MRC-NIHR Trials Methodology Research Partnership: Webinar recording

Randomisation: Current practice for method selection

Presented, on behalf of the UK Trial Managers' Network, by:

Cydney Bruce (Nottingham University)

12 December 2023

The slides are available below.

For any queries, please contact uktmn@nottingham.ac.uk

https://youtu.be/vwu5tw6MmrE

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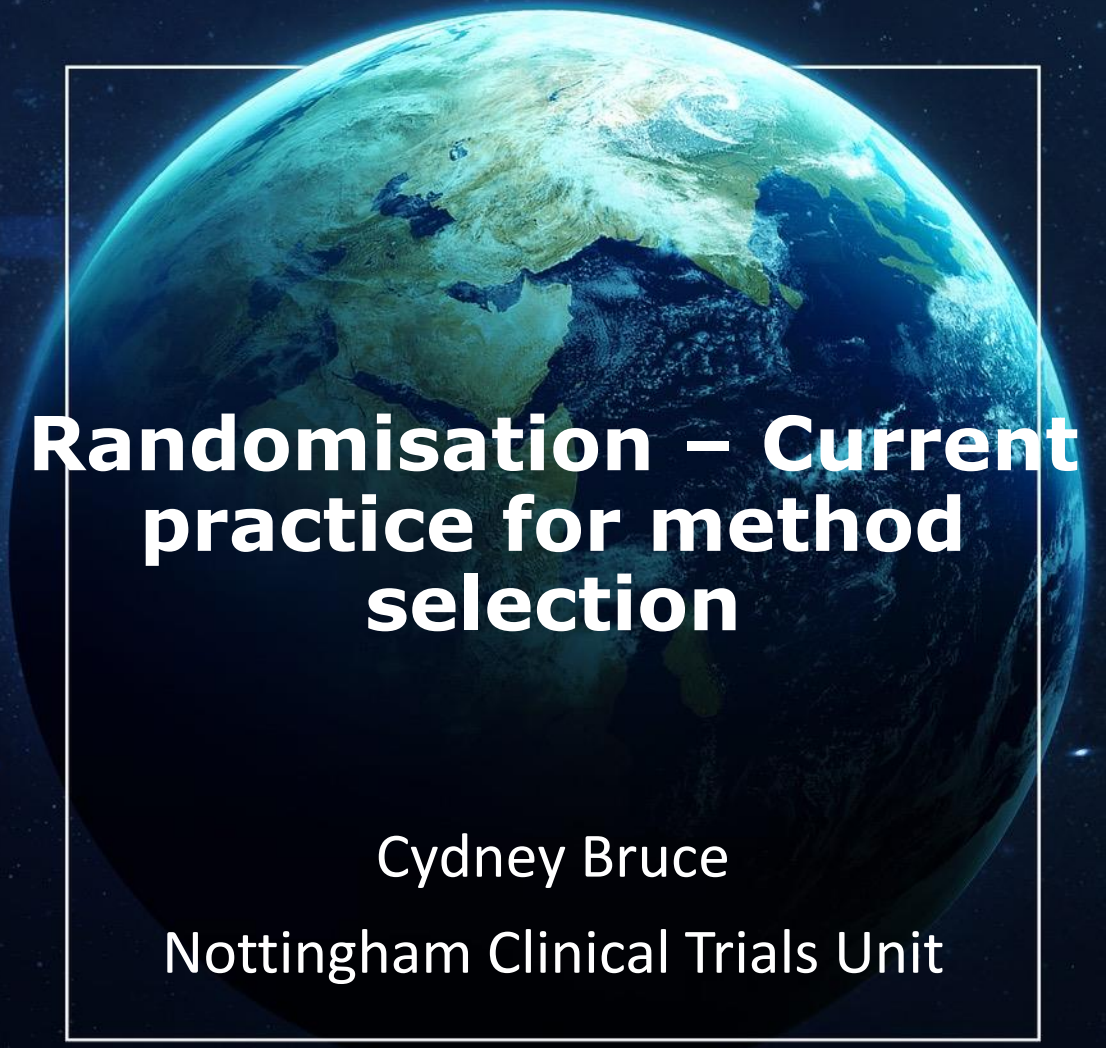


Randomisation – Current practice for method selection

Cydney Bruce

Nottingham Clinical Trials Unit

Trials Methodology TMRP Research Partnership

Acknowledgements

Supervisory Team

Christopher Partlett, NCTU

Reuben Ogollah , NCTU

Alan Montgomery , NCTU

Additional Researchers

Kirsty Sprange, NCTU

Mais Iflaifel, NCTU

Contents

1. Background of randomisation
2. Previous work
3. Researcher Focus Groups
4. What's Next
5. A simulation Study

Background of randomisation

Study motivation

Balance vs predictability (?)

