National Institute for Health and Care Excellence

Guideline version (Draft for consultation)

Rehabilitation for chronic neurological disorders including acquired brain injury

NICE guideline <number>

Methods

April 2025

NICE guideline: methods

Draft for Consultation

Evidence reviews were developed by NICE

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Development of the guideline

Remit

NHS England asked NICE to develop a new guideline about rehabilitation for chronic neurological disorders that are expected to be long term, including acquired brain injury.

To see “What this guideline covers” and “What this guideline does not cover” please see the guideline scope.

Methods

This guideline was developed using the methods described in the 2018 NICE guidelines manual.

Declarations of interest were recorded according to the NICE conflicts of interest policy.

Developing the review questions and outcomes

The review questions developed for this guideline were based on the key areas identified in the guideline scope. They were drafted by the NICE technical team, and refined and validated by the guideline committee.

The review questions were based on the following frameworks:

- population, intervention, comparator and outcome (PICO) for reviews of interventions
- qualitative reviews – using population, phenomenon of interest and context (PICo)

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

The review questions and evidence reviews corresponding to each question (or group of questions) are summarised below.

Table 1: Summary of review questions and index to evidence reviews

Evidence review	Review question	Type of review
[A] Rehabilitation delivery	Based on the views and preferences of everyone involved, what works well and what could be improved in the delivery of rehabilitation?	Qualitative
[B] Identification and referral	What are the barriers and facilitators to identifying people with rehabilitation needs due to chronic neurological disorders and enabling access to appropriate services, including referral?	Qualitative
[C] Assessment, planning and review	Based on the views and preferences of everyone involved, what works well and what could be improved in assessing and reviewing rehabilitation needs and formulating, agreeing and reviewing rehabilitation plans?	Qualitative
[D] Personal care and activities of daily living	What is the effectiveness of approaches for improving or maintaining independence in activities of daily living for	Intervention

Evidence review	Review question	Type of review
	people with chronic neurological disorders?	
[E] Stability, mobility and upper limb function	What is the effectiveness of interventions and approaches for improving and sustaining stability, mobility and upper limb functioning for people with chronic neurological disorders?	Intervention
[F] Speech, language and communication	What is the effectiveness of interventions and approaches for improving or supporting speech, language and communication?	Intervention
[G] Cognitive function	What is the effectiveness of interventions and approaches for improving and maintaining cognitive function?	Intervention
[H] Emotional health and wellbeing	What is the effectiveness of interventions and approaches for improving and sustaining emotional health and mental wellbeing?	Intervention
[I] Clinical case management	What is the effectiveness of clinical case management in the delivery of rehabilitation for people with chronic neurological disorders?	Intervention
[J] Fatigue management	What is the effectiveness of multi modal (i.e. combined physical and psychological) rehabilitation for fatigue management for people with chronic neurological disorders?	Intervention
[K] Access to support for education, employment and social participation	Based on the views and preferences of everyone involved, what works well and what makes it difficult to access support for education, employment, and social participation?	Qualitative
[L] Support to access education	What is the effectiveness of interventions or approaches for supporting people to enter, remain in, return to or leave education and training?	Intervention
[M] Support to access employment	What is the effectiveness of interventions or approaches for supporting people to enter, remain in, return to or leave employment and volunteering?	Intervention

Evidence review	Review question	Type of review
[N] Support for social participation	What is the effectiveness of interventions or approaches for supporting people's social participation (for example leisure, family life, sex and relationships)?	Intervention
[O] Access to physical activity	What is the effectiveness of rehabilitation interventions to support access to physical activity, exercise or sport, for people with chronic neurological disorders?	Intervention

[1]*Original health economic analysis conducted*

The COMET database was searched for core outcome sets relevant to this guideline. No core outcome sets were identified and therefore the outcomes were chosen based on committee discussions.

Additional information related to development of the guideline is contained in:

- Supplement 2 (Economics)
- Supplement 3 (NICE staff list).

Searching for evidence

Scoping search

During the scoping phase, searches were conducted for previous guidelines, economic evaluations, health technology assessments, systematic reviews, randomised controlled trials, observational studies and qualitative research.

Systematic literature search

Systematic literature searches were undertaken to identify published evidence relevant to each review question.

Databases were searched using subject headings, free-text terms and, where appropriate, study type filters. Where possible, searches were limited to retrieve studies published in English. All the searches were conducted in the following databases: Medline, Cochrane Central Register of Controlled Trials (CCTR), Cochrane Database of Systematic Reviews (CDSR), Social Policy and Practice, PsycInfo and Embase.

A combined search was conducted for reviews A and C. A combined search was conducted for reviews L and M.

Searches were run once for all reviews during development. Searches for the following question were updated in June 2024, 17 weeks in advance of the final committee meeting.

- What is the effectiveness of interventions and approaches for improving and maintaining cognitive function? (Review G)

Details of the search strategies, including the study-design filters used and databases searched, are provided in Appendix B of each evidence review.

