Beyond Blocks: A New Era of Randomization

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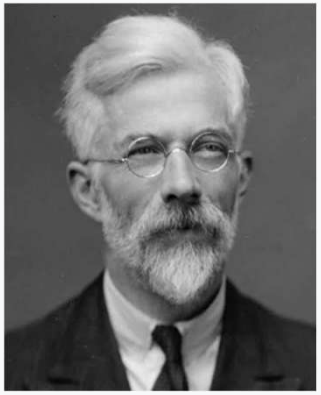
Contents



Fisher described a design for potatoes in 1931 at Rothamsted: **9 blocks of 9 plots each**, testing 3 levels of nitrogen × 3 levels of potash in the field.

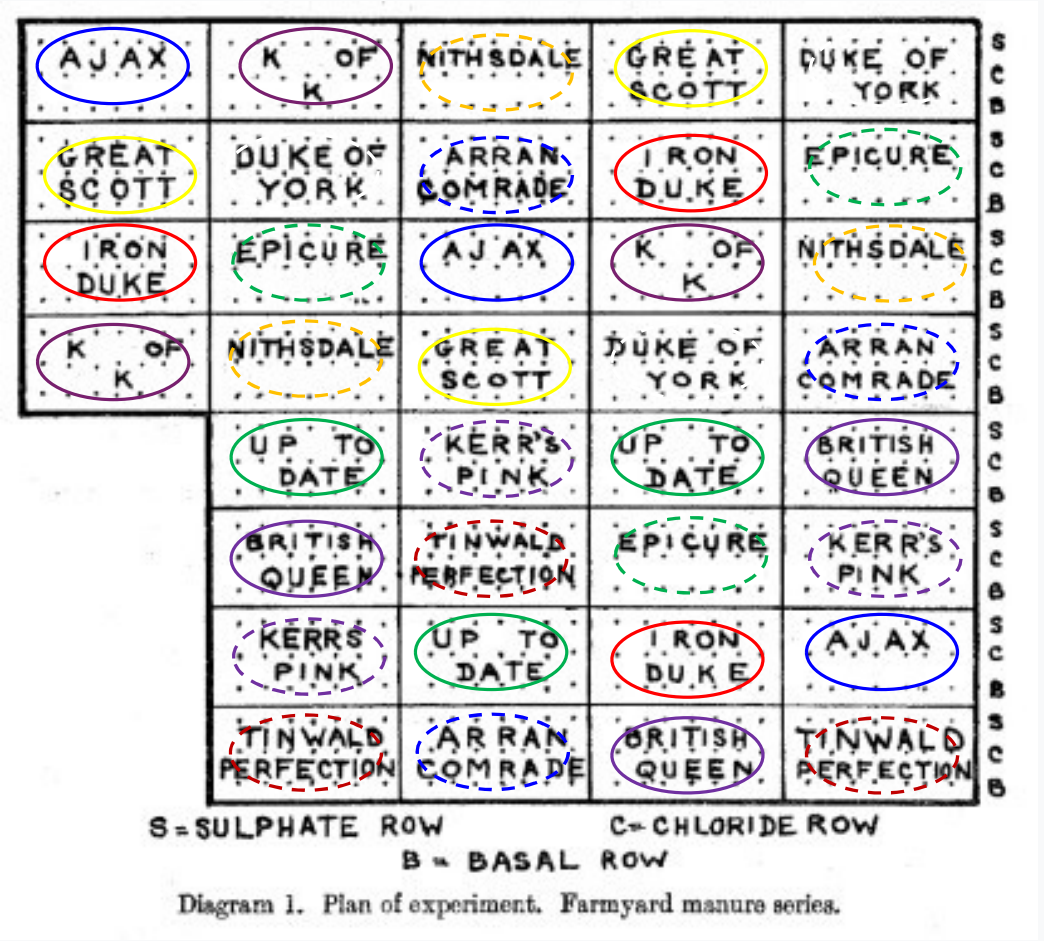
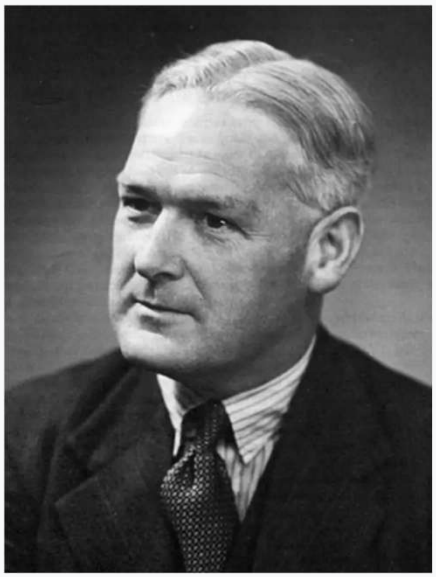


Diagram 1. Plan of experiment. Farmyard manure series.



The 1948 streptomycin trial for pulmonary tuberculosis, run by the UK Medical Research Council, is widely recognized as the first modern randomized controlled clinical trial (RCT).

They used a random numbers table prepared by statistician Austin Bradford Hill.

BRITISH MEDICAL JOURNAL

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STREPTOMYCIN TREATMENT OF PULMONARY TUBERCULOSIS

A MEDICAL RESEARCH COUNCIL INVESTIGATION

The following gives the short-term results of a controlled investigation into the effects of streptomycin on one type of pulmonary tuberculosis. The inquiry was planned and directed by the Streptomycin in Tuberculosis Trials Committee, composed of the following members: Dr. Geoffrey Marshall (chairman), Professor J. W. S. Blacklock, Professor C. Cameron, Professor N. B. Capon, Dr. R. Cruickshank, Professor J. H. Gaddum, Dr. F. R. G. Heaf, Professor A. Bradford Hill, Dr. L. E. Houghton, Dr. J. Clifford Hoyle, Professor H. Raistrick, Dr. J. G. Scadding, Professor W. H. Tytler, Professor G. S. Wilson, and Dr. P. D'Arcy Hart (secretary). The centres at which the work was carried out and the specialists in charge of patients and pathological work were as follows:

Brompton Hospital, London.—Clinician: Dr. J. W. Crofton, Streptomycin Registrar (working under the direction of the honorary staff of Brompton Hospital); Pathologists: Dr. J. W. Clegg, Dr. D. A. Mitchison.

Colindale Hospital (L.C.C.), London.—Clinicians: Dr. J. V. Hurford, Dr. B. J. Douglas Smith, Dr. W. E. Snell; Pathologists (Central Public Health Laboratory): Dr. G. B. Forbes, Dr. H. D. Holt.

Harefield Hospital (M.C.C.), Harefield, Middlesex.—Clinicians: Dr. R. H. Brent, Dr. L. E. Houghton; Pathologist: Dr. E. Nassau.

Bangour Hospital, Bangour, West Lothian.—Clinician: Dr. I. D. Ross; Pathologist: Dr. Isabella Purdie.

Killingbeck Hospital and Sanatorium, Leeds.—Clinicians: Dr. W. Santon Gilmour, Dr. A. M. Reevie; Pathologist: Professor J. W. McLeod.

Northern Hospital (L.C.C.), Winchmore Hill, London.—Clinicians: Dr. F. A. Nash, Dr. R. Shoulman; Pathologists: Dr. J. M. Alston, Dr. A. Mohun.

Sully Hospital, Sully, Glam.—Clinicians: Dr. D. M. E. Thomas, Dr. L. R. West; Pathologist: Professor W. H. Tytler.

The clinicians of the centres met periodically as a working subcommittee under the chairmanship of Dr. Geoffrey Marshall; so also did the pathologists under the chairmanship of Dr. R. Cruickshank. Dr. Marc Daniels, of the Council's scientific staff, was responsible for the clinical co-ordination of the trials, and he also prepared the report for the Committee, with assistance from Dr. D. A. Mitchison on the analysis of laboratory results. For the purpose of final analysis the radiological findings were assessed by a panel composed of Dr. L. G. Blair, Dr. Peter Kerley, and Dr. Geoffrey S. Todd.

Introduction

When a special committee of the Medical Research Council undertook in September, 1946, to plan clinical trials of streptomycin in tuberculosis the main problem faced was that of investigating the effect of the drug in pulmonary tuberculosis. This antibiotic had been discovered two years previously by Waksman (Schatz, Bugie, and Waksman, 1944); in the intervening period its power of inhibiting tubercle bacilli *in vitro*, and the results of treatment in experimental tuberculous infection in guinea-pigs, had been reported; these results were strikingly better than those with any previous chemotherapeutic agent in tuberculosis. Preliminary results of trials in clinical tuberculosis had been published (Hinshaw and Feldman, 1945; Hinshaw, Feldman, and Pfuetze, 1946; Keefer *et al.*, 1946); the clinical results in pulmonary tuberculosis were encouraging but inconclusive.

The natural course of pulmonary tuberculosis is in fact so variable and unpredictable that evidence of improvement or cure following the use of a new drug in a few cases cannot be accepted as proof of the effect of that drug. The history of chemotherapeutic trials in tuberculosis is filled with errors due to empirical evaluation of drugs (Hart, 1946); the exaggerated claims made for gold treatment, persisting over 15 years, provide a spectacular example. It had become obvious that, in future, conclusions regarding the clinical effect of a new chemotherapeutic agent in tuberculosis could be considered valid only if based on adequately controlled clinical trials (Hinshaw and Feldman, 1944). The one controlled trial of gold treatment (and the only report of an adequately controlled trial in tuberculosis we have been able to find in the literature reported negative therapeutic results (Amberson, McMahon and Pinner, 1931). In 1946 no controlled trial of streptomycin in pulmonary tuberculosis had been undertaken in the U.S.A. The Committee of the Medical Research Council decided then that a part of the small supply of streptomycin allocated to it for research purposes would be best employed in a rigorously planned investigation with concurrent controls.

The many difficulties of planning and conducting a trial of this nature are important enough to warrant a full description here of the methods of the investigation.

Plan and Conduct of the Trial

Type of Case

A first prerequisite was that all patients in the trial should have a similar type of disease. To avoid having to make allowances for the effect of forms of therapy other than bed-rest, the type of disease was to be one not suitable for other forms of therapy. The estimated chances of spontaneous regression must be small. On the other hand, the type of lesion should be such as to offer some prospect of action by an effective chemotherapeutic agent; for this reason old-standing disease, and disease with thick-walled

cavities, should be excluded. Finally the age group must be reasonably limited, since the total number of patients in the trial could not be large.

Such closely defined features were considered indispensable, for it was realized that no two patients have an identical form of the disease, and it was desired to eliminate as many of the obvious variations as possible. For these several reasons the type of case to be investigated was defined as follows: acute progressive bilateral pulmonary tuberculosis of presumably recent origin, bacteriologically proved, unsuitable for collapse therapy, age group 15 to 25 (later extended to 30).

The selection of this type of disease constituted full justification for having a parallel series of patients treated only by bed-rest, since up to the present this would be considered the only suitable form of treatment for such cases. Additional justification lay in the fact that all the streptomycin available in the country was in any case being used, the rest of the supply being taken up for two rapidly fatal forms of the disease, miliary and meningeal tuberculosis.

Recruitment and Admission of Cases

Co-operation in the trial was obtained in the first place from Brompton Hospital (drawing on London County Council cases), Colindale Hospital (London County Council), and Harefield County Hospital (Middlesex County Council). The L.C.C. and the M.C.C. gave full co-operation, permitting recruitment of suitable cases from the areas served by them, covering a population of nearly six million persons. Accordingly letters were sent, through the tuberculosis departments of these authorities, to tuberculosis officers and to medical superintendents of general hospitals outlining the proposed trial and asking that particulars and *x*-ray films of possibly suitable patients be sent to the co-ordinator of the trials for consideration. Visits were paid to the tuberculosis clinics and hospitals to show by representative *x*-ray films the type of case sought and to explain in detail the nature of the controlled trial. When cases were submitted the clinical particulars and *x*-ray films were taken to the Committee's selection panel for consideration. When a patient had been accepted as suitable, request was made through the local authority for admission to one of the streptomycin centres; in spite of long waiting-lists these patients were given complete priority, and the majority were admitted within a week of approval.

The first patients to be accepted were admitted to the centres in January, 1947. At first the impression was that cases of the type defined are seen often. In fact, such cases are not common. As it became evident after three months that enough cases could not be found in the London and Middlesex areas, other authorities were approached. The Welsh National Memorial Association, the Department of Health for Scotland, and the Leeds Tuberculosis Service made available centres at Sully, Bangour, and Killingbeck, and cases were recruited to those centres from the respective areas. In addition, another centre was opened in the London area, at the Northern Hospital (L.C.C.).

By September, 1947, 109 patients had been accepted, and no more were admitted to this trial. Two patients had died within the preliminary observation week; these are excluded from the analysis. Of the remaining 107 patients 55 had been allocated to the streptomycin group and 52 to the control group.

The Control Scheme

Determination of whether a patient would be treated by streptomycin and bed-rest (S case) or by bed-rest alone (C case) was made by reference to a statistical series based on random sampling numbers drawn up for each sex at each centre by Professor Bradford Hill; the details of the series were unknown to any of the investigators or to the co-ordinator and were contained in a set of sealed envelopes, each bearing on the outside only the name of the hospital and a number. After acceptance of a patient by the panel, and before admission to the streptomycin centre, the appropriate numbered envelope was opened at the central office; the card inside told if the patient was to be an S or a C case, and this information was then given to the medical officer of the centre. Patients were not told before admission that they were to get special treatment. C patients did not know throughout their stay in hospital that they were control patients in a special study; they were in fact treated as they would have been in the past, the sole difference being that they had been admitted to the centre more rapidly than was normal. Usually they were not in the same wards as S patients, but the same regime was maintained

It was important for the success of the trial that the details of the control scheme should remain confidential. It is a matter of great credit to the many doctors concerned that this information was not made public throughout the 15 months of the trial, and the Committee is much indebted to them for their co-operation.

By definition, cases accepted for the trial were unsuitable for collapse therapy; clinicians were therefore asked to adopt collapse therapy only if the course of the disease so changed that some collapse measure became indispensable and urgent. In the S cases collapse therapy was in fact never applied during the four treatment months. It was given to five of the 52 C cases during that period.

Observation and Treatment Period

Each patient was to remain in bed at the centre for at least six months, and the results were to be assessed on the clinical status at the end of that period. In addition to the usual hospital records, clinical observations were entered on standard record forms designed particularly for this trial; these forms provided for details of history, criteria of acceptance, examination on admission, monthly routine re-examinations with assessment of progress since last examination, observation of toxic reactions, temperature and treatment records, and finally a pathological record form. Instructions on required frequency of examinations were given.

Clinicians and pathologists' meetings were held during the trials to discuss the work as it proceeded. The co-ordinator visited centres and was constantly in touch with the clinicians concerned to discuss the progress of the trial and the problems arising. The working subcommittee of pathologists established the technical laboratory procedures, discussed the findings at intervals, and arranged for independent checking of sensitivity tests of tubercle bacilli and streptomycin levels in the blood.

Analysis of Results

The general trend of results during the course of the trial was followed through the monthly reports from the centres. The analysis of results up to six months after the patient's admission is presented here; it is based on information from the standard record forms completed for each patient and on the *x*-ray films which have been made available by the hospitals concerned.

The films have been viewed by two radiologists and a clinician, each reading the films independently and not knowing if the films were of C or S cases. One of the radiologists had been attached to a centre taking part in the trial; the other two specialists had not been connected with the trial in any way. There was fair agreement among the three; at a final session they met to review and discuss

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- Randomization sequences are created for each sex-center stratum.
- 7 hospitals, 2 sex category, a total 14 strata.
- Final distribution: 55 in treatment arm and 52 in control arm.
- No detail on how the random numbers were drawn.
- Under simple randomization, the chance to have this imbalance is 0.3.

THE CLINICAL TRIAL

A. BRADFORD HILL Ph.D. D.Sc.

Professor of Medical Statistics
London School of Hygiene and Tropical Medicine

Honorary Director, Statistical Research Unit
Medical Research Council

" Therapeutics ", said Professor Pickering in his Presidential Address to the Section of Experimental Medicine and Therapeutics of the Royal Society of Medicine, " is the branch of medicine that, by its very nature, should be experimental. For if we take a patient afflicted with a malady, and we alter his conditions of life, either by dieting him, or by putting him to bed, or by administering to him a drug, or by performing on him an operation, we are performing an experiment. And if we are scientifically minded we should record the results. Before concluding that the change for better or for worse in the patient is due to the specific treatment employed, we must ascertain whether the result can be repeated a significant number of times in similar patients, whether the result was merely due to the natural history of the disease or in other words to the lapse of time, or whether it was due to some other factor which was necessarily associated with the therapeutic measure in question. And if, as a result of these procedures, we learn that the therapeutic measure employed produces a significant, though not very pronounced, improvement, we would experiment with the method, altering dosage or other detail to see if it can be improved. This would seem the procedure to be expected of men with six years of scientific training behind them. But it has not been followed. Had it been done we should have gained a fairly precise knowledge of the place of individual methods of therapy in disease, and our efficiency as doctors would have been enormously enhanced " (Pickering, 1949).

It would be difficult to put the case for the clinical trial more cogently or more clearly. It is the gradual development of this attitude of mind coupled with the concurrent introduction of one antibiotic, one modern drug, after another, that has led in the past few years to the highly organized and efficiently controlled therapeutic trial of new remedies. For instance, as Marc Daniels (1950) wrote of one field, " it is now becoming generally accepted that scientific appraisement of new drugs in tuberculosis is a fundamental necessity, but it is hard to realize that this particular progress has been made almost entirely within the past five years ". Its absence in the past led, he suggests, to the many years of inconclusive work on gold therapy, while Pickering stresses the much earlier and positively dangerous methods of therapeutics, such as bloodletting, purging and starvation, of which the dangers could not have failed to be exposed by comparative observations, impartially made. In more recent years much work has, of course, been done on the efficacy of methods of treatment, e.g. the use of artificial pneumothorax in pulmonary tuberculosis. But many of these studies, as was pointed out in the review of fifty years of medicine published by the *British Medical Journal* (1950), suffer from the handicap that no comparative observations were made, sometimes for ethical reasons, but too often because their importance was not appreciated.

