



# Tackling research waste

**Hywel Williams**

University of Nottingham and  
National Institute of Health Research Health Technology Assessment Programme

German National Convention for Outcomes Research  
October 9, 2019 in Berlin

\*I have no financial or research associations with pharmaceutical companies\*

# What I am going to do

- Some **personal** background
- Describe the **anatomy of research waste** with examples from dermatology
- Consider the **reasons** for research waste
- Say **how we have tackled research waste** at our Centre of Evidence-Based Dermatology
- End with some **solutions and reflections**

# My methodology journey



Chief Investigator seven pragmatic RCTs

Set up international Cochrane Skin Group

Systematic reviews incl. IPD and DTA

Set up Centre of Evidence-Based Dermatology

Directed a Research Design Service and Clinical Trials Unit

Lots of methodological collaborations esp. core outcome sets CS-COUSIN

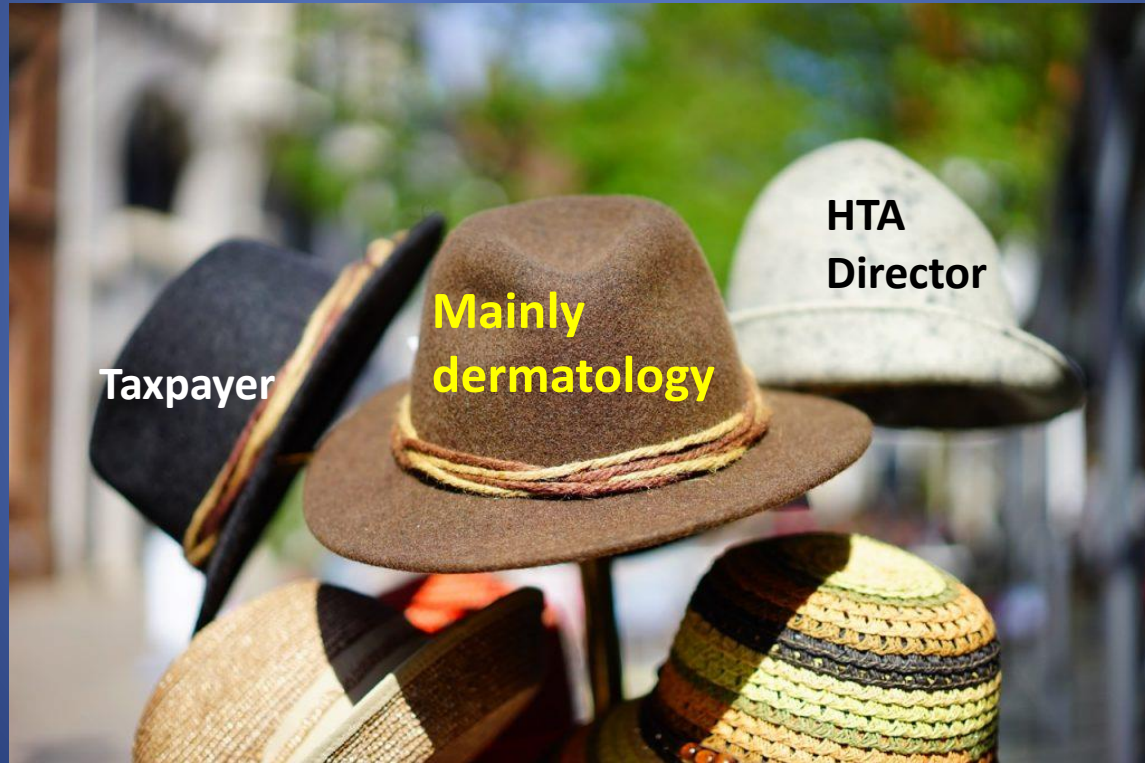
Passionate about reducing avoidable research waste

Knowledge mobilisation

Published 500+ peer-reviewed papers

85,727 citations, h-index 110, i10-index 647 (October 2019)

# What hat am I wearing today?

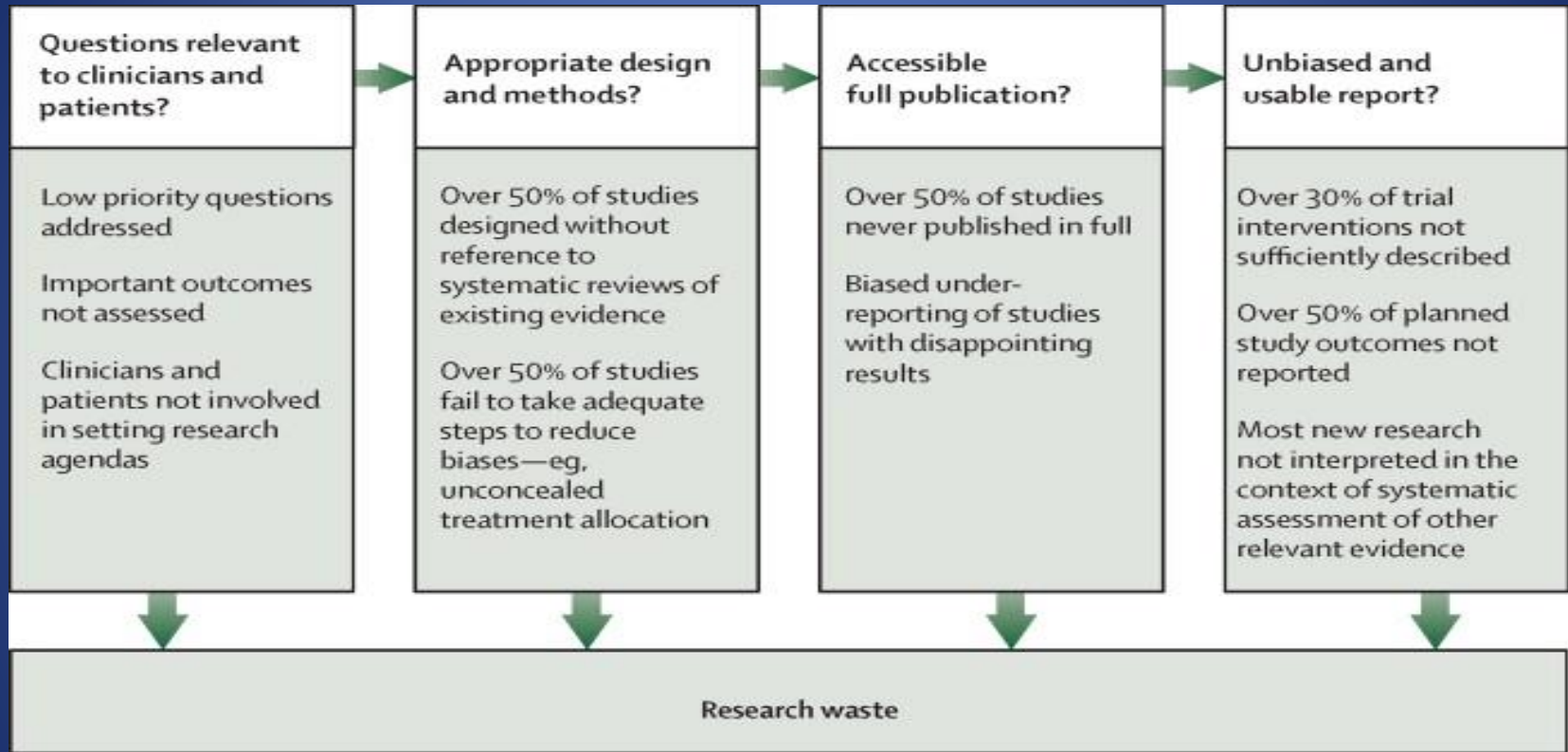


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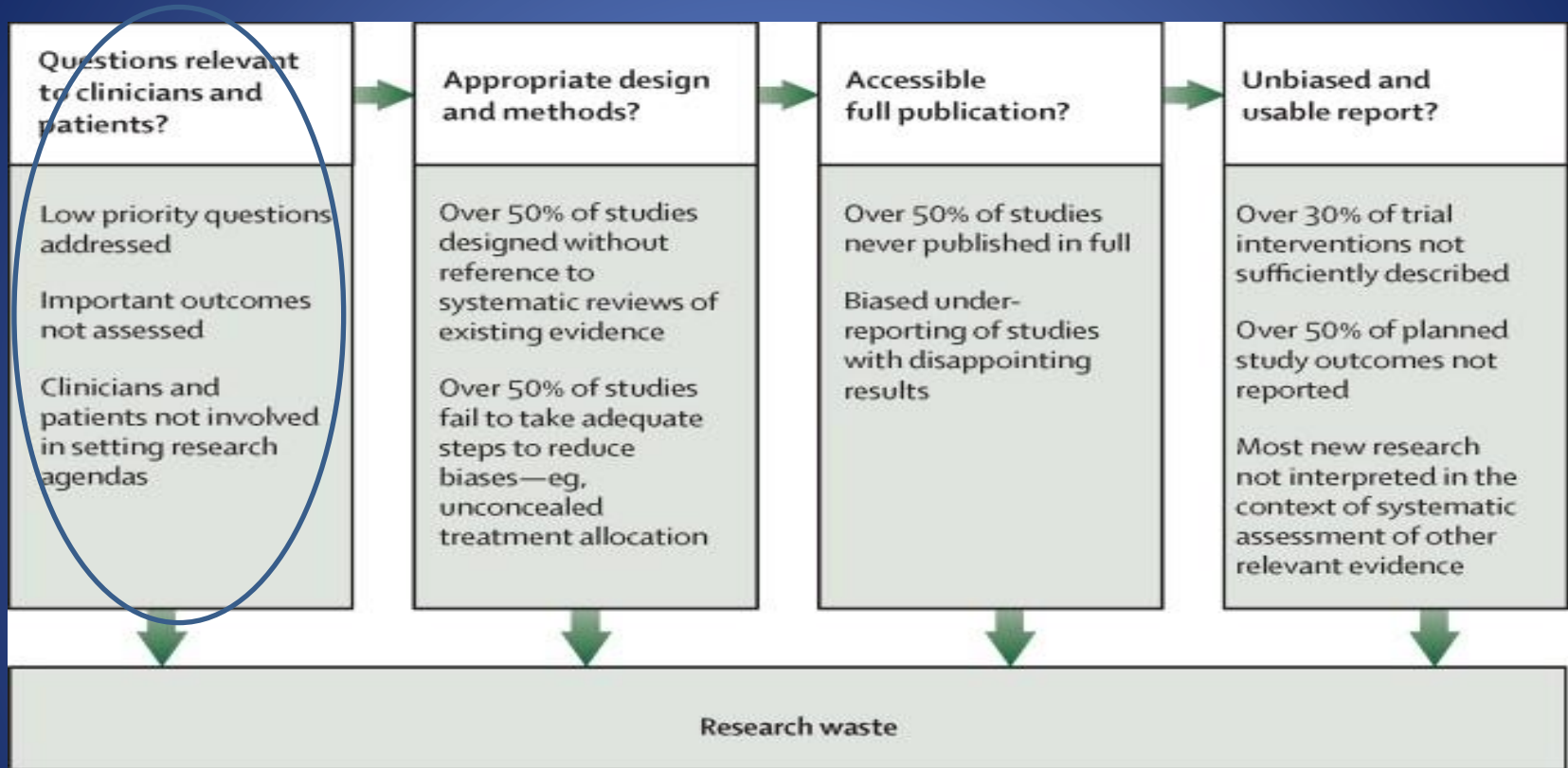


