Post-traumatic stress disorder

Methods

NICE guideline NG116
Supplement 1
December 2018

These evidence reviews were developed by the National Guideline Alliance, hosted by the Royal College of Obstetricians and Gynaecologists
Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

Copyright
© NICE, 2018. All rights reserved. Subject to Notice of rights.

ISBN: 978-1-4731-3181-1
Contents

Development of the guideline .................................................................................................................. 5
  Remit .................................................................................................................................................. 5
  What this guideline covers .................................................................................................................. 5
    Groups that will be covered ........................................................................................................... 5
    Settings that will be covered ........................................................................................................... 5
    Key areas that will be covered ........................................................................................................ 5
  What this guideline does not cover ..................................................................................................... 5
    Settings that will not be covered ...................................................................................................... 5

Methods .................................................................................................................................................. 7
  Developing the review questions and outcomes ................................................................................ 7
  Reviewing research evidence ............................................................................................................. 15
    Type of studies and inclusion/exclusion criteria ........................................................................... 15
    Type of studies and inclusion/exclusion criteria ........................................................................... Error! Bookmark not defined.
  Methods of combining evidence ......................................................................................................... 16
    Data synthesis for intervention studies ......................................................................................... 16
    Data synthesis for qualitative reviews ......................................................................................... 16
  Appraising the quality of evidence .................................................................................................... 16
    Intervention studies ....................................................................................................................... 16
    Qualitative reviews ........................................................................................................................ 20
    Evidence statements ....................................................................................................................... 21
    Formal consensus methods ............................................................................................................ 22
  Reviewing economic evidence ........................................................................................................... 22
    Inclusion and exclusion of economic studies ................................................................................ 22
    Appraising the applicability and quality of economic evidence .................................................... 23
    Inclusion and exclusion of health state utility studies ..................................................................... 24
  Health economic modelling ................................................................................................................ 24
    Cost effectiveness criteria ............................................................................................................... 25
  Developing recommendations ............................................................................................................ 25
    Guideline recommendations .......................................................................................................... 25
    Research recommendations ............................................................................................................ 26
  Validation process ............................................................................................................................... 26
  Updating the guideline ......................................................................................................................... 26
  Funding ................................................................................................................................................ 26

References .............................................................................................................................................. 27
  Appendix A - PRISMA flowchart for global economic evidence ....................................................... 28
Development of the guideline

Remit

The National Institute for Health and Care Excellence (NICE) commissioned the National Guideline Alliance (NGA) to produce the update for this guideline.

The remit for this guideline update is to revise the NICE clinical guideline on the management of Post-Traumatic Stress Disorder (PTSD) in children, young people and adults.

What this guideline covers

Groups that will be covered

- Adults, children and young people at risk of or with PTSD.
- Family members and carers of people with PTSD: the guideline will recognise their role in the treatment and support of people with PTSD.
- Adults, children and young people with PTSD who have coexisting conditions, such as drug and alcohol misuse, common mental health disorders or personality disorders.

Settings that will be covered

- All NHS and social care commissioned services where care is provided for people at risk of or with a diagnosis of PTSD.

Key areas that will be covered

- Psychological and psychosocial interventions for the prevention and treatment of PTSD.
- Pharmacological interventions for the prevention and treatment of PTSD. Note the guideline recommendations will normally fall within licensed indications; exceptionally, and only if clearly supported by evidence, use outside a licensed indication may be recommended. The guideline will assume that prescribers will use a medicine’s summary of product characteristics to inform decisions made with individual patients.
- Principles of care for all people with PTSD.
- Support for families and carers.
- Practical and social support.
- Care for people with coexisting conditions.

What this guideline does not cover

Settings that will not be covered

- Theatres of military conflict.
Areas from the published guideline that will not be updated

- Recognition
- Assessment
- Language and culture
- Disaster planning

Recommendations in areas that are not being updated may be edited to ensure that they meet current editorial standards, and reflect the current policy and practice context.

Areas not covered by the published guideline or the update

- Inoculation interventions for people who may be at risk of experiencing, but have not experienced, a traumatic event
Methods

This chapter sets out in detail the methods used to review the evidence and to generate recommendations in the guideline. This guideline was developed using the methods described in Developing NICE guidelines: the manual.

Declarations of interest were recorded according to the 2014 and 2018 NICE Conflicts of interest policy.

For further information on methods used to develop CG26 please refer to section 4 of the full guideline.

Developing the review questions and outcomes

The 13 review questions developed for this guideline were based on the key areas identified in the https://www.nice.org.uk/guidance/gid-ng10013/documents/draft-scope. They were drafted by the NGA, and refined and validated by the guideline committee. They covered all areas of the scope and were signed-off by NICE. These questions are outlined in Table 1.

The review questions were based on the following frameworks:
- intervention reviews: population, intervention, comparator and outcome (PICO)
- qualitative reviews – using population, area of interest and themes of interest.

These frameworks guided the development of the review protocols, the literature searching process, the critical appraisal and synthesis of evidence and facilitated the development of recommendations by the committee.

Full literature searches, critical appraisals and evidence reviews were completed for all review questions.

