# Identifying problematic studies: the INSPECT-SR project

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Steering group: Calvin Heal, George Antoniou, Ella Flemyng, Lisa Bero, Jamie Kirkham

Some of the research discussed in this presentation is funded by the NIHR Research for Patient Benefit programme (NIHR203568). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

MANCHESTER 1824
The University of Manchester

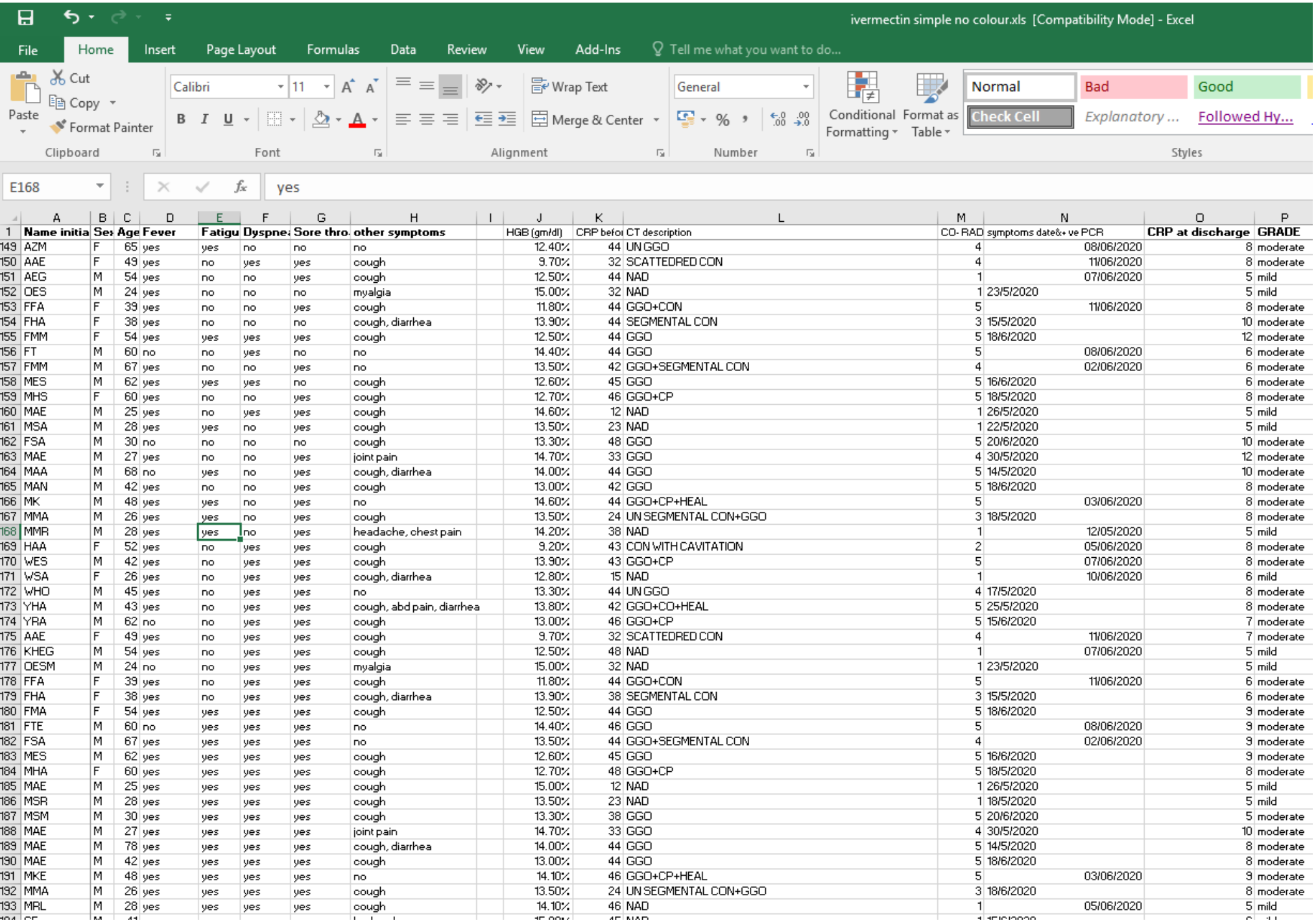
INSPECT SR

# For the lawyers

- I'm not accusing anyone of fraud, data fabrication/falsification, or any other form of research misconduct here.

- I will say that some trials are unlikely to be authentic or are not trustworthy. The data or results do not appear to be compatible with a genuine RCT.

- I make no claims that this is due to deliberate action on behalf of investigators/ authors (vs catastrophic errors in data management, for example).



