3 Methods used to develop this guideline

3.1 Overview

The development of this guideline drew upon methods outlined by NICE (NICE, 2001; Eccles & Mason, 2001). A team of experts, professionals and patients, known as the Guideline Development Group (GDG), with support from NCCMH staff, undertook the development of a patient-centred, evidence-based guideline. There are six basic steps in the process of developing a guideline:

- Define the scope, which sets the parameters of the guideline and provides a focus and steer for the development work
- Define clinical questions considered important for practitioners and patients
- Develop criteria for evidence searching and search for evidence
- Design validated protocols for systematic review and apply to evidence recovered by search
- Synthesise and (meta-) analyse data retrieved, guided by the clinical questions, and produce evidence statements
- Answer clinical questions with evidence-based recommendations for clinical practice.

The clinical practice recommendations made by the GDG are, therefore, derived from the most up-to-date and robust evidence base for the clinical and cost effectiveness of the treatments and services used in the management of depression. In addition, to ensure a patient and carer focus, the concerns of patients and carers regarding clinical practice have been highlighted and addressed by good practice points and recommendations agreed by the whole GDG. The evidence-based recommendations and good practice points are the core of this guideline.

3.2 The Guideline Development Group

The GDG consisted of patients, and professionals and academic experts in psychiatry, clinical psychology and general practice. NCCMH staff undertook the clinical and health economics literature searches, reviewed and presented the evidence to the GDG, managed the process and contributed to the drafting of the guideline.

3.2.1 Guideline Development Group meetings

Twenty-six GDG meetings were held between November 2001 and October 2003. During each day-long GDG meeting clinical evidence was reviewed and assessed to develop

statements and recommendations. At each meeting all GDG members declared any potential conflict of interests. Patient and carer concerns were routinely discussed as part of a standing agenda.

3.2.2 Topic groups

The GDG divided its workload along clinically relevant lines in order to deal with the large volume of evidence efficiently. GDG members formed three topic groups: the Service topic group covered questions relating to the presentation of services to users, including screening, exercise and guided self-help; the Pharmacology topic group covered pharmacological treatments for depression; and the Psychology topic group covered psychotherapies. Each topic group was chaired by a GDG member with expert knowledge of the topic area. Topic groups refined the clinical definitions of treatment interventions, reviewed and prepared the evidence with the NCCMH review team. Topic group leaders reported the status of their group's work as part of the GDG standing agenda. They also assisted in drafting the section of the guideline relevant to the work of each topic group.

3.2.3 Patients and carers

Individuals with direct experience of services gave an integral patient focus to the GDG and the guideline. The GDG included three patients. They contributed as full GDG members to writing the clinical questions, helping to ensure that the evidence addressed their views and preferences, highlighting sensitive issues and terminology associated with depression, and bringing service-user research to the attention of the GDG. In drafting the guideline, they contributed to the editing of the first draft of the guideline's introduction and identified good practice points from the patient and carer perspective; their suggestions were incorporated before distributing the draft to the GDG for further review.

3.2.4 Special advisers

Special advisers who had specific expertise in one or more aspects of treatment and management relevant to the guideline assisted the GDG, commenting on specific aspects of the developing guideline and making presentations to the GDG. Appendix 2 lists those who agreed to act as special advisers.

3.2.5 National and international experts

National and international experts in the area under review were identified through the literature search and through the experience of the GDG members. These experts were contacted to recommend unpublished or soon-to-be published studies in order to ensure up-to-date evidence was included in the evidence base for the guideline. Appendix 5 lists researchers who were contacted.

3.3 Clinical questions

Clinical questions were used to guide the identification and interrogation of the evidence base. The questions were developed using a modified nominal group technique. The process began by asking each member of the GDG to submit as many questions as possible. The questions were then collated and refined by the review team. At a subsequent meeting, the guideline chair facilitated a discussion to further refine the questions. At this point, the GDG members were asked to rate each question for importance. The results of this process were then discussed and consensus reached about which questions would be of primary importance and which would be secondary. The GDG aimed to address all primary questions, while secondary questions would only be covered time permitting. Appendix 6 lists the clinical questions.

