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Cochrane Skin

COUSIN
Core Outcome Set Initiative

Individual participant data meta-analysis

Annual Cochrane Skin Group Meeting & CS-COUSIN
2019 Meeting

Dr Maeve Kelleher & Dr Suzie Cro

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What is individual data meta-analysis

- Individual patient data
- relates to the data record for individual participants in a study
- original source data from trialists

Versus

- Aggregate data
- Information averaged or estimated across all individuals in the study

- One of first IPD described Lancet 1993 - cisplastin therapy in ovarian cancer

Stewart LA, Parmar MKB. Meta-analysis of the literature or of individual patient data: is there a difference? *The Lancet*. 1993;341(8842):418-22.

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Aims of an IPD meta-analysis

- Similar aims as a aggregate meta- analysis – summarise the evidence on a particular clinical question based on similar trials
- Inform evidence based practice
- Pooled level of evidence
- How treatment effect is modified by study or participant factors

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Advantages of IPD

Quantity and quality

- More trials and participants
- Verification of results of individual studies
- Checking of original data
- Standardisation of outcomes

Statistical analysis

- May allow for more up to date follow up of participants
- Results for poorly reported outcomes can be calculated
- Results of unpublished studies can be calculated and incorporated
- Standardised statistical methods

Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data: rationale, conduct, and reporting. *BMJ*. 2010;340:c221
Stewart LA, Tierney JF. To IPD or not to IPD?:Advantages and Disadvantages of Systematic Reviews Using Individual Patient Data. Evaluation & the Health Professions. 2002;25(1):76-97

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Advantages of IPD

Who does the intervention work for?

- Consistent exclusion and inclusion criteria
- Adjust for baseline characteristics
- Meta- analysis for specific sub groups – each participant is analysed in the correct subgroup
- Prognostic modelling

Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data: rationale, conduct, and reporting. *BMJ*. 2010;340:c221
Stewart LA, Tierney JF. To IPD or not to IPD?:Advantages and Disadvantages of Systematic Reviews Using Individual Patient Data. Evaluation & the Health Professions. 2002;25(1):76-97

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Disadvantages of IPD

- Time & Effort
- Ethical or confidentiality concerns about using participant level data
- Data issues – clean data, consistent format
- Resources for team collecting data but also original authors
- Quality of data is dependent on the quality of original study

Potential Biases

- Study selection bias
- Publication bias
- Availability bias

Tierney JF, Vale C, Riley R, Smith CT, Stewart L, Clarke M, et al. Individual Participant Data (IPD) Meta-analyses of Randomised Controlled Trials: Guidance on Their Use. PLoS medicine. 2015;12(7):e1001855-e.

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When is aggregate data enough?

- When there is already detailed and clear reporting of trials
- For short term outcomes
- For binary outcomes
- Simple analysis
- Trials already have clear outcome measures
- Subgroups less important
- if all the required aggregate data can be obtained in full from authors or the published papers themselves

Stewart LA, Tierney JF. To IPD or not to IPD?:Advantages and Disadvantages of Systematic Reviews Using Individual Patient Data. Evaluation & the Health Professions. 2002;25(1):76-97.

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Example of IPD versus aggregate data meta- analysis

Laproscopic verus Open hernia repair for reducing pain.

- Aggregate data meta-analysis

→ statistically significant benefit *in favour of open repair* (odds ratio 2.03, 95% CI 1.03 to 4.01)

- Individual data meta-analysis

→ *laparoscopic repair* significantly reduced persistent pain compared with open repair (odds ratio 0.54, 95% CI 0.46 to 0.64

<u>Reason for differences</u>

- IPD included and additional 17 trials
- Few usable published aggregate data studies available
- IPD Re-analysis of one trial showed marked differences compared to aggregate results.

McCormack K, Grant A, Scott N. Value of updating a systematic review in surgery using individual patient data. *Br J Surg* 2004;91:495-9.

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Growth in IPD meta- analysis

- First reported in 1992
- Now recognised as “gold standard” for systematic review
- Increased publication of IPD meta- analysis
- Increasing promotion of publishing all trial data, and maximising use of clinical data from trials.