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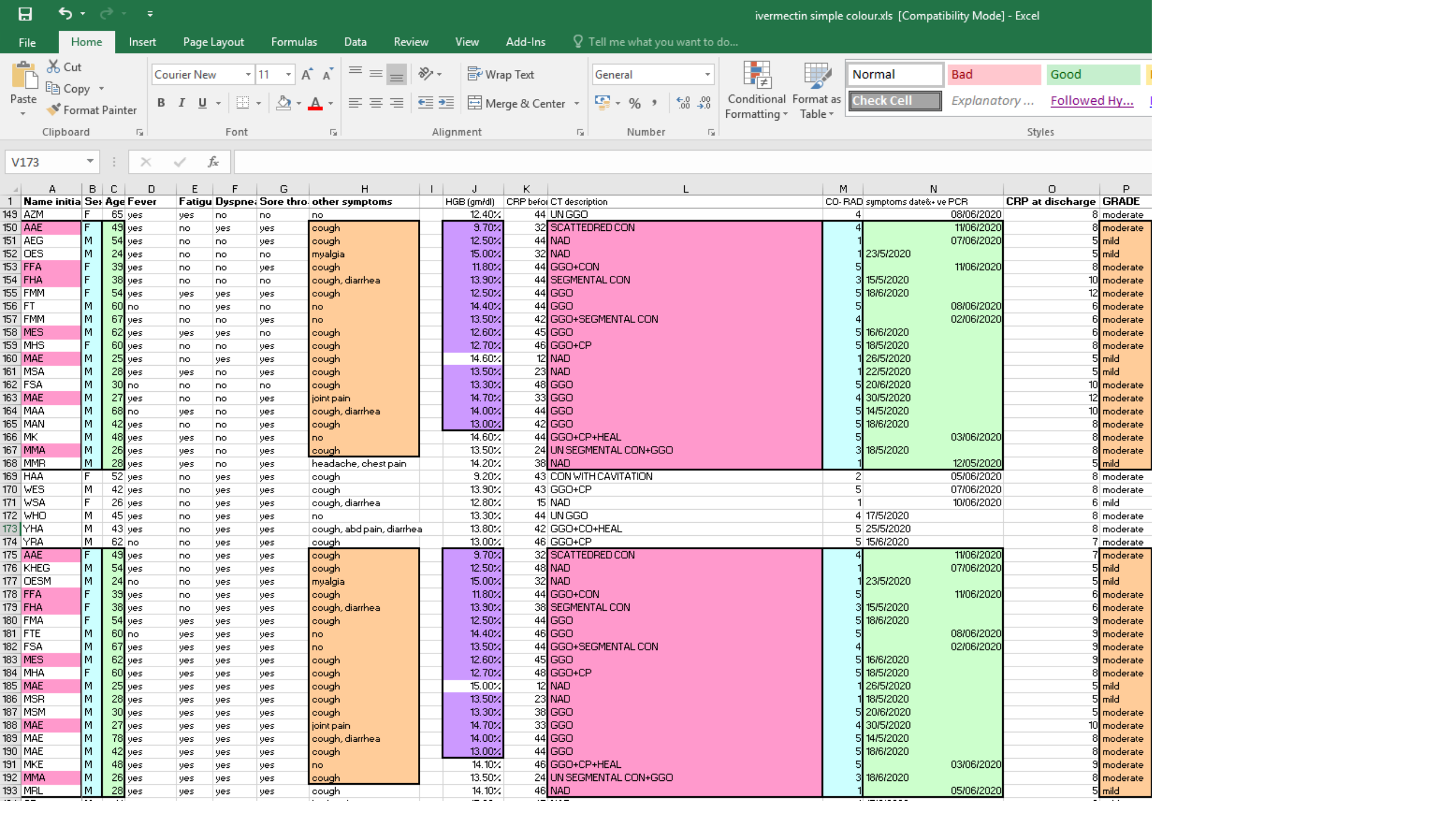
- Data from an RCT of ivermectin for COVID-19.
- Included in systematic reviews
- e.g. Bryant et al., 2021 found risk ratio (95% CI) for death:

  0.38 (0.19 to 0.73).



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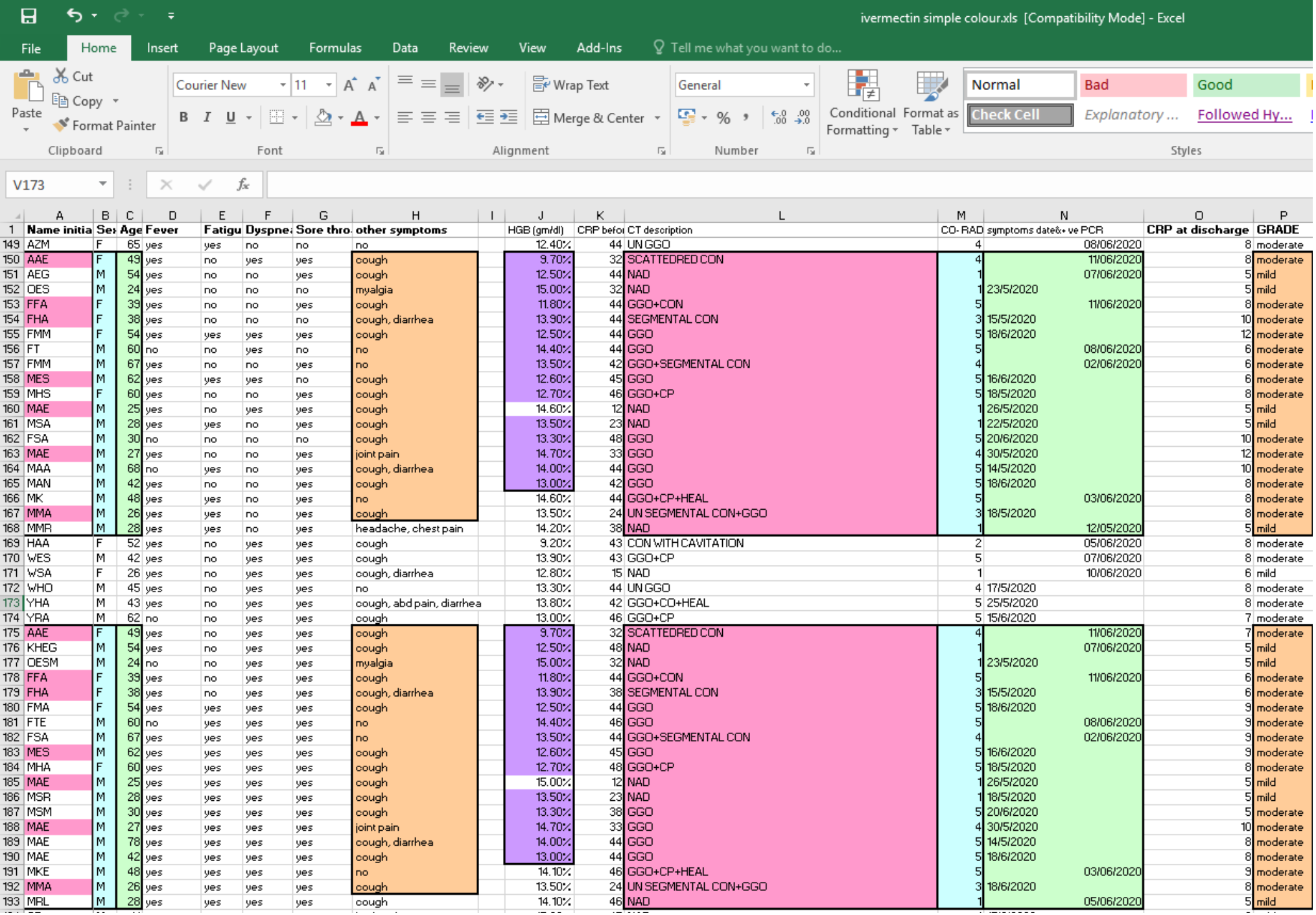


