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Developing a tool for detecting problematic RCTs in health systematic reviews: the INSPECT-SR project

Jack Wilkinson, Centre for Biostatistics, University of Manchester. @jd_wilko

Steering Group: Calvin Heal, Georgios Antoniou, Stephanie Boughton, Lisa Bero, Jamie Kirkham.

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Disclosures

- Currently hold or have recently held grants from NIHR, Health Research Council of New Zealand, UK Government, British Skin Foundation, Wellcome Trust.

- Stats Editor roles at Cochrane Gynaecology and Fertility, Fertility and Sterility, BJOG, Reproduction and Fertility, Journal of Hypertension

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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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Outline

1. Detecting problematic studies in the context of health systematic reviews: the INSPECT-SR project.

2. Some principles for investigating potentially problematic RCTs.

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1. Detecting problematic studies in the context of health systematic reviews: the INSPECT-SR project.

Ivermectin for COVID-19

Ivermectin for Prevention and Treatment of COVID-19 Infection: A Systematic Review, Meta-analysis, and Trial Sequential Analysis to Inform Clinical Guidelines

Bryant, Andrew MSc[1,*]; Lawrie, Theresa A. MBBCh, PhD[2]; Dowswell, Therese PhD[2]; Fordham, Edmund J. PhD[2]; Mitchell, Scott MBChB, MRCS[3]; Hill, Sarah R. PhD[1]; Tham, Tony C. MD, FRCP[4]

[Bryant et al., 2021]

Risk ratio for death:

0.38 (95% CI 0.19 to 0.73)

15 trials

Meta-analysis of Randomized Trials of Ivermectin to Treat SARS-CoV-2 Infection

Andrew Hill,[1] Anna Garratt,[2] Jacob Levi,[3] Jonathan Falconer,[4] Leah Ellis,[5] Kaitlyn McCann,[5] Victoria Pilkington,[6] Ambar Qavi,[5] Junzheng Wang,[5] and Hannah Wentzel[5]

[Hill et al., 2021]

Risk ratio for death:

0.49 (95% CI 0.28 to 0.86)

12 trials

Ivermectin for COVID-19

- SRs widely covered in media and social media.
- Used by antivax groups

Our Systematic Review…

Our peer-reviewed study clearly shows that ivermectin prevents and treats Covid-19 and has the potential to save and improve countless lives.

- **2.6 million views**
- **Ranked 7th of 20 million articles of a similar age.**

Read More

A just-published, peer-reviewed study already clearly shows that ivermectin prevents and treats Covid-19 and has the potential to save and improve countless lives in the UK and worldwide right now.

The strength of evidence for ivermectin has this week been supercharged by publication of a gold standard review of 24 randomised trials conducted in 15 countries among more than 3400 people worldwide proving infections fall and deaths are dramatically reduced when ivermectin is administered. Published in the American Journal of Therapeutics the most rigorous statistical standards were applied by world-leading researchers biostatistician Mr Andrew Bryant and medical doctor and researcher Dr. Tess Lawrie.

Tweeted by 45388

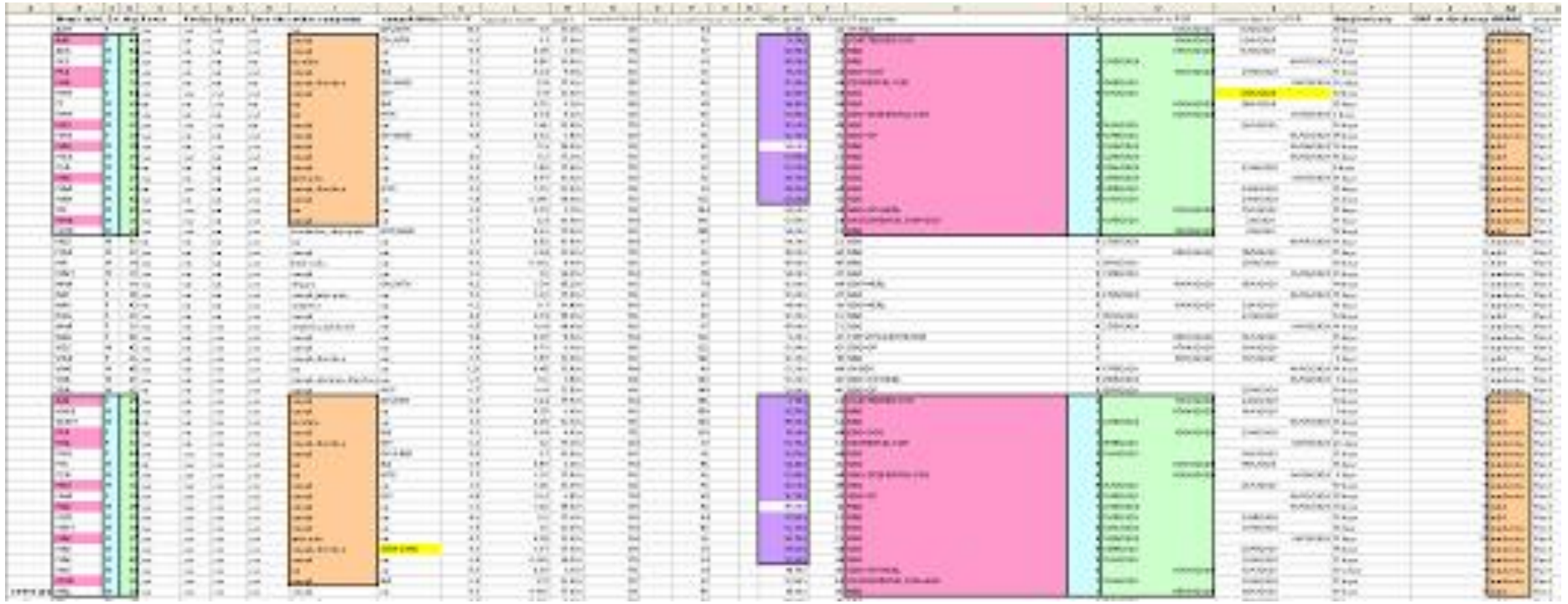
Blogged by 13

On 17 Facebook pages

Picked up by 102 news outlets

The catch…

- It now appears that several of the trials were not authentic



Analysis by Nick Brown (@sTeamTraen) at steamtraen.blogspot.com

Meta-analyses restricted to ‘credible’ trials

Hill et al., retracted their systematic review (👍):

- “The significant effect of ivermectin on survival was dependent on the inclusion of studies with a high risk of bias or potential medical fraud.”

- Risk ratio for death 0.96 (95% CI 0.56 to 1.66, 4 studies)

Popp et al., 2022 (Cochrane) excluded seven trials overall

- Asymptomatic or mild disease: Risk ratio for death 0.77 (95% CI 0.47 to 1.25, 6 trials)

- Moderate to severe disease: Risk ratio for death 0.60 (95% CI 0.14 to 2.51, 3 trials, 1 with no events)

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.

Cochrane Database of Systematic Reviews

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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- Do not include studies until serious concerns about trustworthiness have been resolved.
- How do we define a ‘problematic study’?

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Managing potentially problematic studies

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- Do not include studies until serious concerns about trustworthiness have been resolved.
- How do we define a ‘problematic study’?
- How can we detect them?

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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.

1. Convene a panel of people with expertise and experience of investigating problematic studies.
2. Create an extensive list of methods for detecting problematic studies.
3. Apply the list to a sample of systematic reviews (feasibility, impact on review conclusions)
4. Enter the items into a Delphi process
5. Prospective testing in production and update of systematic reviews.

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Making an extensive list of methods

Methods to assess research misconduct in health-related research: A scoping review

Esmee M Bordewijk • Wentao Li • Rik van Eekelen • ... Marian Showell • Ben W Mol • Madelon van Wely • Show all authors

Published: May 22, 2021 • DOI: https://doi.org/10.1016/j.jclinepi.2021.05.012 • Check for updates

Experts identified warning signs of fraudulent research: a qualitative study to inform a screening tool

Lisa Parker • Stephanie Boughton • Rosa Lawrence • Lisa Bero

102 checks or tests identified

- Implemented as online survey of experts
- “Are we missing anything?”

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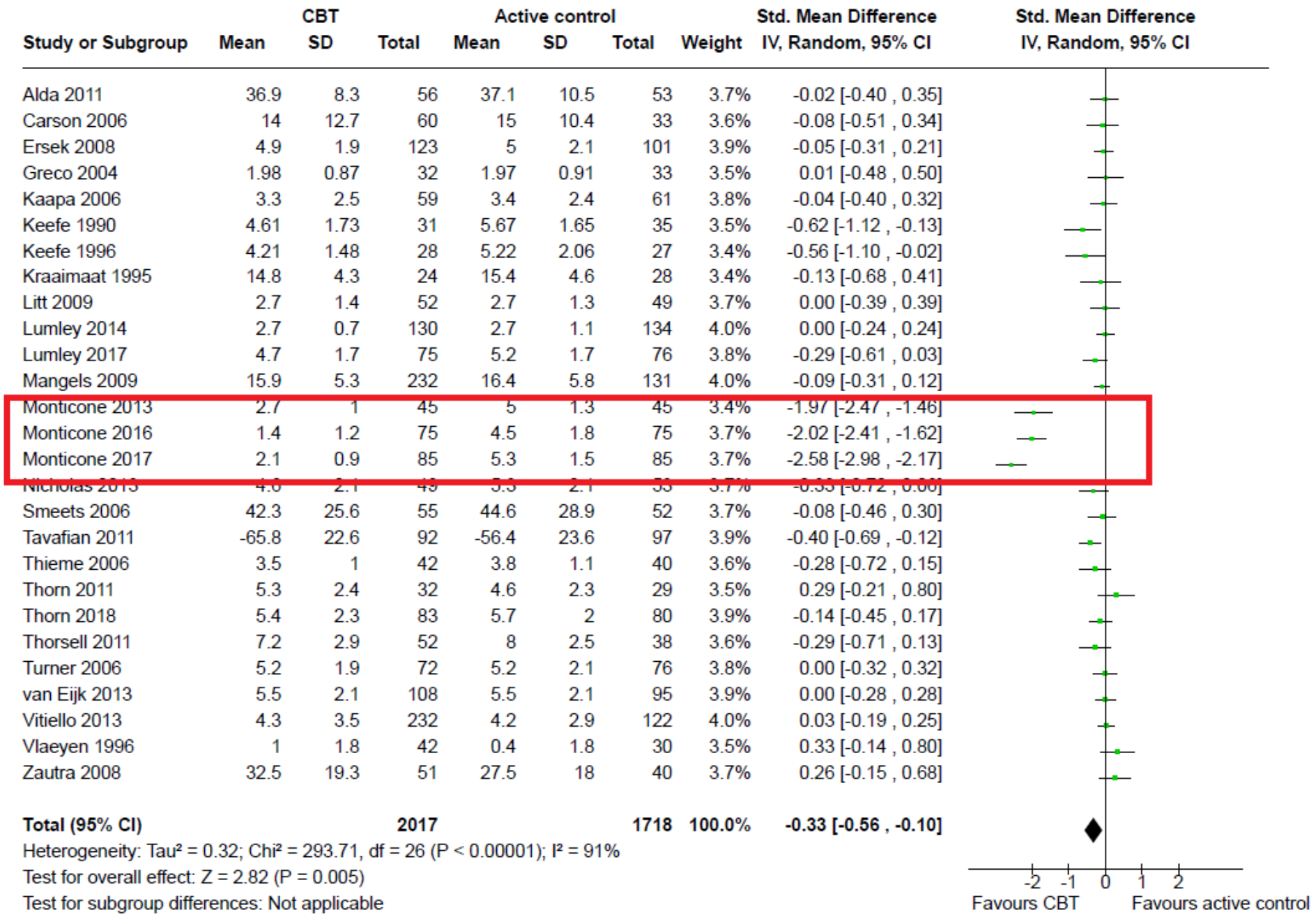
Preliminary classifications and examples

Inspecting results in the paper
Are the results substantially divergent from others in the meta-analysis?
Inspecting conduct, governance and transparency
Is the recruitment of participants plausible within the stated time frame for the research?
Inspecting the research team
Have other studies by the research team been retracted, or do they have expressions of concern?
Inspecting text and publication details
Is there evidence of copied work, such as duplicated or partially duplicated tables?
Inspecting individual participant data
Does the dataset contain repeated sequences of baseline values?