3.4 Systematic clinical literature review

The aim of the clinical literature review was to identify and synthesise systematically all relevant evidence in order to answer the clinical questions developed by the GDG. Thus, clinical practice recommendations are evidence-based as far as possible.

Where an existing NICE Technology Appraisal addressed one of the clinical questions, the GDG was obliged to adopt the relevant existing recommendations. If evidence was not available, then informal consensus methods were used (see Section 3.4.4) and the need for future research was specified.

A stepwise, hierarchical approach was taken to locating and presenting evidence to the GDG. The NCCMH developed the methodology for this process with advice from the National Guidelines Support and Research Unit (NICE) and after considering recommendations from a range of other sources. These included:

- Centre for Clinical Policy and Practice of the New South Wales Health Department (Australia)
- Clinical Evidence Online
- Cochrane Collaboration
- New Zealand Guideline Group
- NHS Centre for Reviews and Dissemination
- Oxford Centre for Evidence-Based Medicine
- Scottish Intercollegiate Guidelines Network (SIGN)
- United States Agency for Health Research and Quality
- Oxford Systematic Review Development Programme.

3.4.1 The review process

Since most of the clinical questions for this guideline concerned interventions, much of the evidence base was formed from high quality randomised controlled trials (RCTs). Although there are a number of difficulties with the use of RCTs in the evaluation of interventions in mental health, this research design remains the most important method for establishing treatment efficacy (see introductions to later chapters for fuller discussions of this issue).

The review process involved:

- Developing search filters
- Searching for existing systematic reviews
- Searching for new RCTs
- Selecting studies
- Synthesising the evidence.

3.4.1.1 Developing search filters

The review team developed search filters to search electronic databases that combined subject headings with free-text phrases. A filter was developed for the general topic 'depression', which was combined with specific filters for each clinical question. These were also combined with filters developed for 'systematic reviews' or 'RCTs' (or other research designs as appropriate) (Appendix 7).

3.4.1.2 Searching for existing systematic reviews

The NCCMH review team undertook searches for existing systematic reviews of RCTs published in English since 1995 (an arbitrary cut-off date to reduce the number of references found and to ensure recency), which would answer the clinical questions posed by the GDG. The initial searches were undertaken in December 2001 and January 2002, with update searches being carried out every two months until May 2002. A search of PubMed (MEDLINE) was also undertaken weekly beginning in April 2003 until the end of the guideline development process. The following databases were searched: EMBASE, MEDLINE, PsycINFO, Cochrane Library, CINAHL, Web of Science.

Systematic reviews were assessed for quality and eligibility (Appendices 8 and 9) before being assessed by the GDG for relevance to a clinical question. Searches were undertaken for RCTs published too late to be included in chosen systematic reviews beginning two years before the publication date of the review in question. Where authors stated the date searches had been undertaken, the NCCMH review team undertook new searches from the beginning of that year. Each study included in an existing review was subjected to the same quality checks as those located through NCCMH searches, and the data were re-extracted according to NCCMH protocols (see below). Where existing reviews had been undertaken using Review Manager (any version) authors were approached for data sets, although any used were checked for accuracy. For clinical questions where no existing systematic review was identified, searches were undertaken for all relevant evidence.

3.4.1.3 Searching for RCTs

For Service and Pharmacology topic area clinical questions, searches for RCTs were undertaken for each clinical question individually. However, RCTs to answer the clinical questions posed by the Psychology topic group were searched for together.
For all questions the following electronic databases were searched: EMBASE, MEDLINE, PsycINFO, Cochrane Library, CINAHL. For the pharmacological review of St John's Wort, AMED was also searched. In addition, hand searches were also made of the reference lists of all eligible RCTs, as well as of the list of evidence submitted by registered stakeholders (Appendix 3). Known experts in the field (see Appendix 5), based both on the references identified in earlier steps and on advice from GDG members, were approached for unpublished RCTs.[1] Studies were considered provided a full trial report was available. Studies published in languages other than English were used provided a native speaker was available.