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- Blocks of data are repeated
- This is not authentic data
- One possible explanation – it has been fabricated, by copying and pasting blocks of data into a spreadsheet.
- This analysis was done by Nick Brown
- [Nick Brown's blog (steamtraen.blogspot.com)]
- Similar problems with other ivermectin RCTs!

# Systematic reviews: Fake data to patient care pipeline

1

**Attempt to identify all RCTs on the review topic**

- Problematic trials will be included

2

**Critically appraise study methodology, include in meta-analysis**

- Assess risk of bias
- But do not consider authenticity
- Many (not all) fake trials report sound methods

3

**Make conclusions, recommendations, on basis of evidence**

- SRs seen as gold standard
- Included in guidelines
- Influence patient care

# Vitamin K and the Prevention of Fractures

*Systematic Review and Meta-analysis of Randomized Controlled Trials*

*Sarah Cockayne, MSc; Joy Adamson, PhD; Susan Lanham-New, PhD; Martin J. Shearer, PhD, MRCPath; Simon Gilbody, DPhil; David J. Torgerson, PhD*

3 out of 5 trials subsequently identified as fake.

# Does tranexamic acid prevent postpartum haemorrhage? A systematic review of randomised controlled trials

**K Ker, H Shakur, I Roberts**

26 trials. 8 had identical or similar text, 2 no ethical approval.

# Psychological therapies for the management of chronic pain (excluding headache) in adults (Review)

Williams ACDC, Fisher E, Hearn L, Eccleston C

3 of 27 trials from one investigator suggested to be implausible (huge effects, no attrition).

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Better health.

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EDITORIAL

# When beauty is but skin deep: dealing with problematic studies in systematic reviews

Stephanie L Boughton, Jack Wilkinson, Lisa Bero

## Managing potentially problematic studies

https://bit.ly/3SsJO9F

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Stephanie L Boughton, Jack Wilkinson, Lisa Bero

## Managing potentially problematic studies

https://bit.ly/3SsJO9F

- Do not include studies until serious concerns about trustworthiness have been resolved.

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- How do we define ‘trustworthiness’?
- How can we identify problematic studies?

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**INveStigating ProblEmatic Clinical Trials in Systematic Reviews**

**Aim: To develop a tool for identifying problematic randomised controlled trials in the context of health systematic reviews.**

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Stage 1: Assemble list of checks for problematic studies (previous studies, new survey of 71 people with experience/ expertise)

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Stage 2: Apply list of checks to RCTs in 50 Cochrane Reviews (feasibility, impact)

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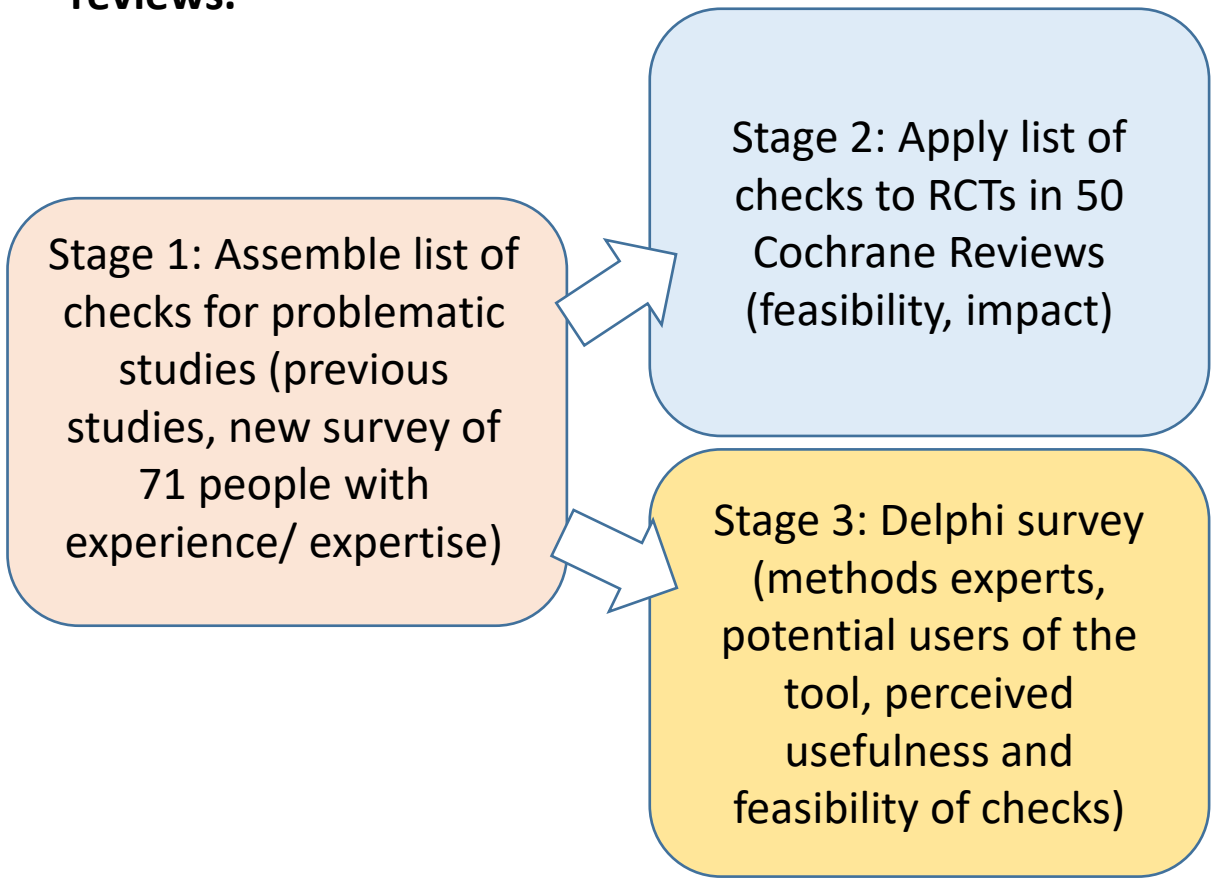