# The problem



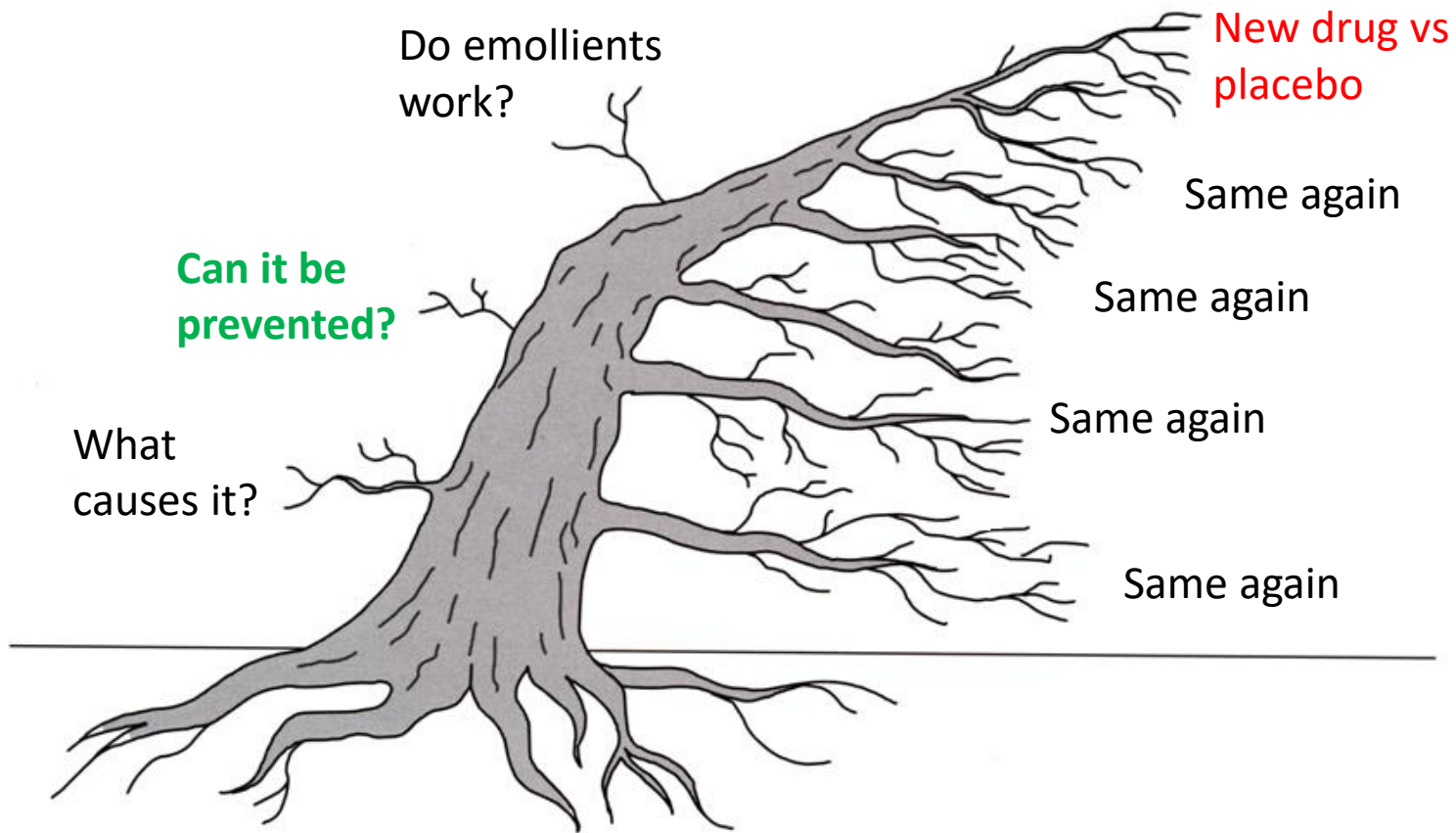
Stages of waste in the production and reporting of research evidence relevant to clinicians and patients

Chalmers I, Glasziou P. Avoidable waste in the production and reporting of research evidence. Lancet 2009; 374:86-89.



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# Look out for seeding trials

- Primary objective - get clinicians familiar using a new drug
- Rather than test a scientific hypothesis
- Many centres in many countries recruiting a few patients
- Often international during new drug launch

# Typical Cochrane Skin Review

This update of the 2010 review includes **96 studies**, 57 from the previous update and 39 new studies, totalling 4512 participants. Most of the studies, covering a wide range of interventions, had fewer than 50 participants. All of the studies assessed repigmentation, however **only five reported on all of our three primary outcomes which were quality of life, > 75% repigmentation and adverse effects**

Whitton M et al Cochrane Library 2015

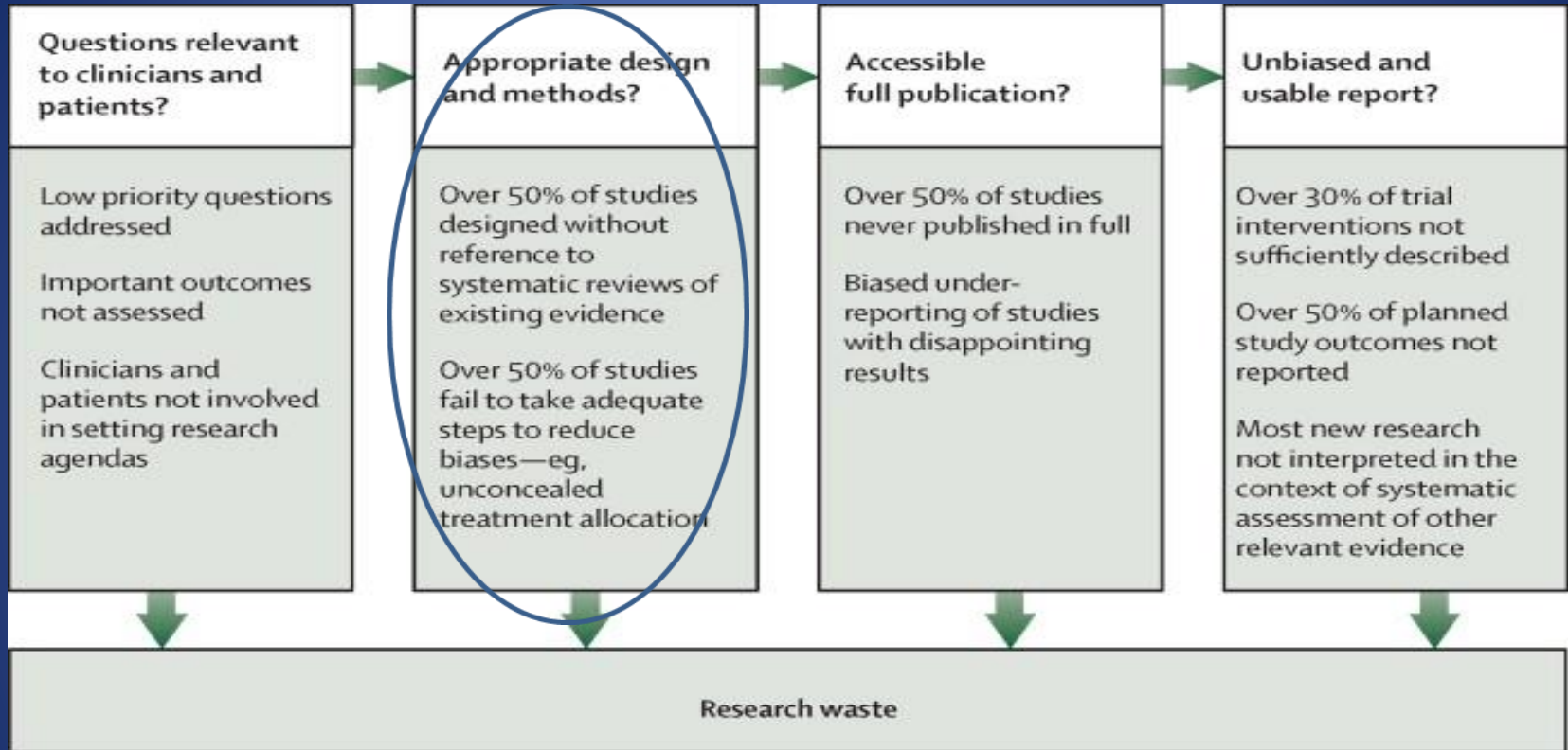


Is % repigmentation best outcome for patients?



# Trialists just do what they like

- Assessed concordance between efficacy outcomes in a random sample of 10 Cochrane Skin systematic reviews and the 220 included trials
- Reviews did not include 742 (68%) of the 1,086 trial outcomes
- Of the 60 outcomes the reviews sought, 17 (28%) were not reported in any trial, while 12 were assessed in <50% of trials
- For 11 of 23 (48%) primary review outcomes, meta-analysis was impossible, because trial outcomes were absent or unclear
- Could be improved by the development and implementation of Core Outcome Sets



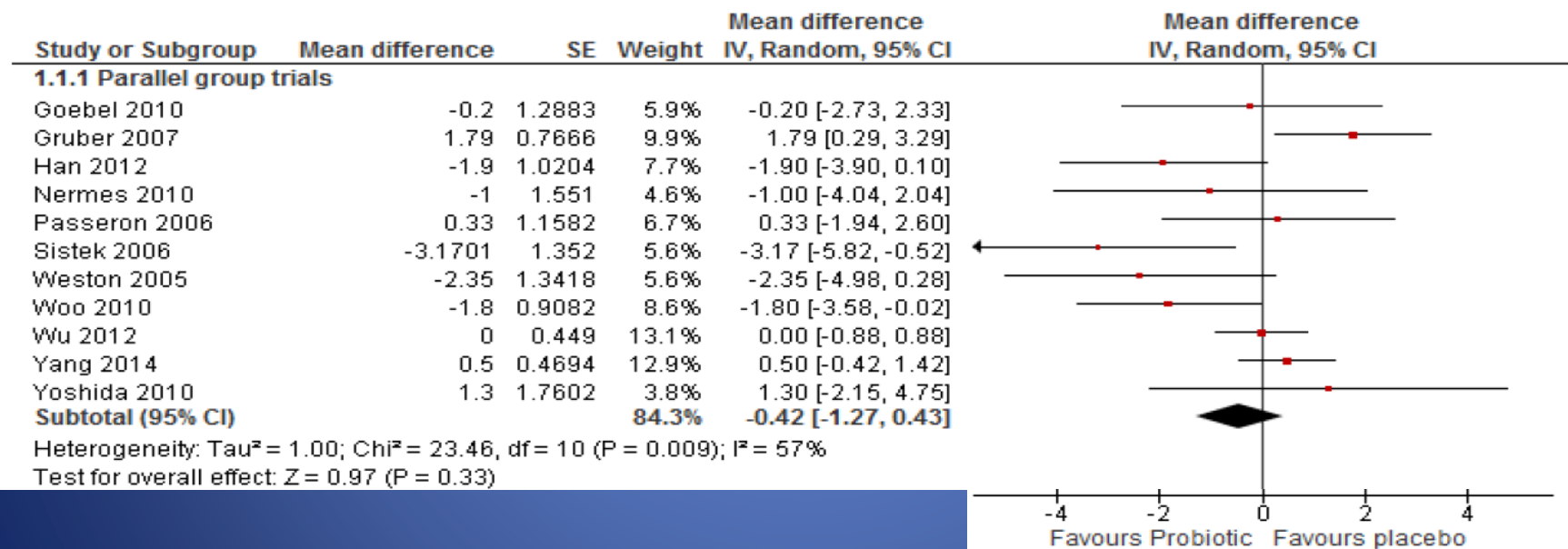
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# Probiotics for Treating Eczema

## 1.1 Participant or parent-rated symptoms of eczema (SCORAD part C) at the end of treatment



# Waste in systematic reviews

- 2019 [Effect of probiotic supplementation during pregnancy and infancy in preventing atopic dermatitis in children: a Meta analysis] (in Chinese)
- 2018 Probiotic supplementation for prevention of atopic dermatitis in infants and children: A systematic review and meta-analysis
- 2018 *Lactobacillus rhamnosus* GG in the primary prevention of eczema in children: A systematic review and meta-analysis
- 2016 Synbiotics for prevention and treatment of atopic dermatitis: a meta-analysis of randomized clinical trials
- 2015 Probiotics and primary prevention of atopic dermatitis: a meta-analysis of randomized controlled studies
- 2015 Long-term effect of early-life supplementation with probiotics on preventing atopic dermatitis: A meta-analysis
- 2015 Probiotics for prevention of atopic diseases in infants: systematic review and meta-analysis
- 2015 Probiotics for the prevention of allergy: a systematic review and meta-analysis of randomized controlled trials

## *Original Investigation*

### The Mass Production of Redundant, Misleading, and Conflicted Systematic Reviews and Meta-analyses

JOHN P.A. IOANNIDIS

*Stanford University School of Medicine; Stanford University School of  
Humanities and Sciences; Meta-Research Innovation Center at Stanford  
(METRICS), Stanford University*

#### **Policy Points:**

- Currently, there is massive production of unnecessary, misleading, and conflicted systematic reviews and meta-analyses. Instead of promoting evidence-based medicine and health care, these instruments often serve mostly as easily produced publishable units or marketing tools.
- Suboptimal systematic reviews and meta-analyses can be harmful given the major prestige and influence these types of studies have acquired.
- The publication of systematic reviews and meta-analyses should be realigned to remove biases and vested interests and to integrate them better with the primary production of evidence.