If no RCTs were found to answer a clinical question the GDG adopted a consensus process (see Section 3.4.4). Future guidelines will be able to update and extend the usable evidence base starting from the evidence collected, synthesised and analysed for this guideline.

3.4.1.4 Study selection

All references located in searches of electronic databases were downloaded into Reference Manager (ISI ResearchSoft, 2002) and searched liberally to exclude irrelevant papers. The titles of excluded papers were double-checked by a second reviewer. All primary-level studies included after the first scan of citations were acquired in full and re-evaluated for eligibility. Appendix 8 lists the standard inclusion and exclusion criteria. Additional eligibility criteria were developed to assess trials of pharmacotherapy, and these are listed in Chapter 7. All eligible papers were critically appraised for methodological quality (see Appendix 10). The eligibility of each study was confirmed by at least one member of the appropriate topic group.

For some clinical questions, it was necessary to prioritise the evidence with respect to the UK context. To make this process explicit, the topic group members took into account the following factors when assessing the evidence:

- Participant factors (e.g. gender, age, ethnicity)
- Provider factors (e.g. model fidelity, the conditions under which the intervention was performed, the availability of experienced staff to undertake the procedure)
- Cultural factors (e.g. differences in standard care, differences in the welfare system).

It was the responsibility of each topic group to decide which prioritisation factors were relevant to each clinical question in light of the UK context, and then decide how they should modify their recommendations.

[1] Unpublished full trial reports were accepted where sufficient information was available to judge eligibility and quality.

3.4.2 Synthesising the evidence

3.4.2.1 Outcomes

The vast majority of data extracted were scores on the Hamilton Rating Scale for Depression (HRSD), Montgomery-Asberg Depression Rating Scale (MADRS) and Beck Depression Inventory (BDI) at the end of treatment and, where available, at follow-up. Both continuous (e.g. mean endpoint scores) and dichotomised data (e.g. number of people achieving below the cut-off for remission) were extracted. The GDG felt it was important to extract a variety of measures since relying on only one can be misleading. For example, dichotomising scores into remission and non-remission creates an artificial boundary, with patients just over the cut-off score often being clinically indistinguishable from those just under the cut-off. The GDG would also have liked to have been able to use quality of life measures as outcomes, but these are rarely reported.

In addition, where possible, sub-analyses were performed for severity of depression. Because very few studies gave information about participants' baseline severity of depression in terms of number of symptoms using the ICD classification (see Chapter 2), the mean depression score at baseline (most commonly an HRSD score) was used as a proxy measure. Scores were categorised mild, moderate, severe or very severe according to American Psychiatric Association criteria (APA, 2000a). Where necessary different versions of the HRSD were standardised using the method for prorating suggested by Walsh *et al.* (2002). The GDG used these categories with caution, mindful of the problematic nature of this proxy measure, in particular the variation in the standard deviation around baseline mean scores. Details of the categories and further information about the depression rating scales are in Appendix 13. When drawing up recommendations the GDG related the APA categories to ICD categories. This method does not take account of the severity of individual symptoms but is nonetheless a rough approximation to clinical severity.

3.4.2.2 Data extraction

Where possible, outcome data from all eligible studies that met quality criteria were extracted using a data extraction form (Appendix 11) and input into Review Manager 4.2 (Cochrane Collaboration, 2003). Where trial reports contained incomplete data and it was possible to contact the original authors, additional information was sought. Where mean endpoint or change scores were extracted and trial reports did not provide standard deviations, standard conversion formulas were used (see Appendix 12).

All dichotomous outcomes were calculated on an intention-to-treat basis (i.e. a 'once-randomised-always-analyse' basis). This assumes that those participants who ceased to engage in the study – from whatever group – had an unfavourable outcome. The effects of high attrition rates (defined as more than 50% of participants in a particular group leaving treatment early) were examined with sensitivity analyses, and studies were removed from efficacy outcomes if the possibility of bias was detected.

