NUFFIELD DEPARTMENT OF
PRIMARY CARE
HEALTH SCIENCES

UNIVERSITY OF
OXFORD

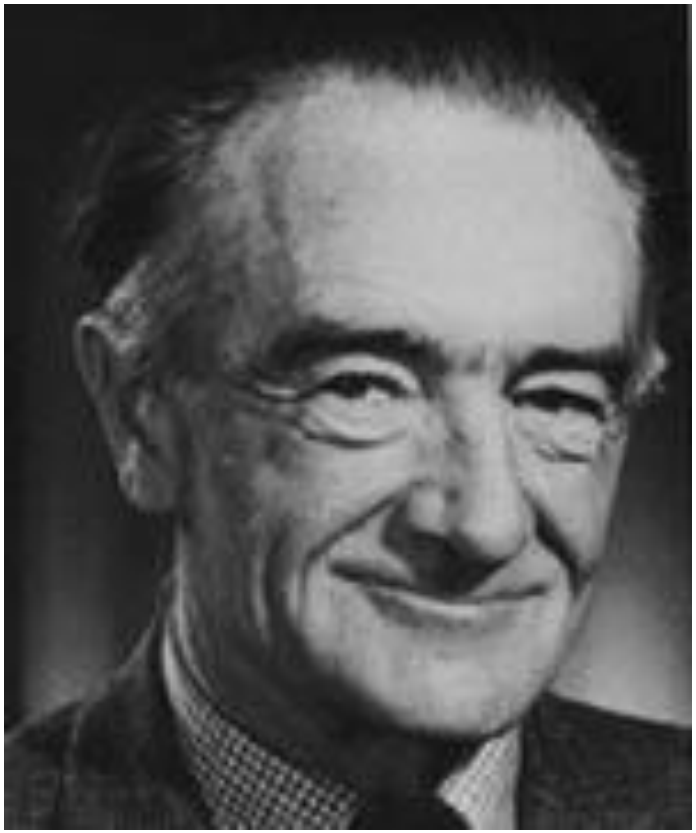
Critical appraisal of randomised controlled trials

Dr Kamal R. Mahtani
BSc PhD MBBS PGDip MRCGP
GP and Deputy Director
Centre for Evidence Based Medicine
University of Oxford

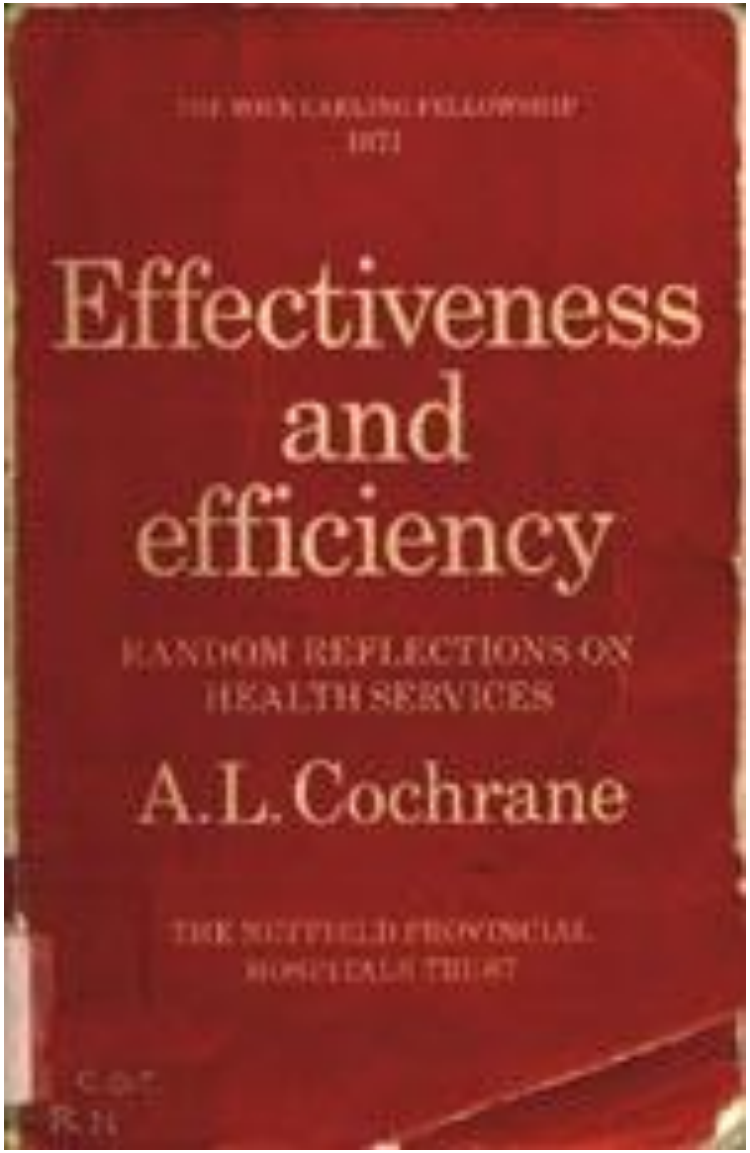
Dec 2015

CEBM

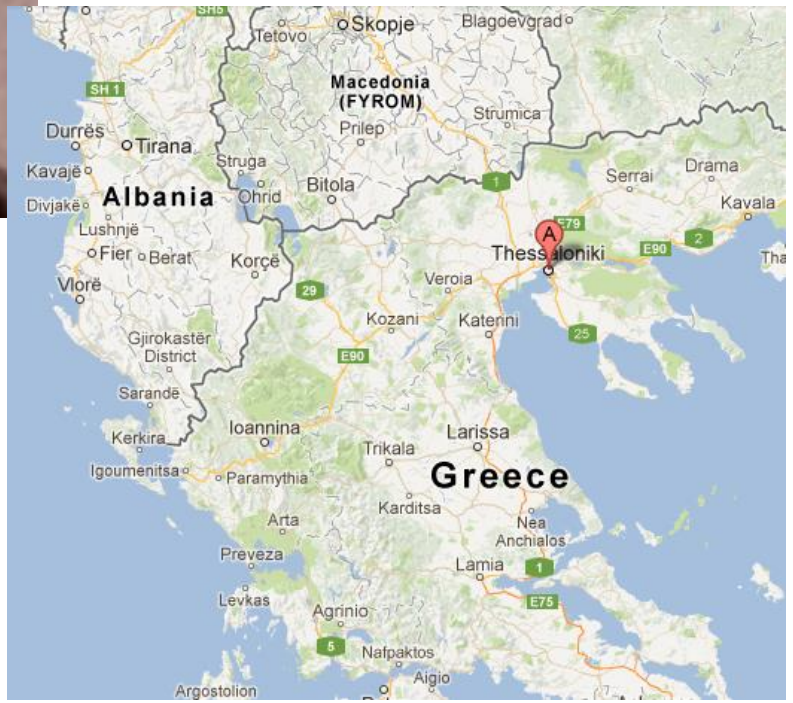
THE COCHRANE COLLABORATION®

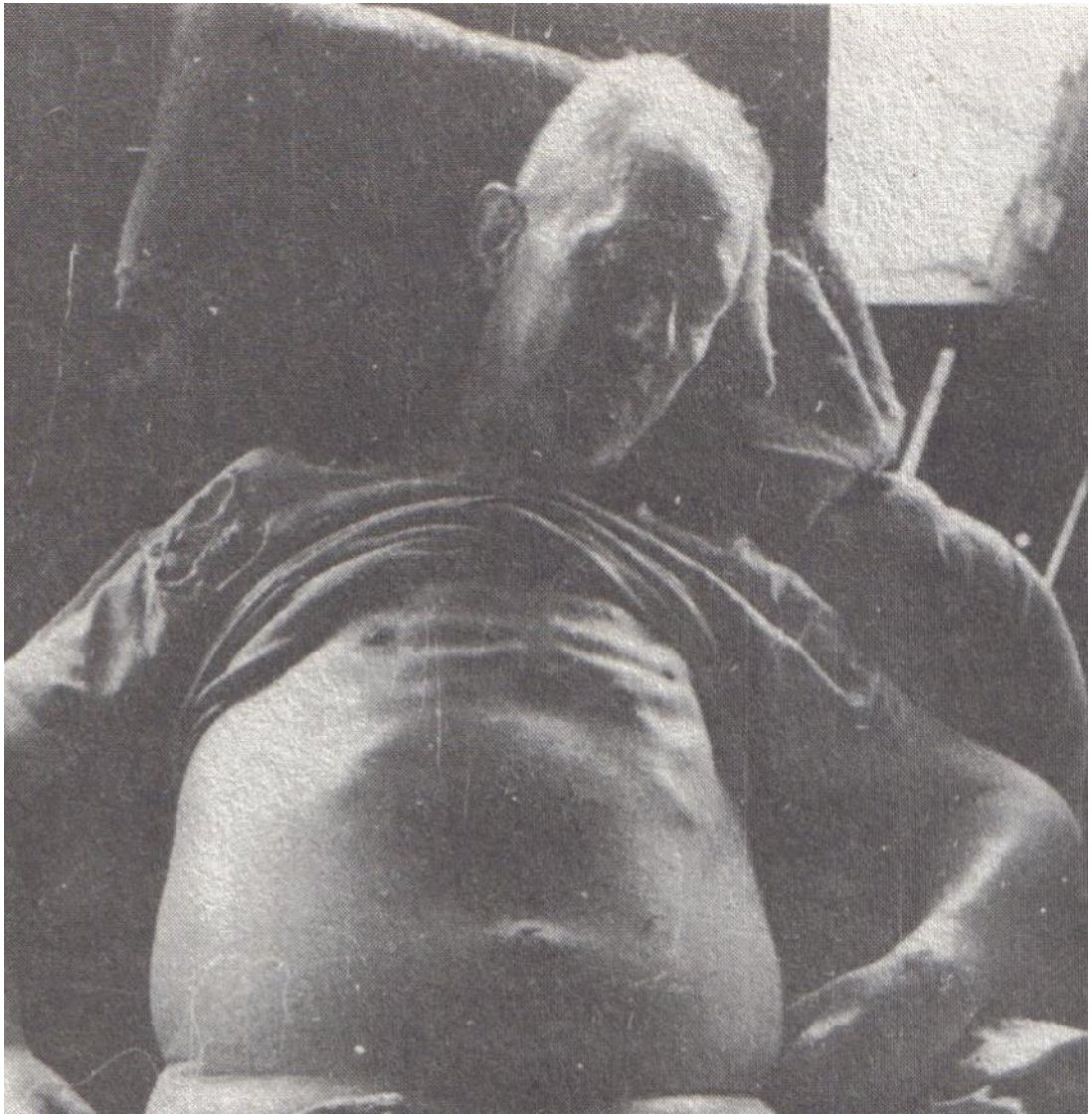


(1909–1988)



In 1979 he wrote, "It is surely a great criticism of our profession that we have not organised a critical summary, by specialty or subspecialty, adapted periodically, of all relevant randomised controlled trials."


Skopje
Tetovo
Blagoevgrad
Macedonia
(FYROM)
Strumica
Prilep
Durrës
Tirana
Kavajë
Struga
Albania
Ohrid
Bitola
Serrai
Drama
Kavala
Divjakë
Lushnjë
Fier
Berat
Korçë
Thessaloniki
Vlorë
Veroia
Kozani
Katerini
Gjirokastër
District
Sarandë
Kerkira
Ioannina
Larissa
Trikala
Igoumenitsa
Paramythia
Greece
Karditsa
Arta
Nea
Anchialos
Preveza
Lamia
Levkas
Agrinio
Nafpaktos
Aigio
Argostolion
SH 1
E79
E90
E75



Sickness in Salonica: my first, worst, and most successful clinical trial-1941.

". . . I recruited 20 young prisoners . . . I gave them a short talk about my medical hero James Lind and they agreed to co-operate in an experiment. I cleared two wards. I numbered the 20 prisoners off: odd numbers to one ward and evens to the other.

Each man in one ward received two spoonfuls of yeast daily. The others got one tablet of vitamin C from my "iron" reserve. The orderlies co-operated magnificently . . . They controlled fluid intake and measured frequency of urination.

. . . There was no difference between the wards for the first two days, but the third day was hopeful, and on the fourth the difference was conclusive . . . there was less oedema in the "yeast" ward. I made careful notes of the trial and immediately asked to see the Germans."

A. L. Cochrane (Br Med J 1984; 289: 1726-7)

“It could be argued that the trial was randomised and controlled, although this last was somewhat inadequate. In those early days, when the randomised controlled trial was little known in medicine, this was something of an achievement.”

BRITISH MEDICAL JOURNAL

LONDON SATURDAY OCTOBER 30 1948

STREPTOMYCIN TREATMENT OF PULMONARY TUBERCULOSIS

A MEDICAL RESEARCH COUNCIL INVESTIGATION

The following gives the short-term results of a controlled investigation into the effects of streptomycin on one type of pulmonary tuberculosis. The inquiry was planned and directed by the Streptomycin in Tuberculosis Trials Committee, composed of the following members: Dr. Geoffrey Marshall (chairman), Professor J. W. S. Blacklock, Professor C. Cameron, Professor N. B. Capon, Dr. R. Cruickshank, Professor J. H. Gaddum, Dr. F. R. G. Heaf, Professor A. Bradford Hill, Dr. L. E. Houghton, Dr. J. Clifford Hoyle, Professor H. Raistrick, Dr. J. G. Scadding, Professor W. H. Tytler, Professor G. S. Wilson, and Dr. P. D'Arcy Hart (secretary). The centres at which the work was carried out and the specialists in charge of patients and pathological work were as follows:

Brompton Hospital, London.—Clinician: Dr. J. W. Crofton, Streptomycin Registrar (working under the direction of the honorary staff of Brompton Hospital); Pathologists: Dr. J. W. Clegg, Dr. D. A. Mitchison.

Colindale Hospital (L.C.C.), London.—Clinicians: Dr. J. V. Hurford, Dr. B. J. Douglas Smith, Dr. W. E. Snell; Pathologists (Central Public Health Laboratory): Dr. G. B. Forbes, Dr. H. D. Holt.

Harefield Hospital (M.C.C.), Harefield, Middlesex.—Clinicians: Dr. R. H. Brent, Dr. L. E. Houghton; Pathologist: Dr. E. Nassau.

Bangour Hospital, Bangour, West Lothian.—Clinician: Dr. I. D. Ross; Pathologist: Dr. Isabella Purdie.

Killingbeck Hospital and Sanatorium, Leeds.—Clinicians: Dr. W. Santon Gilmour, Dr. A. M. Reevie; Pathologist: Professor J. W. McLeod.

Northern Hospital (L.C.C.), Winchmore Hill, London.—Clinicians: Dr. F. A. Nash, Dr. R. Shoulman; Pathologists: Dr. J. M. Alston, Dr. A. Mohun.

Sully Hospital, Sully, Glam.—Clinicians: Dr. D. M. E. Thomas, Dr. L. R. West; Pathologist: Professor W. H. Tytler.

The clinicians of the centres met periodically as a working subcommittee under the chairmanship of Dr. Geoffrey Marshall; so also did the pathologists under the chairmanship of Dr. R. Cruickshank. Dr. Marc Daniels, of the Council's scientific staff, was responsible for the clinical co-ordination of the trials, and he also prepared the report for the Committee, with assistance from Dr. D. A. Mitchison on the analysis of laboratory results. For the purpose of final analysis the radiological findings were assessed by a panel composed of Dr. L. G. Blair, Dr. Peter Kerley, and Dr. Geoffrey S. Todd.

Introduction

When a special committee of the Medical Research Council undertook in September, 1946, to plan clinical trials of streptomycin in tuberculosis the main problem faced was that of investigating the effect of the drug in pulmonary tuberculosis. This antibiotic had been discovered two years previously by Waksman (Schatz, Bugie, and Waksman, 1944); in the intervening period its power of inhibiting tubercle bacilli in vitro and the results of treatment in

if based on adequately controlled clinical trials (Hinshaw and Feldman, 1944). The one controlled trial of gold treatment (and the only report of an adequately controlled trial in tuberculosis we have been able to find in the literature) reported negative therapeutic results (Amberson, McMahon, and Pinner, 1931). In 1946 no controlled trial of streptomycin in pulmonary tuberculosis had been undertaken in the U.S.A. The Committee of the Medical Research Council decided then that a part of the small supply of streptomycin

What's so special about RCTs?

- most rigorous way of determining:
  - a cause-effect relation exists between treatment and outcome and
  - for assessing the cost effectiveness of a treatment
- distributing the characteristics of patients that may influence the outcome randomly between the groups-**no systematic differences between intervention groups**

What's so special about RCTs?

- patients and trialists should **remain unaware of which treatment was given** until the study is completed to avoid influencing the result
- **both arms treated identically** except for the intervention of interest – estimating the size of the difference in predefined outcomes between intervention groups

So are RCTs the gold standard for evidence?