Study or Subgroup	CBT Mean	CBT SD	CBT Total	Active control Mean	Active control SD	Active control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Alda 2011	36.9	8.3	56	37.1	10.5	53	3.7%	-0.02 [-0.40 , 0.35]
Carson 2006	14	12.7	60	15	10.4	33	3.6%	-0.08 [-0.51 , 0.34]
Ersek 2008	4.9	1.9	123	5	2.1	101	3.9%	-0.05 [-0.31 , 0.21]
Greco 2004	1.98	0.87	32	1.97	0.91	33	3.5%	0.01 [-0.48 , 0.50]
Kaapa 2006	3.3	2.5	59	3.4	2.4	61	3.8%	-0.04 [-0.40 , 0.32]
Keefe 1990	4.61	1.73	31	5.67	1.65	35	3.5%	-0.62 [-1.12 , -0.13]
Keefe 1996	4.21	1.48	28	5.22	2.06	27	3.4%	-0.56 [-1.10 , -0.02]
Kraaimaat 1995	14.8	4.3	24	15.4	4.6	28	3.4%	-0.13 [-0.68 , 0.41]
Litt 2009	2.7	1.4	52	2.7	1.3	49	3.7%	0.00 [-0.39 , 0.39]
Lumley 2014	2.7	0.7	130	2.7	1.1	134	4.0%	0.00 [-0.24 , 0.24]
Lumley 2017	4.7	1.7	75	5.2	1.7	76	3.8%	-0.29 [-0.61 , 0.03]
Mangels 2009	15.9	5.3	232	16.4	5.8	131	4.0%	-0.09 [-0.31 , 0.12]
Monticone 2013	2.7	1	45	5	1.3	45	3.4%	-1.97 [-2.47 , -1.46]
Monticone 2016	1.4	1.2	75	4.5	1.8	75	3.7%	-2.02 [-2.41 , -1.62]
Monticone 2017	2.1	0.9	85	5.3	1.5	85	3.7%	-2.58 [-2.98 , -2.17]
Nicholas 2013	4.6	2.1	49	5.3	2.1	33	3.7%	-0.33 [-0.72 , 0.06]
Smeets 2006	42.3	25.6	55	44.6	28.9	52	3.7%	-0.08 [-0.46 , 0.30]
Tavafian 2011	-65.8	22.6	92	-56.4	23.6	97	3.9%	-0.40 [-0.69 , -0.12]
Thieme 2006	3.5	1	42	3.8	1.1	40	3.6%	-0.28 [-0.72 , 0.15]
Thorn 2011	5.3	2.4	32	4.6	2.3	29	3.5%	0.29 [-0.21 , 0.80]
Thorn 2018	5.4	2.3	83	5.7	2	80	3.9%	-0.14 [-0.45 , 0.17]
Thorsell 2011	7.2	2.9	52	8	2.5	38	3.6%	-0.29 [-0.71 , 0.13]
Turner 2006	5.2	1.9	72	5.2	2.1	76	3.8%	0.00 [-0.32 , 0.32]
van Eijk 2013	5.5	2.1	108	5.5	2.1	95	3.9%	0.00 [-0.28 , 0.28]
Vitiello 2013	4.3	3.5	232	4.2	2.9	122	4.0%	0.03 [-0.19 , 0.25]
Vlaeyen 1996	1	1.8	42	0.4	1.8	30	3.5%	0.33 [-0.14 , 0.80]
Zautra 2008	32.5	19.3	51	27.5	18	40	3.7%	0.26 [-0.15 , 0.68]
Total (95% CI)			**2017**			**1718**	**100.0%**	**-0.33 [-0.56 , -0.10]**

Heterogeneity: Tau² = 0.32; Chi² = 293.71, df = 26 (P < 0.00001); I² = 91%
Test for overall effect: Z = 2.82 (P = 0.005)
Test for subgroup differences: Not applicable

Psychological therapies for chronic pain

Williams, et al. 2020
https://pubmed.ncbi.nlm.nih.gov/32794606/

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Preliminary classifications and examples

Inspecting results in the paper
Are the results substantially divergent from others in the meta-analysis?
Inspecting conduct, governance and transparency
Is the recruitment of participants plausible within the stated time frame for the research?
Inspecting the research team
Have other studies by the research team been retracted, or do they have expressions of concern?
Inspecting text and publication details
Is there evidence of copied work, such as duplicated or partially duplicated tables?
Inspecting individual participant data
Does the dataset contain repeated sequences of baseline values?

Results

- 71 participants – 5 continents, but mostly Europe (55%), Australia/ NZ (21%), N America (14%).
- 25 pages of comments: 16 new checks proposed, many suggestions to modify existing checks (e.g. merging, splitting or rewording).

Domain	Number of checks
1. Inspecting results in the paper	28
2. Inspecting the research team and their work	19
3. Inspecting conduct, governance and transparency	22
4. Inspecting text and publication details	7
5. Inspecting individual participant data	41
	117

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Approximately 50 researchers…

Domain	Number of checks
1. Inspecting results in the paper	28
2. Inspecting the research team and their work	19
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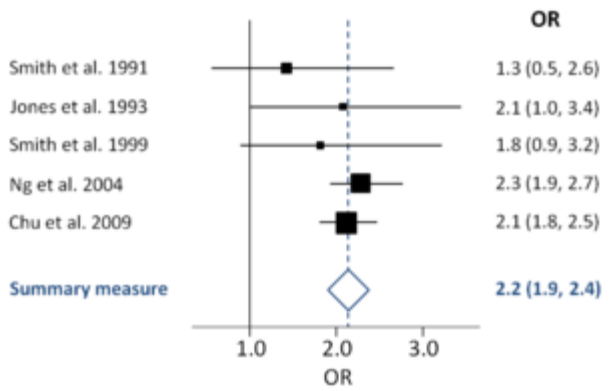
	~~117~~ 76

Applying the long list of checks…



To RCTs in 50 Cochrane Reviews

- How often is each check failed?
- How feasible are the checks?
- What is the impact of removing flagged trials?

Interested?

- Need input and collaboration at all stages – methodologists, trialists, systematic reviewers, editors, publishers, patients, research integrity professionals, or researchers with experience.
- Credible tool needs to be feasible, backed by broad consensus.
- INSPECT-SR Workshop at Colloquium: come and try an early draft version, feedback – join us!
- Need people to participate in Delphi (methods experts and potential users of the tool)
- Need people who would be willing to test the tool while undertaking a systematic review.
- If you have any expertise, experience or interest, please contact me:

- jack.wilkinson@manchester.ac.uk or @jd_wilko

Available tools or frameworks

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Experts identified warning signs of fraudulent research: a qualitative study to inform a screening tool

Lisa Parker • Stephanie Boughton • Rosa Lawrence • Lisa Bero

RESEARCH Open Access

Checklist to assess Trustworthiness in RAndomised Controlled Trials (TRACT checklist): concept proposal and pilot

Ben W. Mol[1,2], Shimona Lai[1], Ayesha Rahim[1], Esmée M. Bordewijk[3], Rui Wang[1], Rik van Eekelen[3,4], Lyle C. Gurrin[5*], Jim G. Thornton[6], Madelon van Wely[3,4,7] and Wentao Li[1]

Cochrane Pregnancy and Childbirth

Identifying and handling potentially untrustworthy trials in Pregnancy and Childbirth Cochrane Reviews

Alfirevic Z, Kellie FJ, Stewart F, Jones L, Hampson L, on behalf of Pregnancy and Childbirth Editorial Board

Research Synthesis Methods

RESEARCH ARTICLE | Open Access

Identifying and managing problematic trials: A research integrity assessment tool for randomized controlled trials in evidence synthesis

Stephanie Weibel, Maria Popp, Stefanie Reis, Nicole Skoetz, Paul Garner, Emma Sydenham

Individual participant data integrity assessment tool

- Tool consisting of a checklist and semi-automated scripts to assess clinical trials for individual participant data meta-analyses (IPD-MA)
- Based on existing literature, mapping exercise and expert consensus
- Pilot tested and refined using two large IPD-MA in child health
- Developed by NextGen Evidence Synthesis Team at NHMRC Clinical Trials Centre, University of Sydney

For more information, or if you are interested in piloting the tool, please contact Kylie Hunter at kylie.hunter@sydney.edu.au

THE UNIVERSITY OF SYDNEY

NHMRC Clinical Trials Centre

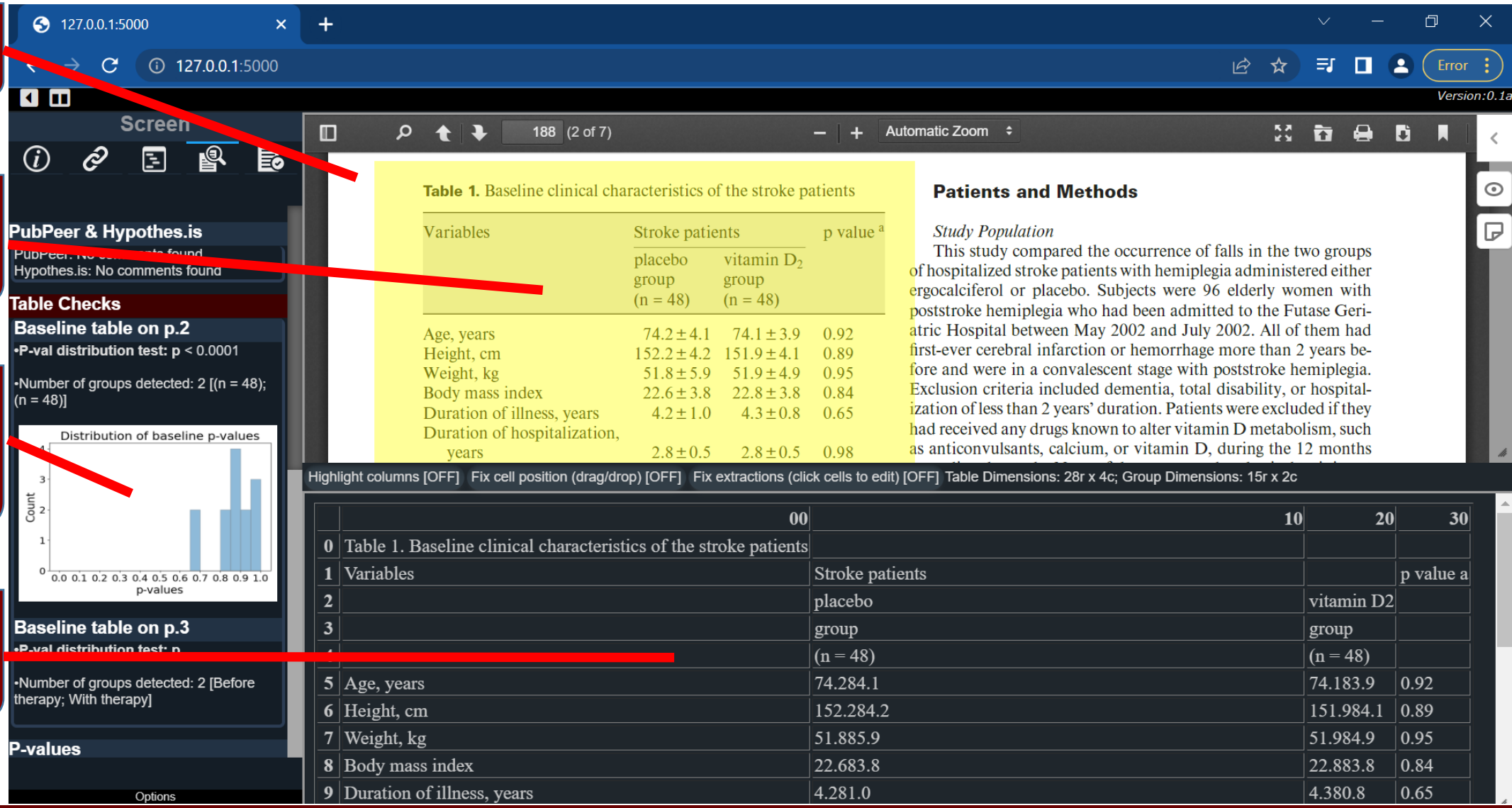
Semi-automated software for analytical forensics: RCT baseline tables as a proof of concept

Upload and view PDF

Automated baseline table identification

Automated p-value extraction and distribution visualization

Manually correct extraction errors



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2. Some principles for investigating potentially problematic RCTs.

Context

- For this part of the talk, drawing on my experience investigating potentially problematic trials for journals and publishers over past four years. Trained by Stephen Evans.

- **Confidentiality** – following examples are illustrative – inspired by real cases, but I have changed details.

- Investigation involves a thorough examination of the manuscript, data, and other sources (registration, correspondence with authors, potentially other papers from the authors).

- Not trying to prove misconduct. Could these data have arisen from a genuine RCT?

Context

- Conclusions based on a **holistic assessment** – not a single statistical test.
- Usually a day's work (at least).
- Illustrating some basic principles here – not comprehensive, not a tutorial!