Description of review questions

Table 1: Description of review questions

<table>
<thead>
<tr>
<th>Chapter or section from the scope</th>
<th>Location in Evidence Reports</th>
<th>Type of review</th>
<th>Review question</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| 1.1                              | A                           | Intervention   | For children and young people at risk of PTSD, what are the relative benefits and harms of psychological, psychosocial or other non-pharmacological interventions targeted at PTSD symptoms? | 1. Efficacy  
   - PTSD symptomology  
   - Diagnosis of PTSD  
  2. Dissociative symptoms  
  3. Personal, social, educational and occupational functioning  
  4. Quality of life  
  5. Acceptability/tolerability  
   - Acceptability of the intervention |
<table>
<thead>
<tr>
<th>Chapter or section from the scope</th>
<th>Location in Evidenc e Reports</th>
<th>Type of review</th>
<th>Review question</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2</td>
<td>B</td>
<td>Intervention</td>
<td>For children and young people with clinically important post-traumatic stress symptoms, what are the relative benefits and harms of psychological, psychosocial or other non-pharmacological interventions targeted at PTSD symptoms?</td>
<td>1. Efficacy • PTSD symptomology • Diagnosis of PTSD • Recovery from PTSD/Remission • Relapse • Global functioning 2. Dissociative symptoms 3. Personal, social, educational and occupational functioning 4. Quality of life 5. Acceptability/tolerability • Acceptability of the intervention • Discontinuation due to adverse effects • Discontinuation due to any reason 6. Coexisting conditions • Symptoms of and recovery from a coexisting condition • Self-harm • Suicide</td>
</tr>
<tr>
<td>1.3</td>
<td>C</td>
<td>Intervention</td>
<td>For adults at risk of PTSD, what are the relative benefits and harms of psychological, psychosocial or other non-pharmacological interventions</td>
<td>1. Efficacy • PTSD symptomology • Diagnosis of PTSD 2. Dissociative symptoms 3. Personal, social, educational and</td>
</tr>
<tr>
<td>Chapter or section from the scope</td>
<td>Locatio n in Evidenc e Reports</td>
<td>Type of review</td>
<td>Review question</td>
<td>Outcomes</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>--------------------------------</td>
<td>----------------</td>
<td>----------------</td>
<td>----------</td>
</tr>
</tbody>
</table>
|                                  |                                | Intervention   | For adults with clinically important post-traumatic stress symptoms, what are the relative benefits and harms of psychological, psychosocial or other non-pharmacological interventions targeted at PTSD symptoms? | occupational functioning  
4. Quality of life  
5. Acceptability/tolerability  
   • Acceptability of the intervention  
   • Discontinuation due to adverse effects  
   • Discontinuation due to any reason  
6. Coexisting conditions  
   • Symptoms of and recovery from a coexisting condition  
   • Self-harm  
   • Suicide |
| 1.4                              | D                              |                | targeted at PTSD symptoms? | occupational functioning  
4. Quality of life  
5. Acceptability/tolerability  
   • Acceptability of the intervention  
   • Discontinuation due to adverse effects  
   • Discontinuation due to any reason  
6. Coexisting conditions  
   • Symptoms of and recovery from a coexisting condition  
   • Self-harm  
   • Suicide |
<table>
<thead>
<tr>
<th>Chapter or section from the scope</th>
<th>Locaton in Evidenc Reports</th>
<th>Type of review</th>
<th>Review question</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| 2.1                              | E                           | Intervention  | For children and young people at risk of PTSD, what are the relative benefits and harms of specific pharmacological interventions? | 1. Efficacy  
- PTSD symptomology  
- Diagnosis of PTSD  
2. Dissociative symptoms  
3. Personal, social, educational and occupational functioning  
4. Quality of life  
5. Acceptability/tolerability  
- Acceptability of the intervention  
- Discontinuation due to adverse effects  
- Discontinuation due to any reason  
6. Coexisting conditions  
- Symptoms of and recovery from a coexisting condition  
- Self-harm  
- Suicide |
| 2.2                              | E                           | Intervention  | For children and young people with clinically important post-traumatic stress symptoms, what are the relative benefits and harms of specific pharmacological interventions? | 1. Efficacy  
- PTSD symptomology  
- Diagnosis of PTSD  
- Recovery from PTSD/Remission  
- Relapse  
- Global functioning  
2. Dissociative symptoms  
3. Personal, social, educational and occupational functioning  
4. Quality of life  
5. Acceptability/tolerability  
- Acceptability of the intervention  
- Discontinuation due to adverse effects  
- Discontinuation due to any reason |
<table>
<thead>
<tr>
<th>Chapter or section from the scope</th>
<th>Location in Evidence Reports</th>
<th>Type of review</th>
<th>Review question</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>6. Coexisting conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Symptoms of and recovery from a coexisting condition</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Self-harm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Suicide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.3 F Intervention</td>
<td></td>
<td>Intervention</td>
<td>For adults at risk of PTSD, what are the relative benefits and harms of specific pharmacological interventions?</td>
<td>1. Efficacy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• PTSD symptomology</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Diagnosis of PTSD</td>
</tr>
<tr>
<td>2.4 F Intervention</td>
<td></td>
<td>Intervention</td>
<td>For adults with clinically important post-traumatic stress symptoms, what are the relative benefits and harms of specific pharmacological interventions?</td>
<td>1. Efficacy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• PTSD symptomology</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Diagnosis of PTSD</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Recovery from PTSD/Remission</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Relapse</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Global functioning</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2. Dissociative symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3. Personal, social, educational and occupational functioning</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4. Quality of life</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5. Acceptability/tolerability</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Acceptability of the intervention</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Discontinuation due to adverse effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Discontinuation due to any reason</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6. Coexisting conditions</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Symptoms of and recovery from a coexisting condition</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Self-harm</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Suicide</td>
</tr>
<tr>
<td>Chapter or section from the scope</td>
<td>Locatio n in Evidenc e Reports</td>
<td>Type of review</td>
<td>Review question</td>
<td>Outcomes</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>---------------------------------</td>
<td>---------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
|                                  |                                 | G             | Intervention For family members (including children and carers) of people at risk of PTSD, do specific psychological, psychosocial or other non-pharmacological interventions result in an improvement in their mental health and wellbeing, a reduction in burden and improved social and occupational outcomes? | • Acceptability of the intervention  
• Discontinuation due to adverse effects  
• Discontinuation due to any reason  
6. Coexisting conditions  
• Symptoms of and recovery from a coexisting condition  
• Self-harm  
• Suicide |
|                                  |                                 | G             | Intervention For family members (including children and carers) of people with clinically important post-traumatic stress symptoms, do specific psychological, psychosocial or other non-pharmacological interventions result in an improvement in their mental health and wellbeing, a reduction in burden and improved social and occupational outcomes? | • Family member/Carer mental health  
• Family member/Carer wellbeing or quality of life  
• Carer burden  
• Employment  
• Housing  
• Lifestyle disruption  
• Relationship difficulties |
<p>| 3.1                              | H                               | Qualitative evidence | For adults, children and young people with clinically Experience and views of services including: | • Access to care |</p>
<table>
<thead>
<tr>
<th>Chapter or section from the scope</th>
<th>Locatio in Evidenc e Reports</th>
<th>Type of review</th>
<th>Review question</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
|                                  |                             |                | important post-traumatic stress symptoms, what factors should be taken into account in order to provide access to care, optimal care and coordination of care? | • Engagement with care  
• Care received  
• Practical support received  
• Social support received  
• Care planning and coordination  
• Content and configuration of services  
• Satisfaction with services  
• Awareness, knowledge and use of wider services  
• A service delivery model change/intervention |
|                                  |                             | Intervention   | Which service delivery models are effective at meeting the needs of adults, children and young people with clinically important post-traumatic stress symptoms? | • PTSD symptomology  
• Quality of life  
• Access to treatment  
• Uptake of treatment  
• Healthcare utilisation  
• Satisfaction, preference  
• Anxiety about treatment |
| 6.1                              | J                            | Intervention   | For adults, children and young people with clinically important post-traumatic stress symptoms, what are the aspects of a clinical care pathway that are associated with better outcomes? | • PTSD symptomology  
• Quality of life  
• Access to treatment  
• Uptake of treatment  
• Healthcare utilisation  
• Satisfaction, preference  
• Anxiety about treatment |