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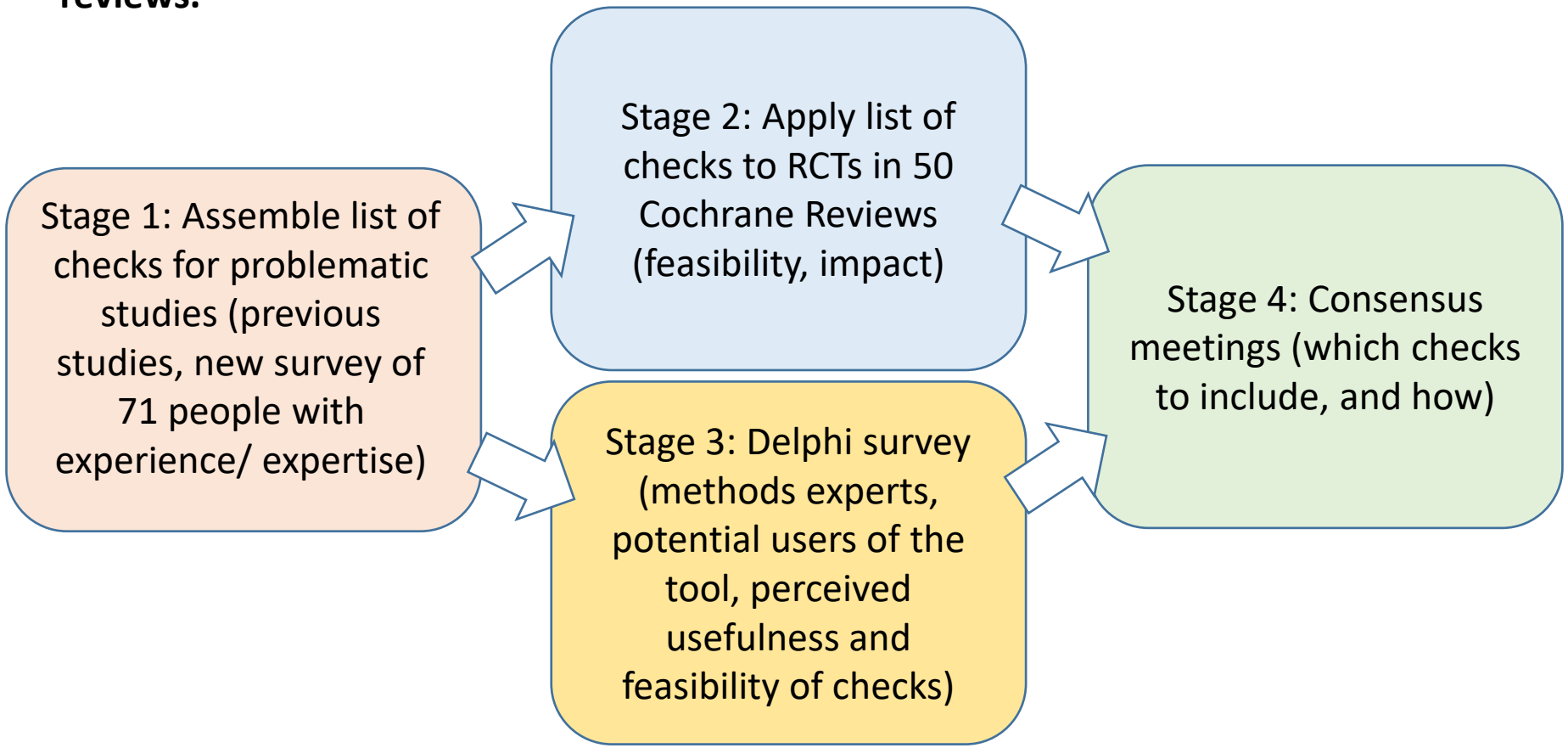