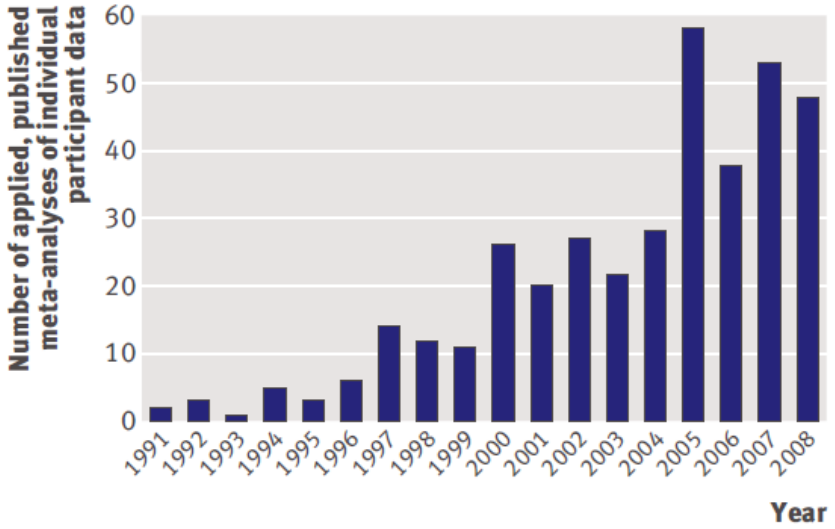

Fig 1 | Number of distinct, applied meta-analyses of individual participant data published up to March 2009,* as identified by a systematic review of Medline, Embase, and the Cochrane Library. *Six articles published in 2009 were identified up to 5 March, when the review was conducted

Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data: rationale, conduct, and reporting. *BMJ*. 2010;340:c221
www.alltrials.net

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IPD & Cochrane

Cochrane Methods
IPD Meta-analysis

Trusted evidence.
Informed decisions.
Better health.

- Typically IPD meta-analysis are not Cochrane led
- IPD analysis methods group provides guidance to those planning an IPD meta-analysis
- Convened in 1994
- Provides workshops at Cochrane Colloquia and training courses.
- Preferred Reporting Items for a Systematic Review and Meta-analysis of Individual Participant Data (PRISMA –IPD)

https://methods.cochrane.org/ipdma/welcome-ipd-meta-analysis-methods-group

Stewart LA, Clarke M, Rovers M, et al. Preferred reporting items for a systematic review and meta-analysis of individual participant data: The prisma-ipd statement. JAMA. 2015;313(16):1657-65.

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How to start?

- Consideration of clinical question – can it be answered by aggregate meta – analysis?
- Prospective *versus* retrospective
- Systematic review approach *versus* a collaboration with other research groups

* *Exclusivity may introduce bias.*

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SCiPAD (Skin care intervention for prevention of atopic disease)

- Skin care interventions for preventing eczema and food allergy: a systematic review and individual participant data meta-analysis

- Rationale:

1. Allergic diseases including eczema, asthma, hay fever and food allergy are the commonest long-term health conditions in children and young people across much of the world with increasing frequency in recent years

2. Recent evidence that early onset skin barrier dysfunction precedes clinical eczema, and that eczema is risk factor for development of food allergy

Will skin care interventions in early infancy prevent eczema and/or food allergy?

Prescott SL, Pawankar R, Allen KJ, Campbell DE, Sinn JKH, Fiocchi A, et al. A global survey of changing patterns of food allergy burden in children. World Allergy Organization Journal. 2013;6(1):1-12.
Tsakok T, Marrs T, Mohsin M, Baron S, du Toit G, Till S, et al. Does atopic dermatitis cause food allergy? A systematic review. J Allergy Clin Immunol. 2016;137(4):1071-8.

