The Royal Society of Medicine

Journal of the Royal Society of Medicine; 2026, Vol. 119(3) 83–88
DOI: 10.1177/01410768261419062

The problematic history of randomised controlled trials Part 3: Mainland, Hill and the future of RCTs

Robert AJ Matthews
Department of Mathematics, Aston University, Birmingham B4 7ET UK
Corresponding author: Robert AJ Matthews. Email: rajm@physics.org

> [I]n much medical literature there is inadequate recognition and treatment of questions of chance, of the allowance to be made for small samples, and of natural variation from sample to sample.[1]

Introduction

In August 1936, the *British Medical Journal* published a critique of a proposed criterion for the surgical treatment of Bell's palsy. It highlighted basic errors in arithmetic and statistical reasoning that undermined the evidence for the criterion, and gave guidance on the design and analysis of studies needed for such work. Entitled 'Problems of chance in clinical work',[1] the critique also included the above quotation, reflecting concern that many medical researchers lacked even the most basic statistical background needed to extract reliable insight from data. Its author was Donald Mainland (1902–1985), who had himself once been in this position. As a young professor of anatomy at Dalhousie University, Canada, he had run into the very issues mentioned in the quotation while performing experimental work in embryology in the late 1920s. Their resolution emerged after a discussion with an agricultural experimentalist who introduced Mainland to Ronald Fisher's seminal text *Statistical Methods for Research Workers*.[2] Despite its contents reflecting its origins in crop research, Mainland saw that Fisher's text addressed key challenges faced by medical researchers.[3] A combination of self-study and both correspondence with Fisher and work in his department at University College, London, led Mainland to a deep understanding of both the theory and practice of randomisation. It also laid the foundation of a distinguished reputation as a statistician, triallist and educator.[4]

In this third and final article of a series revisiting the history of randomised controlled trials (RCTs), Mainland's career serves as a counterpoint to that of Austin Bradford Hill, the British statistician generally credited with having catalysed the widespread adoption of RCTs. What follows does not challenge that reputation. Its aim is to examine the standard narrative of the rise of RCTs in the light of the contrasting approach of Mainland and Hill to the principles that underpin RCTs. The outcome suggests that the evolution of RCTs may have benefited considerably had Mainland's approach enjoyed the same popularity and impact as that of his more famous contemporary.

The contrasting attitudes of Mainland and Hill to Fisher's work

The early careers of Mainland and Hill have several parallels. Both gained DSc degrees in life science-related areas in the early 1930s (in Mainland's case, after graduating in medicine from the University of Edinburgh), and acquired their understanding of statistics by a combination of self-tuition, interaction with others and practical experience. Both also shared a commitment to making statistical techniques accessible to the medical community. However, they had radically different attitudes to the work of Fisher in general, and his theory of randomisation in particular.

This is clear even in their earliest publications. Mainland's 1936 critique of Bell's palsy study appeared a few months before Hill's lecture series in *The Lancet*, which became the basis of his hugely influential *Principles of Medical Statistics*.[5] Mainland's critique contains more, and more sophisticated, concepts in its four pages than Hill conveys in his *Lancet* lectures. Moreover, in what would become a common feature of his publications, Mainland stresses the interplay between randomness and the reliability of statistical inferences, and refers the reader to Fisher's 1925 text for further details. In the 1936 critique, he also acknowledges Fisher's direct input and review of the text. By contrast, and as described in Part 1 of this series, Hill's lectures and early editions of

Correction (February 2026): This paper has been updated to correct the citation in the line: [Hill, quoted in Neuhauser et al.[18]; emphasis added].

Principles are remarkable for their confused notion of randomness and absence of substantive references to Fisher's work, still less the concept of randomisation.

