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PoINT: Patient and public Involvement in Numerical aspects of Trials

Guide to Trial's Numerical Aspects

This guide contains information and explanations about **twelve key numerical aspects of trials**. It was prepared as part of the PoINT project led by Dr Beatriz Goulao at the Health Services Research Unit, University of Aberdeen. The project team included Dr Katie Gillies, Professors Craig Ramsay and Marion Campbell, and public partner Richard Caie. The original aim of the guide was to help support a prioritisation exercise focused on the twelve numerical aspects covered here. The guide can also be used to support discussions with public partners around the numerical aspects.

What is a numerical aspect of a trial?

We defined numerical aspects as any quantifiable or measurable aspect of a trial and/or their interpretation and dissemination.

How were these twelve numerical aspects selected?

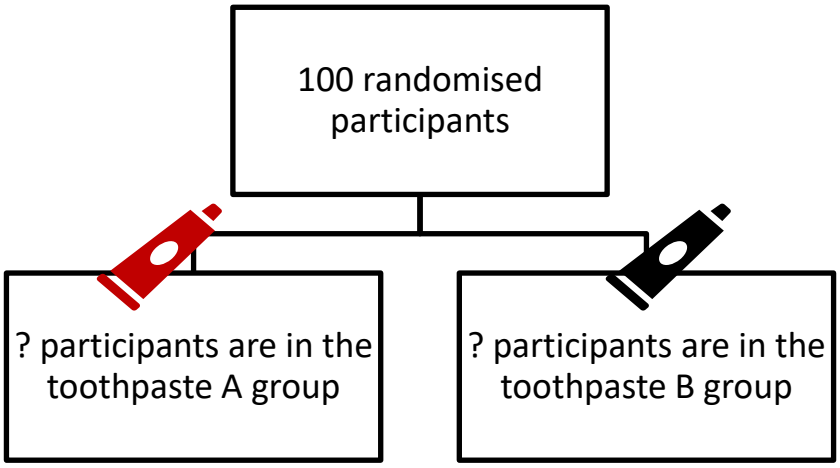
Through a review of the literature along with expert discussion. This is not necessarily an exhaustive list of all possible numerical aspects of trials that patients can be involved in.

What aspects are covered in the guide?

A. Target differences (Clinically meaningful difference, Non-inferiority margins)
B. Expected contamination
C. Clinical equipoise
D. Risk / benefit trade-off
E. Randomisation allocation ratio
F. Discussions about representativeness of sample
G. Recruitment & retention projections
H. Stop / go criteria
I. Data monitoring committee data discussions
J. Estimations of observed data when data is missing
K. Select data to go into health economics models
L. Interpretation of trial results and their dissemination

Motivating example to discuss numerical aspects

We are introducing a fictional trial to illustrate what each of the numerical aspects mean. Our fictional trial aims to test whether a strong **toothpaste A** improves dental pain, measured from 1 (pain free) to 10 (very painful) compared with a weaker **toothpaste B**. In this trial we aim to recruit 100 participants.



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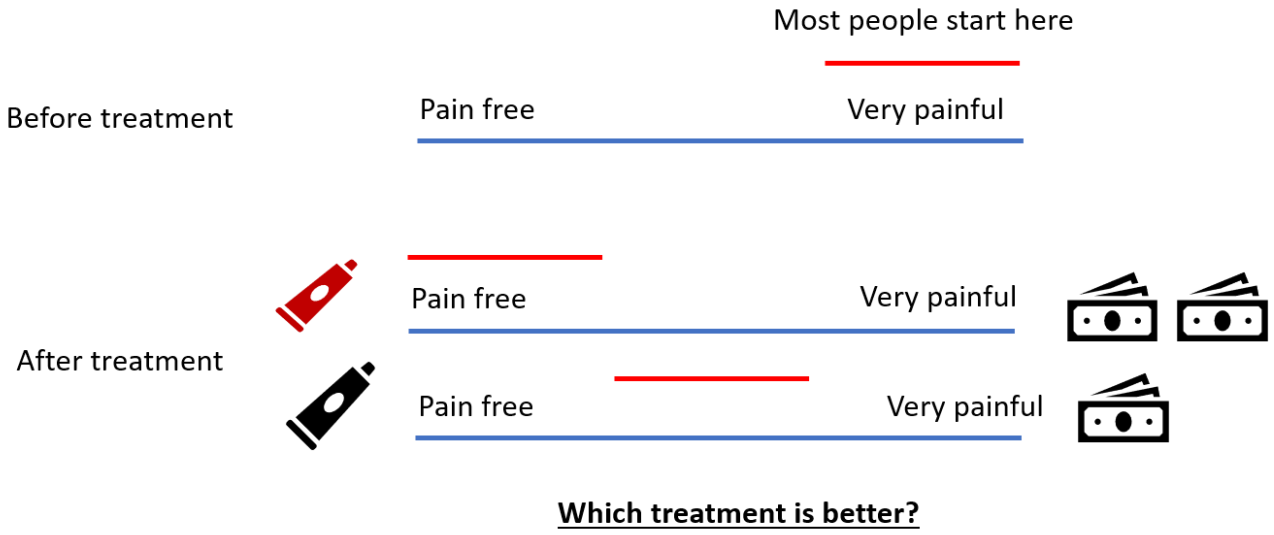
A: Target differences