Economic systematic literature search

Systematic literature searches were also undertaken to identify published economic evidence. Databases were searched using subject headings, free-text terms and, where appropriate, an economic evaluations search filter.

A single search, using the population search terms used in the evidence reviews, was conducted to identify economic evidence in the NHS Economic Evaluation Database (NHS EED) and International HTA database (INAHTA). Another single search, using the population search terms used in the evidence reviews combined with an economic evaluations search filter, was conducted in Medline, CCTR and Embase. Where possible, searches were limited to studies published in English.

Searches were also run for the following review questions using the search strategies derived from the review questions, combined with a search filter for economic evaluations, were conducted in Medline, Medline in Process, CCTR and Embase. A single search, using the population search terms used in the evidence reviews, was also conducted in the NHS Economic Evaluation Database (NHS EED) and HTA. Where possible, searches were limited to studies published in English.

- What is the effectiveness of interventions and approaches for improving or supporting speech, language, and communication? (Review F)
- What is the effectiveness of interventions and approaches for improving and maintaining cognitive function? (Review G)
- What is the effectiveness of interventions or approaches for supporting people to enter, remain in, return to or leave education and training? (Review L)
- What is the effectiveness of interventions or approaches for supporting people to enter, remain in, return to or leave employment and volunteering? (Review M)
- What is the effectiveness of interventions or approaches for supporting people's social participation (for example leisure, family life, sex and relationships)? (Review N)

As with the general literature searches, the economic literature searches were run once for all reviews during development. Searches for the following questions were updated in June 2024, 17 weeks in advance of the final committee meeting.

- What is the effectiveness of interventions and approaches for improving and maintaining cognitive function? (Review G)

Details of the search strategies, including the study-design filter used and databases searched, are provided in Supplement 2 (Health economics).

Quality assurance

Search strategies were quality assured by cross-checking reference lists of relevant studies, analysing search strategies from published systematic reviews and asking members of the committee to highlight key studies. The principal search strategies for each search were also quality assured by a second information scientist using an

adaptation of the PRESS 2015 Guideline Evidence-Based Checklist (McGowan 2016).

Reviewing research evidence

Systematic review process

The evidence was reviewed in accordance with the following approach.

- Potentially relevant articles were identified from the search results for each review question by screening titles and abstracts. Full-text copies of the articles were then obtained. Full-text articles were reviewed against pre-specified inclusion and exclusion criteria in the review protocol (see Appendix A of each evidence review).
- Combined searches were conducted for reviews A and C and for reviews L and M. Search results for these reviews were therefore screened twice on title and abstract; once to assign them to the relevant review and again to include or exclude them for that review, before full-text screening.
- Key information was extracted from each article on study methods and results, in accordance with factors specified in the review protocol. The information was presented in a summary table in the corresponding evidence review and in a more detailed evidence table (see Appendix D of each evidence review).
- Due to the size and complexity of the guideline population (in terms of age range and condition), the review protocols generally included a large number of outcomes, measured using a range of tools, comprising several sub-domains. The approach taken in most instances was to extract total scores only but in reviews with a paucity of evidence and if total scores were unavailable then relevant sub-domain data were extracted. Where several tools were used to measure a particular outcome, data from all of them were extracted but only the data from one measure was pooled with data from other studies; namely the measure with the same polarity as the majority of other measures, the measure most commonly used across studies or the one most widely used in practice. Finally, where studies reported outcome data from multiple follow-ups, all data were extracted but only end of intervention and final follow-up were used in meta-analysis, where pooling was possible.
- Included studies were critically appraised using an appropriate checklist as specified in Developing NICE guidelines: the manual. Further detail on appraisal of the evidence is provided below.
- Summaries of effectiveness evidence by outcome and qualitative evidence by theme were presented in the corresponding evidence review and discussed by the committee.

Review questions were subject to dual screening on title and abstract through a 10% random sample of articles (or 300 records, whichever was smaller). Any discrepancies were resolved by discussion between the first and second reviewers or by reference to a third (senior) reviewer. Internal (NICE) quality assurance processes also included consideration of the outcomes of screening, study selection and data extraction and the committee reviewed the results of study selection and data extraction. The review protocol for each question specifies that dual screening was undertaken for each question. Drafts of all evidence reviews were quality assured by a senior reviewer.

Type of studies and inclusion/exclusion criteria

Inclusion and exclusion of studies was based on criteria specified in the corresponding review protocol. A general rule across reviews was that if some, but not all, of a study's participants were eligible for the review, then the study would be included if at least 66% of its participants met the protocol criteria. A further general rule, agreed after the scope had been published, was to apply a definition of 'chronic' to the study population. A study was included if the intervention was provided to the population at least 3 months after their diagnosis or injury. Exceptions to this rule were considered in reviews with a lack of evidence to support committee decision making. In these circumstances, studies were considered with populations in the acquired injury categories who were between 2 and 3 months since onset because regardless of the time since injury, there can be long lasting cognitive effects. Such studies would be included and downgraded for relevance.