Consultation was used to overcome difficulties with coding. Data from studies included in existing systematic reviews were extracted independently by one reviewer directly into Review Manager and checked by a second reviewer. Where consensus could not be reached, a third reviewer was consulted. Masked assessment (i.e. blind to the journal from which the article comes, the authors, the institution, and the magnitude of the effect) was not used since it is unclear that doing so reduces bias (Jadad *et al.*, 1996; Berlin, 1997).

Information describing each study was also extracted and input into Review Manager 4.2. This was used to generate evidence tables (see Appendix 17 on the CD).

3.4.2.3 Meta-analysis

Where possible, meta-analysis was used to synthesise data. If necessary, sub-analyses were used to answer clinical questions not addressed in the original studies or reviews.

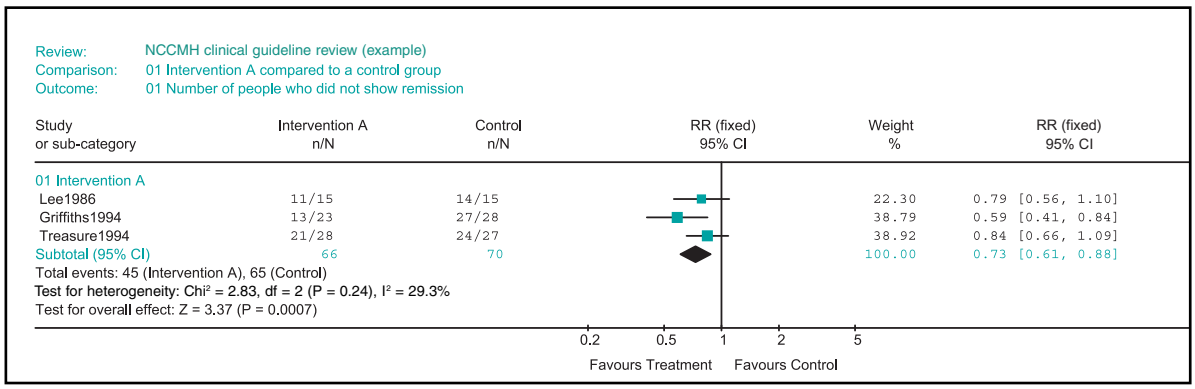
The GDG was given a graphical presentation of the results using forest plots generated with Review Manager. Each forest plot displayed the effect size and 95% confidence interval (CI) for each study as well as the overall summary statistic with its 95% CI. The graphs were organised so that the display of data in the area to the left of the 'line of no effect' indicated a 'favourable' outcome for the treatment in question.[2]

Dichotomous outcomes were presented as relative risks (RR) with the associated 95% CI (see Figure 1). A relative risk (or risk ratio) is the ratio of the treatment event rate to the control event rate. A RR of 1 indicates no difference between treatment and control. In Figure 1, the overall RR of 0.73 indicates that the event rate (i.e. non-remission rate) associated with intervention A is about half of that with the control intervention, or in other words, intervention A reduces non-remission rates by 27%. In addition, the 95% CI around the RR does not cross the 'line of no effect' indicating that this is a statistically significant effect. The CI shows with 95% certainty the range within which the true treatment effect should lie.

It had been planned to calculate the number needed to treat (NNT) (or number needed to harm (NNH)) for dichotomous outcomes with statistically significant effect sizes. However, when the baseline risk (i.e. control group event rate (CER)) or length of follow-up varies, NNT is a poor summary of the treatment effect, especially with low risk or where the CER is dissimilar across studies in a meta-analysis (Deeks, 2002). Since it was not possible to calculate the baseline risk for most outcomes NNT and NNH have not been calculated.