…..depends

Limitations of RCTs

- Excellent vs Poor RCTs – quality varies
  - Impact on interpretation of result (external validity)?
- Expensive and time consuming
  - £250k - £millions over 2-5 years+
- May not always be the right study design to answer that question

A RCT to examine if smoking causes lung cancer

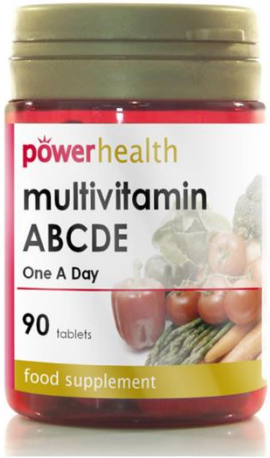
- 30 healthy Volunteers
- Randomise to 2 groups
  - Gp1 smokes 20 cigarettes per day every day
  - Gp2 no smoking

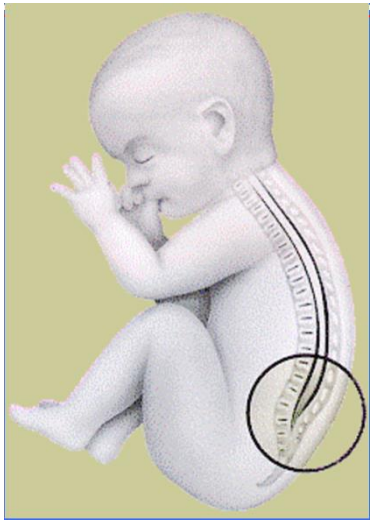
wellcome trust

NHS National Institute for Health Research

MRC Medical Research Council

Ethical issues and RCTs





THE LANCET, FEBRUARY 16, 1980

Preliminary Communication

POSSIBLE PREVENTION OF NEURAL-TUBE DEFECTS BY PERICONCEPTIONAL VITAMIN SUPPLEMENTATION

R. W. SMITHELLS S. SHEPPARD
C. J. SCHORAH
Department of Pædiatrics and Child Health, University of Leeds

M. J. SELLER
Pædiatric Research Unit, Guy's Hospital, London

N. C. NEVIN
Department of Medical Genetics, Queen's University of Belfast

R. HARRIS A. P. READ
Department of Medical Genetics, University of Manchester

D. W. FIELDING
Department of Pædiatrics, Chester Hospitals

Summary Women who had previously given birth to one or more infants with a neural-tube defect (NTD) were recruited into a trial of periconceptional multivitamin supplementation. 1 of 178 infants/fetuses of fully supplemented mothers (0·6%) had an NTD, compared with 13 of 260 infants/fetuses of unsupplemented mothers (5·0%).

British Journal of Obstetrics and Gynaecology
June 1984, Vol. 91, pp. 516–523

Neural-tube defects and vitamins: the need for a randomized clinical trial

NICHOLAS J. WALD *Professor, Department of Environmental and Preventive Medicine, Medical College of St Bartholomew's Hospital* & PAUL E. POLANI *Professor, Paediatric Research Unit, Guy's Medical School, London*

Summary. It has been suggested that taking extra vitamins around the time of conception may reduce the risk of fetal neural-tube defects. We have examined the evidence for this and conclude that there is considerable doubt about the efficacy of such a regimen. Also, it cannot be assumed that the taking of extra vitamins has no adverse medical effects. We give reasons for our view that a large randomized clinical trial is ethical and the only satisfactory way of resolving the matter. The Medical Research Council is currently conducting such a study in centres in Britain and abroad, involving women who have already had a pregnancy with a fetal neural-tube defect. The design of the Medical Research Council study is described briefly.

It has been claimed that the neural-tube defects, anencephaly and spina bifida, may be prevented by folic acid and other vitamin supplementation. The need for further studies designed to investigate this claim has been questioned (*Yorkshire Post* 1982; *The Guardian* 1982). It has been argued that the existing evidence is persuasive and it is therefore unethical to withhold vitamin supplementation from women known to be at risk of having a child with a neural-tube defect.

This has prompted us to review the evidence so far obtained. We have done this and conclude that, though suggestive, the evidence is so inconclusive that it does not justify offering extra vitamins to all women who are at risk.

been found to be lower on average among women who later gave birth to infants with neural-tube defects, than among controls. The quality of diet of women with affected infants has also been assessed and judged to be poor (Laurence *et al.* 1980). The blood vitamin and the dietary evidence is, however, only suggestive since it is relatively non-specific: deficiency of one nutrient is often correlated with deficiencies of other nutrients, as well as with non-nutritional factors such as quality of housing and the associated increased exposure to infection. There is also no suggestion that countries in which the average diet is likely to be lacking in vitamins have unusually high rates of neural-tube defect.

In-vitro experiments with whole embryo cultures have been used to study the effects of

Multivitamins for NTD?

- Original Smithells study open to possible bias
  - Women who were already “healthier” chose to take the multivitamin – self selecting population
- Could multivitamins cause harm?
  - High doses of vitamin A and D could be toxic
- Need to demonstrate what “active ingredient” is?

THE LANCET

Vol 338 Saturday 20 July 1991 No 8760

ORIGINAL ARTICLES

Prevention of neural tube defects: Results of the Medical Research Council Vitamin Study

MRC VITAMIN STUDY RESEARCH GROUP*

A randomised double-blind prevention trial with a factorial design was conducted at 33 centres in seven countries to determine whether supplementation with folic acid (one of the vitamins in the B group) or a mixture of seven other vitamins (A, D, B_1, B_2, B_6, C, and nicotinamide) around the time of conception can prevent neural tube defects (anencephaly, spina bifida, encephalocele). A total of 1817 women at high risk of having a pregnancy with a neural tube defect, because of a previous affected pregnancy, were allocated at random to one of four groups—namely, folic acid, other vitamins, both, or neither. 1195 had a completed pregnancy in which the fetus or infant was known to have or not have a neural tube defect; 27 of these had a known neural tube defect, 6 in the folic acid groups and 21 in the two other groups, a 72% protective effect (relative risk 0·28, 95% confidence interval 0·12–0·71). The other vitamins showed no significant protective effect (relative risk 0·80, 95% CI 0·32–1·72). There was no demonstrable harm from the folic acid supplementation, though the ability of the study to detect rare or slight adverse effects was limited. Folic acid supplementation starting before pregnancy can now be firmly recommended for all women who have had an affected pregnancy, and public health measures should be taken to ensure that the diet of all women who may bear children contains an adequate amount of folic acid.

supplementation might reduce the risk of a recurrence. In the first study,[3] which was not randomised, participating women were given a mixture of eight vitamins which included folic acid (0·36 mg/day), and women who were already pregnant or had declined to take part in the study served as controls. The risk of a recurrence in supplemented women was about one-seventh that in the unsupplemented women.

The second study was a small randomised trial of folic acid supplementation alone (4 mg/day).[4] It yielded inconclusive results when analysed according to randomly allocated treatment group (so avoiding bias), but when analysed after the transfer of women in the folic acid group who did not take their capsules to the control group (ie, ignoring the randomisation and so introducing the possibility of bias) the supplemented women had a significantly lower recurrence rate.

The lower recurrence rate in the supplemented women in these two studies is unlikely to have arisen purely by chance. Two explanations were possible. One is that folic acid or possibly the other vitamins can prevent some cases of neural tube defects. A second plausible explanation is that women who chose to take the vitamins represented a selected group, perhaps with a more affluent or health-conscious diet, who were therefore at low risk of having a further affected pregnancy. Indeed, it is likely that such selection was operating; however, it was not known whether there was also a genuine preventive effect, and, if so, its magnitude and whether the responsible component was folic acid or one of the other vitamins.

Neither further statistical analysis of the results of these studies nor the accumulation of further results without

- The MRC Vitamin Study showed that about 80% of neural tube defects could be prevented by taking 4 mg folic acid immediately before pregnancy

Issue date: March 2008

Quick reference guide

NHS
National Institute for
Health and Clinical Excellence

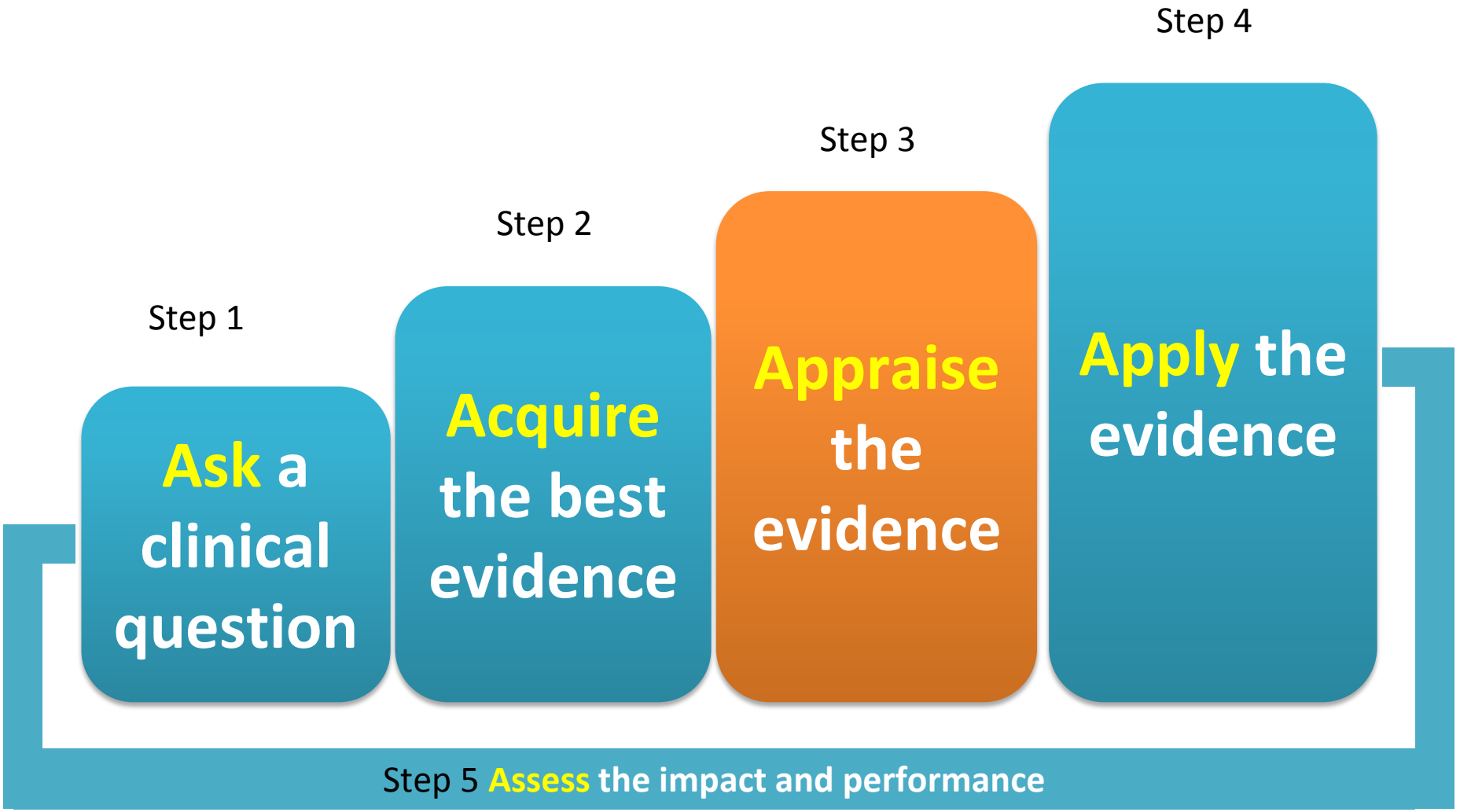
Maternal and child nutrition

July 2011

Recommendations in this guidance have been amended, see page 8 and www.nice.org.uk/guidance/PH11 for details.

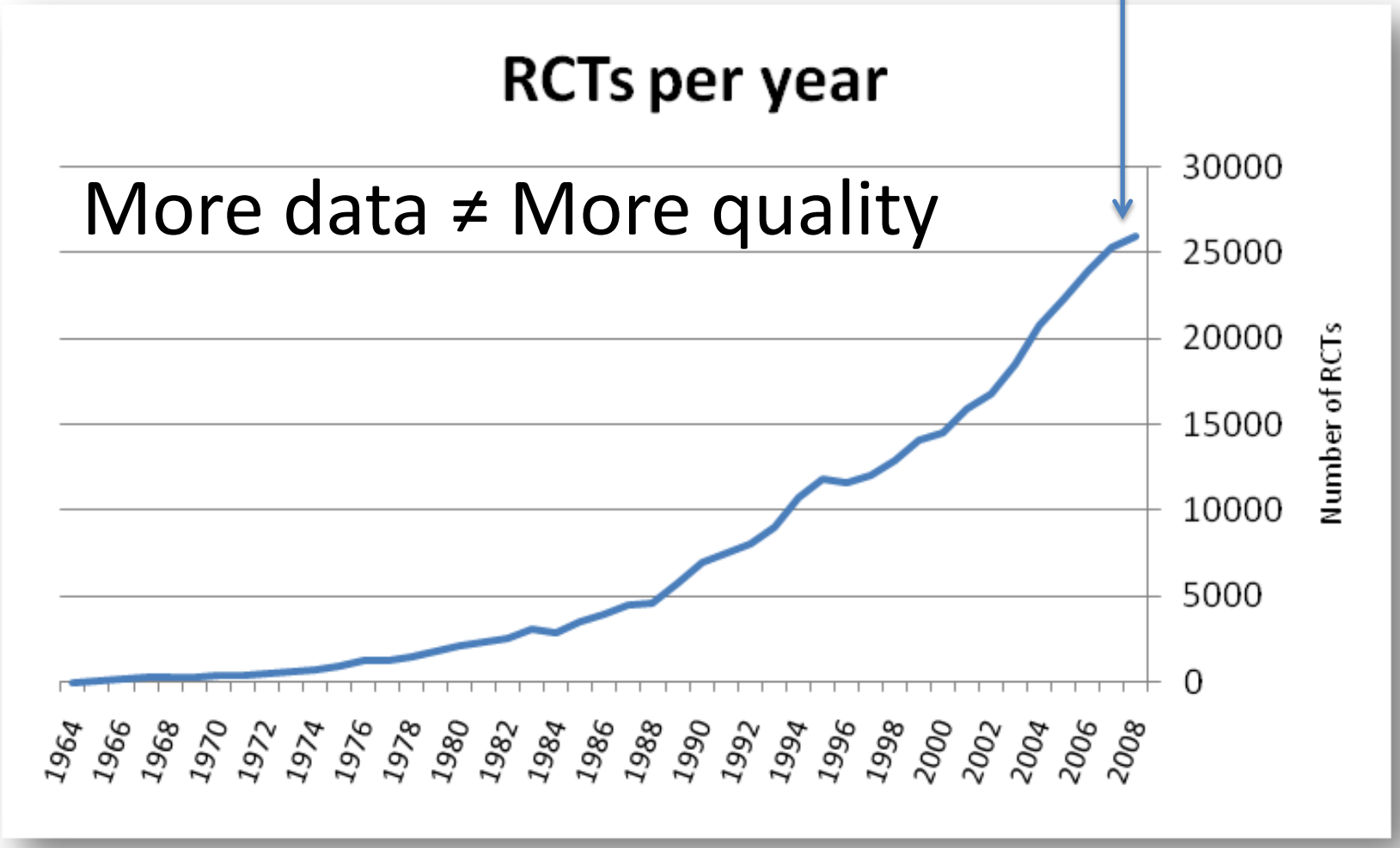
3.15 Folic acid supplements reduce the risk to the fetus of NTDs such as anencephaly and spina bifida. The DH recommends that women who could become pregnant or who are already pregnant take them daily (400 micrograms [µg]) before conception and throughout the first 12 weeks of pregnancy. Higher doses (5 mg daily) are recommended for those who have had a previous NTD pregnancy or who have a family history of NTD. Higher doses are also recommended for women who have (or whose partner may

use of best evidence – the 5 A's



How many randomized trials are published each year

you would have to read 500 RCTS per week in 2008 to cover the published RCTs in PubMed



Risk of Bias

The degree to which the result is skewed away from the truth

Validity of the study

Outside the study: **external** validity

Can the findings be applied to different settings
(e.g. your patient population)?