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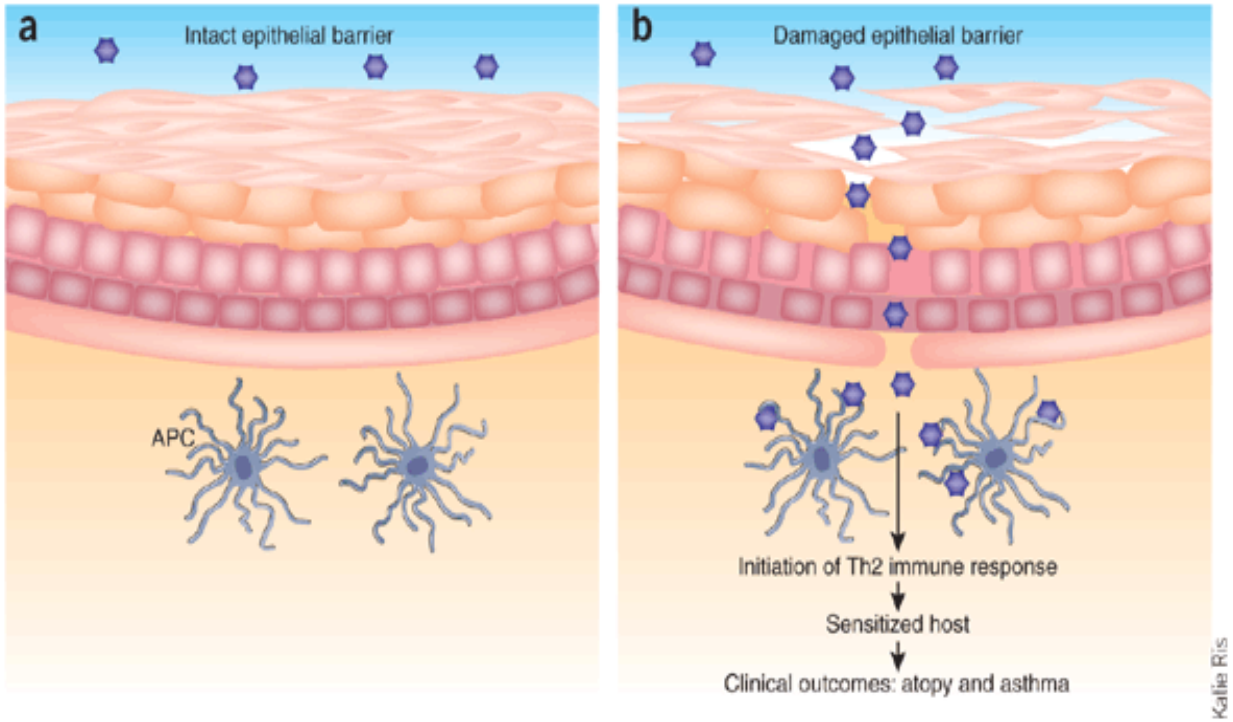
Sensitisation across the skin barrier



Hudson T. *Nature Genetics* **38**, 399 - 400 (2006) doi:10.1038/ng0406-399

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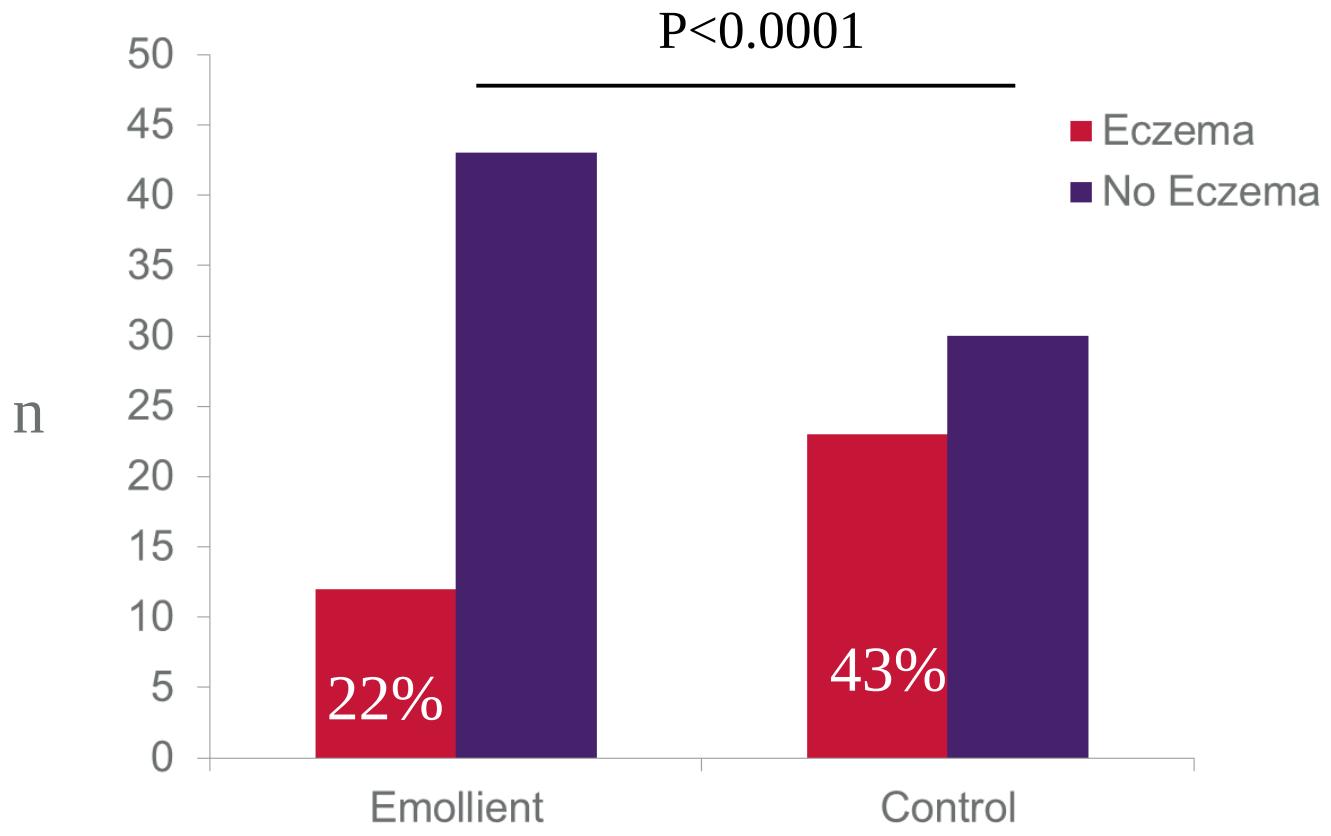
BEEP Pilot study: eczema prevalence at 6 months