1. Imperfect Contrasts

As a result of this situation very many second-best, or even much inferior, " controls " have been put forward. Thus the following ways and means have been used from time to time, and are still used:

i. The treatment of patients with a particular disease is unplanned but naturally varies according to the decision of the physicians in charge. To some patients a specific drug is given, to others it is not. The progress and prognosis of these patients are then compared. But in making this comparison in relation to the treatment the fundamental assumption is made—and must be made—that the two groups are equivalent in all respects relevant to their progress, except for the difference in treatment. It is, however, almost invariably impossible to believe that this is so. Drugs are not ordered by doctors at random, but in relation to a patient's condition when he first comes under observation and also to the subsequent progress of his disease. The two groups are therefore not remotely comparable and more often than not the group given the specific drug is heavily weighted by the more severely ill. No conclusion as to its efficacy can possibly be drawn.

ii. The same objections must be made to the contrasting of volunteers for a treatment with those who do not volunteer, or between those who accept and those who refuse. There can be no knowledge that such groups are comparable; and the onus lies wholly, it may justly be maintained, upon the experimenter to prove that they are comparable, before his results can be accepted. Particularly, perhaps, with a surgical operation the patients who accept may be very different from those who refuse.

iii. The contrast of one physician, or one hospital, using a particular form of treatment, with another physician, or hospital, not adopting that treatment, or adopting it to a lesser degree, is fraught with much the same difficulty—apart from the practicability of being able to find such a situation (with, it must be noted, the same forms of ancillary treatment). It must be proved that the patients are alike in relevant group characteristics, i.e., age, sex, social class, severity of illness, before they can be fairly compared and their relative progress, or lack of progress, interpreted. That proof is clearly hard to come by.

iv. The ' historical ' control relies upon a contrast of past records of the pre-drug days with those of the present treated patients. Of the former group 10 per cent, say, died and 90 per cent recovered while for the present group the ratios are 5 and 95 per cent. If everything else remained constant

- Formally introduced stratified permuted block randomization to clinical trials by Bradford Hill in 1951.

Guidance for Industry

E9 Statistical Principles for Clinical Trials

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
September 1998
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U.S. Department of Health and
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Center for Drug Evaluation and
Center for Biologics Evaluation an
September 1998
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randomization, to administer the assignment of randomized treatment. In addition, clinical assessments should be made by medical staff who are not involved in treating the subjects and who remain blind to treatment. In single-blind or open-label trials every effort should be made to minimize the various known sources of bias and primary variables should be as objective as possible. The reasons for the degree of blinding adopted, as well as steps taken to minimize bias by other means, should be explained in the protocol. For example, the sponsor should have adequate standard operating procedures to ensure that access to the treatment code is appropriately restricted during the process of cleaning the database prior to its release for analysis.

Breaking the blind (for a single subject) should be considered only when knowledge of the treatment assignment is deemed essential by the subject's physician for the subject's care. Any intentional or unintentional breaking of the blind should be reported and explained at the end of the trial, irrespective of the reason for its occurrence. The procedure and timing for revealing the treatment assignments should be documented.

In this document, the blind review (see Glossary) of data refers to the checking of data during the period of time between trial completion (the last observation on the last subject) and the breaking of the blind.

2. Randomization (2.3.2)

Randomization introduces a deliberate element of chance into the assignment of treatments to subjects in a clinical trial. During subsequent analysis of the trial data, it provides a sound statistical basis for the quantitative evaluation of the evidence relating to treatment effects. It also tends to produce treatment groups in which the distributions of prognostic factors, known and unknown, are similar. In combination with blinding, randomization helps to avoid possible bias in the selection and allocation of subjects arising from the predictability of treatment assignments.

The randomization schedule of a clinical trial documents the random allocation of treatments to subjects. In the simplest situation it is a sequential list of treatments (or treatment sequences in a crossover trial) or corresponding codes by subject number. The logistics of some trials, such as those with a screening phase, may make matters more complicated, but the unique preplanned assignment of treatment, or treatment sequence, to subject should be clear. Different trial designs will necessitate different procedures for generating randomization schedules. The randomization schedule should be reproducible (if the need arises).

Although unrestricted randomization is an acceptable approach, some advantages can generally be gained by randomizing subjects in blocks. This helps to increase the comparability of the treatment groups, particularly when subject characteristics may change over time, as a result, for example, of changes in recruitment policy. It also provides a better guarantee that the treatment groups will be of nearly equal

size. In crossover trials, it provides the means of obtaining balanced designs with their greater efficiency and easier interpretation. Care should be taken to choose block lengths that are sufficiently short to limit possible imbalance, but that are long enough to avoid predictability towards the end of the sequence in a block. Investigators and other relevant staff should generally be blind to the block length; the use of two or more block lengths, randomly selected for each block, can achieve the same purpose. (Theoretically, in a double-blind trial predictability does not matter, but the pharmacological effects of drugs may provide the opportunity for intelligent guesswork.)

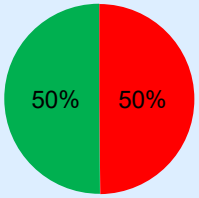
In multicenter trials (see Glossary), the randomization procedures should be organized centrally. It is advisable to have a separate random scheme for each center, i.e., to stratify by center or to allocate several whole blocks to each center. More generally, stratification by important prognostic factors measured at baseline (e.g., severity of disease, age, sex) may sometimes be valuable in order to promote balanced allocation within strata; this has greater potential benefit in small trials. The use of more than two or three stratification factors is rarely necessary, is less successful at achieving balance, and is logistically troublesome. The use of a dynamic allocation procedure (see below) may help to achieve balance across a number of stratification factors simultaneously, provided the rest of the trial procedures can be adjusted to accommodate an approach of this type. Factors on which randomization has been stratified should be accounted for later in the analysis.

The next subject to be randomized into a trial should always receive the treatment corresponding to the next free number in the appropriate randomization schedule (in the respective stratum, if randomization is stratified). The appropriate number and associated treatment for the next subject should only be allocated when entry of that subject to the randomized part of the trial has been confirmed. Details of the randomization that facilitate predictability (e.g., block length) should not be contained in the trial protocol. The randomization schedule itself should be filed securely by the sponsor or an independent party in a manner that ensures that blindness is properly maintained throughout the trial. Access to the randomization schedule during the trial should take into account the possibility that, in an emergency, the blind may have to be broken for any subject. The procedure to be followed, the necessary documentation, and the subsequent treatment and assessment of the subject should all be described in the protocol.

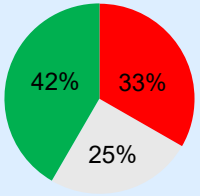
Dynamic allocation is an alternative procedure in which the allocation of treatment to a subject is influenced by the current balance of allocated treatments and, in a stratified trial, by the stratum to which the subject belongs and the balance within that stratum. Deterministic dynamic allocation procedures should be avoided and an appropriate element of randomization should be incorporated for each treatment allocation. Every effort should be made to retain the double-blind status of the trial. For example, knowledge of the treatment code may be restricted to a central trial office from where the dynamic allocation is controlled, generally through telephone

Permuted Block and Selection Bias

b = 2 AB BA



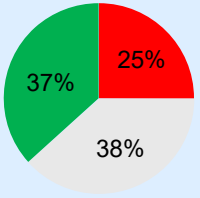
b = 4 AABB ABAB ABBA BAAB BABA BBAA



Number of permutation blocks $= \binom{b}{b/2} = \frac{b!}{(b/2)!^2}$

Proportion of deterministic assignments $= \frac{1}{1+(b/2)}$

b = 6 AAABBB AABABB AABBAB AABBBA ABAABB ABABAB ABABBA ABBBAA BAAABB BAABAB BAABBA BABBAA BBAAAB BBAABA BBABAA BBBAAA



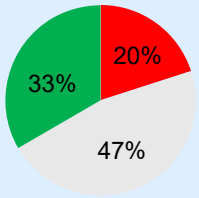
Completely random

Biased coin

Deterministic

b = 8 AAAABBBB AAABABBB AAABBABB AAABBBAB AAABBBBA AABAABBB AABABABB AABABBAB

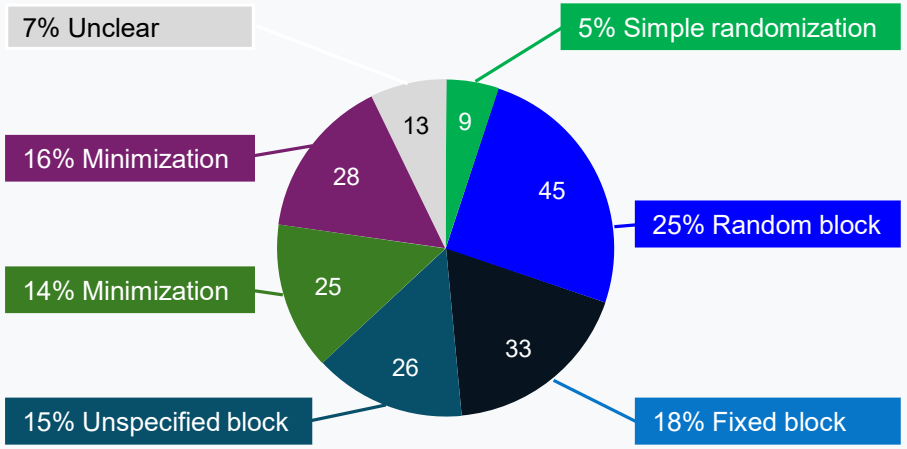
..... BBBAAABA BBBAABAA BBBABAAA BBBBAAAA



Random Block Design - Widely Used

ICH E9 (1998 guideline)

size. In crossover trials, it provides the means of obtaining balanced designs with their greater efficiency and easier interpretation. Care should be taken to choose block lengths that are sufficiently short to limit possible imbalance, but that are long enough to avoid predictability towards the end of the sequence in a block. Investigators and other relevant staff should generally be blind to the block length; the use of two or more block lengths, randomly selected for each block, can achieve the same purpose. (Theoretically, in a double-blind trial predictability does not matter, but the pharmacological effects of drugs may provide the opportunity for intelligent guesswork.)



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Journal of Clinical Epidemiology

REVIEW

A review found small variable blocking schemes may not protect against selection bias in randomized controlled trials

Laura Clark*, Lauren Burke, Rachel Margaret Carr, Elizabeth Coleman, Gareth Roberts, David J. Torgerson

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Accepted 7 September 2021; Available online 11 September 2021

Abstract

Objective: Blocking is associated with prediction of the allocation sequence and subversion. This paper explores if blocking strategies lead to an increase in baseline age heterogeneity (a marker for potential subversion) and, whether the use of blocking is changing over time.

Study Design and Settings: The British Medical Journal, Journal of the American Medical Association, The Lancet and the New England Journal of Medicine were hand searched to identify open RCTs published in January between 2001 and 2020. To explore heterogeneity of baseline age meta-analyses were performed on trials implementing blocking, minimization, and simple randomization.

Results: One hundred seventy-nine open RCTs were identified: nine (5.0%) undertook simple randomization, 104 (58.1%) blocking, 25 (13.9%) minimization, and one (0.6%) both. Baseline age heterogeneity of 24% (P= 0.02) was observed in all trials implementing blocking, 62% (P = 0.001) in trials implementing a fixed block of four, 40% (P = 0.07) implementing variable blocks including a 2 and 0% for both simple randomization and minimization. Small block sizes are implemented in modern trials.

Conclusion: Variable block sizes including two are associated with subversion and should not be implemented. If center only stratification is necessary, it should be used alongside larger blocking schemes. Authors should consider alternative methods to restrict randomization.

Convergent Prediction

Block size	No.	Tx.	b=2	b=4	b=6	b=8	n_B	n_A	Convergent
b=6	1	A	-	-	-	-	0	0	-
	2	B	B	-	-	-	1	0	B
	3	B	-	-	-	-	1	1	-
	4	B	A	A	-	-	1	2	A
	5	A	-	-	A	-	1	3	A
	6	A	B	-	A	-	2	3	A
b=2	7	A	-	B	-	-	3	3	-
	8	B	B	B	-	B	4	3	B
b=2	9	B	-	-	-	-	4	4	-
	10	A	A	-	-	-	4	5	A
b=4	11	A	-	-	-	-	5	5	-
	12	A	B	B	B	-	6	5	B
	13	B	-	-	-	-	7	5	B
	14	B	A	-	-	-	7	6	B
b=4	15	B	-	A	-	-	7	7	-
	16	A	A	A	A	A	7	8	A
	17	B	-	-	A	-	8	8	-
	18	A	A	-	A	-	8	9	A
b=6	19	A	-	-	-	-	9	9	-
	20	B	B	B	-	-	10	9	B
	21	A	-	-	-	-	10	10	-
	22	A	B	-	-	-	11	10	B
	23	B	-	B	B	-	12	10	B
	24	B	A	B	B	B	12	11	B
b=2	25	A	-	-	-	-	12	12	-
	26	B	B	-	-	-	13	12	B
b=6	27	B	-	-	-	-	13	13	-
	28	B	A	A	-	-	13	14	A
	29	A	-	-	A	-	13	15	A
	30	A	B	-	A	-	14	15	A
	31	A	-	B	-	-	15	15	-
	32	B	B	B	-	B	16	15	B
b=4	33	B	-	-	-	-	16	16	-
	34	B	A	-	-	-	16	17	A
	35	A	-	A	A	-	16	18	A
	36	A	B	A	A	-	17	18	A

Prediction Method	Prediction	Prediction Rate (PR)	Correct	Correct Guess Probability (CG)	Selection Bias Risk Score (SBR)
Assume b=2	18	50%	8	44%	-0.0056
Assume b=4	14	39%	9	64%	0.1111
Assume b=6	12	33%	10	83%	0.2222
Assume b=8	4	11%	4	100%	0.1111
Convergent Prediction	23	64%	18	78%	0.3611

$$SBR = PR \cdot (2 \times CG - 1)$$

Over Optimistic Assumptions

Randomization = Blocking

What randomization design is used? → What block size is used?

Knowing block size → Prediction with certainty → Selection bias

The Reality

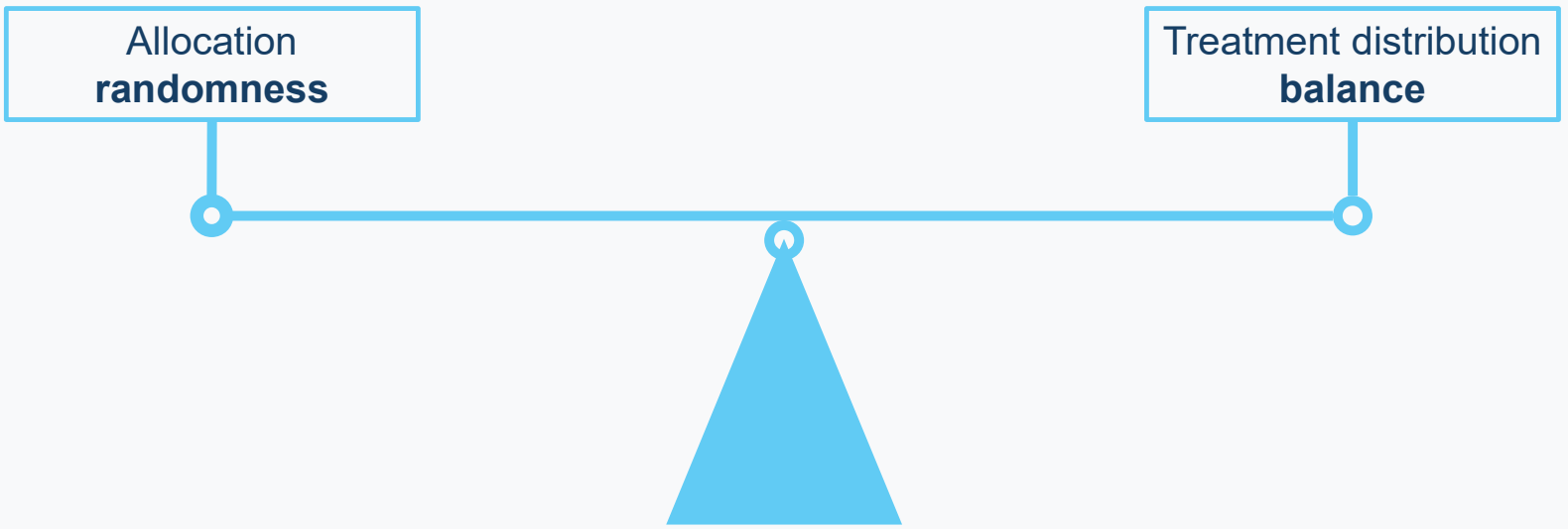
In the word of data, probability is the compass.

Selection bias from prediction could occur unless the assignment is not complete random.

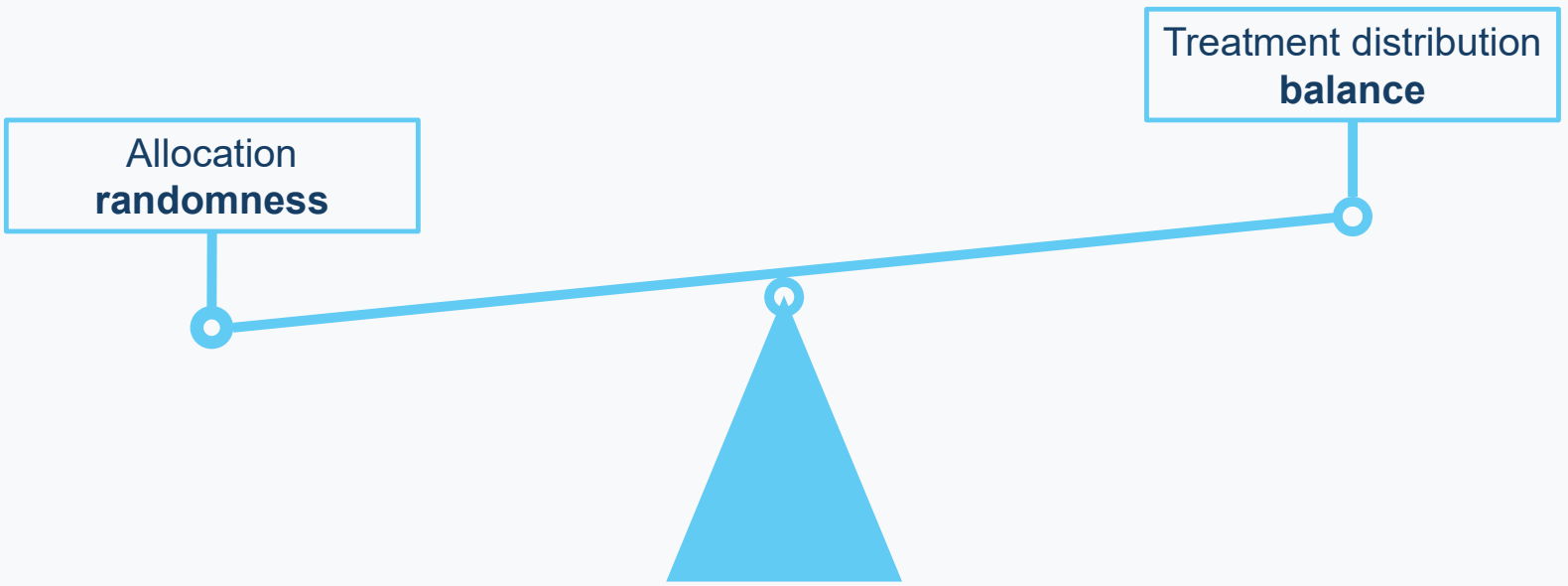
2.