Systematic reviews with meta-analyses or meta-syntheses were considered to be the highest quality evidence that could be selected for inclusion.

For intervention reviews, randomised controlled trials (RCTs) were prioritised for inclusion because they are considered to be the most robust type of study design that could produce an unbiased estimate of intervention effects. This applied to evidence in the adult population but due to the general paucity of research in the children and young people population (particularly RCTs) non-randomised studies (NRS) were also considered for inclusion if there was insufficient evidence from RCTs to inform decision making. Sufficiency was judged taking into account the number, quality and sample size of RCTs, as well as outcomes reported and availability of data from subgroups of interest. When NRS were considered for inclusion, priority was given to studies that controlled for confounding variables (age and chronic neurological disorder).

For qualitative reviews, studies using focus groups, structured interviews or semi-structured interviews were considered for inclusion. Where qualitative evidence was sought, data from surveys or other types of questionnaire were considered for inclusion only if they provided data from open-ended questions, but not if they reported only quantitative data.

The committee was consulted about any uncertainty regarding inclusion or exclusion of studies. A list of excluded studies for each review question, including reasons for exclusion is presented in Appendix J of the corresponding evidence review.

Narrative reviews, posters, letters, editorials, comment articles, unpublished studies and studies published in languages other than English were excluded. Conference abstracts or proceedings were not considered for inclusion because they do not have sufficient information to allow for full critical appraisal. Books, book chapters and theses were also excluded.

Methods of combining evidence

When planning reviews (through preparation of protocols), the following approaches for data synthesis were discussed and agreed with the committee.

Data synthesis for intervention studies

Pairwise meta-analysis

Meta-analysis to pool results from comparative intervention studies was conducted where possible using Cochrane Review Manager software (RevMan5 for all apart from evidence review G. RevMan8 web version was used for evidence review G).

For dichotomous outcomes, such as mortality, the Mantel–Haenszel method with a fixed effect model was used to calculate risk ratios (RRs). For all outcomes with zero events in both arms the risk difference was presented. For outcomes in which the majority of studies had low event rates (<1%), Peto odds ratios (ORs) were calculated as this method performs well when events are rare (Bradburn 2007).

For continuous outcomes, measures of central tendency (mean) and variation (standard deviation; SD) are required for meta-analysis. Data for continuous outcomes, such as quality of life, were meta-analysed using an inverse-variance method for pooling weighted mean differences (WMDs). Mean change from baseline measures were prioritised if reported or calculable, from the information reported in the paper, but where this was not the case, final mean difference was reported and analysed.

Where SDs were not reported for each intervention group, the standard error (SE) of the mean difference was calculated from other reported statistics (p values or 95% confidence intervals; CIs) and then meta-analysis was conducted as described above.

Where continuous outcomes were measured using different tools, these were analysed and presented using standard mean difference (SMD). For ease of interpretation, where meta-analysis was conducted for one or more outcome, then all outcomes in that review (including those based on single studies) were analysed and presented using SMD. The preference was for pooling results from scales with the same polarity. However the SMD method does not correct for differences in the direction of the scale so when this was not possible, then the advice of Cochrane was followed; to multiply the mean values from one set of studies by –1 to ensure that all the scales point in the same direction, before standardization. If a study reported only the summary statistic and 95% CI the generic-inverse variance method was used to enter data into RevMan5. If the control event rate was reported this was used to generate the absolute risk difference in GRADEpro. If multivariable analysis was used to derive the summary statistic but no adjusted control event rate was reported, no absolute risk difference was calculated. Where a study reported multiple adjusted estimates for the same outcome, the one that minimised the risk of bias due to confounding was chosen.

When evidence was based on studies that reported descriptive data or medians with interquartile ranges or p values, this information was included in the corresponding GRADE tables (see below) without calculating relative or absolute effects. Consequently, certain aspects of quality assessment such as imprecision of the effect estimate could not be assessed as per standard methods for this type of evidence and ratings based on sample size cut-offs were considered instead.

For some reviews, evidence was either stratified from the outset, by chronic neurological condition group or separated into subgroups when heterogeneity was encountered. The exception was the progressive neurological disease group, which

was stratified by individual condition, where heterogeneity within that group was significant (Duchenne muscular dystrophy being very different to Parkinson's disease for example). The stratifications and potential subgroups were pre-defined at the protocol stage (see the protocols for each review for further detail). Where evidence was stratified or subgrouped the committee considered on a case by case basis if separate recommendations should be made for distinct groups. Separate recommendations may be made where there is evidence of a differential effect of interventions in distinct groups. If there is a lack of evidence in one group, the committee considered, based on their experience, whether it was reasonable to extrapolate and assume the interventions will have similar effects in that group compared with others.