Inside the study:
internal validity

Was the study carried out correctly?

http://www.indiana.edu/~p1013447/dictionary/int_val.htm

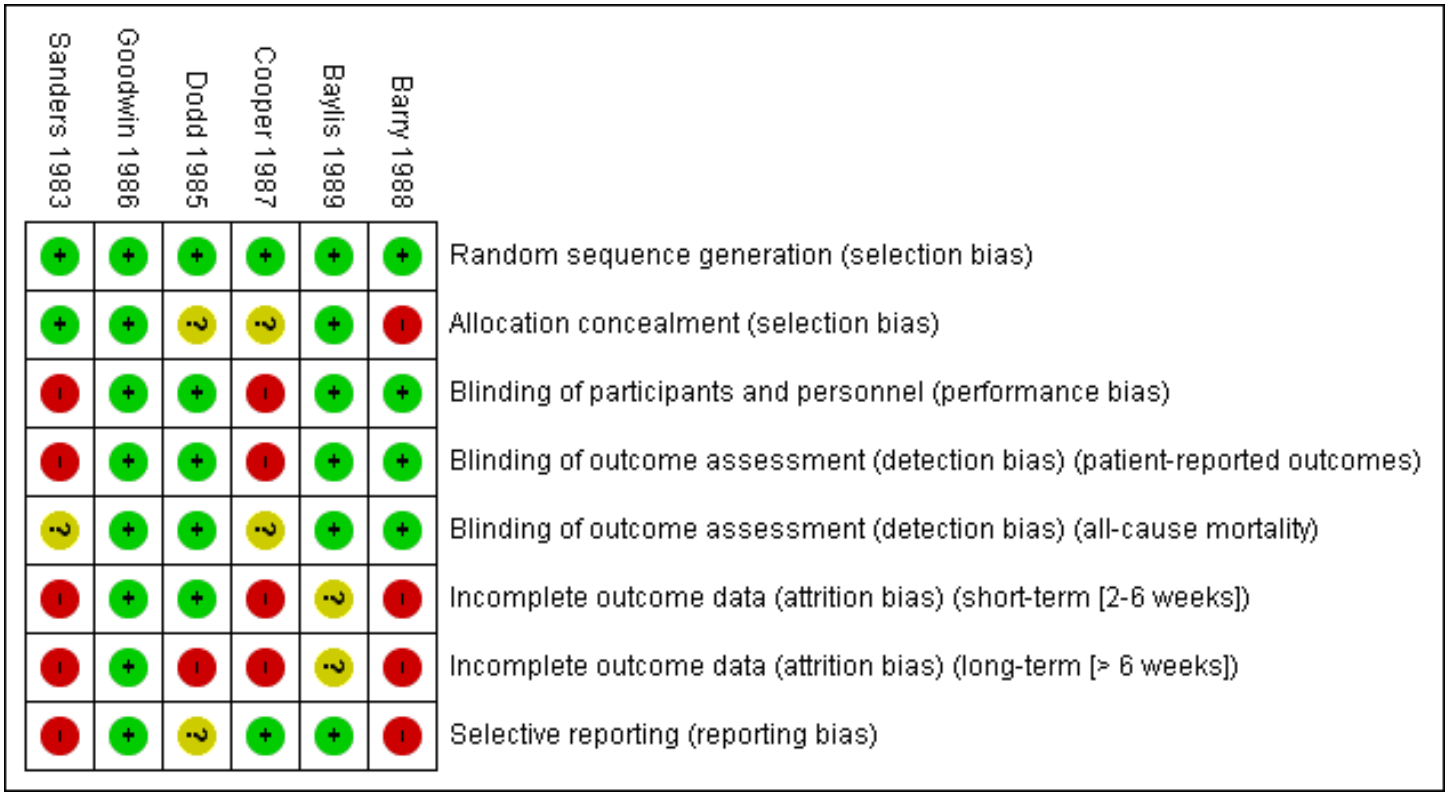
Internal validity

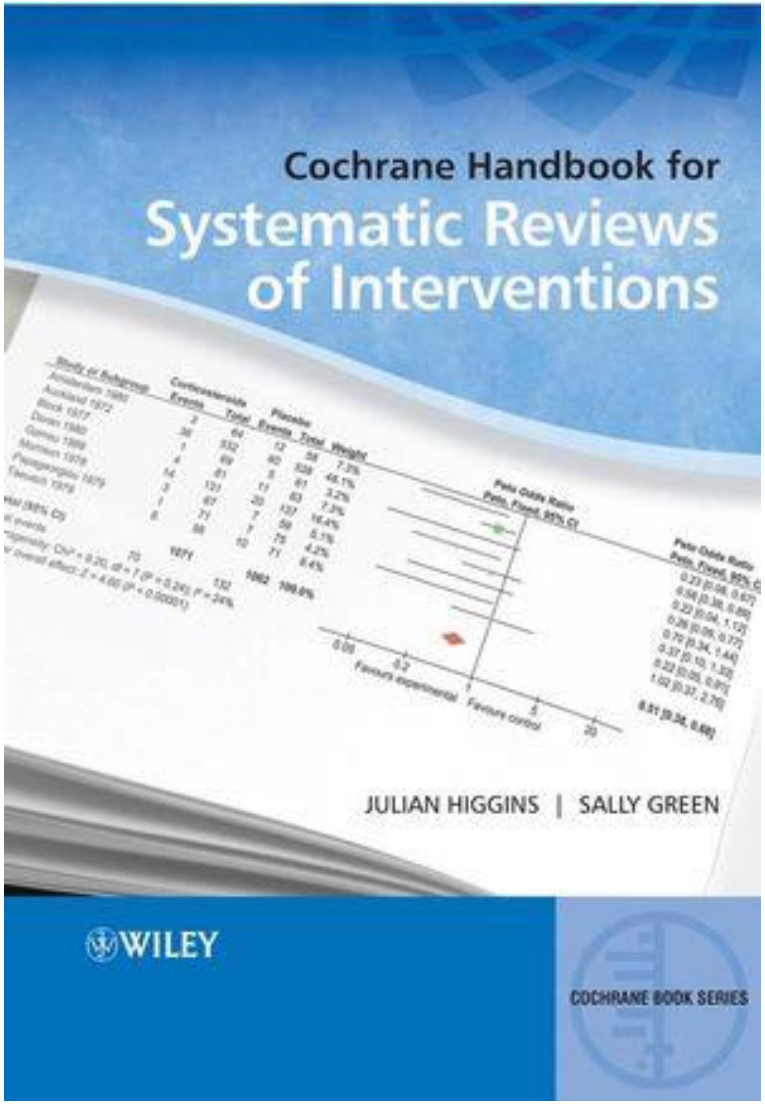
- extent to which observed treatment effects can be ascribed to differences in treatment and not confounding, thereby allowing the inference of causality to be ascribed to a treatment.[1]
- Systematic error (bias) could threaten the internal validity of trials, and all efforts should be made to minimise these in the design, conduct, and analysis of studies.[2]

1. http://www.bmj.com/content/344/bmj.e1004
2. http://www.ncbi.nlm.nih.gov/pubmed/18728521

Types of bias

Type of bias	Description
Selection bias	Systematic differences between baseline characteristics of the groups that are compared.
Performance bias	Systematic differences between groups in the care that is provided, or in exposure to factors other than the interventions of interest
Attrition bias	Systematic differences between groups in withdrawals from a study
Detection bias	Systematic differences between groups in how outcomes are determined
Reporting bias	Systematic differences between reported and unreported findings


Sanders 1983
Goodwin 1986
Dodd 1985
Cooper 1987
Baylis 1989
Barry 1988
Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias) (patient-reported outcomes)
Blinding of outcome assessment (detection bias) (all-cause mortality)
Incomplete outcome data (attrition bias) (short-term [2-6 weeks])
Incomplete outcome data (attrition bias) (long-term [> 6 weeks])
Selective reporting (reporting bias)



http://handbook.cochrane.org/front_page.htm

Assessing risk of bias for an RCT

- Recruitment
  - Were the subjects representative of the target population?
- Random Allocation
  - Were the groups comparable at the start?
- Maintenance
  - Were both groups treated the same bar the intervention
- Measurement
  - Unbiased (Blinded)
  - Objective
- What was the size of the effect?

JAMA The Journal of the American Medical Association

< Previous Article Next Article >

ARTICLE | February 1, 1995

Empirical Evidence of Bias

Dimensions of Methodological Quality Associated With Estimates of Treatment Effects in Controlled Trials

Kenneth F. Schulz, PhD, MBA; Iain Chalmers, MBBS, MSc; Richard J. Hayes, MSc; Douglas G. Altman

[+] Author Affiliations

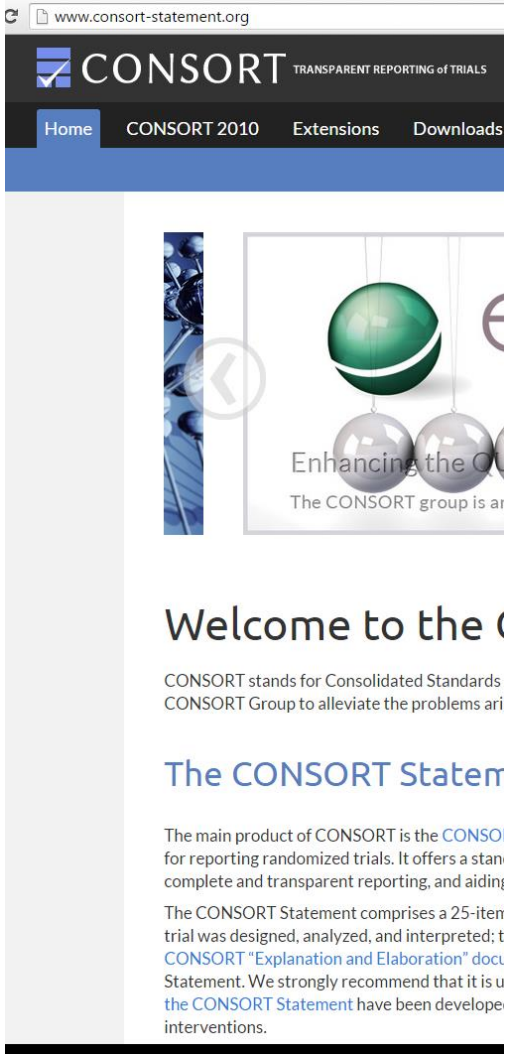
JAMA. 1995;273(5):408-412. doi:10.1001/jama.1995.03520290060030.

Results. —Compared with trials in which authors reported adequately concealed treatment allocation, trials in which concealment was either inadequate or unclear (did not report or incompletely reported a concealment approach) yielded larger estimates of treatment effects ($P<.001$). Odds ratios were exaggerated by 41% for inadequately concealed trials and by 30% for unclearly concealed trials (adjusted for other aspects of quality). Trials in which participants had been excluded after randomization did not yield larger estimates of effects, but that lack of association may be due to incomplete reporting. Trials that were not double-blind also yielded larger estimates of effects ($P=.01$), with odds ratios being exaggerated by 17%.

Main Outcome Measures. —The associations between estimates of treatment effects and inadequate allocation concealment, exclusions after randomization, and lack of double-blinding.

Results. —Compared with trials in which authors reported adequately concealed treatment allocation, trials in which concealment was either inadequate or unclear (did not report or incompletely reported a concealment approach) yielded larger estimates of treatment effects ($P<.001$). Odds ratios were exaggerated by 41% for inadequately concealed trials and by 30% for unclearly concealed trials (adjusted for other aspects of quality). Trials in which participants had been excluded after randomization did not yield larger estimates of effects, but that lack of association may be due to incomplete reporting. Trials that were not double-blind also yielded larger estimates of effects ($P=.01$), with odds ratios being exaggerated by 17%.

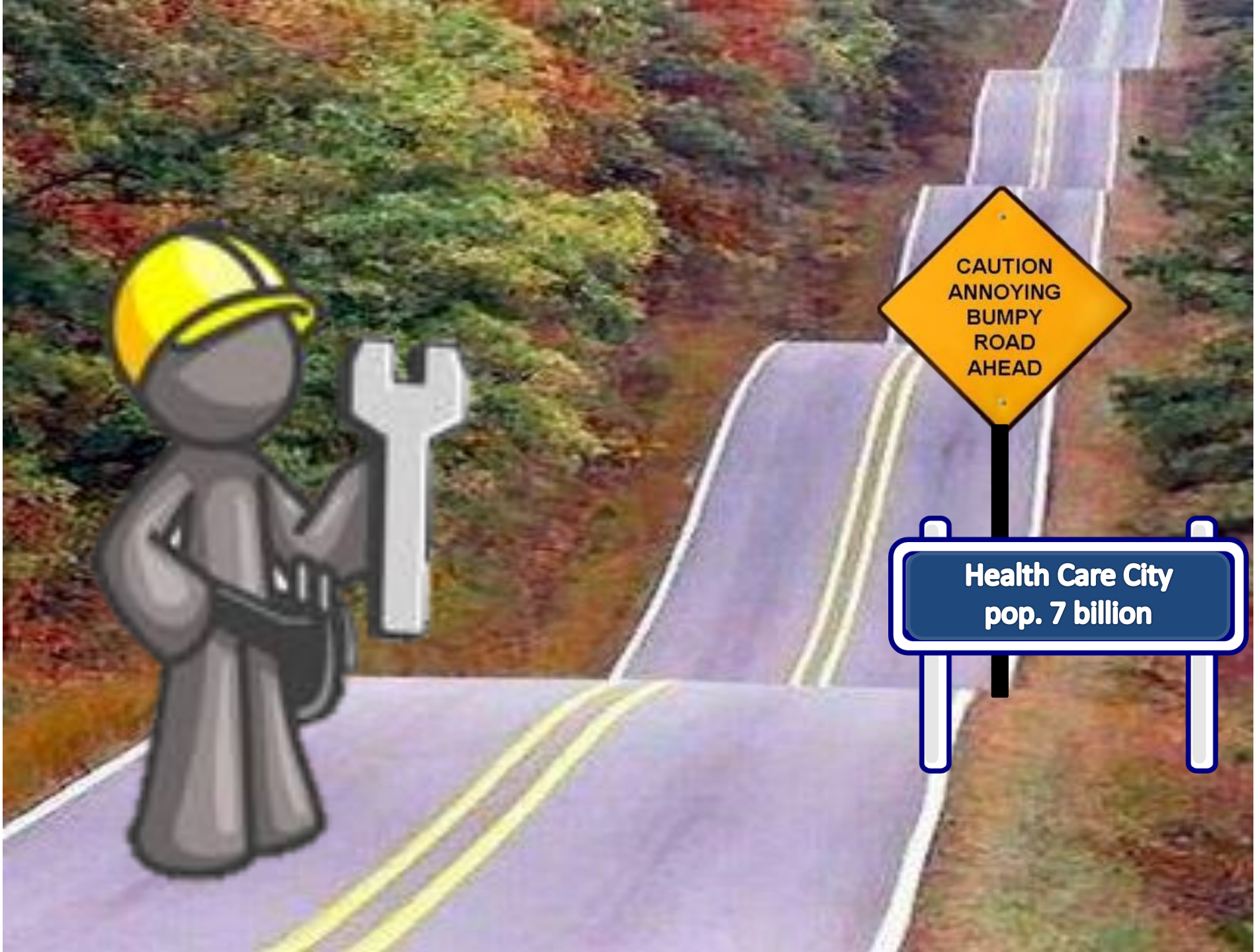
Conclusions. —This study provides empirical evidence that inadequate methodological approaches in



CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item
Title and abstract		
	1a	Identification as a randomised trial in the title
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts[21 31])
Introduction		
Background and objectives	2a	Scientific background and explanation of rationale
	2b	Specific objectives or hypotheses
Methods		
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons
Participants	4a	Eligibility criteria for participants
	4b	Settings and locations where the data were collected
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed
	6b	Any changes to trial outcomes after the trial commenced, with reasons
Sample size	7a	How sample size was determined
	7b	When applicable, explanation of any interim analyses and stopping guidelines
Randomisation:		
Sequence generation	8a	Method used to generate the random allocation sequence
	8b	Type of randomisation; details of any restriction (such as blocking and block size)
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how
	11b	If relevant, description of the similarity of interventions
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses
Results		
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome
	13b	For each group, losses and exclusions after randomisation, together with reasons
Recruitment	14a	Dates defining the periods of recruitment and follow-up
	14b	Why the trial ended or was stopped
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms[28])
Discussion		
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses
Generalisability	21	Generalisability (external validity, applicability) of the trial findings
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence
Other information		
Registration	23	Registration number and name of trial registry
Protocol	24	Where the full trial protocol can be accessed, if available
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders

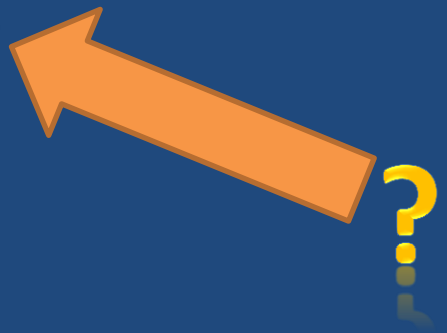
*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration[33] for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials,[11] non-inferiority and equivalence trials,[12] non-pharmacological treatments,[32] herbal interventions,[30] and pragmatic trials.[34] Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.


CAUTION
ANNOYING
BUMPY
ROAD
AHEAD
Health Care City
pop. 7 billion

What is evidence-based medicine?

Evidence-based medicine is the integration of:

- best research evidence
- clinical expertise
- patient values




EAST OXFORD HEALTH CENTRE

The £7 headset that can keep blood pressure low could help thousands of patients

- **Resperate device available on NHS for first time**

By SOPHIE BORLAND FOR THE DAILY MAIL
UPDATED: 00:42, 1 February 2012

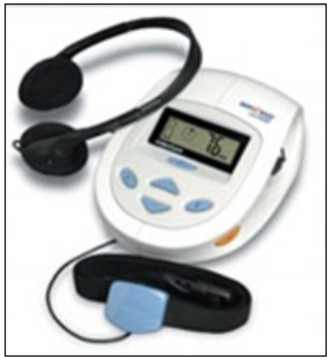
9 View comments

A gadget that controls high blood pressure will be available on the NHS for the first time.