Performance Evaluation Measures

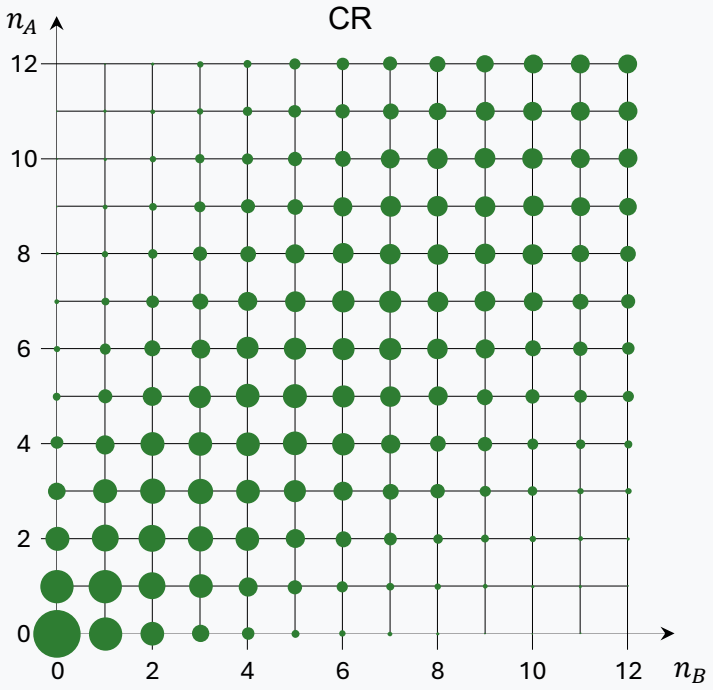
Objectives for Randomization

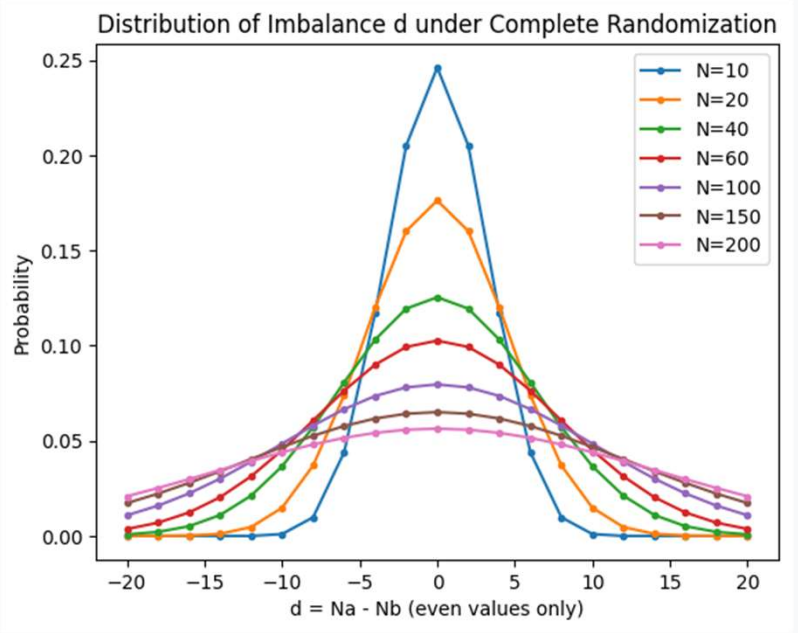


Competing Objectives

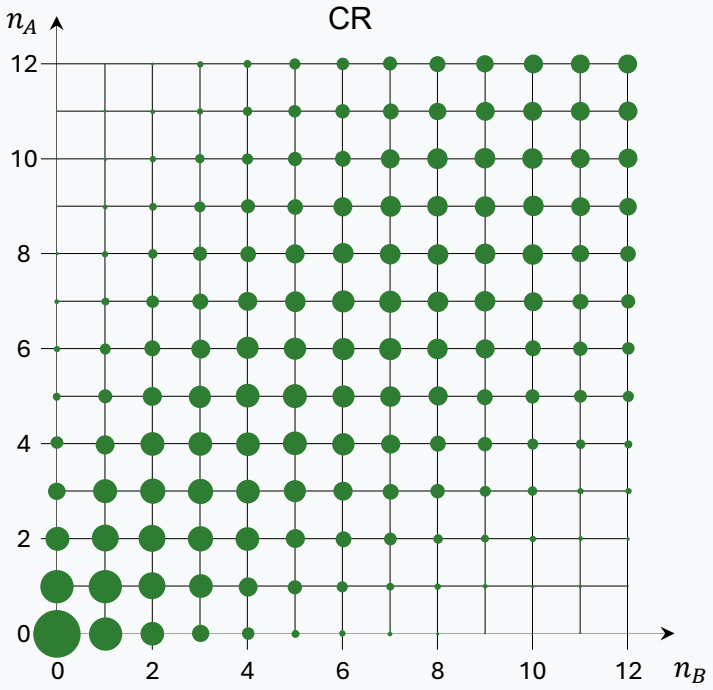


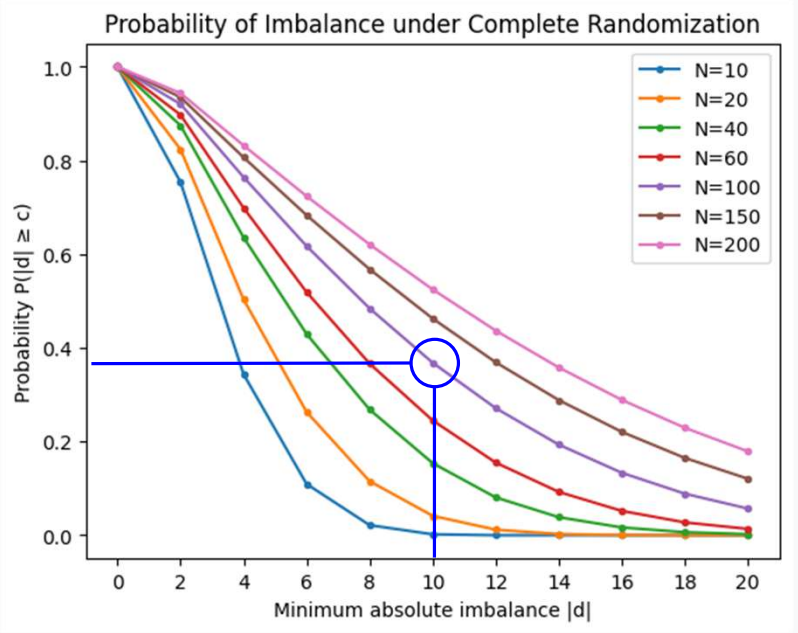
Complete Random Allocation



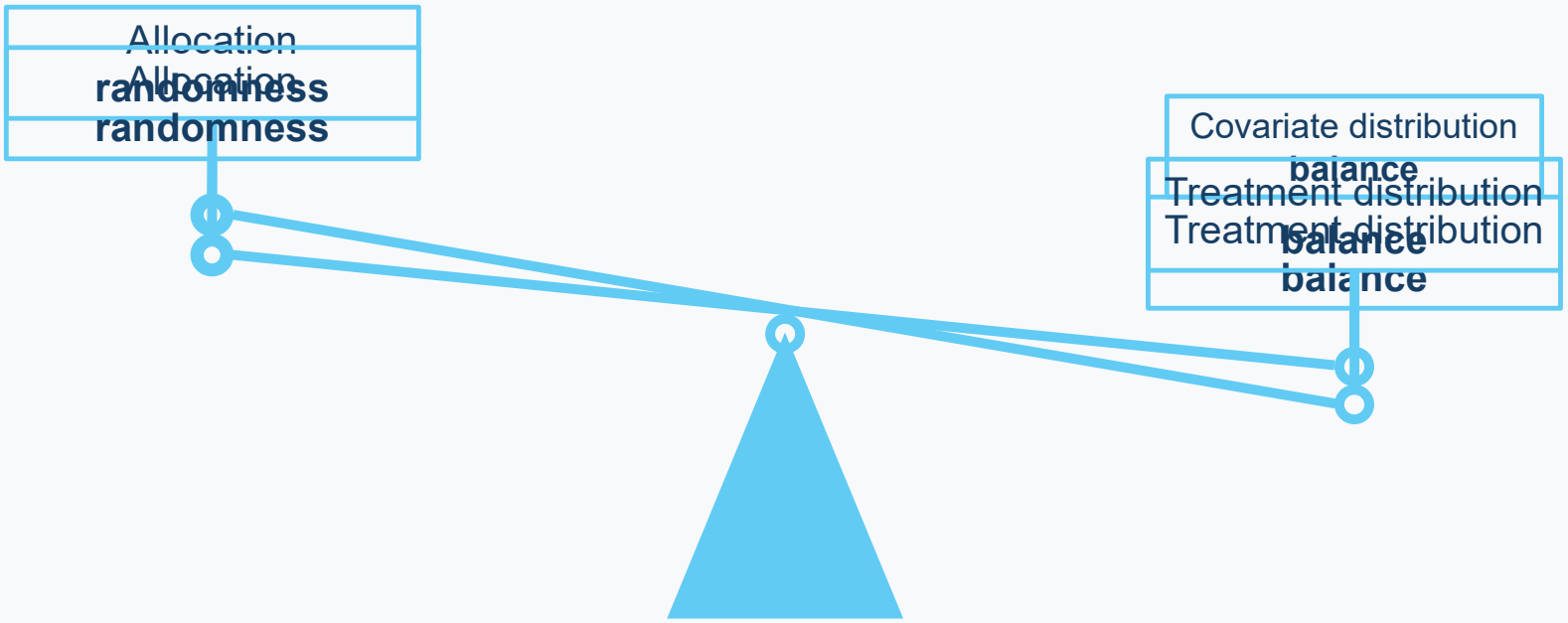


Complete Random Allocation is Vulnerable to Imbalance





Balancing overweighs Randomness



Commonly Studied Randomization Methods

A New Randomization Design

- ✓ *Low allocation predictability.*
- ✓ *With maximum tolerated imbalance control.*
- ✓ *Applicable to all trial settings: two-arm or multi-arm; equal or unequal allocations.*
- ✓ *Easy to implement with explicit conditional allocation probability formula.*

No imbalance control
Complete Randomization

High predictability
Permuted Block Design

Very high predictability
Random Block Design

Predictability not low
Block Urn Design

2-arm equal allocation only
Big Stick Design

2-arm equal allocation only
Biased Coin Design with Imbalance Tolerance

2-arm equal allocation only
Ehrenfest Urn Design

No explicit CAP formular
Maximal Procedure

No explicit CAP formular
Brick Tunnel Design

No explicit CAP formular
Wide Brick Tunnel Design

No fixed imbalance limit
Efron's Biased Coin Desing

No fixed imbalance limit
Merged Block Design

Uneven imbalance limits
Mass-weighted Urn Design

No randomness
Daves' Minimization

No fixed imbalance limit
Wei's Urn Design

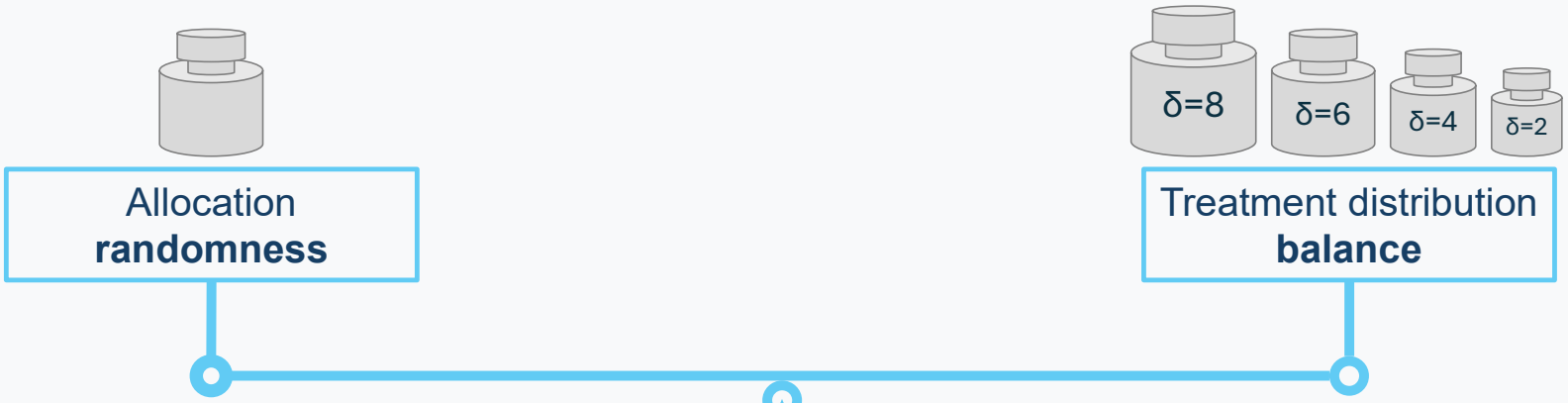
Block size = Sequence length
Random Allocation Rule

High imbalance in middle
Truncated Binomial Design

2-arm only
Asymptotic Maximal Procedure

Low randomness
Pocock & Simon's Minimization

Measures for Imbalance and Randomness



Allocation Prediction Strategies

1. Maximum probability: $T = j$ if $\hat{p}_j = \max(\hat{p}_k)$
2. Deterministic: $T = j$ if $\hat{p}_j = 1$
3. *Most vulnerable to selection bias*?

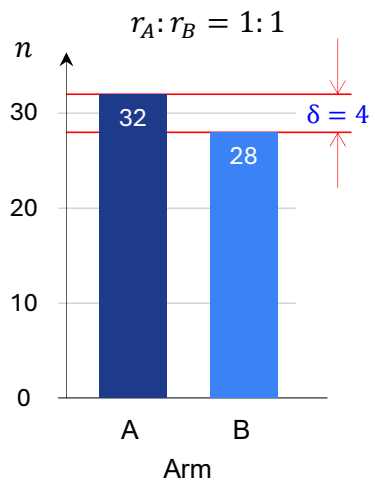
Range of treatment assignments

Two-arm equal allocation: $\delta = |n_A - n_B|$

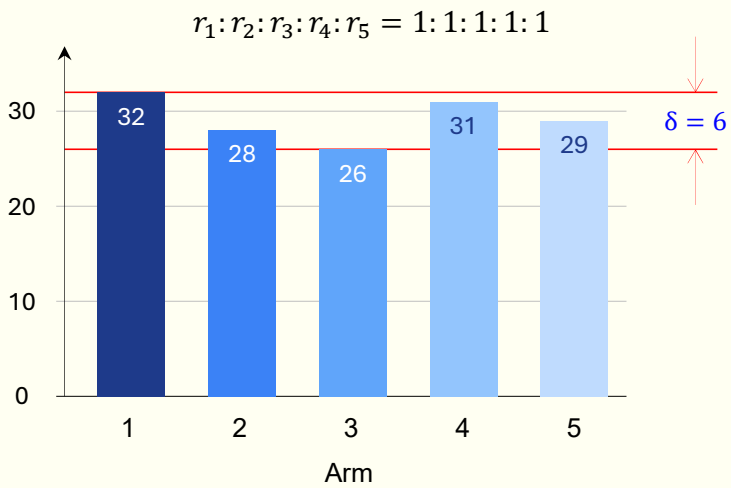
Multi-arm equal allocation: $\delta = max(n_j) - min(n_j)$

Unequal allocation: δ =?