Common randomisation methods

Study motivation

Randomised Controlled Trials (RCTs) are considered the gold standard when evaluating interventions.

Many methods exist: Simple, block, stratification, minimisation.

Methods perform differently in different trial designs, but there is a lack of consensus on which methods are most appropriate.

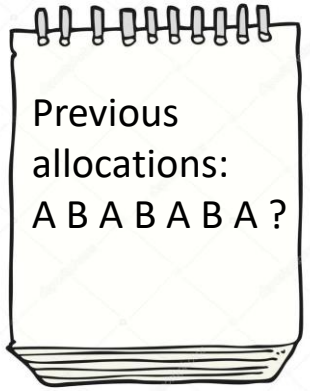
Balance vs Predictability

Balance

Group Size Imbalance

Characteristic Imbalance

Predictability



Randomisation

Simple

Block

Example for a block size of 4:

Dice roll	Block
1	AABB
2	ABAB
3	ABBA
4	BAAB
5	BABA
6	BBAA

2 4 3 6

ABAB BAAB ABBA BBAA

Randomisation

Stratification

		Age	
		< 50	> 50
Sex	Male	A	B
	Female	C	D

Next Allocation: Male / < 50

A	B	C	D
1	2	1	2
2	1	1	2
2	2	2	1
1	1	2	1

Minimisation

		Treatment	
		1	2
Sex	Male	A	E
	Female	B	F
Age	< 50	C	G
	> 50	D	H

Next Allocation: Male / < 50

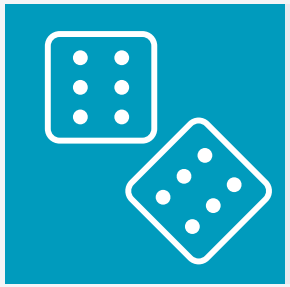
Treatment 1: A + C
Treatment 2: E + G

Allocate to smallest total!

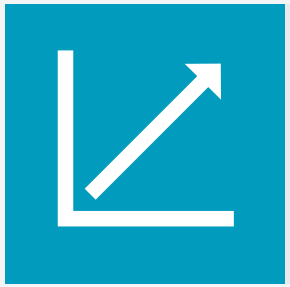
Systematic review of RCTs

A summary

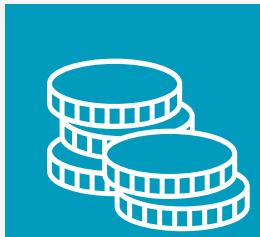
A systematic review of RCTs



Identify commonly used randomisation methods



Identify aspects of trial design associated with choice of method



Compare choice of method with a similar review of trials in 2014

THE LANCET

JAMA
The Journal of the American Medical Association

thebmj

The NEW ENGLAND JOURNAL of MEDICINE

NIHR | National Institute for Health Research

385 papers appropriate for review
123 from The Lancet
85 from JAMA
92 from NEJM
20 from BMJ
65 from NIHR HTA

