The Royal Society of Medicine

Journal of the Royal Society of Medicine; 2026, Vol. 119(2) 55–58
DOI: 10.1177/01410768261419045

The problematic history of randomised controlled trials Part 2: Hill's 'pragmatic' view of randomisation and its origins

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> My skill, if any, was, I believe, in offering the clinician something simple that he could understand - and all that I could understand. If one had started with something abstruse, the answer would have been 'Go to Hell' – and we would still be there.
>
> Austin Bradford Hill, personal communication to Harold Schoolman, 1977.[1]

Introduction

The emergence of the randomised controlled trial (RCT) as the principal means of assessing treatments is generally taken to have begun with the UK Medical Research Council (MRC) trial of streptomycin for treating tuberculosis, published in 1948.[2] According to the standard narrative,[3,4] its defining feature is the use of a concealed random process to assign patients to the trial arms, thereby preventing triallists from influencing allocation and biassing the outcome. As the trial statistician who advocated this approach, Austin Bradford Hill is credited with catalysing one of the greatest advances of 20th-century medicine.

The first part of this study reviewed the historical background to this landmark development and its many puzzling features. These include the persistence of alternation as the means of patient allocation long after its vulnerabilities had become clear, and its frequent conflation with random allocation, not least by Hill himself. The reasons for Hill's advocacy of random allocation were also explored, including the common claim that he had been influenced by the theoretical arguments developed by the statistician Ronald Fisher.[5,6]

As noted in Part 1, Hill himself denied that Fisher's seminal theory of randomisation had any substantive influence on his advocacy.[7,8] Yet Hill's approach to Fisher's theory hints at a general lack of understanding of both its foundations and its implications. Even in his hugely influential *Principles of Medical Statistics*,[9] Hill showed a striking reluctance even to mention Fisher's work on randomisation, still less describe its practical consequences beyond prevention of allocation bias. Hill's focus on the practical necessity of concealed random allocation is rightly celebrated. However, it has led to a narrative that uncritically accepts Hill's neglect of these other consequences, despite their relevance to clinical trial design and analysis.

This second of three articles examines these elements of the history of RCTs in more detail. The outcome suggests that a more nuanced view of Hill's relationship with statistical theory is merited. In particular, it is argued that his celebrated 'pragmatism' in clinical trial design and impatience with theoretical arguments reflect his self-confessed limitations concerning technical aspects of statistical inference.

Hill's understanding of randomisation

As noted in Part 1, a perplexing feature of early editions of Hill's influential *Principles* is his repeated conflation of alternation with random allocation of patients to the arms of a trial. It was not until 1955 and the publication of the sixth edition – almost a decade after implementing its use in the streptomycin RCT – that Hill gave his reasons for preferring concealed random allocation over alternation. Even then, they seem equivocal:

> In many trials this allocation [alternation] has been successfully made by putting patients, as they present themselves, alternately into the treatment and control groups. Such a method may, however, be insufficiently random if the admission or non-admission of a case to the trial turns upon a difficult assessment of the patient and if the clinician involved knows whether the patient, if accepted, will pass to the treatment or control group. By such knowledge he may be biased, consciously or unconsciously, in his acceptance or rejection; or through fear of being biased, his judgement may be influenced. The latter can be just as important a source of

> error as the former but is more often overlooked. For this reason, it is better to avoid the alternating method and to adopt the use of random sample numbers; in addition the allocation of the patient to treatment or control should be unknown to the clinician until *after* he has made his decision upon the patient's admission. Thus he can proceed to that decision – admission or rejection – without any fear of bias.[10]

Hill's characteristic pragmatism is clear: concealed random allocation is necessary to prevent clinician-induced allocation bias. There is, however, no reference to Fisher's theory of randomisation and its implication that random allocation is a *sine qua non* for reliable inference from clinical trials. Also clear is Hill's flawed understanding of the difference between alternation and random allocation of patients presenting for potential inclusion in a trial. By its very nature, alternation *per se* cannot induce randomness. As such, alternation can only be 'sufficiently' random if one presumes the original patient series was *already* randomised. This presumption constitutes the Quasirandomness Fallacy, described in Part 1. Remarkably, in a memoir written a year before his death in 1991, Hill shows he had yet to shake off this fallacy:

> At the outset, I think I pleaded that trials should be made using alternate cases. I suspect if (and its a very large IF) if that, in fact, were done *strictly* they would be random. (typos and emphasis in original).[11]

He goes on to account for the absence of any mention of Fisher's concept of randomisation in the first edition of *Principles*:

> I deliberately left out the words 'randomization' and 'random sampling numbers' at that time, because I was trying to persuade the doctors to come into controlled trials in the very simplest form and I might have scared them off. I think the concepts of 'randomization' and 'random sampling numbers' are slightly odd to the layman, or, for that matter, to the lay doctor, when it comes to statistics. I thought it would be better to get doctors to walk first, before I tried to get them to run.[11]

It is unclear why Hill regarded these concepts as 'slightly odd to the layman'. Random numbers are familiar from coin-tosses and dice-throwing, while randomisation is no more 'odd' than shuffling a deck of cards to ensure a fair deal. In contrast, Hill had no such qualms about exposing his readers to more subtle yet unfamiliar concepts like standard error, correlation and statistical significance.

