EbM Kongress, March 2018

Non-drug treatments
and the waste in research

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Summary

- Effective Non-Drug treatments:
  many developed and tested,
  but most are poorly described and little used

- Waste in Research:
  over 85%, due to poor design, non-publication, and poor reporting

HANDI Making non-drug interventions easier to find and use

Know any breathing exercises?

GP patient:

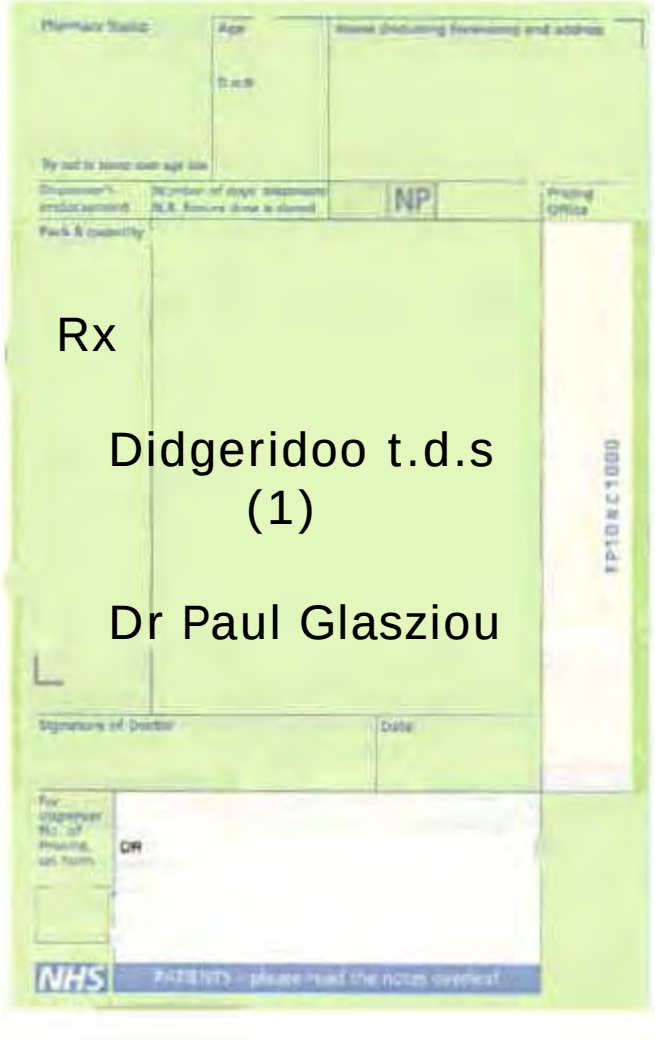
Long term smoker with chronic obstructive airways disease has recently quit smoking.

Has tried medications but does not like any.

Asks: *are any “breathing exercises” I can recommend?*

19 Beaumont St, Oxford

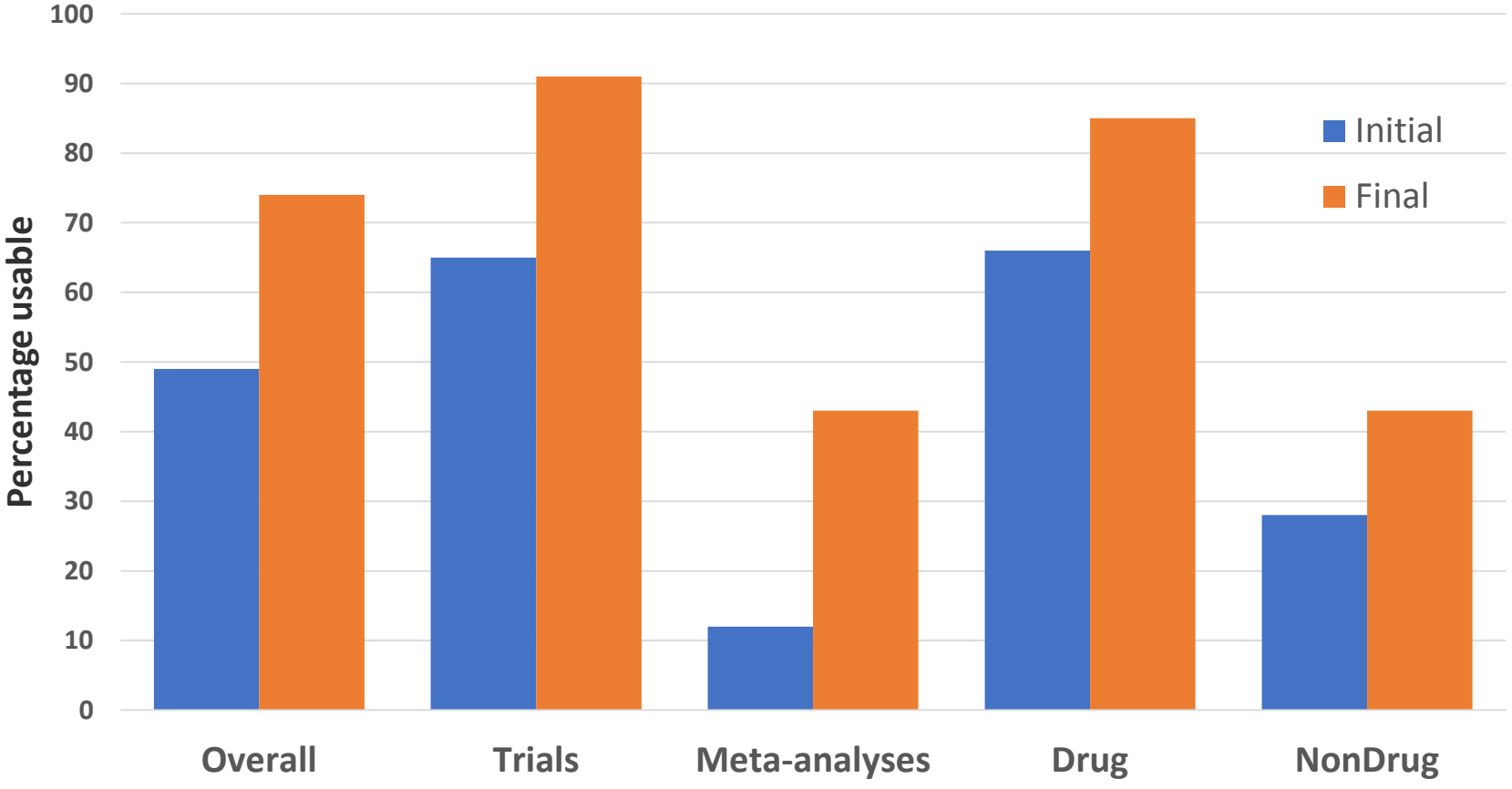
What about didgeridoo playing?



Puhan M, et al. BMJ, 2006

Inadequate treatment descriptions Analysis of 80 studies in EBM journal

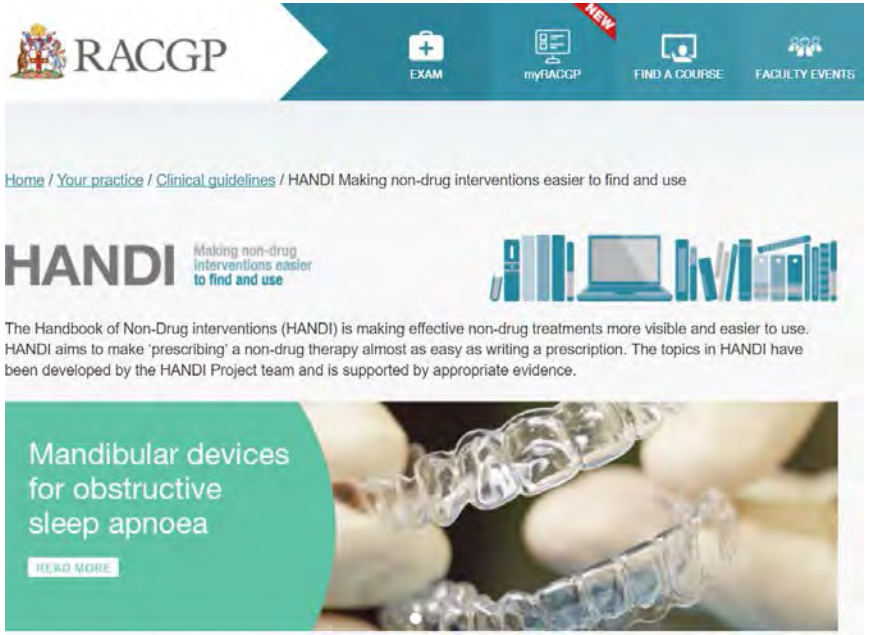
"Could you use this treatment with a patient tomorrow?"