*PTSD: post-traumatic stress disorder*
Searching for evidence

Clinical search literature

Systematic literature searches were undertaken to identify all published clinical evidence relevant to the review questions. All relevant studies from existing reviews (all reviews except recognition, assessment, language and culture, and disaster planning) were carried over.

Databases were searched using relevant medical subject headings, free-text terms and study type filters where appropriate. Studies published in languages other than English were not reviewed. All searches were conducted in MEDLINE, Embase, PsycINFO, CINAHL and The Cochrane Library.

Searches for treatment and prevention reviews were initially undertaken between October 2016 and January 2017 and re-runs performed in January 2018. Searches for all other reviews were undertaken between September and November 2017.

Search strategies were quality assured by cross-checking reference lists of highly relevant papers, analysing search strategies in other systematic reviews and asking the group members to highlight any additional studies. The questions, the filters applied and the databases searched can be found in Appendix F in each Evidence Report. The years covered can be found in the review protocols.

Searches for grey literature or unpublished literature were not undertaken. Searches for electronic, ahead-of-print publications were routinely undertaken for all review questions.

During the scoping stage, a search was conducted for guidelines, systematic reviews and reports on websites of organisations relevant to the topic. All references suggested by stakeholders at the scoping consultation were considered.

Health economics search literature

A global search of economic evidence was undertaken in Medline, Embase, HTA database and NHS EED in December 2016 and re-run in March 2018. Evidence resulting from the search was screened to reflect the final dates of the searches that were undertaken for the clinical reviews (see review protocols).

Further to the database searches, the committee was contacted with a request for details of relevant published and unpublished studies of which they may have had knowledge; reference lists of key identified studies were also reviewed for any potentially relevant studies.

The search strategy for existing economic evaluations combined terms capturing the target condition (PTSD) and, for searches undertaken in MEDLINE and EMBASE, terms capturing PTSD and economic evaluations. No restrictions on language or setting were applied to any of the searches, but a standard exclusions filter was applied (letters, animals, etc.). Full details of the search strategies are presented in Appendix F of each Evidence Report.

Call for evidence

No call for evidence was made.
Reviewing research evidence

Type of studies and inclusion/exclusion criteria

The evidence was reviewed following these steps.

