Hypertension in adults: diagnosis and management

[H] Evidence review for relaxation therapies

NICE guideline NG136

Intervention evidence review

August 2019

This evidence review was developed by the National Guideline Centre
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, where appropriate, their carer or guardian.

Local commissioners and 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.

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1 Relaxation therapies

1.1 Review question: What is the clinical and cost-effectiveness of relaxation therapies for the management of primary hypertension in adults?

1.2 Introduction

Blood pressure is affected by many physiological parameters including the actions of the kidneys, blood vessels and level of arousal. It is known that blood pressure increases at times of stress, and this forms the basis of the recommendation that individuals should sit quietly for a short period of time before blood pressure measurement. Participation in relaxation therapies (for example, biofeedback, meditation or yoga) may therefore have a sustained blood pressure lowering effect thus leading to a reduction in cardiovascular events. Relaxation therapies for hypertension are not part of current practice in the treatment of hypertension. This chapter assesses the evidence as to whether relaxation therapies are clinically and cost effective for the management of hypertension.

1.3 PICO table

For full details, see the review protocol in appendix A.

Table 1: PICO characteristics of review question

<table>
<thead>
<tr>
<th>Population</th>
<th>Adults (aged over 18 years) with primary hypertension who do or do not also have type 2 diabetes.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interventions</td>
<td>Intervention designed to promote relaxation (relaxation therapies).</td>
</tr>
<tr>
<td></td>
<td>Mind-body and relaxation techniques:</td>
</tr>
<tr>
<td></td>
<td>• Biofeedback</td>
</tr>
<tr>
<td></td>
<td>• Breathing</td>
</tr>
<tr>
<td></td>
<td>• Meditation</td>
</tr>
<tr>
<td></td>
<td>• Mindfulness</td>
</tr>
<tr>
<td></td>
<td>• Muscle relaxation</td>
</tr>
<tr>
<td></td>
<td>• Relaxation imagery</td>
</tr>
<tr>
<td></td>
<td>• Yoga</td>
</tr>
<tr>
<td>Comparisons</td>
<td>Control* including:</td>
</tr>
<tr>
<td></td>
<td>• No active treatment (usual care or blood pressure [BP] monitoring)</td>
</tr>
<tr>
<td></td>
<td>• Sham or placebo therapy</td>
</tr>
<tr>
<td></td>
<td>*Note that studies combining a control intervention with additional interventions will be allowed where all participants (including the intervention arm[s]) received the same additional interventions.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Assessed at 12 or more months (using final endpoint)</td>
</tr>
<tr>
<td></td>
<td>Critical</td>
</tr>
<tr>
<td></td>
<td>• All-cause mortality</td>
</tr>
<tr>
<td></td>
<td>• Health-related quality of life</td>
</tr>
<tr>
<td></td>
<td>• Stroke (ischaemic or haemorrhagic)</td>
</tr>
<tr>
<td></td>
<td>• Myocardial infarction (MI)</td>
</tr>
</tbody>
</table>
Hypertension in adults: Final
Relaxation therapies

Important
- Heart failure needing hospitalisation
- Vascular procedures (including both coronary and carotid artery procedures)
- Angina needing hospitalisation
- Cessation or reduction of medication
- [Combined cardiovascular disease outcomes in the absence of MI and stroke data]
- [Coronary heart disease outcome in the absence of MI data]

| Study design | Randomised control trials (RCT) and systematic reviews (SR) |

1.4 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A.

Declarations of interest were recorded according to NICE’s 2018 conflicts of interest policy.

1.5 Clinical evidence

1.5.1 Included studies

One study was included in the review, which is summarised in Table 2 below. Evidence from this study is summarised in the clinical evidence summary below.

This RCT compared relaxation therapy to no treatment with outcomes reported at 1 year.

See also the study selection flow chart in appendix C, study evidence tables in appendix D, forest plots in appendix E and GRADE tables in appendix F.

1.5.2 Excluded studies

One Cochrane review relevant to this review question was identified. This was excluded due to having a less than a minimum duration follow up; a median duration of treatment was 8 weeks (range: 5 to 26 weeks).

See the excluded studies list in appendix I. Table 20 outlines the full excluded studies list, and Table 19 provides additional detail of studies that were included in the previous guideline iteration (CG127) but excluded from this update.
1.5.3 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention and comparison</th>
<th>Population</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patel, 1988 ⁷⁸</td>
<td>Relaxation therapy (breathing exercises, deep muscle relaxation and simple meditation), n=49 versus no treatment, n=54</td>
<td>Adults (n=103)</td>
<td>At 12 months:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aged 35 to 64 years</td>
<td>• Myocardial infarction (MI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Stroke</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Angina</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prescence of population with diabetes</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>not given.</td>
<td></td>
</tr>
</tbody>
</table>

See appendix D for full evidence tables.

1.5.4 Quality assessment of clinical studies included in the evidence review

Table 3: Clinical evidence summary: Relaxation therapy versus no treatment

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No of Participants (studies) Follow up</th>
<th>Quality of the evidence (GRADE)</th>
<th>Relative effect (95% CI)</th>
<th>Anticipated absolute effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Risk with No treatment</td>
</tr>
<tr>
<td>Stroke at 12 months</td>
<td>103 (1 study) 12 months</td>
<td>VERY LOW¹,² due to risk of bias, imprecision</td>
<td>Peto OR 8.18 (0.16 to 414.3)</td>
<td>0 per 1,000</td>
</tr>
<tr>
<td>Myocardial infarction at 12 months</td>
<td>103 (1 study) 12 months</td>
<td>VERY LOW¹,² due to risk of bias, imprecision</td>
<td>Peto OR 0.15 (0 to 7.52)</td>
<td>19 per 1,000</td>
</tr>
<tr>
<td>Angina at 12 months</td>
<td>103 (1 study) 12 months</td>
<td>VERY LOW¹,² due to risk of bias, imprecision</td>
<td>Peto OR 0.15 (0 to 7.52)</td>
<td>19 per 1,000</td>
</tr>
</tbody>
</table>

¹Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
*Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

See appendix F for full GRADE tables.
1.6 Economic evidence

1.6.1 Included studies
No relevant health economic studies were identified.

1.6.2 Excluded studies
No health economic studies that were relevant to this question were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in appendix G.

1.6.3 Resource costs
The resource use involved in providing the relaxation intervention from the clinical evidence included has been costed below for illustration.

The unit costs of the staff involved are shown in Table 4, with the resource use and total costs demonstrated in Table 5.

### Table 4: Staff costs

<table>
<thead>
<tr>
<th>Resource</th>
<th>Detail</th>
<th>Unit cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>GP time</td>
<td>Cost per minute of patient contact (including qualifications and direct care staff costs)</td>
<td>£4.05</td>
</tr>
<tr>
<td>Nurse (GP practice) time</td>
<td>Cost per hour including qualifications</td>
<td>£42</td>
</tr>
</tbody>
</table>

*Source: PSSRU 2018*

### Table 5: Intervention cost

<table>
<thead>
<tr>
<th>Resource use</th>
<th>Cost of resource use</th>
<th>Total cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>GP time of 30 minutes per session</td>
<td>£122</td>
<td></td>
</tr>
<tr>
<td>Nurse time of 30 minutes per session</td>
<td>£21</td>
<td></td>
</tr>
<tr>
<td>Total staff cost per 1 hour session</td>
<td>£143</td>
<td></td>
</tr>
<tr>
<td><strong>Total group cost for 8 sessions</strong></td>
<td><strong>£1,140</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Total per person cost for 8 sessions</strong></td>
<td><strong>£114</strong></td>
<td></td>
</tr>
</tbody>
</table>

*Note: Each session was 1 hour over 8 weeks. 10 people per group.*

This illustrated cost does not include preparation time for staff and can vary depending on the grade of staff involved.

Similar interventions from the PSSRU 2017 include mindfulness based cognitive behavioural therapy, costing £88 per hour of direct contact. The lower cost reflecting a psychological therapist providing the intervention rather than a GP.
1.7 Evidence statements

1.7.1 Clinical evidence statements

Very low quality evidence from 1 study with 103 participants showed a clinically important benefit of relaxation therapy compared to no treatment for occurrence of myocardial infarction and angina at 12 months.