Glasziou P, et al. BMJ 2008;336:1472-74

Handbook of **N**on-**D**rug **I**nterventions

60 entries;
15 new / year
Free access at
www.racgp.org.au/handi/
Indexed in PubMedHealth




Paul Glasziou | Marie Pirotta | John Bennett | Tammy Hoffman | Jane Gunn

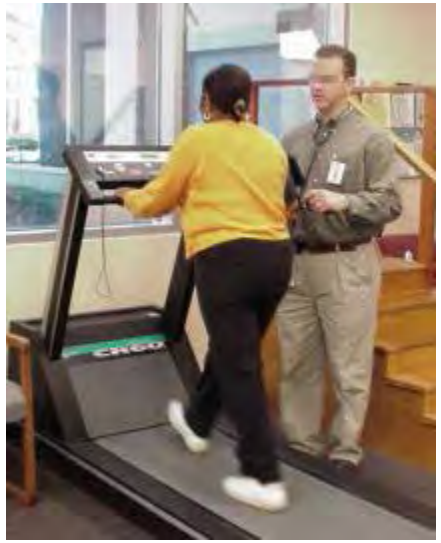

Peter Greenberg | Sally Green | Kim Bennell | Dan Ewald | Ben Ewald

and Raquel Newman (medical writer); Joanna Ong & Gisele Rocha (RACGP senior project officers)

HANDI Committee
GPs, Occupational Therapist, Physiotherapist, Physician

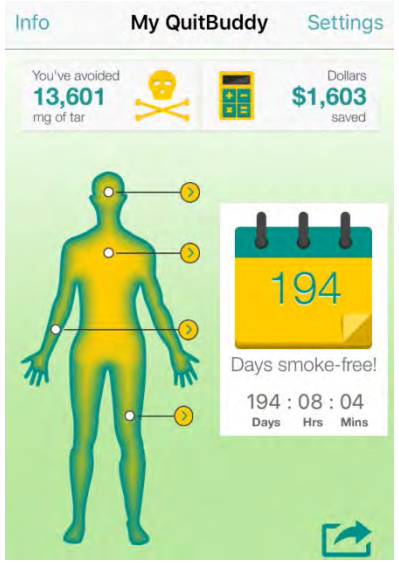
Types of treatments in HANDI

DEVICES
Nasal Balloon
Mandibular splint
Pedometers



EXERCISE
Heart Failure
COPD
Cancer Fatigue
Depression

PROCEDURES
Plantar stretch
Epley for BPPV
Wet combing
Pelvic floor training



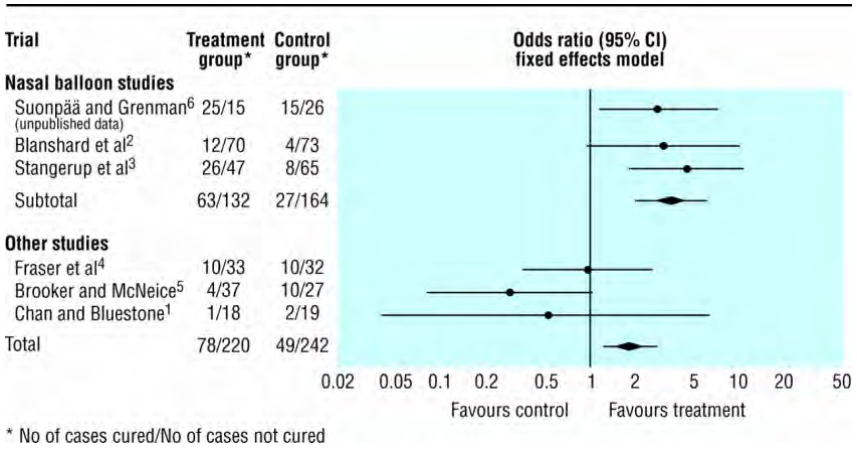
APPS
Quit Smoking
CBT for Anxiety
Insomnia

Many methodological problems to overcome

1. Devices: autoinflation for glue ear

Cochrane review, 2006

- Some small RCTs
- “Promising; inconclusive”



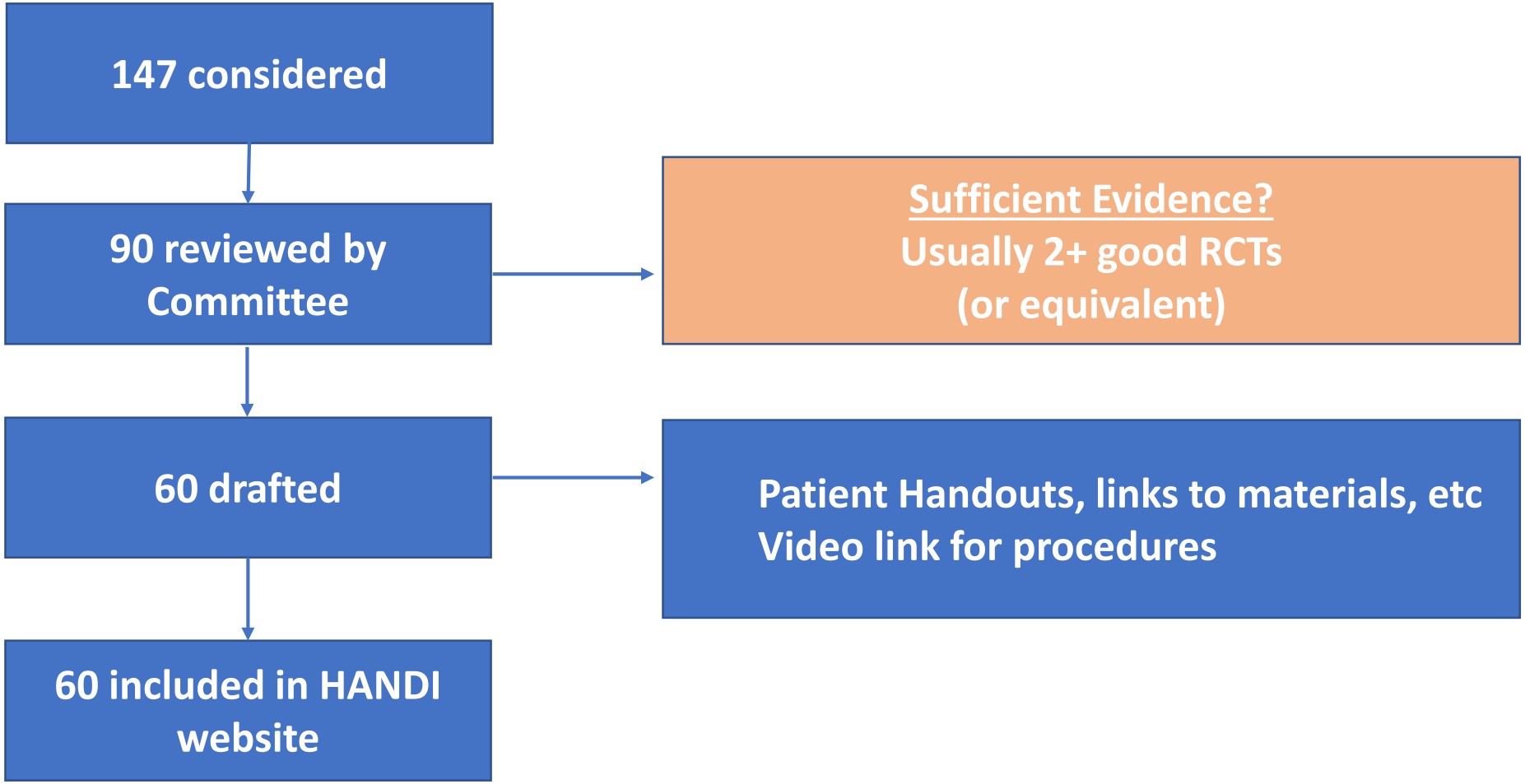
UK HTA-funded trial of 320 kids, 2015

- Effective (NNT=10)