Human Reproduction, Vol.36, No.1, pp. 87–98, 2021
Advance Access Publication on December 8, 2020 doi:10.1093/humrep/deaa268

human reproduction ORIGINAL ARTICLE *Infertility*

Endometrial scratching in women with one failed IVF/ICSI cycle—outcomes of a randomised controlled trial (SCRaTCH)

N.E. van Hoogenhuijze[1,*], F. Mol[2], J.S.E. Laven[3], E.R. Groenewoud[4], M.A.F. Traas[5], C.A.H. Janssen[6], G. Teklenburg[7], J.P. de Bruin[8], R.H.F. van Oppenraaij[9], J.W.M. Maas[10], E. Moll[11], K. Fleischer[12], M.H.A. van Hooff[13], C.H. de Koning[14], A.E.P. Cantineau[15], C.B. Lambalk[16], M. Verberg[17], A.M. van Heusden[18], A.P. Manger[19], M.M.E. van Rumste[20], L.F. van der Voet[21], Q.D. Pieterse[22], J. Visser[23], E.A. Brinkhuis[24], J.E. den Hartog[25], M.W. Glas[26], N.F. Klijn[27], S. van der Meer[28], M.L. Bandell[29], J.C. Boxmeer[30], J. van Disseldorp[31], J. Smeenk[32], M. van Wely[33], M.J.C. Eijkemans[1,34], H.L. Torrance[1], and F.J.M. Broekmans[1]

[1]Department of Gynaecology & Reproductive Medicine, University Medical Centre Utrecht, Utrecht University, PO Box 85500, 3508 GA, Utrecht, the Netherlands [2]Amsterdam UMC, University of Amsterdam, Center for Reproductive Medicine, Reproduction and Development, Meibergdreef 9, Amsterdam, the Netherlands [3]Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynaecology, Erasmus Medical Centre Rotterdam, 3015 GD, Rotterdam, the Netherlands [4]Department of Obstetrics, Gynaecology & Reproductive Medicine, Noordwest Ziekenhuisgroep, 1782 GZ, Den Helder, the Netherlands [5]Department of Gynaecology, Gelre Hospital, 7334 DZ, Apeldoorn, the Netherlands [6]Department of Gynaecology, Groene Hart Hospital, 2803 HH, Gouda, the Netherlands [7]Isala Fertility Clinic, Isala Hospital, 8025 AB, Zwolle, the Netherlands [8]Department of Gynaecology & Obstetrics, Jeroen Bosch Hospital, 5223 GZ, Den Bosch, the Netherlands [9]Department of Gynaecology, Maasstad Hospital, 3079 DZ, Rotterdam, the Netherlands [10]Department of Gynaecology - Maxima Medical Centre, 5504 DB, Veldhoven, the Netherlands [11]Department of Gynaecology, Onze Lieve Vrouwe Gasthuis, 1061 AE, Amsterdam, the Netherlands [12]Department of Obstetrics & Gynaecology, Radboud University Medical Centre, 6525 GA, Nijmegen, the Netherlands [13]Department of Gynaecology, Franciscus Gasthuis en Vlietland, 3045 PM, Rotterdam, the Netherlands [14]Department of Gynaecology, Tergooi Hospital, 1213 XZ, Hilversum, the Netherlands [15]University of Groningen, University Medical Center Groningen, Hanzeplein 1, Groningen, the Netherlands [16]Department of Reproductive Medicine, Amsterdam UMC, Vrije Universiteit Amsterdam, 1081 HV, Amsterdam, The Netherlands [17]Fertility Clinic, Fertility Clinic Twente, 7556 BN, Hengelo, the Netherlands [18]Fertility Clinic, Medisch Centrum Kinderwens, 2353 GA, Leiderdorp, the Netherlands [19]Department of Gynaecology, Diakonessenhuis, 3582 KE, Utrecht, the Netherlands [20]Department of Gynaecology, Catharina Hospital, 5623 EJ, Eindhoven, the Netherlands [21]Department of Gynaecology, Deventer Hospital, 7416 SE, Deventer, the Netherlands [22]Fertility Center, Haga Hospital, 2545 AA, The Hague, the Netherlands [23]Department of Gynaecology & Obstetrics, Amphia Hospital, 4818 CK, Breda, the Netherlands [24]Department of Gynaecology & Obstetrics, Meander Hospital, 3813 TZ, Amersfoort, the Netherlands [25]Department of Obstetrics & Gynaecology, Maastricht University Medical Centre, 6229 HX, Maastricht, the Netherlands [26]Fertility clinic, Wilhelmina Hospital Assen, 9401 RK, Assen, the Netherlands [27]Department of Gynaecology, Leiden University Medical Centre, 2333 ZA, Leiden, the Netherlands [28]Department of Gynaecology, Haaglanden Medical Centre, 2512 VA, The Hague, the Netherlands [29]Department of Gynaecology, Albert Schweitzer Hospital, 3364 DA, Sliedrecht, the Netherlands [30]Department of Gynaecology, Reinier de Graaf Gasthuis, 2625 AD, Delft, the Netherlands [31]Department of Gynaecology & Obstetrics, St. Antonius Hospital, 3435 CM, Nieuwegein, the Netherlands [32]Department of Reproductive Medicine, Elisabeth-TweeSteden Hospital, 5042 AD, Tilburg, the Netherlands [33]Dutch Consortium for Healthcare Evaluation and Research in Obstetrics and Gynaecology – NVOG Consortium 2.0 [34]Julius Centre for Health Sciences and Primary Care, Department of Medical Humanities, University Medical Centre Utrecht, Utrecht University, PO Box 85500, 3508 GA, Utrecht, the Netherlands

*Correspondence address. Department of Gynaecology & Reproductive Medicine, University Medical Centre Utrecht, Utrecht University, PO Box 85500, 3508 GA Utrecht, the Netherlands. E-mail: n.a.vanhoogenhuijze@umcutrecht.nl

Submitted on June 6, 2020; resubmitted on July 27, 2020; editorial decision on August 26, 2020

NIH U.S. National Library of Medicine
ClinicalTrials.gov

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Stage 1: Concerns with study

- Usually on the basis of published or submitted information (manuscript, trial registration)

Human Reproduction, Vol.36, No.1, pp. 87–98, 2021
Advance Access Publication on December 8, 2020 doi:10.1093/humrep/deaa268

human reproduction ORIGINAL ARTICLE Infertility

Endometrial scratching in women with one failed IVF/ICSI cycle—outcomes of a randomised controlled trial (SCRaTCH)

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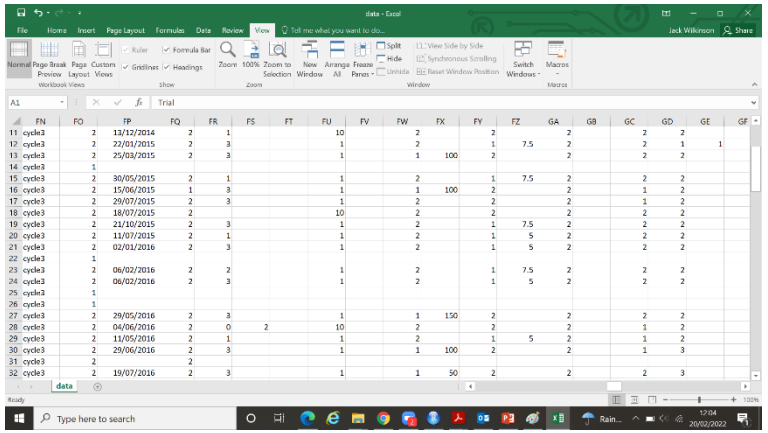

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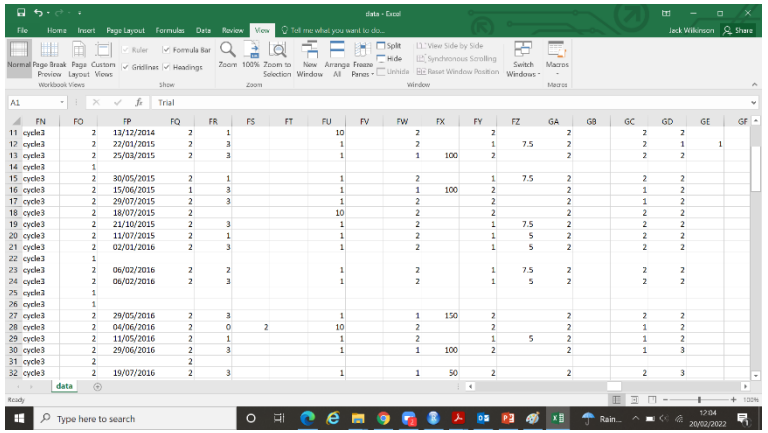

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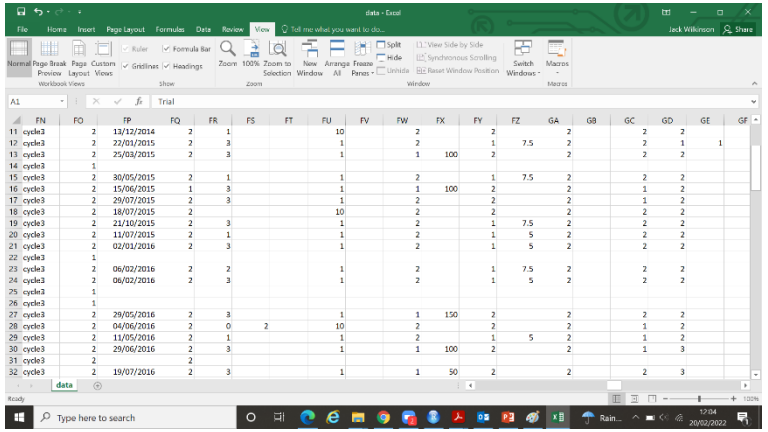

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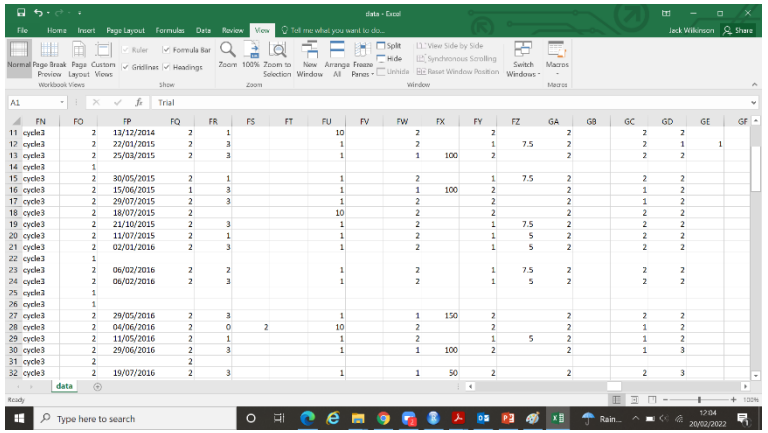

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- Usually on the basis of published or submitted information (manuscript, trial registration)

How?

INSPECT SR

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human reproduction ORIGINAL ARTICLE Infertility

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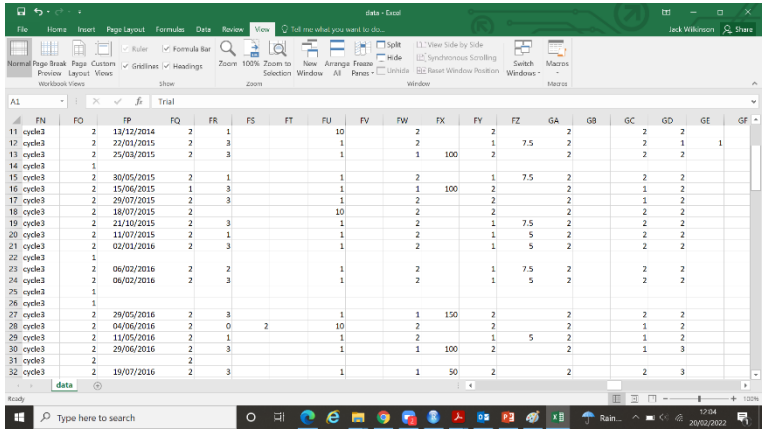

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Recruitment and allocation to treatments in an RCT

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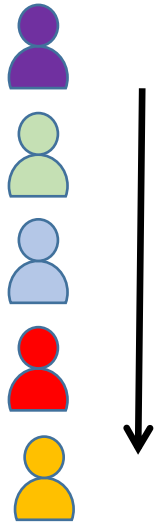

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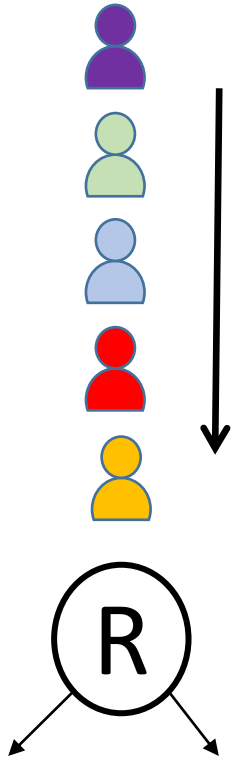

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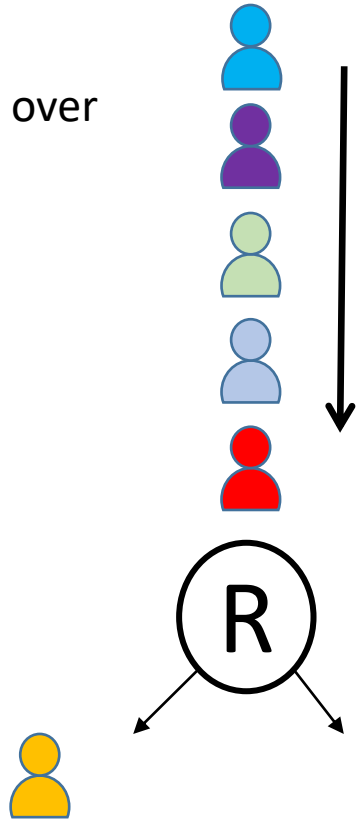

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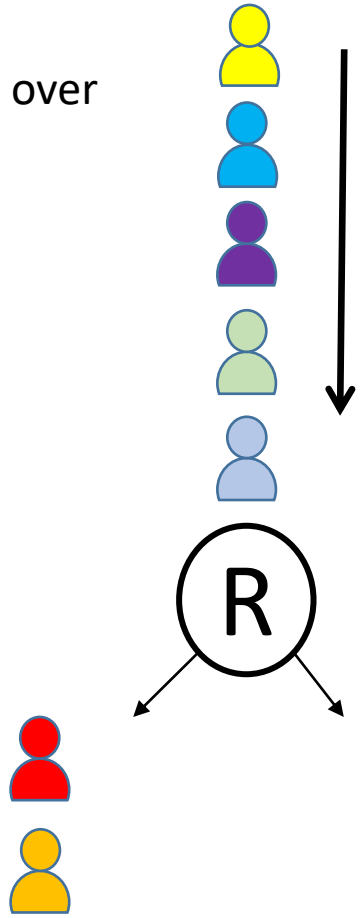