When meta-analysis was undertaken, the results were presented visually using forest plots generated using RevMan5 (see Appendix E of relevant evidence reviews).

Data synthesis for qualitative reviews

Where possible, a meta-synthesis was conducted to combine evidence from more than one study into a theme or sub-theme. Whenever studies identified a qualitative theme relevant to the protocol, this was extracted and the main characteristics were summarised. When all themes had been extracted from studies, common concepts were categorised and tabulated. This included information on how many studies had contributed to each theme identified by the NICE technical team.

The technical team were guided in their data extraction, synthesis and formulation of review findings, or themes, by a framework of phenomena developed by the guideline committee. This framework consisted of the themes that the committee anticipated would be covered by the included studies and these were set out a priori in the corresponding review protocol. As well as guiding the data extraction and synthesis, the framework also underpinned the approach referred to in the protocol as 'thematic saturation'. Essentially, data or themes from included studies would not be extracted if they contributed to review findings which were judged to be 'adequate' and 'coherent' following assessment using the GRADE-CERQual approach; that is, they were not downgraded for either domain. Themes identified from the included studies, which were not set out in the protocol but which were considered relevant to answering the review question, were also extracted and the same approach to 'thematic saturation' would have been applied. Thematic saturation was not reached for any themes in any of the qualitative reviews in this guideline. Therefore, all relevant data from all included qualitative studies were extracted and analysed.

Themes from individual studies were integrated into a wider context and, when possible, overarching categories of themes with sub-themes were identified. Themes were derived from data presented in individual studies. When themes were extracted from 1 primary study only, theme names used in the guideline mirrored those in the source study. However, when themes were based on evidence from multiple studies, the theme names were assigned by the NICE technical team. The names of overarching categories of themes were also assigned by the NICE technical team.

Emerging themes were placed into a thematic map representing the relationship between themes and overarching categories. The purpose of such a map is to show relationships between overarching categories and associated themes.

Appraising the quality of evidence

Intervention studies

Pairwise meta-analysis

GRADE methodology for intervention reviews

For intervention reviews, the evidence for outcomes from included RCTs and comparative non-randomised studies was evaluated and presented using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology developed by the international GRADE working group.

When GRADE was applied, software developed by the GRADE working group (GRADEpro) was used to assess the quality of each outcome, taking account of individual study quality factors and any meta-analysis results. Results were presented in GRADE profiles (GRADE tables).

The selection of outcomes for each review question was agreed during development of the associated review protocol in discussion with the committee. The evidence for each outcome was examined separately for the quality elements summarised in Table 2. Criteria considered in the rating of these elements are discussed below. Each element was graded using the quality ratings summarised in Table 3. Footnotes to GRADE tables were used to record reasons for grading a particular quality element as having a 'serious' or 'very serious' quality issue. The ratings for each component were combined to obtain an overall assessment of quality for each outcome as described in Table 4.

The initial quality rating was based on the study design: RCTs and NRS assessed by ROBINS-I start as 'high' quality evidence, other non-randomised studies start as 'low' quality evidence. The rating was then modified according to the assessment of each quality element (Table 2). Each quality element considered to have a 'serious' or 'very serious' quality issue was downgraded by 1 or 2 levels respectively (for example, evidence starting as 'high' quality was downgraded to 'moderate' or 'low' quality). In addition, there was a possibility to upgrade evidence from non-randomised studies (provided the evidence for that outcome had not previously been downgraded) if there was a large magnitude of effect, a dose–response gradient, or if all plausible confounding would reduce a demonstrated effect or suggest a spurious effect when results showed no effect.

Table 2: Summary of quality elements in GRADE for intervention reviews

Quality element	Description
Risk of bias ('Study limitations')	This refers to limitations in study design or implementation that reduce the internal validity of the evidence
Inconsistency	This refers to unexplained heterogeneity in the results
Indirectness	This refers to differences in study populations, interventions, comparators or outcomes between the available evidence and inclusion criteria specified in the review protocol

Quality element	Description
Imprecision	This occurs when a study has few participants or few events of interest, resulting in wide confidence intervals that cross minimally important thresholds
Publication bias	This refers to systematic under- or over-estimation of the underlying benefit or harm resulting from selective publication of study results

Table 3: GRADE quality ratings (by quality element)

Quality issues	Description
None or not serious	No serious issues with the evidence for the quality element under consideration
Serious	Issues with the evidence sufficient to downgrade by 1 level for the quality element under consideration
Very serious	Issues with the evidence sufficient to downgrade by 2 levels for the quality element under consideration

Table 4: Overall quality of the evidence in GRADE (by outcome)

Overall quality grading	Description
High	Further research is very unlikely to change the level of confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on the level of confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on the level of confidence in the estimate of effect and is likely to change the estimate
Very low	The estimate of effect is very uncertain

Assessing risk of bias in intervention reviews

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

Risk of bias in RCTs was assessed using the Cochrane risk of bias tool (RoB 2; see Appendix H in Developing NICE guidelines: the manual).