348 individually randomised trials

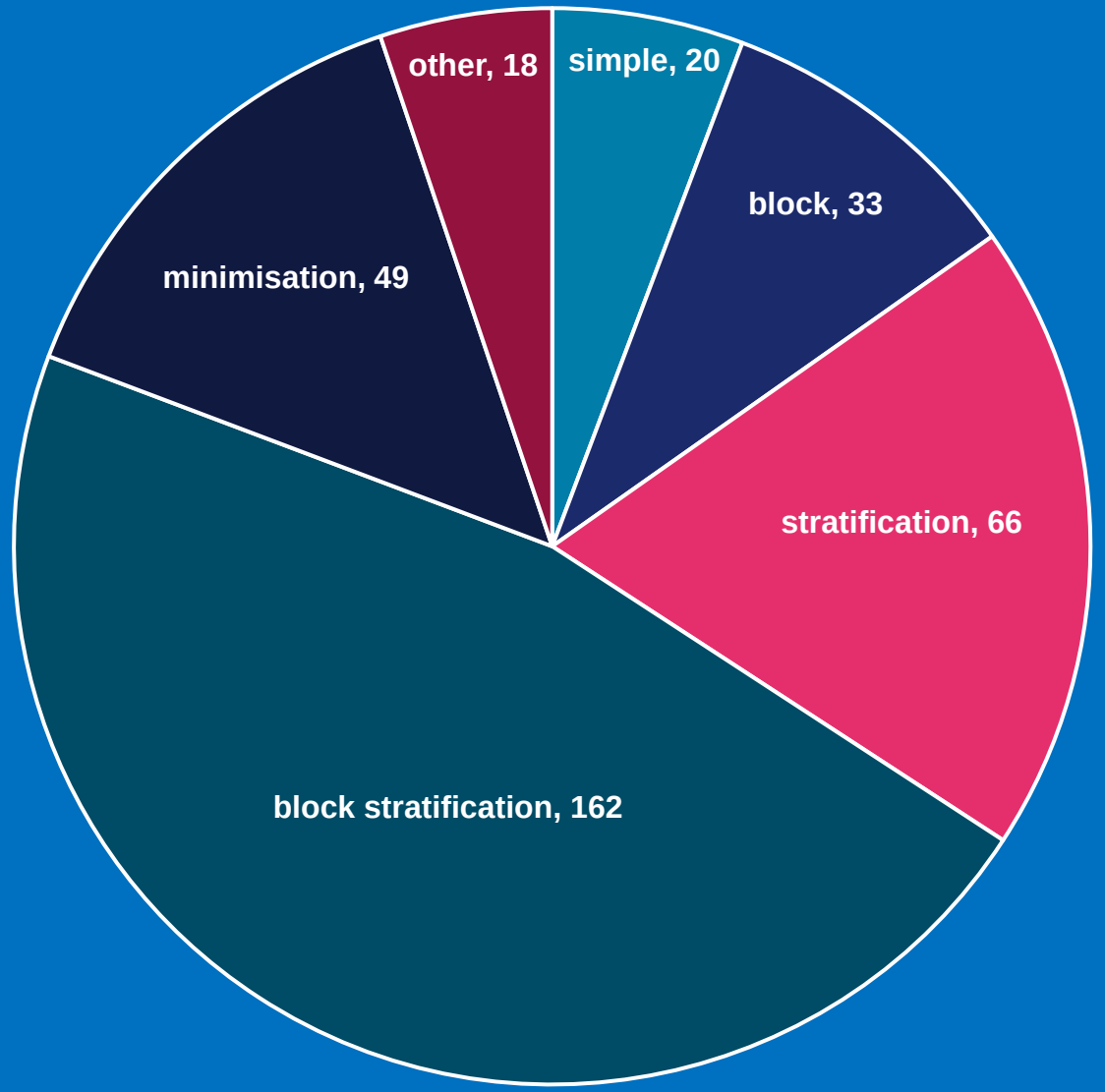
Randomisation method use in 2019

Randomisation method use in individually randomised studies in BMJ, NEJM, JAMA, The Lancet and the NIHR HTA library in 2019

95% of trials used simple, block, stratification or minimisation.

47% of trials used block stratification

67% of trials used stratification in their randomisation



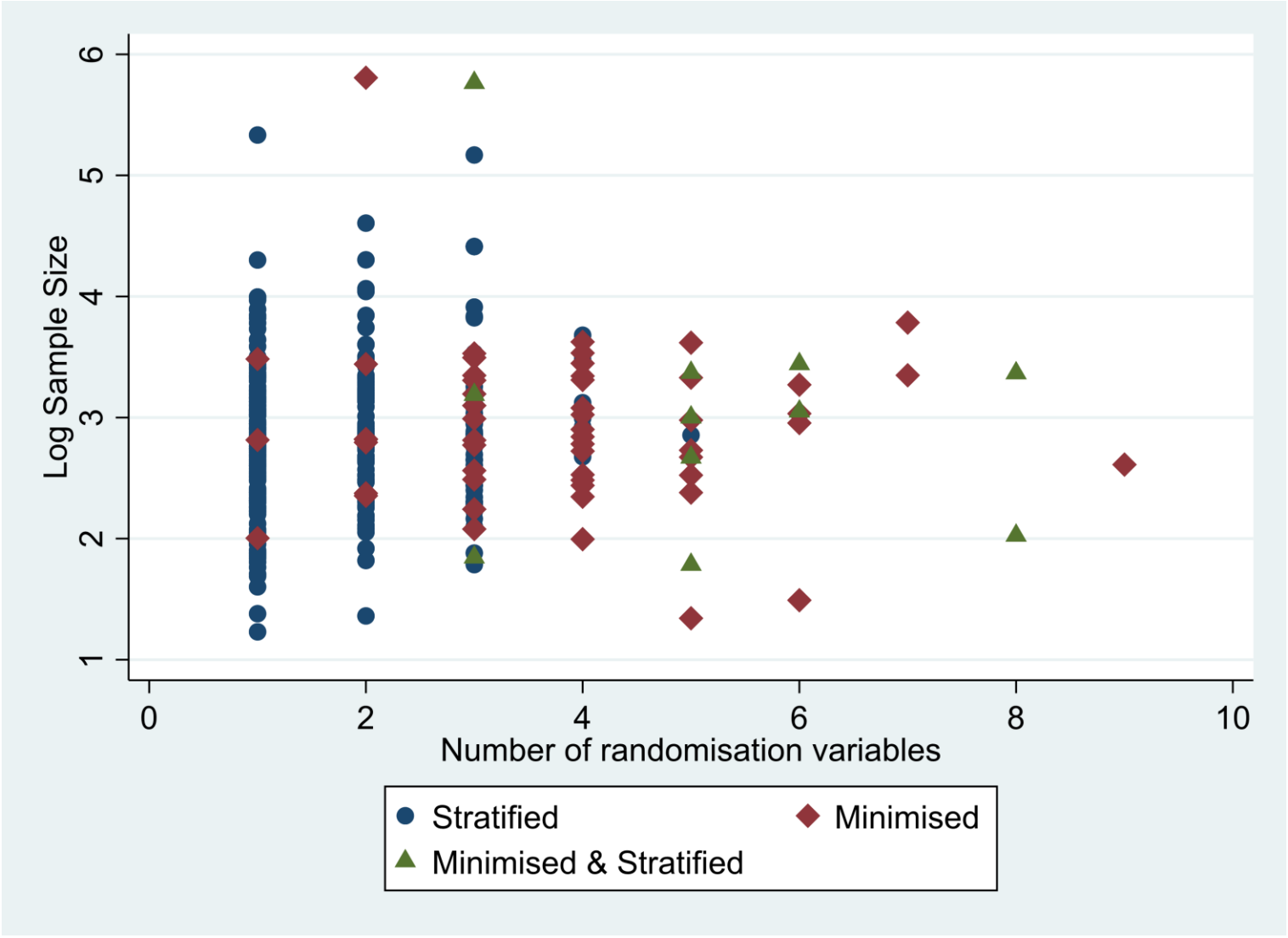
Other includes:
6 – stratified minimisation
12 - Other (including 4 dynamic/adaptive, 3 Bayesian, a big stick and 1 biased coin)