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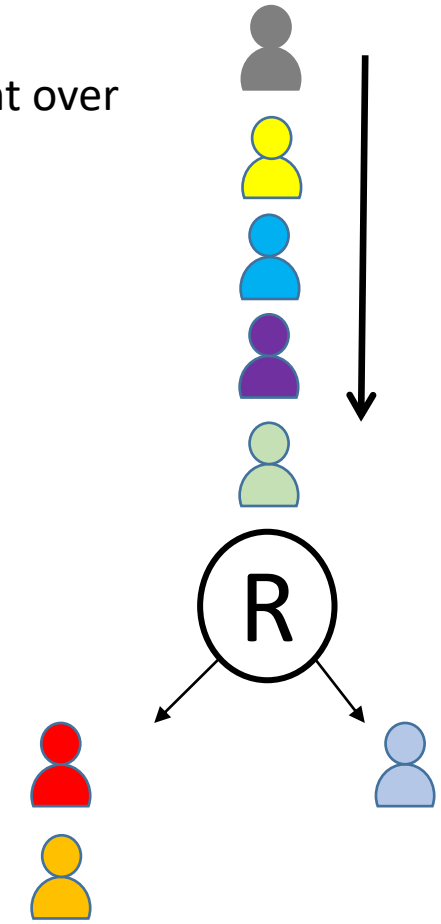

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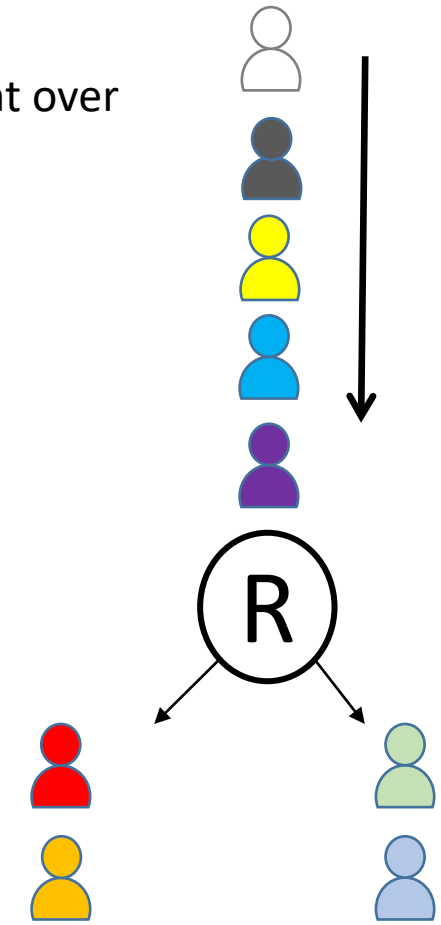

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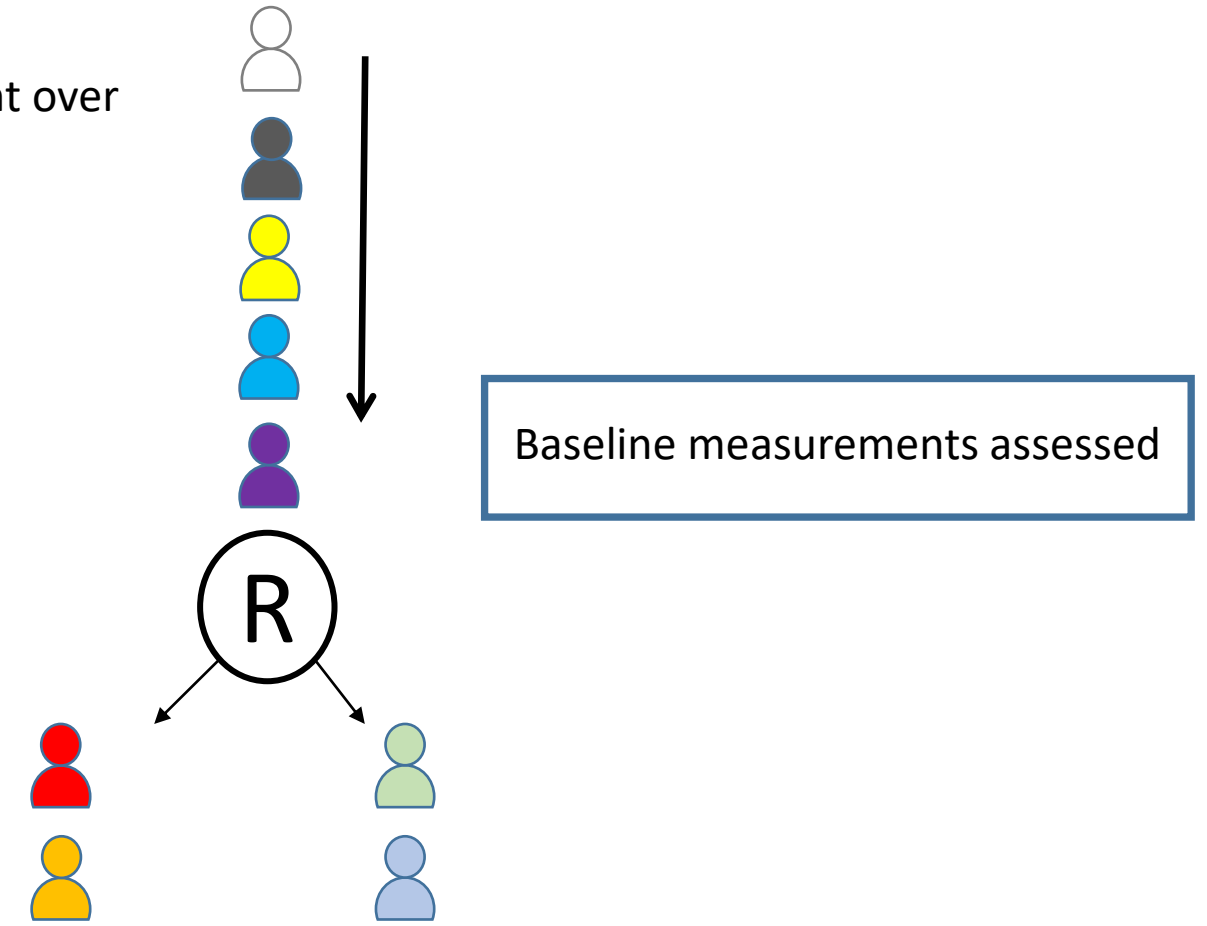

- No systematic differences between groups in baseline characteristics.
- Any patterns in baseline characteristics over time should appear in both groups…

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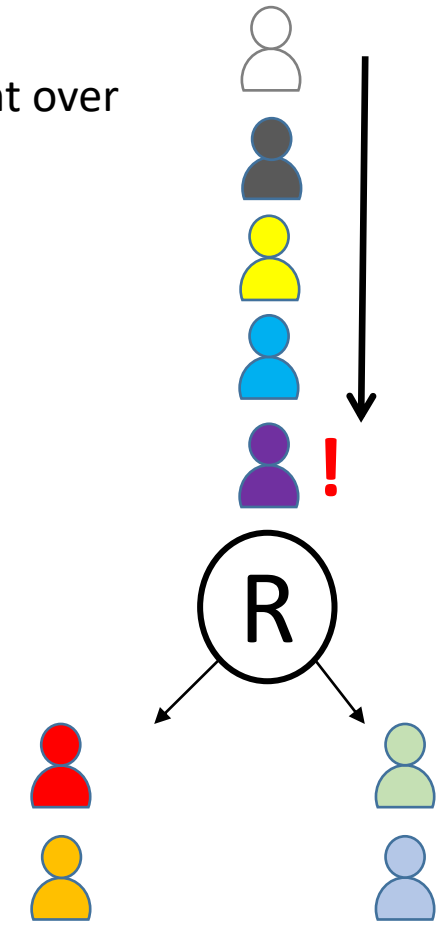

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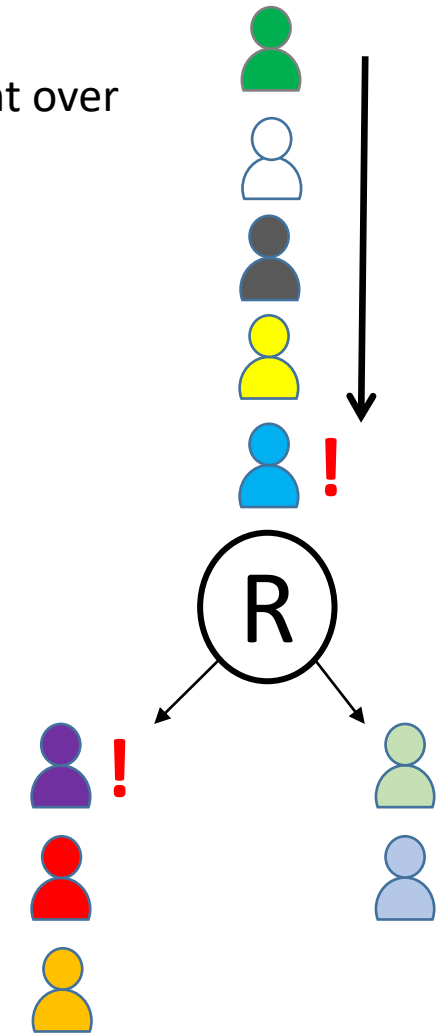

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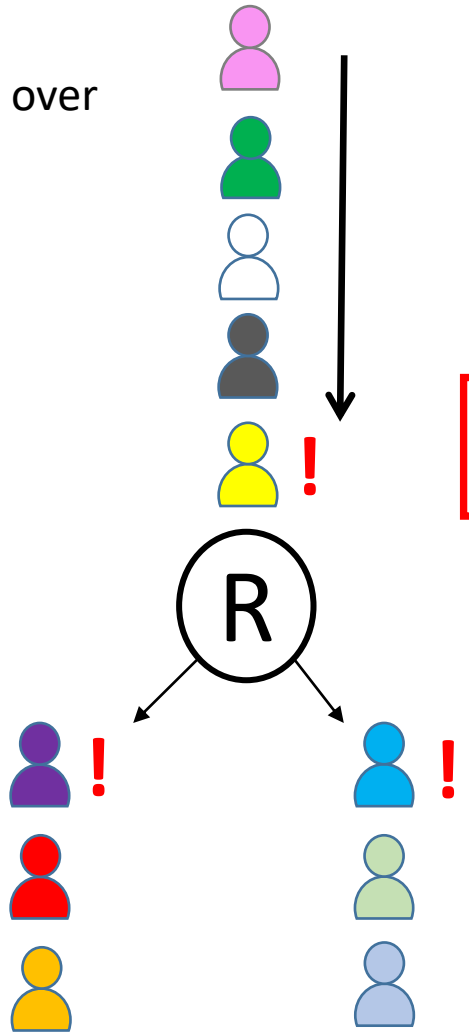

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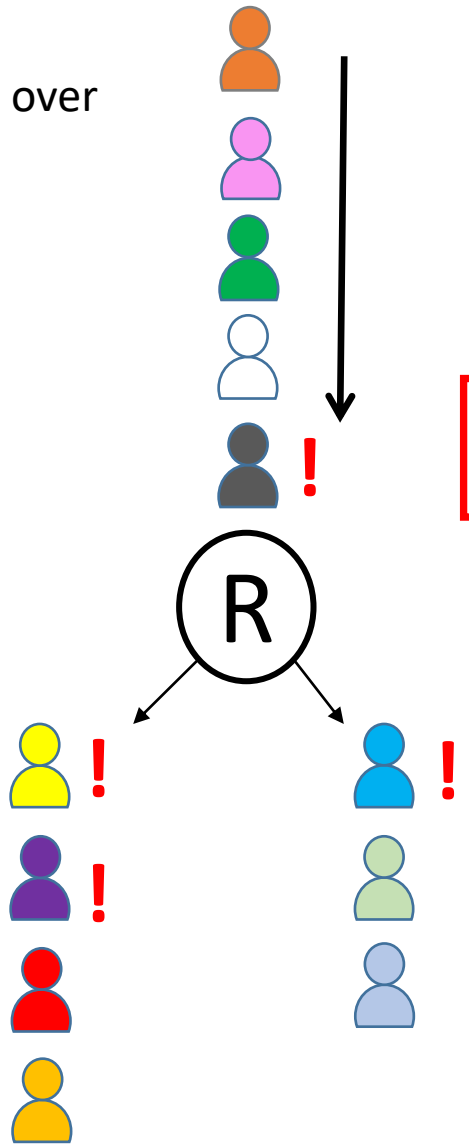