The conflations and omissions in Hill's *Principles* are all the more striking given that they remained for years after the publication in 1948 of the UK Medical Research Council's landmark streptomycin RCT (MRC 1948),[6] which featured Hill's celebrated use of concealed random allocation of patients. The report itself carries no explanation of why randomisation had been chosen over the usual method of alternation, described in Part 1. In contrast, Mainland had by this time already written on the role of random selection in experimental work and specifically warned against the presumption of randomness – that is, the Quasirandomness Fallacy discussed in the first paper of this series – prior to allocation:

> [Random selection] does not mean a *haphazard* choice, or the selection of any patients or animals that happen to come along, or a sampling that we believe to be random because we cannot think of any reason why it should not be random.(p. 6)[7]

In 1952, with Hill's *Principles* still bizarrely failing to advocate randomised allocation, the first edition of Mainland's best-known textbook, *Elementary Medical Statistics* (henceforth *EMS*),[8] appeared (a comprehensive review of which is currently in preparation by Farewell (2025, personal communication). This stressed the importance of eliminating bias in allocating patients to trial arms, and why this is best achieved through Fisher's concept of randomisation:

> Since we cannot distribute the various types of patient (i.e., sets of factors) equally to our two samples, we must allocate them in such a way that we can tell what allowance to make for the inequalities. The only way to do this is to make chance decide for us; i.e., *we must allocate the treatments strictly at random*.(p. 103)[8]

Mainland explained that the crucial problem with allocation by alternation is that it 'may, or may not, clear an experiment of bias', and even if it did somehow mimic strictly random allocation 'it would permit manipulation' (p. 268).[8] This led him to explain the imposition of true randomisation using tables of random numbers, all of this appearing 3 years before being mentioned by Hill in the sixth edition of *Principles.*

The second, and radically re-structured, edition of *EMS*[9] makes clear that Mainland's advocacy of randomisation flowed from his understanding of Fisher's theory rather than the simple 'pragmatism' of Hill. He gives a clear exposition of the difference between an experiment like an RCT and a survey (which would now be called an observational study), explaining the role of randomisation by analogy of card-shuffling (pp. 19–23).[9] He then highlights the fundamental error in blithely assuming clinical trials can be analysed using the standard random sampling model. Noting the myriad pathways and commonalities of patients admitted to a clinical trial he states:

> [W]e see very good reasons to conclude that no group of patients investigated by an individual physician, or in a clinic or in a hospital, is likely to be equivalent to a strictly random sample of the population which, by diagnostic label, it purports to represent. (p. 37).

Mainland then invokes Fisher's theory of randomisation, and its implications:

> The point to remember is that Nature does not *try* to randomize . . . And so, after learning that strictly random sampling is nearly always essential if we are to make a reliable estimate of the possible error in our conclusions, we learn that most of the samples that come to us are not strictly random samples of the populations to which we wish to generalize (p. 37).[9]

In these two sentences, Mainland makes clear his recognition of two key issues that forever eluded Hill: recognition that simple random sampling theory is inappropriate for clinical trials, and the impact of the Quasirandomness Fallacy on inferences based on their outcomes.

Mainland sympathised with triallists who found it 'very discouraging' to learn that the generalisability of their findings was undermined by a seemingly abstruse technicality. He blamed the (unnamed) authors of introductory texts for failing to explain the concept of bias sufficiently well (p. 75).[9] He also had little patience for those who failed to see the point of using randomisation rather than alternation in clinical trials:

> To omit randomisation because one cannot see clearly how bias could occur is like trusting that glassware in chemistry is clean because it does not look dirty (pp. 138–145).[10]

In general, Mainland's writings recognise the concerns of those unfamiliar with the challenge of dealing with the biases and random error: '[S]tudents have asked: "How can one ever hope to draw any reliable conclusions?"(p. 41)[8] Mainland's grasp of Fisher's theory allowed him to answer the students' 'despairing question' by appeal to the power of randomisation, rather than via standard random sampling arguments propped up by the Quasirandomness Fallacy. He explained how to begin by purposively grouping individuals according to obvious sources of potential bias, such as sex, and then using randomisation to deal with all the others, including allocation bias:

> Let us even suppose that, unknown to anyone, there is some major factor that influences strongly the outcome of a disease, and is present in some patients but not in others. The

> only method by which the physician can exert control over this factor is by allocating it strictly at random to his treatment samples. Then he will know that his samples will differ, with respect to that factor, as well as to the others, only to the extent caused by chance (p. 104).[8]