Associated study characteristics

		Total (n = 330)	Simple (n = 20)	Block (n = 33)	Stratified (n = 66)	Block Stratified (n = 162)	Minimisation (n = 49)
Number of Centres	**Single Centre**	27 (8)	4 (20)	5 (15)	4 (6)	13 (8)	1 (2)
	2-10	81 (25)	4 (20)	11 (34)	10 (15)	51 (31)	5 (10)
	11-25	65 (20)	7 (35)	4 (12)	4 (6)	40 (25)	10 (20)
	26-50	45 (14)	1 (5)	4 (12)	13 (20)	13 (8)	14 (29)
	51-100	39 (12)	1 (5)	4 (12)	11 (17)	15 (9)	8 (16)
	101+	70 (21)	3 (15)	5 (15)	24 (36)	27 (17)	11 (23)
	Median (IQR)	22 (7, 86)	15 (4, 29)	11 (4, 51)	61 (17, 153)	16 (6, 53)	42 (14, 90)
	Mean (SD)	72 (144)	59 (127)	121 (324)	111 (137)	51 (97)	62 (64)
Size of Study	**< 200**	60 (18)	6 (30)	10 (30)	15 (23)	23 (14)	5 (10)
	201-1000	159 (48)	9 (45)	15 (46)	26 (39)	86 (53)	24 (49)
	1001-10,000	103 (31)	4 (20)	6 (18)	24 (36)	49 (30)	20 (41)
	10,001+	8 (3)	1 (5)	2 (6)	1 (2)	4 (3)	0
	Median (IQR)	648 (241, 1468)	354 (133, 1445)	417 (154, 782)	690 (225, 1672)	653 (253, 1326)	694 (334, 2135)
	Mean (SD)	1702 (3835)	1493 (2910)	1845 (3980)	1844 (3275)	1748 (4581)	1346 (1343)

Associated Study characteristics

Sample size vs Number of variables



Summary of results

- These 4 randomisation methods make up 95% of method usage in these 5 journals
- Stratification is the most commonly used randomisation method
- Number of centres, sample size and number of randomisation variables are all associated with choice of method

Focus Group Results

Aims

Methods

Results

Conclusion

Strengths and limitations

Focus groups with researchers

Gain a deeper insight into how the randomisation method is currently selected in trials

Identify randomisation method features considered most important to measure by researchers.

Research Aims

Methods – Topic guide development

Section 1

This section of the discussion is aimed specifically at better understanding the motivations behind current practice when selecting randomisation methods.