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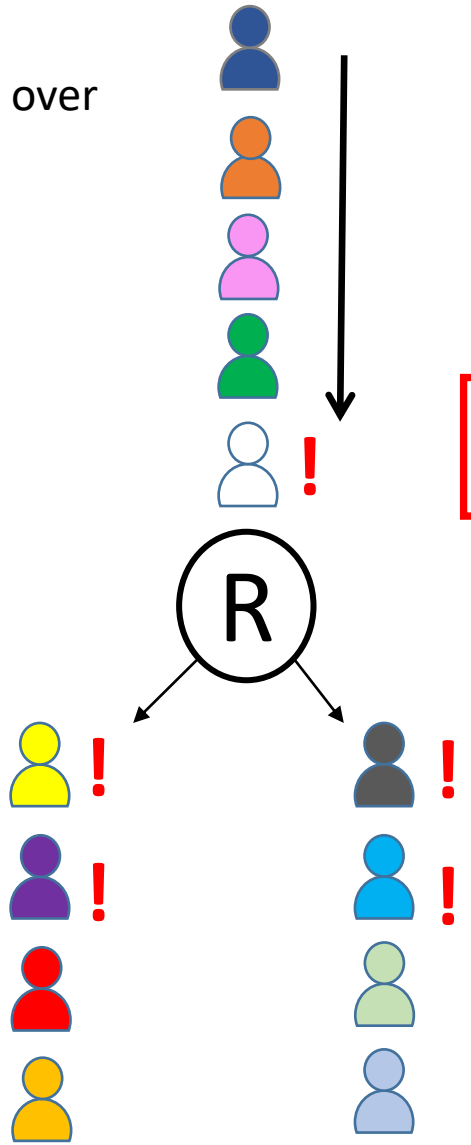
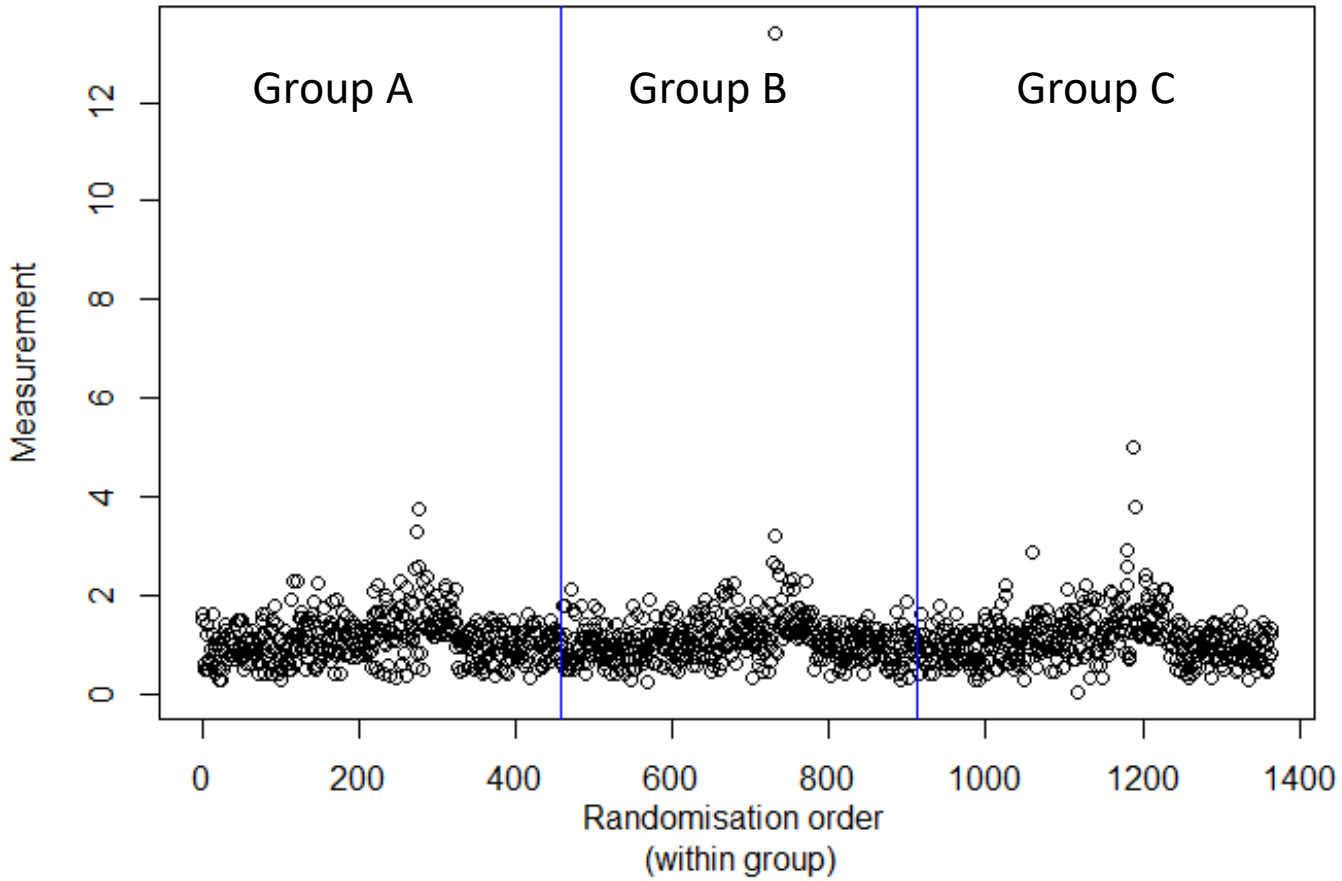


Change in process

3. Patterns in baseline characteristics should be apparent in both arms.

Example – genuine data

3-arm RCT. Blue lines divide into treatment groups – plotted in randomisation order.



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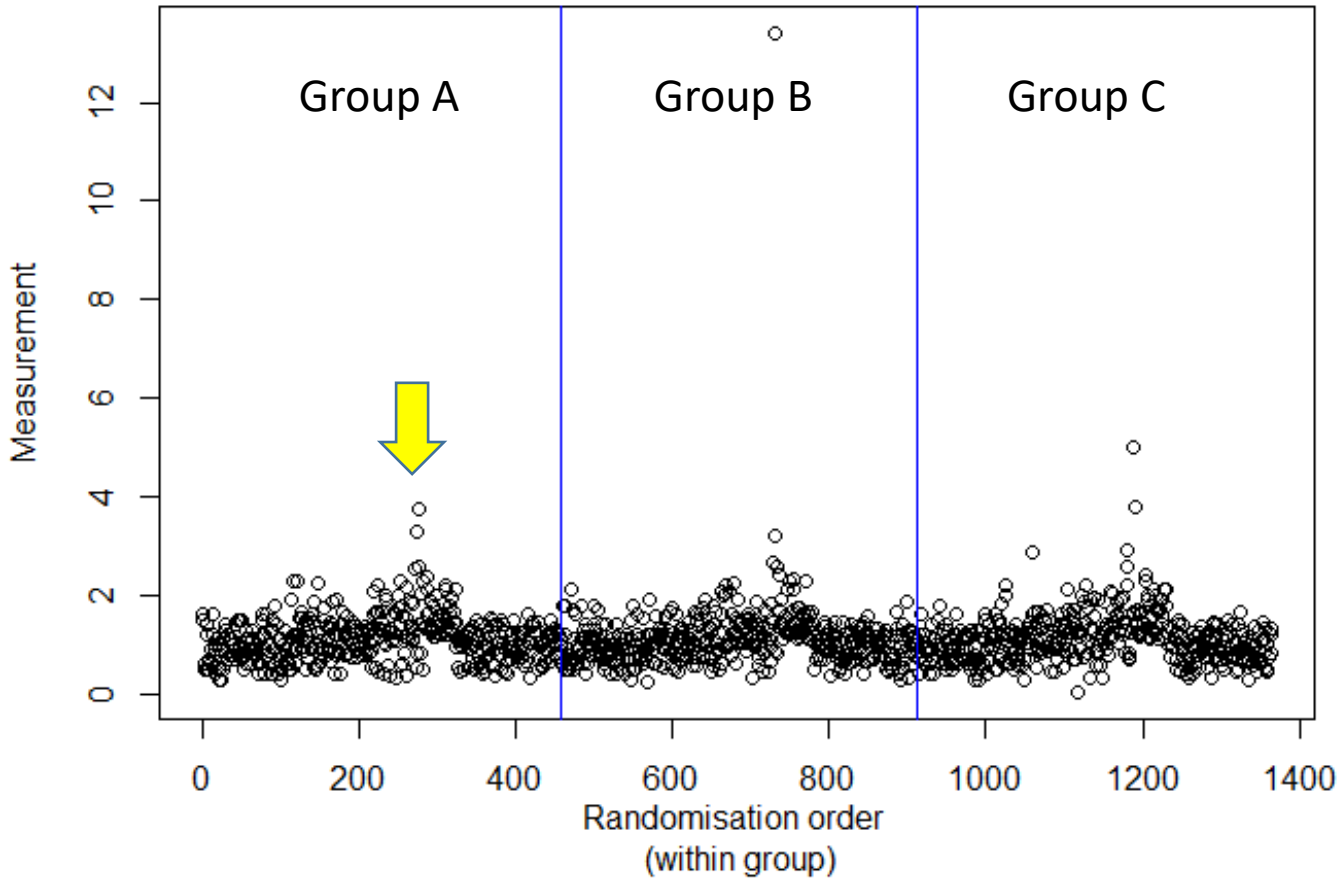

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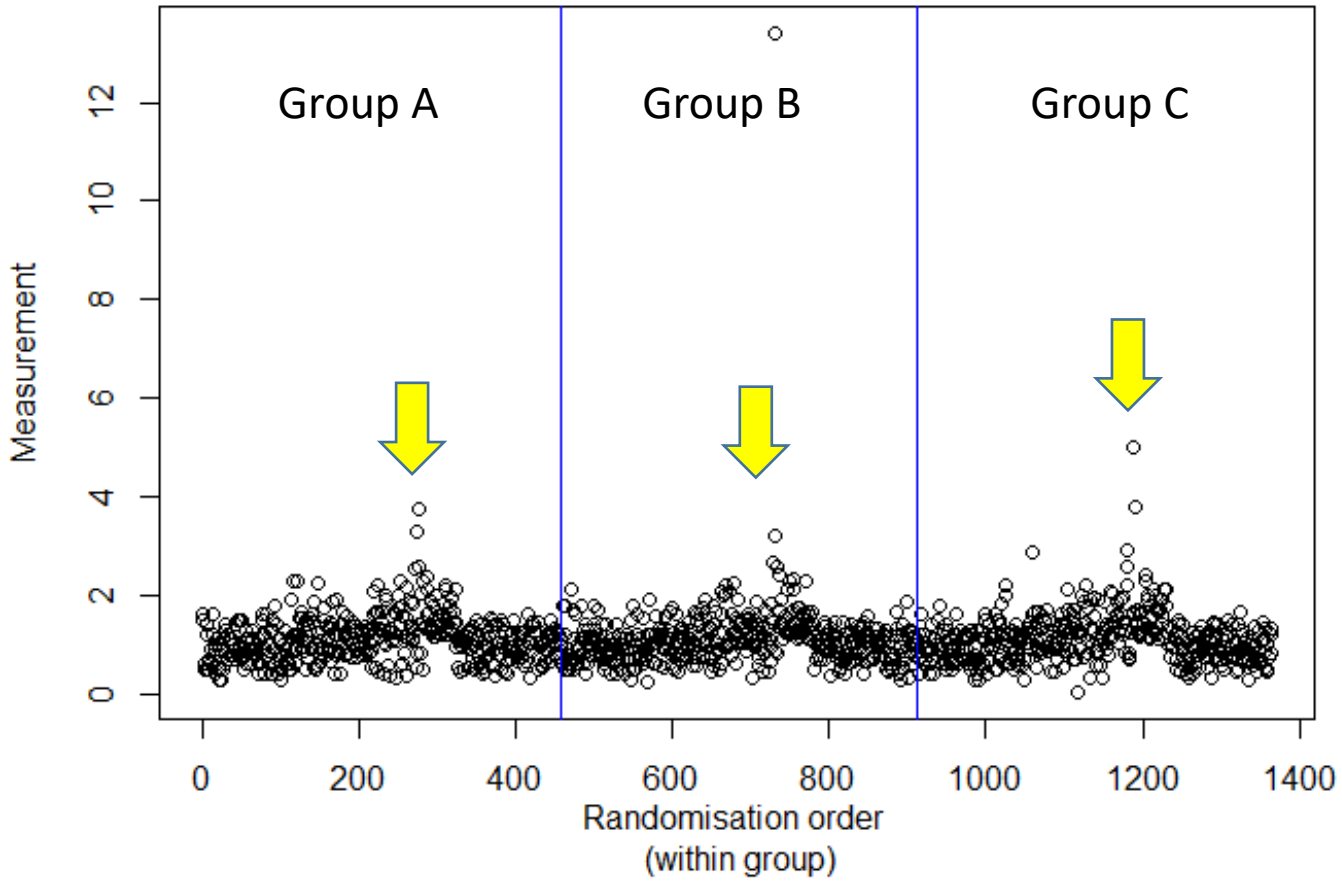
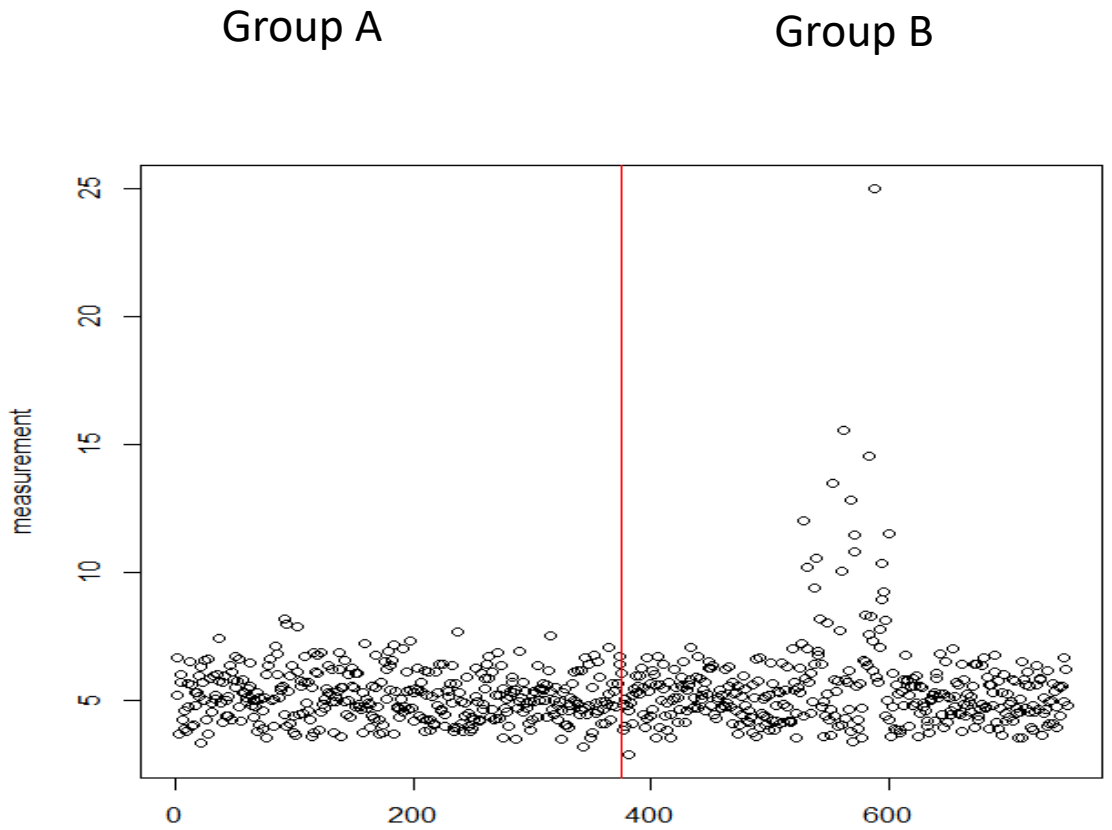


