How to start a conversation with public partners about estimands:

a practical tool

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Acknowledgments

- HEALTHY STATS public involvement group:
  Ania Henley (Co-chair)
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Trials Methodology TMRP Research Partnership

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Outline

- What is an estimand & why should we consider involving patients?
- Public partner's perspectives on the importance of discussing estimands
- How to start a conversation about estimands: A practical tool
- A simpler and more accessible language to use
- Summary & next steps

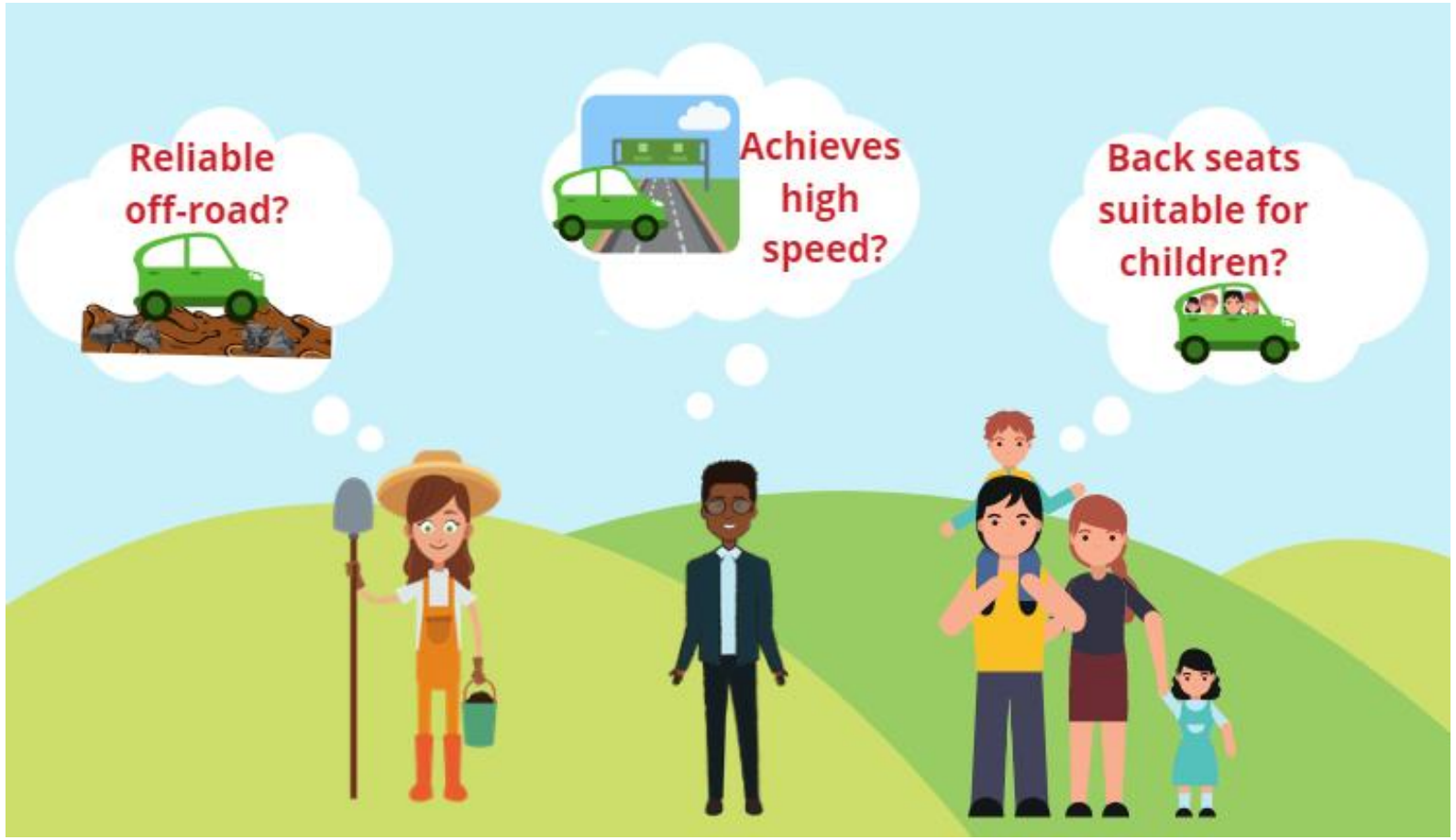
Clinical Trials

What *precisely* are we aiming to calculate and find out?