Treatment Imbalance for Equal Allocation



Range of assignments : $\delta = 4$



Range of assignments : $\delta = 6$

Standard Deviation: $S = 2.39$

Euclidian distance between expected and observed: $E = 4.77$

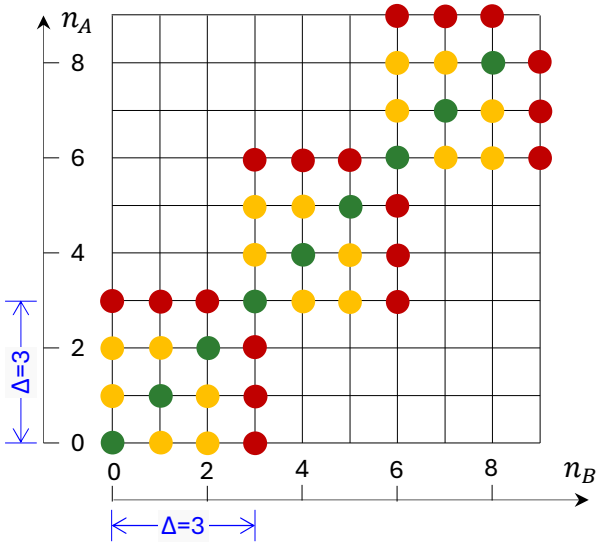
Treatment Imbalance for trials with equal allocation = Range of assignments

$$\delta = max(n_j) - min(n_j)$$

Allocation-adjusted Treatment Assignments

a. Permuted Block Design ($b = 6$)

allocation $r_A : r_B = 1:1$



$$d = |n_A - n_B|$$

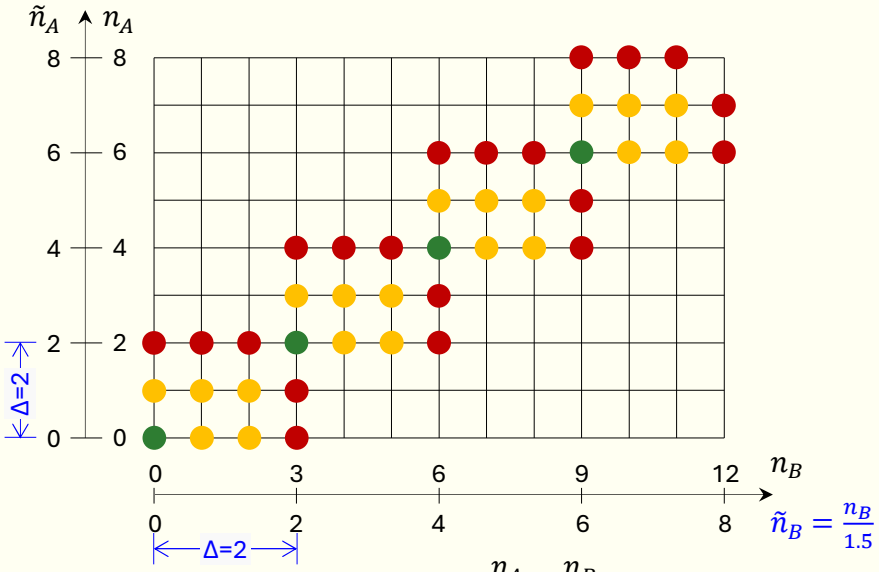
Complete random

Biased coin

Deterministic

b. Permuted Block Design ($b = 5$)

allocation $r_A : r_B = 1:1.5$

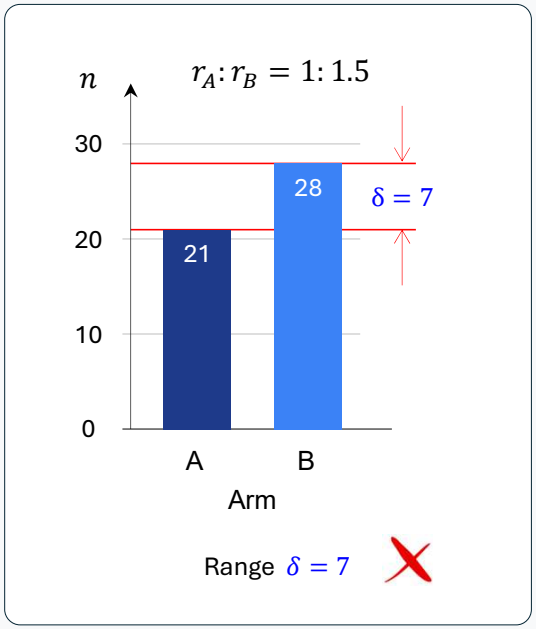


$$\delta = |\tilde{n}_A - \tilde{n}_B| = |\frac{n_A}{1} - \frac{n_B}{1.5}|$$

Treatment Imbalance = Allocation-adjusted assignment difference between the two arms

Treatment Imbalance for Two-arm Unequal Allocation

Raw Assignments

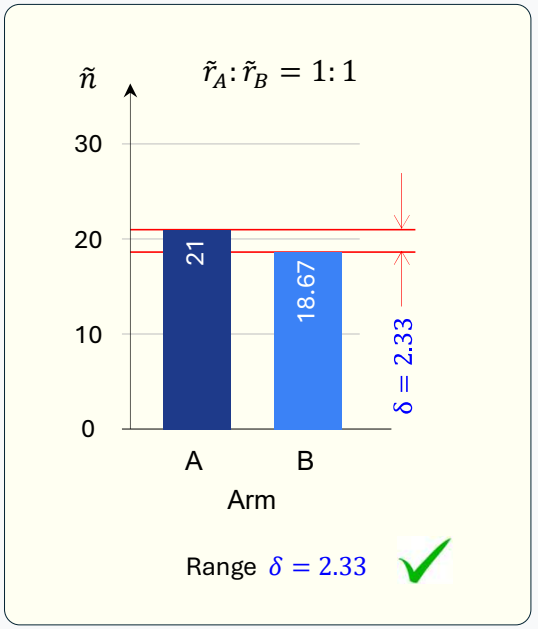


Allocation adjustment converts Unequal Allocation to Equal Allocation

$$\tilde{n}_A = \frac{n_A}{r_A},\ \tilde{n}_B = \frac{n_B}{r_B}$$

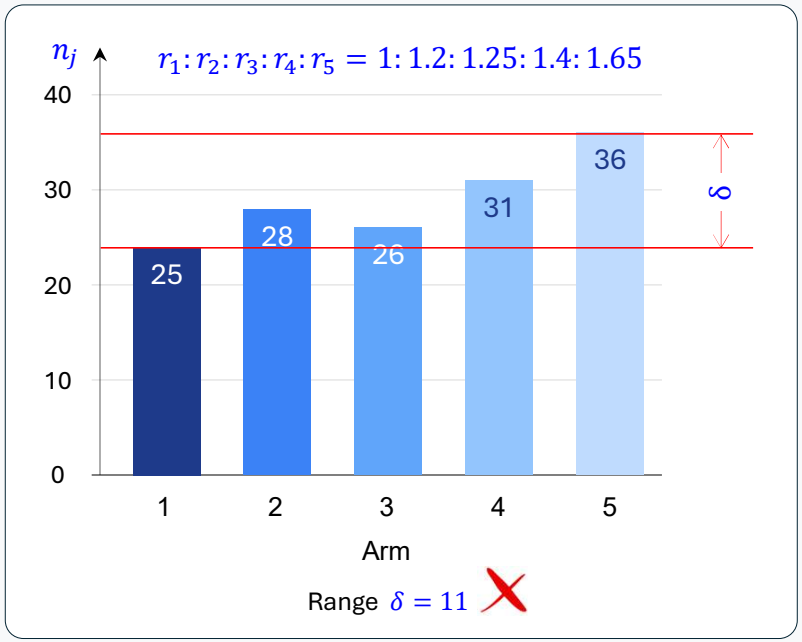
$$\delta = |\tilde{n}_A - \tilde{n}_B|$$

Allocation-Adjusted Assignments



Treatment Imbalance for Multi-arm Unequal Allocations

Raw Assignments



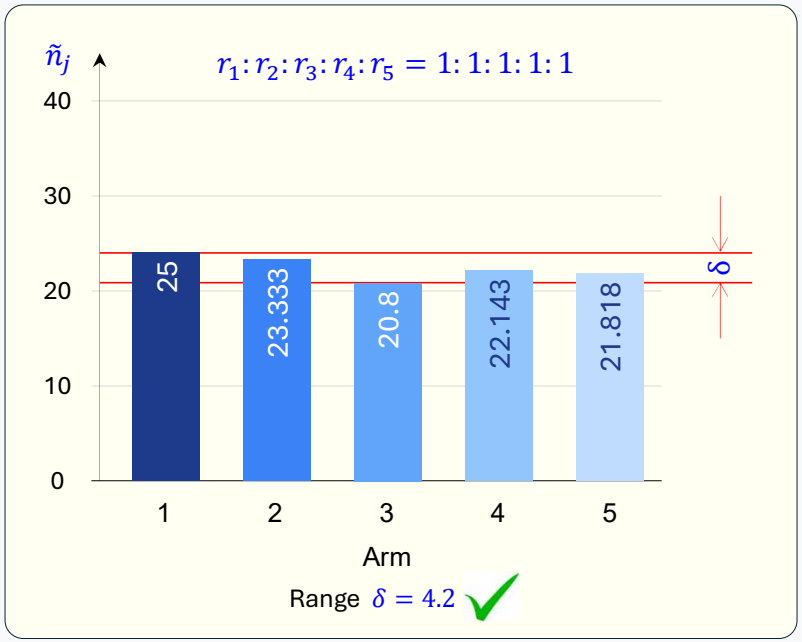
Allocation adjustment

$\tilde{n}_j = n_j / r_j$

Treatment imbalance

$\delta = max(\tilde{n}_j) - min(\tilde{n}_j)$

Allocation-Adjusted Assignments



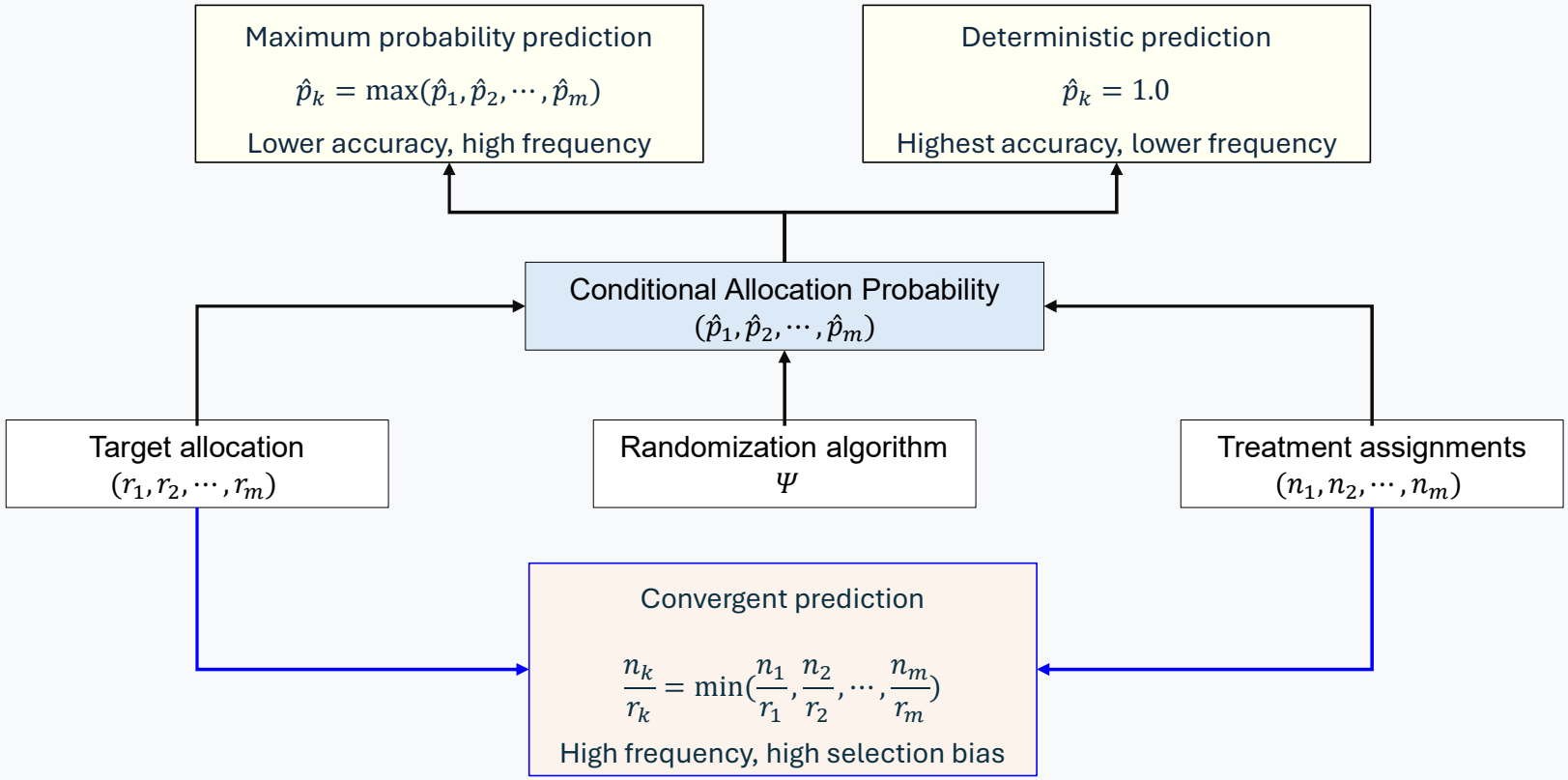
Universal Measure for Treatment Imbalance

Treatment imbalance = range of allocation-adjusted treatment assignments

$$\delta = max(n_j/r_j) - min(n_j/r_j)$$

Allocation Scenario	Two-arm Equal	Two-arm Unequal	Multi-arm Equal	Multi-arm Unequal	Multi-arm Irrational
Target allocation	1, 1	1, 1.5	1, 1, 1	1, 2, 3	$1, \sqrt{2}, \sqrt{3}$
Treatment Assignments	12, 10	9, 16	7, 8, 9	11, 17, 25	12, 15, 19
Allocation-adjusted assignments	**12**, **10**	**9**, **10.67**	**7**, 8, **9**	**11**, 8.5, **8.33**	**12**, **10.61**, 10.97
Treatment imbalance	2	1.67	2	2.67	1.39

Allocation Randomness and Prediction Strategies



[1]: Blackwell, D, Hodges, JL. Design for the Control of Selection Bias. *Ann Math Stat*. 1957; 28(2), 449–460.

Definition of Selection Bias Risk

$$SBR = E\left[\sum_{j=1\sim m} v_j \left(\frac{\hat{p}_j - p_j}{1 - p_j}\right)\right]$$

p_j: target allocation probability for arm j.

$\hat{p}_j$: conditional allocation probability for arm j = prediction accuracy.

v_j: frequency of prediction under the specific strategy.

SBR : selection bias risk

Example #1:
Using complete randomization, $\hat{p}_j \equiv p_j (j = 1,2,\cdots,m)$. Therefore, $SBR = 0.$

Example #2:
Two-arm equal allocation trial, using permuted block design with block size 2, and deterministic prediction.
Assignments in odd places have $\hat{p}_A = \hat{p}_B = 0.5$; assignments in even places have $\hat{p}_A = 1$ or $\hat{p}_B = 1$. Therefore, $SBR = 0.5$

Example #3: Two-arm Trial with1:2 allocation Using PBD (b=6)

Block	Allocation	$\hat{p}_A$	$\delta = \frac{n_A}{r_A} - \frac{n_B}{r_B}$	Maximum Probability	Deterministic Prediction	Convergent Prediction
1	AABBBB	1/3,1/5,0,0,0,0	0,1,2,1.5,1,0.5	BBBBBB	OOBBBB	OBBBBB
2	ABABBB	1/3,1/5,1/4,0,0,0	0,1,0.5,1.5,1,0.5	BBBBBB	OOOBBB	OBBBBB
3	ABBABB	1/3,1/5,1/4,1/3,0,0	0,1,0.5,0,1,0.5	BBBBBB	OOOOBB	OBBOBB
4	ABBBAB	1/3,1/5,1/4,1/3,1/2,0	0,1,0.5,0,-0.5,0.5	BBBBOB	OOOOOB	OBBOAB
5	ABBBBA	1/3,1/5,1/4,1/3,1/2,1	0,1,0.5,0,-0.5,-1	BBBBOA	OOOOOA	OBBOAA
6	BAABBB	1/3,2/5,1/4,0,0,0	0,-0.5,0.5,1.5,1,0.5	BBBBBB	OOOBBB	OABBBB
7	BABABB	1/3,2/5,1/4,1/3,0,0	0,-0.5,0.5,0,1,0.5	BBBBBB	OOOOBB	OABOBB
8	BABBAB	1/3,2/5,1/4,1/3,1/2,0	0,-0.5,0.5,0,-0.5,0.5	BBBBOB	OOOOOB	OABOAB
9	BABBBA	1/3,2/5,1/4,1/3,1/2,1	0,-0.5,0.5,0,-0.5,-1	BBBBOA	OOOOOA	OABOAA
10	BBAABB	1/3,2/5,1/2,1/3,0,0	0,-0.5,-1,0,-0.5,0.5	BBOBBB	OOOOBB	OAAOBB
11	BBABAB	1/3,2/5,1/2,1/3,1/2,0	0,-0.5,-1,0,-0.5,0.5	BBOBOB	OOOOOB	OAAOAB
12	BBABBA	1/3,2/5,1/2,1/3,1/2,1	0,-0.5,-1,0,-0.5,-1	BBOBOA	OOOOOA	OAAOAA
13	BBBAAB	1/3,2/5,1/2,2/3,1/2,0	0,-0.5,-1,-1.5,-0.5,0.5	BBOAOB	OOOOOB	OAAAAB
14	BBBABA	1/3,2/5,1/2,2/3,1/2,1	0,-0.5,-1,-1.5,-0.5,-1	BBOAOA	OOOOOA	OAAAAA
15	BBBBAA	1/3,2/5,1/2,2/3,1,1	0,-0.5,-1,-1.5,-2,-1	BBOAAA	OOOOAA	OAAAAA

A, B: Correct prediction A, B: Incorrect prediction O: No prediction

Example #3: Two-arm Trial with1:2 allocation Using PBD (b=6)

Arm	Target Allocation Probability	Assessment	Maximum Probability Prediction	Deterministic Prediction	Convergent Prediction
A	$p_A = \frac{1}{3}$	Prediction Accuracy	8/9=88.9%	6/6=100%	19/33=57.6%
		Prediction Frequency	9/90=10%	6/90=6.7%	33/90=36.7%
		Selection Bias Risk	0.083	0.067	0.133
B	$p_B = \frac{2}{3}$	Prediction Accuracy	52/67=77.6%	20/20=100%	30/33=90.9%
		Prediction Frequency	67/90=74.4%	20/90=22.2%	33/90=36.7%
		Selection Bias Risk	0.244	0.222	0.267
Overall		Selection Bias Risk	0.328	0.289	0.400

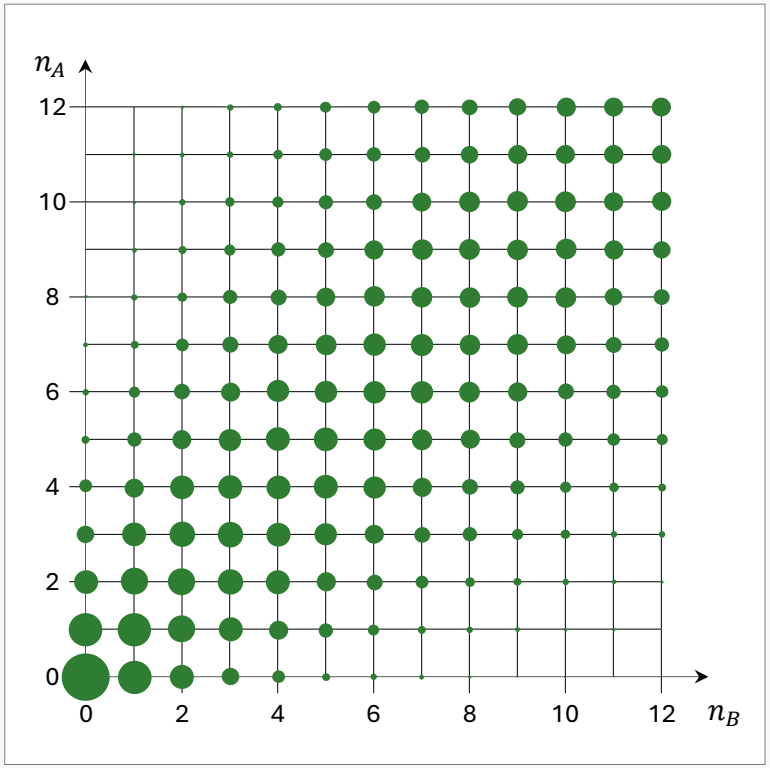
Most vulnerable prediction to selection bias

