dis. Child. 90, 849–852.

Akobeng, A.K., 2005. Principles of evidence based medicine. Arch. Dis. Child. 90, 837–840.

Akobeng, A.K., 2005. Understanding randomised controlled trials. Arch. Dis. Child. 90, 840–844.

Akobeng, A.K., 2005. Understanding systematic reviews and meta-analysis. Arch. Dis. Child. 90, 845–848.
An excellent series of articles downloadable as a single PDF, which provide a useful introduction to evidence-based practice.

Pandis, N., Cobourne, M.T., 2013. Clinical trial design for orthodontists. J. Orthod. 40, 93–103.

Pandis, N., 2015. Biostatistics in Orthodontics. Design, analysis, reporting and synthesis of clinical studies. Zmk bern. Zahnmedizinische Kliniken der Universität Bern.

Papageorgiou, S.N., Xavier, G.M., Cobourne, M.T., 2015. Basic study design influences the results of orthodontic clinical investigation. J. Clin. Epidemiol. [Epub ahead of print].

The Internet has now produced a number of blog pages dedicated to evidence-based dentistry and orthodontics, the sites listed below represent two very interesting resources, that are continually being updated:
Kevin O' Brien's Orthodontic Blog <http://kevinobrienorthoblog.com>.
Dental Elf <http://www.thedentalelf.net>.

References

Cochrane, A.L., 1972. Effectiveness and Efficiency. Random Reflections on Health Services. Nuffield Provincial Hospitals Trust, London. Reprinted in 1989 in association with the BMJ, Reprinted in 1999 for Nuffield Trust by the Royal Society of Medicine Press, London (ISBN 1-85315-394-X).

Harrison, J.E., O'Brien, K.D., Worthington, H.V., 2007. Orthodontic treatment for prominent upper front teeth in children. Cochrane Database Syst. Rev. (3), CD003452.

Higgins, J.P., Thompson, S.G., Deeks, J.J., et al., 2003. Measuring inconsistency in meta-analysis. BMJ 327, 557–560.

Meikle, M.C., 2005. Guest editorial: what do prospective randomized clinical trials tell us about the treatment of class II malocclusions? A personal viewpoint. Eur. J. Orthod. 27, 105–114.

Moher, D., Liberati, A., Tetzlaff, J., et al., 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 339, b2535.

Schulz, K.F., Altman, D.G., Moher, D., CONSORT Group, 2010. Statement: updated guidelines for reporting parallel group randomised trials. BMJ 340, c332.

Straus, S.E., Glasziou, P., Richardson, W.S., et al., 2011. Evidence-Based Medicine, fourth ed. Elsevier, Philadelphia.

Schroll, J.B., Moustgaard, R., Gøtzsche, P.C., 2011. Dealing with substantial heterogeneity in Cochrane reviews. Cross sectional study. BMC Med. Res. Methodol. 11, 22.

Thiruvenkatachari, B., Harrison, J.E., Worthington, H., et al., 2013. Orthodontic treatment for prominent upper front teeth (class II malocclusion) in children. Cochrane Database Syst. Rev. (11), CD003452. doi:10.1002/14651858.CD003452.pub3.

Von elm, E., Altman, D.G., Egger, M., et al., 2007. STROBE Initiative. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. BMJ 335, 806–808.