Imagine buying a new car…

“Would this car suit my lifestyle?”

Imagine buying a new car…



Trials can ask different questions about treatments

- For example:

'What is the treatment effect for all patients even if the treatment is not taken exactly as instructed?'

'What is the treatment effect for only those patients who could tolerate treatment?'

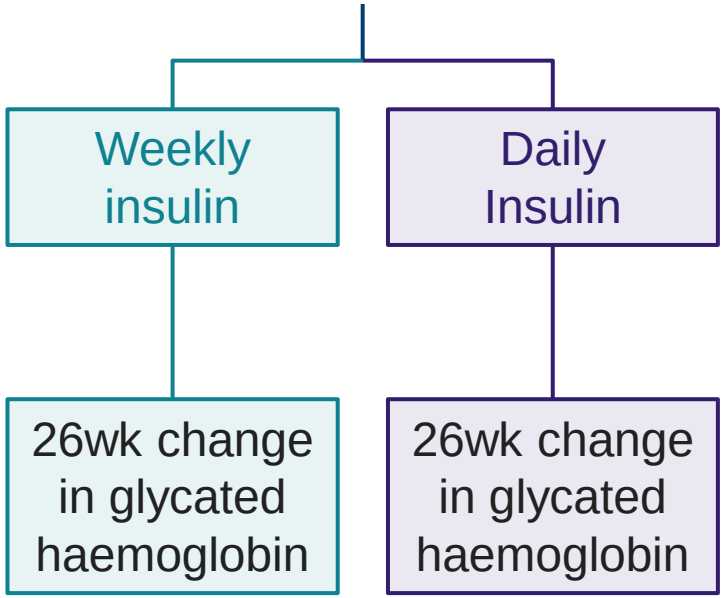
'What is the treatment effect if all patients take the treatment exactly as they are asked?'

Why does this matter?

- Answers to different questions may lead to quite different impressions about how useful a treatment is

- Like how understanding the exact conditions a car works well under, may lead to different conclusions on how useful a car is

Example: diabetes trial



Example: diabetes trial

Weekly insulin

Daily Insulin

Ancillary medication

Ancillary medication

26wk change in glycated haemoglobin

26wk change in glycated haemoglobin

Example: diabetes trial

Weekly insulin

Daily Insulin

Ancillary medication

Treatment discontinuation

STOP

26wk change in glycated haemoglobin

26wk change in glycated haemoglobin

Different effects → different conclusions

- What was the mean difference in glycated haemoglobin for a once-weekly insulin regimen compared to a once-daily regimen…

…regardless of the amount of randomised treatment or ancillary treatment received?
-0.09 percentage points (95% CI -0.29 to 0.20, p=0.35)

Different effects → different conclusions

- What was the mean difference in glycated haemoglobin for a once-weekly insulin regimen compared to a once-daily regimen…

…regardless of the amount of randomised treatment or ancillary treatment received?
-0.09 percentage points (95% CI -0.29 to 0.20, p=0.35)

….if all participants had hypothetically adhered to the treatment regimens and not received ancillary treatment?
-0.18 percentage points (95% CI -0.38 to 0.02, p=0.08)

Estimands

= A precise description of exactly ***what*** *treatment effect* you **want (or *demand)*** to find out