However there was a clinically important harm of relaxation therapy compared to no treatment for the occurrence of stroke at 12 months.

1.7.2 Health economic evidence statements

No relevant economic evaluations were identified.

1.8 The committee’s discussion of the evidence

1.8.1 Interpreting the evidence

1.8.1.1 The outcomes that matter most

The committee considered all-cause mortality, quality of life, stroke and myocardial infarction to be critical outcomes for decision-making. Heart failure, vascular procedures, angina and reduction in medication were also considered important for decision-making. There was no evidence addressing all-cause mortality, quality of life, heart failure and vascular events. There was also no evidence to determine whether or not relaxation therapies could result in a cessation or reduction of medication.

1.8.1.2 The quality of the evidence

Only 1 study was identified to include in the review. The evidence was rated as very low quality due to imprecision and risk of bias. Due to the small sample size, the committee considered that in isolation this evidence was underpowered to detect differences in cardiovascular event rates. The committee also considered the age of the included study and noted that clinical diagnoses in 1988 differ to those in the present day. In particular, the committee highlighted that myocardial infarction outcomes may have previously included conditions such as angina and therefore this may overestimate the effect of reduction in this outcome when compared to the current definition. In addition, the device used for blood pressure measurement was a random 0 sphygmomanometer, which is no longer a validated measurement. Furthermore, it was noted that there was a significant imbalance between the 2 groups in their baseline systolic blood pressure. The improvement in blood pressure for the group receiving relaxation therapy may therefore be the result of regression towards the mean, and must be interpreted with caution. When considering all of these factors, the committee agreed that the available evidence was insufficient to inform recommendations.

1.8.1.3 Benefits and harms

There was a clinically important benefit of relaxation therapy for hypertension with the outcomes of angina and myocardial infarction at 1 year, and conversely there was a clinically important harm for the outcome of stroke at 1 year. However, there were only a small number of participants included within the evidence, which was considered insufficient to determine differences in cardiovascular events. The very low quality of the evidence and low numbers of events occurring led to considerable uncertainty in the effect size. The committee agreed this was insufficient to determine the effectiveness of relaxation therapies.
Based on the available evidence, the committee agreed it could not justify retaining the recommendation that had been made in the previous guideline for relaxation therapies. The committee was aware of some RCTs that had suggested benefits of relaxation therapies in reducing blood pressure; however, these did not meet the protocol inclusion criteria to be included in this review where the surrogate measure of blood pressure reduction was not considered critical to decision-making. A previous iteration of the guideline in 2004 (CG18) identified some evidence to suggest that relaxation therapies could reduce blood pressure at a short follow-up, however, this was a small reduction and the long term effectiveness of relaxation therapies was not determined. This evidence was not sufficient to determine whether or not relaxation therapies could also reduce cardiovascular events, and the additional evidence reviewed in this update was also not sufficient to determine this. Given the lack of evidence for hard outcomes, the committee considered whether there would be some merit in recommending further research in this area. The committee discussed the study designs that could be utilised for further research and agreed that a well-designed RCT would require extensive resources in order to answer the question of whether relaxation therapies are a clinically effective treatment for hypertension. This would need to be significantly larger than those in the current literature. Due to the small changes in blood pressure that are associated with the interventions, a large number of participants would be required in order to detect any differences between interventions. The committee agreed a research recommendation may be useful.

1.8.2 Cost effectiveness and resource use

No economic evidence was identified for this question.

The clinical study identified had a relaxation intervention conducted by GPs and nurses. Relaxation therapies involve a lot of staff time to provide the exact cost varying depending on the length of the sessions, the length of the course, the number of people attending, and the grade of staff involved. To estimate, costing up the course from the clinical trial led to over £1,000 for a course of treatment for a group and over £100 per person if there are 10 people per group.

The committee agreed there was no benefit demonstrated from the intervention, as there was only 1 event in 1 arm and no events in the other arm for each outcome. There were also serious methodological flaws with the evidence.
2 References


42. Hafer DG. Self-directed relaxation as a treatment for essential hypertension (imagery, autogenic, progressive relaxation). Denton, TE. North Texas State University. 1984. Ph.D.


100. Sun J, Buys N. Community-based mind-body meditative tai chi program and its effects on improvement of blood pressure, weight, renal function, serum lipoprotein, and quality of life in Chinese adults with hypertension. American Journal of Cardiology. 2015; 116(7):1076-1081


Appendices

Appendix A: Review protocols

<table>
<thead>
<tr>
<th>Table 6: Review protocol: Relaxation therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Field</td>
</tr>
<tr>
<td>Review question</td>
</tr>
<tr>
<td>Type of review question</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Objective of the review</td>
</tr>
<tr>
<td>Eligibility criteria – population / disease / condition / issue / domain</td>
</tr>
<tr>
<td>Eligibility criteria – intervention(s) / exposure(s) / prognostic factor(s)</td>
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<tr>
<td>Eligibility criteria – comparator(s) / control or reference (gold) standard</td>
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<tr>
<td>Outcomes and prioritisation</td>
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<tr>
<td>Critical</td>
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<td></td>
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<tr>
<td>Important</td>
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</tbody>
</table>
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References

<table>
<thead>
<tr>
<th>Eligibility criteria – study design</th>
<th>RCTs and SRs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other inclusion exclusion criteria</td>
<td>Minimum follow up time: 1 year</td>
</tr>
<tr>
<td>Exclusions:</td>
<td>Papers that evaluate relaxation therapies combined with other interventions such as diet or exercise or stable drug therapy. Unless all participants (including control) received the same additional interventions. This includes studies allowing participants to adjust antihypertensive medication.</td>
</tr>
<tr>
<td></td>
<td>Studies including participants with type 1 diabetes or chronic kidney disease (A3 or above [heavy proteinuria]). For the Type 2 diabetes strata studies including participants with chronic kidney disease (A2 or above [heavy proteinuria]).</td>
</tr>
<tr>
<td></td>
<td>Indirect populations with secondary causes of hypertension such as tumours or structural vascular defects (Conn's adenoma, phaeochromocytoma, renovascular hypertension)</td>
</tr>
<tr>
<td></td>
<td>Pregnant women</td>
</tr>
<tr>
<td></td>
<td>Crossover trials</td>
</tr>
<tr>
<td></td>
<td>Children (aged under 18 years)</td>
</tr>
</tbody>
</table>

| Proposed sensitivity / subgroup analysis, or meta-regression | Subgroups analysis for heterogeneity |
|                                                           | Age (75 as a cut off)* |
|                                                           | Family origin (African and Caribbean, White, South Asian) |
|                                                           | Concomitant pharmacological therapy for hypertension (Y/N) |
|                                                           | Severity of hypertension |

*To note that we will also extract evidence in those >80 years old if this evidence is reported separately.

| Selection process – duplicate screening / selection / analysis | A senior research fellow will undertake quality assurance prior to completion. |
| Data management (software) | Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). |
|                          | GRADEpro will be used to assess the quality of evidence for each outcome. |
|                          | Endnote will be used for bibliography, citations, sifting and reference management. |

| Information sources – databases and dates | Medline, Embase, the Cochrane Library, CINAHL and AMED Language: Restrict to English only |

| Identify if an update | Yes, it is an update |
| Author contacts | https://www.nice.org.uk/guidance/cg127 |
| Highlight if amendment to previous protocol | For details, please see section 4.5 of Developing NICE guidelines: the manual. |
| Search strategy – for one database | For details, please see appendix B |
| Data collection process – forms / duplicate | A standardised evidence table format will be used, and published as appendix D of the evidence report. |
**Table 7: Health economic review protocol**

<table>
<thead>
<tr>
<th>Review question</th>
<th>All questions – health economic evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objectives</strong></td>
<td>To identify health economic studies relevant to any of the review questions.</td>
</tr>
</tbody>
</table>
| **Search criteria** | • Populations, interventions and comparators must be as specified in the clinical review protocol above.  
  • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis).  
  • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) |
• Unpublished reports will not be considered unless submitted as part of a call for evidence.
• Studies must be in English.

Search strategy
A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below. No date cut-off from the previous guideline was used.

Review strategy
Studies not meeting any of the search criteria above will be excluded. Studies published before 2002, abstract-only studies and studies from non-OECD countries or the US will also be excluded.