Table 3: Tympanometric resolution at 1 month and 3 months, by study group

Variable	No. (%) of children*	
	Standard care *n* = 160	Autoinflation *n* = 160
1-month analysis	*n* = 132	*n* = 131
Tympanometric resolution of ≥ 1 type-B ear per child at 1 mo‡	47 (35.6)	62 (47.3)

Question 1: What is sufficient evidence?
Answer: Usually 2+ randomized trials



2. Exercise – for chronic illnesses

<u>CURRENT ENTRIES</u>

✓COPD

✓Cancer fatigue

✓Chronic Fatigue

✓Claudication

✓Heart Failure

✓Depression

<u>POSSIBLES</u>

•Anxiety

Committee presentations of possible entries

PAUL GLASZIOU, HANDI, NOVEMBER 2015

Exercise for Cancer Fatigue

References

1. Cramp F1, Byron-Daniel J. Exercise for the management of cancer-related fatigue in adults. Cochrane Database Syst Rev. 2012 Nov 14;11:CD006145.

2. Kampshoff CS et al. Randomized controlled trial of the effects of high intensity and low-to-moderate intensity exercise on physical fitness and fatigue in cancer survivors: results of the Resistance and Endurance exercise After ChemoTherapy (REACT) study. BMC Med. 2015;13:275.

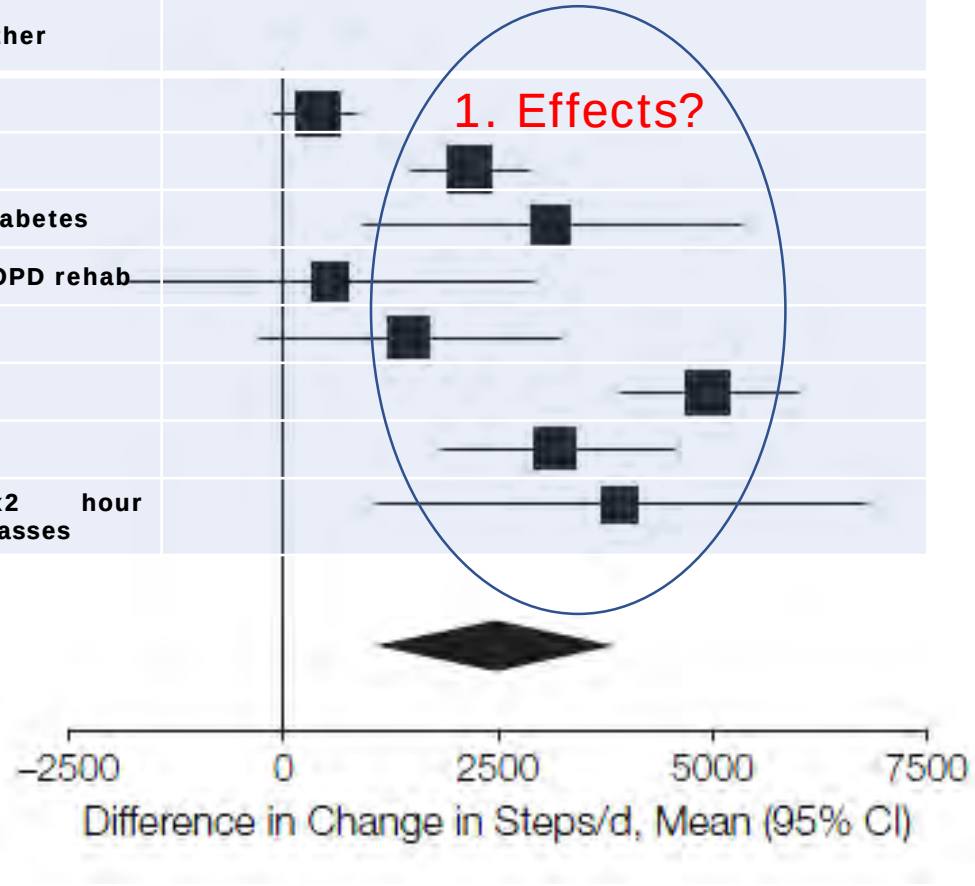
Is there sufficient evidence?

Question 2: Which treatment to use?
Answer: Consider treatments of single trials

Author	Initial Step Target/day	Increments	Diary	Other
Butler, 2004	3,000	To 4,000	No	
Hultquist, 2005	10,000	-	Yes	
Araiza, 2006	10,000		Yes	Diabetes
De Blok, 2006	Individual	Individual	Yes	COPD rehab
Talbot, 2003	Individual	+30% @12wks	Yes	
Moreau, 2001	Individual	Individual	Yes	
Izawa, 2005	No Goal		Yes	
Ransdell, 2004	3 times/wk	Step wise	Yes	2x2 hour Classes

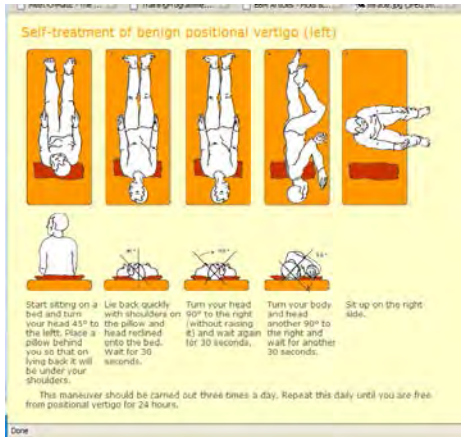
1. Effects?

2. Adequate description?
3. Local Feasibiity?
4. Local Costs?



Glasziou et al. Intervention synthesis: a missing link between a systematic review and practical treatment(s). PLoS Med. 2014

3. Procedures



Epley for BPPV

Pulled elbow manipulation

Stretches for plantar fasciitis

(Several randomized trials to support these)

Question 3: Are randomized trials <u>always</u> required?
Answer: Not for some "dramatic" effects

<u>The "Mother's Kiss" technique</u>

Child with nasal foreign body

- Dislodged with Parent Kiss method
- Case series of success 15/19

  (Botma J Laryngol Otol 2000)
- Systematic review of series

Cook SC, Burton DM & Glasziou P. Efficacy and safety of the "mother's kiss" technique: a systematic review of the case reports and case series. CMAJ 2012

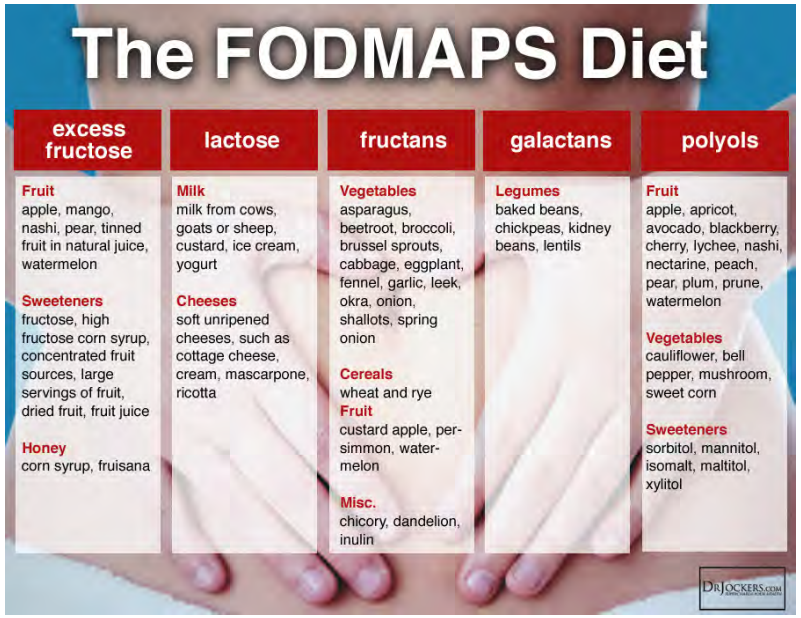
When are randomised trials unnecessary? Picking signal from noise. Glasziou P, Chalmers I, Rawlins M, McCulloch P. BMJ. 2007;334:349-51.