Example – dubious data

2-arm RCT



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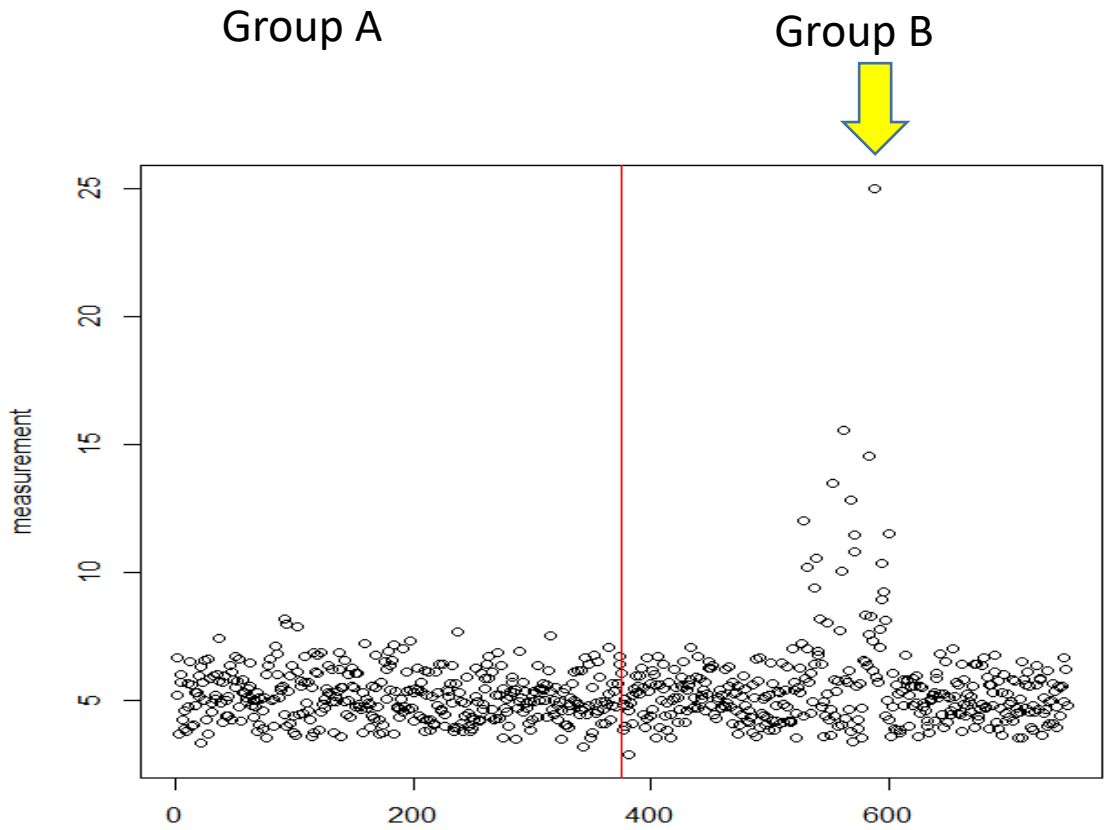

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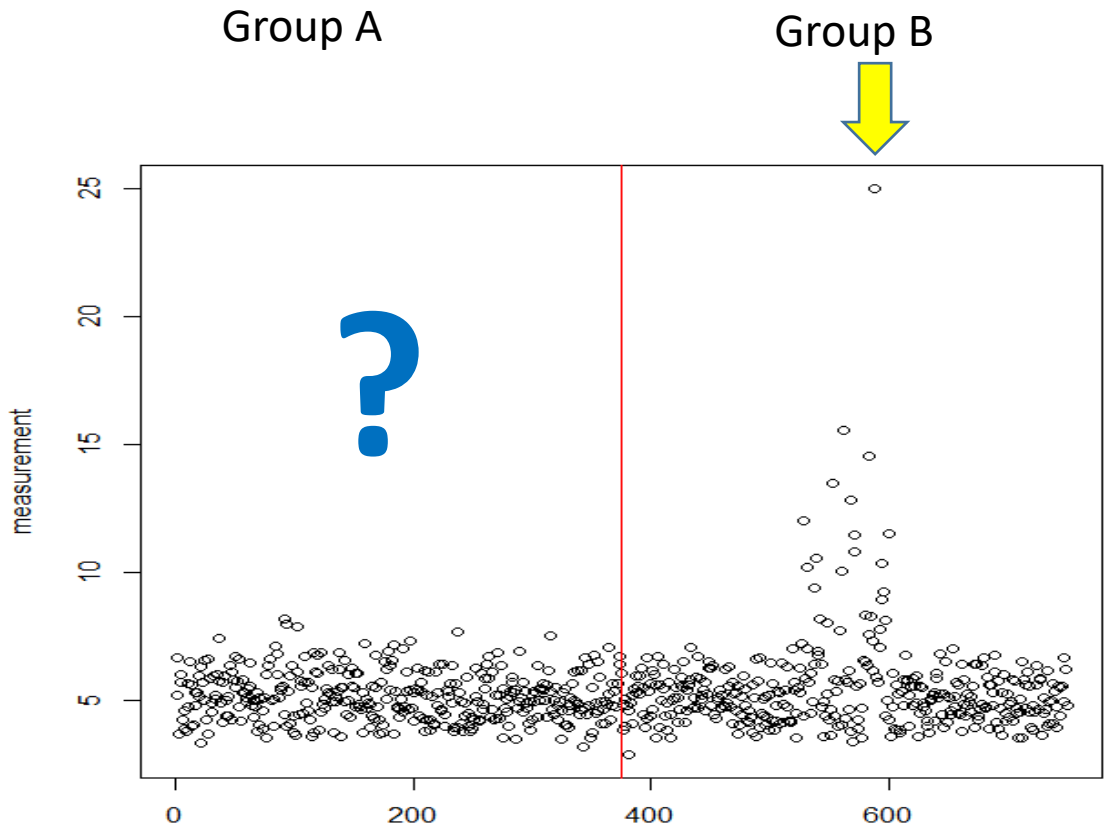
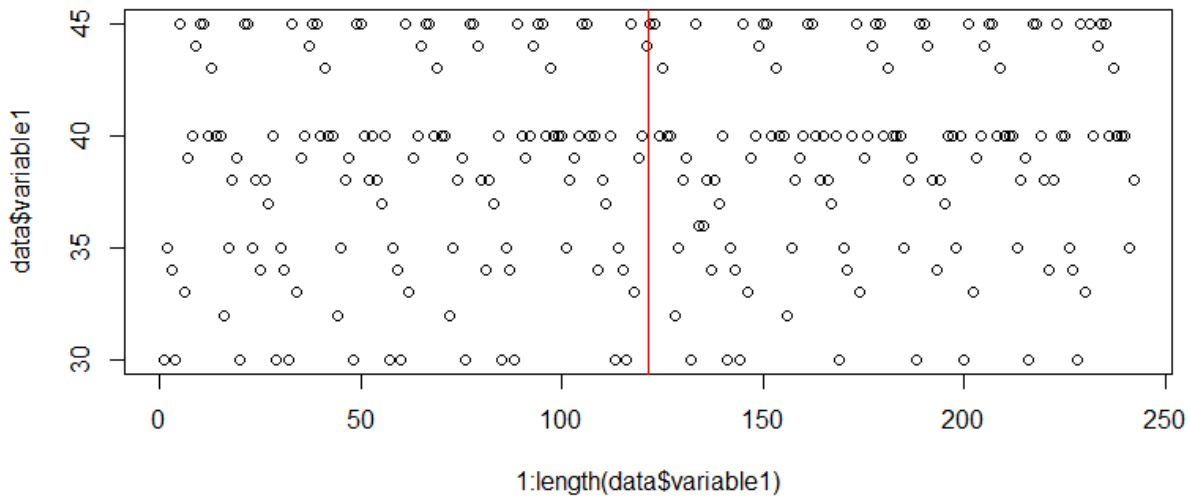


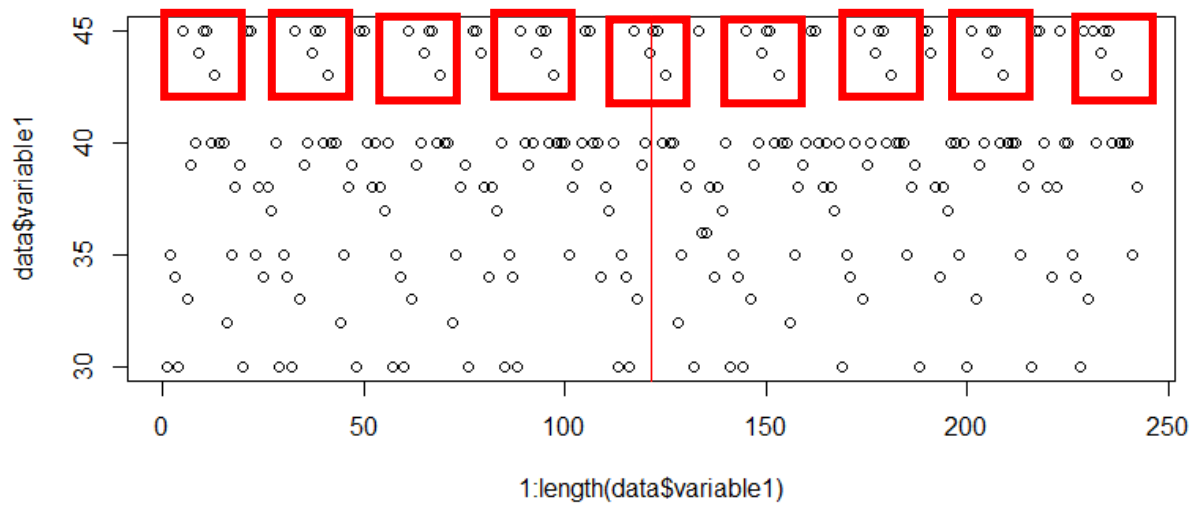
INSPECT SR

Other problems can be revealed by these plots



Take a moment – can you spot any problems?