The ability of randomisation to go beyond combating allocation bias and handle even unknown biases and confounders is the most important aspect of Fisher's theory as applied to clinical trials, and Mainland was surely right to emphasise it. His understanding of Fisher's theory allowed him to go further still, however. The introduction to his first textbook on medical statistics, *The Treatment of Clinical and Laboratory Data*,[11] states its aim as being to provide clinicians with methods for assessing their own findings, critiquing the claims of others, and 'to give a simple introduction to some parts of Dr Fisher's work'. This became a recurring theme in his textbooks, and again sets them apart from Hill's *Principles*, which reflect its author's belief that Fisher's arguments could and should be treated as unnecessary technicalities.

As Altman[4] notes in his biographical review of Mainland's career, his works are remarkable for their clarity and lack of jargon: 'he wrote really well for his target readership'. He was also undaunted by the challenge of introducing his readership to unfamiliar or relatively advanced concepts if he thought them valuable. Altman provides a list of examples, ranging from the use of confidence intervals[7] and cluster randomisation[8] to methods of dealing with missing data.[9]

On topics specific to Fisher's theory, Mainland made much of how randomisation allows valid inference to be performed without assuming the effect of interest follows a normal distribution. This is especially valuable in small clinical trials, where the assumption of normality is most questionable. In his 1938 text, Mainland mentions what at the time was a novel and conceptually related method now known as Fisher's Exact Text, and demonstrates its use via Yates's modification to the standard chi-square formula. In contrast, Hill's *Principles* long contained only oblique reference to the concept of exact tests and their use with small trials.

The contrasting pedagogical approaches of Mainland and Hill

Considering that both Hill and Mainland had the same target readership of working clinicians, the difference in approach is remarkable. Mainland's confident command of statistical methods in general and Fisher's theory in particular underpinned his clarity of exposition. It also meant he was able to take on the task of 'translating' Fisher's methods – some devised originally for crop research – for use in clinical medicine. This allowed Mainland to make clinicians aware of powerful techniques such as factorial designs and Analysis of Variance. The approach taken by Hill, in contrast, was one of 'clarity by omission'. One could ascribe this to Hill having a lower opinion of his readers' technical abilities than did Mainland. To judge by the evidence provided in Part 2 of this series, however, they seem to reflect Hill's avowedly low opinion of his own.

Despite the pedagogical differences between Mainland and Hill, there are also important similarities. The most fundamental is their shared belief in the primacy of appropriate study design and the dangers of an unthinking application of statistical methods. They also both stressed the dangers of mis-interpreting statistical significance, a concept which remains a contentious issue to this day.[12]

It should be noted that Mainland admired Hill's introduction of concealed random allocation to clinical research, describing it as 'a beacon' leading to the improvement of medical experimentation:

> . . .not only by devices such as randomization and the balancing of samples, borrowed from other biological fields, but by methods specially appropriate to investigation on human beings, such as the 'double blind' method, to avoid bias both from the patient and the observer.[3]

Like Hill, Mainland was highly regarded for his expository skill. In 1970, Yale University epidemiologist Alvan Feinstein wrote: 'With his textbook . . . and his many other writings, [Mainland] has probably contributed as much as any single person to the statistical sensibility of clinical investigators in North America'.[13] Yet such praise cannot conceal the reality that the Mainland's *EMS* never seriously challenged the influence of Hill's *Principles.* As noted in the second article in this series, from the start of his career, Hill benefited from personal connections to some of the most influential statisticians of his day. His statistical lectures in the internationally respected *The Lancet* won plaudits on both sides of the Atlantic, leading to their rapid re-publication as *Principles.* Hill's key role in the landmark streptomycin RCT of 1948 raised his international profile still higher. Around this time, statisticians fully conversant with Fisher's approach began to emerge in American institutions, and Mainland gained some prominence via the publication in 1952 of *EMS* and the second edition in 1963. By this time, Hill had retired, and yet *Principles* remained in print for another 30 years and his writings continued to be highly cited.[14] As a 2010 review put it: 'Hill's book stands out as making a worldwide contribution to the understanding and teaching of medical statistics over the last 70 years'.[15] Neither *EMS* nor its thesis that Fisher's theory of randomisation holds the key to the effectiveness of RCTs ever achieved such traction.