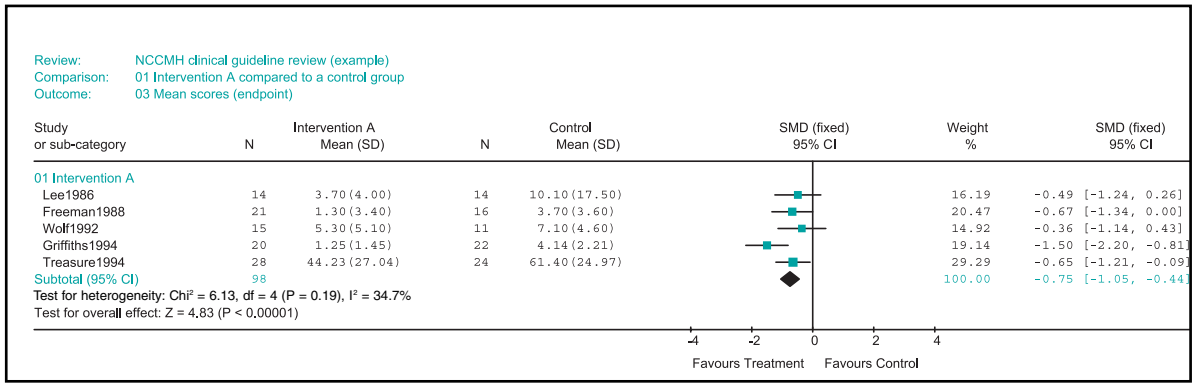
Continuous outcomes were analysed as weighted mean differences (WMD) or standardised mean differences (SMD) when different measures (or different versions of the same measure) were used in different studies to estimate the same underlying effect (see Figure 2).

Figure 1: Example of a forest plot displaying dichotomous data.



[2] The exceptions to this are: the review of amitriptyline, for which the GDG were provided with a data set for an existing systematic review (Barbui & Hotopf, 2001), and the overview of TCA data.

Figure 2: Example of a forest plot displaying continuous data.



To check for heterogeneity between studies, both the I^2 test of heterogeneity and the chi-squared test of heterogeneity ($p<0.10$), as well as visual inspection of the forest plots, were used. The I^2 statistic describes the proportion of total variation in study estimates that is due to heterogeneity (Higgins & Thompson, 2002). An I^2 of less than 30% was taken to indicate mild heterogeneity and a fixed effects model was used to synthesise the results. This assumes that the underlying effect is the same (Egger *et al.*, 2001). An I^2 of more than 50% was taken as notable heterogeneity. In this case, an attempt was made to explain the variation. If studies with heterogeneous results were found to be comparable, a random effects model was used to summarise the results (DerSimonian & Laird, 1986). In the random effects analysis, heterogeneity is accounted for both in the width of CIs and in the estimate of the treatment effect. With decreasing heterogeneity the random effects approach moves asymptotically towards a fixed effects model. An I^2 of 30% to 50% was taken to indicate moderate heterogeneity. In this case, both the chi-squared test of heterogeneity and a visual inspection of the forest plot were used to decide between a fixed and random effects model.

To explore the possibility that the results entered into each meta-analysis suffered from publication bias, data from included studies were entered, where there were sufficient data, into a funnel plot. Asymmetry of the plot was taken to indicate possible publication bias and was investigated further.

3.4.3 Developing statements and graded recommendations

The summary statistics (effect sizes (ES)) and evidence tables formed the basis for developing clinical statements and recommendations.

3.4.3.1 Developing statements

For each outcome a clinical statement describing the evidence found was developed. To do this both the statistical and the clinical significance (i.e. the likely benefit to patients) of the summary statistic were taken into account.

Assessing statistically significant summary statistics

To assess clinical significance where a statistically significant summary was obtained (after controlling for heterogeneity) the GDG adopted the following 'rules of thumb', in addition to taking into account the trial population and nature of the outcome:

For dichotomous outcomes a RR of 0.80 or less was considered clinically significant (see Section 3.4.2.3).

For continuous outcomes for which an SMD was calculated (for example, when data from different versions of a scale are combined), an effect size of ~0.5 (a 'medium' effect size; Cohen, 1988) or higher was considered clinically significant. Where a WMD was calculated, a between group difference of at least three points (two points for treatment-resistant depression) was considered clinically significant for both BDI and HRSD.

Once clinical significance had been established the strength of the evidence was assessed by examining the 95% CIs surrounding the ES. For level I evidence, where the effect size was judged clinically important for the full range of plausible estimates, the result was characterised as 'strong evidence' (i.e. S1, Flowchart 1: Guideline Statement Decision Tree). For non-level I evidence or in situations where the CI also included clinically unimportant effects, the result was characterised as 'some evidence' (i.e. S2).