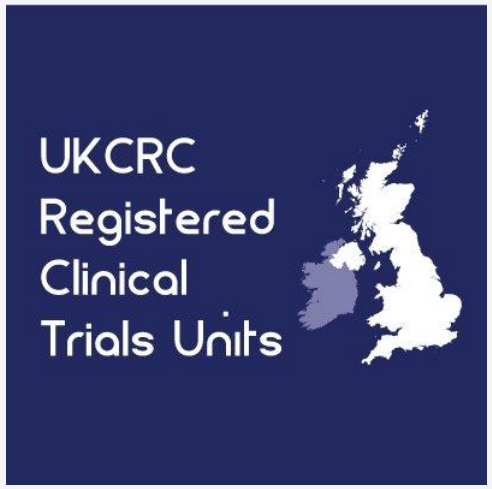
1. **How do you currently select a randomisation method?**

   For instance:
   - Is there a standard preferred method?
     - Does clinical area affect this?
     - Or organisation policy?
   - What roles are involved in this decision process?
     - Just statisticians or does IT/ the trial team have input into this
   - Do unit resources affect this choice?
     - Would staffing issues/expertise lead to less complex method selection?
   - Are there specific circumstances where each method is used?
     - For example does study design affect this choice?
       - Sample size
       - Number/type of prognostic factors
       - Number of centres
       - Parallel or multiarm
       - Individually or cluster randomised
       - Blinded or unblinded (who is blinded)

2. **Do you have any specific opinions with respect to certain methods?**

   For instance:
   - Are simpler methods more effective?
   - Do you prefer to include balancing factors?
   - What are your views on Response Adaptive/Bayesian Adaptive methods?
     - (Response adaptive methods are a group of methods where the ratio of participants assigned to each of the outcomes is adjusted based on interim data obtained from the trial.)

Methods – Recruitment



For and on behalf of Cydney Bruce, Nottingham CTU

Dear All,

I am currently conducting a PhD at the University of Nottingham within the Nottingham Clinical Trials Unit. My research focuses on evaluating the different methods of allocating participants to treatments/interventions during a randomised controlled trial.

As part of this research, I want to conduct focus groups with researchers who are involved in the randomisation process with two main aims in mind:

- To understand how the decision of which randomisation method to use is currently made
- To identify the most important features of the method to evaluate the performance of the methods.

We are seeking out researchers working on clinical trials who would be willing to share their opinions on these topics and fall into the following groups:

- Statisticians
- IT/programmers
- Other trials researchers (e.g., trial managers or CIs)

More information is given in the attached participant information sheet.

The provisional plan is for the meetings to happen remotely (via Microsoft Teams) in May/June 2022.

Methods – Conduct

- Focus groups had 4 – 8 participants
- Held on teams
- During recruitment, information on role and institution was collected so that focus groups could be built with a variety of roles from different CTUs
- We went through the topic guide, but allowed participants to move direct the conversation and only intervened if conversation moved away from topic guide topics
- All focus groups were led be myself and attended by at least one other researcher who took notes on key themes they noticed coming through

Methods - Analysis

- All scripts were printed and underwent an open analysis, where manuscripts were reviewed, and topics and ideas grouped. From here the main topics were identified and full thematic analysis was conducted in NVivo.

- For many results, findings were grouped based on how many institutions or participants discussed a topic or had a general thought to allow us to get a good idea of how many participants held specific views.

Results – The Focus groups

Table 1 – The roles of participants and number of unit they came from summarised by focus group.

Role	Pilot FG (n = 6)	FG 1 (n = 5)	FG 2 (n = 9)	FG 3 (n = 5)
Statisticians	4	4	7	5
IT/Programmers	2	0	2	0
Other	0	1	0	0
Number of CTUs represented	4	5	8	5

Results – The themes

- **Question 1** – Selection of randomisation method
- **Question 2** – Opinions of the different randomisation methods
- **Question 3** – Desirable features of a randomisation method
- **Question 4** – Measuring/quantifying features of a randomisation method

Results – Current randomisation method selection

Table 2: Summary of randomisation method selection themes

Sub-theme [a]	FG 1 [b] (n=6)	FG 2 [b] (n=5)	FG 3 [b] (n=9)	FG 4 [b] (n=5)	Total [b] (n = 25)
Unit Standard	4	2	1	3	10
Expertise	1	1	1	1	4
Cost and time	2	1	0	1	4
Study design	3	2	3	2	10
Sample size	3	1	1	1	6
Number of variables	3	1	1	1	6

Related Quote:

"…there's like a default institutional sort of preference. The last place I worked there was also a default institutional preference as well for minimisation."

(Programmer 3)

Results – Current randomisation method selection

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Related Quote:

"We have like an in-house system that we use so it doesn't really make any difference. Obviously at the start like when it was first created there was, you know, how are we going to design minimisation."