Simpson E et al. J Allergy Clin Immunol 2014

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SCiPAD – why IPD?

- Food allergy is less prevalent than eczema

(Around 15 % of children have eczema whereas around 1-4 % have food allergy)

- Food allergy outcomes can be difficult to classify
- Reported reaction ?
- Blood test ?
- Skin test ?
- Oral food challenge ?

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SCiPAD – why IPD?

- Study factors

- Which intervention works best?
- When to implement intervention, for how long?

- Participant factors

- Which patients were most likely to benefit from intervention – sex, age, family history?

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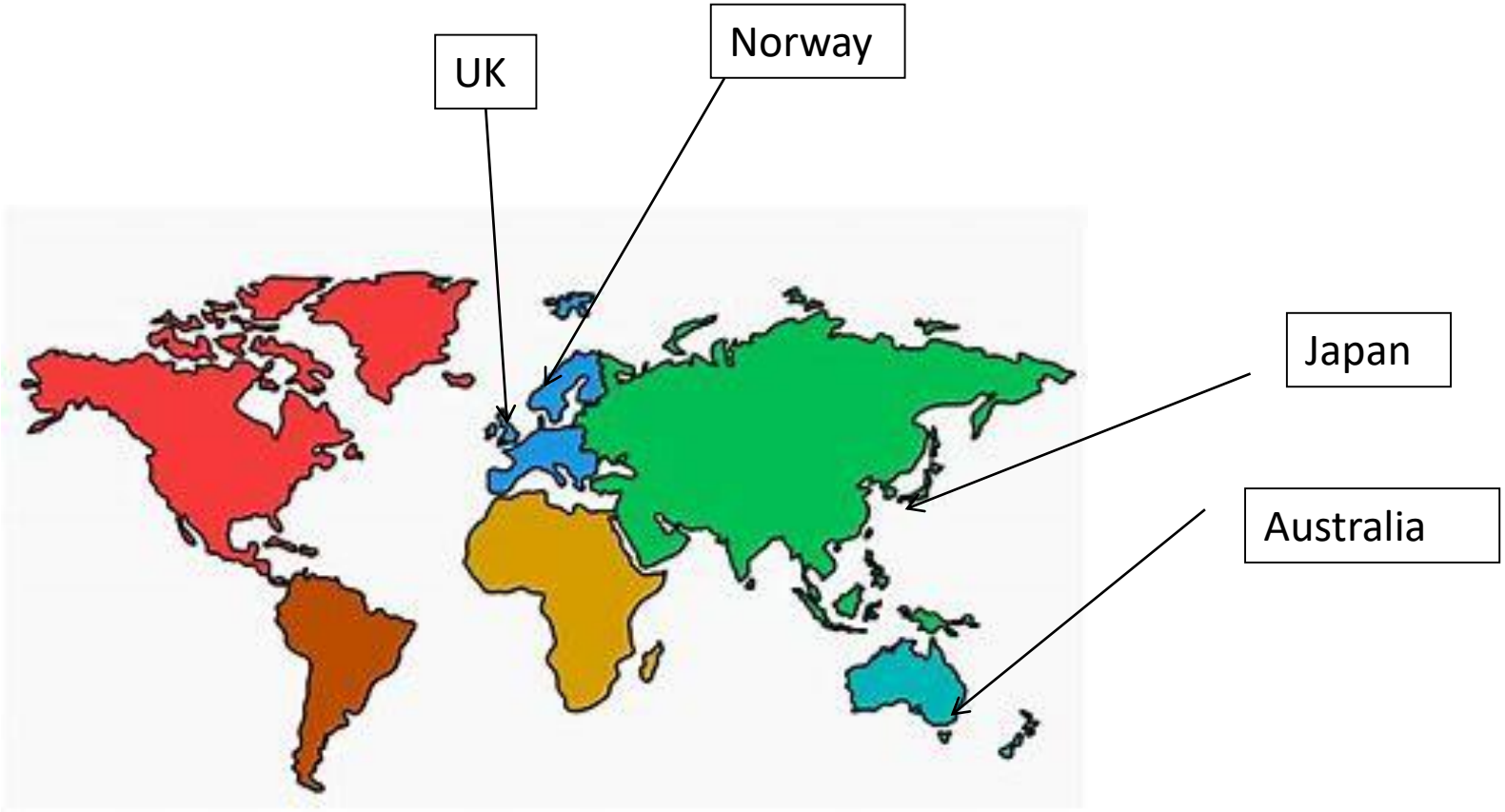
SCiPAD