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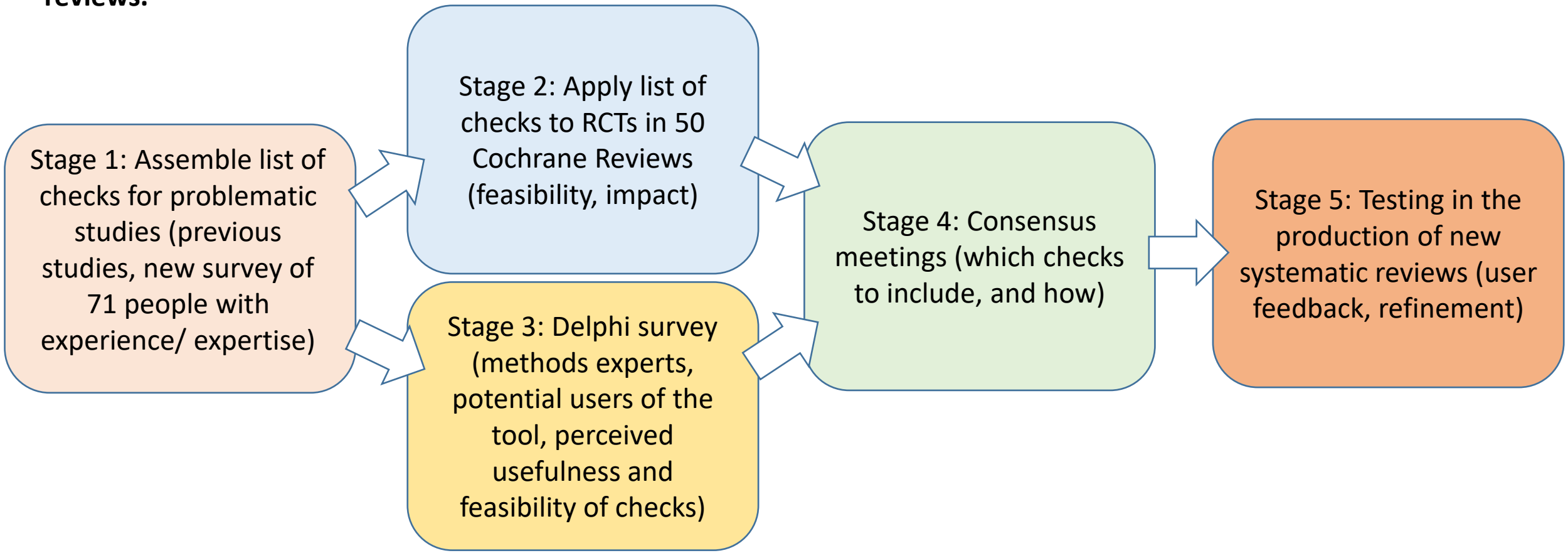

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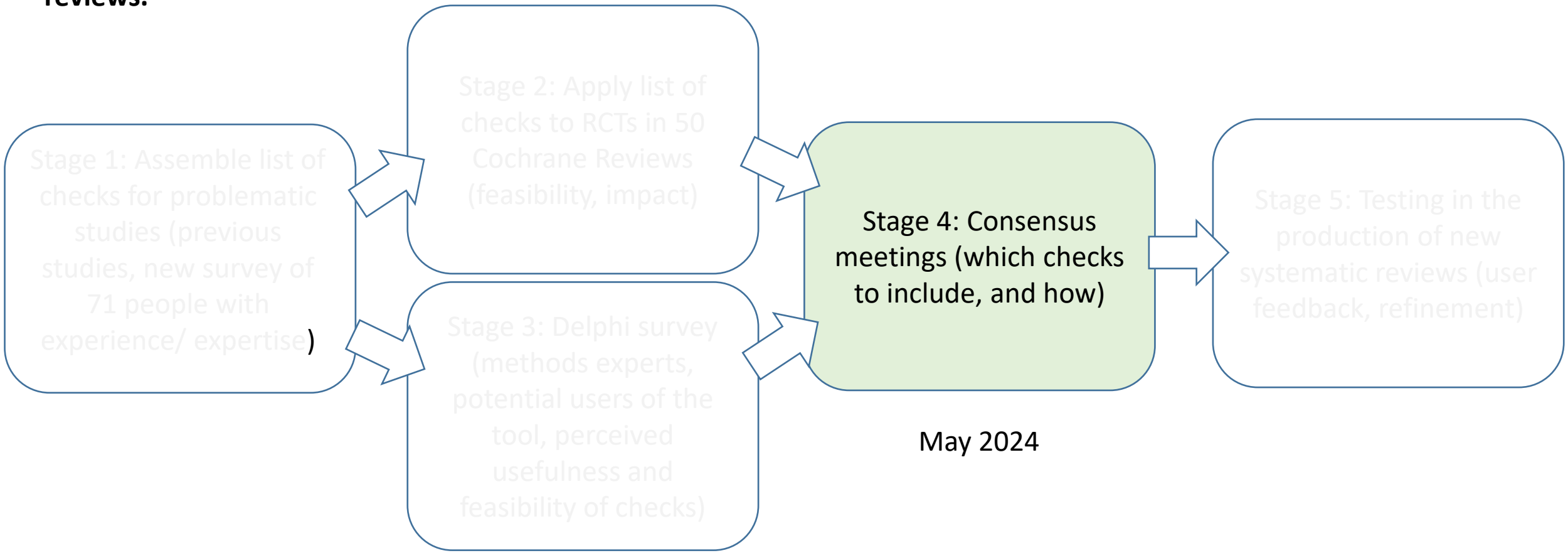