(Statistician 8)

Results – Current randomisation method selection

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Related Quote:

"I guess there might be an element of cost that we need to consider because obviously minimisation would cost more"

(Statistician 13)

Results – Current randomisation method selection

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Related Quote:

"You look at the trial design and talk to the investigators"

(Statistician 7)

Results – Current randomisation method selection

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Related Quote:

"You're going to base it on your sample size. And also like, the number of factors that you wanted to cater for"

(Statistician 15)

Results – Current randomisation method selection

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[a] Note that categories are not mutually exclusive. Some participants that discussed having a unit standard also discussed a personal view that study design should be considered.

[b] Each cell denotes the number of participants who mentioned this theme during focus groups.

Related Quote:

"I tend to question protocols when I see more than two variables and the word stratification, I think why are you doing this basically"

(Programmer 2)

Results – Current randomisation method selection

“I would echo that disparity between what happens in practice and what happens in reality.”

(Statistician)

I've tried to engage other members of trial teams when designing trials so that designing randomisation is very much a multidisciplinary process”

(Statistician)

Results – Method opinions

Table 4: Summary of concerns regarding randomisation methodology

Method	Unit standard [a] [c]	Negative opinions [b]	Method concerns
Simple randomisation	0	6	Balance not ensured
			Non statistical team members uncomfortable with the method
			Difficult to validate in early stages
Stratified block randomisation	5	5	Does not ensure balance if number of strata is too large
			More predictable sequence
Minimisation	3	5	May lead to overcomplicated designs
			Can balance known predictors of the primary outcome but not those that are unknown
			More predictable sequence

[a] number of participants who reported the method was a standard at their unit
[b] number of participants who reported concerns
[c] Two researchers reported using simpler methods – however this was not defined specifically as simple randomisation hence was not counted here.

ICH E9 Statistical Principals

2.3.2 Randomisation

Randomisation 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, randomisation helps to avoid possible bias in the selection and allocation of subjects arising from the predictability of treatment assignments.

The randomisation 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 pre-planned assignment of treatment, or treatment sequence, to subject should be clear. Different trial designs will require different procedures for generating randomisation schedules. The randomisation schedule should be reproducible (if the need arises).

Although unrestricted randomisation is an acceptable approach, some advantages can generally be gained by randomising 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 multicentre trials (see Glossary) the randomisation procedures should be organised centrally. It is advisable to have a separate random scheme for each centre, i.e. to stratify by centre or to allocate several whole blocks to each centre. More generally, stratification by important prognostic factors measured at baseline (e.g. severity of disease, age, sex, etc.) 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 randomisation has been stratified should be accounted for later in the analysis.

The next subject to be randomised into a trial should always receive the treatment corresponding to the next free number in the appropriate randomisation schedule (in the respective stratum, if randomisation is stratified). The appropriate number and associated treatment for the next subject should only be allocated when entry of that subject to the randomised part of the trial has been confirmed. Details of the randomisation that facilitate predictability (e.g. block length) should not be contained in the trial protocol. The randomisation 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 randomisation 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 randomisation 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 contact. This in turn permits additional checks of eligibility criteria and establishes entry into the trial, features that can be valuable in certain types of multicentre trial. The usual system of pre-packing and labelling drug supplies for double-blind trials can then be followed, but the order of their use is no longer sequential. It is desirable to use appropriate computer algorithms to keep personnel at the central trial office blind to the treatment code. The complexity of the logistics and potential impact on the analysis should be carefully evaluated when considering dynamic allocation.

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ICH E9 Statistical Principals

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"The use of more than two or three stratification factors is rarely necessary, is less successful at achieving balance and is logistically troublesome."

"Deterministic dynamic allocation procedures should be avoided and an appropriate element of randomisation should be incorporated for each treatment allocation."

Results – Current randomisation method selection

Table 3 – Model for randomisation method selection most considered.

Characteristic		Method
Sample Size	> 100 / > 1000	Simple
	< 100 / < 1000	Consider restrictive methods
Number of variables	< 3	Block Stratified
	> 3	Minimisation

Results – Important method features

Table 5: Participant opinions of whether balance or unpredictability is most important.

Feature	Number of participants who discussed a preference [a]
Balance	1
Unpredictability	7
Both	1
Neither	2

[a] Note – other participants did not specify a preference during discussions.

Results – Important method features

Table 5: Participant opinions of whether balance or unpredictability is most important.