The Cochrane risk of bias tool assesses the following possible sources of bias:

- risk of bias arising from the randomization process
- risk of bias due to deviations from the intended interventions
- risk of bias due to missing outcome data
- risk of bias due to measurement of the outcome
- risk of bias in selection of the reported result.

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 the chosen design and methodology will impact on the estimation of the intervention effect.

More details about the Cochrane risk of bias tool can be found in Section 8 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011).

For systematic reviews of RCTs the ROBIS checklist would have been used (see Appendix H in Developing NICE guidelines: the manual). Note that no systematic reviews met the protocol criteria for any reviews in this guideline; systematic reviews were used only for reference harvesting.

For non-randomised controlled studies, cohort studies or historical controlled studies the ROBINS-I checklist was used (see Appendix H in Developing NICE guidelines: the manual).

Assessing inconsistency in intervention reviews

Inconsistency refers to unexplained heterogeneity in results of meta-analysis. When estimates of 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 truly applicable when statistical meta-analysis is conducted (that is, results from different studies are pooled). When outcomes were derived from a single study the rating 'no serious inconsistency' was used when assessing this domain, as per GRADE methodology (Santesso 2016).

Inconsistency was assessed visually by inspecting forest plots and observing whether there was considerable heterogeneity in the results of the meta-analysis (for example if the point estimates of the individual studies consistently showed benefits or harms). This was supported by calculating the I-squared statistic for the meta-analysis with an I-squared value of more than 50% indicating serious heterogeneity, and more than 80% indicating very serious heterogeneity. When serious or very serious heterogeneity was observed, possible reasons were explored and subgroup analyses were performed as pre-specified in the review protocol where possible. In the case of unexplained heterogeneity, sensitivity analyses were planned based on the quality of studies, eliminating studies at high risk of bias (in relation to randomisation, allocation concealment and blinding, and/or missing outcome data).

When no plausible explanation for the serious or very serious heterogeneity could be found, the quality of the evidence was downgraded in GRADE for inconsistency and the meta-analysis was re-run using the Der-Simonian and Laird method with a random effects model and this was used for the final analysis.

Assessing indirectness in intervention reviews

Directness refers to the extent to which populations, interventions, comparisons and outcomes reported in the evidence are similar to those defined in the inclusion criteria for the review and was assessed by comparing the PICO elements in the studies to the PICO defined in the review protocol. Indirectness is important when such differences are expected to contribute to a difference in effect size, or may affect the balance of benefits and harms considered for an intervention.

Assessing imprecision and importance in intervention reviews

Imprecision in GRADE methodology refers to uncertainty around the effect estimate and whether or not there is an important difference between interventions (that is, whether the evidence clearly supports a particular recommendation or appears to be consistent with several candidate recommendations). Therefore, imprecision differs

from other aspects of evidence quality because it is not concerned with whether the point estimate is accurate or correct (has internal or external validity). Instead, it is concerned with uncertainty about what the point estimate actually represents. 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 the procedure to be repeated. The larger the study, the smaller the 95% CI will be and the more certain the effect estimate.

Imprecision was assessed in the guideline evidence reviews by considering whether the width of the 95% CI of the effect estimate was relevant to decision making, considering each outcome independently. This is illustrated in Figure 1, which considers a positive outcome for the comparison of two treatments. Three decision-making zones can be differentiated, bounded by the thresholds for minimal importance (minimally important differences; MIDs) for benefit and harm.

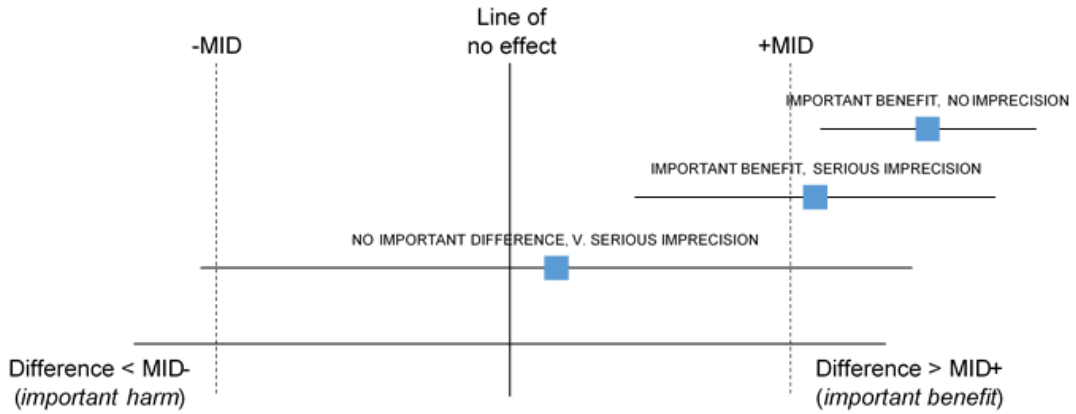
When the CI of the effect estimate is wholly contained in 1 of the 3 zones there is no uncertainty about the size and direction of effect, therefore, the effect estimate is considered precise; that is, there is no imprecision.