Where an ES was statistically significant, but *not* clinically significant and the CI excluded values judged clinically important, the result was characterised as 'unlikely to be clinically significant' (S3). Alternatively, if the CI included clinically important values, the result was characterised as 'insufficient to determine clinical significance' (S6).

Assessing non-statistically significant summary statistics

Where a non-statistically significant ES was obtained, the GDG reviewed the trial population, nature of the outcome, size of the effect and, in particular, the CI surrounding the result. If the CI was narrow and excluded a clinically significant ES, this was seen as indicating evidence of 'no clinically significant difference' (S4), but where the CI was wide this was seen as indicating 'insufficient evidence' to determine if there was a clinically significant difference or not (S5).

In order to facilitate consistency in generating and drafting the clinical statements the GDG utilised a statement decision tree (see Flowchart 1 overleaf). The flowchart was designed to assist with, but not replace, clinical judgement.

3.4.3.2 Developing graded recommendations

Once all evidence statements relating to a particular clinical question were finalised and agreed by the GDG, the associated recommendations were produced and graded. Recommendations were graded A to C based on the level of associated evidence, or noted as coming from a previous NICE guideline or health technology appraisal (see Table 1 overleaf).

Grading allowed the GDG to distinguish between the level of evidence and the strength of the associated recommendation. It is possible that a statement of evidence would cover only one part of an area in which a recommendation was to be made or would cover it in a way that would conflict with other evidence. In order to produce more comprehensive recommendations suitable for people in England and Wales, there were times when the GDG had to extrapolate from the available evidence based on their combined clinical experience. The resulting recommendations were then graded with a lower grade (e.g. a 'B' grade where data were based upon Level I evidence).
This allowed the GDG to moderate recommendations based on factors other than the

Flowchart 1: Guideline Statement Decision Tree.