Estimands

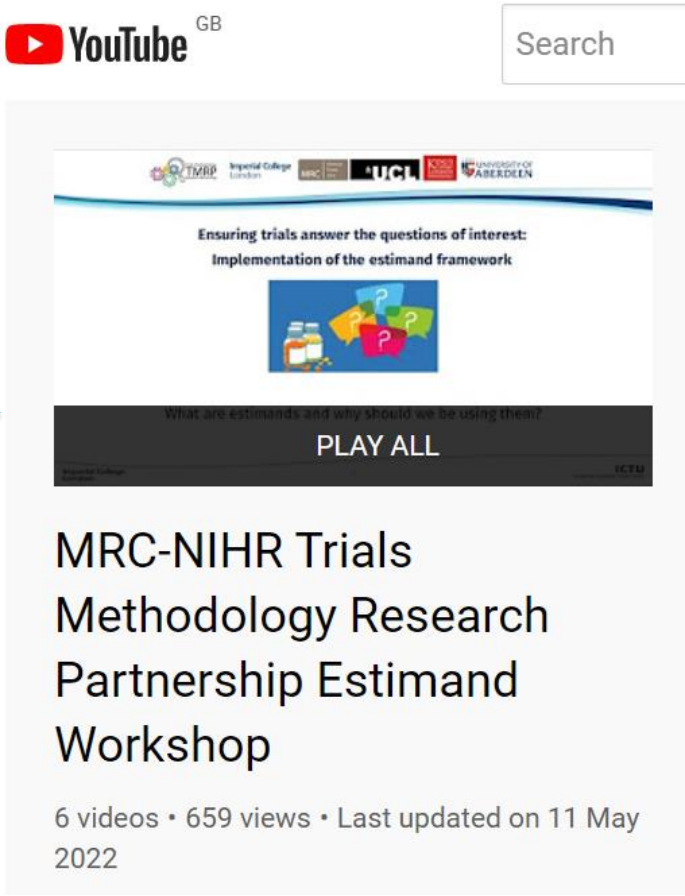
= A precise description of exactly ***what*** *treatment effect* you **want (or *demand)*** to find out

- Captures what patient population and under what conditions particular treatment regimens are being compared

- Trial design/conduct/analysis should be aligned to the estimand(s) of interest (ICH E9 R1 November 2019)

Why should we consider involving patients/public ?

- Patients/public want a say in the research question/direction being involved in defining the estimand is essential to achieve that
- MRC-NIHR TMRP online estimand workshop
- Professor Amanda Adler *"Estimands are for patients and for the people that will benefit from them the most"* and we need to *"provide rationale to select one strategy over another"*



Initial work in this field with HEALTHY STATS PPI group

- Research Question: Do public partners want to be involved in estimand discussions?

- Public partners = patients or members of the public part of the research team

- Methods:

  -Online meeting with public partners from an established statistical trial methodology project (HEALTHY Stats)

  -Five public partners aged between 20 and 70 years of mixed ethnicities and sex; four facilitators to facilitate breakout discussions

Aims of meeting

1. Co-develop a practical tool with public partners that helps explain what an estimand is and what impact it may have in trial results

2. Explore public partner's perspectives on the importance of discussing estimands with public partners when designing a trial

Results – tool development

- Draft 2-page leaflet explaining estimands was presented and discussed

- Feedback:
  - The estimand term felt to be a piece of **“statistical jargon”, “uninteresting””**
  - Public partners found the tool useful to start a discussion about what question a trial is answering in a trial design context
  - They recommended the use of storytelling, analogies and visual aids
  - It was felt that the tool should be shared and a chance to discuss it with the trial team/statistician provided
  - Public partners raised that this tool would not be indicated for potential trial participants, unsure if they might need/want to know about the estimand of the trial

Estimand explainer tool

Clinical Trials: What exactly are we trying to find out?

So, you've been asked to help design a clinical trial…what exactly do clinical trials try to find out?

Imagine buying a new car, if you asked the salesperson *'would this car suit my lifestyle?'* you might not get the answer you were after as the question is too general

What you or I want to know might be quite different, depending on who we are and how we intend to use the car

To find a suitable car, you need to ask a more precise question…

Like buying a car, clinical trials ask different and very specific questions to find suitable new treatments for patients, for instance:

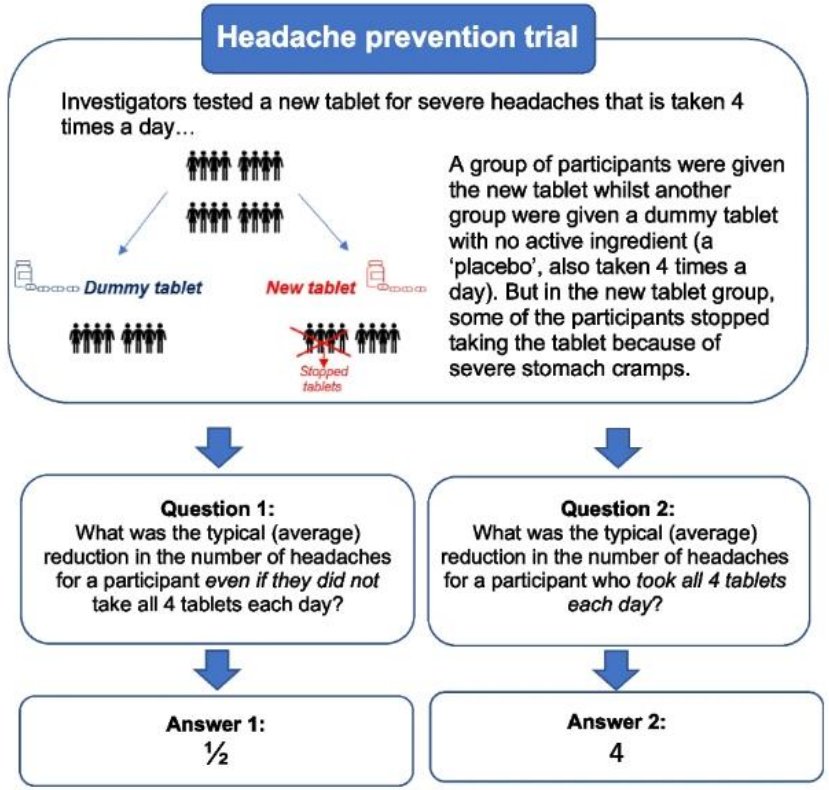
'Does the treatment work for all patients even if it is not taken exactly as instructed?'
'Does the treatment work for just those who could tolerate treatment?'
'Does the treatment work for all patients if they take it exactly as they are asked?'

Why do we need to think about this?

Just as asking different questions might lead you to different impressions about whether a car is suitable for your lifestyle

Asking different questions about a new treatment may lead to different impressions about how useful the treatment is for you

Let's look at an example…



As different questions can lead to different impressions, it is important when helping with a clinical trial you know what questions are going to be asked

Researchers would like your opinion on this so that the question that matters most to you will be addressed

You may hear researchers call the exact question a trial is aiming to answer as the **'estimand'**

Estimand explainer tool

Analogy

Visual story

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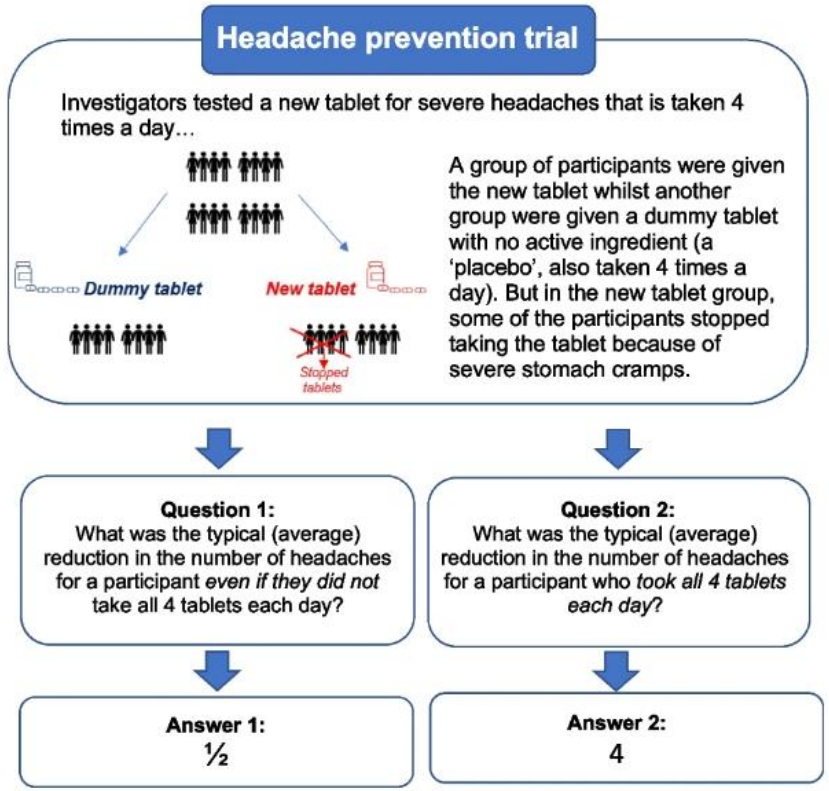