4. Diet & Nutrition

✓Mediterranean diet for CHD prevention

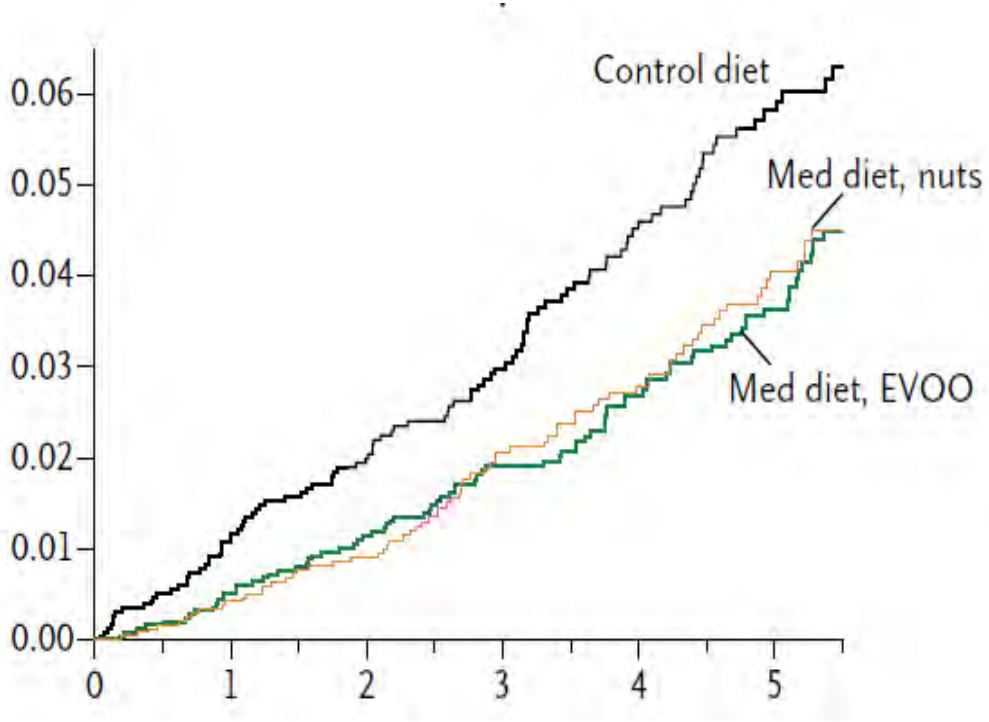
✓Early introduction of peanuts to prevent allergy development

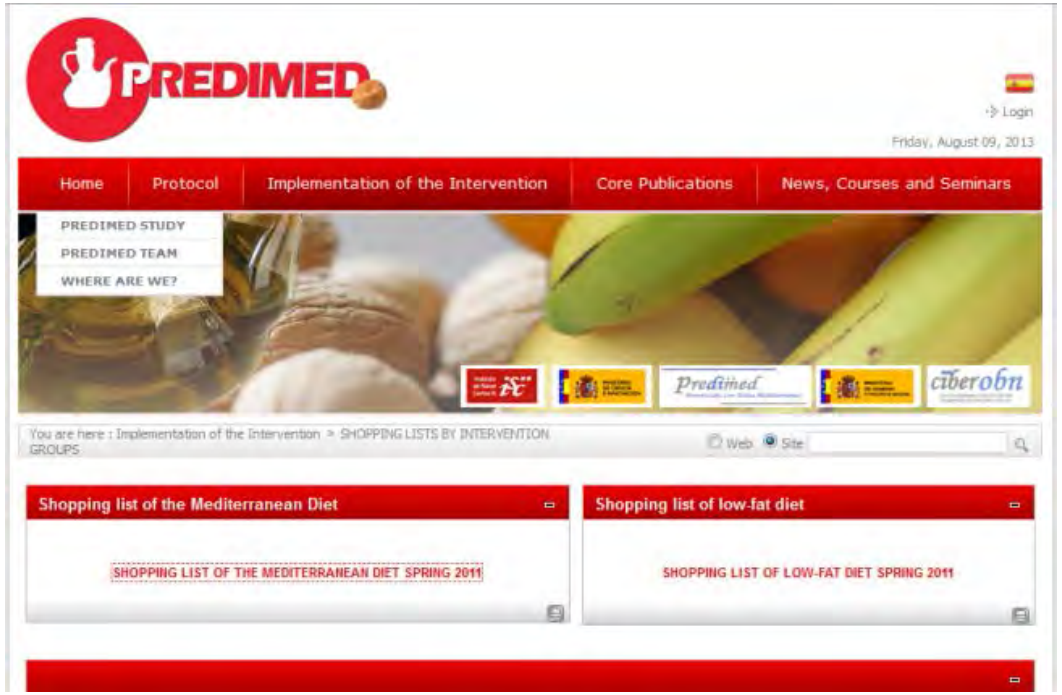
✓FODMAP diet for Irritable Bowel Syndrome



Evidence: 2+ randomized trials Mediterranean Diet

1. Lyon Heart Study (Lancet, 1994) RCT showed lower mortality
2. PREDIMED randomized trial: 7447 men & women 55-80 years of age without CV disease; type 2 diabetes mellitus or ≥ 3 major risk factors. (NEJM)





HANDI Making non-drug interventions easier to find and use

Mediterranean diet: reducing cardiovascular disease risk

In 2010, UNESCO officially recognised the Mediterranean diet pattern to be part of the cultural heritage of Italy, Greece, Spain and Morocco.

Give feedback on this topic

Intervention

A change in overall dietary pattern to increase intake of fresh fruits, vegetables, grains, nuts and fish and decrease intake of meat and dairy, known as the Mediterranean diet.

Total energy intake is adapted to meet individual needs. There is no specific fat restriction, as long as fat is mostly derived from fatty fish and plant sources (particularly olive oils or nuts). Patients view the Mediterranean diet as tastier and more filling than low-fat diets, which leads to increased long-term compliance.

Indication

Prevention of subsequent cardiovascular events in patients who have had myocardial infarction.

Description

The Mediterranean diet comprises:

- high monounsaturated (eg olive oil) to saturated (eg fatty red meat) ratio – at least 2:1
- high intake of legumes
- high intake of fruits and vegetables
- high intake of grains and cereals
- moderate quantities of fish, white meat and low-fat dairy
- low to moderate consumption of red wine
- low intake of red meat, processed meat and eggs
- low intake of sweets, sweet desserts and sweet drinks.

Refer to the Consumer resources for food group portion guide.

Simple guidelines for implementing the MedDiet in clinical practice

- Assess adherence to a Mediterranean diet using the PREDIMED 14-item Questionnaire. This tool can also be used for monitoring changes at future clinical consultations
- Introduce simple changes to the patient's diet, such as:
  - using olive oil instead of other oils/ fats for cooking and dressing salads and cooked vegetables

Format similar to Drug Formulary

Handouts on "how to" as pdf

What is the “Mediterranean” Diet?