- Potentially relevant studies were identified for each review question from the relevant search results by reviewing titles and abstracts. Full papers were then obtained.
- Full papers were reviewed against pre-specified inclusion and exclusion criteria as outlined in the review protocols (in appendix A of each evidence review chapter).
- Key information was extracted on the study’s methods, according to the factors specified in the protocols and results. These were presented in summary tables (in each review chapter) and evidence tables (in appendix F of each evidence review chapter).
- Relevant studies were critically appraised using the appropriate checklist as specified in Developing NICE guidelines: the manual.
- Summaries of evidence were generated by outcome (included in the relevant review chapters) and were presented to the committee as follows.
  - Randomised studies: meta-analysis was carried out where appropriate and results were reported in Grading of Recommendations Assessment, Development and Evaluation (GRADE) profiles (for intervention reviews).
  - Qualitative studies: each study was summarised by theme and themes were then presented in summary tables with quality ratings based on the study checklists. CERQUAL, an adapted GRADE approach, was also used to assess the confidence in the qualitative review findings
- All drafts of reviews were checked by a senior reviewer.

For intervention reviews in this guideline, randomised controlled trials (RCTs) were prioritised because they are considered the most robust type of study design for unbiased estimate of intervention effects.

In the qualitative reviews, studies using focus groups, or structured or semi-structured interviews were considered for inclusion. Survey data or other types of questionnaires were only included if they provided analysis from open-ended questions, but not if they reported descriptive quantitative data only.

For quality assurance of study identification, titles and abstracts of identified studies were screened by two reviewers for inclusion against criteria, until a good inter-rater reliability was observed (percentage agreement =>90% or Kappa statistics, K>0.60). Initially 10% of references were double-screened. If inter-rater agreement was good then the remaining references were screened by one reviewer. All primary-level studies included after the first scan of citations were acquired in full and re-evaluated for eligibility at the time they were entered into a study database (standardised template created in Microsoft Excel). At least 10% of data extraction were double-coded. Discrepancies or difficulties with coding were resolved through discussion between reviewers or the opinion of a third reviewer was sought. Non-English-language papers were excluded (unless data were obtained from an existing review). For further details, please refer to Appendix A of the relevant Evidence Report.
Methods of combining evidence

Data synthesis for intervention studies

Pair-wise meta-analyses were conducted where possible, to combine the results of studies for each review question using Cochrane Review Manager 5 (RevMan5) software.

For binary outcomes, such as occurrence of adverse events, the Mantel-Haenszel method of statistical analysis was used to calculate risk ratios (relative risk, RRIs) with 95% confidence intervals (CIs).

For continuous outcomes, measures of central tendency (mean) and variation (standard deviation, SD) are required for meta-analysis. Data for continuous outcomes (such as health-related quality of life or improvement of symptoms) were analysed using an inverse-variance method for pooling weighted standard mean differences.

Statistical heterogeneity was assessed by visually examining the forest plots and by considering the chi-squared test for significance at p<0.1 or an I-squared inconsistency statistic (with an I-squared value of more than 50% indicating high heterogeneity). Where considerable heterogeneity was present, predefined subgroup analyses were performed.

Assessments of potential differences in effect between subgroups were based on the chi-squared tests for heterogeneity statistics between subgroups. If no sensitivity analysis was found to resolve statistical heterogeneity (i.e., bring I² below 50%), then a random-effects (DerSimonian 2015) model was employed to provide a more conservative estimate of the effect. For heterogeneity, the quality of the evidence was downgraded in GRADE by 1 or 2 levels for the domain of inconsistency, depending on the extent of heterogeneity in the results.

Data synthesis for qualitative reviews

Where appropriate, qualitative data synthesis was guided by a “best fit” framework synthesis approach (Carroll 2011). The distinguishing characteristic of this type of approach, and the aspect in which it differs from other methods of qualitative synthesis such as meta-ethnography (Campbell, 2003) is that it is primarily deductive involving a priori theme identification and framework construction against which data from included studies can be mapped.

CERQual was used to evaluate the overall quality in the evidence.

Appraising the quality of evidence

Intervention studies

GRADE methodology

For intervention reviews, the evidence for outcomes from the included RCTs was evaluated and presented using GRADE, which was developed by the international GRADE working group.
The software developed by the GRADE working group (GRADEpro) was used to assess the quality of each outcome, taking into account individual study quality factors and the meta-analysis results. The clinical/economic evidence profile tables include details of the quality assessment and pooled outcome data, where appropriate, an absolute measure of intervention effect and the summary of quality of evidence for that outcome. In this table, the columns for intervention and control indicate summary measures of effect and measures of dispersion (such as mean and SD or median and range) for continuous outcomes and frequency of events (n/N; the sum across studies of the number of patients with events divided by sum of the number of completers) for binary outcomes. Reporting or publication bias was only taken into consideration in the quality assessment and included in the clinical evidence profile tables if it was apparent.

The selection of outcomes for each review question was decided when each review protocol was discussed with the guideline committee, and was informed by committee discussion and key papers.

The evidence for each outcome in the intervention reviews was examined separately for the quality elements listed and defined in Table 2. Each element was graded using the quality levels listed in Table 3.

The main criteria considered in the rating of these elements are discussed below. Footnotes were used to describe reasons for grading a quality element as having serious or very serious limitations. The ratings for each component were summed to obtain an overall assessment for each outcome (Table 4).