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SCiPAD

- Initial collaboration group established in 2017 when protocol for IPD meta-analysis registered on PROSPERO
- Protocol development to be published through Cochrane in 2019
- For prospective meta-analysis, collaboration with main groups to align outcomes
- Meeting for mutual agreements, trust, collaboration
- Updated search of register
- Data sharing agreements, data sharing
- Scheduled for completion in late 2020

Boyle RJ et al. {Prospectively planned meta-analysis of skin barrier studies for the prevention of eczema and associated health conditions. PROSPERO 2017 CRD42017056965 Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017056965

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How do we do IPD meta-analysis?

Study 1:

Study	Patient	sex	eczema	Treatment
1	1	male	Yes	Skin care
1	2	female	Yes	Skin care
1	3	male	No	Skin care
1	4	male	Yes	Control
1	5	female	No	Control
⋮	⋮	⋮	⋮	⋮

Study 2:

Study	Patient	sex	eczema	Treatment
2	1	male	No	Skin care
2	2	female	Yes	Control
2	3	female	No	Skin care
2	4	male	No	Control
2	5	female	No	Skin care
⋮	⋮	⋮	⋮	⋮

Study 3:

Study	Patient	sex	eczema	Treatment
3	1	female	No	Control
3	2	female	Yes	Skin care
3	3	male	No	Skin care
3	4	male	Yes	Skin care
3	5	female	No	Control
⋮	⋮	⋮	⋮	⋮

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Two stage IPD meta-analysis

- **Stage 1:** Analyse each study data set separately, using the same analysis model appropriate to the type of outcome data → for each study obtain one treatment effect and estimate of variance

- **Stage 2:** Combine treatment effects across studies using standard meta-analysis methods (weighted average of treatment effects – typically weights correspond to inverse of treatment effect variance):

  - Fixed effect model: assumes each study is estimating exactly the same intervention effect

  - Random effects model: assumes the studies are not all estimating same intervention effect, intervention effects follow a distribution across studies

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Two stage IPD meta-analysis

Stage 1: For each study, use a binomial regression model to obtain RR for eczema adjusted for sex and family history

Study	Patient	sex	eczema	Treatment
1	1	male	Yes	Skin care
1	2	female	Yes	Skin care
1	3	male	No	Skin care
1	4	male	Yes	Control
1	5	female	No	Control
⋮	⋮	⋮	⋮	⋮

↓

Analyse study 1
RR = 0.8

Study	Patient	sex	eczema	Treatment
2	1	male	No	Skin care
2	2	female	Yes	Control
2	3	female	No	Skin care
2	4	male	No	Control
2	5	female	No	Skin care
⋮	⋮	⋮	⋮	⋮

↓

Analyse study 2
RR = 1.0

Study	Patient	sex	eczema	Treatment
3	1	female	No	Control
3	2	female	Yes	Skin care
3	3	male	No	Skin care
3	4	male	Yes	Skin care
3	5	female	No	Control
⋮	⋮	⋮	⋮	⋮

↓

Analyse study 3
RR = 1.2

Stage 2: Pool treatment effects using a random effects model with studies weighted by the inverse of their treatment effect variance

RR = ?