Requirements for delivering the diet

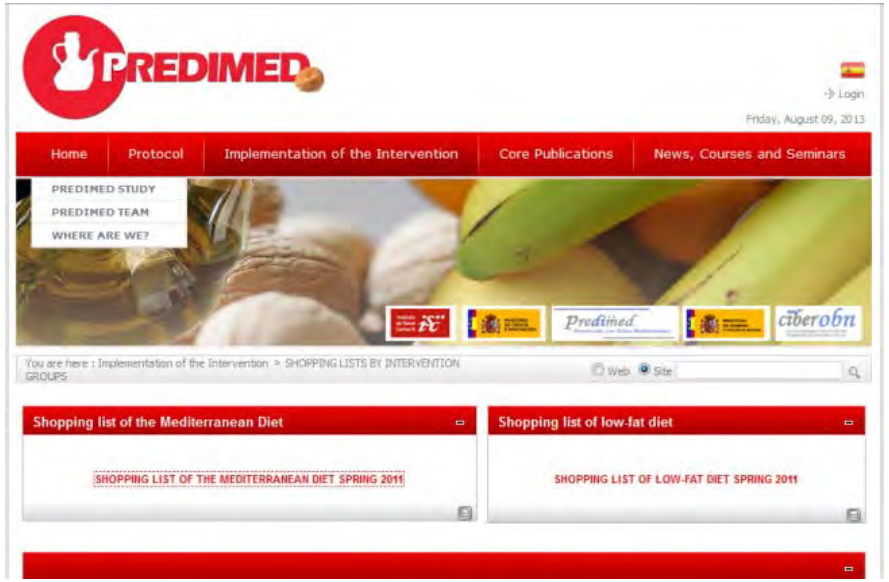
1. Compliance Score sheets

Table S1. Quantitative Score of Compliance with the Mediterranean Diet.

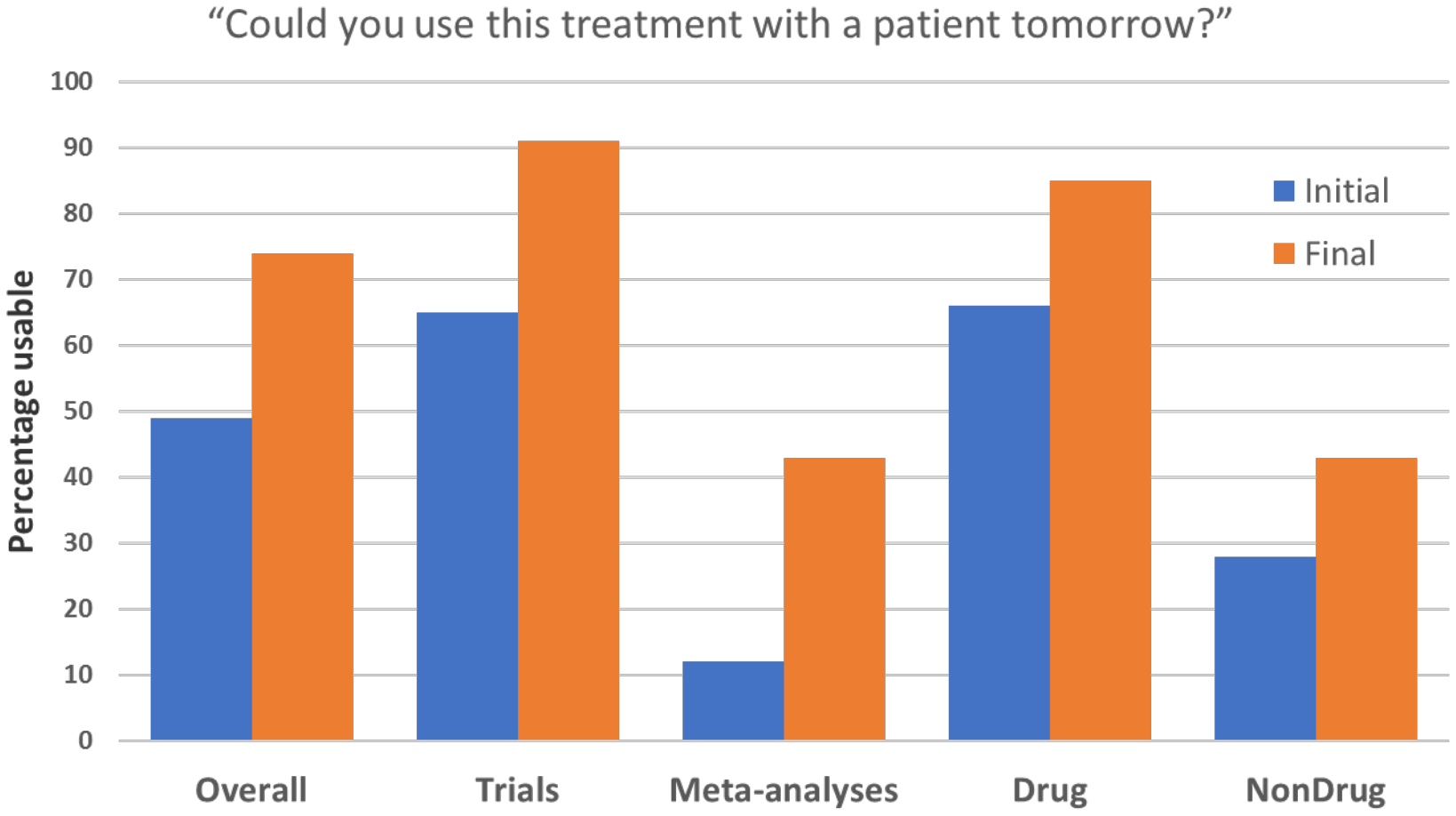
	Foods and frequency of consumption	Criteria for 1 point*
1	Do you use olive oil as main culinary fat?	Yes
2	How much olive oil (pglaszio / olive oil) you consume in a given day (including oil used for frying, salads, out of house meals, etc.)?	4 or more tablespoons
3	How many vegetable servings do you consume per day? *(1 serving = 200g - consider side dishes as 1/2 serving)*	2 or more *(at least 1 portion raw or as salad)*
4	How many fruit units (including natural fruit juices) do you consume per day?	3 or more
5	How many servings of red meat, hamburger, or meat products (ham, sausage, etc.) do you consume per day? *(1 serving = 100-150 g)*	Less than 1
6	How many servings of butter, margarine, or cream do you consume per day? *(1 serving = 12 g)*	Less than 1
7	How many sweet/carbonated beverages do you drink per day?	Less than 1
8	How much wine do you drink per week?	7 or more glasses
9	How many servings of legumes do you consume per week? *(1 serving = 150 g)*	3 or more
10	How many servings of fish or shellfish do you consume per week? (1 serving: 100-150 g fish, or 4-5 units or 200 g shellfish)	3 or more
11	How many times per week do you consume commercial sweets or pastries (not homemade), such as cakes, cookies, biscuits, or custard?	Less than 3
12	How many servings of nuts (including peanuts) do you consume per week? *(1 serving = 30 g)*	3 or more
13	Do you preferentially consume chicken, turkey or rabbit meat instead of veal, pork, hamburger or sausage?	Yes
14	How many times per week do you consume vegetables, pasta, rice, or other dishes seasoned with *sofrito* (sauce made with tomato and onion, leek, or garlic, simmered with olive oil)?	2 or more

* 0 points if these criteria are not met.

2. PREDIMED materials
Translated from Spanish



Inadequate treatment descriptions Analysis of 80 studies in EBM journal



Glasziou P, et al. BMJ 2008;336:1472-74

Summary (so far)

Effective Non-Drug treatments

- many developed and tested in RCTs
- but the treatment is often poorly described
- little usage
- (Hence development of www.racgp.org.au/handi)

HANDI Making non-drug interventions easier to find and use

Going from research to patient benefits?

Questions relevant to clinicians & patients?

Low priority questions

Unbiased and usable report?

Over 30% of trial

Avoidable waste in the production and reporting of research evidence

Iain Chalmers, Paul Glasziou www.thelancet.com **Published online June 15, 2009**

agendas

not interpreted in the

Questions relevant to clinicians and patients?	→	Appropriate design and methods?	→	Accessible full publication?	→	Unbiased and usable report?