May 2024

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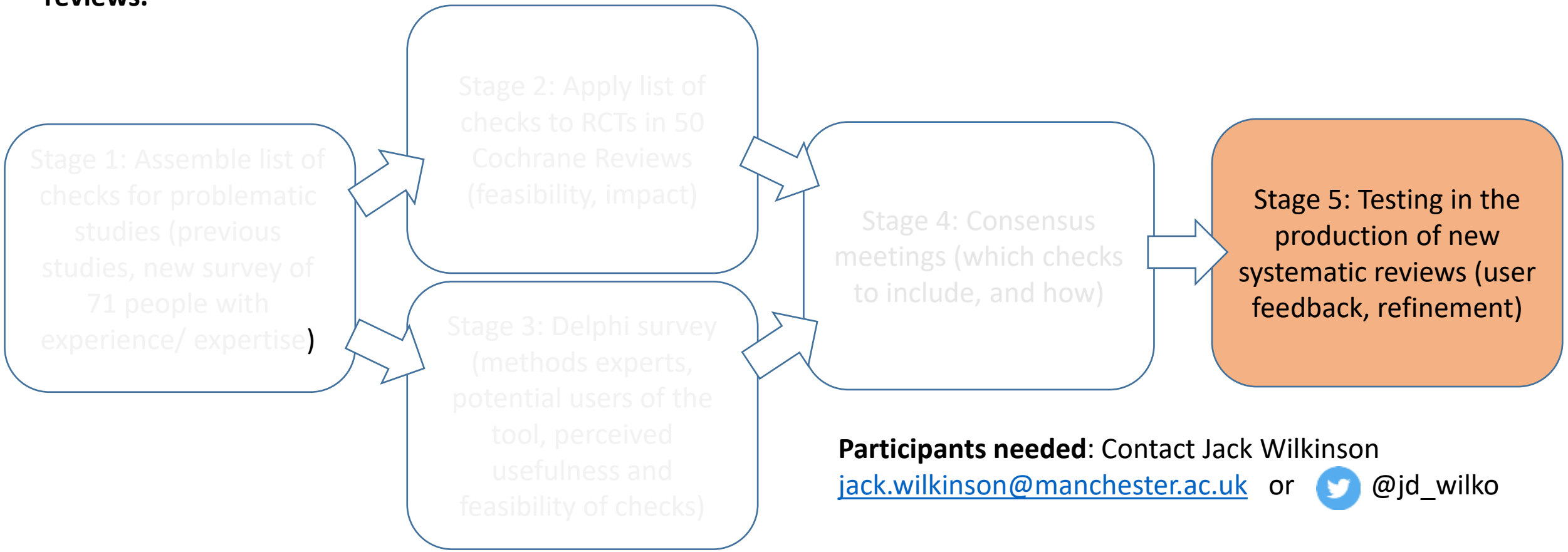


**Participants needed**: Contact Jack Wilkinson
jack.wilkinson@manchester.ac.uk or @jd_wilko

INSPECT SR

Long list of checks under consideration, grouped into five domains:

| Domain | Number of checks |
|---|---|
| Inspecting text and publication details | 10 |
| Inspecting results in the paper | 26 |
| Inspecting the research team and their work | 16 |
| Inspecting conduct, governance and transparency | 17 |
| Inspecting individual participant data | 41 |
| | 110 |

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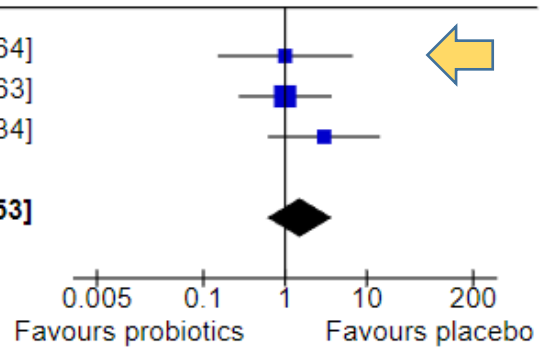
INSPECT IPD

Our task: select which checks to include (and how). **One** example of each now.

## Hypertensive disorders

| Study or Subgroup | Probiotics Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Badehnoosh 2018 | 2 | 30 | 2 | 30 | 25.0% | 1.00 [0.15 , 6.64] |
| Karamali 2018 | 4 | 30 | 4 | 30 | 50.0% | 1.00 [0.28 , 3.63] |
| Lindsay 2015 | 6 | 68 | 2 | 68 | 25.0% | 3.00 [0.63 , 14.34] |
| **Total (95% CI)** | | **128** | | **128** | **100.0%** | **1.50 [0.64 , 3.53]** |
| Total events: | 12 | | 8 | | | |

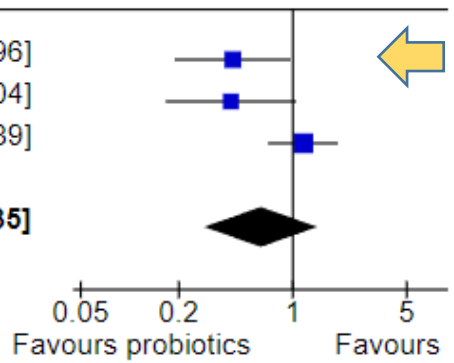
Heterogeneity: Chi² = 1.31, df = 2 (P = 0.52); I² = 0%
Test for overall effect: Z = 0.93 (P = 0.35)
Test for subgroup differences: Not applicable