Studies published after 2002 that were included in the previous guideline(s) will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified.

Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014). 68

Inclusion and exclusion criteria
• If a study is rated as both ‘Directly applicable’ and with ‘Minor limitations’, then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile.
• If a study is rated as either ‘Not applicable’ or with ‘Very serious limitations’, then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile.
• If a study is rated as ‘Partially applicable’, with ‘Potentially serious limitations’ or both, then there is discretion over whether it should be included.

Where there is discretion
The health economist will make a decision based on the relative applicability and quality of the available evidence for that question in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to exclude selectively the remaining studies. All studies excluded based on applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below.

The health economist will be guided by the following hierarchies.

Setting:
• UK NHS (most applicable).
• OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).
• OECD countries with predominantly private health insurance systems (for example, Switzerland).
• Studies set in non-OECD countries or in the US will be excluded before being assessed for applicability and methodological limitations.

Health economic study type:
• Cost–utility analysis (most applicable).
• Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis).
• Comparative cost analysis.
- Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations.

Year of analysis:
- The more recent the study, the more applicable it will be.
- Studies published in 2002 or later (including any such studies included in the previous guideline(s)) but that depend on unit costs and resource data entirely or predominantly before 2002 will be rated as ‘Not applicable’.
- Studies published before 2002 (including any such studies included in the previous guideline(s)) will be excluded before being assessed for applicability and methodological limitations.

Quality and relevance of effectiveness data used in the health economic analysis:
- The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review, the more useful the analysis will be for decision-making in the guideline.
- Generally, economic evaluations based on excludes from the clinical review will be excluded.
Appendix B: Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual 2014, updated 2017.

For more detailed information, please see the Methodology Review.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 8: Database date parameters and filters used

<table>
<thead>
<tr>
<th>Database</th>
<th>Dates searched</th>
<th>Search filter used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medline (OVID)</td>
<td>1946 – 02 October 2018</td>
<td>Exclusions Randomised controlled trials Systematic review studies</td>
</tr>
<tr>
<td>Embase (OVID)</td>
<td>1974 – 02 October 2018</td>
<td>Exclusions Randomised controlled trials Systematic review studies</td>
</tr>
<tr>
<td>The Cochrane Library (Wiley)</td>
<td>Cochrane Reviews to Issue 8 of 12, August 2018, CENTRAL to Issue 7 of 12, July 2018, DARE and NHSEED to Issue 2 of 4, April 2015, HTA to Issue 4 of 4, October 2016</td>
<td>None</td>
</tr>
<tr>
<td>CINAHL, Current Nursing and Allied Health Literature (EBSCO)</td>
<td>Inception – 02 October 2018</td>
<td>Exclusions</td>
</tr>
<tr>
<td>AMED, Allied and Complementary Medicine (OVID)</td>
<td>Inception – 02 October 2018</td>
<td>Exclusions Randomised controlled trials Systematic review studies</td>
</tr>
</tbody>
</table>

Table 9: Medline (Ovid) search terms

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
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<tbody>
<tr>
<td>1</td>
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</tr>
<tr>
<td>2</td>
<td>hypertens*.ti,ab.</td>
</tr>
<tr>
<td>3</td>
<td>(elevat* adj2 blood adj pressur*).ti,ab.</td>
</tr>
<tr>
<td>4</td>
<td>(high adj blood adj pressur*).ti,ab.</td>
</tr>
<tr>
<td>5</td>
<td>(increase* adj2 blood pressur*).ti,ab.</td>
</tr>
<tr>
<td>6</td>
<td>((systolic or diastolic or arterial) adj2 pressur*).ti,ab.</td>
</tr>
<tr>
<td>7</td>
<td>or/1-6</td>
</tr>
<tr>
<td>8</td>
<td>exp pregnancy/</td>
</tr>
<tr>
<td>9</td>
<td>exp Hypertension, Pregnancy-Induced/ not exp Hypertension/</td>
</tr>
<tr>
<td>10</td>
<td>(pre eclampsia or pre-eclampsia or preeclampsia).ti,ab.</td>
</tr>
<tr>
<td>11</td>
<td>exp Hypertension, Portal/ not exp Hypertension/</td>
</tr>
<tr>
<td>12</td>
<td>exp Hypertension, Pulmonary/ not exp Hypertension/</td>
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</tbody>
</table>
13. exp Intracranial Hypertension/ not exp Hypertension/
14. exp Ocular Hypertension/ not exp Hypertension/
15. exp Diabetes Mellitus, Type 1/ not exp Diabetes Mellitus, Type 2/
16. or/8-15
17. 7 not 16
18. letter/
19. editorial/
20. news/
21. exp historical article/
22. Anecdotes as Topic/
23. comment/
24. case report/
25. (letter or comment*).ti.
26. or/18-25
27. randomized controlled trial/ or random*.ti,ab.
28. 26 not 27
29. animals/ not humans/
30. exp Animals, Laboratory/
31. exp Animal Experimentation/
32. exp Models, Animal/
33. exp Rodentia/
34. (rat or rats or mouse or mice).ti.
35. or/28-34
36. 17 not 35
37. (exp child/ or exp pediatrics/ or exp infant/) not (exp a dolescent/ or exp adult/ or exp middle age/ or exp aged/)
38. 36 not 37
39. limit 38 to English language
40. exp Mind-Body Therapies/
41. (mind body or mindbody).ti,ab.
42. ((relax* or breath*) adj3 (behavior* or behaviour* or therap* or technic*or technique* or practic* or educat* or manag* or train* or method*)).ti,ab.
43. ((stress* or cognitive or talk* or assertiveness or anger) adj3 (treatment* or therap* or train* or educat* or manag* or technique*)).ti,ab.
44. ((behaviour* or behavior*) adj3 (intervention* or therap* or train* or educat* or manag*)).ti,ab.
45. Feedback, Psychological/
46. (biofeedback or bio feedback or neurofeedback or neuro feedback or myofeedback or myo feedback).ti,ab.
47. ((physiologic* or psychophysiologic*) adj2 (feedback or feed back)).ti,ab.
48. exp Meditation/
49. (meditat* or meditation* or mindful*).ti,ab.
50. autogenic*.ti,ab.
51. ((hypnosis or hypnot* or reverie or trance) adj2 (therap* or train* or technique* or relax* or guide* or led or lead* or treatment* or intervention*)).ti,ab.
52. ((imagery or imagination or imagining) adj3 (relax* or guide* or led or lead*)).ti,ab.
53. (yoga* or yogic or pilates).ti,ab.
54. Muscle Relaxation/
Hypertension in adults: Final
References

55. ((muscle* or muscular*) adj3 (relax* or stretch* or flex* or exercise*)).ti,ab.
56. or/40-55
57. 39 and 56
58. randomized controlled trial.pt.
59. controlled clinical trial.pt.
60. randomi#ed.ti,ab.
61. placebo.ab.
62. randomly.ti,ab.
63. Clinical Trials as topic.sh.
64. trial.ti.
65. or/58-64
66. Meta-Analysis/
67. exp Meta-Analysis as Topic/
68. (meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
69. ((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
70. (reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
71. (search strategy or search criteria or systematic search or study selection or data extraction).ab.
72. (search* adj4 literature).ab.
73. (medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
74. cochrane.jw.
75. ((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
76. or/66-75
77. 65 or 76
78. 57 and 77