**Context:** Currently, most systematic reviews and meta-analyses are done retrospectively with fragmented published information. This article aims to explore

# The “systematic review” sausage machine



# Interventions for melasma

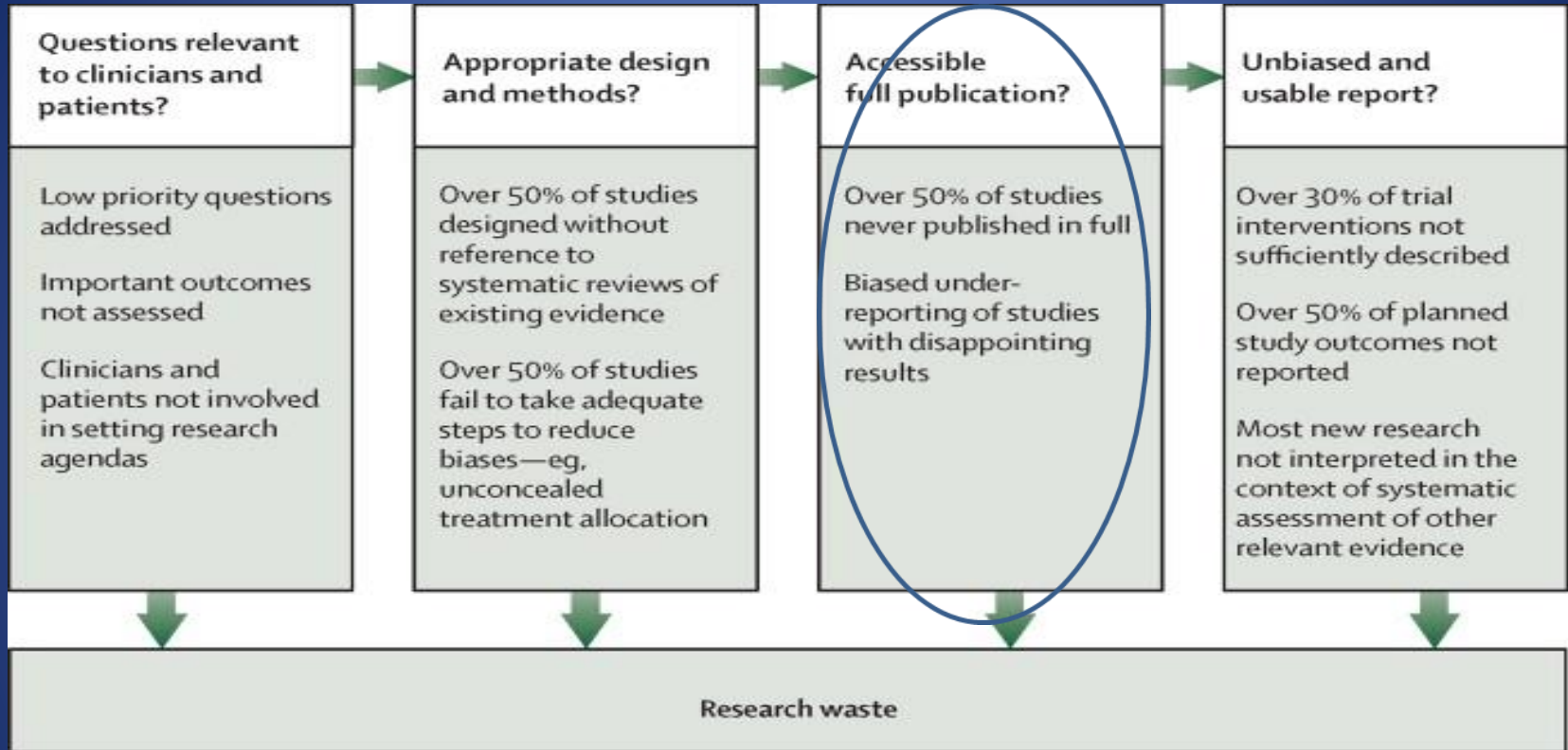
	Adequate sequence generation?	Allocation concealment?	Blinding?	Incomplete outcome data addressed?	Free of selective reporting?	Compliance to treatment assessed	Aims/interventions and outcomes clear	Reliable outcome measure
Baliña 1991b	?	?	+	-	?	?	?	?
Chan 2008	+	?	+	+	+	+	+	+
Ejaz 2008	+	?	+	?	?	+	+	+
Ennes 2000	+	+	+	?	?	+	+	?
Espinal-Perez 2004	?	?	+	+	?	?	?	+
Francisco-Diaz 2004	+	+	+	?	?	?	+	+
Griffiths 1993	+	?	+	-	+	?	?	+
Guevara 2003	+	+	+	?	?	?	?	+
Huh 2003	+	?	+	?	?	?	?	+
Hurley 2002	+	?	+	?	?	+	+	+
Khemis 2007	+	+	+	?	-	?	?	?
Kimbrough-Green 1994	+	?	+	?	?	?	+	+
Leenutaphong 1999	+	?	+	-	?	?	?	+
Lim 1997	+	?	+	?	?	?	?	?
Lim 1999	?	?	+	?	?	?	+	?
Sivayathorn 1995	?	?	+	?	?	?	?	?
Taylor 2003	?	?	+	+	-	?	+	+
Thirion 2006	?	?	+	?	?	?	?	?
Vázquez 1983	+	?	+	?	-	+	?	?
Wang 2004	?	?	-	?	?	?	?	+



# Study reporting and quality

	Study quality	
Reporting quality	Good	Flawed
Clear	May be helpful for clinical practice	At least you can tell it is flawed and make a judgment on utility
Poor	A sparkling diamond – but how do you know?	Difficult to distinguish from a good but poorly reported study

Williams HC. Cars, CONSORT 2010, and clinical practice.  
Trials. 2010 Mar 24;11:33.

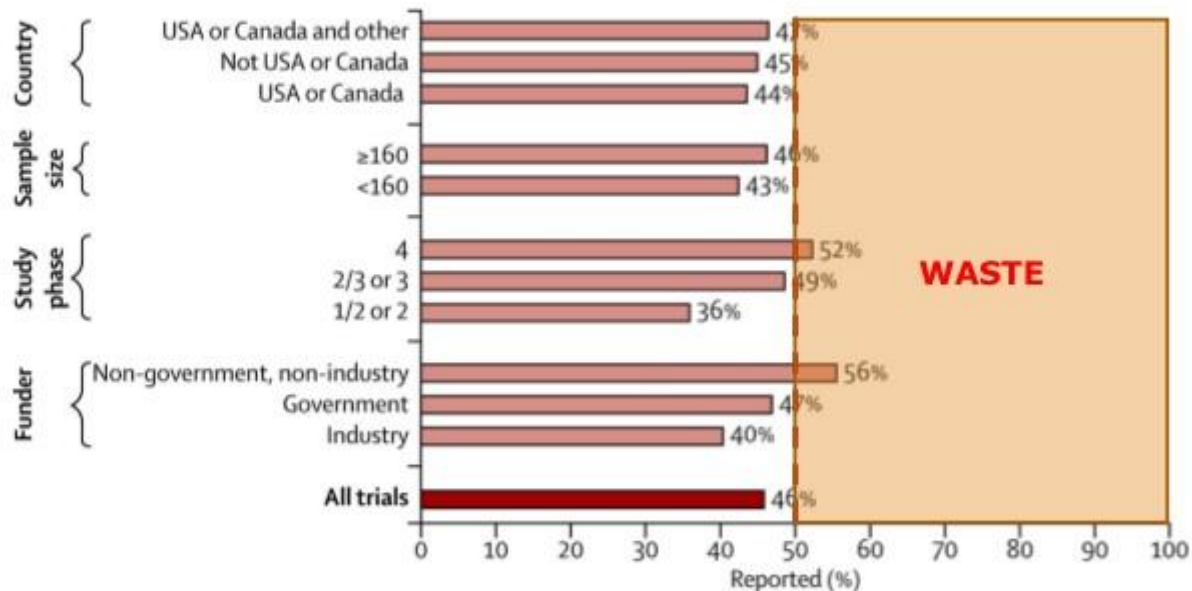


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# 50% of research is not published

*But similar across countries, size, phase, ...*



*Lancet* 2014;383:257-66

# Imiquimod for mollusca story

- Two large pivotal trials of 702 children
- Completed 2006
- Study 1494-IMI 24% imiquimod vs 26% vehicle
- Study 1495-IMI 24% imiquimod vs 28% vehicle
- No benefit shown in either study
- Missed in two subsequent systematic reviews and in Paed Derm 2017 review
- Why????

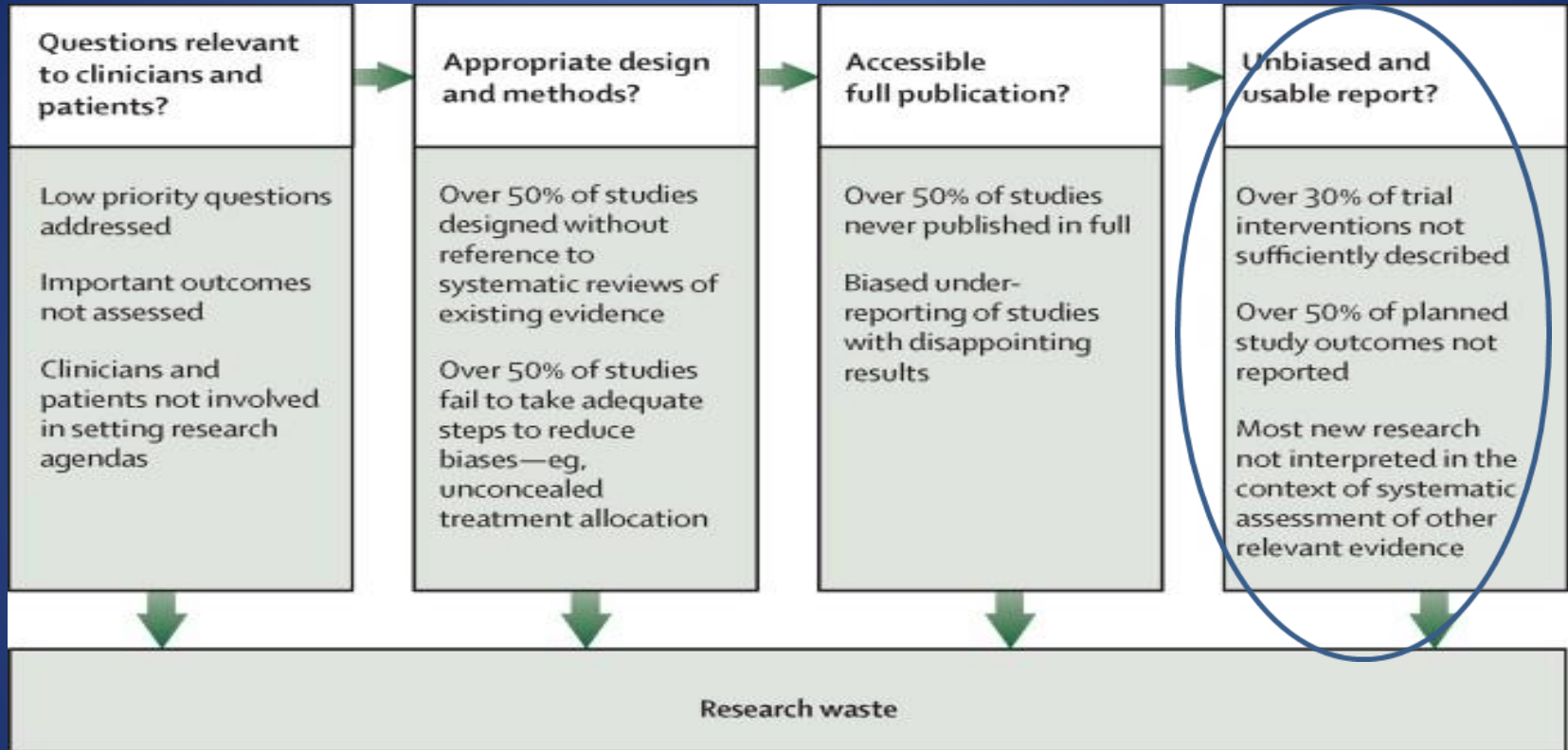
Katz KA. Imiquimod is not an effective drug for molluscum contagiosum. Lancet Infect Dis. 2014;14:372-3

# They were never published!



Katz KA, Williams HC, van der Wouden JC. Imiquimod cream for molluscum contagiosum: Neither safe nor effective. *Pediatr Dermatol.* 2018 Mar;35(2):282-283.

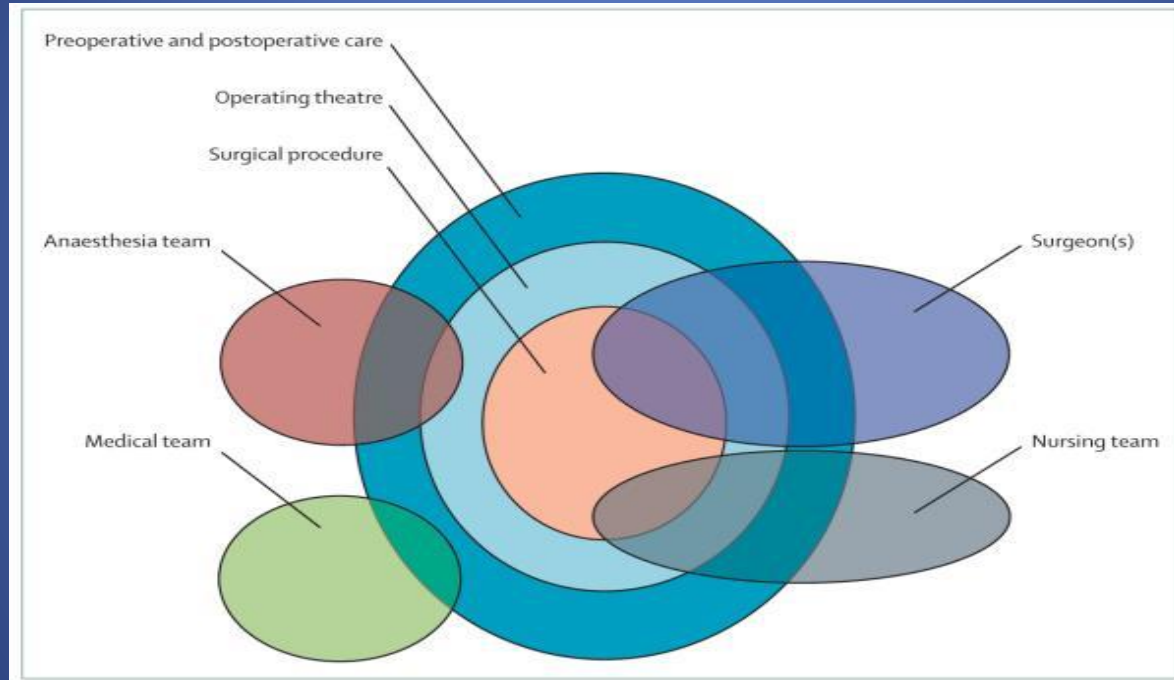




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# Surgery is a complex intervention