Hill's role in the evolution of clinical trial design and analysis

In his 1991 obituary of Hill in the *Journal of the Royal Statistical Society*, Peter Armitage describes his former colleague as 'responsible, more than any other single person, for the widespread acceptance of the randomised trial as a basic tool of medical research'.[16] The following year, the distinguished statistician CR Rao declared that Fisher's work on the design of experiments was his 'most outstanding contribution' to statistics.[17]

Hill and Fisher remain universally and justifiably regarded as giants in their respective fields. Given that randomisation plays a major role in their enduring eminence, it is perhaps understandable that attempts have been made to connect their respective advocacy of it. This is, however, one of several problematic aspects of the standard narrative of the rise of the RCT addressed in these articles. As Chalmers has long maintained, there is no reason to believe that Fisher's theoretical work on randomisation lay behind Hill's advocacy of random allocation in clinical trials. Hill himself repeatedly rejected the suggestion, never more clearly than at a meeting held at the Royal Society of Medicine on 14 June 1982. On the specific issue of the use of randomisation in the landmark 1948 streptomycin trial he stated:

> Well, nor did this come out of Fisher's teaching. I said no it didn't. I knew what Fisher was teaching with agricultural experiments. But it came out of what I was taught by Karl Pearson and Greenwood. We got these ideas in our heads all along before Fisher. Fisher was too elaborate anyway for medicine. (quoted in Neuhauser et al.[18]; online appendix therein)

Hill is here both confirming that Fisher played no role in his advocacy of random allocation, and explaining why: he believed Fisher's work had little to add to the conduct of clinical trials beyond the methods already used by himself and his mentors. This is consistent with Hill having failed to understand both Fisher's advocacy of randomisation and its consequences for clinical trials. As for the motivation of Hill's advocacy, the most plausible source remains that suggested by Chalmers,[19–21] namely, Hill's investigation in 1933 of the notorious multi-centre trial of a treatment for lobar pneumonia described in Part 1 of this series. This involved patient allocation by alternation, which cannot lead to a genuinely random allocation unless one believes the patient series has somehow already been randomised, a presumption which underpins the Quasirandomness Fallacy. At some point between 1933 and his work on the streptomycin trial over a decade later, Hill recognised that the *imposition* of concealed randomisation would combat allocation bias. What Hill seems never to have recognised is that this did more than eliminate this particular threat to the reliability of clinical trials. He had unwittingly also unlocked the inferential benefits of randomisation demonstrated by Fisher.

Given Hill's clear antipathy to Fisher's theoretical work and his insistence that it played no role in his adoption of random allocation, claims to the contrary seem unjustified. The standard narrative of the emergence of RCTs would also benefit from a broader assessment of Hill's influence on clinical trials, and specifically the consequences of his attitude towards Fisher's work. As Mainland made clear, Fisher showed randomisation provides more than just a means of preventing allocation bias, the pragmatic issue underpinning Hill's advocacy. It also resolves another pragmatic challenge described in Part 2 of this series: the messy realities of the presentation, admission and allocation of patients to a trial, which undermine the validity of standard random sampling theory for extracting reliable insights from trial outcomes. Had Hill possessed Mainland's grasp of Fisher's theory, clinicians might have been alerted to the issues surrounding alternation and random sampling theory a decade before the streptomycin trial, and almost 20 years before Hill's oddly delayed advocacy of random allocation in *Principles*.

Hill is rightly revered for putting randomisation front and centre of the RCT. Yet even today randomisation is often seen as a 'rote exercise',[22] its role still regarded as primarily that of preventing allocation bias. As a result, 'many clinical researchers today do not conceptualise the assumption of randomisation as fundamental to the validity of the statistical methods that they use'.[18] A closely related manifestation of Hill's legacy is the continuing lack of awareness of randomisation-based inference. Rather than presuming the existence of some population from which the randomly allocated patients are drawn, the act of randomisation is made the basis of a distribution-free model applicable even to small studies.[23] Despite computational barriers to its general use having been overcome, this approach remains 'often forgotten, ignored or left untaught'.[22] Rosenberger cites various reasons, starting with the historical development of statistical methods for clinical trials, and the influence of Hill '. . .who rarely did anything other than descriptive analyses'.[24]