85% Research waste = over $100 Billion / year

Lancet series: Adding Value, Reducing Waste 2014

www.researchwaste.net

Five stages of waste in research

Annual waste in research is estimated to be 85% - from avoidable design flaws (50%), non-publication (50%) and unusable reports (50%) – for a global total of over $140 Billion/year.

http://blogs.bmj.com/bmj/2016/01/14/paul-glasziou-and-iain-chalmers-is-85-of-health-research-really-wasted/

Lancet series: Adding Value, Reducing Waste 2014

www.researchwaste.net

Five stages of waste in research

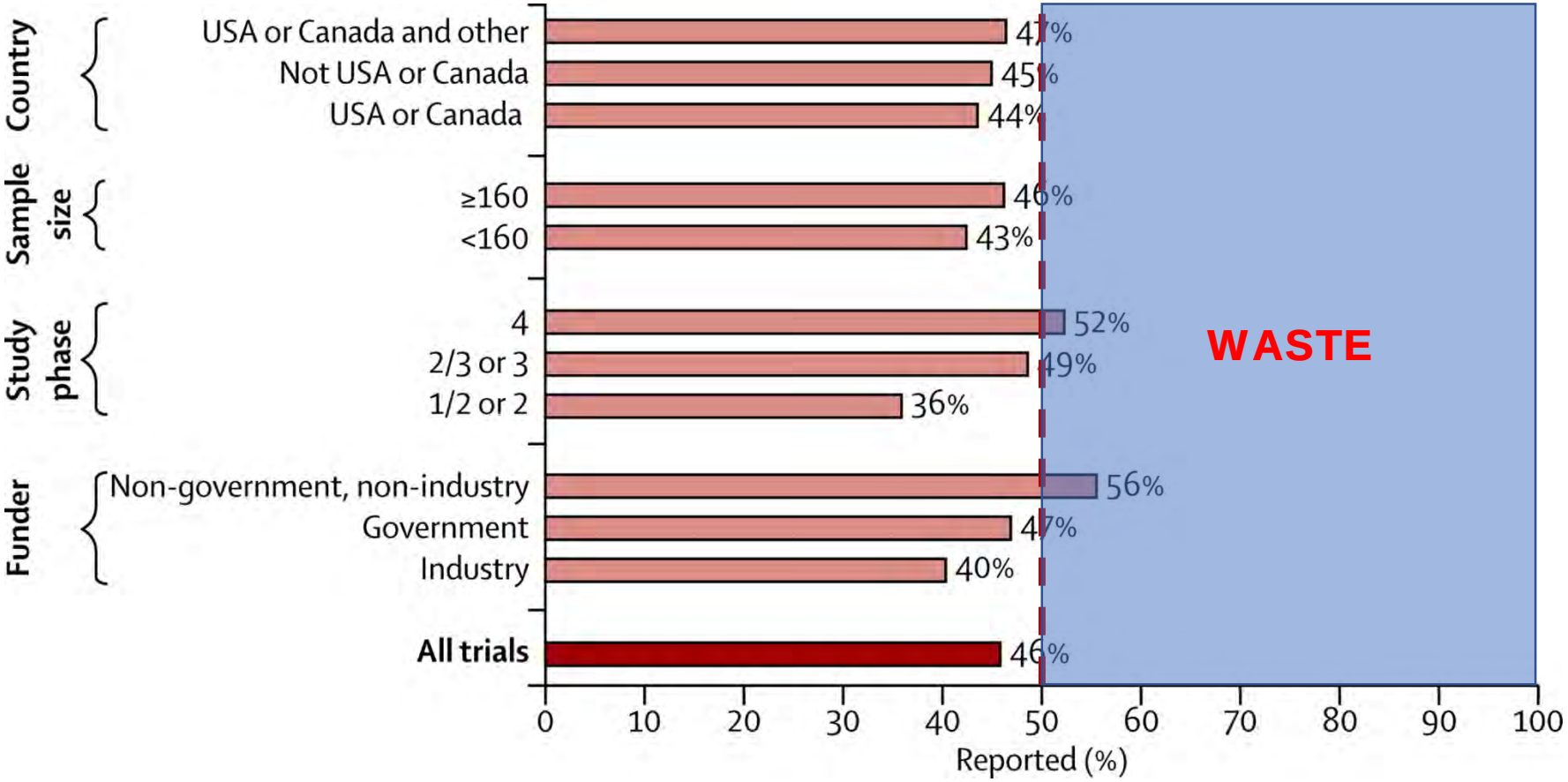
Lancet series: Adding Value, Reducing Waste 2014

www.researchwaste.net

Five stages of waste in research

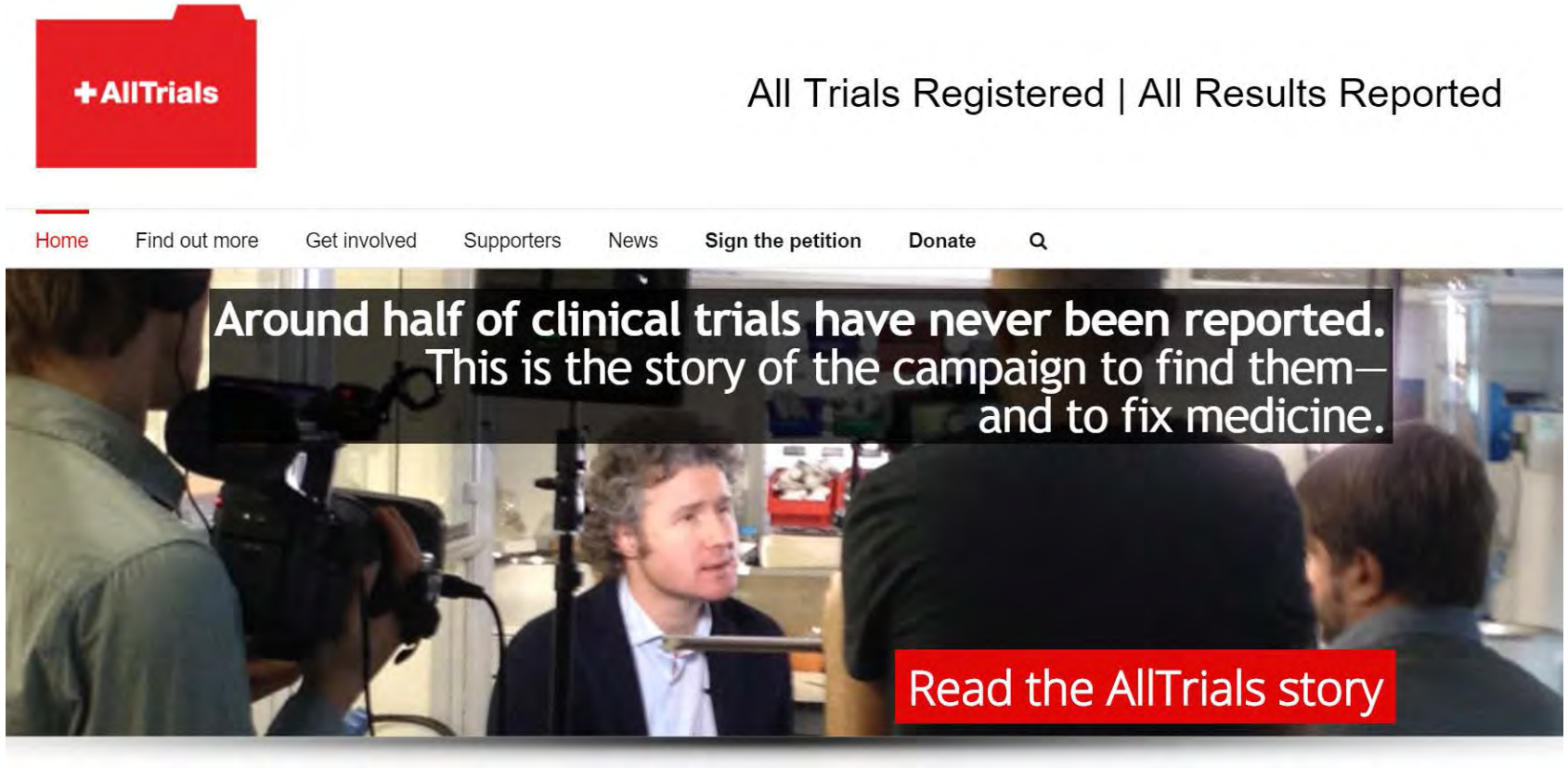
50% of research is not published

But similar across countries, size, phase, …



Lancet 2014;383:257–66

Non-Publication: a solution*



www.alltrials.net/

Monitoring “the solution” Automated tracking by institution

Who's not sharing their trial results?