Ergina et al Lancet 2009;374:1097-1104

# MSLT-1



- Final report of sentinel node biopsy plus lymphadenectomy vs. observation in melanoma NEJM 2014
- Registered primary outcome = overall survival
- Completely missing from final report
- But you can work it out from the data
- Absolute risk reduction = 0.005 (-0.039 to 0.051)



Sladden M et al Br J Dermatol. 2015;172:566-71

# Probiotics for atopic eczema

- Viljanen et al randomised 230 infants with AD and cow's milk allergy to *Lacto rham* GG, or mix of four probiotics or inert cellulose and concluded

*“Treatment with LGG may alleviate atopic dermatitis symptoms in IgE-sensitised infants but not in non-IgE sensitised infants”*

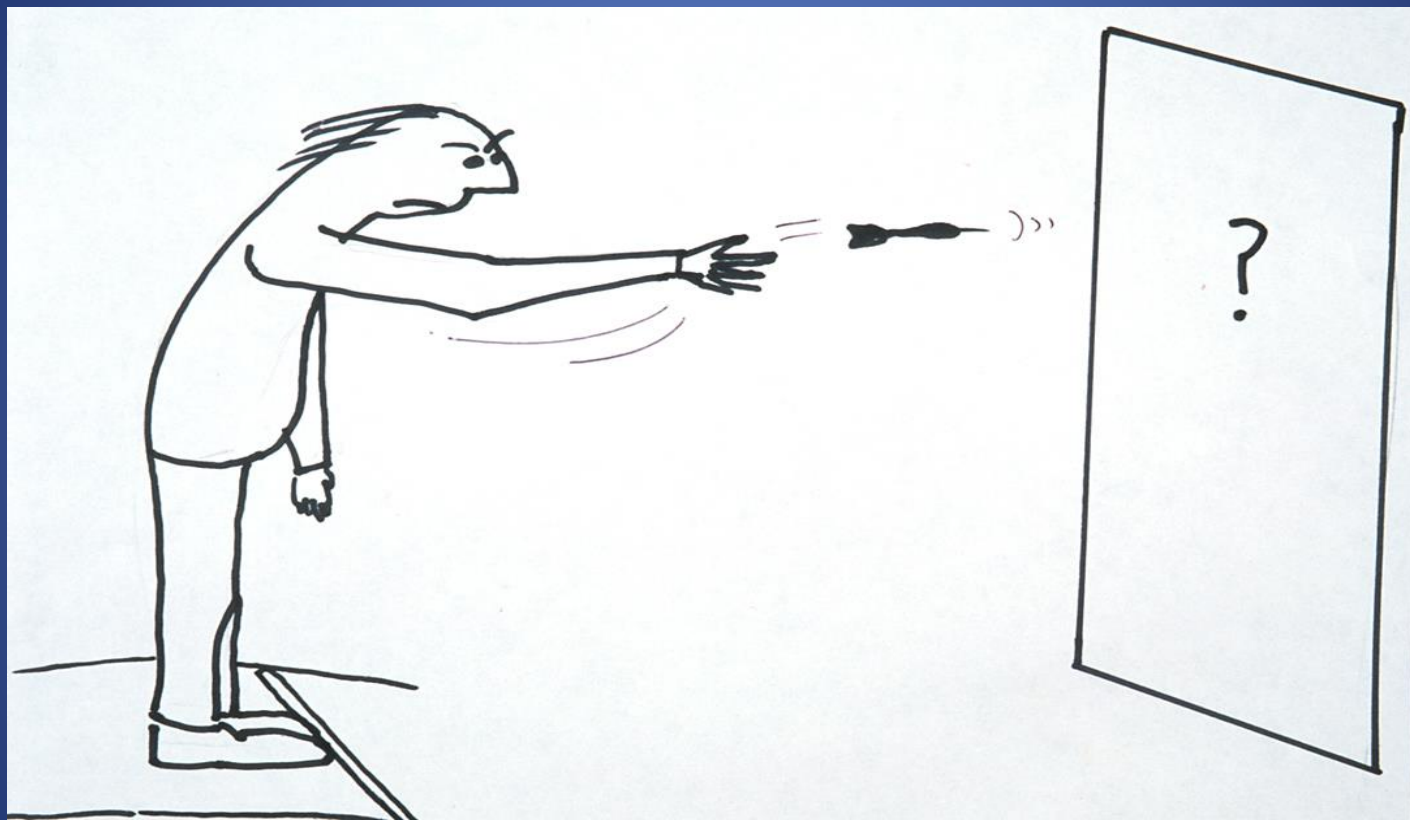
Viljanen et al *Allergy* 2005;60:494-500

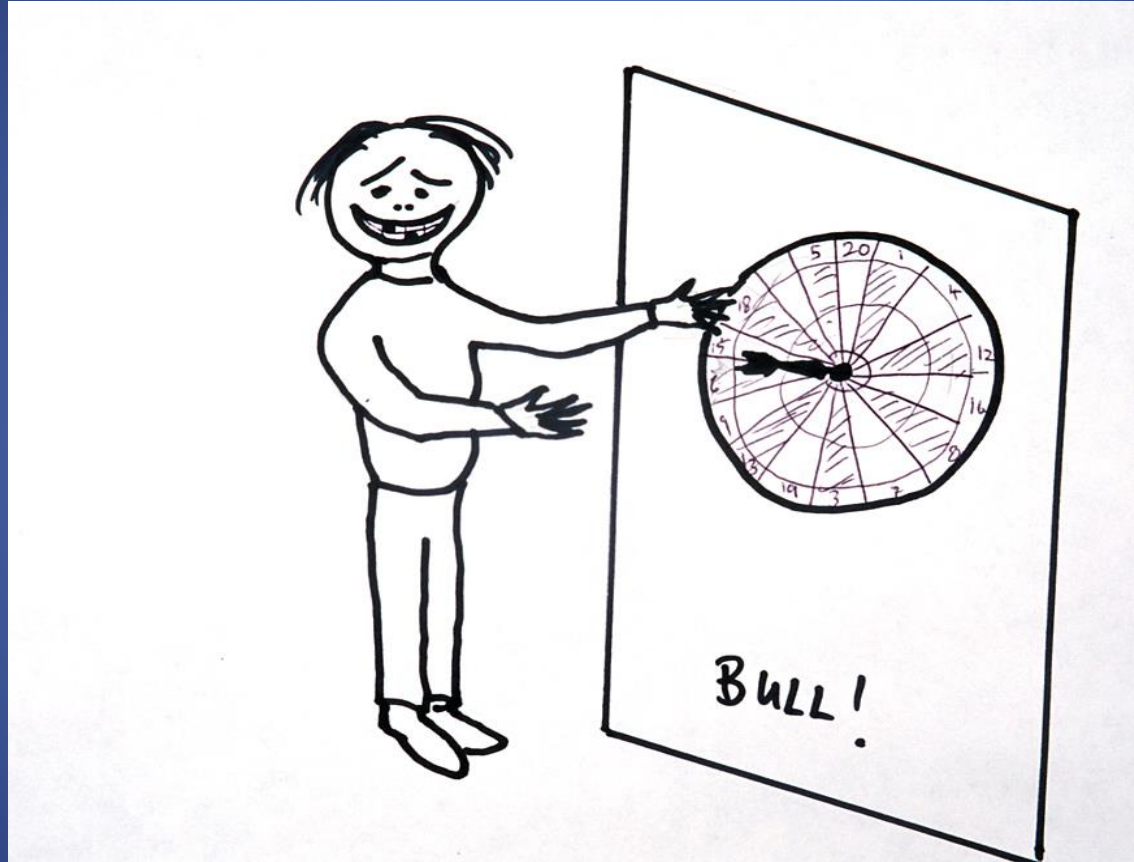
# But if you read the paper...

- Viljanen – main analysis for primary outcome not significant.
- Instead, they emphasised exploratory analysis in a subgroup 4 weeks after main assessment
- It's a bit like....

Williams HC. Two “positive studies of probiotics for atopic dermatitis – or are they?  
Arch Dermatol 2006;142:1201-3







Beware of post hoc findings

# Spin – another type of research waste

- 95% multiple primary outcomes
- 95% inappropriate extrapolation from specific to global improvement
- 75% focus on within-group improvement
- 65% focus on interim findings

**Analysis of Spin in the Reporting of Studies of Topical Treatments of Photoaged Skin. Motosko et al JAAD 2018 April 21 [Epub]**

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# Reasons for research waste?

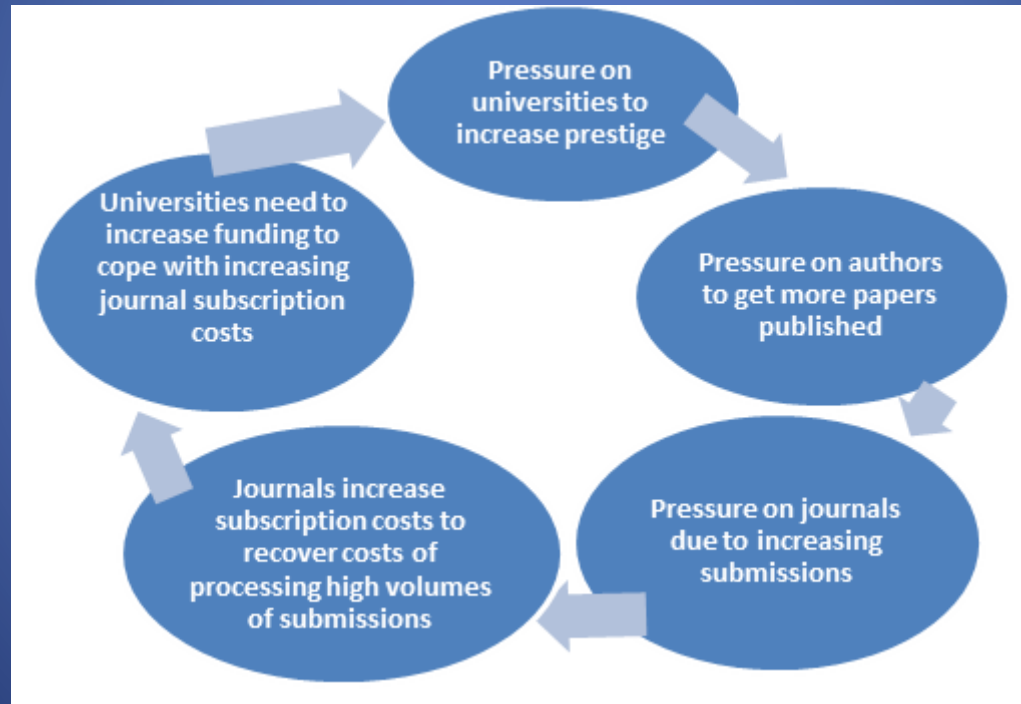
- Lack of researcher and research-user training
- Failure of funders to identify, prioritise and commission research
- University pressure to publish
- Journal editors
- Financial interests
- Lack of public awareness





This one doesn't even know how to appraise a clinical trial!

# Academic systems encourage obsession with publishing and impact factor



# Researcher behaviour



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# 1. Mapped systematic review evidence

oups/cebd/index.aspx Centre of Evidence Based D... Google

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University of Nottingham > Research > Groups > Centre of Evidence Based Dermatology

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Get involved

Resources

News and Events

Division of Rheumatology, Orthopaedics & Dermatology

School of Medicine


### Welcome to CEBD

We conduct independent research into the treatment and prevention of skin disease that is of direct relevance to patients, clinicians and NHS managers.

The centre has an international reputation for skin research and evidence based practice. We produce around 40-50 peer-reviewed publications per year and are one of the highest income generators for non-commercial dermatology research in the world.


About us ▶

#### Our Research




Details of our current and previous research projects.

#### Learn with us



Online and face-to-face courses about evidence-based research.


#### Our Resources



For clinicians, researchers and patients.


#### Connect with us

##### Twitter



We tweet about issues related to evidence based skin research.

##### Evidence updates



Monthly emails summarising the latest dermatology publications.

#### Patient opportunities

If you have a skin condition (or care for someone who does) there are many ways you can get involved in research, whether that's taking part in a study or joining a patient panel.

For more information about participating in research, see our [get involved](#) page.

#### News and Events

[Editorial Trainee for the British Journal of Dermatology](#)

[Topical cream is potential alternative to surgery for common type of skin cancer, study finds](#)

[NIHR Trainees Meeting 2016 Award](#)



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[School of Medicine](#)



CEBD produces free tools and resources of relevance to those who have or research skin conditions.

## Clinical Tools

[UK Diagnostic criteria for Atopic Dermatitis](#) A practical manual for researchers wishing to define atopic eczema (with photos)

[Nottingham Eczema Record Sheet](#)  
A useful form for young patients to complete before their first outpatient appointment [PDF](#)

[Skinsafe Interactive Tool](#) A downloadable application about malignant melanoma and skin-examinations

[Psychology & Eczema](#) A choice of 4 stories that can be personalised for children about eczema management

[Using hand-held light devices](#) A guide on how UV light devices can be used safely at home for vitiligo

[Minimal Erythema Dose \(MED\) testing](#) A guide on how to perform

## Outcome Measures

[Patient Oriented Eczema Measure \(POEM\)](#) A patient-reported outcome measure for monitoring atopic eczema severity

[Nottingham Eczema Severity Score \(NESS\)](#) An eczema severity measure based on the Rajka and Langeland grading

[Vitiligo Outcome Measures](#) A page giving information about vitiligo outcome measures, including the Vitiligo Noticeability Scale.