When the CI crosses 2 zones, it is uncertain in which zone the true value of the effect estimate lies and therefore there is uncertainty over which decision to make. The CI is consistent with 2 possible decisions, therefore, the effect estimate is considered to be imprecise in the GRADE analysis and the evidence is downgraded by 1 level ('serious imprecision').

When the CI crosses all 3 zones, the effect estimate is considered to be very imprecise because the CI is consistent with 3 possible decisions and there is therefore a considerable lack of confidence in the results. The evidence is therefore downgraded by 2 levels in the GRADE analysis ('very serious imprecision').

Implicitly, assessing whether a CI is in, or partially in, an important zone, requires the guideline committee to estimate an MID or to say whether they would make different decisions for the 2 confidence limits.

Figure 1: Assessment of imprecision and importance in intervention reviews using GRADE



MID, minimally important difference

Defining minimally important differences for intervention reviews

The committee was asked whether there were any recognised or acceptable MIDs in the published literature and community relevant to the review questions under consideration. The committee was not aware of any MIDs that could be used for the guideline.

In the absence of published or accepted MIDs, the committee agreed to use the GRADE default MIDs to assess imprecision. For dichotomous outcomes minimally important thresholds for a RR of 0.8 and 1.25 respectively were used as default MIDs in the guideline. The committee also chose to use 0.8 and 1.25 as the MIDs for ORs & HRs in the absence of published or accepted MIDs. ORs were predominantly used in the guideline when Peto OR were indicated due to low event rates, at low event rates OR are mathematically similar to RR making the extrapolation appropriate. While no default MIDs exist for HR, the committee agreed for consistency to continue to use 0.8 and 1.25 for these outcomes.

If risk difference had been used for meta-analysis, for example if the majority of studies had zero events in either arm, imprecision would have been assessed based on sample size using 200 and 400 as cut-offs for very serious and serious imprecision respectively. The committee would have used these numbers based on commonly used optimal information size thresholds but this scenario did not arise in any of the evidence reviews.

The same thresholds were used as default MIDs in the guideline for all dichotomous outcomes considered in intervention evidence reviews. For continuous outcomes default MIDs are equal to half the median SD of the control groups at baseline (or at follow-up if the SD is not available a baseline).

Assessing publication bias in intervention reviews

If 10 or more studies had been included as part of a single meta-analysis, a funnel plot would have been produced to graphically assess the potential for publication bias. This did not arise in any of the evidence reviews, so in practice, with fewer than 10 studies included for any outcome, the committee subjectively assessed the likelihood of publication bias based on factors such as the proportion of trials funded by industry and the propensity for publication bias in the topic area.

Qualitative studies

GRADE-CERQual methodology for qualitative reviews

For qualitative reviews an adapted GRADE Confidence in the Evidence from Reviews of Qualitative research (GRADE-CERQual) approach (Lewin 2018) was used. In this approach the quality of evidence is considered according to themes in the evidence. The themes may have been identified in the primary studies or they may have been identified by considering the reports of a number of studies. Quality elements assessed using GRADE-CERQual are listed and defined in Table 5. Each element was graded using the levels of concern summarised in Table 6.

The ratings for each component were combined (as with other types of evidence) to obtain an overall assessment of quality for each theme as described in Table 7. ‘Confidence’ in this context refers to the extent to which the review finding is a reasonable representation of the phenomenon of interest set out in the protocol.

Similar to other types of evidence all review findings start off with 'high confidence' and are rated down by one or more levels if there are concerns about any of the individual CERQual components. In line with advice from the CERQual developers, the overall assessment does not involve numerical scoring for each component but in order to ensure consistency across and between guidelines, the NICE technical team established some guiding principles for overall ratings. For example, a review finding would not be downgraded (and therefore would be assessed with 'high' confidence) if at least 2 of the individual components were rated as 'no or very minor; and none of the components were rated as having moderate or serious concerns.

At the other extreme, a review finding would be downgraded 3 times (to 'very low') if at least 2 components had serious concerns or 3 had moderate concerns (as long as the 4th component was rated 'serious') or if all components had moderate concerns . A basic principle was that if any components had any serious concerns then overall confidence in the review finding would be downgraded at least twice, to low. Transparency about overall judgements is provided in the CERQual tables, with explanations for downgrading given in the individual domain cells.