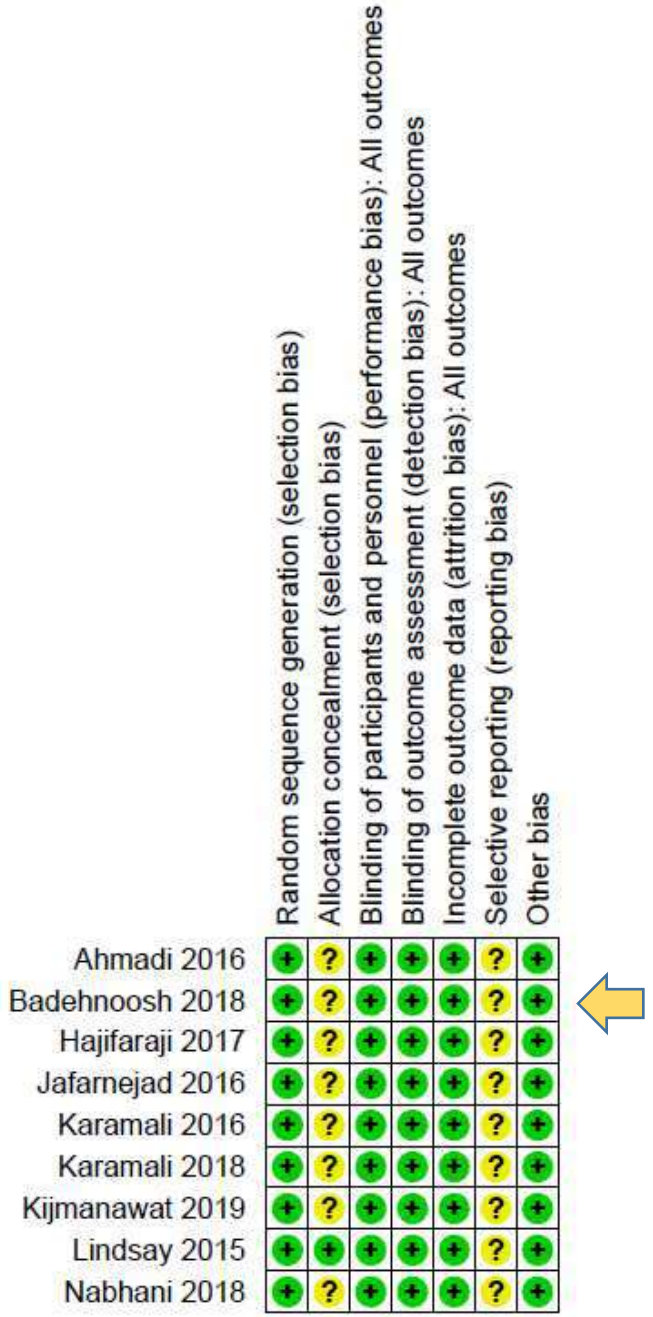



## Caesarian deliveries

| Study or Subgroup | Probiotics Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Badehnoosh 2018 | 6 | 30 | 14 | 30 | 31.1% | 0.43 [0.19 , 0.96] |
| Karamali 2018 | 5 | 30 | 12 | 30 | 28.4% | 0.42 [0.17 , 1.04] |
| Lindsay 2015 | 24 | 73 | 21 | 74 | 40.4% | 1.16 [0.71 , 1.89] |
| **Total (95% CI)** | | **133** | | **134** | **100.0%** | **0.64 [0.30 , 1.35]** |
| Total events: | 35 | | 47 | | | |

Heterogeneity: Tau² = 0.30; Chi² = 6.47, df = 2 (P = 0.04); I² = 69%
Test for overall effect: Z = 1.18 (P = 0.24)
Test for subgroup differences: Not applicable



# Domain 1: Inspecting text and publication details

## *Has the study been retracted or does it have an expression of concern?*

Online version has link to **Expression of concern** for several articles, including this one (not very prominent!):



**Expression of Concern**

Page 4030 | Published online: 27 Jan 2021

Download citation https://doi.org/10.1080/14767058.2020.1842963

Since publication of these articles, serious concerns have been raised about the integrity of the reported methods, results and analysis. We have contacted the authors and the ethics committee of the institution to respond to the concerns raised and they are cooperating with the investigation. However, the authors have not been able to provide the original data associated with this article, and so as we continue to work through the issues raised, we advise readers to interpret the information presented in the article with due caution. We will provide an update following the conclusion of our investigation. The authors have been notified about this Expression of Concern.

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Review authors would not have had this information

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## Domain 2: Inspecting the results in the paper

*Are the means and variances of integer data possible?*

Table 5. The association of probiotic supplementation with pregnancy outcomes.

| | Placebo group ($n = 30$) | Probiotic group ($n = 30$) | $p$[a] |
|---|---|---|---|
| Cesarean section (%) | 14 (46.7) | 6 (20.0) | .054[b] |
| Preterm delivery (%) | 1 (3.3) | 2 (6.7) | >.999[b] |
| Need to insulin therapy after intervention (%) | 3 (10.0) | 2 (6.7) | >.999[b] |
| Pre-eclampsia (%) | 2 (6.7) | 2 (6.7) | >.999[b] |
| Polyhydramnios (%) | 1 (3.3) | 0 (0) | >.999[b] |
| Maternal hospitalization (%) | 2 (6.7) | 0 (0) | .492[b] |
| Macrosomia >4000 g (%) | 3 (10.0) | 0 (0) | .237[b] |
| Gestational age (weeks) | 39.1 ± 1.1 | 39.1 ± 2.5 | .948 |
| Newborns' weight (g) | 3438.0 ± 398.4 | 3321.7 ± 443.5 | .290 |
| Newborns' length (cm) | 51.2 ± 1.9 | 50.4 ± 2.8 | .223 |
| Newborns' head circumference (cm) | 36.0 ± 1.5 | 35.8 ± 1.8 | .624 |
| LGA (%) | 9 (30.0) | 5 (16.7) | .360[b] |
| 1-min Apgar score | 8.93 ± 0.25 | 8.96 ± 0.18 | .561 |
| 5-min Apgar score | 9.93 ± 0.18 | 9.96 ± 0.18 | .561 |
| Newborns' hyperbilirubinemia (%) | 8 (26.7) | 2 (6.7) | .080[b] |
| Newborns' hospitalization (%) | 8 (26.7) | 2 (6.7) | .080[b] |
| Newborns' hypoglycemia (%) | 3 (10.0) | 2 (6.7) | >.999[b] |

Values are means ± SDs for continuous measures and are number (%) for dichotomous variables.
[a]Obtained from independent *t*-test.
[b]Obtained from Fisher's exact test.
LGA: large for gestational age.

| | | | |
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Apgar score is a variable which only takes **integer values** (1,2,3,4,5,6,7,8,9,10).

There are a limited number of possible mean and SD values for integer data for a given sample size (**GRIM** DOI: 10.1177/1948550616673876 and **GRIMMER** https://doi.org/10.7287/peerj.preprints.2400v1 )

# Applying GRIM and GRIMMER to Apgar score data

| | | | |
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- 1-min Apgar score mean probiotic group (8.96) could not occur for n = 30.
- Same for 5-min Apgar (9.96)
- Also can't have combination of mean of 9.93 and SD of 0.18. Smallest SD would be 0.25.
- Here I used the online tool at http://www.prepubmed.org/grimmer
- Also implemented in Lukas Jung's scrutiny package in R.