[Eczema flares](#) A collection of information on how flares could be captured in clinical trials.

[Harmonizing Outcome Measures for Eczema \(HOME\) initiative](#) A consensus based core outcome measure set for eczema - includes EASI guidance

## Collation of Evidence

[GREAT Database](#) Contains details of randomised controlled trials of eczema treatments published from 2000 onward.

[Systematic review of eczema treatments](#) Comprehensive reports evaluating eczema treatment trials and reviews

[CEBD Evidence Updates](#)  
Monthly emails summarising the latest dermatology publications

[Annual Evidence Updates](#)  
Summary papers collating recently published systematic reviews

[Maps of systematic reviews](#)  
Systematic reviews by topic: eczema, acne, psoriasis, vitiligo, cellulitis, hidradenitis suppurativa

[Skin Conditions in the UK: a Health Care Needs Assessment](#) A



# Systematic review maps



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**Breastfeeding**



**Dietary & supplements (for prevention)**



**Aeroallergen reduction (for prevention)**



**Other prevention**



## Topical treatments

**Topical corticosteroids**



2016 [Efficacy and safety of wet wrap therapy for patients with atopic dermatitis: a systematic review and meta-analysis](#)

2016 [What is the evidence-base for atopic eczema treatments? A summary of published randomised controlled trials](#)

2016 [Systematic review of published trials: long-term safety of topical corticosteroids and topical calcineurin inhibitors in pediatric patients with atopic dermatitis](#)

2016 [Scoping systematic review of treatments for eczema](#)

2016 [Systematic review and meta-analysis of randomized clinical trials \(RCTs\) comparing topical calcineurin inhibitors with topical corticosteroids for atopic dermatitis: A 15-year experience](#)

2015 [Topical corticosteroid-induced skin atrophy: a comprehensive review](#)

2015 [Safety of topical corticosteroids in pregnancy](#) (Cochrane Review)

2015 [A systematic review of topical corticosteroid withdrawal \("steroid addiction"\) in patients with atopic dermatitis and other dermatoses](#)

2015 [Risk of lymphoma in patients with atopic dermatitis and the role of topical treatment: A systematic review and meta-analysis](#)

2014 [Guidelines of care for the management of atopic dermatitis: section 2. Management and treatment of atopic dermatitis with topical therapies](#) (AAD guideline)

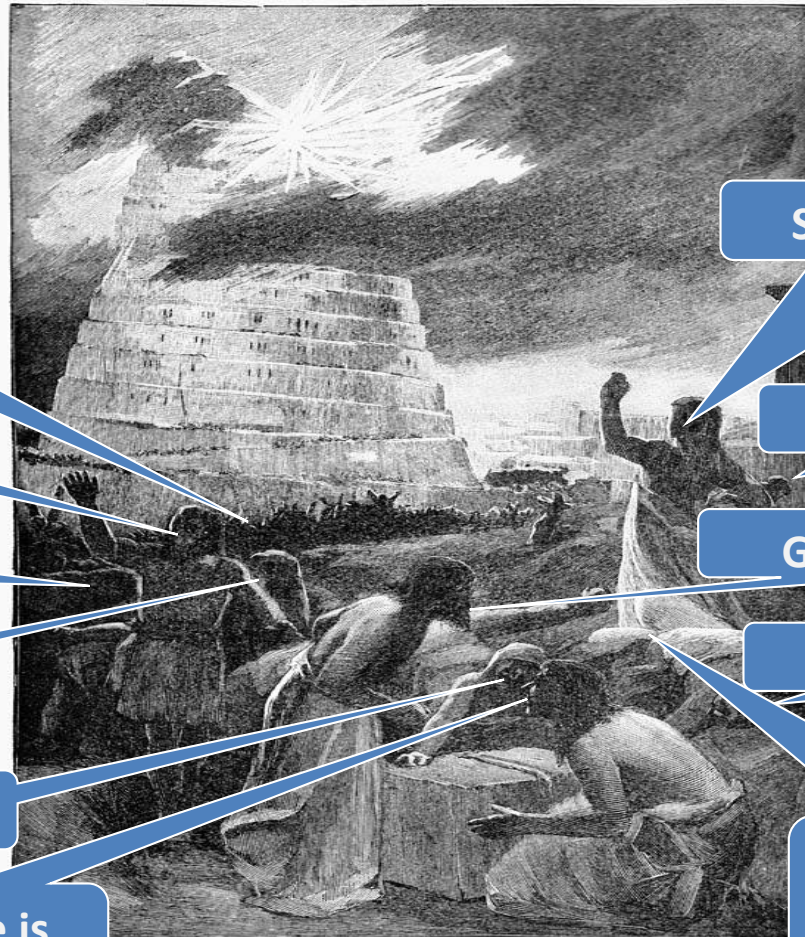
2014 [Guidelines of care for the management of atopic dermatitis: Section 4. Prevention of disease flares and use of adjunctive therapies and approaches](#) (AAD guideline)

## 2. Updated overarching systematic reviews

- 7 databases searched
- 287 new trials since 2000 HTA review
- 92 treatments
- Only 8% low risk of bias
- Hardly any done in primary care



# The tower of eczema outcomes research



What's all the  
FSSS about?

Take it EASI

TIS a right  
mess

Me too!

Meet my SIS

My name is  
ADAM

SCORAD scores again

SASSAD rules OK

Give me a POEM

ADASI tonight?

IGADA bad  
headache

Engraving by "Patriarchus and Proprius."

THE TOWER OF BABEL.

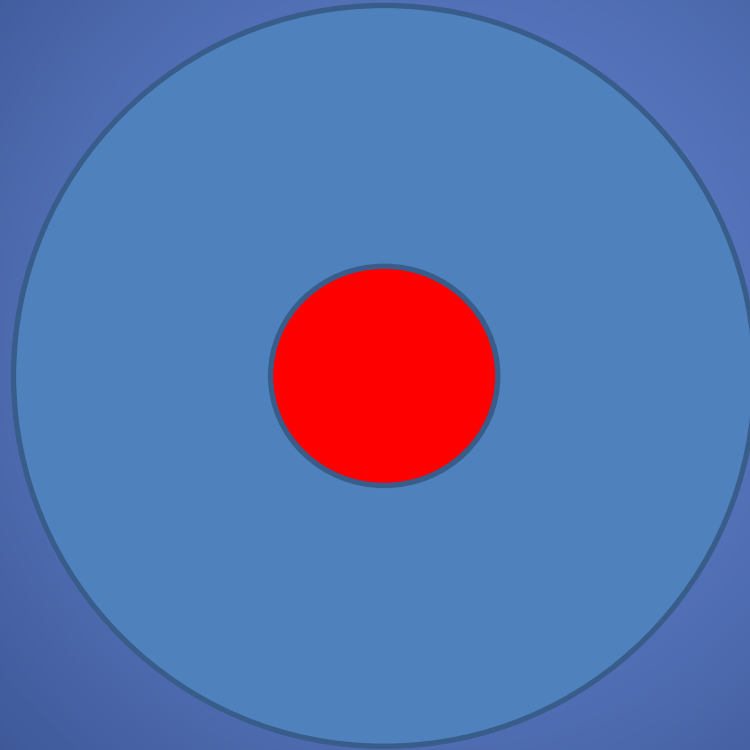
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# Outcome measures for atopic dermatitis

## – a mess

- Too many – over 20 named scales
- Many not tested at all
- Some are only partly tested (validity, repeatability, sensitivity change, consistency, interpretability)

# *Core* outcomes that are used in all trials



Schmitt J et al Cochrane Skin Core Outcome Set Initiative. Cochrane Reviews and Dermatological Trials Outcome Concordance: Why Core Outcome Sets Could Make Trial Results More Usable. J Invest Dermatol. 2019 May;139(5):1045-1053.



# Core outcome sets

[not secure](#) | [homeforeczema.org](http://homeforeczema.org)

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## Harmonising Outcome Measures for Eczema (HOME)

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Anyone with an interest in atopic eczema outcomes can join HOME. We have 345 members worldwide.

**Core Outcome Set (COS) and core outcome instruments (for clinical trials)**

- Clinical signs:** Eczema Area and Severity Index (EASI)
- Patient-reported symptoms:** Patient-oriented Eczema Measure (POEM) and NRS-11 for peak itch over past 24 hours)
- Long term control:** (Recap of Atopic Eczema (RECAP) or Atopic Dermatitis Control Test (ADCT))
- Quality of Life:** DLQI (adults), CDLQI (children), IDQoL (infants)




About HOME




Patient Associations

*These videos were recorded by the Association Française de l'Eczéma*




Core Outcomes for Eczema

The core outcome set (COS) and core outcome instruments




Meetings

Past and future HOME meetings




Patients

We're proud to have patients as an integral part of HOME




Publications

Articles, reviews and meeting reports from HOME



Background

Background to the HOME initiative



Links

Links to other core outcomes related projects

**AIM of HOME:** To agree a set of core outcome measures for eczema for use in **all** clinical trials. Ultimately, the aim is to have just *one instrument* per domain for:

1. Signs
2. Symptoms
3. Quality of Life
4. Measure of long term control of flares

	Stage 1 →	Stage 2 →	Stage 3 →			Stage 4 →	Stage 5
Task	Identify all instruments previously used to measure the domain.	Establish the extent and quality of testing of the identified instruments.	Determine which instruments are good enough quality meet the requirements of the OMERACT filter and be shortlisted for further consideration.			Carry out validation studies on shortlisted scales.	Finalise core outcome(s) for domain.
Methodology	Systematic review of outcome instruments used.	Systematic review of validation studies of the long-list of identified instruments. Highlight any gaps in validation.	Apply OMERACT filter; Truth, discrimination and feasibility:			Consensus discussion and voting to determine what validation studies will be conducted on short-listed instruments. Gaps in testing were highlighted in stage 2 (systematic review). Appropriate methods used to fill the gaps in validation.	Re-apply the OMERACT filter with the results of the completed validation studies. Consensus discussion and voting on core outcome to be recommended.
			<b>Truth</b> <i>"Is the measure truthful, does it measure what it intends to measure? Is the result unbiased and relevant?"</i> Consensus discussion and voting on truth: 1. Face validity 2. Content validity 3. Construct validity 4. Criterion validity	<b>Discrimination</b> <i>"Does the measure discriminate between situations that are of interest?"</i> Consensus discussion and voting on discrimination: 1. Reliability 2. Sensitivity to change	<b>Feasibility</b> <i>"Can the measure be applied easily in it's intended setting, given constraints of time, money, and interpretability?"</i> Consensus discussion and voting on feasibility: 1. Time taken 2. Cost 3. Interpretability		
Output	Long-list of all instruments previously used to measure the domain.	Summary of which instruments have been tested and the quality, extent and results of any testing.	Short-list of potential instruments that meet the requirements of the OMERACT filter.			Short-list of fully tested instruments.	Recommended core outcome(s) for the domain.



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CORE OUTCOME SET

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## > PROJECT GROUPS ONGOING

- > ACNE CORE OUTCOMES RESEARCH NETWORK (ACORN)
- > CORE OUTCOME MEASURES IN CHRONIC SPONTANEOUS URTICARIA
- > DEVELOPING A CORE OUTCOME SET FOR CHRONIC WOUNDS
- > HARMONISING OUTCOME MEASURES FOR ECZEMA (HOME)
- > CORE OUTCOME SET FOR THE APPEARANCE OF FACIAL AGING
- > HECOS: DEVELOPMENT OF A HAND ECZEMA CORE OUTCOME SET
- > DEVELOPMENT OF A CORE OUTCOME SET IN HIDRADENITIS SUPPURATIVA (HS)
- > CONSIDER - CORE OUTCOME SET IN IAD RESEARCH PROJECT: DEVELOPMENT OF A CORE SET OF OUTCOMES AND MEASUREMENT INSTRUMENTS FOR INCONTINENCE ASSOCIATED DERMATITIS (IAD) RESEARCH
- > DEVELOPING A CORE OUTCOME SET FOR MELANOMA TRIALS
- > DEVELOPMENT OF A CORE OUTCOME SET IN NAIL PSORIASIS
- > CORE OUTCOME SET FOR ROSACEA
- > THE OUTCOMES FOR PRESSURE ULCEER TRIALS

## Project groups ongoing

### Acne Core Outcomes Research Network (ACORN)



Acne is one of the most prevalent diseases worldwide, being one of three dermatoses in the global top ten (Hay R et al. J Invest Dermatol 2014; 134: 1527-34). Despite this, the quality of the evidence base for the comparative efficacy of acne treatments is poor. Numerous ...

> Mehr...

### Core Outcome Measures in Chronic Spontaneous Urticaria



Chronic spontaneous urticaria (CSU) is a frequent, distressing, embarrassing and often disabling skin condition which can last for years. Its estimated point prevalence is 0.5-1% of the total population.[1]

> Mehr...