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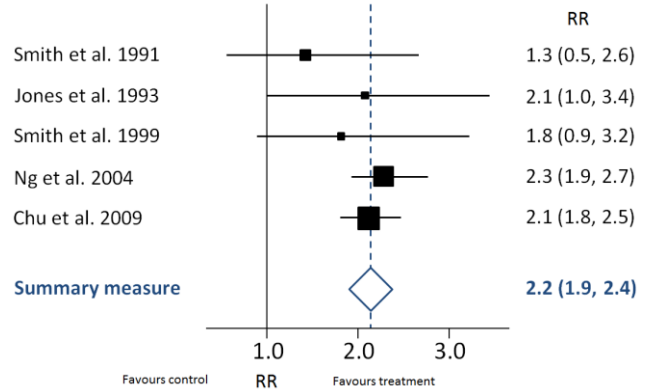
Two stage IPD meta-analysis

- Benefits:
  - Simple, employs traditional/familiar meta-analysis methods
  - Can be readily implemented in standard statistical software
  - Immediately obtain individual study effects and the overall pooled effect to display on a forest plot
  - Straight forward to incorporate Aggregate Data (AD) for trials where IPD is not available (add in at stage 2)

- Disadvantages:
  - Reduces patient information to study level summaries
  - Stage 2 may be poor approximation if small numbers and/or rare events

Forest plot



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One stage IPD meta-analysis

Study	Patient	sex	eczema	Treatment
1	1	male	Yes	Skin care
1	2	female	Yes	Skin care
1	3	male	No	Skin care
1	4	male	Yes	Control
1	5	female	No	Control
⋮	⋮	⋮	⋮	⋮
2	1	male	No	Skin care
2	2	female	Yes	Control
2	3	female	No	Skin care
2	4	male	No	Control
2	5	female	No	Skin care
⋮	⋮	⋮	⋮	⋮
3	1	female	No	Control
3	2	female	Yes	Skin care
3	3	male	No	Skin care
3	4	male	Yes	Skin care
3	5	female	No	Control
⋮	⋮	⋮	⋮	⋮

- Create one large data set – data from each trial stacked one on top of the other
- Fit *one analysis model* using the entire collection of IPD appropriate to type of data of data being synthesised e.g logistic (OR)/binomial (RR) model for binary data or linear regression model for continuous data.
- The single analysis model must adjust for study!

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One stage IPD meta-analysis

Study	Patient	sex	eczema	Treatment
1	1	male	Yes	Skin care
1	2	female	Yes	Skin care
1	3	male	No	Skin care
1	4	male	Yes	Control
1	5	female	No	Control
⋮	⋮	⋮	⋮	⋮
2	1	male	No	Skin care
2	2	female	Yes	Control
2	3	female	No	Skin care
2	4	male	No	Control
2	5	female	No	Skin care
⋮	⋮	⋮	⋮	⋮
3	1	female	No	Control
3	2	female	Yes	Skin care
3	3	male	No	Skin care
3	4	male	Yes	Skin care
3	5	female	No	Control
⋮	⋮	⋮	⋮	⋮

- SCiPAD Binary outcome (eczema): Fit *one binomial regression model* using the entire collection of IPD to obtain pooled RR for treatment directly

- Include study using either a:
  - Fixed study effect
  - Random study effect: allows for variability in baseline risk across studies

- The treatment effect may be fixed or vary randomly across studies (depends on meta-analysis assumption of one common treatment effect across studies or allowing for variability in treatment effect)

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One stage IPD meta-analysis

- Benefits
  - One stage models allow more flexible, multi-parameter modeling
  - Potentially more exact than two-stage approach with small event numbers
  - Becoming more popular as can be implemented in statistical software
  - Combining IPD and non-IPD is also possible in one stage approach

- Disadvantages:
  - Combining IPD and non-IPD requires careful model specification
  - More opportunity to go wrong: do not ignore clustering by study!
  - May face computational difficulties
  - Individuals study effects available to construct a forest plot, but not immediately

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One stage or two stage approach?