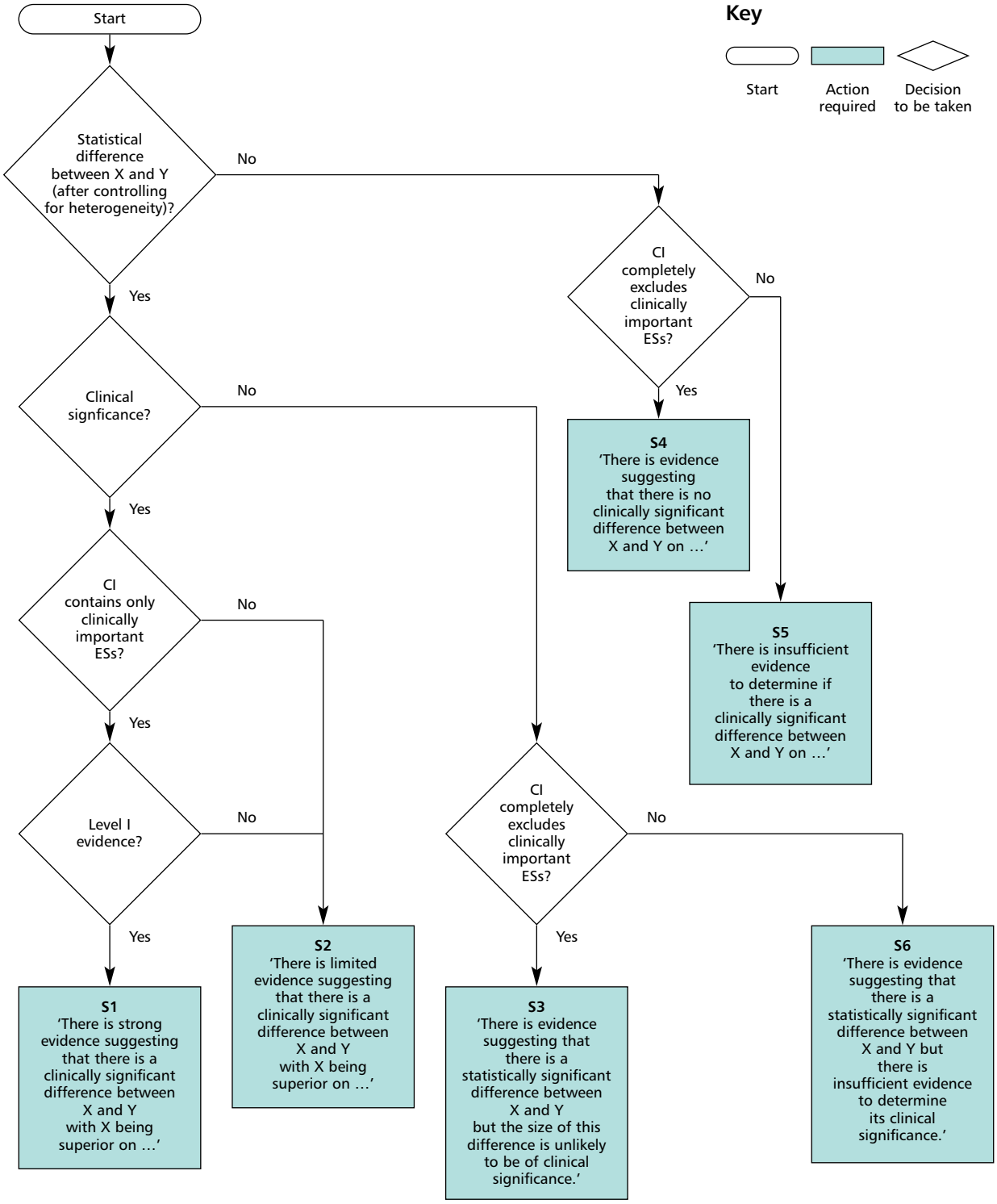


Table 1: Hierarchy of evidence and recommendations grading scheme.

Level	Type of evidence	Grade	Evidence
I	Evidence obtained from a single randomised controlled trial or a meta-analysis of randomised controlled trials	**A**	At least one randomised controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation (evidence level I) without extrapolation
IIa	Evidence obtained from at least one well-designed controlled study without randomisation	**B**	Well-conducted clinical studies but no randomised clinical trials on the topic of recommendation (evidence levels II or III); or extrapolated from level I evidence
IIb	Evidence obtained from at least one other well-designed quasi-experimental study		
III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case-control studies		
IV	Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities	**C**	Expert committee reports or opinions and/or clinical experiences of respected authorities (evidence level IV) or extrapolated from level I or II evidence. This grading indicates that directly applicable clinical studies of good quality are absent or not readily available
		GPP	Recommended good practice based on the clinical experience of the GDG
NICE	Evidence from NICE guideline or Technology Appraisal	**NICE**	Evidence from NICE guideline or Technology Appraisal

Adapted from Eccles, M. & Mason, J. (2001), How to develop cost-conscious guidelines. *Health Technology Assessment, 5*(16); Department of Health (1996), *Clinical Guidelines: Using clinical guidelines to improve patient care within the NHS*. Leeds: NHS Executive.

strength of evidence. Such considerations include the applicability of the evidence to the people in question, economic considerations, values of the development group and society, or the group's awareness of practical issues (Eccles *et al.*, 1998).

3.4.4 Method used to answer a clinical question in the absence of appropriately designed, high-quality research

In the absence of level I evidence (or a level that is appropriate to the question), or where the GDG were of the opinion (on the basis of previous searches or their knowledge of the literature) that there was unlikely to be such evidence, an informal consensus process was adopted. This process focused on those questions that the GDG considered a priority.

3.4.4.1 Informal consensus

The starting point for this process of informal consensus was that a member of the topic group identified, with help from the systematic reviewer, a narrative review that most directly addressed the clinical question. Where this was not possible, a brief review of the recent literature was initiated.

This existing narrative review or new review was used as a basis for beginning an iterative process to identify lower levels of evidence relevant to the clinical question and to lead to written statements for the guideline. The process involved a number of steps:

1. A description of what is known about the issues concerning the clinical question was written by one of the topic group members.