### Developing a Core Outcome Set for Chronic Wounds



Based on "The German national consensus on wound documentation and outcomes: Rationale, working program and current status" an international consensus and data base should be developed.

> Mehr...

### Harmonising Outcome Measures for Eczema (HOME)



The Harmonising Outcome Measures for Eczema (HOME) project is an international group working together to agree a core outcome set (COS) for atopic eczema clinical trials.

> Mehr...

### Core Outcome Set for the Appearance of Facial Aging

"While aging is not a disease, it is treated as a condition in the context of efforts to treat aging by interventions like cosmetics, cosmeceuticals

Website durchsuchen



Cochrane  
Skin



Core Outcome Set Initiative

## Nachrichten

05.09.2016

>SAVE THE DATE: CSG-COUSIN Meeting 2017 - 9th and 10th January 2017 - Berlin, Germany

15.06.2016

>Second CSG-COUSIN Newsletter is online

26.02.2016

>COS development-guidance is online

23.02.2016

>Meeting-Report is online

23.10.2015

>Newsletter is online

## 4. National collection of eczema trials?







# Global Resource for Eczema Trials



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Browse the GREAT database

Search the GREAT database

A comprehensive collection of detailed information on systematic reviews and randomised controlled trials of eczema treatments  
**GREAT database last updated: Sunday 1st of May 2016**

## Background



Eczema is a complex, chronic and relapsing inflammatory skin disease affecting children and adults worldwide...

## Aims



To provide a comprehensive, easy to use and access resource...

## Collaboration



The data contained within this database is just part of a much larger data set being collected...

## Methods



The database contains records of RCTs published since the inception of MEDLINE/EMBASE and systematic reviews published since 2000

## Search strategy



The search for the RCTs contained in this database is based on the Cochrane Sensitive search strategy...

## How to cite



For those who use this database in their work, it should be cited as...



All trials (Filter)

All treatments

Antihistamines and Mast Cell Stabilisers

Antimicrobial and Antiseptic Agents

Complementary therapies

Dietary interventions

Non-pharmacological treatments

Oral Steroids

Other comparators

Other interventions

Other topical agents

Systemic immunomodulatory agents

Topical corticosteroids

Topical immunomodulatory agents

## All treatments

Choose a treatment from the full listing below, or browse treatment categories by clicking the left menu items. The figures in brackets indicate the number of trials associated with each treatment.

Prevention of eczema RCTs are not included in the database.

Acrivastine [1]	Acupressure [1]	Acupuncture [1]	Alclometasone [8]
Allergen-antibody complexes of house dust mite [2]	AN0128 [1]	AN2728/AN2898 [2]	Analogous blood therapy [3]
Antihistamines [2]	Antimicrobials [2]	Antioxidants [1]	Aquaphilus dolomiae [1]
Aromatherapy [2]	Ascomycin [1]	Ass's milk [1]	Atopidclair [5]
Atorvastatin [1]	Avoidance of enzyme-rich detergents [1]	Azathioprine [3]	Azelastine [2]
Bacterial lysate [3]	Balneotherapy [2]	Bath additives [5]	Beclometasone [2]
Benzalkonium chloride [2]	Betamethasone [41]	Bioresonance [1]	Black seed oil [1]
Borage oil [6]	Budesonide [1]	Bufexamac [1]	Butyl flufenamate [1]
Calcipotriol [2]	Camellia oil [1]	Camomile extract [1]	Capric acid [1]
Caprylic acid [1]	Carbohydrate derived fulvic acid [1]	Cefadroxil [1]	Cetirizine [10]
Change in altitude [1]	Chinese herbal medicine [26]	Chlorhexadine [1]	Chlorpheniramine [4]
Chymase Inhibitor [1]	Ciclopiroxolamine [1]	Cimetidine [3]	Cipamfylline [1]
Clarythromycin [1]	Clobetasol [8]	Clobetasone [7]	Clofibrate [1]
Control [14]	Cooling pillow [1]	Cow's milk [1]	Cow's milk formula [1]
Cyclosporin [22]	Defensamide [1]	Dermatologist consultation [3]	Dermatology nurse consultation [2]
Desonide [13]	Desoximetasone [1]	Desoximetasone [2]	Dietary restriction [9]
Dietary supplements [1]	Dietician advice [1]	Diflorasone [1]	Diflorasonediacetate [2]



**Number of participants randomised**

60, 30 in the montelukast group and 30 in the placebo group

**Follow up**

At the end of the single blind placebo phase and at 4 weeks and 8 weeks of randomised treatment

**Inclusion criteria**

Eczema defined according to the Hanifin and Rajka criteria, moderate disease severity defined as a SASSAD score between 12 and 50 at visits 1 and 2 (the 2 week single blind placebo phase). Aged 16 to 60.

**Exclusion criteria**

Pregnancy and lactation, known sensitivity or contraindication to montelukast and any co-existing skin disease, illness or other condition likely to require admission to hospital or impair assessments or influence treatment response.

**Description of randomisation and allocation concealment**

Treatment was supplied by the sponsor in containers labelled with sequential subject numbers containing medication in computer-generated randomized sequence. Treatment was allocated to the participants in strict numerical sequence.

**Description of blinding**

Investigators and participants were blinded to the treatment allocation throughout the study.

**Intention to treat**

An evaluable 'intention-to-treat' population of 29 participants is described for each group as one participant in each group was lost to follow up after baseline. It is stated in a graph that missing data was imputed by last observation carried forward.

**Withdrawals/dropouts**

One patient in each treatment was lost to follow-up. Between 4 and 8 weeks two further subjects in each group were lost to follow-up. In addition, one patient receiving montelukast was withdrawn due to dizzy spells, and one subject in the placebo group was withdrawn for to worsening of eczema.

**Outcome A**

Investigator assessed response to treatment (7 point scale)

**Outcome B**

Participant assessed response to treatment (7 point scale)

**Outcome C**

Severity (SASSAD)

# 5. Independent new drug commentaries with UKDCTN Fellows

- ☐ [After Decades Without any Developments, New Drugs May Revolutionize the Treatment of Atopic Dermatitis.](#)  
11. Morgado-Carrasco D, Fustà-Novell X, Riera-Monroig J, Iranzo P.  
Actas Dermosifiliogr. 2018 Jun;109(5):443-444. doi: 10.1016/j.ad.2017.08.011. Epub 2017 Nov 21. English, Spanish.  
No abstract available.  
PMID: 29169558  
[Similar articles](#)
- ☐ [Crisaborole Ointment 2%: A Review in Mild to Moderate Atopic Dermatitis.](#)  
12. Hoy SM.  
Am J Clin Dermatol. 2017 Dec;18(6):837-843. doi: 10.1007/s40257-017-0327-4. Review.  
PMID: 29076116  
[Similar articles](#)
- ☐ [Atopic dermatitis: emerging therapies.](#)  
13. Simpson E, Udkoff J, Borok J, Tom W, Beck L, Eichenfield LF.  
Semin Cutan Med Surg. 2017 Sep;36(3):124-130. doi: 10.12788/sder.2017.0137.  
PMID: 28895959  
[Similar articles](#)
- ☐ [Therapeutic pipeline for atopic dermatitis: End of the drought?](#)  
14. Paller AS, Kabashima K, Bleber T.  
J Allergy Clin Immunol. 2017 Sep;140(3):633-643. doi: 10.1016/j.jaci.2017.07.006. Review.  
PMID: 28887947  
[Similar articles](#)
- ☐ [Novel Therapeutic Approaches to Atopic Dermatitis.](#)  
15. Osinka K, Dumycz K, Kwiek B, Feleszko W.  
Arch Immunol Ther Exp (Warsz). 2018 Jun;66(3):171-181. doi: 10.1007/s00005-017-0487-1. Epub 2017 Aug 31.  
Review.  
PMID: 28861617  
[Similar articles](#)
- ☐ [Crisaborole. A new and effective nonsteroidal topical drug for atopic dermatitis.](#)  
16. Kailas A.  
Dermatol Ther. 2017 Sep;30(5). doi: 10.1111/dth.12533. Epub 2017 Aug 23. No abstract available.  
PMID: 28834023  
[Similar articles](#)
- ☐ [Long-term safety of crisaborole ointment 2% in children and adults with mild to moderate atopic dermatitis.](#)  
17. Eichenfield LF, Call RS, Forsha DW, Fowler J Jr, Hebert AA, Spellman M, Stein Gold LF, Van Syoc M, Zane LT, Tschien E.  
J Am Acad Dermatol. 2017 Oct;77(4):641-649.e5. doi: 10.1016/j.jaad.2017.06.010. Epub 2017 Aug 18.  
PMID: 28823881 **Free Article**  
[Similar articles](#)

# Look out for new topicals...crisaborole

- Two pivotal studies – mild to moderate eczema in children N=759 and N=763
- Well reported and registered
- Study 1: success active = 32.8% vs 25.4% vehicle (number needed to treat = 13)
- Study 2: success active = 51.7% vs 40.6% vehicle (number needed to treat = 9)
- Need active comparators eg 1% hydrocortisone

Ahmed A, Solman L, Williams HC. Magnitude of benefit for topical crisaborole in the treatment of atopic dermatitis in children and adults does not look promising: a critical appraisal. Br J Dermatol. 2018;178:659-662.

## 6. Filling the research gaps








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[School of Medicine](#)

## Eczema Priority Setting Partnership



### Key Facts

-  [1. What did the priority setting exercise involve?](#)
-  [2. How many people took part?](#)
-  [3. What were the results?](#)
-  [4. What next?](#)
-  [5. Who led this project?](#)



### Overview

Eczema is a common condition yet there are numerous uncertainties in its treatment. More research is needed on how to treat the condition effectively, but it is unusual for patients and clinicians to set the research agenda.

In order to involve both those who have eczema, and those who treat eczema, a priority setting partnership was formed to tackle this issue. The Partnership was overseen by the James Lind Alliance and included patients, clinicians and researchers. Its central task was to identify uncertainties about treatments for eczema and to [prioritise the top selected issues](#) for future research.

### Outcomes

#### Publications

- Batchelor JM, Ridd MJ, Clarke T, Ahmed A, Cox M, Crowe S, Howard M, Lawton S, McPhee M, Rani A, Ravenscroft JC, Roberts A, Thomas KS. [The Eczema Priority Setting Partnership: A collaboration between patients, carers, clinicians and researchers to identify and prioritise important research questions for the treatment of eczema](#) *Br J Dermatol.* 2013;168:577-82.
- [Newsletter \(final\)](#) 
- [Study Protocol](#) 

#### Conferences

Eczema PSP findings have been presented orally and through posters at various conferences including the British Dermatology Nursing Group Annual Conference, the Royal College of General Practitioner's Annual Conference, the European Academy of Dermatology



# Identifying answerable questions important to patients and carers



[www.ukdctn.org](http://www.ukdctn.org)



# Top 14

## Shared priorities

- What is the **best and safest way of using topical steroids** for eczema?
- What is the **long term safety** of applying steroids to the skin for eczema?
- What role might **food allergy tests** play in treating eczema?
- Which **emollient** is the most effective and safe in treating eczema?

## Patient and carer priorities

- What is the best **psychological treatment** for itching/scratching in eczema ?
- Which is the best way for people with eczema to **wash**: frequency of washing, water temperature, bath versus shower ?
- What are the best and safest **natural products** to apply to the skin for eczema?
- How much does **avoidance of irritants and allergens** help people with eczema ?
- What is the **role of diet in treating eczema**: exclusion diets and nutritional supplements ?

## Health professional priorities

- Which is more effective in the management of eczema: **education programmes**, GP care, nurse-led care, dermatologist-led care or multi disciplinary care?
- Which is safer and more effective for treating eczema; **steroids or calcineurin inhibitors**?
- How effective are **interventions to reduce skin infections** in the management of eczema?
- **Which should be applied first** when treating eczema, emollients or topical steroids?
- What is the best and safest way of using **drugs that suppress the immune system** when treating eczema?

# Uncertainties investigated in RCTs

- Antibiotics for infected eczema (CREAM)
- Silk clothing (CLOTHES)
- Bath emollients (BATHE)
- Eczema Online Education (ECO)
- Systemic treatments (TREAT)
- Best emollients for eczema (BEE)
- Emollients for the prevention of eczema (BEEP)





James  
Lind  
Alliance

Priority Setting Partnerships


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About PSPs

How do I set up a PSP?

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JLA Advisers

History

What people say

## About Priority Setting Partnerships

“This PSP has been a truly collaborative effort and everybody has had a voice. It has widened horizons and will shape clinical research for brain cancer patients and the people who look after them. This means that in future clinical research will be relevant, focused and cohesive. It’s been a fabulous experience”

*Helen Bulbeck, Director of [braintrust](#), about the [Neuro-oncology PSP](#)*

[Priority Setting Partnerships \(PSPs\)](#) enable clinicians, patients and carers to work together to identify and prioritise evidence uncertainties in particular areas of health and care that could be answered by research. While the [James Lind Alliance \(JLA\)](#) facilitates these partnerships, the funding and organising is done by the PSP itself.