Below, we present two examples of target differences used in trial design.

A1: Clinically meaningful difference

- **What does it mean?**

This is the difference that will make researchers and clinicians conclude a treatment really is better than another treatment, i.e. it will lead to a change of treatment.

- **How could patients be involved?**

Patients could help us define the clinically meaningful difference, so it is acceptable to them.

- **Example**

To decide if the toothpaste A is any better than the toothpaste B, we will have to define a meaningful difference in pain. For example, the meaningful difference could be a difference of 2 points in a pain scale from 1 to 10. If participants in the toothpaste A group had a score of 3 points in the pain scale and participants in the toothpaste B group had a score of 5.5 points, we decide that toothpaste A is a better treatment. Should we involve patients in deciding how big the difference needs to be to conclude toothpaste A is better than toothpaste B?

A2: Non-inferiority margins

- **What does it mean?**

A “normal” clinical trial tries to find out whether a new treatment is better than the current treatment.

A non-inferiority trial tries to show the new treatment is not worse than the current treatment by a defined margin (the non-inferiority margin). The trial doesn't need to find out that the new treatment is better than the current treatment. The non-inferiority margin will define whether a new treatment is considered to be "good enough" to replace the current treatment. The new treatment may come with other benefits, such as being cheaper or having less adverse events.

- **How could patients be involved?**

Patients could help us define the non-inferiority margin, so it is acceptable to them.

- **Example**

If toothpaste A is potentially better than toothpaste B, but more expensive and likely to cause tooth stains, we might need to decide whether we are willing to accept a cheaper toothpaste without side effects that is not worse than the stronger toothpaste by a pre-defined margin. For example, toothpaste B can be worse than toothpaste A by 5 points in the pain scale to be considered acceptable given its other advantages. Should we involve patients in deciding how big the non-inferiority margin needs to be to conclude toothpaste B is not worse than toothpaste B?

B: Risk/benefit trade-off

- **What does it mean?**

In a clinical trial, we usually test to find out whether a treatment gives more benefit than another. However, there could be risks or burdens to the patient there are different depending on the treatment. When trying to consider both benefits and risks of a treatment, we talk about assessing a risk/benefit trade-off.

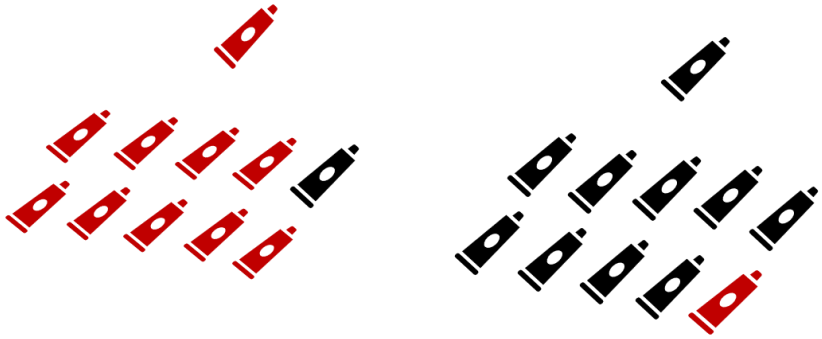
- **How could patients be involved?**

Patients could be asked to help decide the frequency and intensity of side effects they are willing to accept for added benefit of one treatment over another.

- **Example**

Toothpaste A and toothpaste B have known side effects, but patients might be willing to accept some side effects for more treatment benefit. For example, either toothpaste can lead to pain-free teeth in patients for 1 month, 3 months, 6 months; but they will result in tooth stains (mild, moderate, severe) and bleeding gums (mild, moderate, severe). Should patients be involved in deciding how acceptable side effects are, to achieve a pain-free mouth for longer?