Table 10: Embase (Ovid) search terms

<table>
<thead>
<tr>
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<td>(high adj blood adj pressur*).ti,ab.</td>
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<td>5</td>
<td>(increase* adj2 blood pressur*).ti,ab.</td>
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<td>((systolic or diastolic or arterial) adj2 pressur*).ti,ab.</td>
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<td>7</td>
<td>or/1-6</td>
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<td>8</td>
<td>exp pregnancy/</td>
</tr>
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<td>exp Maternal Hypertension/</td>
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<td>10</td>
<td>(pre eclampsia or pre-eclampsia or preeclampsia).ti,ab.</td>
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<tr>
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<td>or/8-15</td>
</tr>
<tr>
<td>17</td>
<td>7 not 16</td>
</tr>
<tr>
<td>18</td>
<td>letter.pt. or letter/</td>
</tr>
<tr>
<td>19</td>
<td>note.pt.</td>
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<td>Number</td>
<td>Term</td>
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<td>case report/ or case study/</td>
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<td>22</td>
<td>(letter or comment*).ti.</td>
</tr>
<tr>
<td>23</td>
<td>or/18-22</td>
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<td>randomized controlled trial/ or random*.ti,ab.</td>
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<td>exp Animal Experiment/</td>
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<td>animal model/</td>
</tr>
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<td>31</td>
<td>exp Rodent/</td>
</tr>
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<td>32</td>
<td>(rat or rats or mouse or mice).ti.</td>
</tr>
<tr>
<td>33</td>
<td>or/25-32</td>
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<td>37</td>
<td>limit 36 to English language</td>
</tr>
<tr>
<td>38</td>
<td>*Alternative medicine/</td>
</tr>
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<td>39</td>
<td>(mind body or mindbody).ti,ab.</td>
</tr>
<tr>
<td>40</td>
<td>((relax* or breath*) adj3 (behavior* or behaviour* or therap* or technic* or technique* or practic* or exerc* or educat* or manag* or train* or method*)).ti,ab.</td>
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<td>41</td>
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<td>((behaivation* or behavior*) adj3 (intervention* or therap* or train* or educat* or manag*).ti,ab.</td>
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<tr>
<td>43</td>
<td>*feedback system/</td>
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<td>44</td>
<td>(biofeedback or bio feedback or neurofeedback or neuro feedback or myo feedback or myo feedback).ti,ab.</td>
</tr>
<tr>
<td>45</td>
<td>((physiologic* or psychophysiological*) adj2 (feedback or feed back)).ti,ab.</td>
</tr>
<tr>
<td>46</td>
<td>exp *Meditation/</td>
</tr>
<tr>
<td>47</td>
<td>Transcendental, meditation/</td>
</tr>
<tr>
<td>48</td>
<td>(meditat* or meditation* or mindful*).ti,ab.</td>
</tr>
<tr>
<td>49</td>
<td>autogenic*.ti,ab.</td>
</tr>
<tr>
<td>50</td>
<td>((hypnosis or hypnot* or reverie or trance) adj2 (therap* or train* or technique* or relax* or guide* or led or lead* or treatment* or intervention*)).ti,ab.</td>
</tr>
<tr>
<td>51</td>
<td>((imagery or imagination or imagining) adj3 (relax* or guide* or led or lead*).ti,ab.</td>
</tr>
<tr>
<td>52</td>
<td>(yoga* or yogic or pilates).ti,ab.</td>
</tr>
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<td>53</td>
<td>*Muscle Relaxation/</td>
</tr>
<tr>
<td>54</td>
<td>((muscle* or muscular*) adj3 (relax* or stretch* or flex* or exercise*)).ti,ab.</td>
</tr>
<tr>
<td>55</td>
<td>or/38-54</td>
</tr>
<tr>
<td>56</td>
<td>37 and 55</td>
</tr>
<tr>
<td>57</td>
<td>random*.ti,ab.</td>
</tr>
<tr>
<td>58</td>
<td>factorial*.ti,ab.</td>
</tr>
<tr>
<td>59</td>
<td>(crossover* or cross over*).ti,ab.</td>
</tr>
<tr>
<td>60</td>
<td>((doubi* or singl*) adj blind*).ti,ab.</td>
</tr>
<tr>
<td>61</td>
<td>(assign* or allocat* or volunteer* or placebo*).ti,ab.</td>
</tr>
<tr>
<td>62</td>
<td>crossover procedure/</td>
</tr>
</tbody>
</table>
63. single blind procedure/
64. randomized controlled trial/
65. double blind procedure/
66. or/57-65
67. systematic review/
68. meta-analysis/
69. (meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
70. ((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
71. (reference list* or bibliography* or hand search* or manual search* or relevant journals).ab.
72. (search strategy or search criteria or systematic search or study selection or data extraction).ab.
73. (search* adj4 literature).ab.
74. (medline or pubmed or cochrane or embase or psyclit or psychnfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
75. cochrane.jw.
76. ((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
77. or/67-76
78. 66 or 77
79. 56 and 77

<table>
<thead>
<tr>
<th>Table 11: Cochrane Library (Wiley) search terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1. MeSH descriptor: [Hypertension] explode all trees</td>
</tr>
<tr>
<td>#2. hypertens*:ti,ab</td>
</tr>
<tr>
<td>#3. (elevat* near/2 blood next pressur*):ti,ab</td>
</tr>
<tr>
<td>#4. (high near/1 blood near/1 pressur*):ti,ab</td>
</tr>
<tr>
<td>#5. (increase* near/2 blood pressur*):ti,ab</td>
</tr>
<tr>
<td>#6. ((systolic or diastolic or arterial) near/2 pressur*):ti,ab</td>
</tr>
<tr>
<td>#7. (or #1-#6)</td>
</tr>
<tr>
<td>#8. MeSH descriptor: [Mind-Body Therapies] explode all trees</td>
</tr>
<tr>
<td>#9. (mind body or mindbody):ti,ab</td>
</tr>
<tr>
<td>#10. ((relax* or breath*) near/3 (behavior* or behaviour* or therap* or technic* or technique* or practic*: or exerc*: or educat*: or manag*: or train*: or method*))):ti,ab</td>
</tr>
<tr>
<td>#11. ((stress* or cognitive or talk* or assertiveness or anger) near/3 (treatment* or therap* or train*: or educat*: or manag*: or technique*)):ti,ab</td>
</tr>
<tr>
<td>#12. ((behaviour* or behavior*) near/3 (intervention* or therap* or train*: or educat*: or manag*)):ti,ab</td>
</tr>
<tr>
<td>#13. MeSH descriptor: [Feedback, Psychological] explode all trees</td>
</tr>
<tr>
<td>#14. (biofeedback or bio feedback or neurofeedback or neuro feedback or myo feedback):ti,ab</td>
</tr>
<tr>
<td>#15. ((physiologic* or psychophysiologic*) near/2 (feedback or feed back)):ti,ab</td>
</tr>
<tr>
<td>#16. MeSH descriptor: [Meditation] explode all trees</td>
</tr>
<tr>
<td>#17. (meditat* or meditation* or mindful*):ti,ab</td>
</tr>
<tr>
<td>#18. autogenic*:ti,ab</td>
</tr>
<tr>
<td>#19. ((hypnosis or hypnot* or reverie or trance) near/2 (therap* or train* or technique* or relax* or guide* or led or lead* or treatment* or intervention*)):ti,ab</td>
</tr>
<tr>
<td>#20. ((imagery or imagination or imagining) near/3 (relax* or guide* or led or lead*)):ti,ab</td>
</tr>
<tr>
<td>#21. (yoga* or yogic or pilates):ti,ab</td>
</tr>
</tbody>
</table>
Table 12: CINAHL (EBSCO) search terms