The device – which looks like a portable CD player – slows down breathing by playing relaxing music through headphones.

Researchers claim it could help tens of thousands of patients control high blood pressure without having to take endless drugs with unpleasant side effects.

Called the Resperate, it works by first checking a patient's breathing via a strap tied around the chest. It then creates a tune and patients breathe in and out in time with certain notes.



Alternative to pills? The Resperate machine which controls blood pressure by slowing down breathing by playing relaxing music through headphones

The music then gradually slows down – as does the patients' breathing. From today, it will be available for GPs to prescribe to patients at a cost of £7.40 a time.

Experts are cautious and say it should not replace any high blood pressure drugs.

Maker Intercure, however, claims it has helped patients come off their medication.

Patients are advised to use the Resperate for at least 40 minutes a week – four sessions of ten minutes.

Risk: Around 16million Britons have high blood pressure, which can lead to heart attacks and strokes (posed by models)

The average person takes 18 breaths a minute, but to lower pressure you have to take ten or fewer – which is helped by the Resperate.

But experts point out there is no evidence to suggest it could replace medication.

A Blood Pressure Association spokesman said: 'As with any adjunct therapy, it must not be used as a replacement for any treatments prescribed by a GP.'

Around 16million Britons have high blood pressure. It can lead to heart attacks and strokes.

Many patients are able to control it through diet and exercise but others are forced to take a cocktail of drugs including ACE inhibitors, beta blockers and alpha blockers.

Some can have unpleasant side effects including swollen ankles, dizziness and tiredness.

RESPeRATE
TO LOWER BLOOD PRESSURE

Healthcare Professionals | Site map | About Us | LIVE HELP CHAT NOW | ORDER BY PHONE 0800-177-7778

HOME | HOW IT WORKS | REVIEWS | SUPPORT | BUY

LOWER YOUR BLOOD PRESSURE

Without Additional Medication

Clinically Proven, Doctor Recommended

See How It Works

Doctor Reviews

Get 10 Free Daily Tips to lower your blood pressure

Email SUBMIT Privacy Policy

In addition to 10 tips about lowering high blood pressure, you'll also receive occasional updates about RESPeRATE.

FREE Blood Pressure Monitor

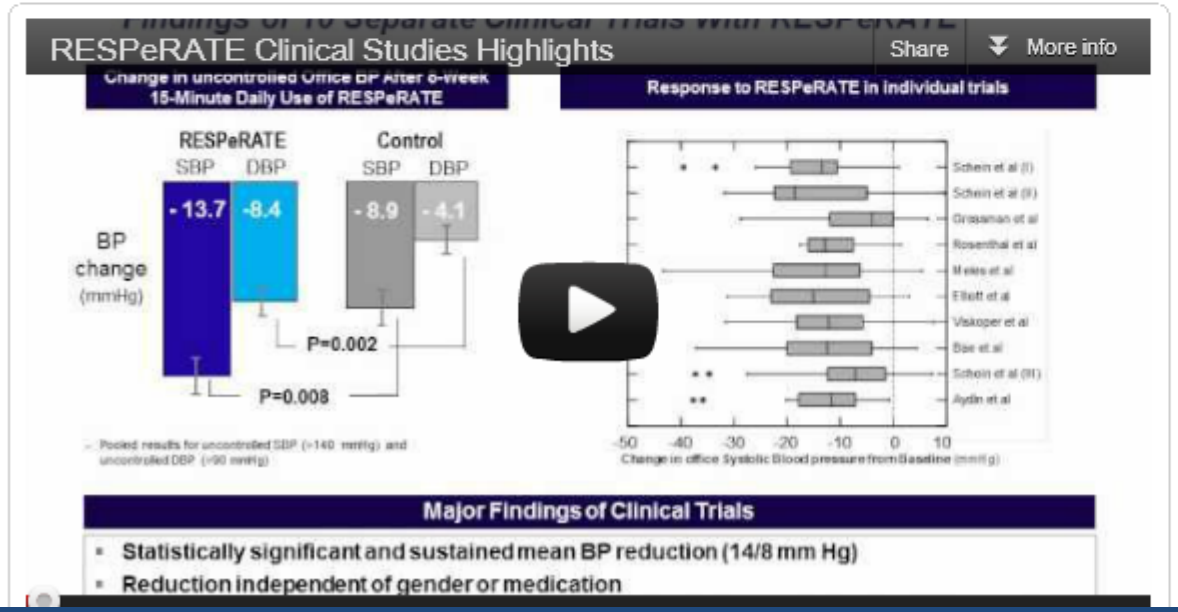
Get a FREE BP Monitor with RESPeRATE.
(While Supplies Last.)

LEARN MORE

Clinical Studies

Validated to Lower Blood Pressure in 10 Clinical Studies

- Ten clinical studies with peer-reviewed, published results have assessed the safety and efficiency of lowering high blood pressure in patients, whether taking medication or not.
- Over 200,000 users prior to NHS decision to include on UK's drug tariff.



Recent Publications

RESPeRATE: nonpharmacological treatment of hypertension. Cardiology in Review. 2011;19:47-51.

Impact of device-guided slow breathing on symptoms of chronic heart failure: a randomized, controlled feasibility study. European Journal of Heart Failure 2011;13:1000-1005.

Sympathetic nerve activity is decreased during device-guided slow breathing. Hypertension Research. 2010;33:708-712

Pooled characteristics of study patient population on enrollment

Pooled # of patients**		507
% Male		56%
Age (average)		57±11
Age in Years (%)	<40	4%
	40-60	54%

n/Resperate_873109/

Feedback | A-Z brands | Store locator | Help | Advantage Card

Boots

Prescriptions Basket
0 prescriptions

Basket
0 items 00.00
View Basket

My Account
Sign In or Register

Find
in All departments
Go

Pharmacy & Health | Beauty | Fragrance | Mother & Baby | Toiletries | Men | Electrical | Photo | Opticians | Toys | Gift | New | Offers

You are here: Home > Beauty > Electrical > Health Equipment > Tests & Monitors > Heart Rate Monitors > Resperate

Resperate 5669022

Write the First Review

Resperate a proven way to lower blood pressure - without side effects.

View full product information

Save 25% on Resperate

Collect 608 points with this purchase

£152.43

Save £50.81

Was £203.24

Sorry currently out of stock

Collect your order from store for free when you spend over £20

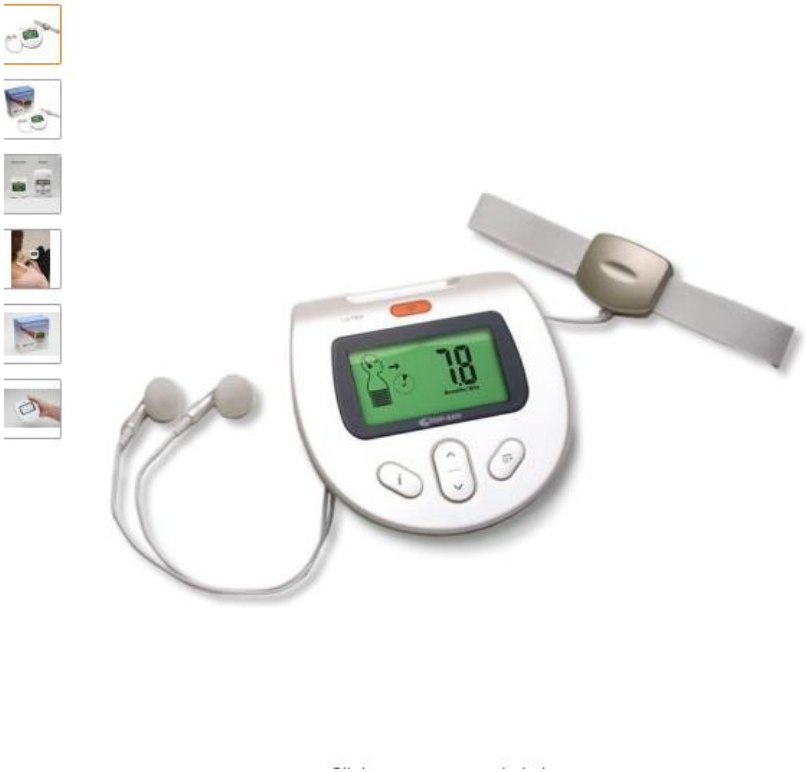
Free standard delivery in 4 working days

View full delivery information

Related categories

- Blood Glucose Monitors
- Blood Pressure Monitors
- Heart Rate Monitors
- Thermometers
- Home Test Kits

Add to Favourites | Add to Wishlist | Print this page | Email this page | SHARE | Like | One like. Sign Up to see what your friends like.



RESPeRATE To Lower Blood Pressure

by RESPeRATE

4.0 out of 5 stars 28 customer reviews | 3 answered questions

Price: £118.95 (£13.11 / 100 g) Prime

Only 9 left in stock.

Sold by Tower Health and Fulfilled by Amazon. Gift-wrap available.

Want it today, 29 June? Order it within **44 mins** and choose **Evening Delivery** at checkout. Details

8 new from £115.00

- Natural non-drug way to lower blood pressure
- Proven in 10 clinical trials
- Only Blood Pressure Lowering Device FDA Cleared and CE Approved to Lower Blood Pressure
- No Side Effects Associated with Medications
- Also indicated to manage stress

NHS Makes £200 Non-Drug Hypertension Treatment Device Available on Prescription

LONDON, February 1, 2012 /PRNewswire/ --

From today, an innovative non-drug, non-invasive treatment for high blood pressure will be made available to all hypertensive patients on NHS prescription. RESPeRATE is an interactive respiratory modulation device clinically-proven to lower blood pressure. When used for just 15 minutes a day, at least four times a week, RESPeRATE has demonstrated a significant, all-day blood pressure reduction beyond that seen with concurrent medication and lifestyle modification such as diet and exercise.

The NHS decision to make the £200 medical device available to patients on prescription [at the standard prescription charge of £7.40] is a clear reflection of the Department of Health's belief in RESPeRATE's potential as a new treatment option.

Dr Benjamin Gavish, inventor of RESPeRATE and Chief Scientist of InterCure (manufacturer of RESPeRATE), said: "We are delighted that patients in the UK can now obtain RESPeRATE on prescription. We hope that this pioneering move by the NHS to set up a new device category to supplement the currently available treatment options for hypertension will encourage GPs to integrate RESPeRATE into their hypertension standard of care."

High blood pressure affects over 16 million people in the UK and is the direct cause of half of all strokes and heart attacks in the country.
Failure to control blood pressure to target levels results in over 60,000 unnecessary deaths every year.
Despite many recent advances in the medical treatment of hypertension and public health campaigns aimed at highlighting awareness of the dangers of high blood pressure, it remains a significant public health problem in the UK.

RESPeRATE is most likely to be initially prescribed for patients aged 65+ with not-yet-at-target blood pressure - in spite of medication, those who have diabetes with hypertension and those who either refuse medication or suffer side effects with current medications. The good news is that there are no known contraindications for, and have been no adverse reactions to the use of RESPeRATE.

For patients who wish to self-pay, RESPeRATE is also available, at a cost of £200, direct from the manufacturer (http://www.resperate.co.uk) or through selected pharmacies.

About RESPeRATE®

- RESPeRATE is a non-drug, portable, battery operated, medical device clinically-proven to lower blood pressure.
- It consists of a small computerised control unit, a breathing sensor mounted on an adjustable strap for wrapping around the abdomen and a set of earphones.
- RESPeRATE enables patients to harness the power of therapeutic breathing, to reduce neural sympathetic activity to dilate constricted blood vessels which in turn helps to lower blood pressure - all patients have to do is breathe along with RESPeRATE.
- Its breathing sensor, placed on the upper abdomen, automatically analyses the patient's breathing pattern and in real-time creates a personalised melody composed of two distinct tones - one for inhalation, the other for exhalation - the 'guiding tones'.
- The patient simply listens to the melody through the headphones, and the body's natural tendency to follow external rhythms

www.ppa.org.uk/edt/May_2012/mindex.htm

NHS Electronic Drug Tariff

NHS Business Services Authority

Contents | Index | Search

resperate Go!

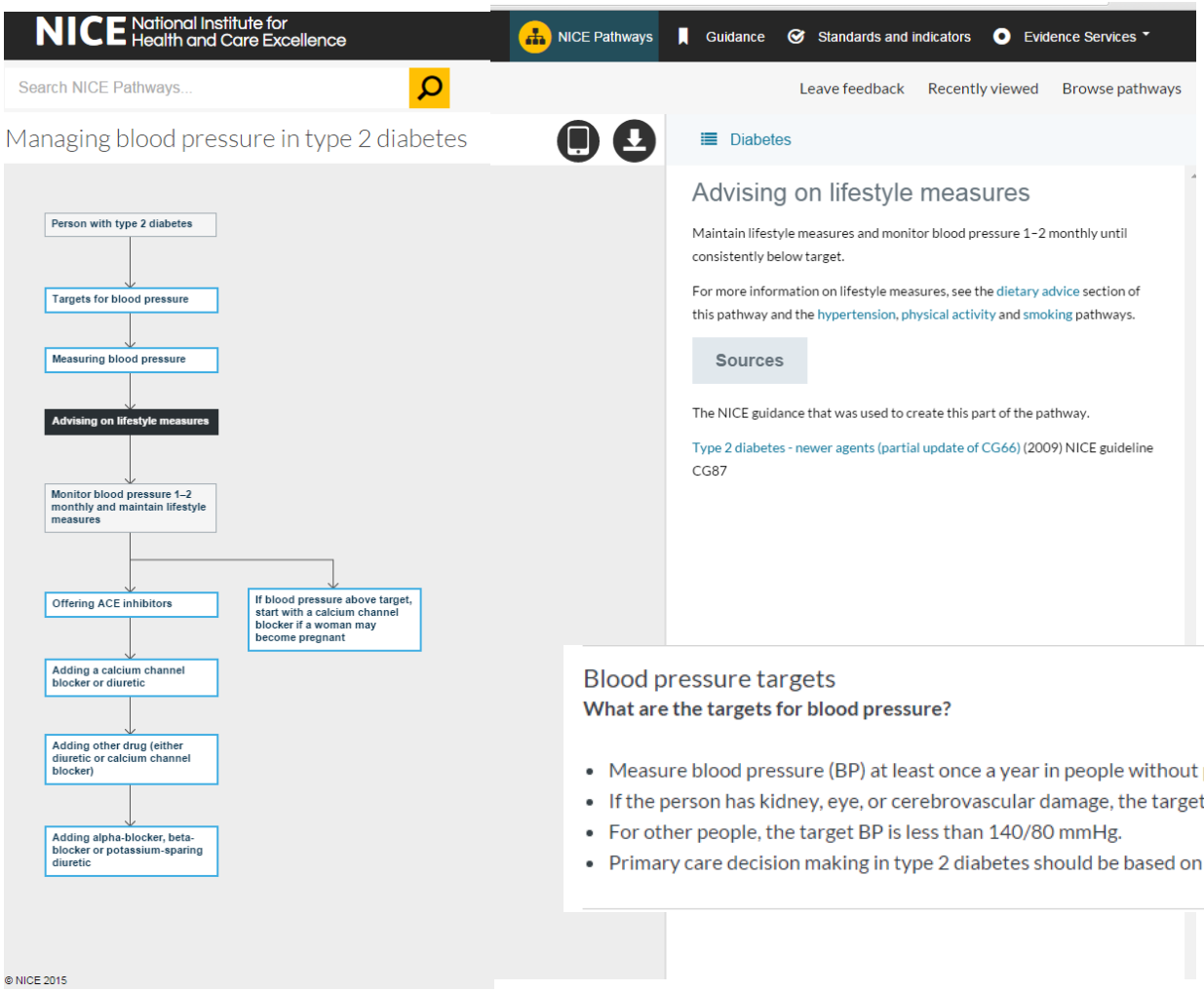
Rank Title

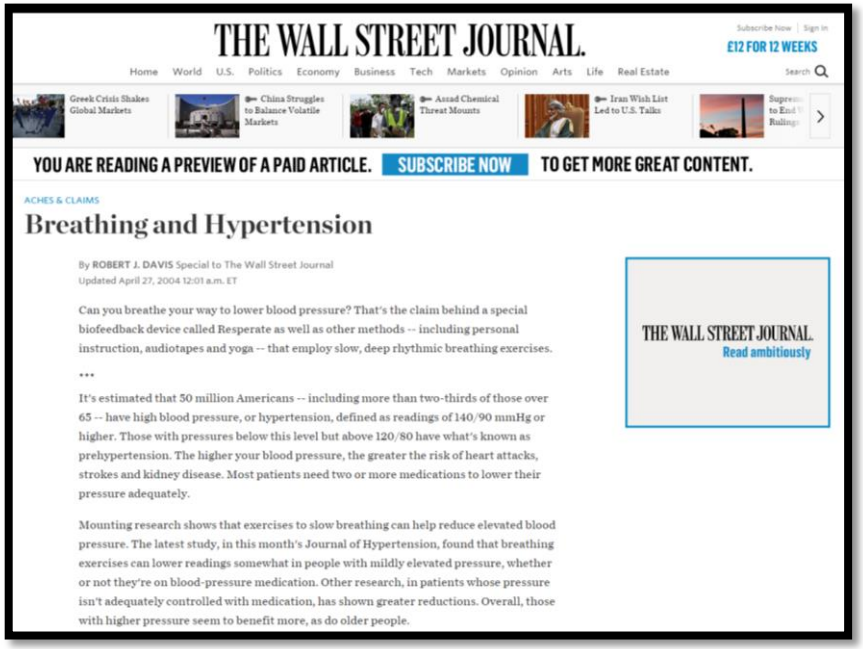
100. Part IXA-Appliances

Ortho All-Flex Diaphragm		
Arcing - Arcing Spring (Type C)	65-80mm (rising in 5mm)	835
		pack of 3
CYCLOIDAL VIBRATION ACCESSORIES		
Vibro-Pulse		1500
		each
DEVICES FOR ADJUNCTIVE TREATMENT OF HYPERTENSION		
RESPeRATE		13200
DOUCHES		
With Rectal and Vaginal fittings		
Plastic Douche - Rigid plastics container, with 2m approx. flexible plastics tubing, a tap and vulcanite or rigid plastics rectal pipe and plastics vaginal pipe.	1 litre approx	665
Spare Plastics Tubing	2m approx.	108

Where type not specified by the prescriber, plastics tubing to be supplied

Hypertension Management in T2DM





THE WALL STREET JOURNAL.