### Table 2: Description of quality elements in GRADE for intervention reviews

<table>
<thead>
<tr>
<th>Quality element</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of bias (study limitations)</td>
<td>Limitations in the study design and implementation may bias the estimates of the treatment effect. High risk of bias for the majority of the evidence decreases confidence in the estimate of the effect.</td>
</tr>
<tr>
<td>Inconsistency</td>
<td>Inconsistency refers to an unexplained heterogeneity of results or findings.</td>
</tr>
<tr>
<td>Indirectness</td>
<td>Indirectness refers to differences in study population, intervention, comparator and outcomes between the available evidence and the review question, or recommendation made, such that the effect estimate is changed. This is also related to applicability or generalisability of findings.</td>
</tr>
<tr>
<td>Imprecision</td>
<td>Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of the effect. Imprecision results if the confidence interval includes the clinically important threshold.</td>
</tr>
<tr>
<td>Publication bias</td>
<td>Publication bias is a systematic underestimate or an overestimate of the underlying beneficial or harmful effect due to the selective publication of studies.</td>
</tr>
</tbody>
</table>

### Table 3: Levels of quality elements in GRADE

<table>
<thead>
<tr>
<th>Levels of quality elements in GRADE</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>None/no serious</td>
<td>There are no serious issues with the evidence.</td>
</tr>
<tr>
<td>Serious</td>
<td>The issues are serious enough to downgrade the outcome evidence by 1 level.</td>
</tr>
</tbody>
</table>
Levels of quality elements in GRADE

<table>
<thead>
<tr>
<th>Description</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Very serious</td>
<td>The issues are serious enough to downgrade the outcome evidence by 2 levels.</td>
</tr>
</tbody>
</table>

Table 4: Levels of overall quality of outcome evidence in GRADE

<table>
<thead>
<tr>
<th>Overall quality of outcome evidence in GRADE</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Further research is very unlikely to change our confidence in the estimate of effect.</td>
</tr>
<tr>
<td>Moderate</td>
<td>Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.</td>
</tr>
<tr>
<td>Low</td>
<td>Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.</td>
</tr>
<tr>
<td>Very low</td>
<td>Any estimate of effect is very uncertain.</td>
</tr>
</tbody>
</table>

Assessing risk of bias in intervention reviews

Bias is a systematic error, or a consistent deviation from the truth in the results. When a risk of bias is present the true effect can be either under- or over-estimated.

Risk of bias in intervention studies was assessed using the Cochrane Risk of Bias Tool (see Appendix H in Developing NICE guidelines: the manual).

The possible sources of bias in intervention studies in the Cochrane risk of bias tool fit with the following 5 categories: selection bias, performance bias, attrition bias, detection bias and reporting bias.

It should be noted that a study with a poor methodological design does not automatically imply high risk of bias; the bias is considered individually for each outcome and it is assessed whether this poor design will impact on the estimation of the intervention effect.

For risk of bias, outcomes were downgraded if the randomisation and/or allocation concealment methods were unclear or inadequate. Outcomes were also downgraded if no attempts were made to blind the assessors or participants. Outcomes were also downgraded if there was considerable missing data (see below).

Handling missing data:
- where possible an intention to treat approach was used
- outcomes were downgraded if there was a dropout of more than 20%, or if there was a difference of >20% between the groups.

Assessing inconsistency in intervention reviews

Inconsistency refers to unexplained heterogeneity of results of meta-analysis. When estimates of the treatment effect vary widely across studies (that is, there is heterogeneity or variability in results), this suggests true differences in underlying effects. Inconsistency is, thus, only applicable when statistical meta-analysis is conducted (that is, results from different studies are pooled). However, ‘no inconsistency’ is nevertheless used to describe this quality assessment in the
GRADE profiles for outcomes from a single study as per GRADE methodology (Santesso 2016).

Statistical heterogeneity was assessed by calculating the I-squared statistic for the meta-analysis. I-squared values of more than 50% and 80% were considered to indicate high and very high heterogeneity, respectively. When high or very high heterogeneity was observed, possible reasons for it were explored and subgroup analyses were performed as pre-specified in the review protocol.

The quality of the evidence was downgraded in GRADE by 1 (I-squared > 50%) or 2 (I-squared > 80%) levels for the domain of inconsistency, depending on the extent of heterogeneity in the results.

**Assessing indirectness in intervention reviews**

Directness refers to the extent to which the populations, intervention, comparisons and outcome measures are similar to those defined in the inclusion criteria for the reviews. Indirectness is important when these differences are expected to contribute to a difference in effect size, or may affect the balance of harms and benefits considered for an intervention.

**Assessing imprecision and clinical significance in intervention reviews**

Imprecision in guidelines concerns whether the uncertainty (CI) around the effect estimate means that it is not clear whether there is a clinically important difference between interventions or not (that is, whether the evidence would clearly support one recommendation or appear to be consistent with several different types of recommendations). Therefore, imprecision differs from the other aspects of evidence quality because it is not really concerned with whether the point estimate is accurate or correct (has internal or external validity). Instead, it is concerned with the uncertainty about what the point estimate actually is. This uncertainty is reflected in the width of the CI.

The 95% CI is defined as the range of values within which the population value will fall on 95% of repeated samples, were this procedure to be repeated. The larger the trial, the smaller the 95% CI and the more certain the effect estimate.

For imprecision: outcomes were downgraded according to the following criteria:

**Step 1:** If the 95% CI was imprecise i.e. crossed 0.8 or 1.25 (for dichotomous outcomes) or -0.5 or 0.5 (for continuous outcomes). Outcomes were downgraded one or two levels depending on how many lines it crossed.