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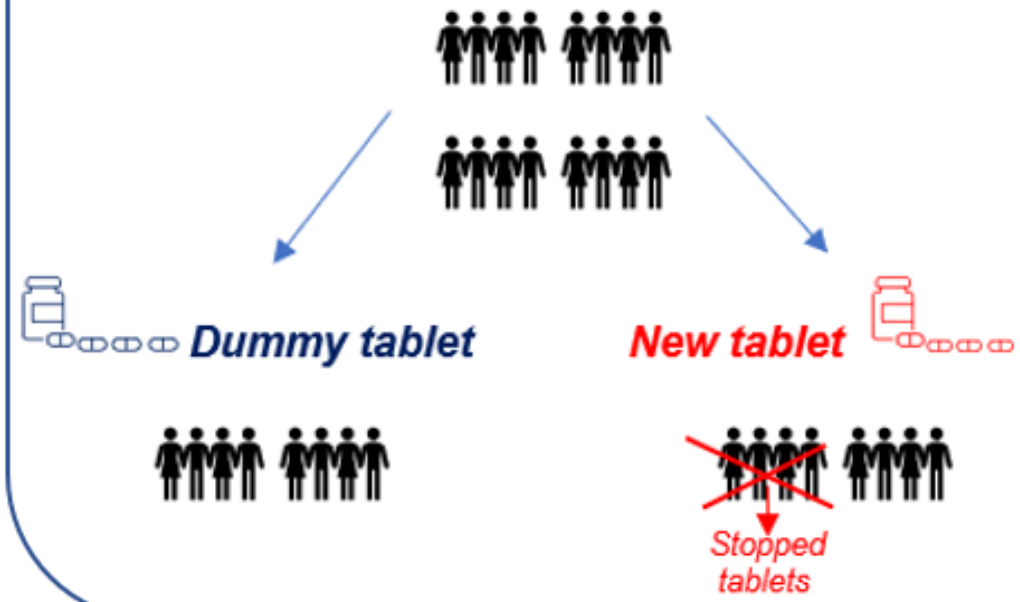
Estimand explainer tool – example

An example (application of estimands)