Other problems can be revealed by these plots



Looking at outcome variables

- Outcomes are a bit different
- They are influenced by treatment, so we do expect to see differences
- But plotting against randomisation order can still reveal improbable patterns…

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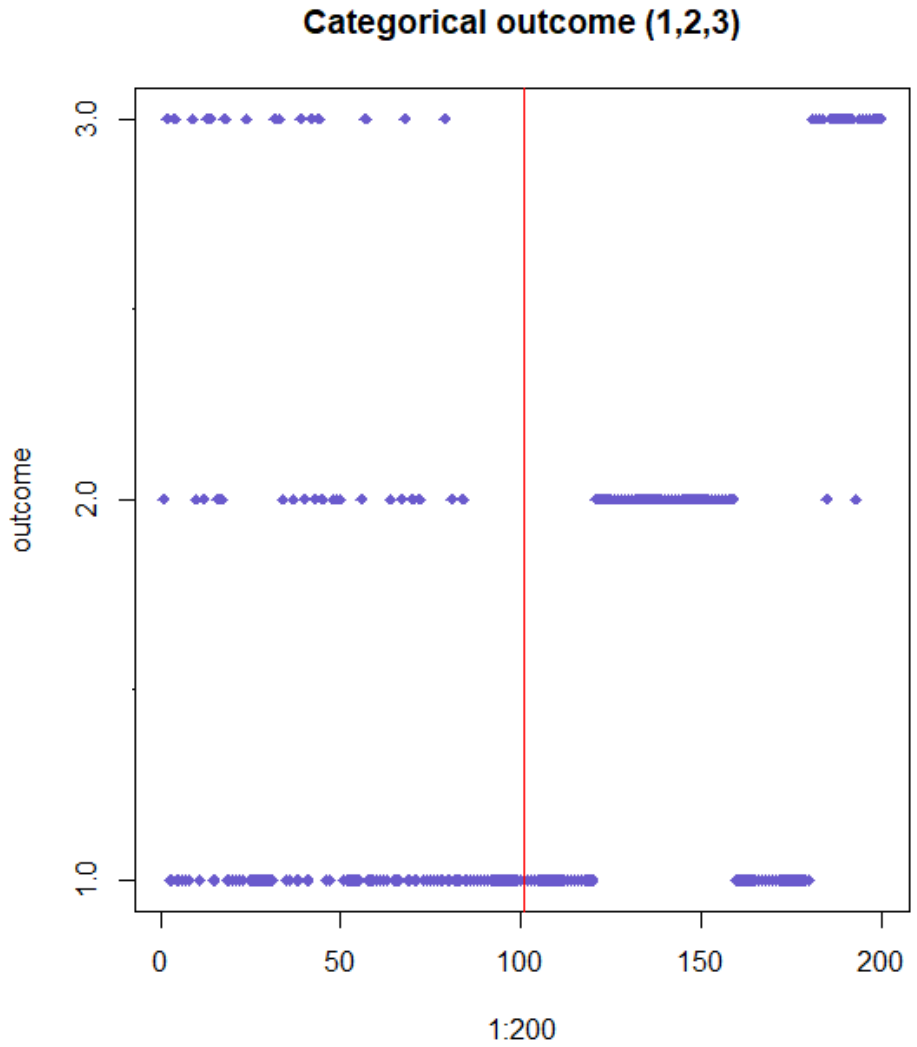

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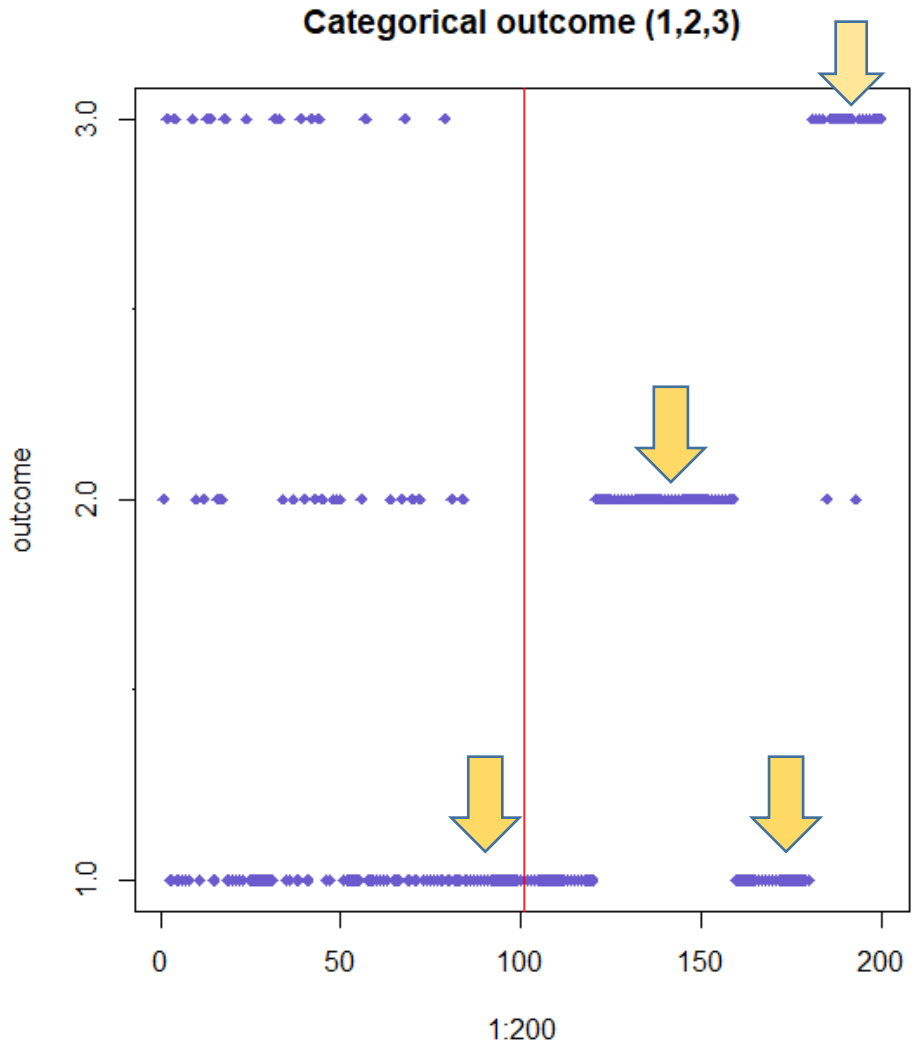


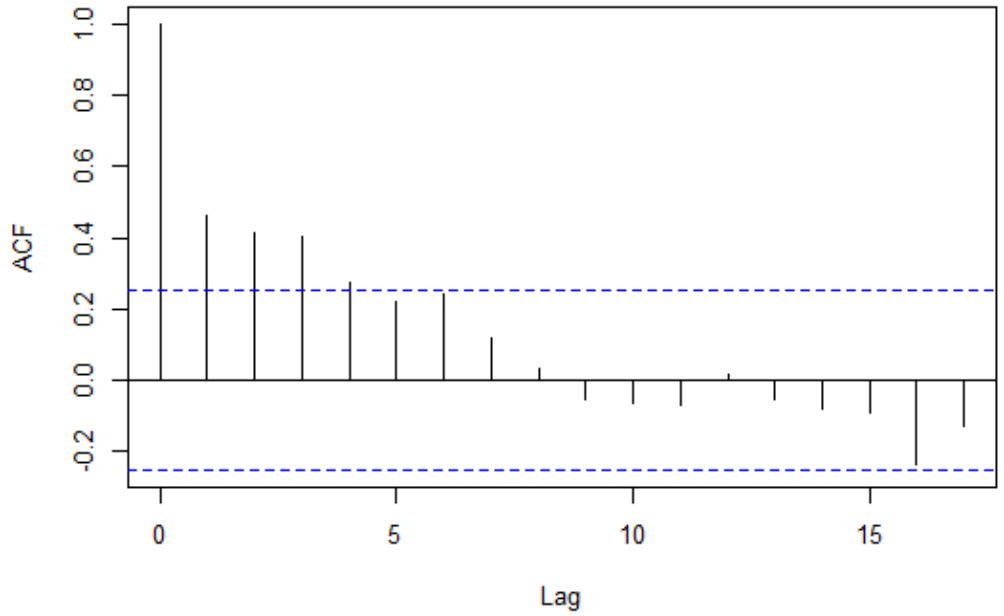
Correlation across rows in the dataset

- We don't expect to see substantial correlation between the baseline values of successive participants.
- E.g. each participant's duration of infertility shouldn't be related to the duration of infertility of the person recruited after them, or to the next person's, or the next person's etc.
- We do expect correlation across rows if someone has typed (fabricated) values into the column – people are poor random number generators.
- Certainly don't expect this to differ between randomised groups.

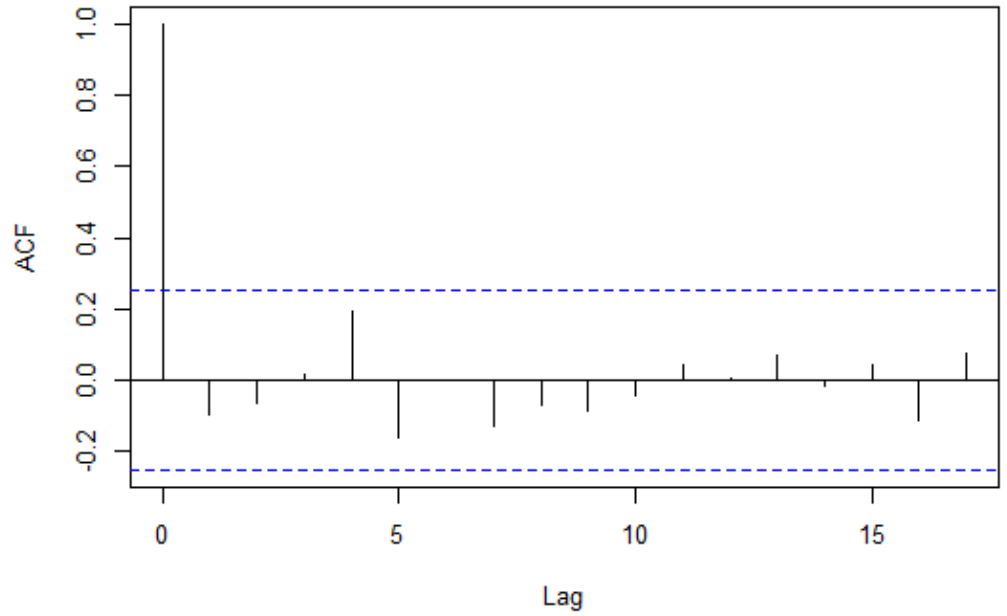
Study ID	InfertilityDuration
1	12
2	8
3	8
4	3
5	1
6	3
7	9
8	3
9	7
10	6
11	5
12	1
13	4
14	6
15	2

Autocorrelation plot

Treatment group



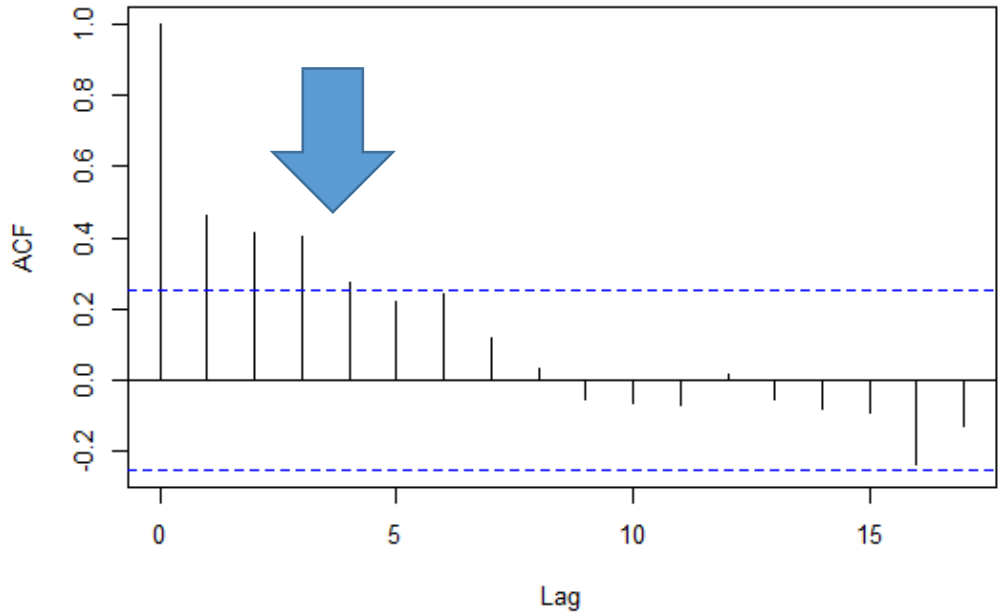
Control group



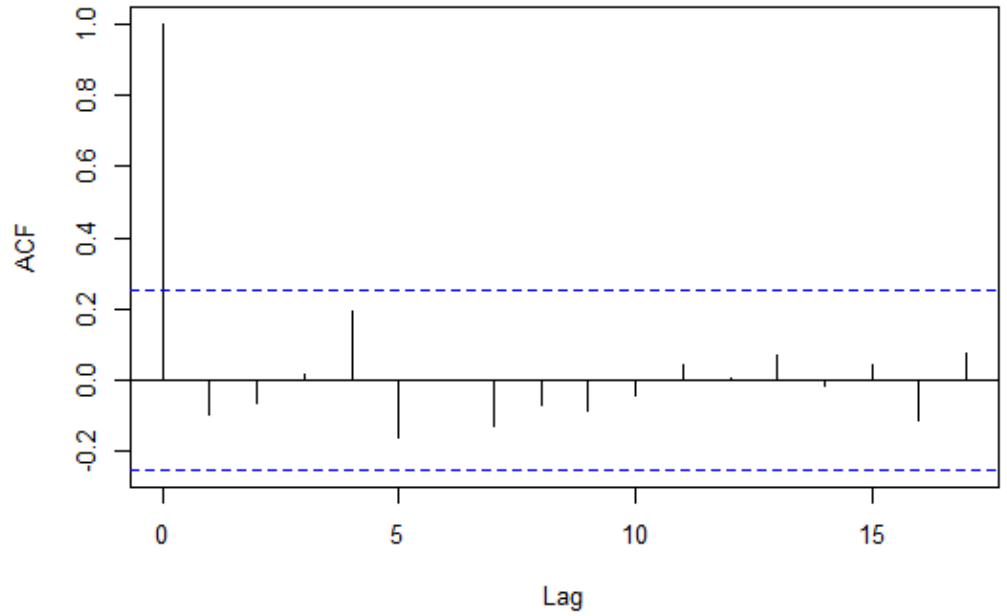
- Plot of correlation between duration of infertility values 1 row apart (Lag =1), 2 rows apart (Lag = 2), 3 rows apart etc.