Table 5: Adaptation of GRADE quality elements for qualitative reviews

Quality element	Description
Methodological limitations	Limitations in study design and implementation may bias interpretation of qualitative themes identified. High risk of bias for the majority of the evidence reduces our confidence that the review findings reflect the phenomena of interest. Qualitative studies are not usually randomised and therefore would not be downgraded for study design from the outset (they start as high quality)
Relevance (or applicability) of evidence	This refers to the extent to which the context of the studies supporting the review findings is applicable to the context specified in the review question
Coherence of findings	This refers to the extent to which review findings are well grounded in data from the contributing primary studies and provide a credible explanation for patterns identified in the evidence. If the data from the underlying studies are ambiguous or contradict the review finding this would reduce our confidence in the finding.
Adequacy of data (theme saturation or sufficiency)	This corresponds to a similar concept in primary qualitative research, that is, 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 the particular theme. Judgements are not based on the number of studies but do take account of the quantity and also richness of data underpinning a finding. The more complex the finding, the more detailed the supporting data need to be. For simple findings, relatively superficial data would be considered adequate to explain and explore the phenomenon being described.

Table 6: CERQual levels of concern (by quality element)

Level of concern	Definition
None or very minor concerns	Unlikely to reduce confidence in the review finding
Minor concerns	May reduce confidence in the review finding

Level of concern	Definition
Moderate concerns	Will probably reduce confidence in the review finding
Serious concerns	Very likely to reduce confidence in the review finding

Table 7: Overall confidence in the evidence in CERQual (by review finding)

Overall confidence level	Definition
High	It is highly likely that the review finding is a reasonable representation of the phenomenon of interest
Moderate	It is likely that the review finding is a reasonable representation of the phenomenon of interest
Low	It is possible that the review finding is a reasonable representation of the phenomenon of interest
Very low	It is unclear whether the review finding is a reasonable representation of the phenomenon of interest

Assessing methodological limitations in qualitative reviews

Methodological limitations in qualitative studies were assessed using the Critical Appraisal Skills Programme (CASP) checklist for qualitative studies (see appendix H in Developing NICE guidelines: the manual). Overall methodological limitations were derived by assessing the methodological limitations across the 6 domains summarised in Table 8.

Table 8: Methodological limitations in qualitative studies

Aim and appropriateness of qualitative evidence	This domain assesses whether the aims and relevance of the study were described clearly and whether qualitative research methods were appropriate for investigating the research question
Rigour in study design or validity of theoretical approach	This domain assesses whether the study approach was documented clearly and whether it was based on a theoretical framework (such as ethnography or grounded theory). This does not necessarily mean that the framework has to be stated explicitly, but a detailed description ensuring transparency and reproducibility should be provided
Sample selection	This domain assesses the background, the procedure and reasons for the method of selecting participants. The assessment should include consideration of any relationship between the researcher and the

	participants, and how this might have influenced the findings
Data collection	This domain assesses the documentation of the method of data collection (in-depth interviews, semi-structured interviews, focus groups or observations). It also assesses who conducted any interviews, how long they lasted and where they took place
Data analysis	This domain assesses whether sufficient detail was documented for the analytical process and whether it was in accordance with the theoretical approach. For example, if a thematic analysis was used, the assessment would focus on the description of the approach used to generate themes. Consideration of data saturation would also form part of this assessment (it could be reported directly or it might be inferred from the citations documented that more themes could be found)
Results	This domain assesses any reasoning accompanying reporting of results (for example, whether a theoretical proposal or framework is provided)

Assessing relevance of evidence in qualitative reviews

Relevance (applicability) of findings in qualitative research is the equivalent of indirectness for quantitative outcomes, and refers to how closely the aims and context of studies contributing to a theme reflect the objectives outlined in the guideline review protocol.

Assessing coherence of findings in qualitative reviews

For qualitative research, a similar concept to inconsistency is coherence, which refers to the way findings within themes are described and whether they make sense. This concept was used in the quality assessment across studies for individual themes. This does not mean that contradictory evidence was automatically downgraded, but that it was highlighted and presented, and that reasoning was provided. Provided the themes, or components of themes, from individual studies fit into a theoretical framework, they do not necessarily have to reflect the same perspective. It should, however, be possible to explain these by differences in context (for example, the views of health or social care professionals might not be the same as those of family members, but they could contribute to the same overarching themes).

Assessing adequacy of data in qualitative reviews

Adequacy of data (theme saturation or sufficiency) corresponds to a similar concept in primary qualitative research in which consideration is made of whether a theoretical point of theme saturation was achieved, meaning that no further citations or observations would provide more insight or suggest a different interpretation of the theme concerned. As noted above, it is not equivalent to the number of studies

contributing to a theme, but it does take account of the quantity of data supporting a review finding (for instance whether sufficient quotations or observations were provided to underpin the findings) and in particular the degree of 'richness' of supporting data. Concerns about richness arise when insufficient details are provided by the data to enable an understanding of the phenomenon being described. Generally, if a review finding is fairly simple then relatively superficial data will be needed to understand it. Data underpinning a more complex finding would need to offer greater detail, allowing for interpretation and exploration of the phenomenon being described. Therefore in assessing adequacy our downgrading involved weighing up the complexity of the review finding against the explanatory contribution of the supporting data.