Visual representation

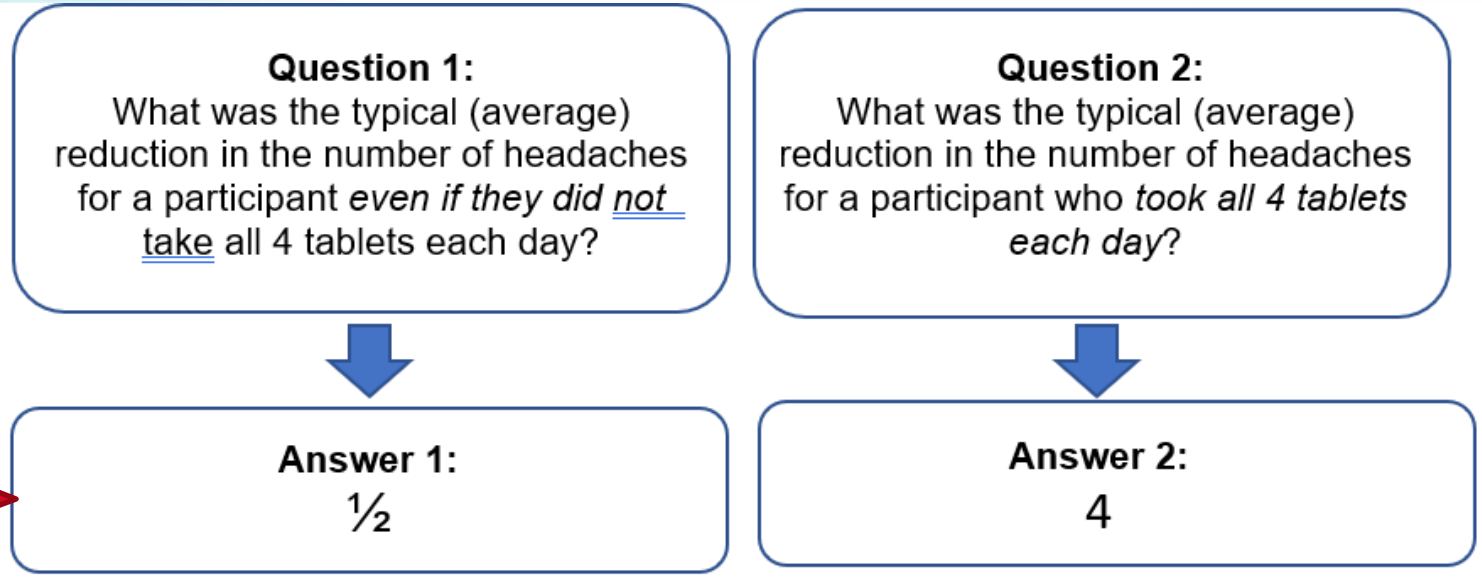
Headache prevention trial

Investigators tested a new tablet for severe headaches that is taken 4 times a day…



A group of patients were given the new tablet whilst another group were given a dummy tablet with no active ingredient (a 'placebo', also taken 4 times a day). But in the new tablet group, some of the participants stopped taking the tablet because of severe stomach cramps.

Estimand explainer tool – example (cont)



What are the implications of choosing one estimand over another?

Why it is important to get involved

As different questions can lead to different impressions, it is important when helping with a clinical trial you know what questions are going to be asked

Researchers would like your opinion on this so that the question that matters most to you will be addressed

Definition of estimand

You may hear researchers call the exact question a trial is aiming to answer as the **'estimand'**