# Domain 3: Inspecting the research team and their work

*Does consideration of other studies from members of the research team highlight causes for concern*

Search Retraction Watch database for last author: Zatollah Asemi

http://retractiondatabase.org/

# *Does consideration of other studies from members of the research team highlight causes for concern?*

- Search on Asemi has to limit results to first **50** results (retractions, expressions of concern, corrections). Does include some before the publication of the Cochrane Review, so these could be picked up if we introduced this check

**28 February 2020** The Editors-in-Chief are currently investigating this article [Afshar Ebrahimi, F., Foroozanfard, F., Aghadavod, E. et al. The Effects of Magnesium and Zinc Co-Supplementation on Biomarkers of Inflammation and Oxidative Stress, and Gene Expression Related to Inflammation in Polycystic Ovary Syndrome: a Randomized Controlled Clinical Trial. Biol Trace Elem Res 184, 300–307 (2018). https://doi.org/10.1007/s12011-017-1198-5] as concerns have been raised about integrity of the clinical trial reported here. There is also an ongoing investigation by the Iranian National Committee for Ethics in Biomedical Researches. Further editorial action will be taken as appropriate once the investigation into the concerns is complete and all parties have been given an opportunity to respond in full.

# Domain 4: Inspecting conduct, governance and transparency.

*Is the recruitment plausible?*

- Paper: 6 month recruitment.
- Retrospective registration: 1 month recruitment (one of several inconsistencies)
- Requires good domain knowledge to make an informed judgement.

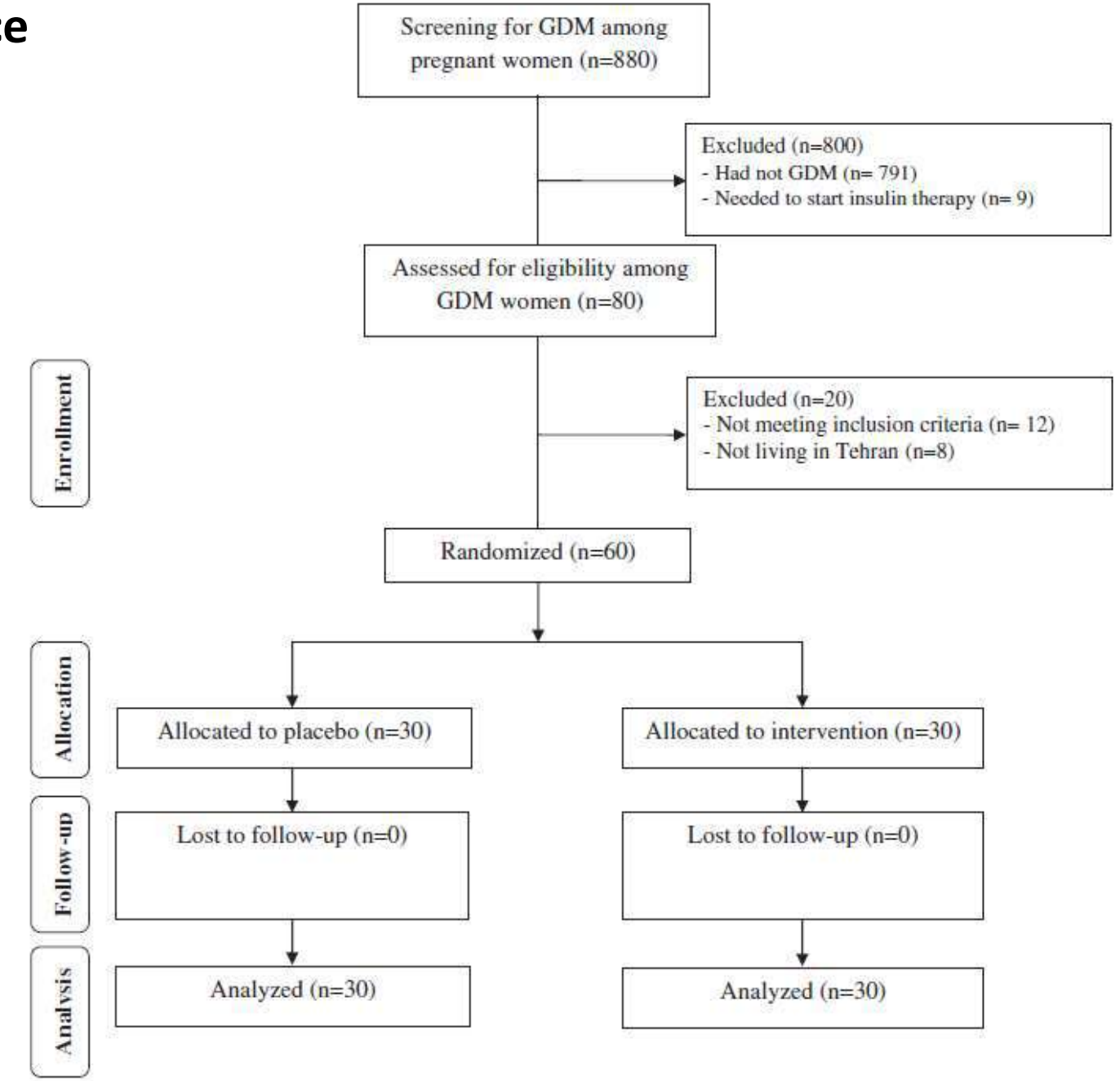


Figure 1. Summary of patient flow diagram.

# Some closing remarks

- INSPECT-SR will **not** be a diagnostic test for fraud.

- It will guide the reviewer through a series of checks to help them make a **judgement** about trustworthiness, and to articulate the basis for that judgement.

- If you'd be interested in testing during a systematic review (new or update, Cochrane or otherwise) and providing some feedback contact jack.wilkinson@manchester.ac.uk