Hill's claim to have omitted references to randomisation for fear of scaring off readers thus seems somewhat disingenuous. This raises the possibility that the statistician generally credited with introducing random allocation into clinical trials failed fully to appreciate the potency of randomisation, and thus the true impact of what he had done.

Support for this view can be found in the first edition of *Principles*. Hill describes other pragmatic challenges in clinical trial design beyond allocation bias, such as balancing covariates (p. 8) using small samples (p. 57) and dealing with unknown biases (p. 158), but fails to point out that these are all encompassed by Fisher's theory. This remains the case even in the sixth edition, the first in which Hill makes the case for concealed random allocation. This apparent indifference towards Fisher's theory is underlined by Hill's statement in this same edition of what he regards as the 'three great advantages' of random allocation (Sixth edition, p. 241): protection against allocation bias, prevention of over-compensation for suspected bias, and immunity from accusations that the allocation has been rigged. There is no reference to the patently pragmatic benefits of randomisation stressed by Fisher, such as its ability to accommodate even unknown biases and small sample sizes in the statistical analysis. Despite this, previous authors have argued that Hill's views on Fisher's theory were not the result of ignorance:

> [H]e was certainly aware of Fisher's views on the theoretical justification for random allocation . . . Hill simply did not accord randomisation the special status that Fisher and other statistical theorists did.[7]

Hill's erstwhile colleague Peter Armitage similarly dismissed the suggestion of ignorance but hinted at another reason for Hill's view of Fisher's work: 'Hill would have been less than impressed by Fisher's emphasis on exactness in statistical analysis'.[12] The impatience of a pragmatist when confronted with technicalities is also suggested by another of Hill's distinguished former colleagues, Richard Doll, who stated that Hill adopted randomisation in the streptomycin trial purely to eliminate allocation bias and 'not for any esoteric statistical reason'.[13] Yet these observations again overlook the fact that randomisation has valuable pragmatic consequences beyond the control of one form of bias. Given that these would have greatly strengthened Hill's case for making the crucial switch from alternation to randomisation, why did he never point them out? As noted above, the standard argument of wanting to spare others any exposure to complexity is far from compelling. A more nuanced explanation emerges from consideration of Hill's relationship with the technical aspects of statistical inference.

The origins of Hill's 'pragmatic' view of randomisation

The success of *Principles* owes much to Hill's use of real-life examples and minimal mathematical formalism. The result was a practical guide written by a statistician clearly sympathetic to the needs of 'an essentially innumerate

medical profession'.[14] This mirrors Hill's background. Prevented by illness from pursuing a medical career, Hill initially studied economics, and then, via a family connection, obtained a position at the MRC research group led by Major Greenwood, the leading medical statistician of his day. When Greenwood took up a professorship at the London School of Hygiene and Tropical Medicine (LSHTM) in 1927, Hill was among those who went with him. Over the years, his colleagues included such luminaries as Armitage, Doll and Oscar Irwin – a former colleague of Karl Pearson and Fisher regarded as the leading theorist in medical statistics during the 1930s. Hill took over Greenwood's professorship on the latter's retirement in 1945, by which time his celebrated *Principles* was already in its third edition. The publication of the MRC streptomycin trial 3 years later was followed by election to the presidency of the Royal Statistical Society (1950), the award of its highest honour (1953) and election to the Royal Society (1954).

Given such imposing credentials, it is perhaps unsurprising that previous authors have largely confined themselves to noting Hill's conflations and omissions concerning randomisation and arguing that whatever their cause, it was 'not because he was statistically naïve'.[7] Yet by his own admission, Hill was never comfortable with the technical aspects of statistics. Required by Greenwood to acquire at least a basic understanding of the principles, Hill attended Pearson's lectures in the early 1920s. Having found them 'mathematical and entirely over my head',[15] he resorted to teaching himself using Yule's popular *Introduction to the Theory of Statistics*.[16] A decade later, on learning that Fisher had been appointed to the Galton chair at University College, London, Hill wrote to express his delight at having Fisher '. . .within reach when my statistical woes are too much for me, and your mathematics defeats me (which is invariable)'.[17] In his Royal Statistical Society obituary of Hill, Armitage recalled that 'As a statistician he was out of sympathy with mathematical formalism'.[18] This could manifest itself in dramatic fashion, as Hill himself makes clear in an unpublished memoir written for the Librarian of the LSHTM a few years before his death.[16] He recounts ordering a visiting Australian statistician to 'get out of my department and don't come back' for having the temerity even to draft a paper for a medical journal that Hill deemed too technical.[19] Yet in the same memoir, Hill states that 'having no mathematical knowledge I needed first-class statisticians', which led to his recruitment of, among others, Peter Armitage.