**Step 2:** If the clinical decision threshold was not crossed, it was considered whether the criterion for Optimal Information Size was met, if not, the outcome was downgraded one level for the following:

- for dichotomous outcomes: <300 events
- for continuous outcomes: <400 participants

For clinical effectiveness, if studies reported outcomes using the same scale mean differences were considered, if not standardized mean differences (SMDs) were considered and the following criteria was used:

- SMD <0.2 too small to likely show an effect
- SMD 0.2 small effect
- SMD 0.5 moderate effect
- SMD 0.8 large effect
- RR <0.8 or >1.25 clinical benefit

Anything less (RR >0.8 and <1.25), the absolute numbers were looked at to make a decision on whether there may be a clinical effect.

It must be noted that ‘clinically important’ is also used in another context in this guideline. In reference to PTSD symptoms, it is defined as a diagnosis of PTSD according to DSM, ICD or similar criteria or clinically-significant PTSD symptoms as indicated by baseline scores above clinical threshold on a validated scale.

**Minimally important differences**

The committee members were asked whether they were aware of any recognised MIDs in the clinical community.

As no published or recognised MIDs were identified, the committee decided that it was clinically acceptable to use the GRADE default MID to assess imprecision. For binary outcomes, clinically important thresholds for a RR of 0.8 and 1.25 were used (due to the statistical distribution of this measure this means that this is not a symmetrical interval). For continuous outcomes, clinically important thresholds were standardised mean differences (SMD) of -0.5 or 0.5 were used. The committee considered outcomes that were statistically significant but where the effect size fell below the threshold for a clinically important effect. However, these effects were only considered meaningful where there was a large number of studies and participants and effects were highly consistent.

**Optimal information size**

Evaluating the CI is not sufficient to assess imprecision. When there are a small number of events, the CI can be narrow but the results may be fragile. Therefore, it is suggested that in addition to considering whether the CI crosses thresholds for MIDs, the optimal information size (OIS), representing the number of patients generated by a conventional single-trial sample size calculation, should be considered (Schünemann, 2013). In statistical hypothesis testing alpha is probability of rejecting the null hypothesis given that it is true and beta is the probability of failing to reject the null hypothesis given that it is false. For continuous outcomes, using the standard alpha and beta values of 0.05 and 0.20 respectively, a total sample size (across both arms) of approximately 400 would be required to detect an effect size of 0.2; therefore if N < 400 for an outcome, the evidence would be considered imprecise and downgraded by 1 level (‘serious imprecision’). For binary outcomes, evidence should be considered imprecise and downgraded by 1 level (‘serious imprecision’) if the total number of events (across both arms) is less than 300. For outcomes where any statistically significant change was considered by the committee to be clinically important, imprecision was rated based on OIS alone; for all other outcomes, imprecision was determined based on the width of the CI and the OIS.

**Qualitative reviews**

For qualitative evidence, quality was assessed using a checklist for qualitative studies (see Appendix H in Developing NICE guidelines: the manual). This was based on the Critical Appraisal Skills Programme (CASP) checklist for qualitative
The quality rating for risk of bias (low, high and unclear) was derived by assessing the risk of bias across 6 domains.

The evidence was then assessed by theme using the ratings on the CASP checklist across studies taking into account any identified limitations as described in Table 5 and labelled as low (more than one study limitation identified), moderate (one study limitation identified) or high quality (no study limitations identified).

### Table 5: Summary of CASP tool for qualitative studies

<table>
<thead>
<tr>
<th>Risk of bias</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aim and appropriateness of qualitative evidence.</td>
<td>This refers to an assessment of whether the aims and relevance of the study were clearly described and whether qualitative research methods were appropriate for investigating the research question.</td>
</tr>
<tr>
<td>Rigour in study design or validity of theoretical approach</td>
<td>This domain assesses whether the study approach has been clearly described and is based on a theoretical framework (for example ethnography or grounded theory). This does not necessarily mean that the framework has to be explicitly stated, but that at least a detailed description is provided which makes it transparent and reproducible.</td>
</tr>
<tr>
<td>Sample selection</td>
<td>The background, the procedure and reasons for the chosen method of selecting participants should be stated. It should also be assessed whether there was a relationship between the researcher and the informant and if so, how this may have influenced the findings that were described.</td>
</tr>
<tr>
<td>Data collection</td>
<td>Consideration was given to how well the method of data collection (in-depth interviews, semi-structured interviews, focus groups or observations) was described, whether details were provided and how the data were collected (who conducted the interviews, how long did they last and where did they take place).</td>
</tr>
<tr>
<td>Data analysis</td>
<td>For this criterion it is assessed whether sufficient detail is provided about the analytical process and whether it is in accordance with the theoretical approach. For instance, if a thematic analysis was used, it is assessed whether there was a clear description of how the theme was arrived at. Data saturation is also part of this section. This refers to whether a theoretical point of theme saturation was achieved at which point no further citations or observations would provide more insight or suggest a different interpretation of this theme. This could be explicitly stated, or it may be clear from the citations presented that it may have been possible to find more themes.</td>
</tr>
<tr>
<td>Results</td>
<td>In relation to this section the reasoning about the results are important, for instance whether a theoretical proposal or framework is provided rather than being restricted to citations / presentation of data.</td>
</tr>
</tbody>
</table>

**Evidence statements**

Evidence statements are summary statements that are presented after the GRADE profiles highlighting the key features of the clinical evidence presented. The wording of the evidence statements reflects the certainty or uncertainty in the estimate of effect. The evidence statements are presented by outcome or theme and encompass the following key features of the evidence:

- the quality of the evidence (GRADE rating)
- the number of studies and/or the number of participants for a particular outcome (or theme in the case of qualitative evidence)
- a brief description of the participants
• the clinical significance of the effect and an indication of its direction (for example, if a treatment is clinically significant (beneficial or harmful) compared with another, or whether there is no clinically significant difference between the tested treatments).