- Research indicates that in most cases very similar results will be obtained from a one-stage and two-stage analysis
- Where differences are reported this is generally because:
  1. Researchers have knowingly or unknowingly made different modelling assumptions
  2. And/or used different estimation methods and different methods to derive CI's
- Burke et al, Statistics in medicine, 2016: 10 key reasons why one-stage and two-stage approaches may differ
- Where assumptions/estimation methods do not vary the two approaches will give similar results: analysts free to choose most convenient procedure to fit the required model

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SCiPAD: Two stage IPD meta-analysis

- Will utilise both prospective and retrospectively acquired data: we hope all trials will provide IPD but there is the potential not all will

- Primary meta-analysis will use all data including IPD where available and Aggregate Data where IPD could not be provided to avoid *"availability bias"*

- A two-stage approach to analysis will be taken for all primary and secondary analyses:
  - Readily combine IPD and non-IPD
  - Individual study effects immediately available for forest plot

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Subgroup analysis

- Often interested in factors which cause patients to respond better to treatment e.g. high or low/normal risk for atopy based on filaggrin genotype

- Access to IPD enables the impact of individual patient characteristics on the treatment effect to be assessed

- Two stage approach:

  Stage 1: Estimate the interaction between the covariate of interest and treatment effect in each study separately

  Stage 2: Pool interaction effects using standard meta-analysis methods (weighted average of interaction effects)

- One stage approach: fit one large model which includes treatment by covariate interaction effect of interest in the model

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Efficacy analysis

- With IPD we have the potential to estimate not only the effect of allocation to intervention which is typically reported in RCTs (Intention-to-treat analysis)
- Can use IPD to estimate alternative *estimands/treatment effects* of interest: e.g. treatment effect in individuals who start and comply with the treatment
- Newly published ICH E9 (R1) *addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials* has brought the estimation of other estimands into sharp focus in the clinical trial arena
- → Meta-analysis arena: pool alternative treatment estimands of interest

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Efficacy analysis

- Following a two-stage approach:

Stage 1: For each trial estimate the alternative estimand of interest

e.g. in SCiPAD for each trial estimate the complier average causal effect (CACE):

- CACE = statistically valid estimate as analysis includes all randomized patients unlike a per protocol analysis which excludes individuals who don't comply (compliers/non-compliers may have different baseline characteristics)
- CACE estimated in each trial using instrumental variable analysis methods
- Randomisation used an instrument for intervention received and a two-stage residual estimator approach employed for estimation
- Requires compliance data from trials & a definition of a complier

Stage 2: Pool alternative estimand of interest using standard meta-analysis methods

e.g. SCiPAD: Pool CACE effects using as a weighted average of CACE estimates – weighted by inverse variance – using random effects model

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Efficacy analysis

- SCiPAD: we will initially define a ‘complier’ as an individual who completes ≥80% of the prescribed intervention
- The pooled CACE estimate will be compared against the primary treatment effect estimating the effect of being assigned to the intervention for the subset of trials where compliance data is available
- Subsequently we will explore the impact of different threshold values for defining compliance