Subscribe Now | Sign In

£12 FOR 12 WEEKS

Home World U.S. Politics Economy Business Tech Markets Opinion Arts Life Real Estate

YOU ARE READING A PREVIEW OF A PAID ARTICLE. SUBSCRIBE NOW TO GET MORE GREAT CONTENT.

ACHES & CLAIMS

Breathing and Hypertension

By ROBERT J. DAVIS Special to The Wall Street Journal
Updated April 27, 2004 12:01 a.m. ET

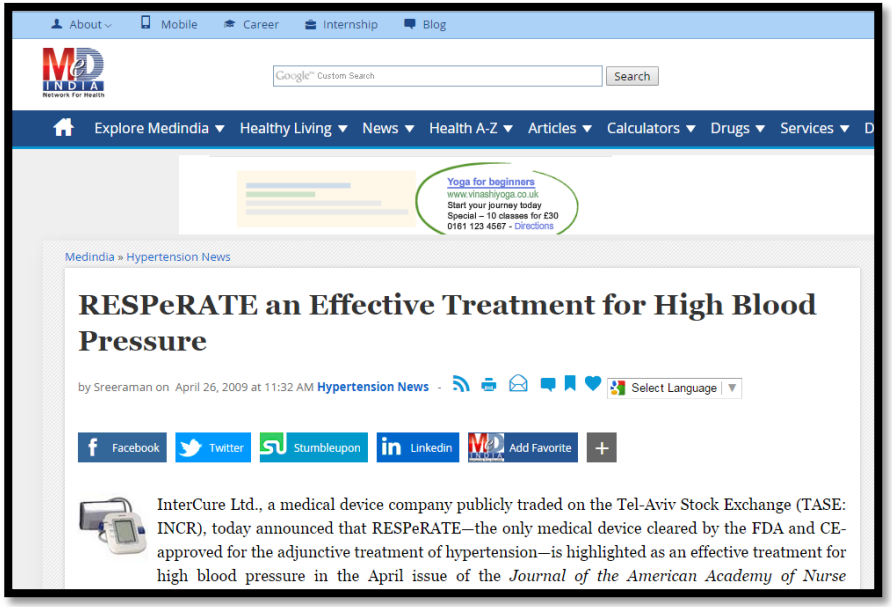
Can you breathe your way to lower blood pressure? That's the claim behind a special biofeedback device called Resperate as well as other methods -- including personal instruction, audiotapes and yoga -- that employ slow, deep rhythmic breathing exercises.

...

It's estimated that 50 million Americans -- including more than two-thirds of those over 65 -- have high blood pressure, or hypertension, defined as readings of 140/90 mmHg or higher. Those with pressures below this level but above 120/80 have what's known as prehypertension. The higher your blood pressure, the greater the risk of heart attacks, strokes and kidney disease. Most patients need two or more medications to lower their pressure adequately.

Mounting research shows that exercises to slow breathing can help reduce elevated blood pressure. The latest study, in this month's Journal of Hypertension, found that breathing exercises can lower readings somewhat in people with mildly elevated pressure, whether or not they're on blood-pressure medication. Other research, in patients whose pressure isn't adequately controlled with medication, has shown greater reductions. Overall, those with higher pressure seem to benefit more, as do older people.

THE WALL STREET JOURNAL.
Read ambitiously



About Mobile Career Internship Blog

MD INDIA Network For Health

Search

Explore Medindia Healthy Living News Health A-Z Articles Calculators Drugs Services

Yoga for beginners
www.vinashiyoga.co.uk
Start your journey today
Special – 10 classes for £30
0161 123 4567 - Directions

Medindia » Hypertension News

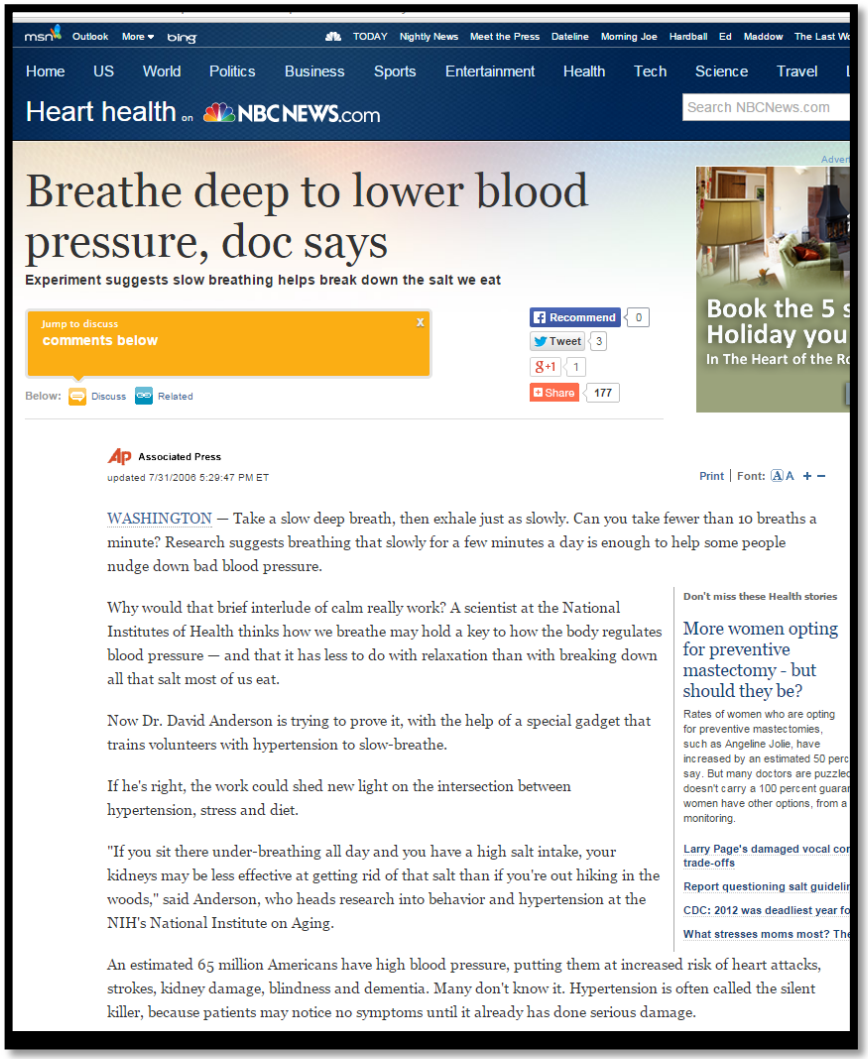
RESPeRATE an Effective Treatment for High Blood Pressure

by Sreeraman on April 26, 2009 at 11:32 AM Hypertension News

Select Language

Facebook Twitter Stumbleupon Linkedin Add Favorite

InterCure Ltd., a medical device company publicly traded on the Tel-Aviv Stock Exchange (TASE: INCR), today announced that RESPeRATE—the only medical device cleared by the FDA and CE-approved for the adjunctive treatment of hypertension—is highlighted as an effective treatment for high blood pressure in the April issue of the *Journal of the American Academy of Nurse*



msn Outlook More bing TODAY Nightly News Meet the Press Dateline Morning Joe Hardball Ed Maddow The Last W

Home US World Politics Business Sports Entertainment Health Tech Science Travel

Heart health on NBCNEWS.com

Search NBCNews.com

Breathe deep to lower blood pressure, doc says

Experiment suggests slow breathing helps break down the salt we eat

Jump to discuss
comments below

Below: Discuss Related

Recommend 0 Tweet 3 +1 1 Share 177

Book the 5 s
Holiday you
In The Heart of the Rc

AP Associated Press
updated 7/31/2006 5:29:47 PM ET

Print | Font: A A + –

WASHINGTON — Take a slow deep breath, then exhale just as slowly. Can you take fewer than 10 breaths a minute? Research suggests breathing that slowly for a few minutes a day is enough to help some people nudge down bad blood pressure.

Why would that brief interlude of calm really work? A scientist at the National Institutes of Health thinks how we breathe may hold a key to how the body regulates blood pressure — and that it has less to do with relaxation than with breaking down all that salt most of us eat.

Now Dr. David Anderson is trying to prove it, with the help of a special gadget that trains volunteers with hypertension to slow-breathe.

If he's right, the work could shed new light on the intersection between hypertension, stress and diet.

"If you sit there under-breathing all day and you have a high salt intake, your kidneys may be less effective at getting rid of that salt than if you're out hiking in the woods," said Anderson, who heads research into behavior and hypertension at the NIH's National Institute on Aging.

An estimated 65 million Americans have high blood pressure, putting them at increased risk of heart attacks, strokes, kidney damage, blindness and dementia. Many don't know it. Hypertension is often called the silent killer, because patients may notice no symptoms until it already has done serious damage.

Don't miss these Health stories

More women opting for preventive mastectomy - but should they be?

Rates of women who are opting for preventive mastectomies, such as Angeline Jolie, have increased by an estimated 50 perc say. But many doctors are puzzle doesn't carry a 100 percent guara women have other options, from a monitoring.

Larry Page's damaged vocal cor trade-offs

Report questioning salt guideli

CDC: 2012 was deadliest year fo

What stresses moms most? The

The £7 headset that can keep blood pressure low could help thousands of patients

- **Resperate device available on NHS for first time**

By SOPHIE BORLAND FOR THE DAILY MAIL
UPDATED: 00:42, 1 February 2012

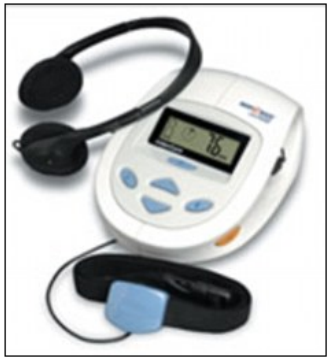
9 View comments

A gadget that controls high blood pressure will be available on the NHS for the first time.

The device – which looks like a portable CD player – slows down breathing by playing relaxing music through headphones.

Researchers claim it could help tens of thousands of patients control high blood pressure without having to take endless drugs with unpleasant side effects.

Called the Resperate, it works by first checking a patient's breathing via a strap tied around the chest. It then creates a tune and patients breathe in and out in time with certain notes.



Alternative to pills? The Resperate machine which controls blood pressure by slowing down breathing by playing relaxing music through headphones

The music then gradually slows down – as does the patients' breathing. From today, it will be available for GPs to prescribe to patients at a cost of £7.40 a time.

Experts are cautious and say it should not replace any high blood pressure drugs.

Maker Intercure, however, claims it has helped patients come off their medication.

Patients are advised to use the Resperate for at least 40 minutes a week – four sessions of ten minutes.

Risk: Around 16million Britons have high blood pressure, which can lead to heart attacks and strokes (posed by models)

The average person takes 18 breaths a minute, but to lower pressure you have to take ten or fewer – which is helped by the Resperate.

But experts point out there is no evidence to suggest it could replace medication.

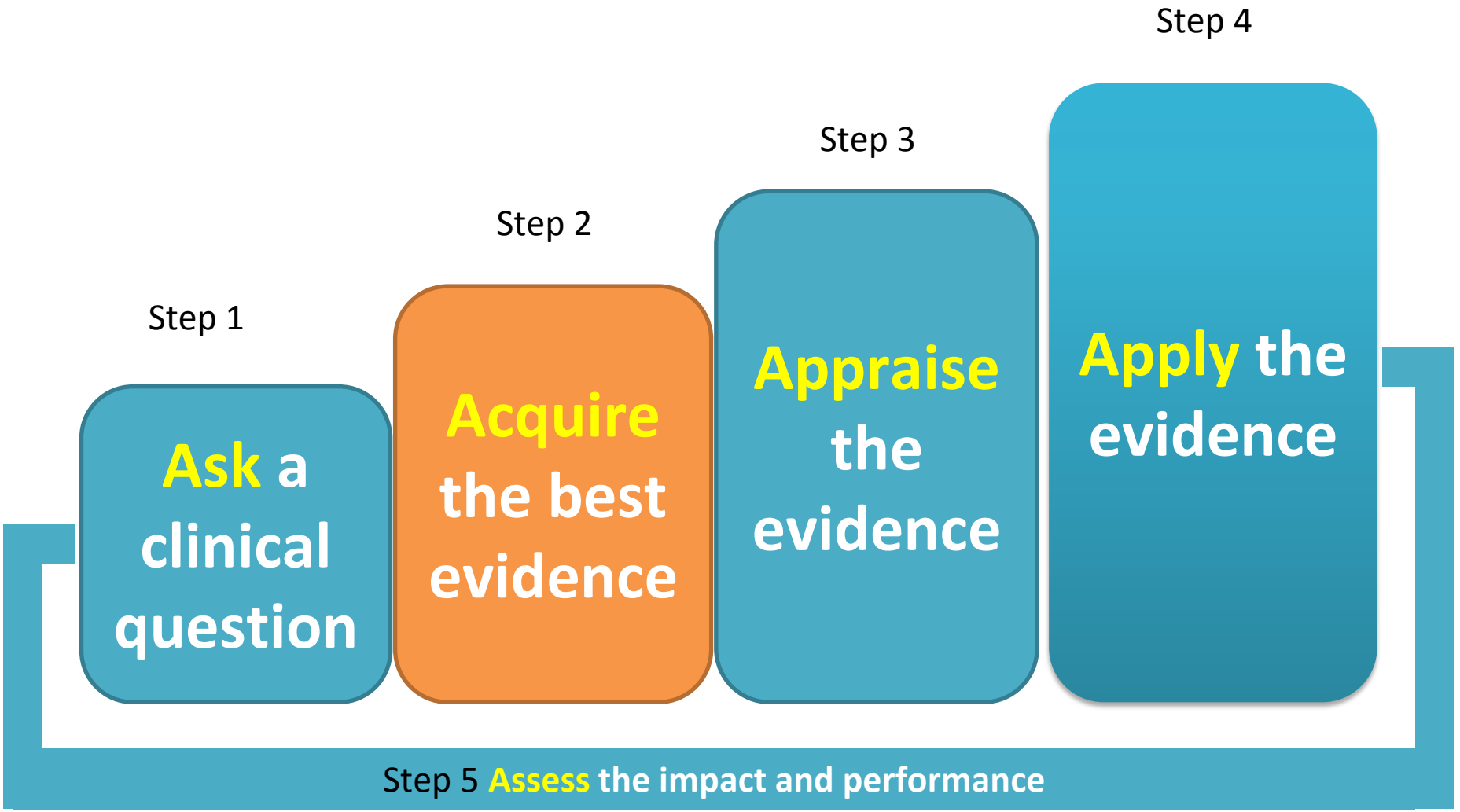
A Blood Pressure Association spokesman said: 'As with any adjunct therapy, it must not be used as a replacement for any treatments prescribed by a GP.'