Trials registered on ClinicalTrials.gov should share results on the site shortly after completing, or publish in a journal. But many organisations fail to report the results of clinical trials. We think this should change. Explore our data (last updated October 2016) to see the universities, government bodies and pharmaceutical companies that aren't sharing their clinical trial results.

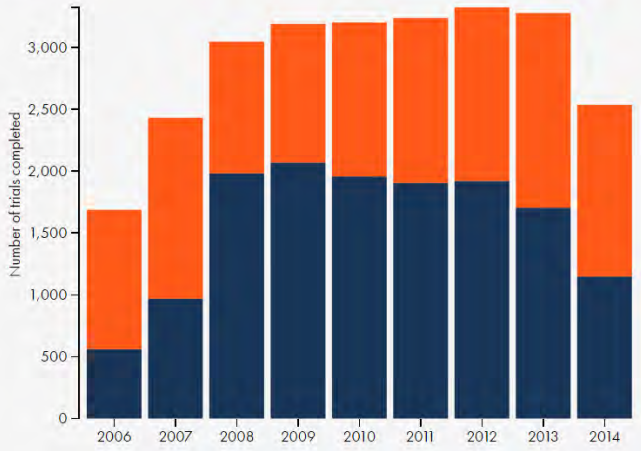
Trial sponsors

We've ranked the major trial sponsors with the most unreported trials registered on ClinicalTrials.gov. Click on a sponsor's name to find out whether it's getting better at reporting completed trials - or worse.

	Name of sponsor	Trials missing results	Total eligible trials	Percent missing
1	Sanofi	285	435	65.5%
2	Novartis Pharmaceuticals	201	534	37.6%
3	National Cancer Institute (NCI)	194	558	34.8%
4	Assistance Publique - Hôpitaux de Paris	186	292	63.7%
5	GlaxoSmithKline	183	809	22.6%
6	Mayo Clinic	157	312	50.3%
7	Yonsei University	139	194	71.6%
8	Seoul National University Hospital	131	207	63.3%
9	Alliance for Clinical Trials in Oncology	129	160	80.6%

Trials by year

Since Jan 2006, **all major trial sponsors** completed 25,927 eligible trials and **haven't published results for 11,714 trials**. That means 45.2% of their trials are missing results.



https://trialstracker.ebmdatalab.net/#/

Lancet series: Adding Value, Reducing Waste 2014

www.researchwaste.net

Five stages of waste in research

New research should build on previous research

Horn J et al. Very Early Nimodipine Use in Stroke (VENUS): a randomized, double-blind, placebo-controlled **TRIAL**. Stroke. 2001
RESULTS: At trial termination, after inclusion of 454 patients (225 nimodipine, 229 placebo), **no effect** of nimodipine was found.

Horn J, et al. Calcium antagonists for acute ischemic stroke. The Cochrane Database of **SYSTEMATIC REVIEWS**. 2001.
RESULTS "46 trials were identified of which 28 were included (7521 patients). **No effect** of calcium antagonists on poor outcome at the end of follow-up (OR 1.07), or on death at end of follow-up (OR 1.10) was found."

Horn J et al. Nimodipine in **ANIMAL** model experiments of focal cerebral ischemia: a **SYSTEMATIC REVIEW** Stroke. 2001 Oct.
"20 studies ... **review did not show convincing evidence** to substantiate the decision to perform trials with nimodipine in large numbers of patients."

Animal systematic reviews & registry

Federatie van medisch wetenschappelijke verenigingen Federa COREON coreon

FederaBulletin

Too valuable to waste

Hoe verkwisten we zo weinig mogelijk waarde van dierproeven en klinische trials? Aanstaande vrijdag behandelen diverse sprekers deze vraag.

Registration

Meer waarde uit dierproeven halen

FederaPrijs voor dr. Janneke Horn, neuroloog-intensivist aan het AMC

Too valuable to waste: Experiments on humans and animals

Human clinical trials and animal experiments for medicine need a sound regulation. That is needed to get valid results and to avoid waste of efforts. However, meetings of clinical trial researchers with animal experiments researchers are taken place very rarely. The FederaDag 2017 will offer knowledge ánd connection to experts in both fields.

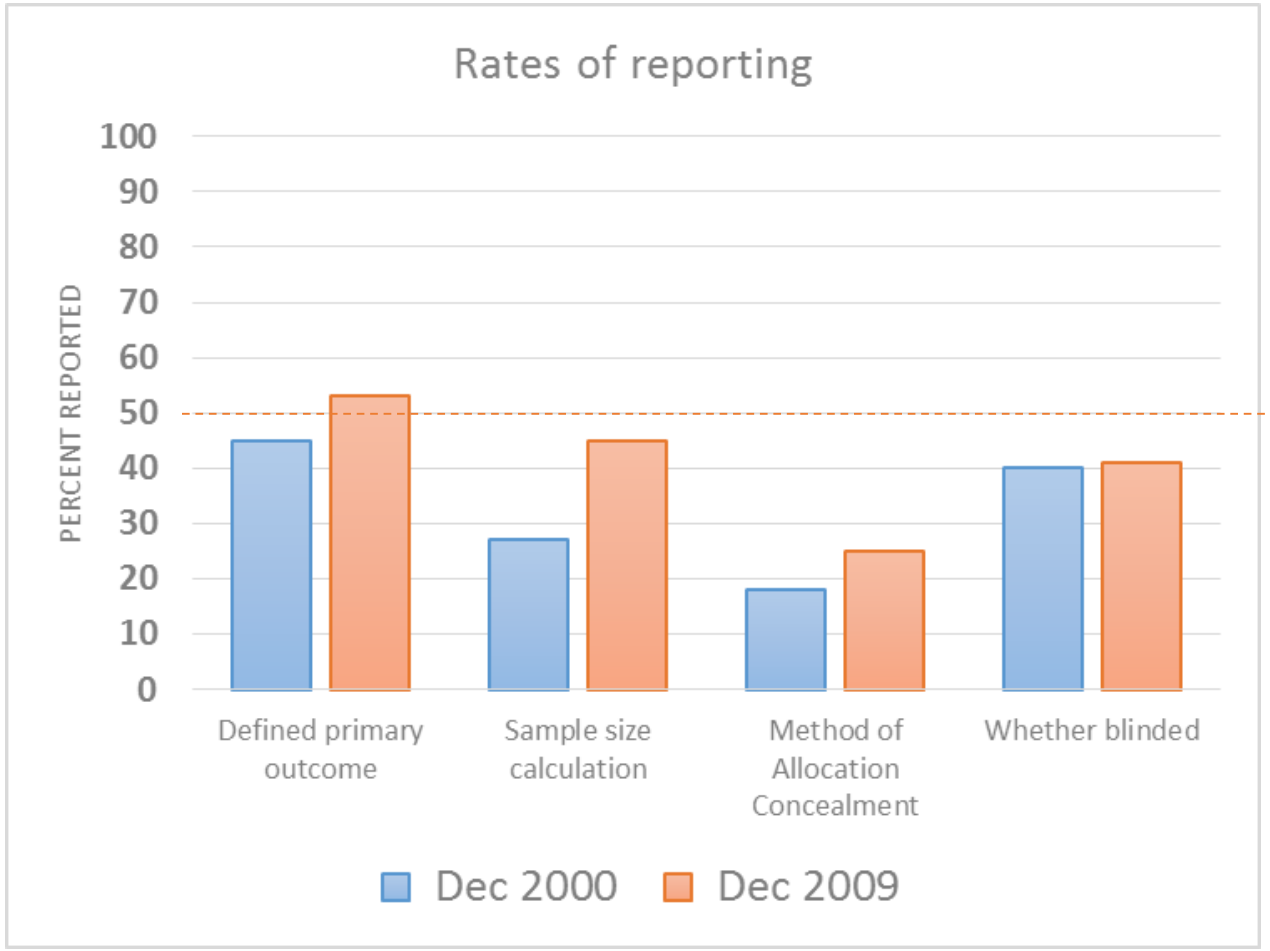
Friday June 16th, the FederaDag 2017 takes place at NWO in The Hague, and is organized by Federa in cooperation with ZonMw.