2. Evidence from the existing review or new review was then presented in narrative form to the GDG and further comments were sought about the evidence and its perceived relevance to the clinical question.

3. Based on the feedback from the GDG, additional information was sought and added to the information collected. This may include studies that did not directly address the clinical question but were thought to contain relevant data.

4. If, during the course of preparing the report, a significant body of primary-level studies (of appropriate design to answer the question) was identified, a full systematic review was done.

5. At this time, subject possibly to further reviews of the evidence, a series of statements that directly addressed the clinical question was developed.

6. Following this, on occasions and as deemed appropriate by the development group, the report was then sent to appointed experts outside of the GDG for peer review and comment. The information from this process was then fed back to the GDG for further discussion of the statements.

7. Recommendations were then developed and could also be sent for further external peer review.

8. After this final stage of comment, the statements and recommendations were again reviewed and agreed upon by the GDG.

3.5 Evidence on safety and harm

In the UK the licensing and post-licensing safety monitoring of medicines is undertaken by the Medicines and Healthcare products Regulatory Agency (MHRA). During the development of this guideline the safety of some drugs used to treat depression (selective serotonin reuptake inhibitors (SSRIs), mirtazapine and venlafaxine) was formally reviewed by the MHRA on behalf of the Committee on Safety of Medicines (CSM). The CSM convened a working group to look at this issue (the SSRI Expert Working Group (EWG)). The EWG's findings were made available to the GDG, and used in addition to the efficacy and safety data reviewed during the guideline development process in drawing up recommendations. In particular, data on discontinuation/withdrawal symptoms, cardiotoxicity, dose, and suicidality and self-harm, were used, together with information on changes to produce licences as a result of the EWG's report to the CSM (MHRA, 2004). The Marketing Authorisation Holder (the pharmaceutical company responsible for the drug in question) analysed data from clinical trials for each relevant drug, in accordance with a protocol specified by the EWG. These reviews formed the basis of the EWG's deliberations, and it should be noted that not all trial data were made available to the EWG (MHRA, 2004). The EWG used other data, including a number of analyses of the General Practice Research Database (for example, Jick *et al.*, 2004), along with spontaneous reporting of adverse drug reactions (via the MHRA's Yellow Card scheme).

3.6 Health economics review strategies

The aim of the health economics review was to contribute to the guideline development process data on the economic burden of depression. Evidence of the cost-effectiveness of different treatment options for depression was collected and assessed in order to help the decision-making process. See Chapter 9, Health economics evidence, for the detailed review strategies.

3.7 Stakeholder contributions

Professionals, patients and companies have contributed to and commented on the guideline at key stages in its development. Stakeholders for this guideline include:

- Patient/carer stakeholders: the national patient and carer organisations that represent people whose care is described in this guideline

- Professional stakeholders: the national organisations that represent healthcare professionals who are providing services to patients
- Commercial stakeholders: the companies that manufacture medicines used in the treatment of depression
- Primary Care Trusts
- Department of Health and Welsh Assembly Government.

Stakeholders have been involved in the guideline's development at the following points:

- Commenting on the initial scope of the guideline and attended a briefing meeting held by NICE
- Contributing lists of evidence to the GDG
- Commenting on the first and second drafts of the guideline.

3.8 Validation of this guideline

This guideline has been validated through two consultation exercises. Drafts of the full and NICE versions of the guideline were submitted to the NICE Guidelines Review Panel and posted on the NICE website (www.nice.org.uk). Stakeholders and other reviewers nominated by the GDG were then informed that the documents were available.

The GDG reviewed comments from stakeholders, the NICE Guidelines Review Panel, a number of health authority and trust representatives and a wide range of national and international experts from the first round of consultation. The GDG then responded to all comments and prepared final consultation drafts of all three versions of the guideline – the full guideline, the NICE guideline, and the information for the public. These were made available on the NICE website, and stakeholders were informed. Following consultation, the drafts were amended and responses to any comments were made. The final drafts were then submitted to NICE to be signed off after review by the Guidelines Review Panel.