Feature	Number of participants who discussed a preference [a]
Balance	1
Unpredictability	7

[a] Note – other parti

"…there's obviously ways for us to prepare analysis for imbalance, but it's much harder to address the potential bias from the allocation concealment, or lack of, from predictability." (Statistician)

Results – Important method features

Table 6: A summary of logistical issues relating to methods

Feature	Description	Number of participants who discussed this
Time and Money	The resource cost of implementing the method. Trial funding can be limited and so this may exclude more costly randomisation methods.	4
Programming expertise	The programming expertise required to implement the method. For example, dynamic methods (such as minimisation) require integration with the trial database.	6
Statistical expertise	The statistical expertise required to implement the method. For example, implementation of adaptive randomisation methods requires specialist statistical knowledge.	6

Results – Measuring method features

“I think, balance might be the tougher one to quantify, because are you going to measure it on relative scales or absolute scales? Are you measuring differences? Are you measuring each variable in your table one in isolation, or are you assuming they're correlated and looking at some multivariate measure?”
(Statistician 10)

“…the horse I will back is the one that's had the less allocations. So if you've seen seven of A and six of B, I’m accepting this only works if it's open label, you will always get more than 50% accuracy by saying, well, the next one is more likely to be B.”
(Statistician 11)

Conclusion

Main Findings

1. Randomisation methods are chosen either based on **method preference** or based on **study characteristics** including sample size.

2. Researcher's opinions of methods are in line with EMA's guidance – even when not followed in practice.

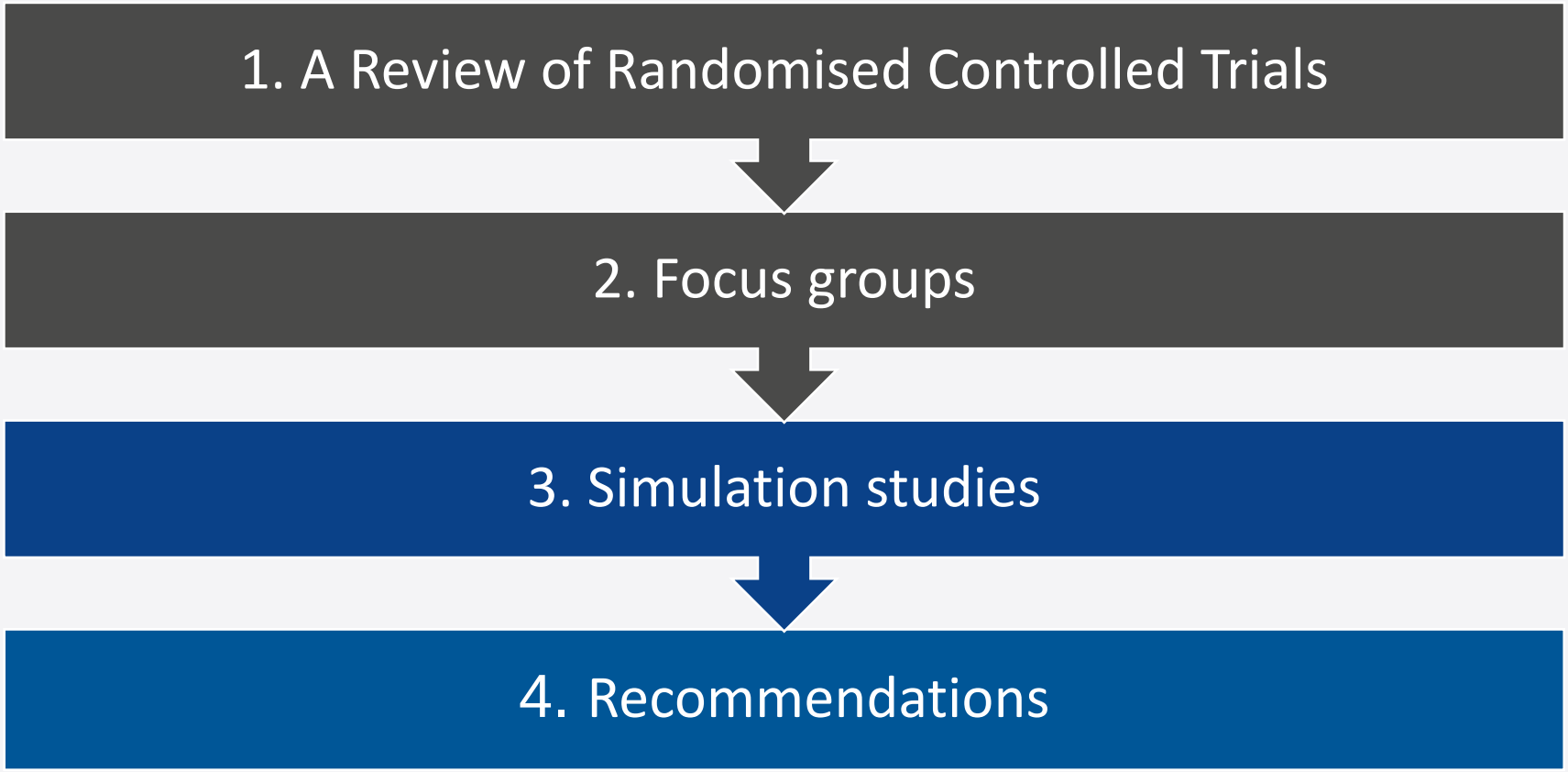
3. Balance and predictability are considered the most important features of a randomisation method, although opinions on their relative importance is varied.