Lancet series: Adding Value, Reducing Waste 2014

www.researchwaste.net

Five stages of waste in research

Reports of Randomized Trials are often missing essential methods



Most < 50% reported

Chen & Altman, Lancet 2005; Hopewell BMJ 2010

What is the treatment?

The paper's description of sodium reduction

- "Individual and weekly group counseling sessions were offered initially, with less intensive counseling and support thereafter, specific to sodium reduction."

What would you tell a patient to do?

TOHP Study BMJ, Apr 2007; 334: 885

What is sodium reduction?

The BMJ paper's description

"Individual and weekly group counseling sessions were offered initially, with less intensive counseling and support thereafter, specific to sodium reduction."

Description in earlier (paywalled) reference:

1. an individual session followed by **10 weekly group 90 minute sessions** with a nutritionist, followed by a transitional stage of some additional sessions

2. Topics in the weekly sessions included Getting Started, sodium basics, the morning meal, midday sources of sodium, the main meal, planning ahead, creative cooking, eating out, food cues, and social support,

3. the sessions included **sampling** of foods, **discussion of articles** on sodium reduction, and problem-solving,

4. patients kept **diaries** at least 6 days per week, and **urine sodiums** were measured.

Poor descriptions of treatments

BMJ

BMJ 2013;347:f3755 doi: 10.1136/bmj.f3755 (Published 10 September 2013) Page 1 of 10

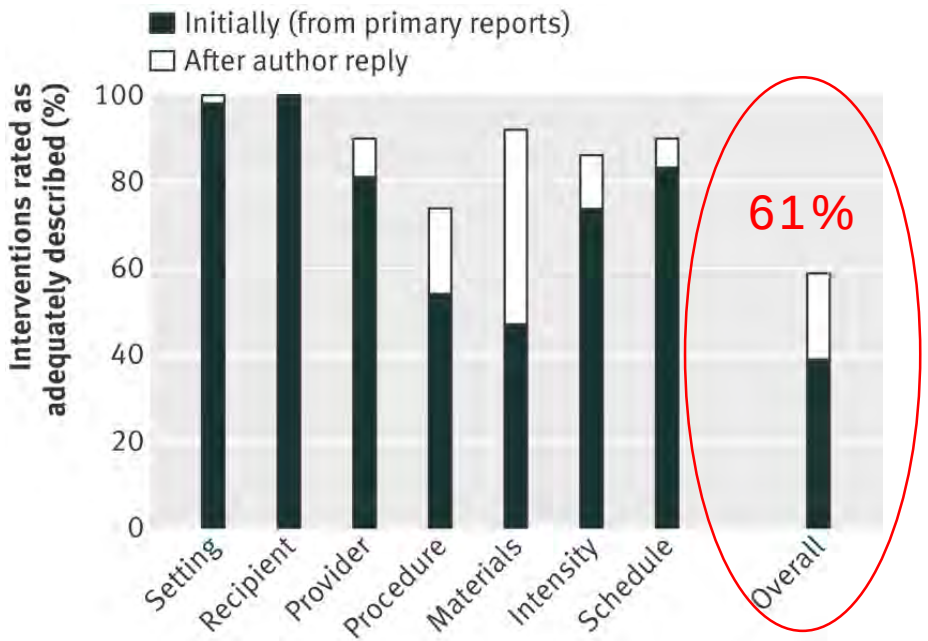
RESEARCH

Poor description of non-pharmacological interventions: analysis of consecutive sample of randomised trials

OPEN ACCESS

Tammy C Hoffmann *associate professor of clinical epidemiology*, Chrissy Erueti *assistant professor*, Paul P Glasziou *professor of evidence-based medicine*

Centre for Research in Evidence-Based Practice, Faculty of Health Sciences and Medicine, Bond University, Qld, Australia, 4229



BMJ

BMJ 2014;348:g1687 doi: 10.1136/bmj.g1687 (Published 6 March 2014) Page 1 of 13

RESEARCH METHODS & REPORTING

Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide

Tammy C Hoffmann *associate professor of clinical epidemiology*[1], Paul P Glasziou *director and professor of evidence based medicine*[1], Isabelle Boutron *professor of epidemiology*[2], Ruairidh Milne *professorial fellow in public health and director*[3], Rafael Perera *university lecturer in medical statistics*[4], David Moher *senior scientist*[5], Douglas G Altman *professor of statistics in medicine*[6], Virginia Barbour *medicine editorial director, PLOS*[7], Helen Macdonald *assistant editor*[8], Marie Johnston *emeritus professor of health psychology*[9], Sarah E Lamb *Kadoorie professor of trauma rehabilitation and co-director of Oxford clinical trials research unit*[10], Mary Dixon-Woods *professor of medical sociology*[11], Peter McCulloch *clinical reader in surgery*[12], Jeremy C Wyatt *leadership chair of ehealth research*[13], An-Wen Chan *Phelan scientist*[14], Susan Michie *professor*[15]

TIDieR Template for Intervention Description and Replication

The TIDieR (Template for Intervention Description and Replication) Checklist*:

Information to include when describing an intervention and the location of the information

Item number	Item	Where located **	
		Primary paper (page or appendix number)	Other † (details)
	BRIEF NAME		
1.	Provide the name or a phrase that describes the intervention.		
	WHY		
2.	Describe any rationale, theory, or goal of the elements essential to the intervention.		
	WHAT		
3.	Materials: Describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or in training of intervention providers. Provide information on where the materials can be accessed (e.g. online appendix, URL).		
4.	Procedures: Describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities.		
	WHO PROVIDED		
5.	For each category of intervention provider (e.g. psychologist, nursing assistant), describe their expertise, background and any specific training given.		
	HOW		
6.	Describe the modes of delivery (e.g. face-to-face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group.		
	WHERE		
7.	Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features.		

Summary

- **Effective NonDrug treatments:**
  many developed and tested, but poorly described and little used
  - www.racgp.org.au/handi

- **Avoidable Waste in Research:**
  over 85%, due to poor design, non-publication, and poor reporting
  - http://rewardalliance.net/

HANDI Making non-drug interventions easier to find and use

Light Therapy
Current Utilisation (in Austria)

Winkler-Pirek E et al. Use of Light Therapy (LT) by Office-Based Physicians. Neuropsychobiology. 2016; 74(4):182-187

A questionnaire-survey of 400 randomly selected office-based doctors in Austria.

Results

Light Therapy (LT) recommended by 67% of physicians, 92% of psychiatrists & 47% of GPs.

The recommended location of treatment was patients' homes in 90%.

Physicians were asked whether they considered LT to be an appropriate treatment for various disorders - affirmative answers:

94% for seasonal affective disorder (SAD)
93% for sub-syndromal SAD
61% for non-seasonal recurrent major depressive disorder
36% for jet lag syndrome,
36% for chronobiological problems with shift work
22% for insomnia, 14% for premenstrual dysphoric disorder
11% for behavioural problems with Alzheimer's disease.