<p>| S1.          | MH hypertension                                      |
| S2.          | TI hypertens* OR AB hypertens*                       |
| S3.          | TI blood pressure* OR AB blood pressure*             |
| S4.          | TI ((high or elevat* or increas*) ) OR AB ((high or elevat* or increas*)) |
| S5.          | TI ( systolic or diastolic or arterial ) AND AB ( systolic or diastolic or arterial ) |
| S6.          | S4 OR S5                                            |
| S7.          | S3 AND S6                                           |
| S8.          | S1 OR S2 OR S7                                      |
| S9.          | (MH &quot;Mind Body Techniques+&quot;) OR (MH &quot;Hypnosis+&quot;) OR (MM &quot;Meditation&quot;) OR (MH &quot;Relaxation Techniques+&quot;) OR (MH &quot;Yoga+&quot;) OR (MM &quot;Buteyko Method&quot;) |
| S10.         | TI ( mind body or mindbody ) OR AB ( mind body or mindbody ) |
| S11.         | TI ( relax* or breath* ) OR AB ( relax* or breath* )   |
| S12.         | TI ( behavior* or behaviour* or therap* or technic<em>or technique</em> or practic* or exerc* or educat* or manag* or train* or method* ) OR AB ( behavior* or behaviour* or therap* or technic* or technique* or practic* or exerc* or educat* or manag* or train* or method* ) |
| S13.         | S11 AND S12                                         |
| S14.         | TI ( stress* or cognitive or talk* or assertiveness or anger ) OR AB ( stress* or cognitive or talk* or assertiveness or anger ) |
| S15.         | TI ( treatment* or therap* or train* or educat* or manag* or technique* ) OR AB ( treatment* or therap* or train* or educat* or manag* or technique* ) |
| S16.         | S14 AND S15                                         |
| S17.         | TI ( behaviour* or behavior* ) OR AB ( behaviour* or behavior* ) |
| S18.         | TI ( intervention* or therap* or train* or educat* or manag* ) OR AB ( intervention* or therap* or train* or educat* or manag* ) |
| S19.         | S17 AND S18                                         |
| S20.         | TI ( (biofeedback or bio feedback or neurofeedback or neuro feedback or myofeedback or myo feedback) ) OR AB ( (biofeedback or bio feedback or neurofeedback or neuro feedback or myofeedback or myo feedback) ) |
| S21.         | TI ( physiologic* or psychophysiologic* ) OR AB ( physiologic* or psychophysiologic* ) |
| S22.         | TI ( feedback or feed back ) OR AB ( feedback or feed back ) |
| S23.         | S21 AND S22                                         |
| S24.         | MH Meditation                                       |
| S25.         | TI ( (meditat* or meditation* or mindful*) ) OR AB ( (meditat* or meditation* or mindful*) ) |
| S26.         | TI autogenic* AND AB autogenic*                      |
| S27.         | TI ( (hypnosis or hypnot* or reverie or trance) ) OR AB ( (hypnosis or hypnot* or reverie or trance) ) |
| S28.         | ( therap* or train* or technique* or relax* or guide* or led or lead* or treatment* or intervention* ) OR AB ( therap* or train* or technique* or relax* or guide* or led or lead* or treatment* or intervention* ) |
| S29.         | S27 AND S28                                         |
| S30.         | TI ( imagery or imagination or imagining ) OR AB ( imagery or imagination or imagining ) |
| S31.         | TI ( relax* or guide* or led or lead* ) OR AB ( relax* or guide* or led or lead* ) |
| S32.         | S30 AND S31                                         |
| S33.         | TI ( (yoga* or yogic or pilates) ) OR AB ( (yoga* or yogic or pilates) ) |</p>
<table>
<thead>
<tr>
<th>S34</th>
<th>MH Muscle Relaxation</th>
</tr>
</thead>
<tbody>
<tr>
<td>S35</td>
<td>TI ( muscle* or muscular* ) OR AB ( muscle* or muscular* )</td>
</tr>
<tr>
<td>S36</td>
<td>TI ( relax* or stretch* or flex* or exercise* ) OR AB ( relax* or stretch* or flex* or exercise* )</td>
</tr>
<tr>
<td>S37</td>
<td>S35 AND S36</td>
</tr>
<tr>
<td>S38</td>
<td>S9 OR S10 OR S13 OR S16 OR S19 OR S20 OR S23 OR S24 OR S25 OR S26 OR S29 OR S32 OR S34 OR S37</td>
</tr>
<tr>
<td>S39</td>
<td>S8 AND S38</td>
</tr>
</tbody>
</table>

Limiters: English Language; Exclude MEDLINE records; Human; Publication Type: Clinical Trial, Journal Article, Meta Analysis, Randomized Controlled Trial, Review, Systematic Review; Age Groups: All Adult; Language: English

**Table 13: AMED (Ovid) search terms**

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<tr>
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<tbody>
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<td>3</td>
<td>(elevat* adj2 blood adj pressur*).ti,ab.</td>
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<td>4</td>
<td>(high adj blood adj pressur*).ti,ab.</td>
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<tr>
<td>5</td>
<td>(increase* adj2 blood pressur*).ti,ab.</td>
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<td>6</td>
<td>((systolic or diastolic or arterial) adj2 pressur*).ti,ab.</td>
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<td>or/1-6</td>
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<tr>
<td>8</td>
<td>case report/</td>
</tr>
<tr>
<td>9</td>
<td>(letter or comment*).ti.</td>
</tr>
<tr>
<td>10</td>
<td>animals/ not humans/</td>
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<td>11</td>
<td>or/8-10</td>
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<tr>
<td>12</td>
<td>7 not 11</td>
</tr>
<tr>
<td>13</td>
<td>(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp Middle Aged/ or exp aged/)</td>
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<tr>
<td>14</td>
<td>12 not 13</td>
</tr>
<tr>
<td>15</td>
<td>limit 14 to English</td>
</tr>
<tr>
<td>16</td>
<td>(mind body or mindbody).ti,ab.</td>
</tr>
<tr>
<td>17</td>
<td>((relax* or breath*) adj3 (behavior* or behaviour* or therap* or technic<em>or technique</em> or practic* or exerc* or educat* or manag* or train* or method*)).ti,ab.</td>
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<td>18</td>
<td>((stress* or cognitive or talk* or assertiveness or anger) adj3 (treatment* or therap* or train* or educat* or manag* or technique*)).ti,ab.</td>
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<td>19</td>
<td>((behaviour* or behavior*) adj3 (intervention* or therap* or train* or educat* or manag* or manag*)).ti,ab.</td>
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<tr>
<td>20</td>
<td>(biofeedback or bio feedback or neurofeedback or neuro feedback or myofeedback or myo feedback).ti,ab.</td>
</tr>
<tr>
<td>21</td>
<td>((physiologic* or psychophysiologic*) adj2 (feedback or feed back)).ti,ab.</td>
</tr>
<tr>
<td>22</td>
<td>(meditat* or meditation* or mindful*).ti,ab.</td>
</tr>
<tr>
<td>23</td>
<td>autogenic*.ti,ab.</td>
</tr>
<tr>
<td>24</td>
<td>((hypnosis or hypnot* or reverie or trance) adj2 (therap* or train* or technique* or relax* or guide* or led or lead* or treatment* or intervention*)).ti,ab.</td>
</tr>
<tr>
<td>25</td>
<td>((imagery or imagination or imagining) adj3 (relax* or guide* or led or lead*)).ti,ab.</td>
</tr>
<tr>
<td>26</td>
<td>(yoga* or yogic or pilates).ti,ab.</td>
</tr>
<tr>
<td>27</td>
<td>((muscle* or muscular*) adj3 (relax* or stretch* or flex* or exercise*)).ti,ab.</td>
</tr>
<tr>
<td>28</td>
<td>breathing therapies/ or mind body medicine/ or yoga/</td>
</tr>
<tr>
<td>29</td>
<td>behavior therapy/ or exp hypnosis/ or imagery/</td>
</tr>
<tr>
<td>30</td>
<td>Complementary therapies/</td>
</tr>
</tbody>
</table>
B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to hypertension in adults population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics, economic modelling and quality of life studies.

<table>
<thead>
<tr>
<th>Database</th>
<th>Dates searched</th>
<th>Search filter used</th>
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<td>Exclusions Health economics studies</td>
</tr>
<tr>
<td>Embase</td>
<td>2014–28 August 2018</td>
<td>Exclusions Health economics studies</td>
</tr>
</tbody>
</table>
| Centre for Research and Dissemination (CRD) | HTA - Inception–28 August 2018  
NHS EED - Inception to March 2015 | None                                    |