Formal consensus methods

Formal consensus methods were used with the committee in instances where relevant clinical evidence was non-existent or insufficient to inform recommendations due to poor quality or lack of evidence for subgroups of interest (review question 7.2). The modified nominal group technique (Bernstein 1992) was selected due to its appropriateness for use within the guideline development process and this method has been identified as the most commonly used for the development of consensus in healthcare (Murphy 1998). Other advantages of this method include that it is effective in quickly obtaining consensus from a range of participants and is transparent, making it possible to trace how a group came to a decision and formed recommendations.

This method required members of the committee to indicate their agreement with a set of statements. The statements were developed by the NGA drawing on available sources of evidence on care pathways, namely previous NICE mental health guidelines (including: the previous PTSD guideline; Common mental health problems: identification and pathways to care; Mental health problems in people with learning disabilities: prevention, assessment and management). Agreement with the statements was rated on a 9-point Likert scale where 1 represented strongly disagree, 5 represented neither agree nor disagree and 9 represented strongly agree. Participants had the option of indicating that they had insufficient knowledge in a given area to provide a rating. The ratings were grouped into three categories: 1 to 3 (disagree), 4 to 6 (neither agree nor disagree), or 7 to 9 (agree).

Statements with greater than or equal to 80% agreement were used to inform drafting of recommendations (taking into account comments from the committee members). Statements where there was 60-80% agreement were redrafted based on the committee’s comments and re-rated following the same procedure as in round 1. Statements with less than 60% agreement in round 1 were generally disregarded unless there were obvious and addressable issues identified from the comments.

Reviewing economic evidence

Systematic reviews of economic literature were conducted for all review questions covered in the guideline, unless economic evidence was not relevant to a review question. In addition, literature on the health-related quality of life of people covered by this guideline was systematically searched to identify studies reporting appropriate health state utility data that could be utilised in a cost-utility analysis.

Inclusion and exclusion of economic studies

The titles and abstracts of papers identified through the searches were independently assessed for inclusion using predefined eligibility criteria defined in Table 6.
Table 6: Inclusion and exclusion criteria for the systematic reviews of economic evaluations

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Only studies from Organisation for Economic Co-operation and Development member countries were included, as the aim of the review was to identify economic information transferable to the UK context.</td>
</tr>
<tr>
<td>Only studies published from 2003 onwards were included in the review. This date restriction was imposed so that retrieved economic evidence was relevant to current healthcare settings and costs.</td>
</tr>
<tr>
<td>Selection criteria based on types of clinical conditions, populations and interventions assessed were identical to the clinical literature review.</td>
</tr>
<tr>
<td>Full economic evaluations that compared 2 or more relevant options and considered both costs and consequences as well as costing analyses that compared only costs between 2 or more interventions.</td>
</tr>
<tr>
<td>Clinical effectiveness data utilised in the analysis should be derived from a clinical trial, a prospective or retrospective cohort study, a study with a before-and-after design, or from a literature review.</td>
</tr>
<tr>
<td>The outcome measure of the economic analysis should be the Quality Adjusted Life Year (QALY) or one of the measures considered in the clinical review.</td>
</tr>
<tr>
<td>Studies should be reporting separately costs from a healthcare perspective.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poster presentations and abstracts in conference proceedings.</td>
</tr>
<tr>
<td>Non-English language papers.</td>
</tr>
<tr>
<td>Non-comparative studies.</td>
</tr>
<tr>
<td>Studies that adopted a non-healthcare perspective and did not consider healthcare costs.</td>
</tr>
</tbody>
</table>

Once the screening of titles and abstracts was complete, full versions of the selected papers were acquired for assessment. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for the search of economic evaluations is presented in Appendix A of this chapter.

Lists of included economic studies with their evidence tables, as well as studies excluded after obtaining full text with reasons for exclusion, are provided in Appendix H and Appendix L of the respective Evidence Review Reports.

Appraising the applicability and quality of economic evidence

The applicability and quality of economic evaluations in this guideline were appraised using the methodology checklist reported in the Developing NICE guidelines: the manual, Appendix H for all studies that met the inclusion criteria.

The methodological assessment of economic studies considered in this guideline has been summarised in economic evidence profiles that were developed for each review question for which economic evidence was available. All studies that fully or partially met the applicability and quality criteria described in the methodology checklist were considered during the guideline development process.

Health economic profiles of all economic studies that were considered during guideline development, including de novo economic analyses undertaken for this guideline, are provided in Appendix J of the respective Evidence Review Reports.
Inclusion and exclusion of health state utility studies

The titles and abstracts of papers identified through the searches were independently assessed for inclusion using predefined eligibility criteria defined in Table 7.