Focusing on specific conditions or healthcare settings, the JLA facilitates PSPs which:

- bring patient, carer and clinician groups together on an equal footing
- identify evidence uncertainties (questions which cannot be answered by existing research) which are important to all groups
- work with all groups to jointly prioritise identified uncertainties
- produce a final list (often a [Top 10](#)) of jointly agreed research priorities, publicise them widely, and make sure that other uncertainties are recorded and available for researchers and research funders to access
- provide a rare and valuable opportunity for patients and clinicians to shape the health research agenda

### Mailing list

Sign up to our newsletter and stay up to date on the latest news from the JLA

[Sign up](#)

### JLA on Twitter

Tweets by [@LindAlliance](#)

[James Lind Alliance](#)  
Retweeted

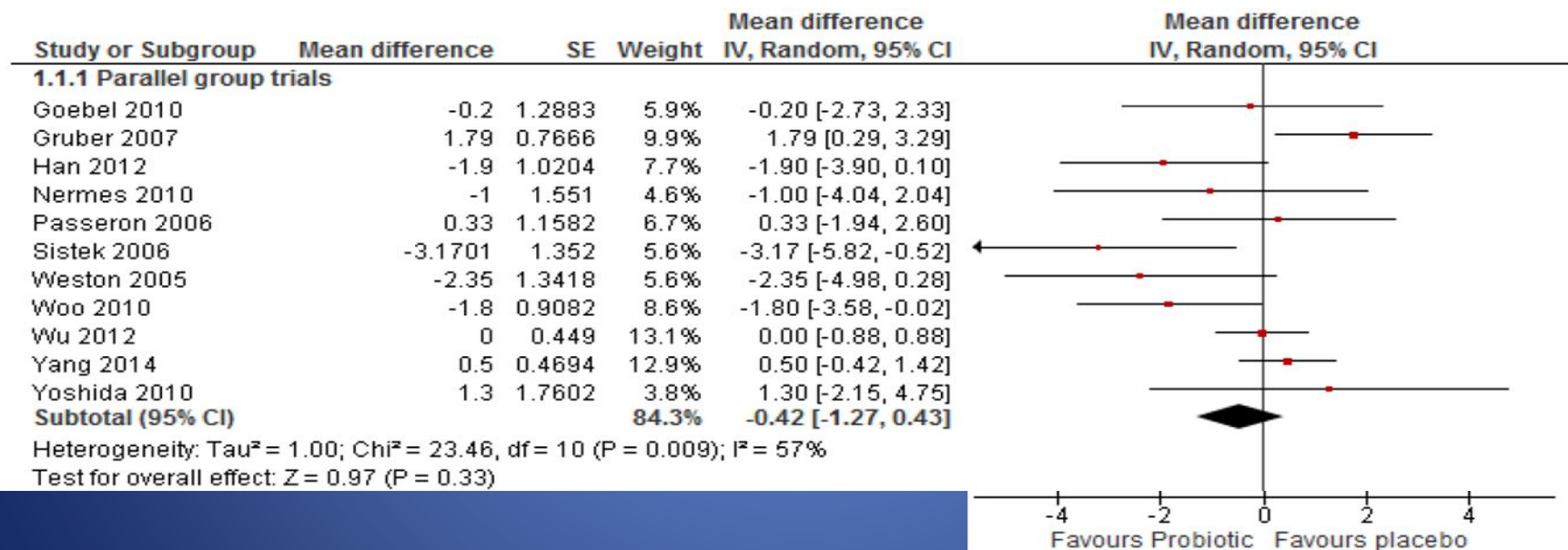


**Gabrielle Rankin**  
[@GabriellePhysio](#)

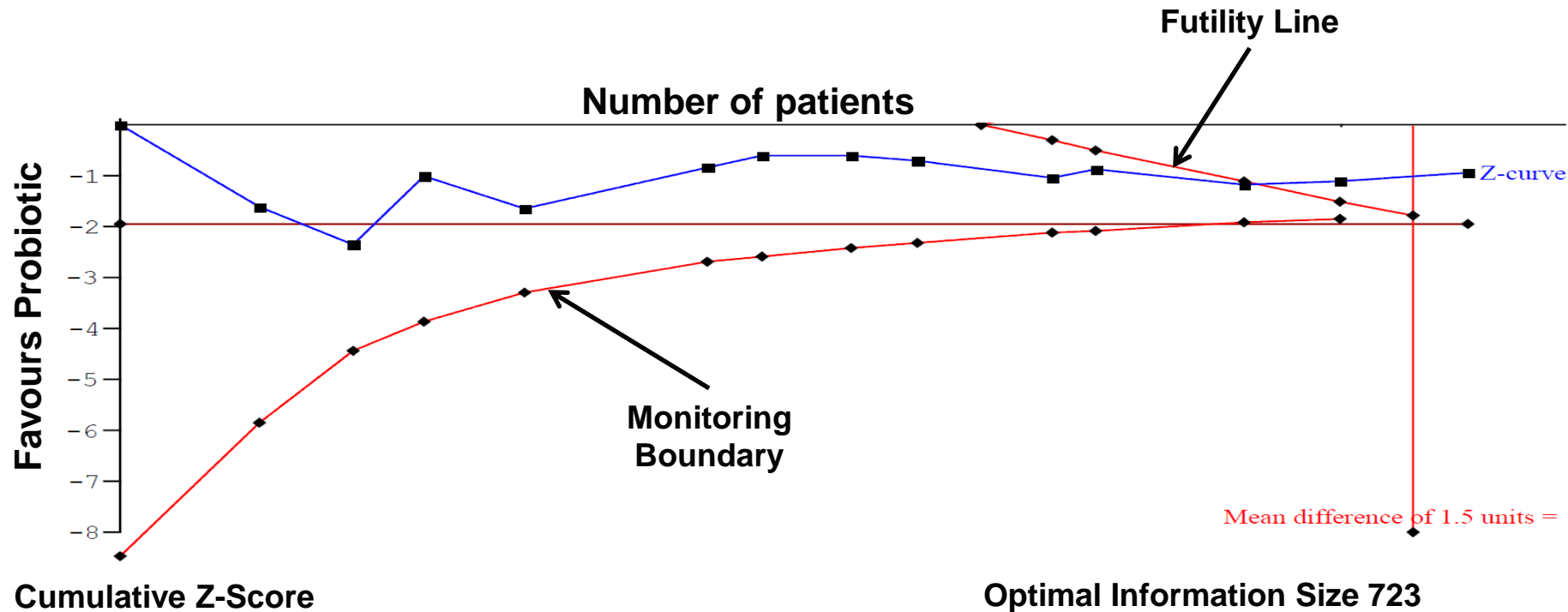
Read about how we set [@thecsp](#) [@LindAlliance](#) research priorities in [@\\_Physiotherapy](#) journal [doi.org/10.1016/j.phys...](#) and don't forget CT Research Priorities Award - closing date 2nd September [bit.ly/327CmXx](#)

# Not wasting time updating Cochrane reviews: trial sequential analysis

## 1.1 Participant or parent-rated symptoms of eczema (SCORAD part C) at the end of treatment

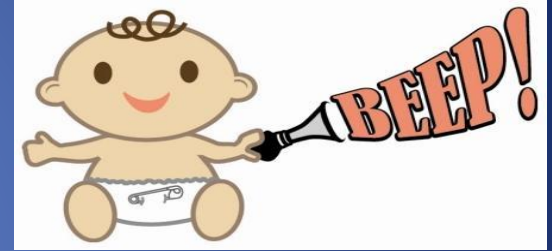


# Probiotics for Treating Eczema



# Prospectively planned meta-analysis

- Barrier enhancement for eczema prevention
- PreventADALL
- Japan
- Two in Germany
- One in US and more.....





# Value of information

- Techniques that use data (control event rate, estimate of effect, incidence data, duration of research, cost and discounting)
- Estimate the value of reducing uncertainty
- Can be done for range of studies and use cost per QALY as common currency

# 7. Trial registration and better reporting with CONSORT

- British Journal of Dermatology
- Journal of Investigative Dermatology
- Journal American Academy of Dermatology
- JAMA Dermatology
- Indian Journal Dermato-Venereology and Leprology
- ActaDV



# Place your bet and show us your hand



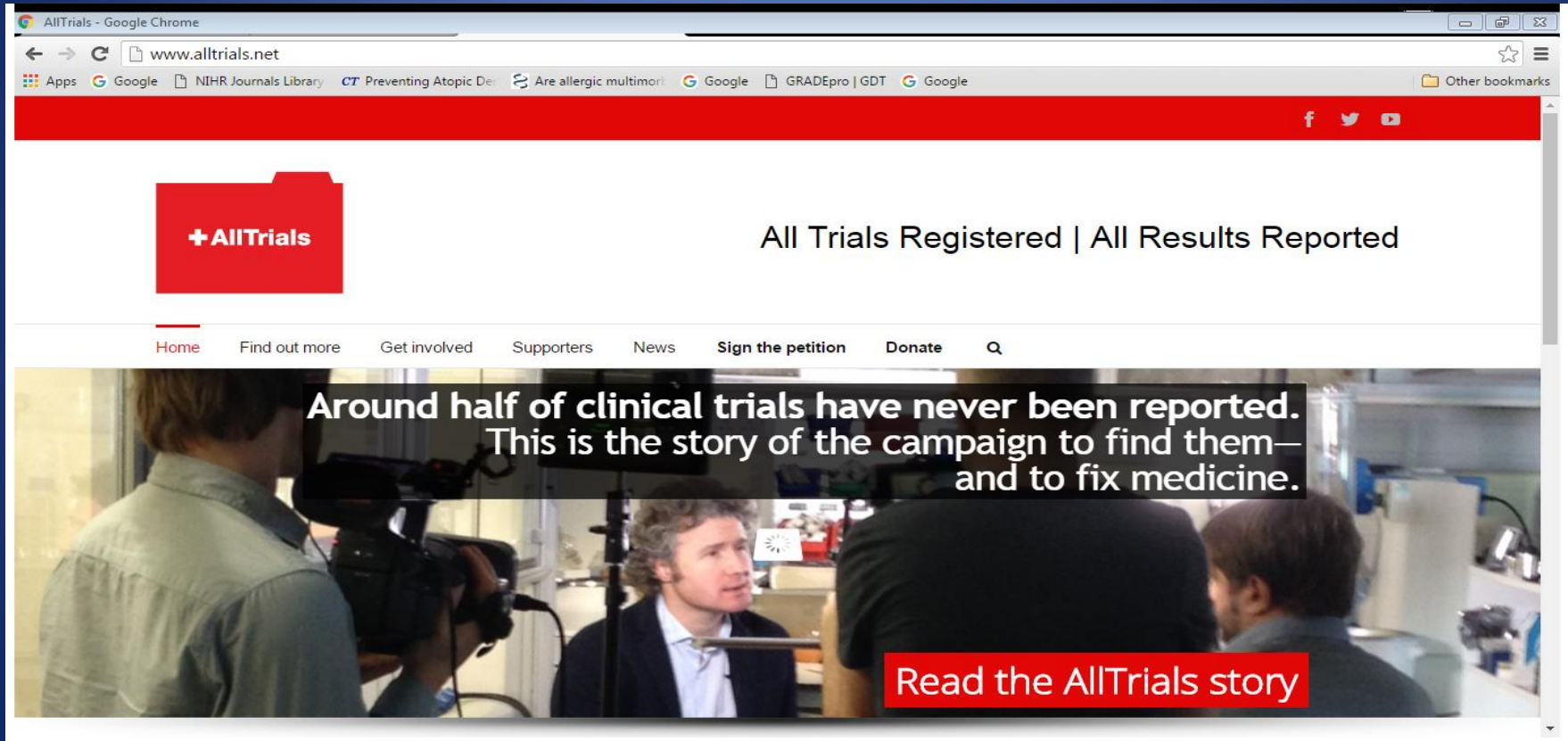
## Rule 1: Place your bet



## Rule 2: Show us your hand

Williams HC, Gilchrest B. Clinical Trials Submitted to the JID: Place Your Bet and Show Us Your Hand. J Invest Dermatol. 2015;135:325-7.