C: Expected contamination



- **What does it mean?**

People in the control group unintentionally take the treatment or people in the treatment group unintentionally do not. For example, participants in the toothpaste A group might share a home with participants in the toothpaste B group. If they use each other's toothpaste we have treatment contamination.

- **How could patients be involved?**

Patients could help understand and quantify how likely contamination is to happen.

- **Example**

In our fictional trial, we might decide to allow for 10% contamination to happen. This means that 10% of participants allocated to toothpaste A may receive toothpaste B and vice-versa. This will have an impact on the trial conduct and on how many participants are recruited to take part. But who should be involved in deciding if 10% contamination is a reasonable expectation?

D: Clinical equipoise

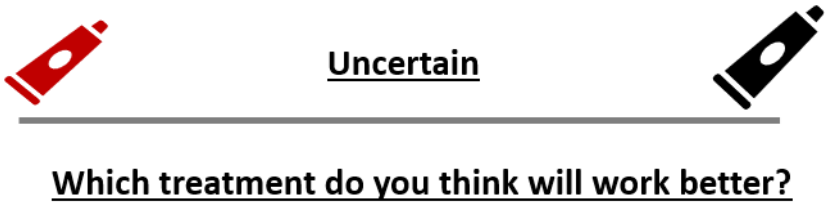
- **What does it mean?**

A state of uncertainty in terms of what treatment option is best. If patients or clinicians have a strong preference for a treatment over another, then a trial might not be feasible and it could be a waste of time and resources.

- **How could patients be involved?**

By providing us with information about how acceptable it is to be randomised to a treatment over another and if they truly believe there is uncertainty about which one is beneficial.

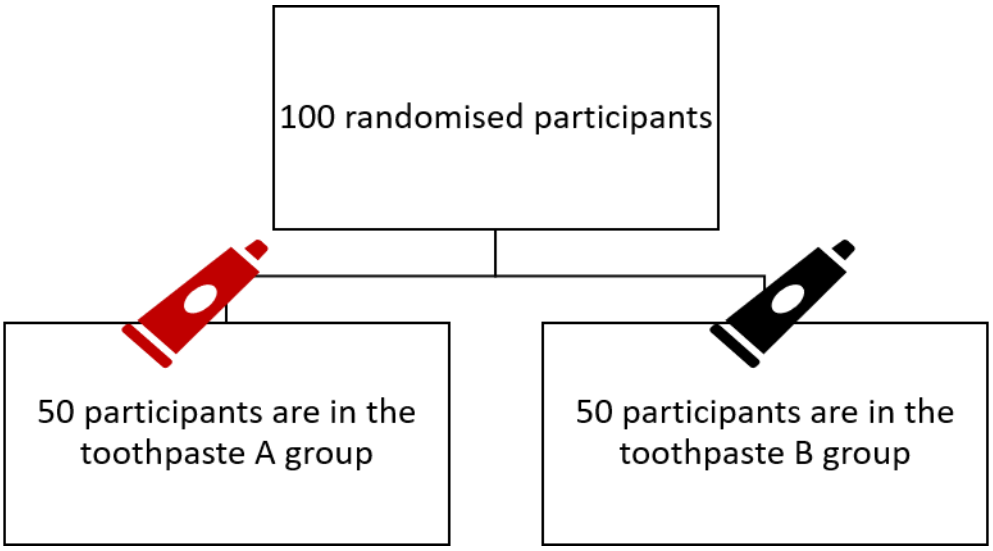
- **Example**



Which treatment do you think will work better?

In our fictional trial, we need to find out whether patients and dentists have a strong preference for toothpaste A or B before the trial starts. Patients and dentists can therefore be asked about their level of certainty about which of the two toothpaste options in different pain scenarios is their preferred option. To do this, respondents can be presented with a linear scale with a treatment option at each end of the scale. The scale is centred on ‘‘completely undecided’’.

E: Randomisation allocation ratio



- **What does it mean?**

Random assignment to treatment arms is usually done on a 1:1 basis which means the same number of people will get randomised to the treatment and the control (as seen in the Figure above). However, trials can use randomisation allocation ratios where the number of patients receiving a treatment exceeds the number of patients in the control arm (called “unequal allocation ratios”, for example 2:1 where the treatment arm has double the number of participants compared with the control arm). Unequal allocation ratios need to recruit more people to reach the same level of certainty about whether a treatment is better than a control. The main reason presented to do them is to facilitate recruitment, although if there is clinical equipoise that should not be the case.