Arguably, the most unfortunate legacy of Hill's 'pragmatic' view of randomisation is the continuing neglect of factorial designs of clinical trials. Such designs were devised by Fisher to allow simultaneous comparisons of several interventions and their interactions in crop research. The same approach can be used to design RCTs able to compare multiple treatments in a single trial. Mainland was certainly convinced of their importance, prefacing his discussion of them in the 1952 edition of *EMS* by stating: 'No-one who is unaware of these

methods knows what the term "modern statistics" means' (p. 194),[8] and gives an outline of how they work, their benefits and limitations. In the second edition of *EMS*, Mainland describes his own experience of using a factorial design and states that once one is familiar with conventional trial design, it is 'very desirable' to at least become acquainted with the factorial approach. In contrast, the contemporaneous editions of Hill's *Principles* include a single sentence simply acknowledging the existence of 'elaborate experiments' without using the term factorial, give two references and then return to the standard single-factor designs. This could be ascribed to Hill again taking a dimmer view of his readership than Mainland. However, a recently published letter from Hill to an American physician in 1982 suggests this example of 'clarity by omission' said more about his antipathy to Fisher's theory:

> I became aware of Fisher's agricultural experiments as any statistician of that day must have been from his book *Statistical Methods for Research Workers*. But I was also aware that much of this work was elaborate with involved experimental designs and intricate analysis (of variance and co-variance, etc.). Any attempt to introduce these into clinical medicine would, in my opinion, have been fatal, and in this respect, *I deliberately turned my back on Fisher's methods*. [Hill, quoted in Neuhauser et al.[18]; emphasis added].

There has long been puzzlement over the neglect of factorial designs of clinical trials,[18,25,26] which still account for less than 1% of all RCTs.[27] Hill's cursory treatment of them has been implicated by several authors,[18,26] with Neuhauser et al. arguing that Hill created 'a methodological echo chamber around single-factor studies that still endures', and asking: 'What might we have accomplished since the RCT emerged in the 1940s had factorial designs been used routinely?' As they point out, some of the most important RCTs of the last 50 years have had factorial designs. Perhaps the most impressive support for Mainland's view of factorial trials over that of Hill is the UK Recovery RCT, which led to as many as four potential treatments for Covid-19 being assessed simultaneously,[28] saving at least a million lives within a year of the pandemic being declared.[29]

Conclusion

The importance of Hill's advocacy of random allocation for the ascendancy of RCTs is beyond doubt. However, the standard narrative of this key episode in the history of medicine places the origins of that advocacy in Hill's pragmatic focus on the prevention of allocation bias. While this is important both historically and operationally, it fails to reflect the full implications and value of Fisher's theory of randomisation for clinical trials. Moreover, the current focus on Hill's advocacy masks the inadequacies of his understanding of Fisher's theory and its implications for RCTs.

A re-balancing of the standard narrative would be of more than just historical value, however. Firstly, it would highlight the powerful consequences of Fisher's theory described by Hill cursorily at best in *Principles* and under-exploited ever since, notably randomisation-based inference and factorial RCTs. Secondly, it would help refocus attention on the role of randomisation at a time of growing concern about the use of often large but non-random sources of 'real world data' when RCTs are inappropriate or infeasible.[30,31] While their size and composition make them potentially complementary to the use of RCTs,[32] their non-random nature raises obvious concerns about their inferential reliability. Recent theoretical and empirical studies of such data sources have shown that even extremely weak correlational structures and biases left intact by the lack of randomisation drastically reduce the reliability of inferences based on them.[33–35] Similar concerns surround the emergence of so-called Randomised Non-Comparative Trials (RNCTs), in which patients are randomly allocated to trial arms which are then never formally compared. This obviates the value of randomisation, reducing it to a performative ritual.[36]

A century after Fisher developed the extraordinarily powerful concept of randomisation, the need to transcend Hill's flawed understanding of its role in clinical research has never been more pressing.