Table 15: Medline (Ovid) search terms

1. exp Hypertension/
2. hypertens*.ti,ab.
<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>3.</td>
<td>(elevat* adj2 blood adj pressur*).ti,ab.</td>
</tr>
<tr>
<td>4.</td>
<td>(high adj blood adj pressur*).ti,ab.</td>
</tr>
<tr>
<td>5.</td>
<td>(increase* adj2 blood pressur*).ti,ab.</td>
</tr>
<tr>
<td>6.</td>
<td>((systolic or diastolic or arterial) adj2 pressur*).ti,ab.</td>
</tr>
<tr>
<td>7.</td>
<td>or/1-6</td>
</tr>
<tr>
<td>8.</td>
<td>letter/</td>
</tr>
<tr>
<td>9.</td>
<td>editorial/</td>
</tr>
<tr>
<td>10.</td>
<td>news/</td>
</tr>
<tr>
<td>11.</td>
<td>exp historical article/</td>
</tr>
<tr>
<td>12.</td>
<td>Anecdotes as Topic/</td>
</tr>
<tr>
<td>13.</td>
<td>comment/</td>
</tr>
<tr>
<td>14.</td>
<td>case report/</td>
</tr>
<tr>
<td>15.</td>
<td>(letter or comment*).ti.</td>
</tr>
<tr>
<td>16.</td>
<td>or/8-15</td>
</tr>
<tr>
<td>17.</td>
<td>randomized controlled trial/ or random*.ti,ab.</td>
</tr>
<tr>
<td>18.</td>
<td>16 not 17</td>
</tr>
<tr>
<td>19.</td>
<td>animals/ not humans/</td>
</tr>
<tr>
<td>20.</td>
<td>exp Animals, Laboratory/</td>
</tr>
<tr>
<td>21.</td>
<td>exp Animal Experimentation/</td>
</tr>
<tr>
<td>22.</td>
<td>exp Models, Animal/</td>
</tr>
<tr>
<td>23.</td>
<td>exp Rodentia/</td>
</tr>
<tr>
<td>24.</td>
<td>(rat or rats or mouse or mice).ti.</td>
</tr>
<tr>
<td>25.</td>
<td>or/18-24</td>
</tr>
<tr>
<td>26.</td>
<td>7 not 25</td>
</tr>
<tr>
<td>27.</td>
<td>limit 26 to English language</td>
</tr>
<tr>
<td>28.</td>
<td>Economics/</td>
</tr>
<tr>
<td>29.</td>
<td>Value of life/</td>
</tr>
<tr>
<td>30.</td>
<td>exp &quot;Costs and Cost Analysis&quot;/</td>
</tr>
<tr>
<td>31.</td>
<td>exp Economics, Hospital/</td>
</tr>
<tr>
<td>32.</td>
<td>exp Economics, Medical/</td>
</tr>
<tr>
<td>33.</td>
<td>Economics, Nursing/</td>
</tr>
<tr>
<td>34.</td>
<td>Economics, Pharmaceutical/</td>
</tr>
<tr>
<td>35.</td>
<td>exp &quot;Fees and Charges&quot;/</td>
</tr>
<tr>
<td>36.</td>
<td>exp Budgets/</td>
</tr>
<tr>
<td>37.</td>
<td>budget*.ti,ab.</td>
</tr>
<tr>
<td>38.</td>
<td>cost*.ti.</td>
</tr>
<tr>
<td>39.</td>
<td>(economic* or pharmaco?economic*).ti.</td>
</tr>
<tr>
<td>40.</td>
<td>(price* or pricing*).ti,ab.</td>
</tr>
<tr>
<td>41.</td>
<td>(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.</td>
</tr>
<tr>
<td>42.</td>
<td>(financ* or fee or fees).ti,ab.</td>
</tr>
<tr>
<td>43.</td>
<td>(value adj2 (money or monetary)).ti,ab.</td>
</tr>
<tr>
<td>44.</td>
<td>or/28-43</td>
</tr>
<tr>
<td>45.</td>
<td>27 and 44</td>
</tr>
</tbody>
</table>

Table 16: Embase (Ovid) search terms

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>exp Hypertension/</td>
</tr>
</tbody>
</table>
Table 17: NHS EED and HTA (CRD) search terms

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>MeSH DESCRIPTOR Hypertension EXPLODE ALL TREES IN NHSEED, HTA</td>
</tr>
<tr>
<td>#2</td>
<td>(Hypertens*) IN NHSEED, HTA</td>
</tr>
<tr>
<td>#3.</td>
<td>(elevat* adj2 blood adj pressur*) IN NHSEED, HTA</td>
</tr>
<tr>
<td>----------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>#4.</td>
<td>(high adj blood adj pressur*) IN NHSEED, HTA</td>
</tr>
<tr>
<td>#5.</td>
<td>(increase* adj2 blood pressur*) IN NHSEED, HTA</td>
</tr>
<tr>
<td>#6.</td>
<td>((systolic or diastolic or arterial) adj2 pressur*) IN NHSEED, HTA</td>
</tr>
<tr>
<td>#7.</td>
<td>#1 OR #2 OR #3 OR #4 OR #5 OR #6</td>
</tr>
</tbody>
</table>
Appendix C: Clinical evidence selection

**Figure 1:** Flow chart of clinical study selection for the review of relaxation therapy

- Records identified through database searching, n=4,047
- Additional records identified through other sources, n=0

- Records screened, n=4,047

- Records excluded, n=3,936

- Full-text papers assessed for eligibility, n=111

- Papers included in review, n=1

- Papers excluded from review, n=110

  Reasons for exclusion: see appendix I
### Appendix D: Clinical evidence tables

<table>
<thead>
<tr>
<th>Study</th>
<th>Patel 1988&lt;sup&gt;78&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study type</strong></td>
<td>RCT (Patient randomised; Parallel)</td>
</tr>
<tr>
<td><strong>Number of studies (number of participants)</strong></td>
<td>(n=104)</td>
</tr>
<tr>
<td><strong>Countries and setting</strong></td>
<td>Conducted in the UK; Setting: General practices</td>
</tr>
<tr>
<td><strong>Line of therapy</strong></td>
<td>First line</td>
</tr>
<tr>
<td><strong>Duration of study</strong></td>
<td>Intervention plus follow up: 8 weeks plus 1 year follow up (FU)</td>
</tr>
<tr>
<td><strong>Method of assessment of guideline condition</strong></td>
<td>Adequate method of assessment or diagnosis</td>
</tr>
<tr>
<td><strong>Stratum</strong></td>
<td>Overall</td>
</tr>
<tr>
<td><strong>Subgroup analysis within study</strong></td>
<td>Stratified then randomised</td>
</tr>
<tr>
<td><strong>Inclusion criteria</strong></td>
<td>All participants had previously taken part in the Medical Research Council's treatment of mild hypertension trial, which was carried out in 192 general practices in Britain and included 17,354 people aged 35–64 years at entry, with phase V diastolic blood pressure in the range of 90–109 mmHg. They were treated with active drugs or placebos. In the second phase, 2,756 early entrants who had completed 6 years of the trial were randomised to continue or discontinue treatment with active drugs or placebos. The last 134 recruits to the second phase, who consented to enter both the second phase and the relaxation trial, were further randomised to receive or not receive relaxation therapy.</td>
</tr>
<tr>
<td><strong>Exclusion criteria</strong></td>
<td>Not reported</td>
</tr>
<tr>
<td><strong>Age, sex and family origin</strong></td>
<td>Age - Range: 35-64. Sex (M: F): 52 male, 51 female. Family origin: N/A</td>
</tr>
<tr>
<td><strong>Further population details</strong></td>
<td>1. Age 2. Concomitant pharmacological treatment 3. Family origin 4. Hypertension severity</td>
</tr>
<tr>
<td><strong>Indirectness of population</strong></td>
<td>No indirectness</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>(n=49) Intervention 1: Meditation. Relaxation therapy - Conducted by GPs. People attended once a week for 1 hour for 8 weeks in groups of 10. During the first 30 minutes, the GP discussed the topics involved and in the last 30 minutes, the nurse carried out training in breathing exercises, deep muscle relaxation and simple meditation using the instruction cassette tape. Each person was also given a relaxation and meditation instruction cassette tape for daily practice at home. Emphasis was placed on the gradual integration of relaxation into everyday life. Duration 8 weeks. Concurrent medication/care: N/A. Indirectness: No indirectness</td>
</tr>
<tr>
<td></td>
<td>(n=54) Intervention 2: Breathing. Control group - no relaxation therapy. Duration 8 weeks. Concurrent</td>
</tr>
<tr>
<td>Study</td>
<td>Patel 1988&lt;sup&gt;78&lt;/sup&gt;</td>
</tr>
<tr>
<td>-------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>medication/care:</td>
<td>N/A. Indirectness: No indirectness</td>
</tr>
<tr>
<td>Funding</td>
<td>Study funded by industry (Supported by the British Heart Foundation)</td>
</tr>
<tr>
<td>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RELAXATION THERAPY versus NO ACTIVE TREATMENT</td>
<td></td>
</tr>
<tr>
<td>Protocol outcome 1: Stroke (ischaemic or haemorrhagic) at ≥12 months</td>
<td>- Actual outcome: Stroke at 12 months; Group 1: 1/49, Group 2: 0/54</td>
</tr>
<tr>
<td>Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Baseline details: Difference in blood pressure; Group 1 Number missing: 5, Reason: 1 died, 2 moved away, 2 didn't attend; Group 2 Number missing: 3, Reason: 1 had MI, 1 moved away, 1 didn't attend</td>
<td></td>
</tr>
<tr>
<td>Protocol outcome 2: Myocardial infarction at ≥12 months</td>
<td>- Actual outcome: Myocardial infarction at 12 months; Group 1: 0/49, Group 2: 1/54</td>
</tr>
<tr>
<td>Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Baseline details: Difference in blood pressure; Group 1 Number missing: 5, Reason: 1 died, 2 moved away, 2 didn't attend; Group 2 Number missing: 3, Reason: 1 had MI, 1 moved away, 1 didn't attend</td>
<td></td>
</tr>
<tr>
<td>Protocol outcome 3: Angina needing hospitalisation at ≥12 months</td>
<td>- Actual outcome: Angina at 12 months; Group 1: 0/49, Group 2: 1/54</td>
</tr>
<tr>
<td>Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Baseline details: Difference in blood pressure; Group 1 Number missing: 5, Reason: 1 died, 2 moved away, 2 didn't attend; Group 2 Number missing: 3, Reason: 1 had MI, 1 moved away, 1 didn't attend</td>
<td></td>
</tr>
<tr>
<td>Protocol outcomes not reported by the study</td>
<td>Health related quality of life at ≥12 months; All-cause mortality at ≥12 months; Heart failure needing hospitalisation at ≥12 months; Vascular procedures (including both coronary and carotid artery procedures) at ≥12 months; Cessation or reduction of medication at ≥12 months</td>
</tr>
</tbody>
</table>
Appendix E: Forest plots