Reviewing economic evidence

Titles and abstracts of articles identified through the economic literature searches were independently assessed for inclusion using the predefined eligibility criteria listed in Table 9.

Table 9: Inclusion and exclusion criteria for systematic reviews of economic evaluations

Inclusion criteria
Intervention or comparators in accordance with the guideline scope
Study population in accordance with the guideline scope
Full economic evaluations (cost-utility, cost effectiveness, cost-benefit or cost-consequence analyses) assessing both costs and outcomes associated with interventions of interest
OECD country [(except USA)] healthcare and personal social services cost perspective
Studies published from 2012 – this cut off has been applied to restrict the reviews to more recent studies which will have more applicable resource use and costs
Exclusion criteria
Conference posters or abstract only studies – these do not provide sufficient information for quality assessment
Non-English language papers
Non-comparative economic analyses including cost-of-illness studies
Studies considering exclusively intervention costs, e.g. intervention costs, without considering wider healthcare costs associated with the management of chronic neurological disorders
Letters, editorials or commentary, or a review of health economic evaluations. (Recent reviews were checked for relevant studies.)

Once the screening of titles and abstracts was completed, full-text copies of potentially relevant articles were requested for detailed assessment. Inclusion and exclusion criteria were applied to articles obtained as full-text copies.

Details of economic evidence study selection, including full list of included and excluded economic studies across all reviews are provided in Supplement 2.

Appraising the quality of economic evidence

The applicability and quality of economic evidence was assessed using the economic evaluations checklist specified in 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.

Economic profiles and economic evidence tables of all economic studies that were considered during guideline development are provided in the respective evidence reviews.

Economic modelling

The aims of the economic input to the guideline were to inform the guideline committee of potential economic issues to ensure that recommendations represented a cost-effective use of healthcare resources. Economic evaluations aim to integrate data on healthcare benefits (ideally in terms of quality-adjusted life-years; QALYs) with the costs of different options. In addition, the economic input aimed to identify areas of high resource impact, as recommendations on these areas need to be supported by robust evidence on cost effectiveness.

The guideline committee prioritised the following review questions for economic modelling where it was thought that economic considerations would be particularly important in formulating recommendations.

- [D] What is the effectiveness of approaches for improving or maintaining independence in activities of daily living for people with chronic neurological disorders?
- [N] What is the effectiveness of interventions or approaches for supporting people's social participation (for example leisure, family life, sex and relationships)?
- The committee agreed that modelling around timing, intensity, and setting would be helpful for any intervention question, making it an overarching priority.

Due to the lack of suitable effectiveness data, no modelling was undertaken for the prioritised areas. As development progressed, the committee requested costings to inform their recommendations for the review question [I] 'What is the effectiveness of clinical case management in the delivery of rehabilitation for people with chronic neurological disorders?'. Due to the lack of effectiveness data, an exploratory threshold analysis was conducted to determine the health benefits (QALY gain) required for clinical case management to be considered cost effective using NICE's cost-effectiveness criteria. The methods and results of this analysis are detailed in Appendix I of the relevant evidence report.

When new economic analysis was not prioritised, the committee made a qualitative judgement regarding cost effectiveness by considering expected differences in resource and cost use between options, alongside effectiveness evidence identified from the effectiveness evidence review.

Cost effectiveness criteria

NICE's report The NICE Principles 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 (provided 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 effective compared with all the other relevant alternative strategies)
- the intervention cost less than £20,000 per QALY gained compared with the next best strategy
- the intervention provided important benefits at an acceptable additional cost when compared with the next best strategy.

The committee's considerations of cost effectiveness are discussed explicitly under the heading 'The committee's discussion of the evidence' under subheading 'Cost effectiveness and resource use' in the relevant evidence reviews.

Developing recommendations

Guideline recommendations

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

The main considerations specific to each recommendation are outlined under the heading 'The committee's discussion of the evidence' within each evidence review.

For further details refer to Developing NICE guidelines: the manual.

Research recommendations

When areas were identified for which evidence was lacking, the committee considered making recommendations for future research. For further details refer to Developing NICE guidelines: the manual and NICE's Research recommendations process and methods guide.

Validation process

This guideline was subject to a 6-week public consultation and feedback process. All comments received from registered stakeholders were responded to in writing and posted on the NICE website at publication. For further details refer to Developing NICE guidelines: the manual.

Updating the guideline

Following publication, NICE will undertake a surveillance review to determine whether the evidence base has progressed sufficiently to consider altering the guideline recommendations and warrant an update. For further details refer to Developing NICE guidelines: the manual.

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