Universal Measure for Allocation Randomness

Selection Bias Risk = Expected chance of making correct prediction above target allocation probability under the convergent prediction strategy

$$SBR = E\left[\sum_{j=1\sim m} v_j \left(\frac{\hat{p}_j - p_j}{1 - p_j}\right)\right]$$

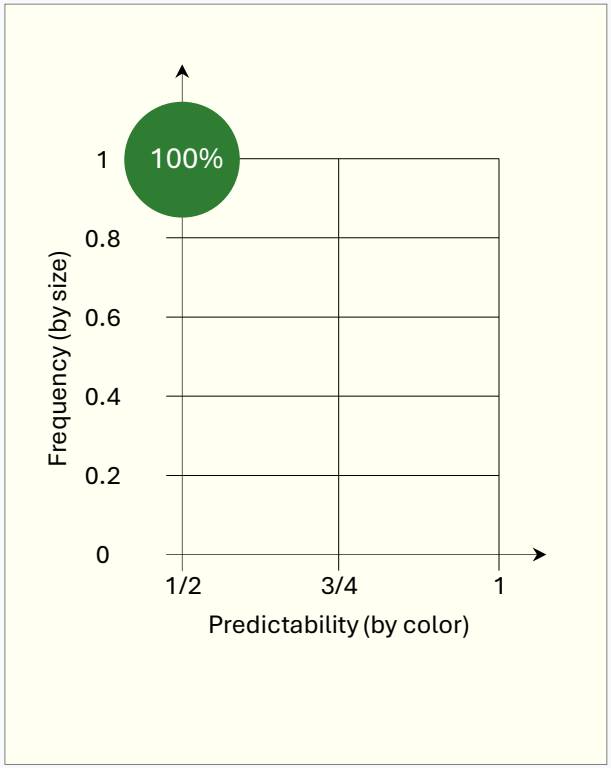
Complete Randomization



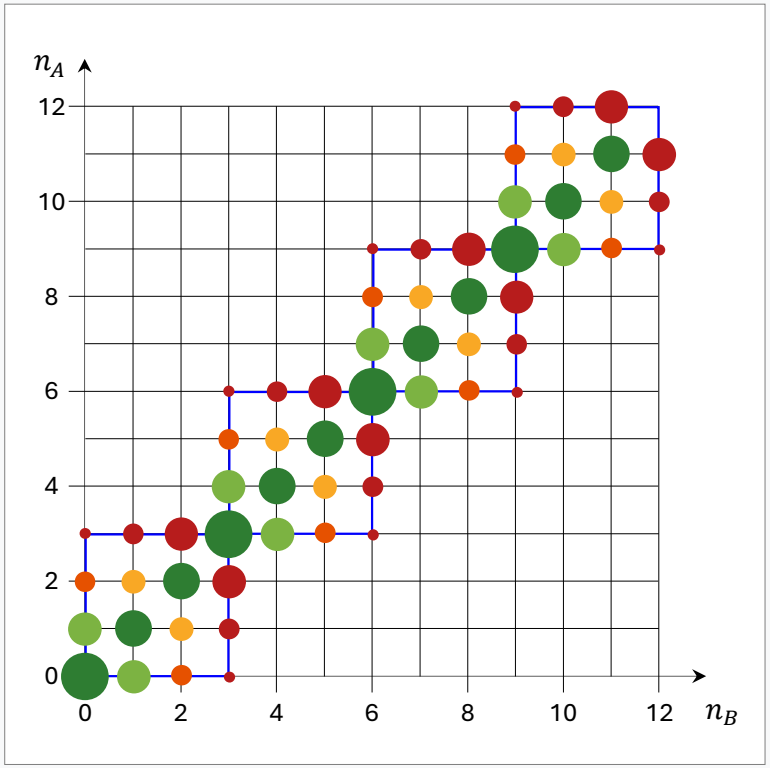
Treatment Imbalance >?

Selection Bias Risk

Frequency	Predictability	SBR
1	1/2	0
Overall SBR		0



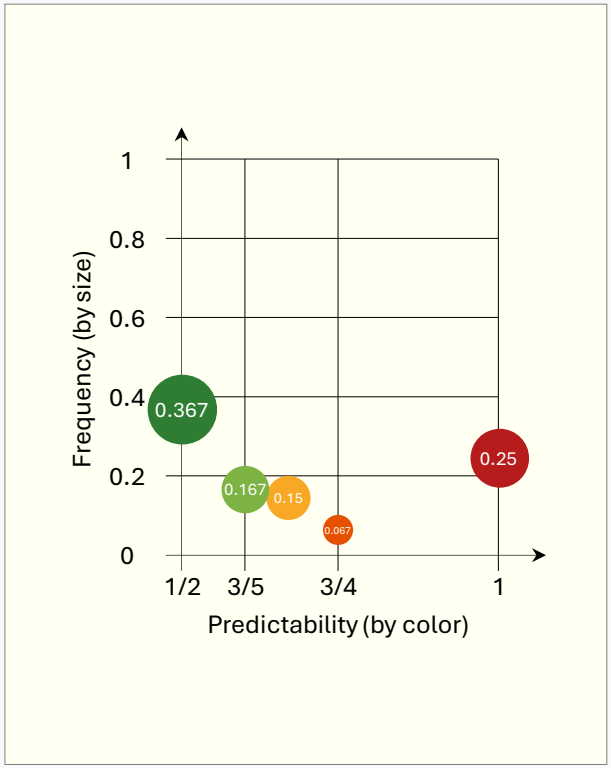
Permuted Block Design, 1:1 Allocation, Block Size 6



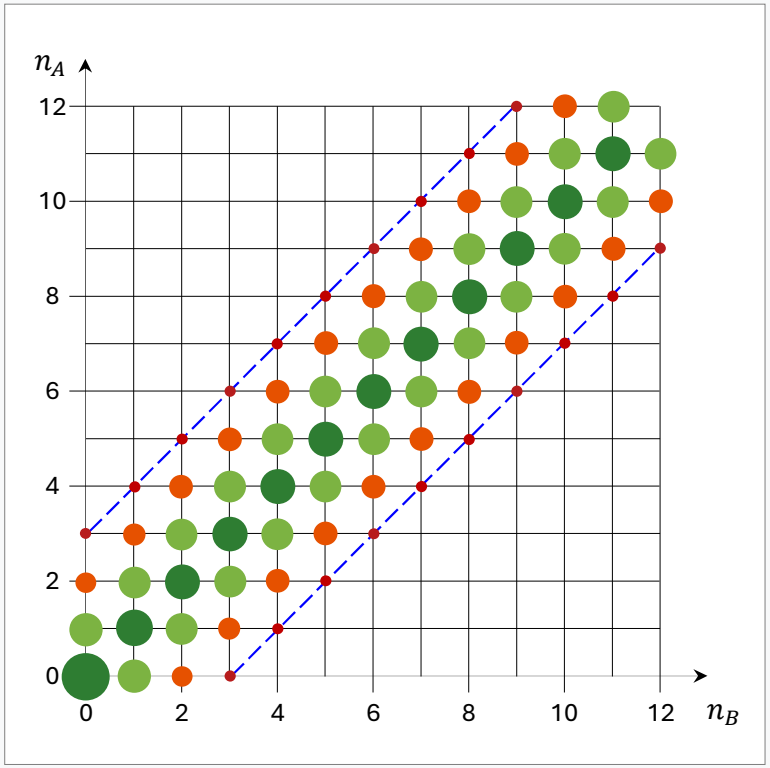
$Treatment\ Imbalance \leq 3$

$Selection\ Bias\ Risk$

Frequency	Predictability	SBR
0.367	1/2	0
0.167	3/5	0.333
0.150	2/3	0.05
0.067	3/4	0.033
0.25	1	0.25
Overall SBR		0.367



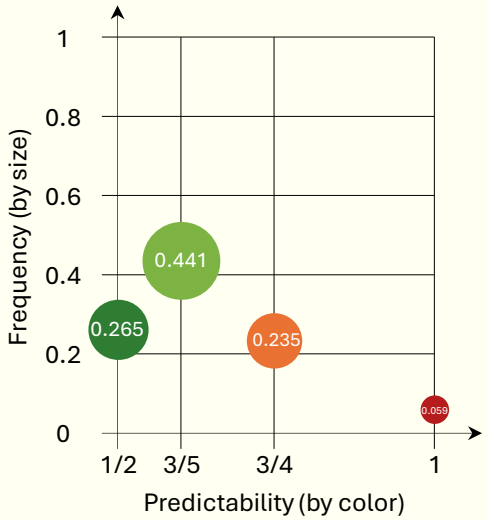
Block Urn Design, 1:1 Allocation, MTI = 3



$Treatment\ Imbalance \leq 3$

$Selection\ Bias\ Risk$

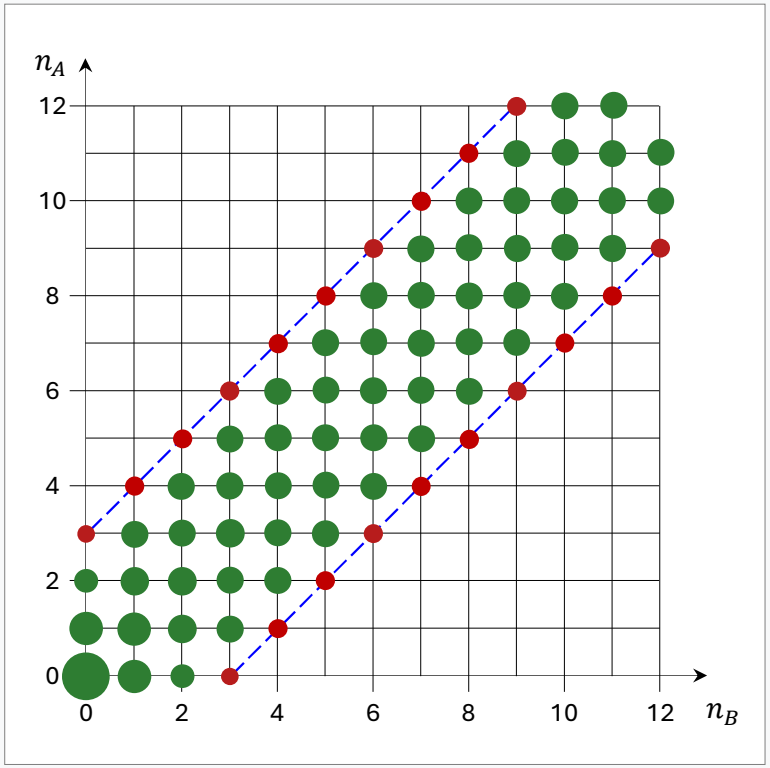
Frequency	Predictability	SBR
0.265	1/2	0
0.441	3/5	0.088
0.235	3/4	0.118
0.059	1	0.059
Overall SBR		0.265



Replace blocks with maximum tolerated imbalance (MTI) boundaries.

[2]: Zhao W, Weng Y. Block urn design - a new randomization algorithm for sequential trials with two or more treatments and balanced or unbalanced allocation. *Contemp Clin Trials*. 2011;32(6):953-961.

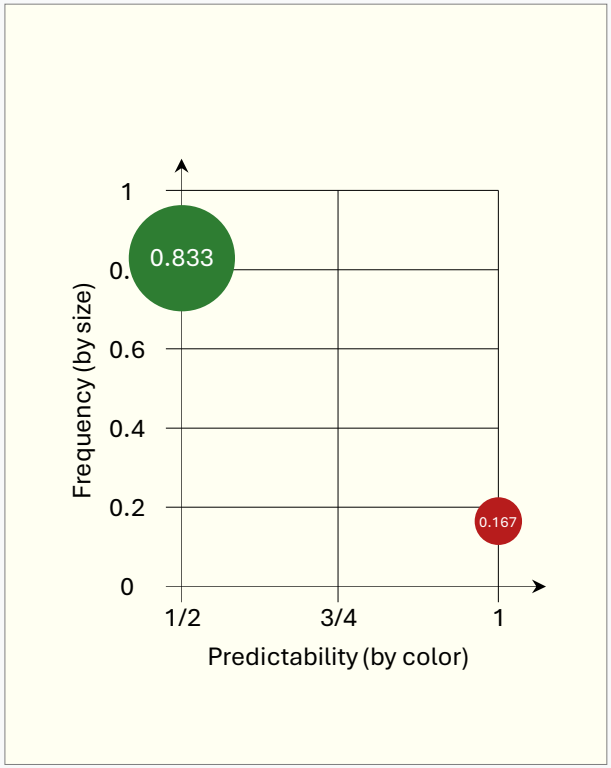
Big Stick Design, 1:1 Allocation, MTI = 3



$Treatment\ Imbalance \leq 3$

$Selection\ Bias\ Risk$

Frequency	Predictability	SBR
0.833	1/2	0
0.167	1	0.167
Overall SBR		0.167



Use complete random assignments until achieved the maximum tolerated imbalance (MTI) boundary.

[3]: Soares JF, Wu CF, Some restricted randomization rules in sequential designs. *Commun Stat*. 1983; 12:2017-2034.

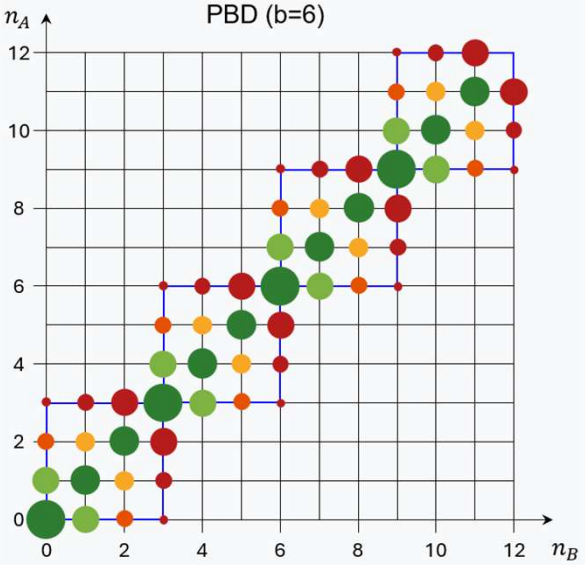
3.

Minimax Allocation Procedure
A new Randomization Algorithm

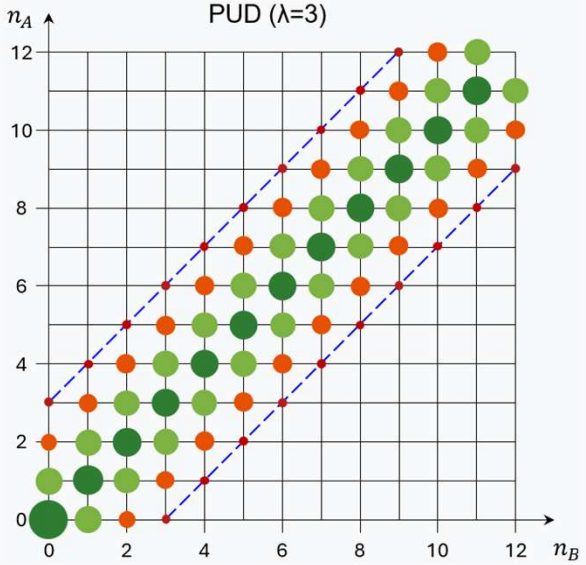
Evolution from Permuted Block to Big Stick

Use **max**imum tolerated imbalance (MTI) to replace blocks.
Use **mini**mal intervention, for ensuring MTI only.

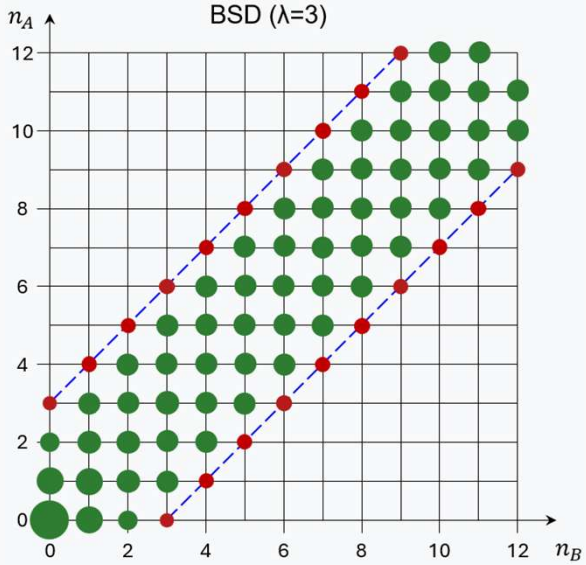
SBR = 0.367



SBR = 0.265



SBR = 0.167



From Big Stick Design to Minimax Allocation Procedure

Define **Minimax Allocation Procedure** as:

With: Target allocation $r = r_1 : r_2 : \cdots : r_m$ where 1= $r_1 \le r_2 \le \cdots \le r_m$.

Maximum tolerated imbalance Δ.

Current treatment assignments $n_1, n_2, \cdots, n_m$.

Do: Step 1: For each arm $j = 1,2,\cdots,m$

Assume $n_j = n_j + 1$.