E.1 Relaxation therapy versus no treatment

Figure 2: Stroke at 12 months

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Relaxation therapy</th>
<th>Control</th>
<th>Peto Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patel, 1988</td>
<td>1</td>
<td>0</td>
<td>8.18 [0.16, 414.30]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>49</td>
<td>54</td>
<td>8.18 [0.16, 414.30]</td>
</tr>
<tr>
<td>Total events</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable
Test for overall effect: Z = 1.05 (P = 0.29)

Figure 3: Myocardial Infarction at 12 months

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Relaxation therapy</th>
<th>Control</th>
<th>Peto Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patel, 1988</td>
<td>0</td>
<td>1</td>
<td>0.15 [0.00, 7.52]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>49</td>
<td>54</td>
<td>0.15 [0.00, 7.52]</td>
</tr>
<tr>
<td>Total events</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable
Test for overall effect: Z = 0.95 (P = 0.34)

Figure 4: Angina at 12 months

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Relaxation therapy</th>
<th>Control</th>
<th>Peto Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patel, 1988</td>
<td>0</td>
<td>1</td>
<td>0.15 [0.00, 7.52]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>49</td>
<td>54</td>
<td>0.15 [0.00, 7.52]</td>
</tr>
<tr>
<td>Total events</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable
Test for overall effect: Z = 0.96 (P = 0.34)
### Appendix F: GRADE tables

#### Table 18: Clinical evidence profile: Relaxation therapy versus no treatment

<table>
<thead>
<tr>
<th></th>
<th>Quality assessment</th>
<th>No of patients</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No of studies</td>
<td>Design</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
<td>Indirectness</td>
</tr>
<tr>
<td>Stroke at 12 months (follow-up 12 months)</td>
<td>1</td>
<td>randomised trials</td>
<td>serious¹</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
</tr>
<tr>
<td>Myocardial Infarction at 12 months (follow-up 12 months)</td>
<td>1</td>
<td>randomised trials</td>
<td>serious¹</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
</tr>
<tr>
<td>Angina at 12 months (follow-up 12 months)</td>
<td>1</td>
<td>randomised trials</td>
<td>serious¹</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
</tr>
</tbody>
</table>

¹Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

²Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
Appendix G: Health economic evidence selection

Figure 5: Flow chart of health economic study selection for the guideline

Records identified through database searching, n=6,194

Records screened in 1st sift, n=6,211

Full-text papers assessed for eligibility in 2nd sift, n=273

Records excluded* in 1st sift, n=5,938

Full-text papers assessed for applicability and quality of methodology, n=38

Papers excluded* in 2nd sift, n=238

Papers included, n=2

Studies included by review:
- Diagnosis: n=1
- Monitoring: n=1
- Initiation threshold: n=0
- Type of target: n=0
- Target level: n=0
- Step 1 treatment: n=0
- Step 2/3 treatment: n=0
- Step 4 treatment: n=0
- Relaxation: n=0
- Same day review: n=0

Papers selectively excluded, n=4

Studies selectively excluded by review:
- Diagnosis: n=2
- Monitoring: n=2
- Initiation threshold: n=0
- Type of target: n=0
- Target level: n=0
- Step 1 treatment: n=0
- Step 2/3 treatment: n=0
- Step 4 treatment: n=0
- Relaxation: n=0
- Same day review: n=0

Reasons for exclusion: see appendix I.2

Papers excluded, n=29

Studies excluded by review:
- Diagnosis: n=1
- Monitoring: n=8
- Initiation threshold: n=4
- Type of target: n=0
- Target level: n=3
- Step 1 treatment: n=5
- Step 2/3 treatment: n=8
- Step 4 treatment: n=0
- Relaxation: n=0
- Same day review: n=0

Reasons for exclusion: see appendix I.2

* Non-relevant population, intervention, comparison, design or setting; non-English language
Appendix H:  Health economic evidence tables

None.

Appendix I:  Excluded studies

I.1  Excluded clinical studies

Table 19: Studies excluded from the clinical review that were included in the previous guideline (CG127)

<table>
<thead>
<tr>
<th>Study</th>
<th>Exclusion details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Achmon 19891</td>
<td>The follow up was at 6 months, not meeting the 12 month minimum follow up specified by the protocol.</td>
</tr>
<tr>
<td>Adsett 19892</td>
<td>This study was excluded for two reasons, one being an inappropriate comparison. Participants were given either a drug treatment or placebo, and this was compared to participants receiving either relaxation training or an education programme. Additionally, the follow up was at 3 months, not meeting the 12 month minimum follow up specified by the protocol.</td>
</tr>
<tr>
<td>Agras 19834</td>
<td>No outcomes reported by the study matched that of the protocol.</td>
</tr>
<tr>
<td>Agras 19875</td>
<td>No outcomes reported by the study matched that of the protocol.</td>
</tr>
<tr>
<td>Bennett 199117</td>
<td>The follow up was at 6 months, not meeting the 12 month minimum follow up specified by the protocol.</td>
</tr>
<tr>
<td>Brauer 197921</td>
<td>The follow up was at 6 months, not meeting the 12 month minimum follow up specified by the protocol. Additionally, no outcomes reported by the study matched that of the protocol.</td>
</tr>
<tr>
<td>Canino 199423</td>
<td>The follow up was for 6 months, not meeting the 12 month minimum follow up specified by the protocol.</td>
</tr>
<tr>
<td>Carson 198825</td>
<td>The follow up was at 8 weeks, not meeting the 12 month minimum follow up specified by the protocol, and no outcomes reported by the study matched that of the protocol.</td>
</tr>
<tr>
<td>Cottier 198429</td>
<td>The follow up was at 22 weeks, not meeting the 12 month minimum follow up specified by the protocol.</td>
</tr>
<tr>
<td>Frankel 197835</td>
<td>The follow up was at 16 weeks, not meeting the 12 month minimum follow up specified by the protocol, and no outcomes reported by the study matched that of the protocol.</td>
</tr>
<tr>
<td>Hatch 198548</td>
<td>This study was excluded for not having any outcomes that matched the protocol, and for incorrect comparisons as it compared diastolic blood pressure biofeedback, progressive deep muscle relaxation training, self-directed relaxation training and medication.</td>
</tr>
<tr>
<td>Hoelscher 198749</td>
<td>The follow up was at 2 months, not meeting the 12 month minimum follow up specified by the protocol.</td>
</tr>
<tr>
<td>Hoelscher 198650</td>
<td>The follow up was at 6 weeks, not meeting the 12 month minimum follow up specified by the protocol.</td>
</tr>
<tr>
<td>Irvine 199151</td>
<td>The follow up was at 12 weeks, not meeting the 12 month minimum follow up specified by the protocol.</td>
</tr>
<tr>
<td>Johnston 199353</td>
<td>No outcomes reported by the study matched that of the protocol.</td>
</tr>
<tr>
<td>Linden 200162</td>
<td>The follow up was at 6 months, not meeting the 12 month minimum follow up specified by the protocol.</td>
</tr>
<tr>
<td>Study</td>
<td>Exclusion details</td>
</tr>
<tr>
<td>---------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>McGrady 1994</td>
<td>The follow up was at 10 months, not meeting the 12 month minimum follow up specified by the protocol.</td>
</tr>
<tr>
<td>Patel 1985</td>
<td>This study was excluded for consisting of a population that did not match the review protocol. They are not stated to have primary hypertension, ‘blood pressure was measured and recalled those with two or more of the following; an average of two measurements of blood pressure of ≥140/90 mm Hg and not taking antihypertensive drugs; non-fasting plasma cholesterol concentration of &gt;6 3 mmol/l (244 mg/100 ml); and a current cigarette consumption of &gt; 10 cigarettes a day’.</td>
</tr>
<tr>
<td>Schein 2001</td>
<td>The follow up was at 8 weeks, not meeting the 12 month minimum follow up specified by the protocol.</td>
</tr>
<tr>
<td>Seer 1980</td>
<td>The follow up was at 25 weeks, not meeting the 12 month minimum follow up specified by the protocol.</td>
</tr>
<tr>
<td>Van Montfrans 1990</td>
<td>No outcomes reported by the study matched that of the protocol.</td>
</tr>
<tr>
<td>Zurawski 1987</td>
<td>This study was excluded for an incorrect comparison as they compared stress management to Galvanic Skin Response (GSR) biofeedback training control condition, and the follow up was at 8 weeks, not meeting the 12 month minimum follow up specified by the protocol. Additionally there were no outcomes reported by the study that matched the protocol.</td>
</tr>
</tbody>
</table>