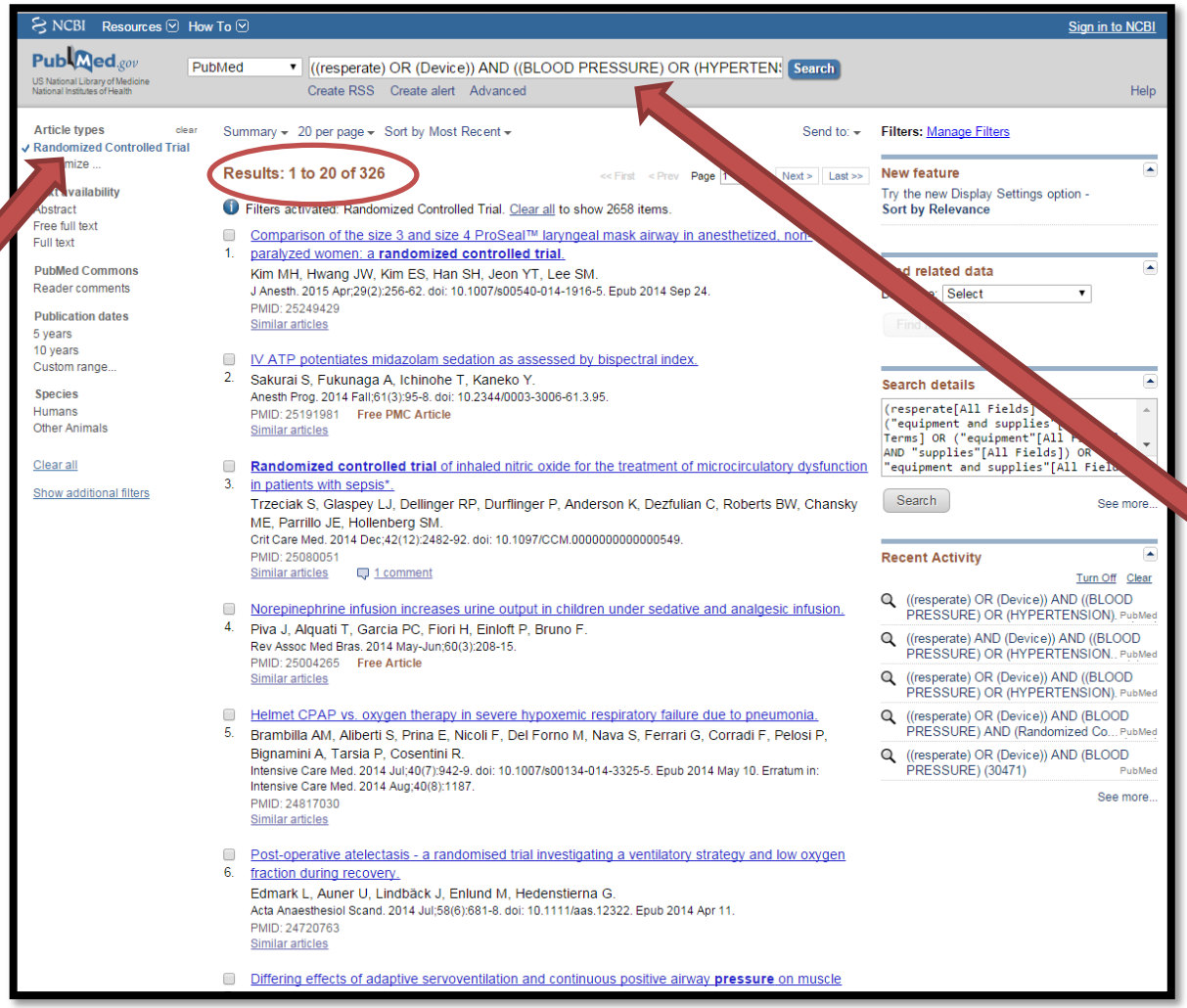
Around 16million Britons have high blood pressure. It can lead to heart attacks and strokes.

Many patients are able to control it through diet and exercise but others are forced to take a cocktail of drugs including ACE inhibitors, beta blockers and alpha blockers.

Some can have unpleasant side effects including swollen ankles, dizziness and tiredness.

use of best evidence – the 5 A's





((RESPERATE) OR (Device)) AND ((BLOOD PRESSURE) OR (HYPERTENSION)) AND (BREATHING)

PICO

Effect of device-guided breathing exercises on blood pressure in hypertensive patients with type 2 diabetes mellitus: a randomized controlled trial

Susan J. Logtenberg[a], Nanne Kleefstra[a,b], Sebastiaan T. Houweling[b], Klaas H. Groenier[c] and Henk J. Bilo[a,b]

Objective **In patients with type 2 diabetes mellitus (DM2), it is hard to reach treatment objectives for blood pressure (BP) with classical treatment options. Recently, reducing breathing frequency has been advocated as a method to reduce BP. We examined if an electronic device such as Resperate, by reducing breathing frequency, would lead to BP reduction in a population of patients with DM2 and hypertension. Our secondary objective was to study the effect of this device on quality of life (QOL).**

Methods **A randomized, single-blind, controlled trial was conducted over a period of 8 weeks to evaluate the effect of this therapy on BP and QOL. The control group listened to music and used no other therapeutic device. BP and QOL changes were studied in 30 patients with DM2 and hypertension.**

Results **There was no significant difference in change in BP between groups; −7.5 [95% confidence interval (CI) −12.7, −2.3]/−1.0 (95% CI −5.5, 3.6) mmHg in the intervention group and −12.2 (95% CI −17.4, −7.0)/−5.5 (95% CI −9.7, −1.4) mmHg in the control group. Whether or not the target breathing frequency of 10 breaths/min was reached did not affect BP. There were no significant changes in QOL.**

Conclusions **The effects of Resperate on BP and QOL were not significantly different from those found in the control group. Furthermore, 40% of patients did not reach the target breathing frequency, making this device less suitable for clinical practice in patients with DM2. *J Hypertens* 25:241–246 © 2007 Lippincott Williams & Wilkins.**

Journal of Hypertension 2007, 25:241–246

Keywords: breathing exercises, hypertension, music, quality of life, type 2 diabetes mellitus

[a]Department of Internal Medicine, Isala Clinics, Zwolle, [b]Langerhans Medical Research Group and [c]Department of General Practice, University Medical Centre Groningen, Groningen, The Netherlands

Correspondence and requests for reprints to Susan J.J. Logtenberg MD, Diabetes Outpatient Clinic, Isala Clinics, Sophia location, PO Box 10400, 8000 GK Zwolle, The Netherlands
Tel: +31 38 4244648; fax: +31 38 4243367; e-mail: s.j.j.logtenberg@isala.nl

Sponsorship: The Medical Research Foundation, Zwolle, The Netherlands, and the Langerhans Foundation provided financial and intellectual support.

Conflict of interest: none.

Received 27 January 2006 **Revised** 22 August 2006
Accepted 29 August 2006

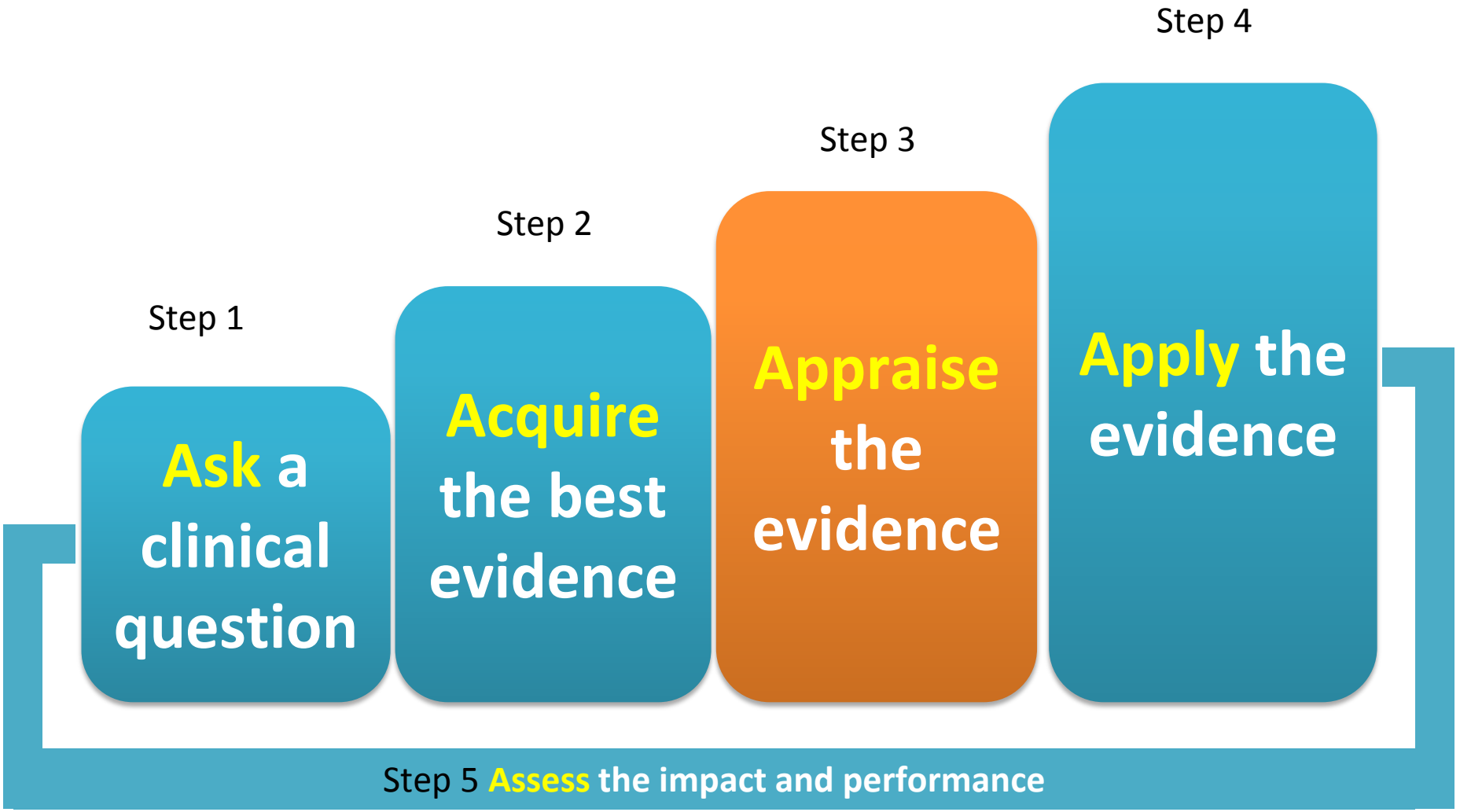
See editorial commentary on page 57

Introduction

Diabetes mellitus type 2 (DM2) and hypertension commonly occur together, with a higher prevalence of hypertension in patients with DM2 than in the general population [1]. Prevalence of hypertension in diabetes patients was 39% in the Hypertension in Diabetes Study (HDS) [1]. In The Netherlands a prevalence of hypertension in the general population (20–70 years) of 27% for men and 22% for women was found (this percentage includes persons taking antihypertensive drugs) [2].

The United Kingdom Prospective Diabetes Study (UKPDS) [illegible] blood pressure (BP) control regimens. The UKPDS showed that in patients with DM2 two or more antihypertensive drugs are often required to attain BP goals [3]. Recently, a new non-pharmacological treatment has been proposed, consisting of breathing exercises guided by an electronic device; the Resperate (InterCure Ltd, Lod, Israel) [5]. The exercises are said to be successful if breathing frequency is less than 10 breaths/min at the end of the exercise. Exercises should be done daily for 10–15 min [5–9]. The rationale behind this therapy is that slow and regular breathing increases the baroreflex sensitivity, which can reduce autonomic imbalance. Autonomic imbalance is thought to be an important factor in the development of hypertension [10].

use of best evidence – the 5 A's



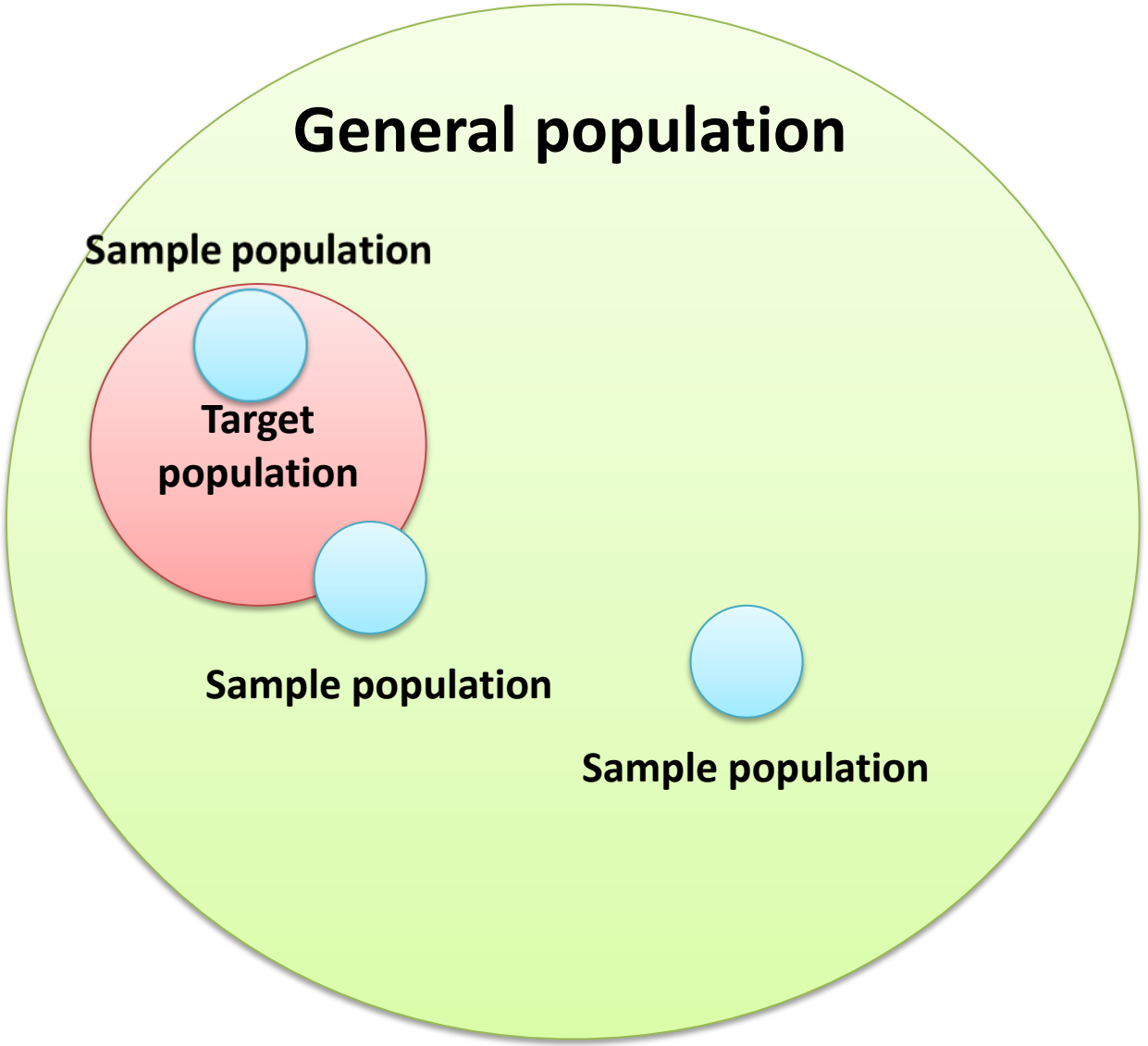
Risk of Bias

The degree to which the result is skewed away from the truth

Assessing risk of bias for an RCT

- Recruitment
  - Were the subjects representative of the target population?
- Random Allocation
  - Were the groups comparable at the start?
- Maintenance
  - Were both groups treated the same bar the intervention
- Measurement
  - Unbiased (Blinded)
  - Objective
- What was the size of the effect?

Recruitment (selection bias)

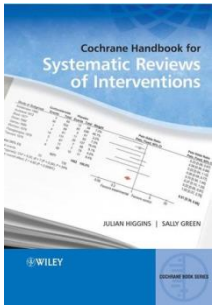


Recruitment (selection bias)

- Were the subjects representative of the target population?
  - What were the inclusion & exclusion criteria?
  - Were they appropriate?
  - How/where were they recruited from?

- Methods participants

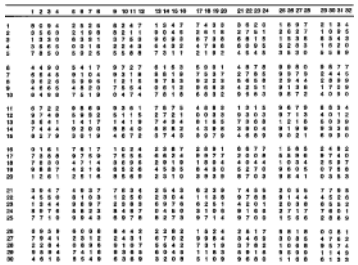
Selection bias



- systematic differences between baseline characteristics of the groups

- Adequate randomisation
  - 1) Sequence generation
  - 2) Allocation concealment

Randomisation (selection bias)



Allocation concealment

How was the randomised sequence implemented?