- **How could patients get involved?**

Patients could be involved in defining the allocation ratio and its rationale if it is different from 1:1.

- **Example**

In our fictional trial, we are interested in ensuring efficiency but want to make sure the allocation ratio does not affect patients’ perceptions of the trial and their willingness to take part. Should we involve patients in the discussion of the randomisation allocation ratio?

F: Representativeness of sample

	Trial participants – n(%)	Overall population – n(%)
Dental health insurance		
Yes	35	50
No	65	50
Ethnicity		
White	80	70
Black	5	15
Asian	5	5
…		

- **What does it mean?**

The people included in research studies and trials might not be representative of the population that has the disease or would be eligible for preventive treatment. In cancer clinical trials, for example, those with health insurance and from higher socio-economic backgrounds can be over-represented, while older patients, ethnic minorities and so-called hard-to-reach groups (often with higher cancer mortality rates) are under-represented. This limits the ability to generalize the results of the trials to all those with cancer (Hannigan, 2018).

- **How could patients get involved?**

Patients can help understand what characteristics should be measured to assess representativeness and contribute to increasing awareness and participation of under-represented groups in trials and therefore help to achieve a population-representative sample.

- **Example**

In our fictional trial, dental health insurance and ethnicity were considered important characteristics to monitor in our sample. Descriptive statistic summaries and graphs are used to present the distributions of the characteristics in the sample. The numbers are discussed to ensure the sample is representative and, if it isn't, when and how to intervene if possible. Should patients be involved in these discussions and in ensuring the trial sample is representative and diverse?

G: Recruitment and retention projections

- **What does it mean?**

Recruitment is the process through which an individual is recruited as a study participant. Participant retention is the engagement of the participant in the research study. For example, in the toothpaste trial we need to find out pain levels at the end. Participant retention is, therefore, the number of participants that provide that information to the trial team. Both recruitment and retention figures (i.e. how many trial participants researchers expect to recruit and how many they expect to continue their engagement with the trial until the end of the trial) are projected at the design stage and updated throughout the trial conduct.

- **How could patients be involved?**

Patients could contribute to the discussions by giving their own estimations of how likely they think centres are to recruit and retain study participants. As part of being involved in those discussions, patients could also help the research team understand emerging recruitment and retention data and assess whether there is need to intervene to improve it.

- **Example**

The toothpaste trial will need to plan how long it will take to recruit 100 participants and monitor recruitment, as it is happening, to ensure there are no issues. If there are delays, the trial team needs to interpret when and how to act. The toothpaste trial will also need to project how many participants will provide their pain measure and monitor those numbers and react to them. Should patients be involved in the estimation of recruitment and retention figures, as well as in their discussion during trial conduct?

H: Stop / go criteria

- **What does it mean?**

Often trials include specific criteria to decide on whether they should move forward, i.e. collect all data as planned or stop due to unfeasibility of recruitment, treatment delivery or due to treatment harm.

- **How could patients be involved?**

Patients could contribute to the discussions of criteria and numbers should be used to decide whether a trial should continue or be stopped.

- **Example**

			
Participants satisfied with toothpaste treatment	20 or more	10-19	Fewer than 10
Participants happy to be randomised	20 or more	10-19	Fewer than 10

In the toothpaste trial, it was decided that from the first 30 participants, 20 or more would have to be happy with any toothpaste treatment and to be randomised in order to continue the trial (green light). Amber light means the trial needs to reassessed and red light that it stops. Should patients be involved in this discussion and defining the number criteria?

I: Data Monitoring committee

- **What does it mean?**

A committee that may be established by the trial sponsor to assess at intervals, the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial. (INVOLVE; webpage consulted in 09/11/2020)

- **How could patients be involved?**

Patients could be part of data monitoring committees and participate in discussions about trial progress, safety and clinical efficacy data.

- **Example**

In the toothpaste trial it was agreed that pain scores, as well as needing to attend the dentist for side effects, would be monitored in the data monitoring committees. Therefore, members of the committee are asked to comment on those data. If data are found to be concerning in any way, a discussion between all committee members needs to happen to decide whether the trial should be paused or stopped. Should patients be part of data monitoring committees?