Autocorrelation plot

Treatment group



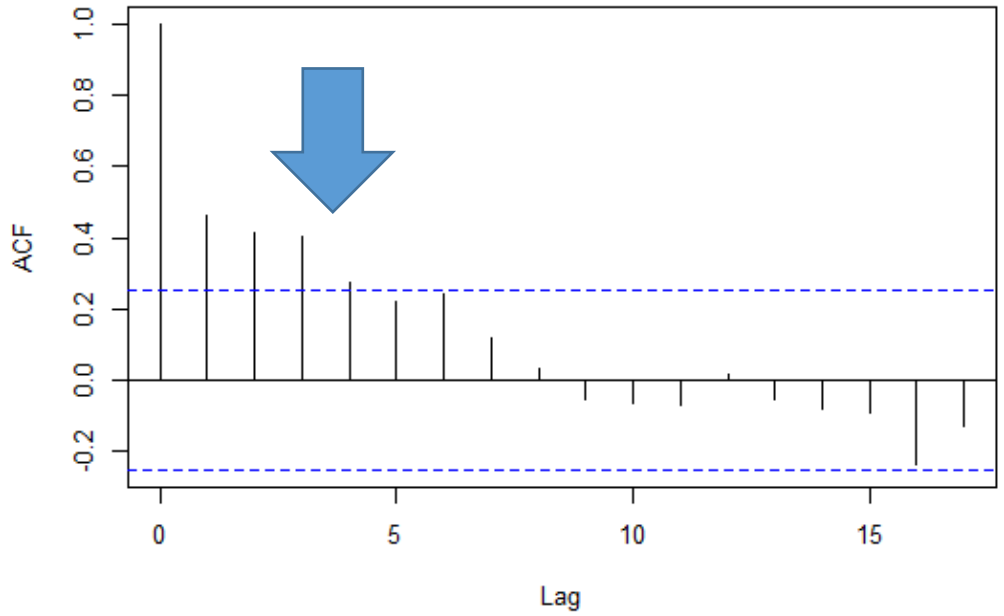
Control group



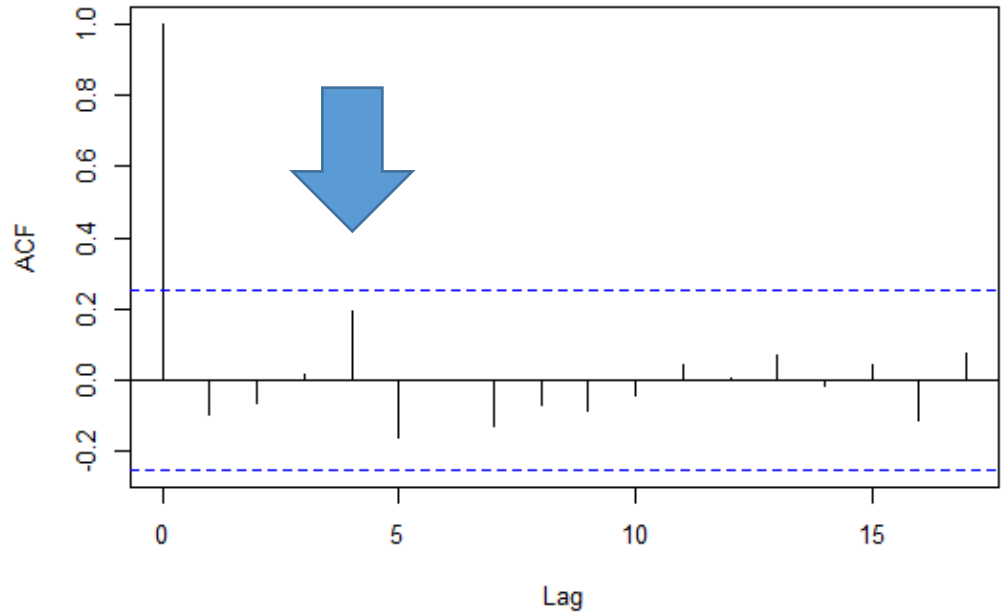
- Plot of correlation between duration of infertility values 1 row apart (Lag =1), 2 rows apart (Lag = 2), 3 rows apart etc.
- In treatment group, there is a correlation between successive rows, which decays as we get further apart.

Autocorrelation plot

Treatment group



Control group



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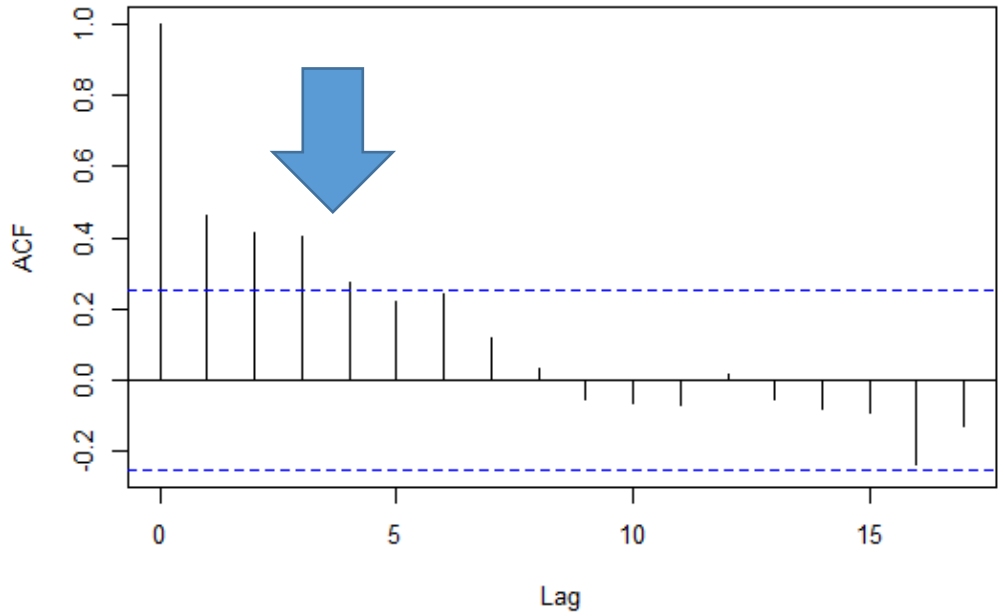
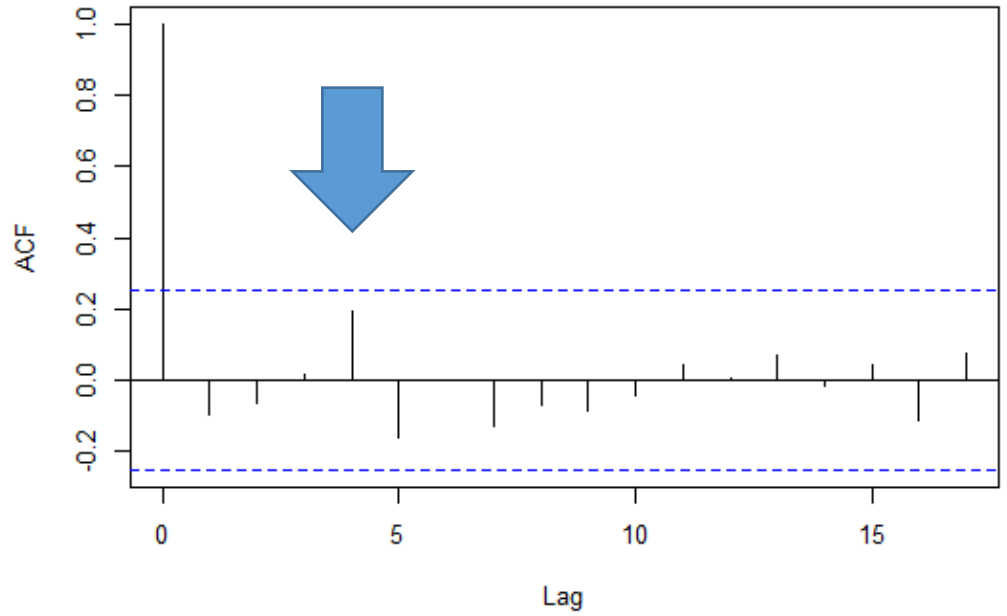
- Control group looks like genuine data – no serial correlation between rows.

Autocorrelation plot

Treatment group



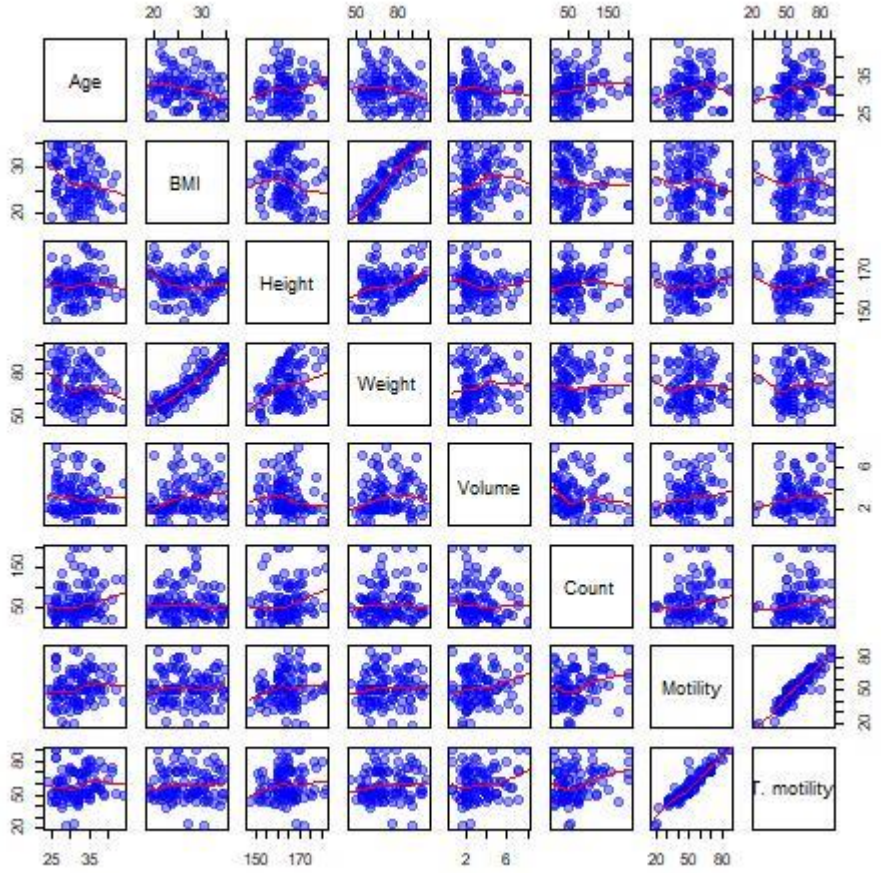
Control group



- Plot of correlation between duration of infertility values 1 row apart (Lag =1), 2 rows apart (Lag = 2), 3 rows apart etc.
- In treatment group, there is a correlation between successive rows, which decays as we get further apart.
- Control group looks like genuine data – no serial correlation between rows.
- The treatment group correlation is suspicious, and the difference between groups is more so.

Relationships between variables

- Are expected relationships between variables present?
- Hard to fake (unless you know what you are doing).
- Requires contextual knowledge (e.g. should we expect relationship between gestational age and birthweight in a particular trial).
- Don’t expect multivariate distribution to differ between randomised groups.



Closing comments

- Have shown just a few basic checks here. Different approaches may be more or less appropriate for particular cases.
- We understand a lot about characteristics of data arising from RCTs. Can use this to assess whether data are (in)compatible with a genuine RCT.
- “Could there be an explanation for this?”
- Sometimes there is clear evidence of fabrication (e.g. certain cases with repeating sequences in the data). Other times, unclear whether misconduct or very poor conduct.
- Either way, may have reservations about using the data to decide how patients are treated.

Thanks to expert panel members

Elizabeth Loder	Toby Lasserson	Kyle Sheldrick	Andrew Grey	Susan Garfinkel
John Carlisle	Tianjing Li	Emily Lam	David Torgerson	Andreas Lundh
Karla Soares-Weiser	Neil O' Connell	Rebecca Jones	Esmée Bordewijk	Lyle Gurrin
Rita Redberg	Lisa Parker	Darren Dahly	Nick Brown	Lene Seidler
Jo Dumville	Virginia Barbour	Alison Avenell	Wentao Li	Kylie Hunter
Mike Clarke	Ben Mol	James Heathers	Richard Stevens	
Emma Sydenham	Barbara Redman	Gideon Meyerowitz-Katz	Rafael Perera-Salazar	
Jane Dennis	Jill Hayden	Madelon van Wely	Sarah Lensen	

- Need people to participate in Delphi.
- Need people who would be willing to test a tool while undertaking a systematic review.
- If you have any expertise, experience or interest, please contact me:
- jack.wilkinson@manchester.ac.uk or @jd_wilko