- patients and investigators enrolling patients cannot foresee assignment

BEST – most valid technique

- Central computer randomization

DOUBTFUL

- Envelopes, etc

Allocation (selection bias)

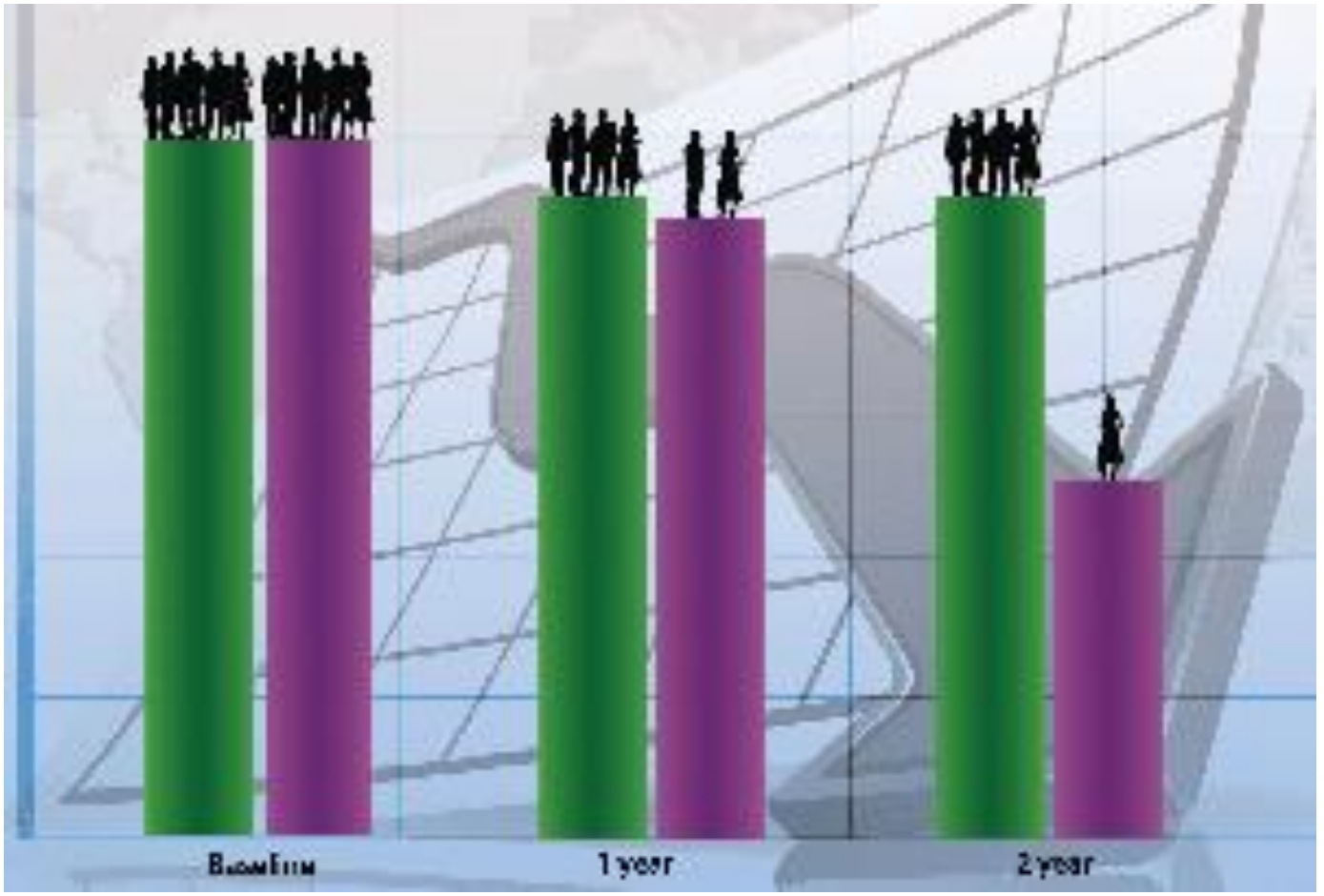
- Were the groups comparable at the start?
  - "Table 1"
- Randomised appropriately?
- Allocation to group concealed beforehand?

- Methods: Randomisation and study design and "Table 1"

Maintenance

- Were both groups comparable throughout the study?
  - Managed equally bar the intervention?
    - What was the intervention?
    - What was the comparator?
- Methods: study design, blood pressure measurement

Adequate follow up? (Attrition bias)



Intention to treat

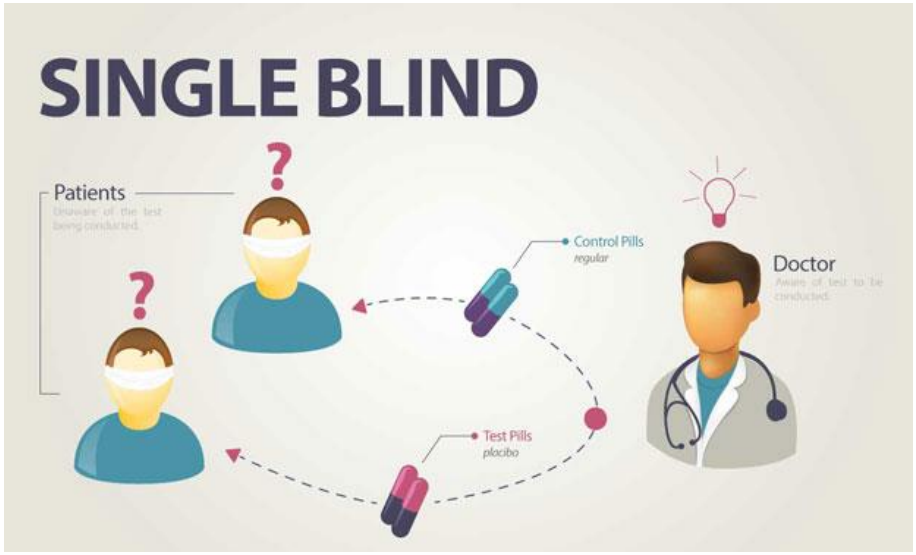
- Once a participant is randomised, they should be analysed to the group they were assigned to
- Pros
  - Maintains randomisation – prognostic factors balanced
  - Reflects “real life” e.g non compliance
  - Unbiased estimate of true effect
  - Maintains sample size thus maintaining statistical power
- Cons
  - Noncompliance provides little data on efficacy
  - Treatment effect may be conservative
  - Dropouts/non-compliant/compliant subjects are different

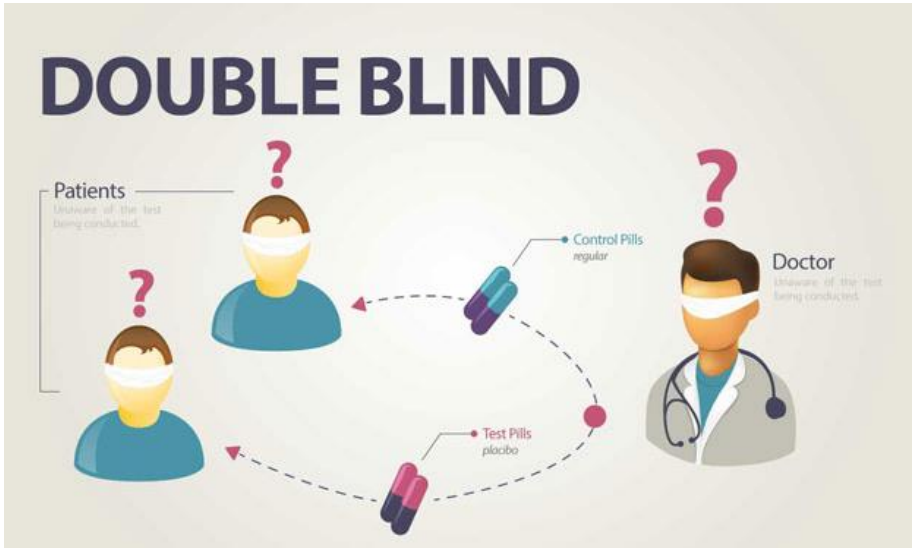
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3159210/

Adequate follow up? (Attrition bias)

- How many people were lost to f/u?
- Why were they lost to f/u?
- Did the researchers use an intention to treat (ITT) principle?
- Figure 1 and Statistical analysis

Measurement – blinding (Performance bias)





UNBLINDED

http://lc.gcumedia.com/hlt362v/the-visual-learner/the-visual-learner-v2.1.html

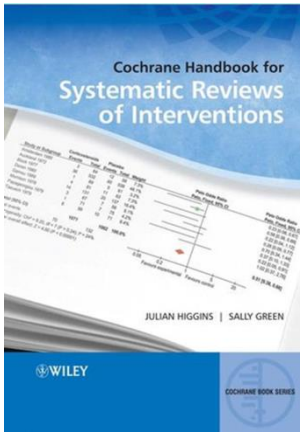
Box 8.11.a: A note on blinding in clinical trials

In general, blinding (sometimes called masking) refers to the process by which study participants, health providers and investigators, including people assessing outcomes, are kept unaware of intervention allocations after inclusion of participants into the study. Blinding may reduce the risk that knowledge of which intervention was received, rather than the intervention itself, affects outcomes and assessments of outcomes.

Different types of people can be blinded in a clinical trial (Gøtzsche 1996, Haahr 2006):

1. participants (e.g. patients or healthy people);
2. healthcare providers (e.g. the doctors or nurses responsible for care);
3. outcome assessors, including primary data collectors (e.g. interview staff responsible for measurement or collection of outcome data) and any secondary assessors (e.g. external outcome adjudication committees);
4. data analysts (e.g. statisticians); and
5. manuscript writers.

The first two type of people are addressed in the tool by the item 'Blinding of participants and personnel'. The third is addressed by the item 'Blinding of outcome assessment'. The last two are not explicitly covered by the tool.



"lack of blinding in randomized trials has been shown to be associated with more exaggerated estimated intervention effects, by **9%** on average, measured as odds ratio"

Measurement – blinding (Performance bias)

- Were the outcomes measured blindly by researchers and participants?

Statistical significance v Clinical significance

- Statistical significance implies that the difference seen in the sample also exists in the population
- Clinical significance implies that the difference between treatments in effectiveness is clinically important, and it is possible that clinical practice will change if such a difference is seen.
- Statistical significance is used to inform clinical significance.

Clinical significance versus statistical significance
BMJ 2014; 348 doi: http://dx.doi.org/10.1136/bmj.g2130 (Published 14 March 2014)

Measurement - outcomes

- What were the outcomes?
  - Primary
  - Secondary
  - Were they appropriate?
- How were the results reported?
- Were they significant?

Clinically meaningful BP difference

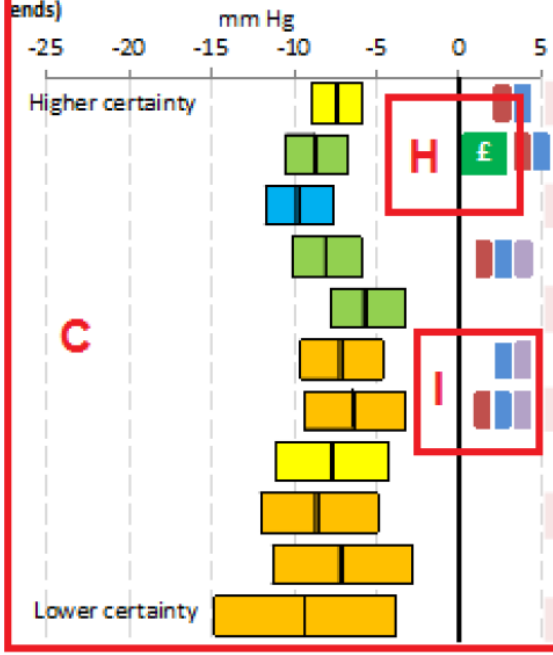
- Powered to detect a 10mmHg difference in SBP
- Reduction in BP by 5mmHg DBP
  - ↓stroke risk 34%
  - ↓IHD risk 21%
- But in all populations?
  - Elderly? – possible harm?
- Risks v benefits

http://www.ncbi.nlm.nih.gov/pubmed/14604498

Angiotensin Converting Enzyme (ACE) Inhibitors

A

This is EEP-1 and displays the effect of selected ACE inhibitors on systolic blood pressure. The performance of each drug is rated in terms of the certainty of its average effect and the quality of the evidence for the effect. B



Dose	Cost	Sample size	Duration
Lowest dose for treatment effects D	UK– Daily E	Participants (Studies) F	Mean follow up G
Trandolapril	1 mg/d	£0.26	1788 (10)	6 weeks
Enalapril	20 mg/d	£0.04	2808 (19)	6.5 weeks
Captopril	37.5 mg/d	£0.08*	1043 (6)	4.9 weeks
Lisinopril	10 mg/d	£0.02	841 (5)	6.5 weeks
Cilazapril	2.5 mg/d	£0.26	1502 (14)	5 weeks
Perindopril	4 mg/d	£0.31*	1054 (6)	4 weeks
Ramipril	5 mg/d	£0.06	747 (6)	7.1 weeks
Fosinopril	20 mg/d	£0.09	649 (6)	4 weeks
Moexipril	15 mg/d†	£0.25	433 (4)	6.6 weeks
Quinapril	Not estimable	£0.07§	196 (3)	5.6 weeks
Imidapril	Not estimable	£0.23#	162 (1)	6.0 weeks

£ = Best buy on performance and cost

Additional benefit in: = heart failure; = diabetes; = myocardial infarction

Outcomes

Table 2 Change in office measurements of blood pressure (BP) and heart rate after 8 weeks

	Treatment group			
	Intervention	Control	P^a	Difference between groups
Change in				
Systolic BP (mmHg)	−7.5 (−12.7, −2.3)	−12.2 (−17.4, −7.0)	0.86	4.7 (−11.7, 2.3)
Diastolic BP (mmHg)	−1.0 (−5.5, 3.6)	−5.5 (−9.7, −1.4)	0.94	4.6 (−10.4, 1.3)
Heart rate (bpm)	−1.7 (−6.3, 2.9)	−1.9 (−9.2, 5.4)	0.97	0.2 (−8.5, 8.1)

Values are mean (95% confidence interval). [a] *P* value of comparison between groups after 8 weeks.

Table 3 Change in home measurements of blood pressure (BP) and heart rate

	Treatment group			
	Intervention	Control	P^a	Difference between groups
Change in				
Systolic BP (mmHg)	−7.8 (−12.6, −3.0)	−8.8 (−14.1, −3.5)	0.77	−1.0 (−7.8, 5.8)
Diastolic BP (mmHg)	−3.3 (−6.7, 0.0)	−4.7 (−8.0, −1.3)	0.55	−1.3 (−5.8, 3.2)
Heart rate (bpm)	0.2 (−3.0, 3.4)	1.9 (−0.5, 4.3)	0.37	1.7 (−2.1, 5.5)

Values are mean (95% confidence interval). [a] *P* value of comparison between groups after 8 weeks.

Table 4 Change in quality of life (QOL) after 8 weeks

	Treatment group			
	Intervention	Control	P^a	Difference between groups
Change in QOL				
SF-12 PCS	−0.2 (−2.5, 2.2)	3.3 (−1.4, 8.0)	0.17	3.5 (−1.6, 8.5)
SF-12 MCS	1.2 (−2.7, 5.1)	1.4 (−3.8, 6.7)	0.94	0.2 (−6.0, 6.5)
PAID	−2.4 (−5.3, 0.5)	2.2 (−4.8, 9.3)	0.19	4.6 (−2.7, 12.1)
WHO-5	4.5 (−5.3, 14.4)	−4.0 (−19.6, 11.6)	0.33	8.5 (−26.2, 9.1)

Values are mean (95% confidence interval). SF-12, 12-item Short Form Health Survey; PCS, physical component score; MCS, mental component score; PAID, Problem Areas In Diabetes; WHO-5, World Health Organization Wellbeing Scale. [a] *P* value of comparison between groups after 8 weeks.

SF-12® Health Survey Scoring Demonstration

This survey asks for your views about your health. This information will help you keep track of how you feel and how well you are able to do your usual activities.

Answer every question by selecting the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

---

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
○	○	○	○	○

---

2. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	○	○	○
b Climbing several flights of stairs	○	○	○

---

3. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	Yes	No
a Accomplished less than you would like	○	○
b Were limited in the kind of work or other activities	○	○

---

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	Yes	No
a Accomplished less than you would like	○	○
b Did work or other activities less carefully than usual	○	○

---

5. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
○	○	○	○	○

---

6. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks...

Conclusions of the study

Discussion

This study shows that breathing exercises guided by an electronic device do not reduce BP in patients with DM2, as measured both in the clinic and at home, to a greater extent than listening to music on a Discman. We chose listening to music with a Discman as our control group to keep the interventions in both groups as similar as possible with the exception of the active lowering of breathing frequency in the intervention group.

External validity/applicability

Mail Online News

The £7 headset that can keep blood pressure low could help thousands of patients

- Resperate device available on NHS for first time

By SOPHIE BORLAND FOR THE DAILY MAIL

Share 9

A gadget that controls high blood pressure will be available on the NHS for the first time.

The device – which looks like a portable CD player – slows down breathing by playing relaxing music through headphones.

Researchers claim it could help tens of thousands of patients control high blood pressure without having to take endless drugs with unpleasant side effects.

Called the Resperate, it works by first checking a patient's breathing via a strap tied around the chest. It then creates a tune and patients breathe in and out in time with certain notes.

The music then gradually slows down – as does the patients' breathing. From today, it will be available for GPs to prescribe to patients at a cost of £7.40 a time.

Experts are cautious and say it should not replace any high blood pressure drugs.

Alternative to pills? The Resperate machine which controls blood pressure by slowing down breathing by playing relaxing music through headphones

Would you change your advice based on this study?