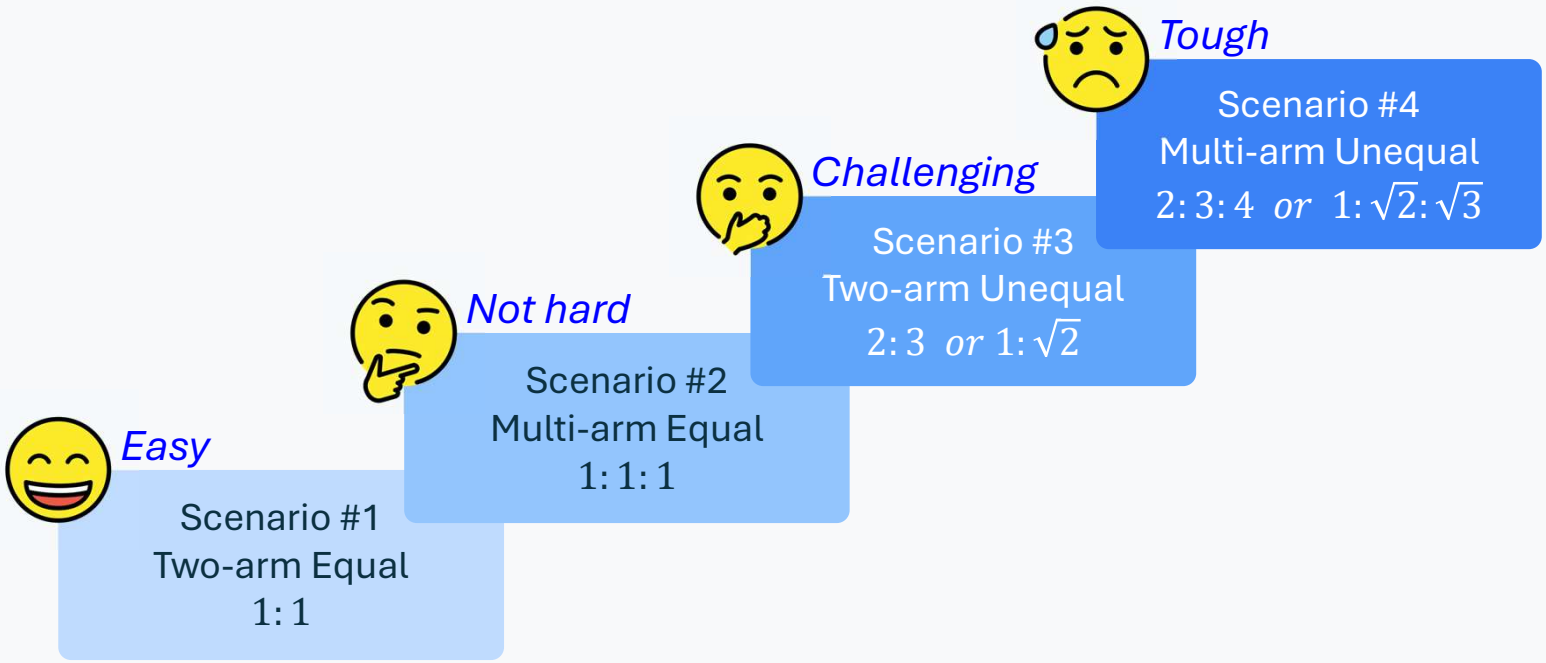
$$\tilde{p}_j = \begin{cases} 0 & \text{if } max\left(\frac{n_k}{r_k}\right) - min\left(\frac{n_k}{r_k}\right) > \Delta \\ r_j & \text{Otherwise} \end{cases}$$

Step 2: Obtain conditional allocation probability $\hat{p}_j = \frac{\tilde{p}_j}{\sum_{k=1}^{m} \tilde{p}_k}$

Step 3: Assign current subject to arm j if $\sum_{k=1}^{j-1} \tilde{p}_k > Rand < \sum_{k=1}^{j} \tilde{p}_k$

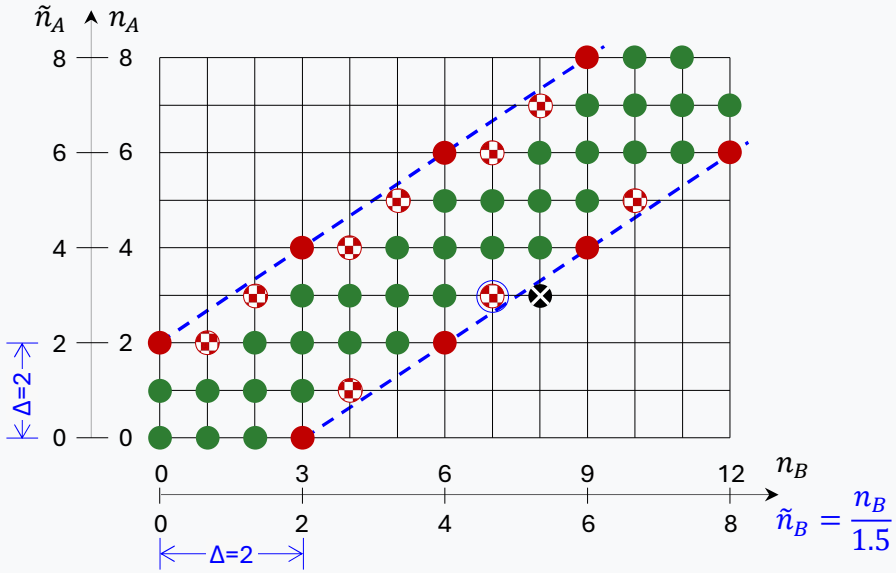
For two-arm equal allocation, Minimax Allocation Procedure is equivalent to Big Stick Design.

Trial Settings Beyond Two-arm Equal Allocation



Minimax Allocation Procedure for Two-arm Unequal Allocations

allocation $r_A : r_B = 1 : 1.5$
Maximum Tolerated Imbalance Δ=2

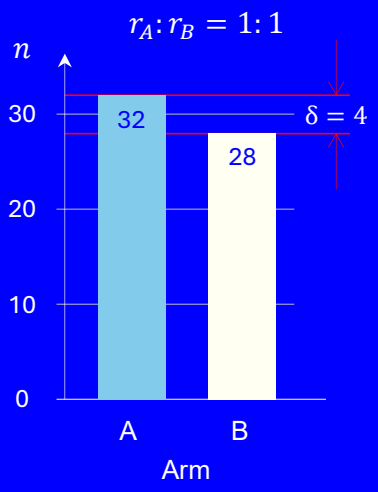


$$\delta = |\tilde{n}_A - \tilde{n}_B| = |\frac{n_A}{1} - \frac{n_B}{1.5}|$$

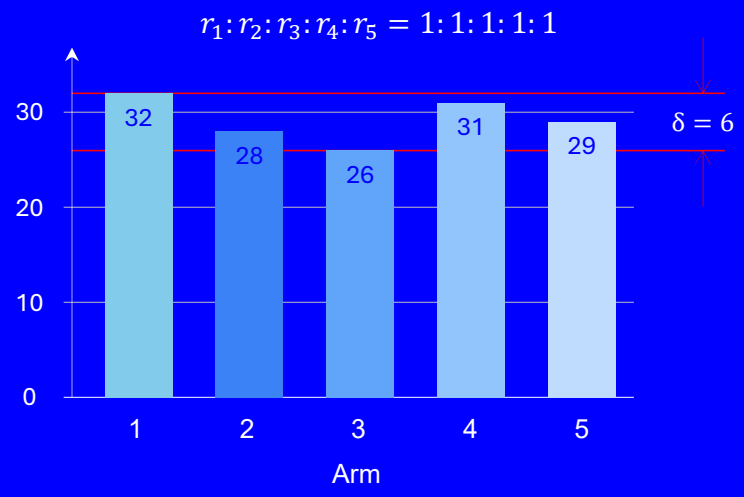
1. Define Δ based on the allocation-adjusted assignments.
2. Use complete random assignment ● by default.
3. Use deterministic assignment ● when δ = Δ.
4. Use deterministic assignment ⊕ to *prevent* δ > Δ.

	Current	After $n_B = n_B + 1$
(n_A, n_B)	$(3, 7)$	$(3, 8)$
$(\tilde{n}_A, \tilde{n}_B)$	$(3, 4.667)$	$(3, 5.333)$
δ	1.4667	$2.333 > 2$

Treatment Imbalance for Equal Allocation



Range of assignments : $\delta = 4$



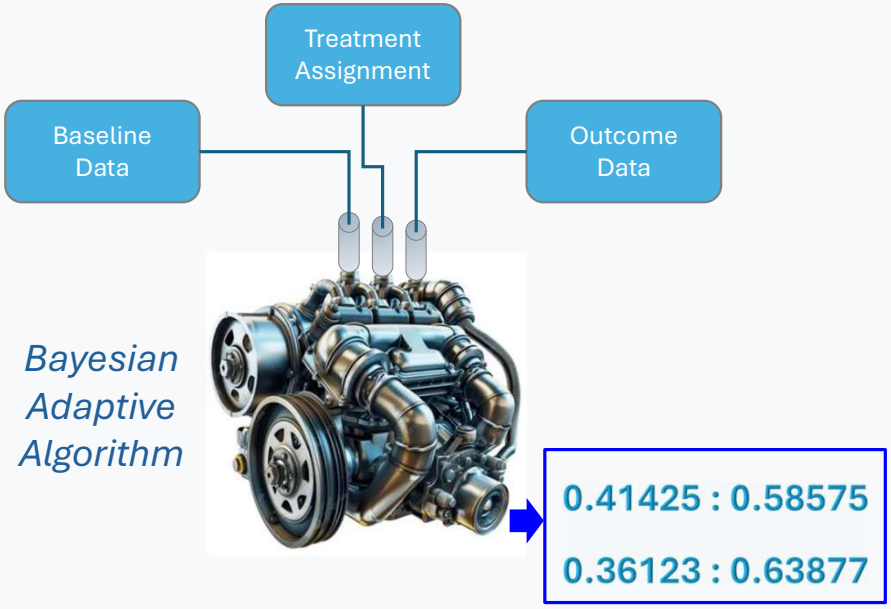
Range of assignments : $\delta = 6$

Treatment Imbalance for trials with equal allocation = Range of assignments

$$\delta = max(n_j) - min(n_j)$$

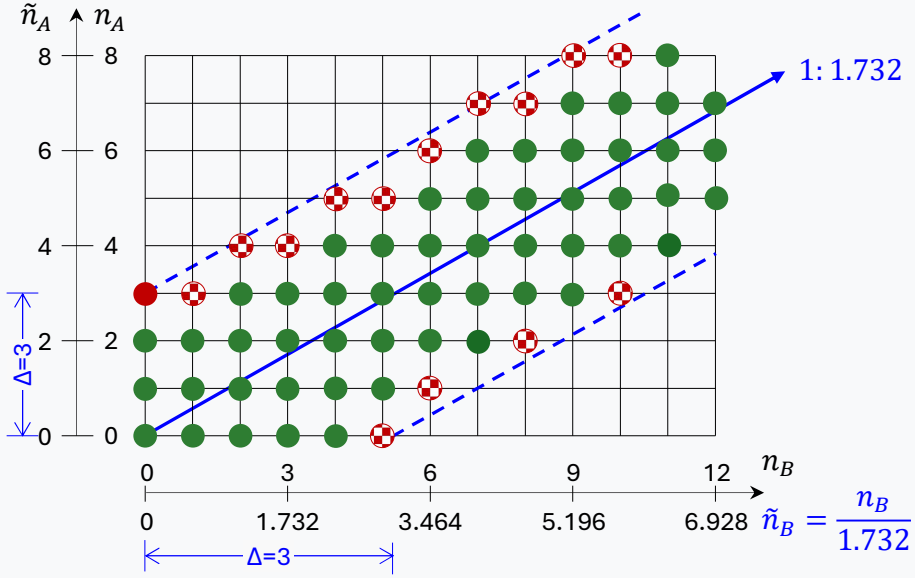
Minimax Allocation Procedure for Two-arm Unequal Allocations

Irrational Allocations in
Response Adaptive Randomization



Minimax Allocation Procedure (Δ=3)

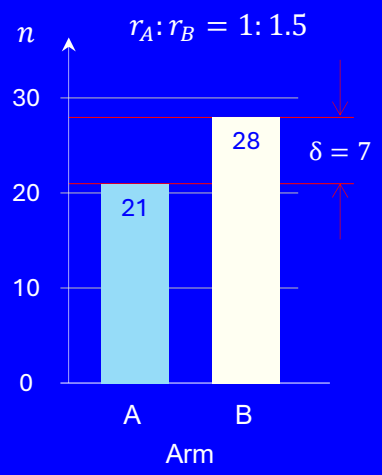
allocation $r_A : r_B = 1 : 1.732$



$$\delta = |\tilde{n}_A - \tilde{n}_B| = |\frac{n_A}{1} - \frac{n_B}{1.732}|$$

Treatment Imbalance for Two-arm Unequal Allocation

Raw Assignments

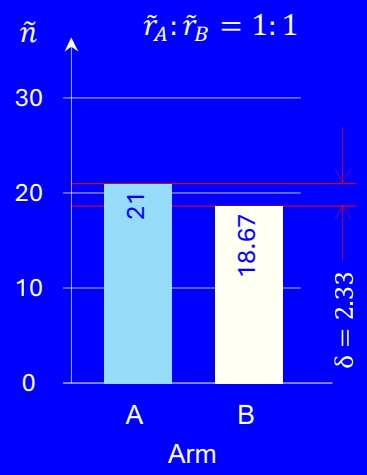


Allocation adjustment converts Unequal Allocation to Equal Allocation

$$\tilde{n}_A = \frac{n_A}{r_A},\ \tilde{n}_B = \frac{n_B}{r_B}$$

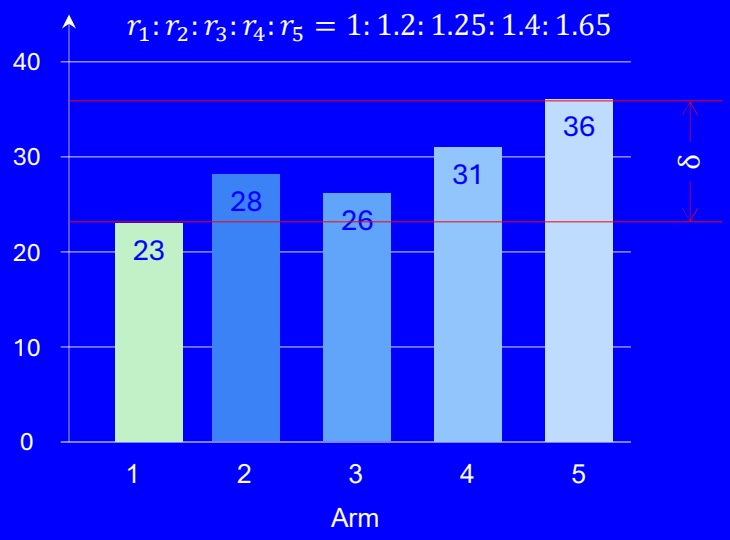
$$\delta = |\tilde{n}_A - \tilde{n}_B|$$

Allocation-Adjusted Assignments



Treatment Imbalance for Multi-arm Unequal Allocations

Raw Assignments



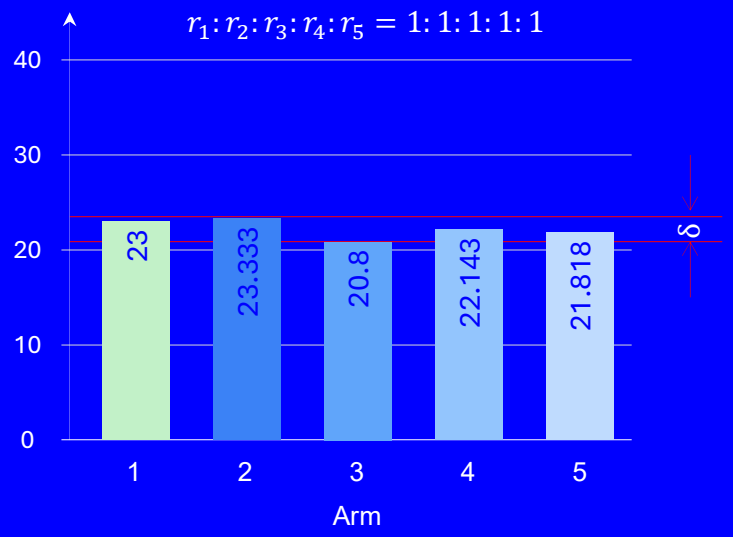
Allocation adjustment

$\tilde{n}_j = n_j / r_j$

Treatment imbalance

$\delta = max(\tilde{n}_j) - min(\tilde{n}_j)$

Allocation-Adjusted Assignments

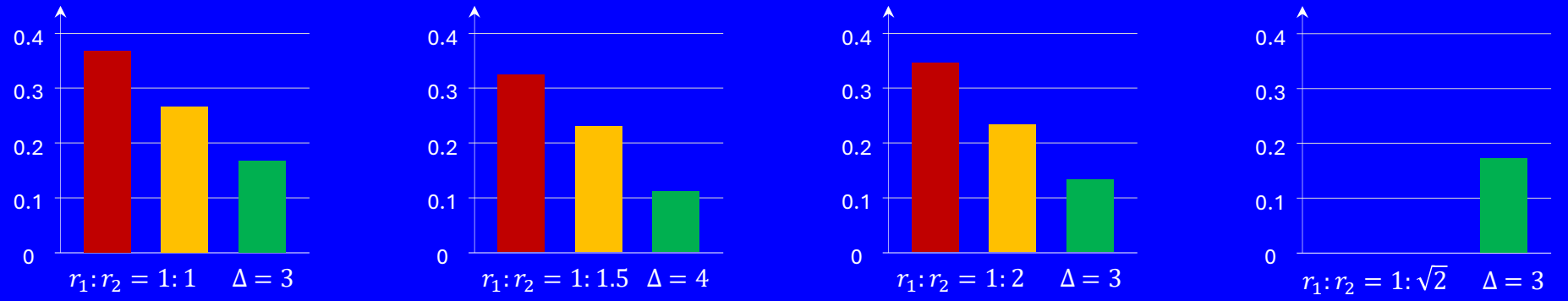


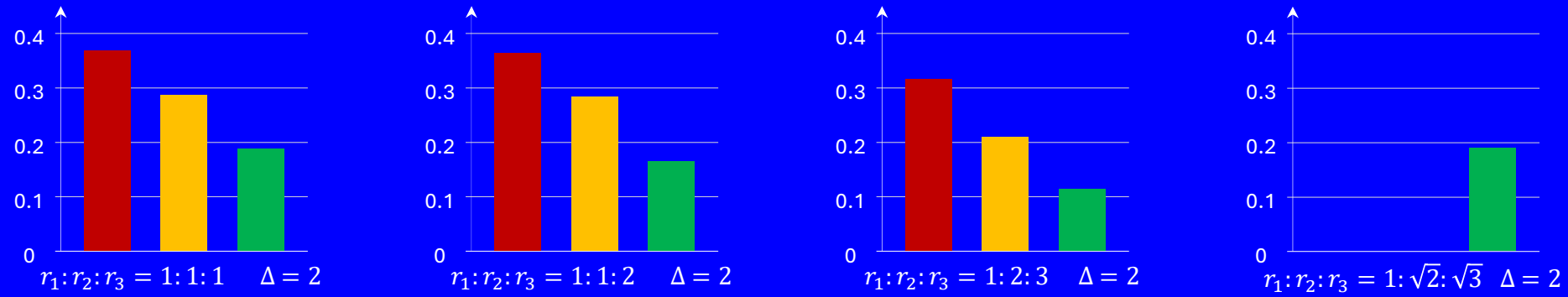
Range $\delta = 2.53$

Selection Bias Risk Comparison

Number of treatment arms = 2					Number of treatment arms = 3				
Target Allocation r	Threshold λ (block size b)	Permuted Block Design	Block Urn Design	Minimax Allocation Procedure	Target Allocation r	Threshold λ (block size b)	Permuted Block Design	Block Urn Design	Minimax Allocation Procedure
(1, 1)	1 (2)	0.5	0.5	0.5	(1, 1, 1)	1 (3)	0.417	0.417	0.336
	2 (4)	0.417	0.337	0.250		2 (6)	0.367	0.285	0.186
	3 (6)	0.367	0.265	0.166		3 (9)	0.220	0.234	0.128
(1, 1.5)	2 (5)	0.417	0.417	0.239	(1, 1, 2)	1 (4)	0.444	0.444	0.351
	3 (na)			0.154		1.5 (na)			0.247
	4 (10)	0.323	0.229	0.110		2 (8)	0.363	0.281	0.163
(1, 2)	1 (3)	0.5	0.5	0.445	(1, 2, 2)	1 (5)	0.383	0.383	0.268
	2 (6)	0.4	0.301	0.205		2 (10)	0.304	0.221	0.126
	2.5 (na)			0.160	(1, 2, 3)	1 (6)	0.377	0.373	0.257
	3 (9)	0.345	0.232	0.131		2 (12)	0.315	0.208	0.114
(1, $\sqrt{2}$)	2			0.282	(1, $\sqrt{2}$, $\sqrt{3}$)	1.4 (na)			0.313
	3			0.171		2 (na)			0.188

Selection Bias Risk Comparison





Minimax Allocation Procedure Summary

Complete random by default.
Intervene for MTI only.
Lowest predictability under convergent strategy.