Hill was thus keenly aware of his technical limitations. This is not to say he lacked any mathematical ability. The preface to Yule's introductory text states that it assumes 'an acquaintance with algebra up to the binomial theorem'[20]; this alone would put it beyond the reach of many of those for whom Hill wrote *Principles.* Moreover, Yule's presentation makes his supposed *Introduction* somewhat daunting for those lacking mathematical confidence. Nevertheless, Hill appears to have succeeded in using it for self-study and referred to it in both his lectures and *Principles.* Hill's limitations appear to have centred not on the 'mechanics' of statistical theory, but the underlying concepts. In particular, he overlooked or perhaps chose to ignore the disparity between the basis of inference used by Yule and his contemporaries – that is, random sampling – and the nature of clinical trials. Random sampling theory leads to valid inferences from clinical trials *if* one presumes they are comparisons of random samples from two patient populations: those getting the specific treatment under study, and the controls. By accepting – consciously or otherwise – the validity of this in the context of clinical trials, Hill rendered Fisher's arguments for randomisation largely irrelevant. Yet, ironically, this presumption is a mathematical idealisation undermined by just the kind of messy practical reality Hill saw as his area of expertise. There is nothing either patently or purely random about the presentation of patients, their acceptance onto trials or their participation.[21,22] As Fisher made clear in Chapter 2 of his landmark text *The Design of Experiments* (1935), the concept of randomisation dispenses with the need to wrestle with these issues by creating the comparison groups via random allocation – in the case of clinical trials, of enrolled patients. The explicit and genuine randomness of this process then permits the use of probabilistic models, enabling statistically valid inferences to be drawn.[23] It is notable that even after Hill began advocating random allocation, he rarely used the term 'randomisation', as one might expect had he accepted Fisher's theory, but continued to refer to 'random samples'. As described in Part 1, he also continued to conflate alternation with randomisation, and never fully rejected the Quasirandomness Fallacy.

As others have stated, Hill was certainly not ignorant of Fisher's theory. He had engaged with it, even if it had no discernible impact on his thinking. A telling insight into why can be found in a 1988 letter to Chalmers in response to an article on the early history of RCTs by Vandenbroucke.[24] On the specific issue of patient allocation, Hill states:

> . . .I may have been influenced by Fisher but not very much – in fact in his famous 'tea and milk' experiment I think he was wrong.[7]

This reference to Fisher's famous tea-tasting experiment is important, as it forms the core of Chapter 2 of *The Design of Experiments*, in which Fisher describes how randomisation works. Hill had thus engaged with Fisher's theory, but had not only failed to see its relevance to clinical trials but also had misgivings about the concept of randomisation-based inference. Chalmers reports being told the nature of these qualms by Hill's son David,

himself a statistician. Briefly put, they centred not on Fisher's analysis, but – unsurprisingly – on a practical issue concerning the experimental design.[7] Chalmers argues Hill's qualms are consistent with his pragmatic approach to trial design. While this may be true, the theory behind Fisher's experiment[25] shows that Hill's approach would lead to inferential ambiguity. As such, his views on Fisher's tea-tasting experiment reflect the same flawed focus on simple pragmatic concerns at the expense of more sophisticated issues, which seem to have led him to underestimate the powers of randomisation.

There seems little reason to doubt the standard narrative account of Hill's advocacy of random allocation as having originated in pragmatic rather than theoretical considerations. As described in Part 1 of this series, a plausible explanation for his advocacy is his investigation of the MRC's lobar pneumonia trial debacle, which led him to see concealed random allocation as a pragmatic solution to the real-world problem of clinician-induced allocation bias.

However, there are grounds for challenging the standard narrative's explanation for Hill's apparent hostility to 'esoteric' statistical arguments in general, and apparent disregard of the theory of randomisation in particular. The evidence presented above suggest Hill's focus on a simple pragmatic argument for random allocation flowed primarily from his inadequate grasp of Fisher's theory of randomisation and its relevance to clinical trials. This had the unfortunate effect of preventing him from recognising its full implications for such trials beyond addressing allocation bias.

Given Hill's influence and stature, this raises two final questions: how might evidence-based medicine have benefited had Hill embraced Fisher's theory and brought its implications to a worldwide readership via his hugely successful *Principles*? Was this even a possibility, given the nature of Fisher's arguments? This is addressed in the third and final part of this series.

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/).

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