J: Missing data

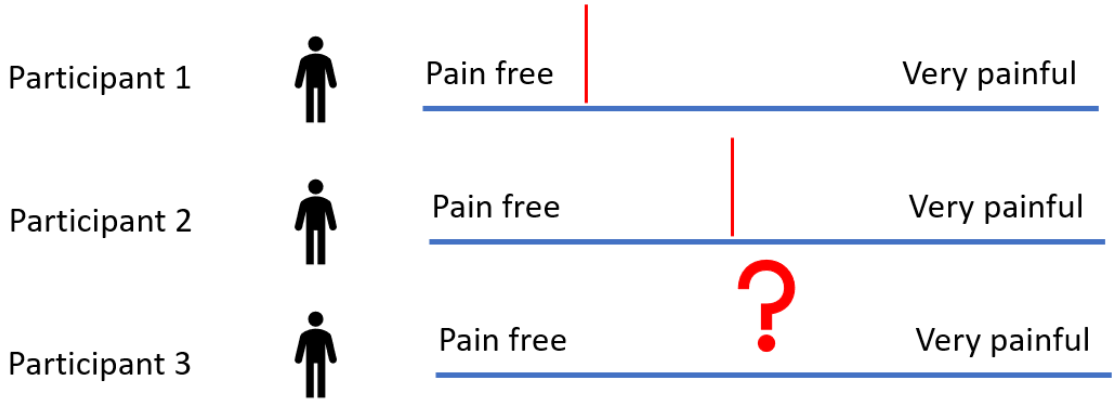
- **What does it mean?**

When a participant outcome is unavailable, due to a missing questionnaire or non-attendance to a trial related clinical appointment, their results are unknown. We call that missing data. In our fictional trial, this would mean we don't know participants pain score at the end. To try to recover those missing values, we use statistical tools that aim to predict what happened to patients that did not provide results, taking into account these predictions are uncertain, ie we do not know for sure what happened to those participants.

- **How could patients be involved?**

Patients can help us predict missing values so we can assess treatment effect with more certainty.

- **Example**



Some participants in the toothpaste trial will have their pain score missing. For those participants and to ensure we investigate different and realistic scenarios, we need to predict what their value might have been, had they answered the question. We have different sources of information to make that prediction, like whether they attended urgent dental treatment and dentists' opinions. However, it is still an informed guess. Should patients help make that informed guess?

K: Cost-effectiveness (value for money)

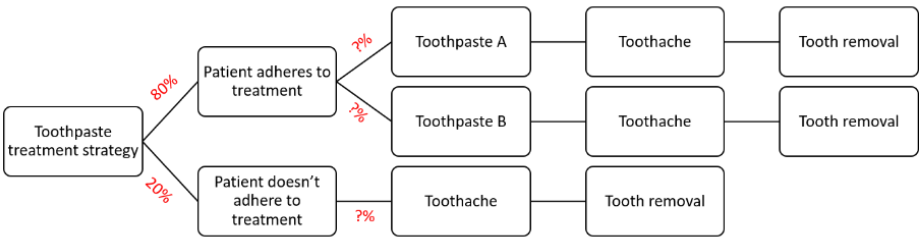
- **What does it mean?**

Cost-effectiveness of a treatment is an economic analysis that views effects in terms of overall health specific to the problem, and describes the costs for some additional health gain (e.g. cost per additional stroke prevented).

- **How could patients be involved?**

Patients could aid the interpretation of cost-effectiveness results, ensuring for example that the calculations capture all relevant costs and benefits to patients. Patients could also provide information that allow different decision strategies to be considered and their impact on costs and quality of life to be estimated.

- **Example**



Selecting a treatment strategy of toothpaste A over toothpaste B can lead to a higher probability of being in pain and, if not treated, a higher probability of having a tooth removed (see Figure above). This probability will be dependent on treatment adherence (ie whether patients use the toothpaste daily or not). Should patients be involved in decisions about probabilities like this and what costs to consider when assessing a toothpaste treatment (for example, days away from work could be considered)?

L: Interpretation of trial results and informing how to disseminate them

- **What does it mean?**

Trial results are presented as numbers (for example, treatment effects) in long and detailed reports.

- **How could patients be involved?**

Patients could contribute to a better understanding of what the findings mean, as well as help co-design dissemination materials that include quantitative trial findings reported in a clear way.

- **Example**

When our toothpaste trial is over, we will have to discuss what the findings mean, how can they be applied in a wider context and we will want to show results to trial participants as well as patients and dentists. In order to do that, we can prepare graphs, reports, podcasts and videos. Whenever numerical information is presented, we will have to make calls on how to report it. Should we involve patients in the interpretation and dissemination of numerical information coming from trials?