$\mathbf{r} = (r_1, r_2, \cdots, r_m)$
where $r_j \in \mathbb{R}^+$

- ✓ *Low allocation predictability.*
- ✓ *With maximum tolerated imbalance control.*
- ✓ *Applicable to all trial settings: two-arm or multi-arm; equal or unequal allocations.*
- ✓ *Easy to implement with explicit conditional allocation probability formula.*

Fixed allocation-adjusted treatment imbalance

Requires basic arithmetic +, -, x, /.

Define **Minimax Allocation Procedure** as:

With: Target allocation $r = r_1 : r_2 : \cdots : r_m$ where $1 = r_1 \leq r_2 \leq \cdots \leq r_m$.

Maximum tolerated imbalance Δ.

Current treatment assignments $n_1, n_2, \cdots, n_m$.

Do: Step 1: For each arm $j = 1,2, \cdots, m$

Assume $n_j = n_j + 1$.

$$\tilde{p}_j = \begin{cases} 0 & \text{if } max\left(\frac{n_k}{r_k}\right) - min\left(\frac{n_k}{r_k}\right) > \Delta \\ r_j & \text{Otherwise} \end{cases}$$

Step 2: Obtain conditional allocation probability $\hat{p}_j = \frac{\tilde{p}_j}{\sum_{k=1}^{m} \tilde{p}_k}$

Step 3: Assign current subject to arm j if $\sum_{k=1}^{j-1} \tilde{p}_k > Rand < \sum_{k=1}^{j} \tilde{p}_k$

Minimax Allocation Procedure Is Not Perfect

- For treatment imbalance control only.
- Fixed imbalance threshold may cost allocation randomness for negligible benefit.
- Unconditional allocation probabilities not consistent across assignments in the allocation sequence.

Define **Minimax Allocation Procedure** as:

With: Target allocation $r = r_1 : r_2 : \cdots : r_m$ where $1 = r_1 \leq r_2 \leq \cdots \leq r_m$.

Maximum tolerated imbalance Δ.

Current treatment assignments $n_1, n_2, \cdots, n_m$.

Do: Step 1: For each arm $j = 1,2, \cdots, m$

Assume $n_j = n_j + 1$.

$$\tilde{p}_j = \begin{cases} 0 & \text{if } max\left(\frac{n_k}{r_k}\right) - min\left(\frac{n_k}{r_k}\right) > \Delta \\ r_j & \text{Otherwise} \end{cases}$$

Step 2: Obtain conditional allocation probability $\hat{p}_j = \frac{\tilde{p}_j}{\sum_{k=1}^{m} \tilde{p}_k}$

Step 3: Assign current subject to arm j if $\sum_{k=1}^{j-1} \tilde{p}_k > Rand < \sum_{k=1}^{j} \tilde{p}_k$

Thank you!

Restricted Randomization Beyond Permuted Blocks

SCT Arizona 2026

Kevin Venner, Diane Uschner

May 2026

Introduction

Outline

1. Why block randomization is increasingly challenged
2. Mathematical perspective on restricted randomization
3. Maximum tolerated imbalance (MTI) framework
4. Practical alternatives to permuted block randomization
5. Predictability under equal MTI constraints
6. Implementation and take-home messages

Why Rethink Permuted Block Randomization?

Block Randomization Under Challenge

- Permuted block randomization has been widely used for decades because it controls treatment imbalance tightly.
- In modern trials, that strong control can come at a cost: higher allocation predictability.
- Predictability increases the risk of selection bias when treatment history can be partially inferred.
- The core question is no longer only balance, but balance versus randomness and robustness.

Dynamic Allocation and Current Trial State

- Treatment assignment is sequential and depends on the current state of the trial.
- In blocked and stratified designs, assignment probabilities are influenced by current within-block imbalance.
- Stratification adds another dynamic layer because covariate strata evolve over enrollment.
- This dynamic dependence is shared by many restricted randomization designs, not only permuted blocks.

Mathematical Framing

Restricted Randomization as a Dynamic Process

- Restricted randomization can be viewed as a stochastic process on imbalance states.
- At each step, the design updates assignment probabilities using current history.
- Design properties are therefore path-dependent, not just determined by the final sample size.
- This framing helps compare designs on predictability, imbalance, and inferential performance.

Dependence on Treatment Balance and Stratum State

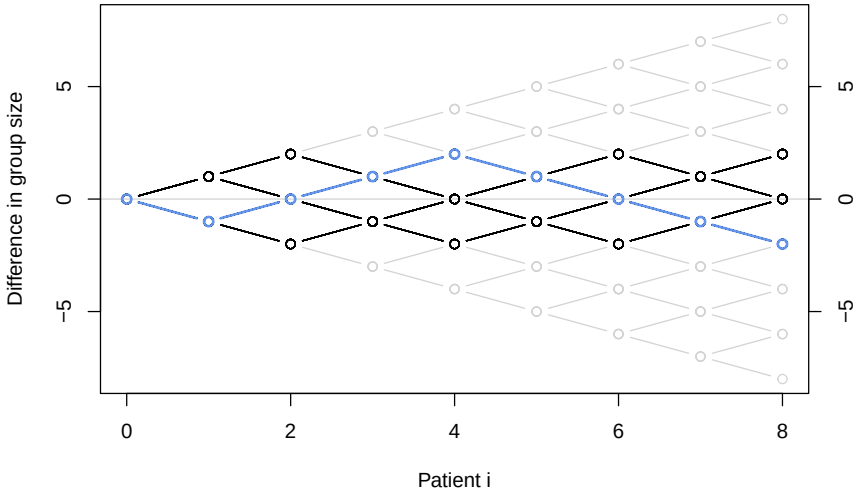
- Let $D_i = N_C(i) - N_E(i)$ denote treatment imbalance after subject i.
- In stratified settings, each stratum has its own imbalance trajectory.
- The next assignment probability is a function of the current imbalance state (and potentially stratum).
- Strong correction toward $D_i = 0$ improves balance but can make assignments easier to guess.

MTI-Based Design Strategy

Maximum Tolerated Imbalance (MTI)

- MTI designs enforce a hard boundary on allowable imbalance: $|D_i| \leq b$.
- Inside the boundary, randomization is flexible; at the boundary, correction is enforced.
- MTI provides a transparent tuning parameter for the balance-randomness trade-off.
- This gives a common framework to compare procedures at the same imbalance tolerance.

Visualization of the MTI tunnel



Releasing Enforced Block-End Perfect Balance

- Permuted blocks force deterministic structure near the end of each block.
- MTI-based alternatives relax this block-end perfect balance requirement.
- The result is lower predictability while still controlling worst-case imbalance.
- In practice, this can reduce selection bias risk without sacrificing operational simplicity.

Alternative Designs

Maximal Procedure

- The maximal procedure is an MTI-constrained restricted randomization design with equi-probable randomization sequences and the contraint of final group balance
- It maximizes randomness subject to the imbalance bound, avoiding fixed block structure.
- Under matched MTI constraints, it is less predictable than permuted block randomization.
- It is a practical option when allocation concealment and anti-predictability as well as exact final balance are priorities.
- Implementation requires knowing the target group sizes in advance.

Big Stick Design

- Big Stick Design randomizes freely until the MTI boundary is reached.
- At the boundary, assignment is forced only to move imbalance back toward zero.
  - As a result, sequences are not equi-probable, but the design is less predictable than permuted blocks.
- This yields less deterministic behavior than permuted blocks while preserving MTI control.
- Operationally, it is straightforward to implement with centralized randomization tools.

Implementation Simplicity and Practical Use

- Big Stick and maximal procedure designs are feasible for routine trial operations.
- They can be pre-specified in SAP/protocol language similarly to existing restricted methods.
- Implementation burden is typically low with modern IWRS/IRT infrastructure.
- Design choice should be justified by expected bias risk, not convenience alone.

Predictability Evidence

Equal-MTI Comparisons Across Designs

- Fair comparisons should match designs on the same MTI level.
  - For the permuted block design, the MTI is half the block size (e.g., MTI=2 for block size 4).
- Under equal MTI, designs can differ meaningfully in allocation predictability.
- Literature shows that predictability is not an unavoidable consequence of imbalance control.
- This supports selecting designs by properties, not by historical default.

Notation

Let N be the total sample size, i the patient index, and $t \in \Omega := \{0,1\}^N$ a randomization sequence, where

$$t_i = \begin{cases} 1 & i \text{ is allocated to } E \\ 0 & i \text{ is allocated to } C \end{cases}$$

We call Ω the set of all sequences. For a sequence t,

$$N_E(i) := N_E(t,i) := \sum_{j=1}^{i} t_j$$

$$N_C(i) := N_C(t,i) := i - \sum_{j=1}^{i} t_j$$

define the number of patients in groups E and C after i allocations.

Predictability Metric: Correct Guesses

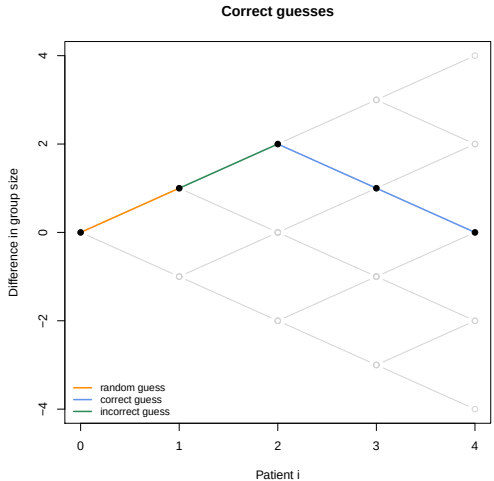
- In the situation of third order selection bias, the investigator can count $N_E(i)$ and $N_C(i)$ respectively.
- Under the assumption that $N_E(N) = N_C(N)$ for all $t \in \Omega$ it makes sense for the investigator to guess

$$g(t_{i+1}) = \begin{cases} 0 & N_E(i) > N_C(i) \\ Ber(0.5) & N_E(i) = N_C(i) \\ 1 & N_E(i) < N_C(i), \end{cases}$$

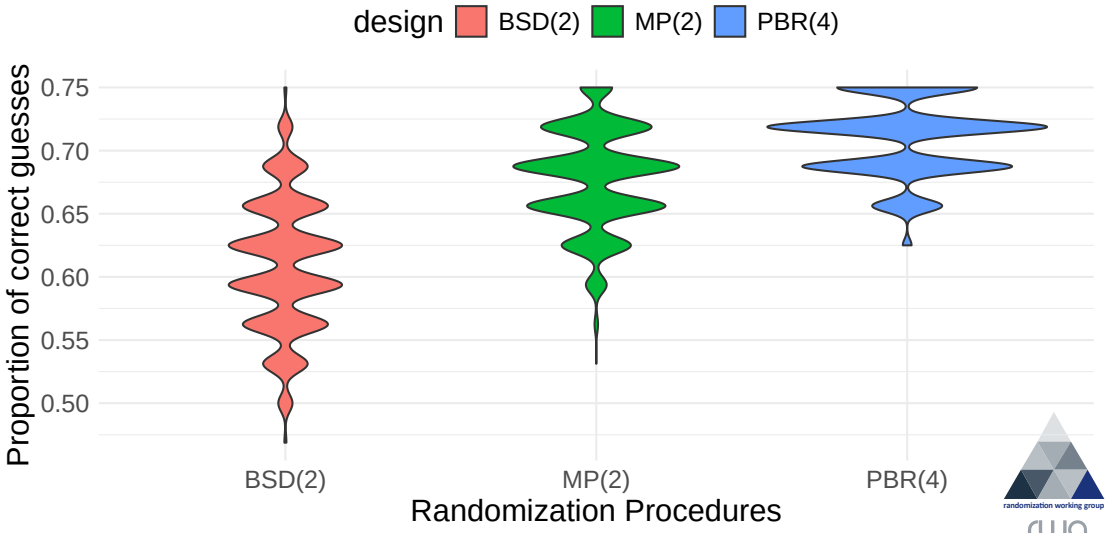
  following the so called *convergence strategy*.
- The number of correct guesses of a randomization sequence is then $CG(t) := \sum_{i=1}^{N-1} g(t_{i+1})$, and the proportion of correct guesses is $CG(t)/N$.

(Blackwell and Hodges 1957)

Visualization Correct Guesses



Design Comparison with respect to Predictability



Why Permuted Block Is Most Predictable Under MTI

- With fixed block structure, remaining allocations become progressively constrained.
- Near block completion, upcoming assignments can often be inferred with high probability.
- Theoretical and empirical work shows permuted blocks are most predictable among equal-MTI designs.
- Therefore, permuted blocks may be inferior when minimizing predictability is a design priority.

Conclusions

Key Messages

- Balance control and allocation unpredictability should be considered jointly.
- Under equal MTI, permuted blocks are generally more predictable than alternatives.
- Big Stick and maximal procedure are practical, implementable, and often preferable options.
- Moving beyond default blocked randomization can improve design robustness.

Discussion

- Which trial settings in our portfolio are most vulnerable to selection bias?
- What MTI level is acceptable from a clinical and operational perspective?
- Should we update internal default randomization recommendations beyond permuted blocks?

Blackwell, D., and J. Hodges. 1957. "Design for the Control of Selection Bias." *Annals of Mathematical Statistics* 25: 449–60.

Welcome

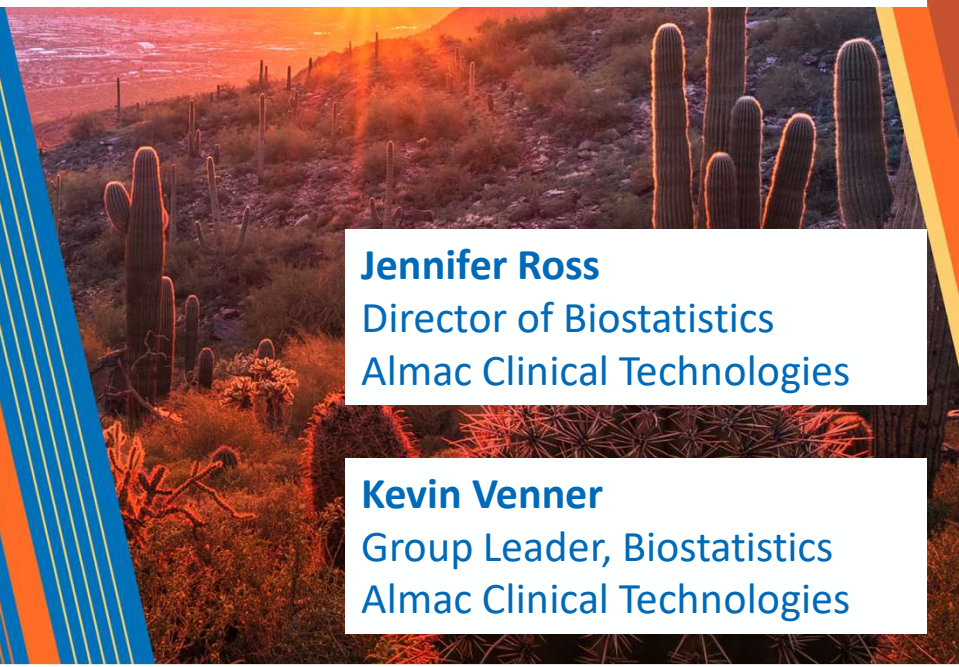
47TH Annual Meeting

PHOENIX

May 17-20, 2026

SCT
SOCIETY FOR CLINICAL TRIALS

Beyond the Blocks: A World of Randomization Possibilities with Modern IRT



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Almac Clinical Technologies

Kevin Venner
Group Leader, Biostatistics
Almac Clinical Technologies

Disclosures

- Nothing to disclose

Agenda

- **Origins of Randomization Procedures / Implementation**
- **IRT Implementation**
  - Blocked Randomization
  - Beyond the Blocks – MTI
  - Beyond the List – Algorithms
- **Modern Day Challenges / Recommendations**

Randomization Procedure Origins
Where it All Began.....

1931 → 1948 → 1951 → 1950s +

Coin Toss

- 1st Rand Element; Coin Toss
- Amberson Tuberculosis Trial
- No Formal Schedule
- No Reproducibility

Random Numbers

- 1st Randomization Schedule
- MRC streptomycin trial; Bradford Hill
- No Blocks / Balance Controls

Blocked Randomization

RandNo	Treatment	BlockNo
10001	Placebo	101
10002	Active	101
10003	Active	101
10004	Placebo	101
10005	Placebo	102
10006	Placebo	102
10007	Active	102
10008	Active	102

- 1st Blocked Randomization List
- Bradford Hill
- Added Controls for Imbalance
- Foreknowledge Risk

Sealed Envelopes

- Added Concealment
- Selection Bias Protection
- Procedure / Process

Randomization Schedules + Sealed Envelopes

Groundbreaking for its time – adding Procedure, Controls for Imbalance / Concealment

But Not Perfect…..