Summary

- RCTs provide an opportunity to deliver answers to the effects if interventions and harms
- May not be the best study design
- Quality of trial conduct and reporting in minimising risk of bias
- Critical appraisal assess this
- Application (external validity) based on your interpretation of results

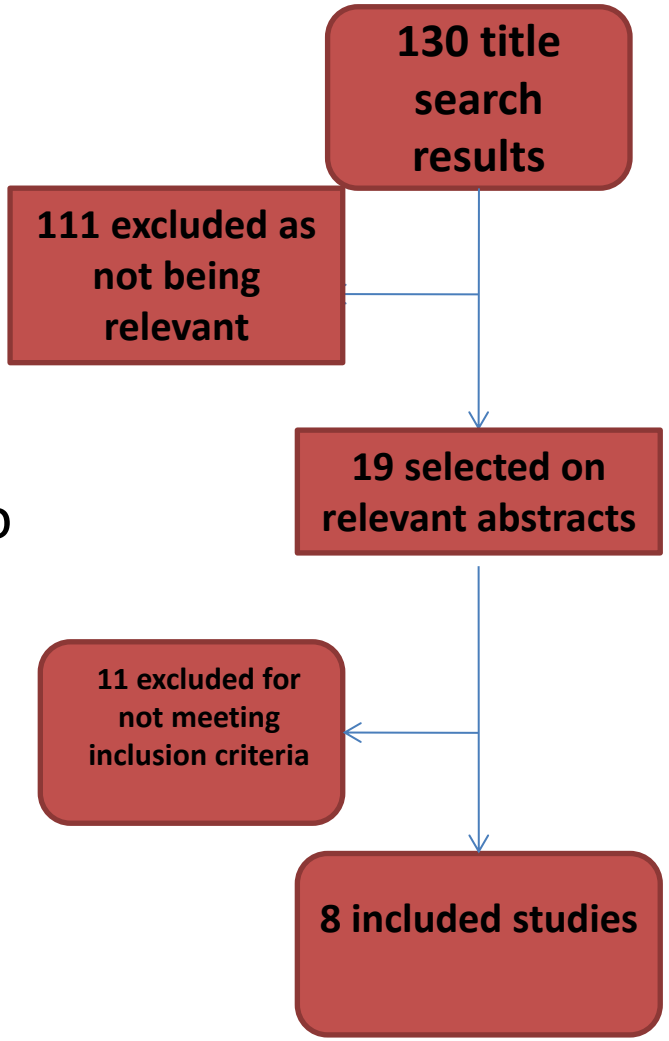
kamal.mahtani@phc.ox.ac.uk

@krmahtani

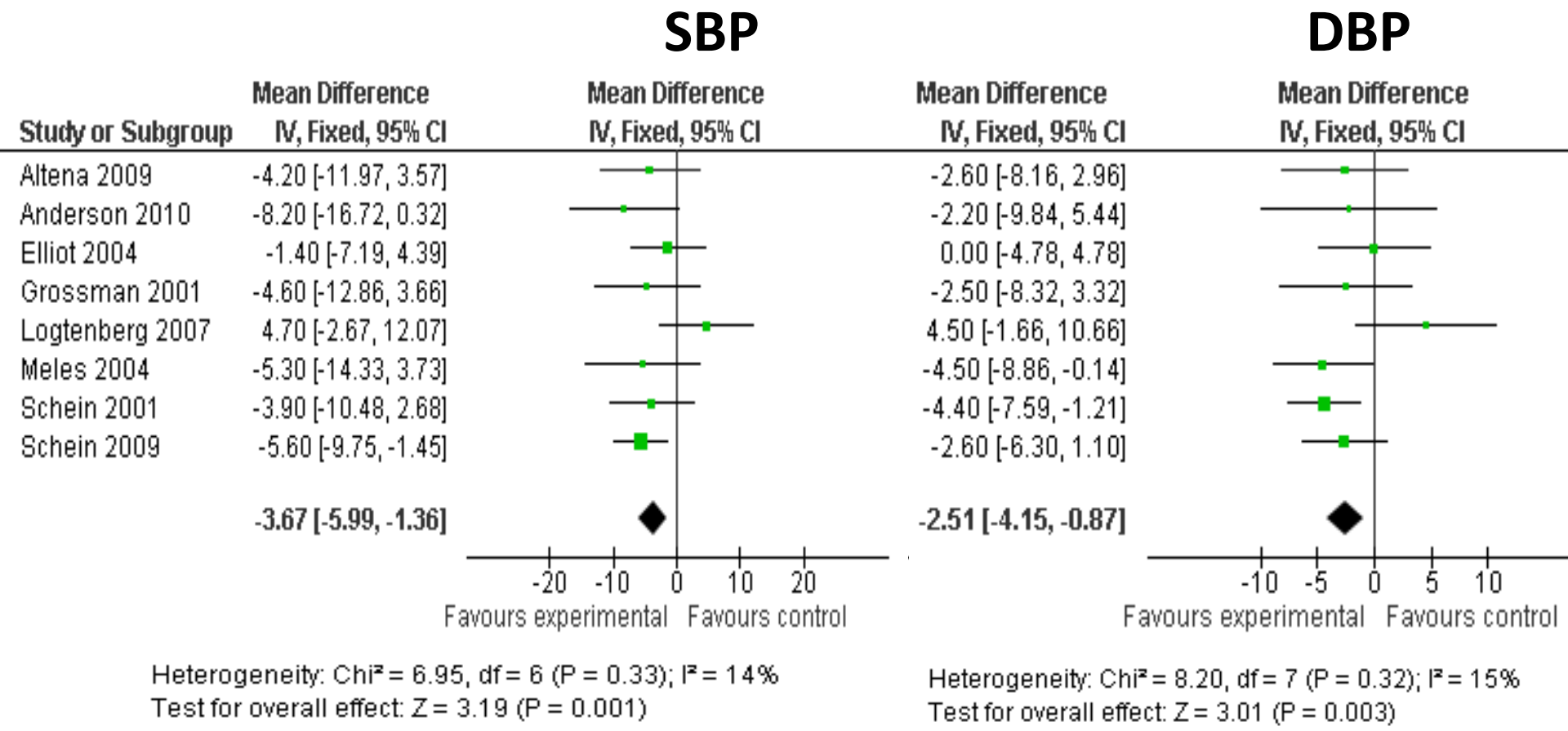
Systematic review: does device guided breathing lower blood pressure?

Inclusion Criteria

- RCTs
- Slow breathing rate device compared to placebo
- adults >18 yrs
- 4 or more weeks of treatment



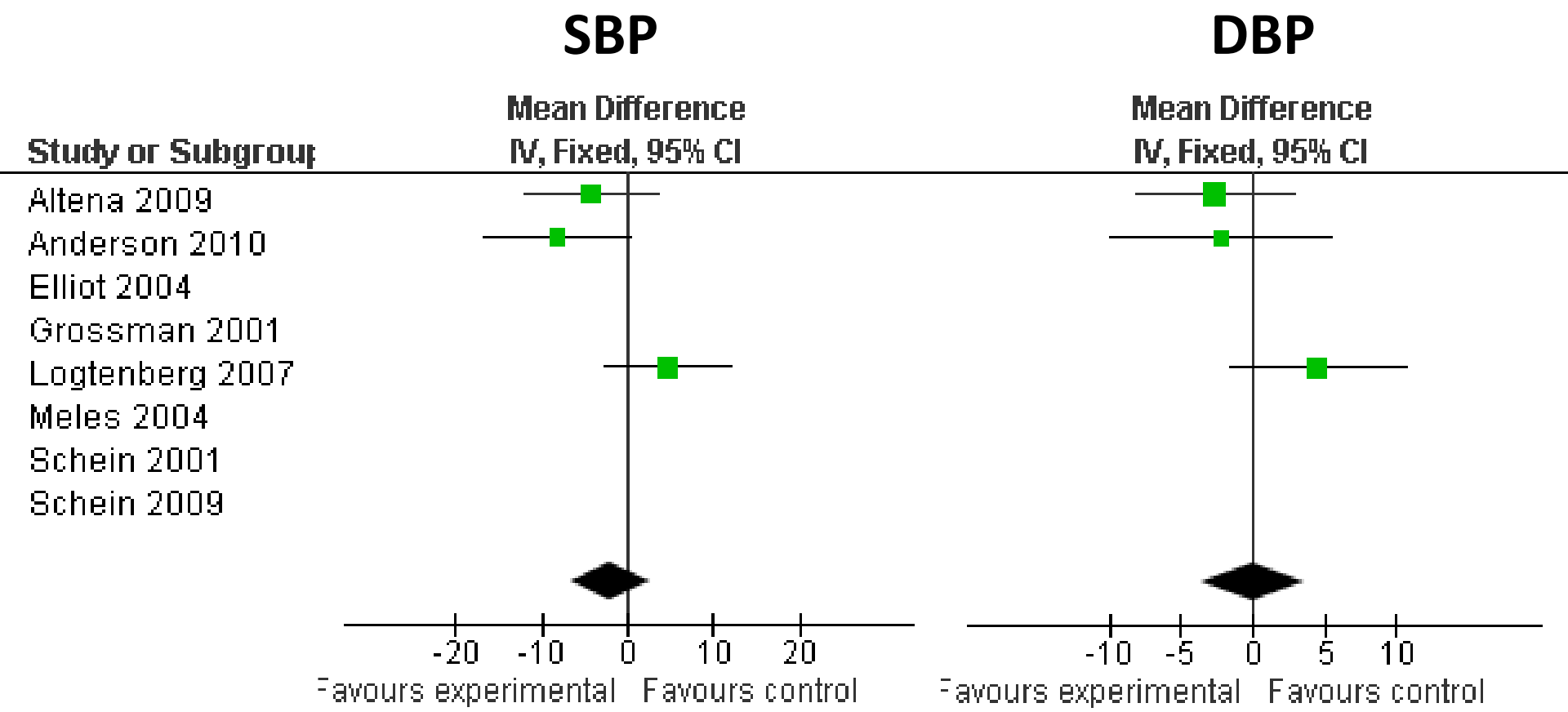
Change in BP


SBP
DBP
Study or Subgroup
Mean Difference
IV, Fixed, 95% CI
Altena 2009 -4.20 [-11.97, 3.57]
Anderson 2010 -8.20 [-16.72, 0.32]
Elliot 2004 -1.40 [-7.19, 4.39]
Grossman 2001 -4.60 [-12.86, 3.66]
Logtenberg 2007 4.70 [-2.67, 12.07]
Meles 2004 -5.30 [-14.33, 3.73]
Schein 2001 -3.90 [-10.48, 2.68]
Schein 2009 -5.60 [-9.75, -1.45]
-3.67 [-5.99, -1.36]
-20 -10 0 10 20
Favours experimental Favours control
Heterogeneity: Chi² = 6.95, df = 6 (P = 0.33); I² = 14%
Test for overall effect: Z = 3.19 (P = 0.001)
Mean Difference
IV, Fixed, 95% CI
-2.60 [-8.16, 2.96]
-2.20 [-9.84, 5.44]
0.00 [-4.78, 4.78]
-2.50 [-8.32, 3.32]
4.50 [-1.66, 10.66]
-4.50 [-8.86, -0.14]
-4.40 [-7.59, -1.21]
-2.60 [-6.30, 1.10]
-2.51 [-4.15, -0.87]
-10 -5 0 5 10
Favours experimental Favours control
Heterogeneity: Chi² = 8.20, df = 7 (P = 0.32); I² = 15%
Test for overall effect: Z = 3.01 (P = 0.003)

Results

- No change in heart rate (5 papers)
- No change in Quality of Life (2 papers)
- No major side effects from use
  - 1 paper reported 1 patient felt dizzy during the trial and was excluded

Sensitivity analysis



April 2012

Review

Device-guided breathing exercises in the control of human blood pressure: systematic review and meta-analysis

Kamal R. Mahtani, David Nunan, and Carl J. Heneghan

Objective: To evaluate whether device-guided breathing (DGB) lowers blood pressure (BP) in adults.

Design: Systematic review and meta-analysis.

Data sources: We searched *Medline* (1950–2010), *Embase* (1980–2010), the *Cochrane Library* including the Cochrane Central register of Controlled Trials (CENTRAL), *AMED* (1985–2010), *CINAHL* (1980–2010) and the Current Controlled Trials registry (as of October 2010).

Outcome measures: Primary outcomes included the mean change in SBP and DBP. Secondary outcomes included change in heart rate, quality of life, compliance with the device and any side effects of the device.

Results: We included eight trials of the Resperate device (InterCure Ltd, Lod, Israel), consisting of 494 adult patients. Use of this device resulted in significantly reduced SBP by 3.67 mmHg [95% confidence interval (CI) = −5.99 to −1.39; $P = 0.002$] and decreased DBP by 2.51 mmHg

estimates predict that hypertension prevalence will increase by approximately 60% by 2025 [2]. As a result there are increasing cost burdens on healthcare systems with antihypertensives accounting for 15% of the total cost of all medications prescribed in primary care [3].

Pharmacological therapies remain the mainstay of antihypertensive treatments. Several large-scale meta-analyses have shown that reductions in SBP and DBP lead to reductions in stroke, coronary events and mortality [3]. These considerable reductions can be achieved through relatively small changes in BP. A recent meta-analysis on the use of BP-lowering drugs estimated a 22% reduction in all coronary events and a 41% reduction in stroke could be achieved for a reduction of 10 mmHg SBP or 5 mmHg DBP [4].

Yet, it has been estimated that less than 50% of hypertensive patients achieve their target BP while on medications [5]. Much of this is thought to be due to a combination of poor compliance with medication and

BHS

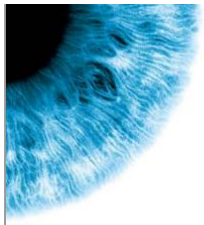
British Hypertension Society

Efficacy of the RESPeRATE Device for Lowering Blood Pressure

Statement from the British Hypertension Society
April 2011

The BHS has received a number of queries regarding this device since it appeared on the NHS Drug Tariff [£132]. A systematic review by Mahtani and Colleagues published in the Journal of Hypertension (May 2012, 30(5):852-860,) found eight trials of the Resperate device, consisting of 494 adult patients (click here to read the abstract, summary below). Use of this device resulted in significantly reduced systolic BP of 3.67mmHg (95% CI [-5.99, -1.39] p=0.002) and decreased diastolic BP of 2.51mmHg (95% CI [-4.15, -0.87] p=0.003). However, the maximum trial duration was only nine weeks and no overall effect was seen on heart rate or quality of life using the device. ***In the opinion of the BHS, such small effects over very short durations of time do not provide sufficient evidence for this equipment to be recommended.***

Mahtani KR., Nunan D. and Heneghan CJ. Device-guided breathing exercises in the control of human blood pressure: systematic review and meta-analysis.



NHS Evidence

Hypertension: Evidence Update March 2013

A summary of selected new evidence relevant to NICE clinical guideline 127 'Clinical management of primary hypertension in adults' (2011)

Device-guided breathing

NICE CG127 does not recommend any device-based methods for the treatment of hypertension.

In a meta-analysis, **Mahtani et al. (2012)** assessed 8 trials (n=494) of a device designed to lower breathing rate (Resperate) with the aim of reducing blood pressure. The device uses a breathing monitor and plays tones via headphones to guide inhalation and exhalation, aiming for less than 10 breaths per minute. Control interventions included meditation exercise, relaxing music, blood pressure monitoring or usual care.

Overall, device-guided breathing resulted in a reduction in systolic (−3.06 mmHg, 95% CI −4.68 to −1.43, p=0.0002) and diastolic blood pressure (−2.35 mmHg, 95% CI −3.47 to −1.22, p=0.0001). However, the risk of bias was assessed as moderate in 6 studies and high in 2 others. The authors noted concern that 5 of the trials were conducted or funded by the manufacturer of the device. Excluding these trials left 3 trials in 100 people, which showed no overall effect on systolic (−1.97, 95% CI −6.50 to 2.56, p=0.39) or diastolic blood pressure (−0.04, 95% CI −3.67 to 3.59).

All trials were short, with a maximum intervention duration of 9 weeks, and the authors noted variable compliance across studies, so current data do not allow any conclusions to be made about long-term efficacy. The authors concluded that the overall positive results of device-guided breathing 'should be interpreted with caution because of study size, cost of device, variability in study quality and potential conflicts of interest from the trial sponsors and the manufacturers of the Resperate device.'

Further independent trials are needed to assess the blood-pressure lowering efficacy of this device. The available evidence does not seem to support the use of this device for the treatment of hypertension and is not likely to influence the recommendations in NICE CG127.

Key reference

Mahtani KR, Nunan, D, Heneghan CJ (2012) Device-guided breathing exercises in the control of human blood pressure: systematic review and meta-analysis. Journal of Hypertension 30: 852–60

Statistical significance

- P values
  - Measure of probability that a result is due to chance
  - The smaller the value (usually $P<0.05$) less likely due to chance
- Confidence intervals
  - Estimate of the range of values that are likely to include the real value
  - 95% chance of including the real value
  - Narrower the range>more reliable
  - If value does not cross 0 for a difference, or 1 for a ratio then pretty sure result is real ($p<0.05$)