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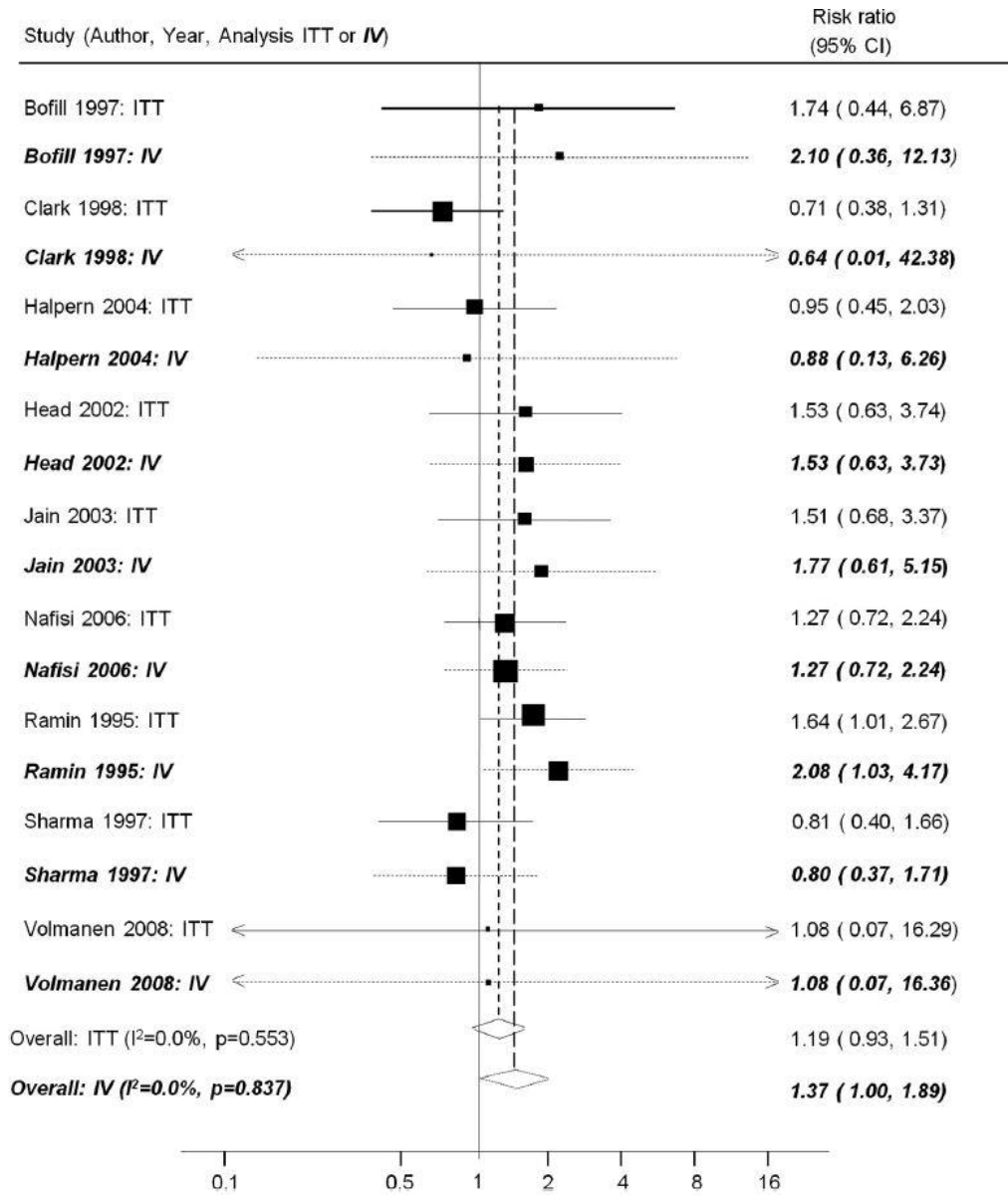
Efficacy analysis

- A review of trials on epidural analgesia in labour found ITT meta-analysis underestimated the effect of receiving epidural analgesia in labour
- IV (CACE): The pooled RR for caesarean section following epidural analgesia was 1.37 [95% CI: 1.00, 1.89, p=0.049]
- ITT: The pooled RR for caesarean section following epidural analgesia was 1.19 [95% CI: 0.93, 1.51, p= 0.16]



Bannister-Tyrell M, Miladinovic B, Roberts CL, Ford JB. Adjustment for compliance behavior in trials of epidural analgesia in labor using instrumental variable meta-analysis. *Journal of clinical epidemiology*. 2014; 68:525-533.

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Sensitivity analysis

- “A repeat of the primary analysis or meta-analysis, substituting alternative decisions or ranges of values for decisions that were arbitrary or unclear” (Cochrane handbook)

- In IPD meta-analysis a decision may be required on whether to include IPD only or IPD + Aggregate Data:
  - Consider availability bias? – Aggregate Data study outcomes/summaries comparable with IPD estimates? – Quality of Aggregate Data studies?

- Sensitivity analysis including/excluding non-IPD studies is recommended

- As in non IPD meta-analysis other useful sensitivity analysis include:
  - By risk of bias
  - To explore heterogeneity

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Conclusions

- IPD meta-analysis is the gold standard approach to meta-analysis to definitively answer a clinical question

- Verification of results of individual studies
- Results for poorly reported outcomes can be calculated
- Standardised statistical methods
- Enables subgroup analysis to identify characteristics of individuals who benefit mos
- Alternative estimands/treatment effects of interest can be explored e.g. compiler average causal effect

- Sound statistical methods have been developed for IPD meta-analysis: one-stage or two stage approach

- But they are time and resource intensive!!