Declarations

Competing Interests: None declared.

Funding: None declared.

Ethics approval: Not applicable.

Guarantor: RAJM.

Contributorship: Sole authorship.

Provenance: Invited article from the James Lind Library.

Acknowledgements: I thank Iain Chalmers for encouraging me to re-examine the standard narrative of the emergence of RCTs. His detailed feedback on early drafts, along with that from Vern Farewell, Stephen Senn, Scott Podolsky, Fabio Molo and Denise Best, is gratefully acknowledged.

For more information on allocation bias, see this entry in the Catalogue of Bias: Catalogue of Bias Collaboration. Spencer EA, Heneghan C, Nunan D. Allocation bias. In: Catalogue of Bias 2017 (https://catalogofbias.org/biases/allocation-bias/).

ORCID iD: Robert AJ Matthews https://orcid.org/0000-0002-1253-6107

References

1. Mainland D. Problems of chance in clinical work. *BMJ* 1936; 2: 221–224.
2. Fisher RA. *Statistical Methods for Research Workers*. Edinburgh: Oliver & Boyd, 1925.
3. Mainland D. The rise of experimental statistics and the problems of a medical statistician. *Yale J Biol Med* 1954; 27: 1–10.
4. Altman DG. Donald Mainland: anatomist, educator, thinker, medical statistician, trialist, rheumatologist. *J R Soc Med* 2020; 113: 28–38. See https://www.jameslindlibrary.org/articles/donald-mainland-anatomist-educator-thinker-medical-statistician-trialist-rheumatologist/ (accessed 17 December 2025).
5. Hill AB. *Principles of Medical Statistics*. 1st ed. London: Lancet. See https://www.jameslindlibrary.org/hill-ab-1937b/ (1937) (accessed 17 December 2025).
6. Medical Research Council. Streptomycin treatment of pulmonary tuberculosis. *BMJ* 1948; 2: 769–782. See https://www.jameslindlibrary.org/medical-research-council-1948b/ (accessed 17 December 2025).
7. Mainland D. Statistical methods in medical research. I. Qualitative statistics (enumeration data). *Can J Res* 1948; 26: 1–166. See https://www.jameslindlibrary.org/mainland-d-1948/ (accessed 17 December 2025).
8. Mainland D. *Elementary Medical Statistics*. Philadelphia: WB Saunders. See https://www.jameslindlibrary.org/mainland-d-1952/ (accessed 17 December 2025) (1952).
9. Mainland D. *Elementary medical statistics*. 2nd ed. Philadelphia: WB Saunders. See https://www.jameslindlibrary.org/mainland-d-1963-2/ (last checked 17 December 2025) (1963).
10. Mainland D. The planning of investigations. *Methods Med Res* 1954; 6: 138–145.
11. Mainland D. *The Treatment of Clinical and Laboratory Data: An Introduction to Statistical Ideas and Methods for Medical and Dental Workers*. Edinburgh: Oliver and Boyd. See https://www.jameslindlibrary.org/mainland-d-1938/ (accessed 17 December 2025) (1938).
12. Wasserstein RL and Lazar NA. The ASA statement on *p*-values: context, process, and purpose. *Am Stat* 2016; 70: 129–133.
13. Feinstein AR. Clinical biostatistics. 1. A new name – and some other changes of the guard. *Clin Pharmacol Ther* 1970; 11: 135–148.
14. Schoolman HM. The clinician and the statistician. *Stat Med* 1982; 1: 311–316.
15. Farewell V and Johnson T. Woods and Russell, Hill, and the emergence of medical statistics. *Stat Med* 2010; 29: 1459–1476. See https://www.jameslindlibrary.org/farewell-v-johnson-t-2010/ (accessed 17 December 2025).
16. Armitage P. Obituary: Sir Austin Bradford Hill, 1897–1991. *J R Stat Soc Ser A* 1991; 154: 482–484.
17. Rao CR. RA Fisher: The founder of modern statistics. *Stat Sci* 1992; 7: 34–48.
18. Neuhauser D, Provost SM and Provost LP. It is time to reconsider factorial designs: how Bradford Hill and RA Fisher shaped the standard of clinical evidence. *Qual Manag Health Care* 2020; 29: 109–122.