Table 20: Studies excluded from the clinical review

<table>
<thead>
<tr>
<th>Study</th>
<th>Exclusion reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>Achmon 1989</td>
<td>Less than minimum duration</td>
</tr>
<tr>
<td>Adsett 1989</td>
<td>Inappropriate comparison</td>
</tr>
<tr>
<td>Agras 1983</td>
<td>No relevant outcomes</td>
</tr>
<tr>
<td>Agras 1984</td>
<td>No relevant outcomes</td>
</tr>
<tr>
<td>Agras 1987</td>
<td>No relevant outcomes</td>
</tr>
<tr>
<td>Ahmadpanah 2016</td>
<td>Less than minimum duration</td>
</tr>
<tr>
<td>Aivazyan 1988</td>
<td>No relevant outcomes</td>
</tr>
<tr>
<td>Alageel 2017</td>
<td>Not review population</td>
</tr>
<tr>
<td>Alexander 1989</td>
<td>Not review population</td>
</tr>
<tr>
<td>Alexander 1996</td>
<td>Less than minimum duration</td>
</tr>
<tr>
<td>Alparslan 2010</td>
<td>Less than minimum duration</td>
</tr>
<tr>
<td>Amigo Vazquez 2001</td>
<td>Not in English</td>
</tr>
<tr>
<td>Anderson 2008</td>
<td>Systematic Review, references checked</td>
</tr>
<tr>
<td>Anonymous 1979</td>
<td>Inappropriate comparison</td>
</tr>
<tr>
<td>Bagga 1983</td>
<td>Less than minimum duration</td>
</tr>
<tr>
<td>Bai 2015</td>
<td>Systematic Review, references checked</td>
</tr>
<tr>
<td>Bennett 1991</td>
<td>Less than minimum duration</td>
</tr>
<tr>
<td>Blom 2014</td>
<td>Less than minimum duration</td>
</tr>
<tr>
<td>Bradley 1980</td>
<td>Less than minimum duration</td>
</tr>
<tr>
<td>Brandani 2017</td>
<td>Systematic Review, references checked</td>
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### I.2 Excluded health economic studies

None.
Appendix J: Research recommendations

J.1 Relaxation therapies

Research question: What is the clinical and cost-effectiveness of relaxation therapies for the management of primary hypertension in adults in terms of reducing cardiovascular events and improving quality of life?

Why this is important:

It is known that blood pressure is increased at times of stress and conversely is reduced when levels of arousal are low. It is unknown whether participation in relaxation therapies can lead to a reduction in cardiovascular events. Relaxation therapies do not form part of current practice in the management of hypertension, as there is a lack of evidence assessing either their clinical- or cost-effectiveness.

Despite the benefits of antihypertensive medication, many individuals with hypertension do not achieve their target blood pressure. The reasons for poorly controlled hypertension are multifactorial, and within this population are individuals who are unable to, or choose not to, take medication. The identification of relaxation therapies as an alternative or complimentary treatment approach may reduce the proportion of individuals with poorly controlled hypertension with consequent improvement in health outcomes.

This research recommendation has been written to guide the design of studies so that the evidence generated is of sufficient, high quality for inclusion in future guidance.

Criteria for selecting high-priority research recommendations:

<table>
<thead>
<tr>
<th>PICO question</th>
<th>Importance to patients or the population</th>
<th>Relevance to NICE guidance</th>
<th>Relevance to the NHS</th>
<th>National priorities</th>
<th>Current evidence base</th>
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<tr>
<td>Population: Adults with primary hypertension.</td>
<td>The current approach to managing hypertension involves combining lifestyle optimisation with antihypertensive medication. The identification of benefit from relaxation therapies would identify a third treatment modality. It is likely that relaxation therapies would be acceptable to people, especially those that are unable to, or choose not to, take medication.</td>
<td>High quality research in this area would generate new evidence and may enable future updates of this guidance to make recommendations on the use of relaxation therapies for the management of hypertension. If studies investigate different methods of relaxation therapies, then it may be possible to make recommendations regarding method and/or intensity of therapy.</td>
<td>Relaxation therapies for the management of hypertension are not currently available on the NHS. Any impact on future service delivery or finances are dependent on the clinical- and cost-effectiveness of the intervention.</td>
<td>No.</td>
<td>Only a single study was included in the evidence review. The evidence from this was graded as ‘very low’ quality due to high risk of bias and imprecision. Several potentially relevant studies were identified in the literature search, but these were excluded due to ineligible populations, short duration or lack of suitable endpoints. Currently, there is no appropriate evidence base on which recommendations for the use of relaxation therapy can make.</td>
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</tbody>
</table>
### Equality
No effect on ‘protected characteristics’ as defined in the Equality Act.

### Study design
- Randomised control trial of a relaxation therapy in addition to usual care, ideally versus sham or placebo.
- Study duration 12 months or more.
- Outcomes to include all-cause mortality, cardiovascular events and health-related quality of life as a minimum.
- Surrogate outcome (for example, blood pressure or user acceptability) may also be included but are unlikely to inform future guidance.

### Feasibility
Hard outcome measures are required for 2 reasons. Firstly, these outcome measures are the standard on which the current guidelines are based. Secondly, it is unlikely that a double-blind study can be conducted into relaxation therapies, and so outcome measures must be selected to minimise potential bias.

To demonstrate a significant difference in outcomes for relaxation therapies in addition to usual care the study will need to recruit many participants for a prolonged period. It is unlikely that the study could be completed in less than 5 years, but this is consistent with other cardiovascular studies. The costs are dependent on the choice of relaxation therapy.

Current guidelines recommend that all hypertensive individuals be offered antihypertensive medication, except those with stage 1 hypertension at low-risk of cardiovascular events. This recommendation is based on evidence of clinical- and cost-effectiveness. It is therefore unlikely to be ethical to randomise people who would normally be offered medication to receive either medication or relaxation therapy. The likely study population would therefore be either low-risk stage 1 hypertensive individuals in whom antihypertensive medication may be considered, or individuals with hypertension who are already taking medication. These limitations will affect the event rate and thus increase the required size or duration of the study.

### Other comments
The study may attract commercial funders including companies developing physical or digital adjuncts for relaxation.

### Importance
Low: the research is of interest and will fill existing evidence gaps.