Table 7: Inclusion and exclusion criteria for the systematic review of health state utility values

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Only studies from Organisation for Economic Co-operation and Development member countries were included, as</td>
</tr>
<tr>
<td>the aim of the review was to identify utility data transferable to the UK context.</td>
</tr>
<tr>
<td>Studies should report utility data for health states associated with PTSD through the care pathway.</td>
</tr>
<tr>
<td>Studies should report health-related quality of life ratings made using a validated generic or PTSD-specific</td>
</tr>
<tr>
<td>preference-based measure directly or via mapping from another validated non-preference-based measure. Utility</td>
</tr>
<tr>
<td>values should have been elicited from the general population using a choice-based method, such as time trade-</td>
</tr>
<tr>
<td>off (TTO) or standard gamble (SG).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poster presentations and abstracts in conference proceedings</td>
</tr>
<tr>
<td>Non-English language papers</td>
</tr>
</tbody>
</table>

OECD Organisation for Economic Co-operation and Development; PICO Population, Intervention, Comparison, and Outcome.

Once the screening of titles and abstracts was complete, full versions of the selected papers were acquired for assessment.

Utility studies that met inclusion criteria and those that were excluded after full text was obtained are reported in Appendix B and Appendix L, respectively, of Evidence Reports for areas that were prioritised for economic modelling (i.e. review questions B and D).

Health economic modelling

The aims of the health economic input to the guideline were to inform the guideline committee of potential economic issues related to the management of adults, children and young people at risk of PTSD or with clinically important PTSD symptoms in order to ensure that recommendations represented a cost-effective use of healthcare resources. Health economic evaluations aim to integrate data on healthcare benefits (ideally in terms of quality-adjusted life-years, QALYs) with the costs of different care options. In addition, the health economic input aimed to identify areas of high resource impact; recommendations which might have a large impact on Clinical Commissioning Group or Trust finances need to be supported by robust evidence on cost effectiveness.

Areas for economic modelling were prioritised by the committee. The rationale for prioritising review questions for economic modelling was set out in an economic plan agreed between NICE, the committee, and members of the Developer's technical team. Economic modelling was undertaken in areas with likely major resource implications, where the current extent of uncertainty over cost effectiveness was significant and economic analysis was expected to reduce this uncertainty. The following economic questions were selected as key issues that were addressed by economic modelling:
• cost effectiveness of interventions for the delayed treatment (>3 months after a traumatic event) of clinically important PTSD symptoms in children and young people
• cost effectiveness of interventions for the delayed treatment (>3 months after a traumatic event) of clinically important PTSD symptoms in adults

The methods and results of the de novo economic analyses are reported in Appendix B of Evidence Reports of the respective review questions. When new economic analysis was not prioritised, the committee made a qualitative judgement regarding cost effectiveness by considering expected differences in resource use and costs between options, alongside clinical effectiveness evidence identified from the clinical evidence review.

Cost effectiveness criteria

NICE’s report Social value judgements: principles for the development of NICE guidance sets out the principles that committees should consider when judging whether an intervention offers good value for money. In general, an intervention was considered to be cost effective if any of the following criteria applied (given that the estimate was considered plausible):

• the intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
• the intervention cost less than £20,000 per QALY gained compared with the next best strategy.

The committee’s considerations of cost-effectiveness are discussed explicitly under the ‘Cost effectiveness and resource use’ headings of the relevant sections.

Developing recommendations

Guideline recommendations

Recommendations were drafted on the basis of the committee’s interpretation of the available evidence, taking into account the balance of benefits, harms and costs between different courses of action. When clinical and economic evidence was of poor quality, conflicting or absent, the committee drafted recommendations based on the members’ expert opinion. The considerations for making consensus-based recommendations include the balance between potential harms and benefits, the economic costs or implications compared with the economic benefits, current practices, recommendations made in other relevant guidelines, patient preferences and equality issues.

The main considerations specific to each recommendation are outlined under the ‘Recommendations and link to evidence’ headings within each Evidence Report.

For further details please refer to the Developing NICE guidelines: the manual.)
Research recommendations

When areas were identified for which good evidence was lacking, the committee considered making recommendations for future research. For further details please refer to the Developing NICE guidelines: the manual.

Validation process

This guidance is subject to a 6-week public consultation and feedback as part of the quality assurance and peer review of the document. All comments received from registered stakeholders are responded to in turn and posted on the NICE website at publication. For further details please refer to the Developing NICE guidelines: the manual.

Updating the guideline

Following publication, and in accordance with the NICE guidelines manual, NICE will undertake a review of whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an update. For further details please refer to the Developing NICE guidelines: the manual.

Funding

The NGA was commissioned by NICE to develop this guideline.
References

Bernstein 1992

Campbell 2003

Carroll 2011

DerSimonian and Laird 2015

Murphy 1998

Santesso 2016

Schünemann 2013
Appendix A - PRISMA flowchart for global economic evidence

A global search was undertaken to identify economic and utility studies for all areas covered in the guideline.

Figure 1 provides an illustration of the process used to select those papers and presents the number of papers identified according to the area in the guideline. Lists of included economic studies, lists of included utility studies, and lists of economic and utility studies excluded after obtaining full text, with reasons for exclusion, are provided in the Evidence Review Reports, as relevant, in Appendix H, Appendix B and Appendix L, respectively.

Figure 1: Flow diagram of selection process for economic evaluations and studies reporting health state utility data

- Titles and abstracts identified, N= 12,650
- Full copies retrieved and assessed for eligibility, N= 24
- Excluded from title and/or abstract N= 12,626
- Publications included, N= 13
  - 10 economic studies [2 including utility data]
  - 3 utility studies
- Publications excluded, N= 11
  - 7 economic studies
  - 4 utility studies