Human Reliance

- Data Integrity Risks – Manipulation; Selection Bias; Unblinding
- Timing Accuracy / Delays

Manual Burden

- Data Entry
- Integrating Data – Rand Sites; Different Sources (e.g., CRF, labs)
- Medication Management

Locally Executed

- Challenging to do Multi-Site / Regions / Global Trials

Limited Oversight

- No Audit Trail
- No Automated Controls
- No Governance

Methodology Limitations

- Primarily Blocked Randomization
- Basic Stratification
- Site Stratification (for different sites)
- Algorithms Rare because of complexity

Randomization Implementation Evolution

The Journey From Physical Procedures to Governed Platforms

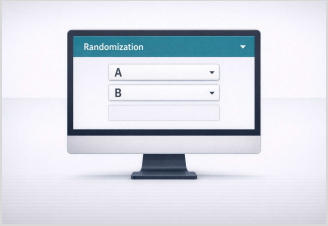
1950s-1990s	1990s-2000s	2000s-2010s	2010s-TODAY
Lists & Sealed Envelopes	IVRS	IWRS	Modern IRT / RTSM

Manual Control

- Local Execution
- High Reliance on User
- Limited Oversight
- No Data Integration

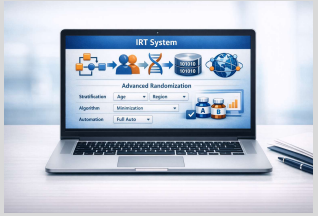
Telephone-Based

- Centralized / Global Allocation
- Basic Automation
- Reduced Manipulation Risk
- Limited Data Integration



Web-Based Systems

- Central / Stratified
- Better Automation
- Eligibility Enforcement
- Better Data Integration



Randomization Platform

- Complex Rand Algorithms
- Robust Automation
- Full Audit Trail / Governance
- Complex Data Integration

Increasing Complexity, Control and Assurance

IRT - Medication Management too!

Performs Both Randomization and Medication Assignments

Randomization List

RandNo	Trt	Participant	DateTime
10001	Active	101	22-Feb-2026 01:21
10002	Control	102	25-Feb-2026 11:18
10003	Control		
10004	Active		
10005	Control		
10006	Active		
10007	Control		
10008	Active		
10009	Control		
10010	Active		
10011	Active		
10012	Control		
10013	Active		
10014	Active		
10015	Control		

Kit List

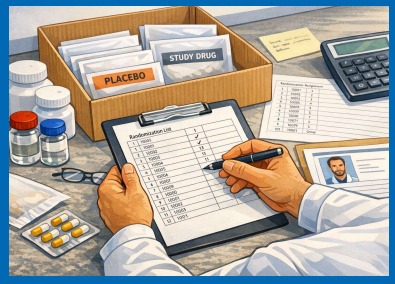
SeqNo	KitNo	KitType	Participant	DateTime
100001	20035	Active	101	22-Feb-2026 01:21
100002	20008	Active		
100003	20034	Active		
100004	20001	Active		
100005	20022	Active		
100006	20009	Active		
100007	20021	Active		
100008	20023	Active		
100009	20024	Active		
100010	20033	Active		
200001	20004	Control	102	25-Feb-2026 11:18
200002	20014	Control		
200003	20005	Control		
200004	20013	Control		
200005	20007	Control		

Medication Management: Shipments, Inventory, Resupplies, Etc.

IRT Medication Management Evolution

The Journey From Physical Procedures to Governed Platforms

Pre-1990	Late 1990s	2000s	2010s-
Schedules / Sealed Envelopes	IVRS	IWRS	Modern IRT / RTSM
Physically / Manually	1st Entered Technology – Dispensing & Resupply	Became Standard – Inventory & Logistics	Reached Full Regulatory Maturity – End-to-End Supply Lifecycle



IRT – Effective Trial Medication Management

Modern IRT Randomization Methods

A World of Randomization Methodologies – from Simple to Highly Complex

List-Based Randomization

- **Central (Study level)**
- **Stratified**
- **Site-based**
- **Blocked Randomization:**
  - Fixed Blocks
  - Variable / Mixed Blocks
  - Pre-Allocated Stratification Blocks
  - On-Demand (dynamically) Allocated
- **Maximum Tolerated Imbalance (MTI)**
- **Other**

Algorithm-Based Randomization

- **Response-Adaptive Randomization**
- **Minimization (Covariate Adaptive Randomization)**
- **Maximum Tolerated Imbalance (MTI)**
- **Backfill Adaptive Randomization Design (BARD)**
- **Custom Algorithms:**
  - Target-Based
  - Ratio-Based
  - Hierarchical
- **Other**

IRT List-Based Implementation Example: Stratified Blocked Randomization

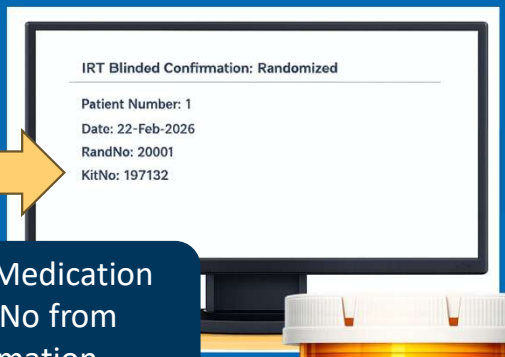
List Generated Upfront / Loaded in IRT

RandNo	Stratum	Trt	BlockNo	Patient	DateTime
10001	1: Trt Naïve	Placebo	101		
10002	1: Trt Naïve	Active	101		
10003	1: Trt Naïve	Active	101		
10004	1: Trt Naïve	Placebo	101		
10005	1: Trt Naïve	Placebo	102		
10006	1: Trt Naïve	Placebo			
10007	1: Trt Naïve	Active	102		
10008	1: Trt Naïve	Active	102		
20001	**2: Trt Experienced**	**Placebo**	**201**	**1**	**22-Feb-2026 01:21**
20002	2: Trt Experienced	Active	201		
20003	2: Trt Experienced				
20004	2: Trt Experienced				
20005	2: Trt Experienced				
20006	2: Trt Experienced				
20007	2: Trt Experienced	Placebo	202		
20008	2: Trt Experienced	Active	202		

Assign Next Available Record in Participant's Stratum

Participant 1 Randomized in IRT

Blinded Confirmation



Dispense Medication with KitNo from Confirmation

Unblinding Information Not Visible to Site or Participant

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Beyond the Blocks

IRT can Implement much more than Blocked Randomization: Maximum Tolerated Imbalance (MTI)

Many MTIs can be generated within a List:

- Maximal Procedure
- Asymptotic Maximal Procedure
- Chen's
- Big Stick Procedure
- Blocked Urn

- Like Blocked Randomization – can be generated through statistical software (SAS, R)
- National Institute of Health (NIH) National Cancer Institute's Clinical Trial Randomization Tool - Generates MTI lists:
  https://prevention.cancer.gov/ctrandomization/

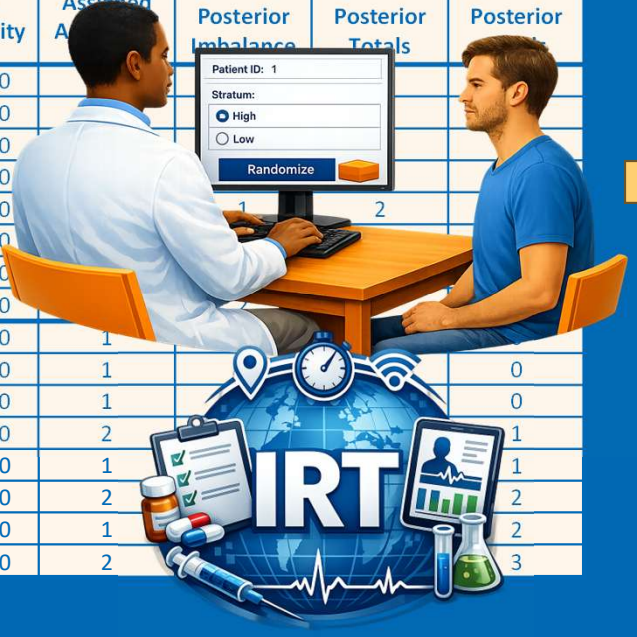
IRT List-Based Implementation Example: Big Stick, MTI 3*

Required Columns Loaded into IRT

RandNo	Stratum	Treat	Patient	DateTime	Arm 2 Probability	Assigned A	Arm 1:Arm 2 Posterior Imbalance	Arm 1 Posterior Totals	Arm 2 Posterior
10001	1: High	Arm 2	1	25-Mar-2026 02:28	0.50000				
10002	1: High	Arm 1			0.50000				
10003	1: High	Arm 2			0.50000				
10004					0.50000				
10005					0.50000		1	2	
10006					0.50000				
10007					0.50000				
10008					0.00000				
20001	2: Low	Arm 1			0.50000	1			
20002	2: Low	Arm 1			0.50000	1			0
20003	2: Low	Arm 1			0.50000	1			0
20004	2: Low	Arm 2			1.00000	2			1
20005	2: Low	Arm 1			0.50000	1			1
20006	2: Low	Arm 2			1.00000	2			2
20007	2: Low	Arm 1			0.50000	1			2
20008	2: Low	Arm 2			1.00000	2			3

Assign Next Available Record in Participant's Stratum

Participant 1 Randomized in IRT



Blinded Confirmation

Dispense Medication with KitNo from Confirmation

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*Example List generated using: Clinical Trial Randomization Tool." The National Cancer Institute's Division of Cancer Prevention, https://prevention.cancer.gov/ctrandomization/. Accessed 1 May. 2026.

Beyond the List - Algorithms

Advanced Randomization Algorithms existed well Before Technology

Response Adaptive Randomization and Minimization were used in clinical trials in 1970s Before Technology, implementing Algorithms had Challenges and Limitations

Modern IRT brings us Beyond the List:

- To effectively Implement Algorithms
- Alleviating these Challenges and Limitations

Implementing RAR without IRT

Initial Randomization

- List / Envelopes Set with Initial Probabilities / Ratio
- Manually Assigns

Challenges / Limitations

- Limited Oversight
- High Human Reliance, etc.
- Human Errors

Participant Response Data

- Site Collects Patient Responses
- Manually Integrates with Rand Data
- Sends to Statistician

Challenges / Limitations

- Manual Burdens for Data Entry & Integrating Rand / Response Data
- Human Errors

RAR Algorithm

- Applies Algorithm / Calculates New Probabilities
- Maps to Block Size / New List

Challenges / Limitations

- Block Size Mapping – Less Precise than Probabilities

Implement New List

- Distribute to Site(s)
- Assign from New List

Challenges / Limitations

- Human Delays
- Human Errors

RAR Assignment Probabilities

What are Assignment Probabilities?

Probability of Participants being Assigned to a Treatment

Treatment	Assignment Probabilities
A	**0.50000**
B	**0.50000**

- 50% Chance of Assignment to A
- 50% Chance of Assignment to B

How are Probabilities Determined?

Initial Probabilities Fixed / Defined in Protocol → Updated by RAR Algorithm Based on Patient Response Data

RAR Probabilities + Mapping

Treatment	Assignment Probabilities
A	0.50000
B	0.50000

Simple:
- Easily Maps to 1:1 ratio / Block Size 4
- Achieves Same as Probabilities

RandNo	Treatment	BlockNo
10001	Placebo	101
10002	Active	101
10003	Active	101
10004	Placebo	101

Treatment	Assignment Probabilities
A	0.75871
B	0.24129

Not as Simple:
- Round / Map to 4:1 ratio, Block Size 5
- Not as Precise as Probabilities

RandNo	Treatment	BlockNo
10001	Active	101
10002	Active	101
10003	Active	101
10004	Placebo	101
10008	Active	101

Treatment	Assignment Probabilities
A	0.54231
B	0.07523
C	0.12478
D	0.25768

Complex:
- Challenging or not possible to map to ratio or acceptable block size
- Rounding can further deviate from expected allocation
- Instead – utilize probabilistic assignment approach with use of Random Numbers

Random Numbers + Probabilities

Random Numbers

List Generated & Loaded Upfront in IRT

SeqNo	Random Number
10001	0.89802
10002	0.65452
10003	0.30436
10004	0.72409
10005	0.69216
10006	0.76218
10007	0.01739
10008	0.86331
10009	0.44058
10010	0.52770

Probabilities

Determine Current Probabilities

Calculate Cumulative Probabilities

Derive Cut-Off Ranges

Treatment	Assignment Probabilities	Cumulative Probabilities	Cut-Off Ranges
A	0.50000	0.50000	0.00001-0.50000
B	0.50000	1.00000	0.50001-1.00000

Assignment Logic

Assign Next Available **Rand Number** to Participant

Compare **Rand Number** to Each Cut-Off Range to Determine Assignment

If **Rand Number** is within **0.00001-0.50000**: Then **Assign A**

If **Rand Number** is within **0.50001-1.00000**: Then **Assign B**

IRT Probabilistic Assignment

Probabilities

Treatment	Assignment Probabilities	Cumulative Probabilities	Cut-Off Ranges
A	0.50000	0.50000	0.00001-0.50000
B	0.50000	1.00000	0.50001-1.00000

Assignment

Assign Next Record → Identify Cut-Off Range → Assign Treatment

SeqNo	Random Number	Participant	Cut-Off Range	Treatment Assigned
10001	0.89802	1	0.50001-1.00000	B
10002	0.65452			
10003	0.30436			
10004	0.72409			
10005	0.69216			
10006	0.76218			
10007	0.01739			
10008	0.86331			
10009	0.44058			
10010	0.52770			

RAR with IRT & Other Systems

Applies Algorithm for Treatment Assignments

Trt Assignment
Data Integration

Electronic Data Capture Collects Participant Response Data

Responses & Trt Assignment
Data Integration

Applies Algorithm for Adjusting Probabilities

- ✓ Able to Utilize Probabilities
- ✓ Real-Time Probabilities Updates
- ✓ No Time Delays

- ✓ Reduces human error
- ✓ Alleviates manual burdens
- ✓ Full audit trail / governance

RAR Probabilities
Data Integration

Minimization without IRT

Differs from RAR –
Probabilities depend on accumulated data
and current state of imbalance

Site Personnel

- Collects Participant Data
- Stratification Factor Levels
- Manually Enters Data
- Calls Statistician to Rand

Statistician

- Manually Perform Imbalance Calculations / Apply Minimization
- Provide Treatment Assignment
- Record Data Manually

Challenges / Limitations

- High Manual Efforts
- Logistical Issues
- Dependent on Statistician's Availability
- Potential Timing Manipulation
- Fragmented record keeping
- Human Error
- Limited Oversight

Minimization with IRT

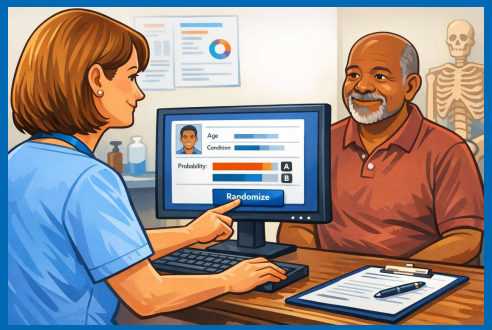
Minimization can be fully implemented within IRT
IRT Logic is programmed to:

- Identify Baseline Details
- Execute Imbalance Calculations
- Determine Probabilities Based on Imbalance Rules
- Calculate Cumulative Probabilities
- Determine Treatment Cut-Off Ranges
- Assign Random Number
- Assign Trt

Participant	Age	T2DM	MATH!	Prob A	Prob B	Cumulative Prob A	Cumulative Prob B	Trt A Cut-Off Range	Trt B Cut-Off Range	Random Number	Treatment
1	<60	Yes		0.50	0.50	0.50000	1.00000	0.00000-0.50000	0.50001-1.00000	0.1234	A
2	<60	Yes		0.20	0.80	0.20000	0.80000	0.80001-1.00000	0.00000-0.80000	0.5612	B
3	<60	No		0.50	0.50	0.50000	1.00000	0.00000-0.50000	0.50001-1.00000	0.8913	B

Minimization with IRT

IRT unifies algorithm logic, execution, and a full audit trail into a single governed system.

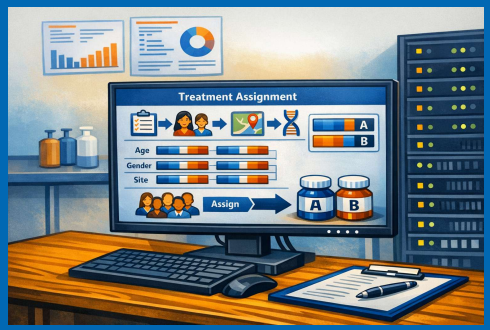


Automated Data Entry

✓ High Quality

Real-Time Minimization Algorithm Execution

✓ No Human Reliance



Immediate Treatment Assignment

✓ No Time Delays

Full Audit Trail

✓ Governance

Modern IRT: Randomization Functionality

In Addition to a World of Randomization Methodology Possibilities with IRT

A World of Randomization Capabilities with IRT Functionality

Specific Purposes / Protocol Objectives	Adaptive Design Features
• Replacement Randomization • Re-Randomization • Multi-Step Randomization • Multi-Phases / Multi-Stages • Capping (e.g., Cohort, Strata, Subgroup, Treatment) • Forced Randomization (Medication Management)	• Cohort Management / Dose Finding / Dose Optimization • Adaptive Trial Designs / Complex Innovative Designs / Master Protocols • Eligibility Controls: (e.g., Site, Participant, Protocol Approval) • Treatment Adaptations (e.g., Add New / Pause / Reopen / Close Adjust Ratios or Probabilities)

Modern Day Challenges / Recommendations

Lack of Knowledge / Awareness	Build Knowledge	Resources out there to learn more! Randomization Working Group: https://randomization-wg.org/ https://www.linkedin.com/groups/14441166/
Vendor Capabilities / Expertise	Assess Vendors	Check vendor capabilities (if able to implement methodology) Check Biostats Expertise of methodology implementation (through IRT vendor, in house, or external Biostats vendor)
Regulatory Concerns	Engage	Keep up to date on Regulatory guidance Engage with Regulatory early / reach out with questions Ensure Biostats support with Regulatory Knowledge
Timelines / Budget	Plan	Start discussions early with stakeholders / vendors • Determine if any additional time is needed • Determine if any additional costs are needed • Account for additional efforts within timelines and budget

Conclusion

With Modern IRT and Effective Planning

We have a World of Randomization Possibilities!