# AllTrials campaign



# The public is now watching us...

Tracking switched outcomes in clinical trials - Tracking switched outcomes in clinical trials - Google Chrome

compare-trials.org

Apps Google NIHR Journals Library CT Preventing Atopic Dermatitis Are allergic multimorbidity GRADEpro | GDT Google Other bookmarks

 **COMPARE**  
TRACKING SWITCHED OUTCOMES IN CLINICAL TRIALS

[METHODS](#) | [RESULTS](#) | [TEAM](#) | [BLOG](#) | [FAQ](#)

## Tracking switched outcomes in clinical trials

Outcome switching in clinical trials is a serious problem. Between October 2015 and January 2016, the COMPare team systematically checked every trial published in the top five medical journals, to see if they misreported their findings:

1. We compared each clinical trial report with its protocol or registry entry. Some trials reported their outcomes perfectly. For the others, we counted how many of the outcomes pre-specified in the protocol or registry were never reported. We also counted how many new

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# 8. Dissemination

- Monthly e-newsletter
- New systematic reviews
- Community of 1000 users
- Many alumni

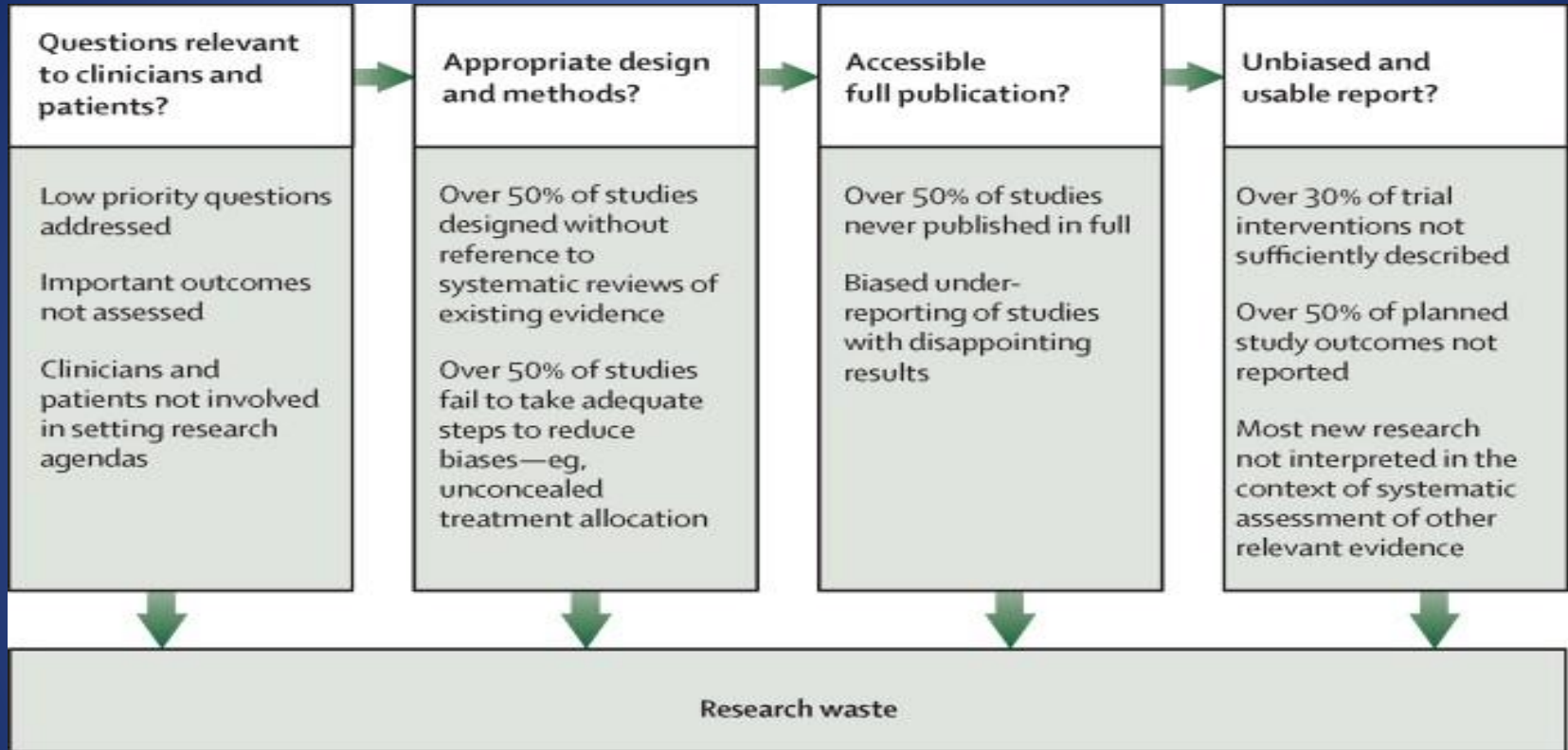


To join, just email Douglas: [douglas.grindlay@nottingham.ac.uk](mailto:douglas.grindlay@nottingham.ac.uk)



# What I am going to do

- Some personal background
- Describe the anatomy of research waste with examples from dermatology
- Consider the reasons for research waste
- Say how we have tackled research waste at our Centre of Evidence-Based Dermatology
- End with some **solutions and reflections**

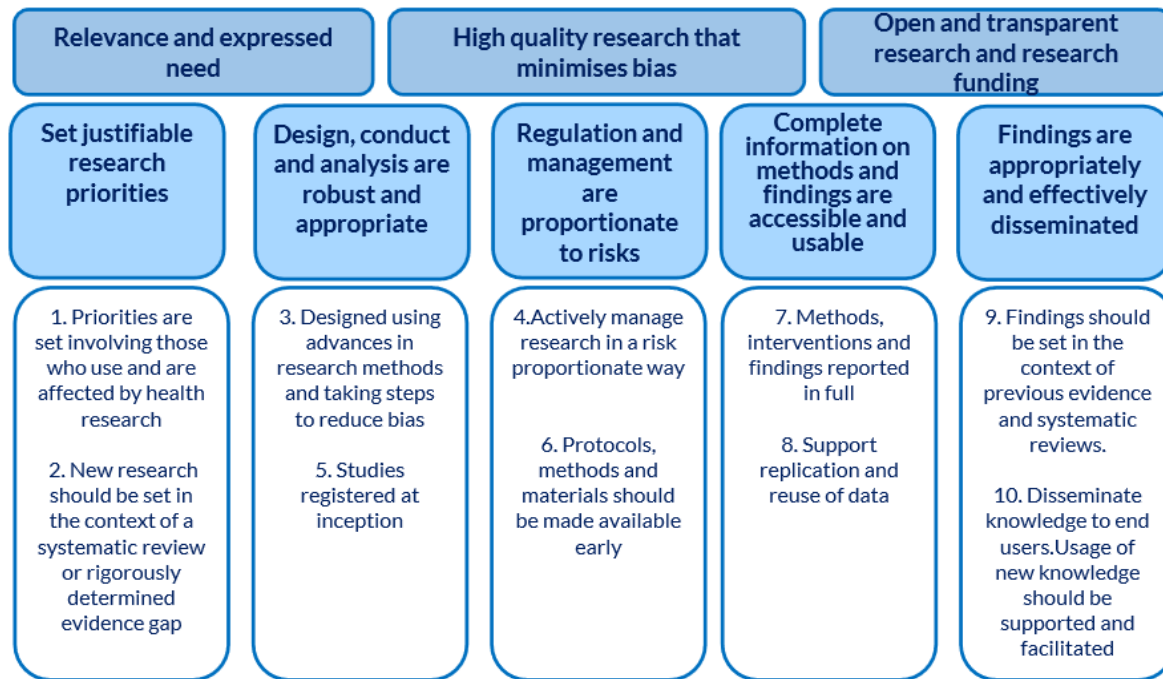


Stages of waste in the production and reporting of research evidence relevant to clinicians and patients

Chalmers I, Glasziou P. Avoidable waste in the production and reporting of research evidence. Lancet 2009; 374:86-89.

# NIHR Adding Value in Research Framework

Raising the probability of benefits to society from health-related research for the tangible and intangible costs involved



WHO value in medical w... EVIR Funders' Forum

Secure sites.google.com/view/evir-funders-forum

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EVIR Funders' Forum

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Ensuring Value in Research (EVIR)

Funders' Collaboration and Development Forum

Organisations from around the world are coming together to advance the practices of health related research and research funding, in order to increase the value of health related research.

The Ensuring Value in Research (EVIR) Funders' Collaboration and Development Forum started in 2017, with meetings in London, Den Haag and Washington DC. In our first year the Funders' Forum developed a [Consensus Statement](#) and [Guiding Principles](#).

As organisations that fund health-related research, represent funders, or set funding policy, we have a responsibility not just to seek to advance knowledge, but also to advance the practices of health-related research and research funding. Through working together and with our respective research communities we are sharing current and developing new approaches to increase the value of health-related research.

Delegates from eight countries have attended meetings so far, with the next meeting of the EVIR Funders' Forum taking place in Cardiff, Wales, UK on 16-17 May 2018.

Members of the forum who have already endorsed the consensus statement and guiding principles include:

- [Forte \(Sweden\)](#)
- [Health and Care Research Wales - Welsh Government \(UK\)](#)
- [Health Research Board Ireland \(Ireland\)](#)
- [Marie Curie \(UK\)](#)
- [Ministry of Health Salute \(Italy\)](#)
- [NIHR - National Institute for Health Research \(UK\)\\*](#)
- [PCORI - Patient Centered Outcomes Research Institute \(USA\)\\*](#)
- [The Scar Free Foundation](#)
- [ZonMW - The Netherlands Organisation for Health Research and Development \(Netherlands\)\\*](#)

*\*Co-convenors of the EVIR Funder's Forum.*

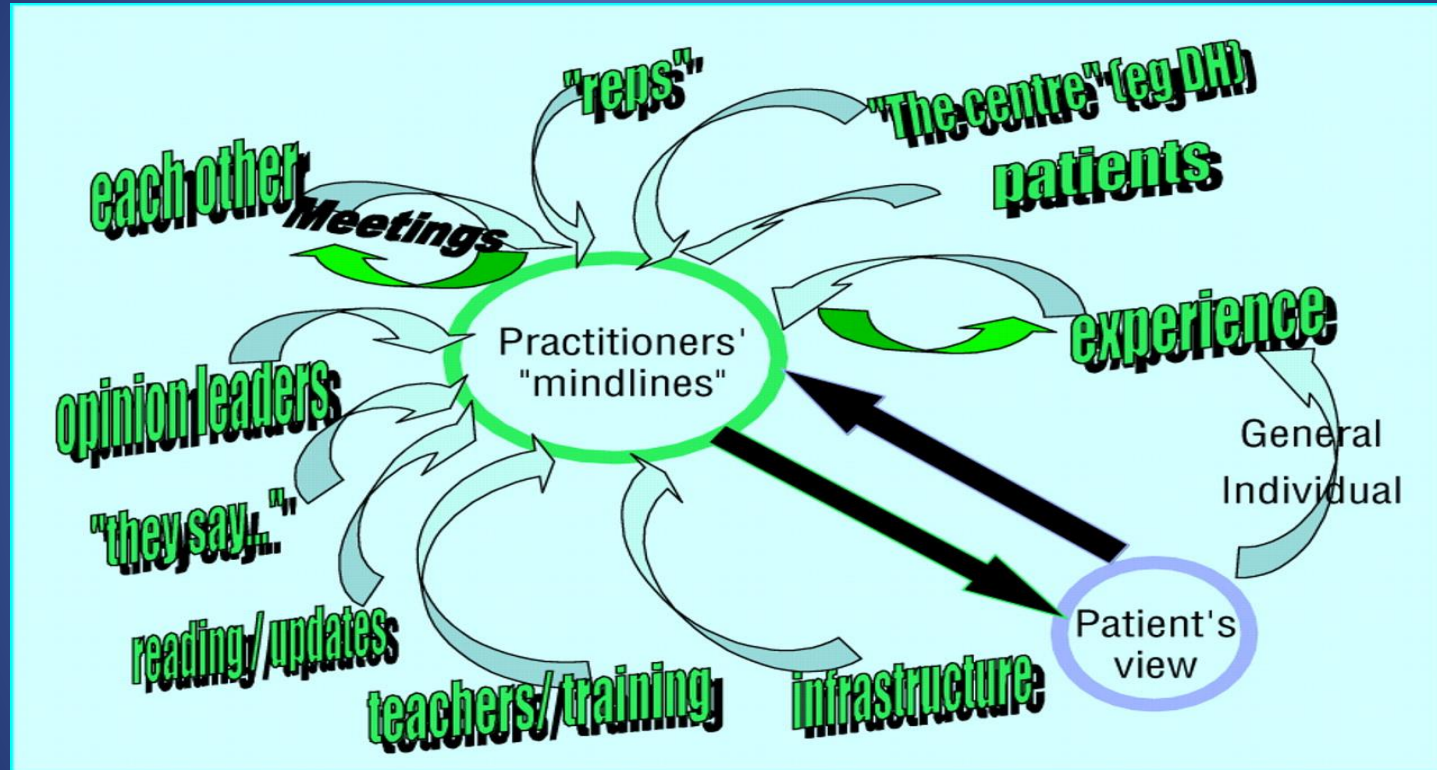
# NIHR track record on reducing research waste – external evidence

- Nasser et al searched 11 international funder websites
- Including UK: NIHR, MRC, Australia: NHMRC, Canada: CIHR, US: NIH, Germany: DFG, France: FOH, ANR, Dutch ZonMw, Denmark: DR, Norway: RH
- On registration, access to protocols, access to completed data, promotion reporting guidelines, support systematic reviews, require SRs of existing evidence, research on research
- Only NIHR achieved 5 green ratings (plus two yellow)
- ZonMw: 2 green, 3 yellow and 2 reds
- NIH 1 green, 3 amber, 3 reds

Nasser M, Clarke M, Chalmers I, et al. What are funders doing to minimise waste in research? Lancet 2017; 389: 1006–07.



# Knowledge mobilisation and mindlines



John Gabbay, and Andrée le May BMJ 2004;329:1013

# Learn something from industry...

- Example: LIBERTY AD CHRONOS
- 161 hospitals
- 14 countries

Blauvelt A et al Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS) ...  
Lancet. 2017;389(10086):2287-2303.

# Solutions to research waste

- **Involve patients and the public** in prioritizing research questions and throughout the research journey
- **Better training in critical appraisal** so that research becomes everybody's business – don't trust academics to do it all
- **Funder prioritization** and contract for registration and publication
- **Culture change**: place your bet and show us your hand
- More emphasis from **universities** on patient/public benefit than impact factor
- **Team science** more than glorification of individuals
- Improve **knowledge mobilization** science



# Less research but better research





Reducing  
research waste  
is everybody's  
business