19. Chalmers I. Why transition from alternation to randomisation in clinical trials was made. *BMJ* 1999; 319: 1372.
20. Chalmers I. Statistical theory was not the reason that randomization was used in the British Medical Research Council's Clinical Trial of streptomycin for pulmonary tuberculosis. In: Jorland G, Weisz G and Opinel A (eds) *Body Counts: Medical Quantification in Historical and Sociological Perspective*. Montreal: McGill-Queen's Press, pp. 309–334.
21. Chalmers I. UK Medical Research Council and multicentre clinical trials: from a damning report to international recognition. *J R Soc Med* 2013; 106: 498–509. See https://www.jameslindlibrary.org/articles/uk-medical-research-council-and-multicentre-clinical-trials-from-a-damning-report-to-international-recognition/ (accessed 17 December 2025).
22. Rosenberger WF, Uschner D and Wang Y. Randomization: The forgotten component of the randomized clinical trial. *Stat Med* 2019; 38: 1–12.
23. Rosenberger WF and Lachin JM. *Randomization in Clinical Trials: Theory and Practice*. Hoboken: John Wiley, 2015.
24. Rosenberger WF. From Fisher to CARA: the evolution of randomization and randomization-based inference. *J R Stat Soc Ser A Stat Soc* 2026; 189: 497–511.
25. Peto R. Clinical trial methodology. *Biomed 28 (special issue)* 1978; 24–36. See https://www.jameslindlibrary.org/peto-r-1978/ (accessed 17 December 2025).
26. Bodmer W. RA Fisher, statistician and geneticist extraordinary: a personal view. *Int J Epidemiol* 2003; 32: 938–942.
27. White IR, Szubert AJ, Choodari-Oskooei B, et al. When should factorial designs be used for late-phase randomised controlled trials? *Clin Trials* 2024; 21: 162–170.
28. Glasziou PP and Tikkinen KA. The RECOVERY trial platform: a milestone in the development and execution of treatment evaluation during an epidemic. *J R Soc Med* 2021; 114: 443–446. See https://www.jameslindlibrary.org/articles/the-recovery-trial-platform-a-milestone-in-the-development-and-execution-of-treatment-evaluation-during-an-epidemic/ (accessed 17 December 2025).
29. NHS News COVID treatment developed in the NHS saves a million lives (press release 23 March 2021). See https://www.england.nhs.uk/2021/03/covid-treatment-developed-in-the-nhs-saves-a-million-lives/ (accessed 17 December 2025).
30. Ramagopalan SV, Simpson A and Sammon C. Can real-world data really replace randomised clinical trials? *BMC Med* 2020; 18: 13.
31. Yaacoub S, Porcher R, Pellat A, et al. Characteristics of non-randomised studies of drug treatments: cross sectional study. *BMJ Med* 2024; 3: e000932.
32. Mayo CS, Matuszak MM, Schipper MJ, et al. Big data in designing clinical trials: opportunities and challenges. *Front Oncol* 2017; 7: 187.
33. Meng X. Statistical paradises and paradoxes in big data (I): law of large populations, big data paradox, and the 2016 US presidential election. *Ann Appl Stat* 2018; 12: 685–726.
34. Bradley VC, Kuriwaki S, Isakov M, et al. (2021). Unrepresentative big surveys significantly overestimated US vaccine uptake. *Nature* 2021; 600: 695–700. See https://www.jameslindlibrary.org/bradley-vc-kuriwaki-s-isakov-m-sejdinovic-d-meng-x-flaxman-s-2021/ (accessed 17 December 2025).
35. Schoeler T, Speed D, Porcu E, et al. Participation bias in the UK Biobank distorts genetic associations and downstream analyses. *Nat Human Behav* 2023; 7: 1216–1227. See https://www.jameslindlibrary.org/schoeler-t-speed-d-porcu-e-pirastu-n-pingault-jb-kutalik-z-2023/ (accessed 17 December 2025).
36. Msaouel P. The curious rise of randomised non-comparative trials. *Significance* 2025; 22: 40–44.