4. Although researchers consider balance and predictability important in trials, they are not measuring these features in practice.

Strengths and limitations

Strengths	Limitations
Variety of levels and roles.	Only one participant not a programmer or statistician.
All focus groups attended by at least 2 researchers.	Coding completed by 1 researcher.

What is next…


1. A Review of Randomised Controlled Trials
2. Focus groups
3. Simulation studies
4. Recommendations

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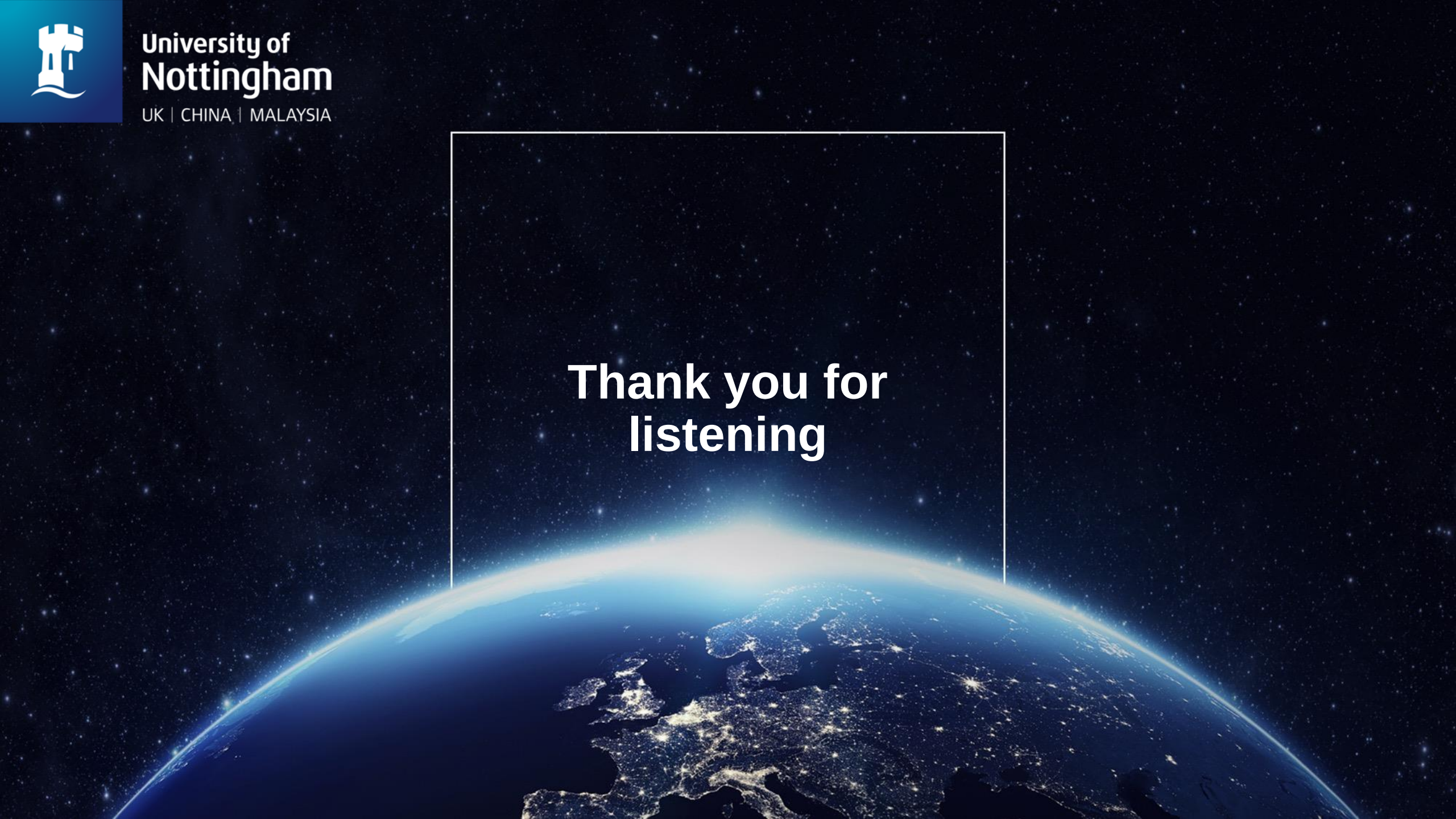
Thank you for listening



References

@CydneyLBruce

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