Results – public partner perspectives

Trials that matter to patients

Involve early on

Education & communication

Change of culture

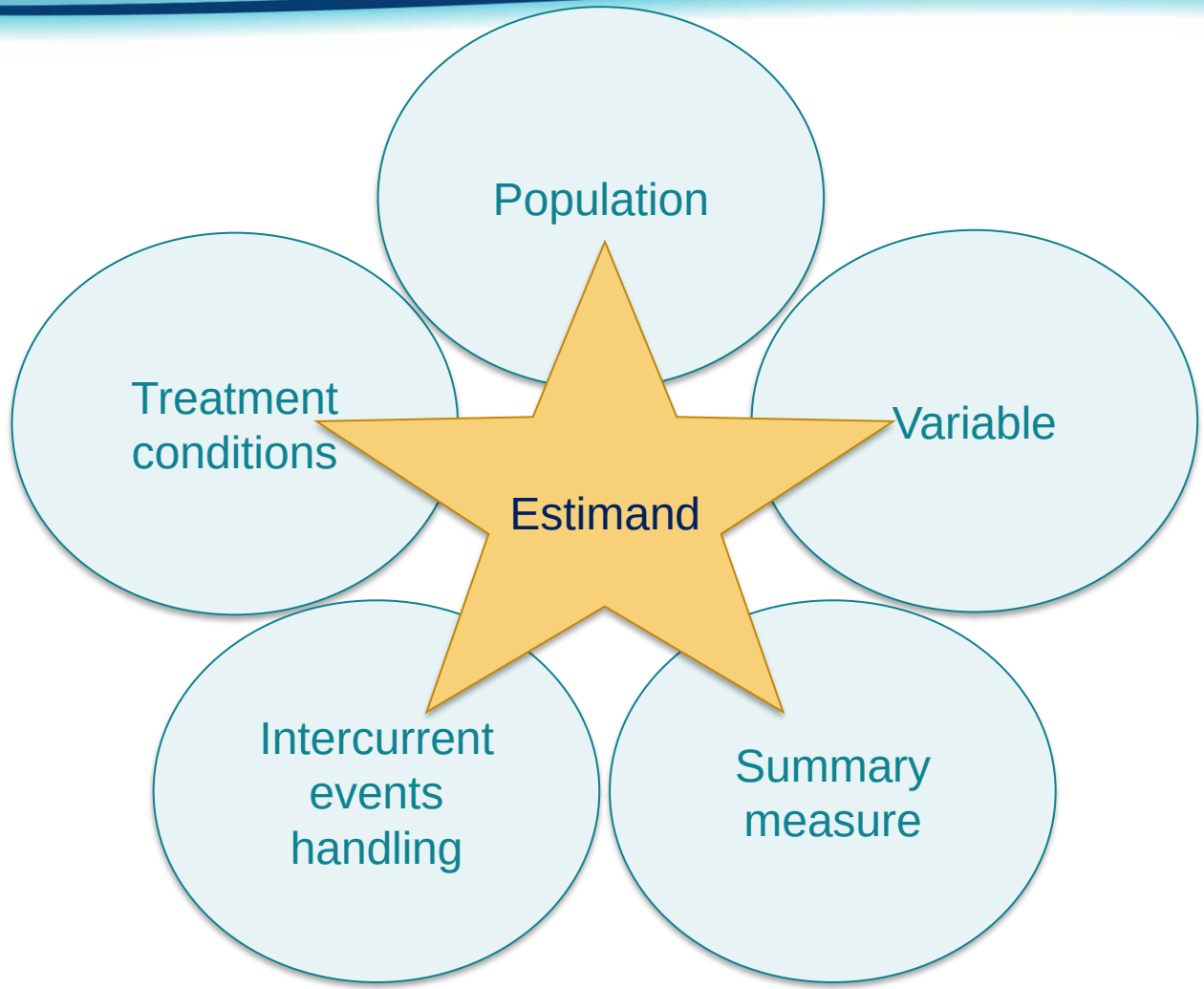
Summary of initial work

- Support from public partners to involve public partners in choosing estimands

- Need to carefully first explain what an estimand is
  - support to use tool co-produced with HEALTHY STATS group to initiate discussions during trial planning about what an estimand is

Estimand language

Estimand


Population
Treatment conditions
Variable
Estimand
Intercurrent events handling
Summary measure

Intercurrent events

- Post-randomisation events which affect the **interpretation** or **occurrence** of outcome data

- Examples
  - Treatment discontinuation
  - Failure to initiate treatment
  - Treatment switching
  - Wrong dose of treatment
  - Use of rescue medication
  - Death

A simpler and more accessible language to use

- Research Question: How can we improve the language used to described 5 parts of an estimand for public partners?

- Methods:
  - 1 x Online meeting followed by 1 x in person meeting with public partners from the HEALTHY Stats group

  -Five public partners aged between 20 and 70 years of mixed ethnicities and sex;

- Aim: Devise new language to use with public partners to describe 5 parts of an estimand

Results – 1st online meeting

- Introduced language researchers use to describe the 5 parts of the estimand (i.e. 5 parts of research question):

Estimand part	Description
Treatment conditions	What treatment conditions are we actually comparing
Population	Who we are answering the question for
Outcome	What measurement are we making the comparison for
Handling of intercurrent events	How are we handling events that happen in the trial and may affect what we are measuring e.g. stopping treatment early
Summary measure	What statistic are we using to look at the difference

Results – 1st online meeting

- Main takeaway – language around the 5 parts of the research question needs to be improved for public partners

- Initial proposal based on group discussions:

~~Estimand Part~~	Important parts of research question
~~Treatment conditions~~	1. What is the trial comparing
~~Population~~	2. For who
~~Outcome~~	3. What difference is being measured
~~Handling of intercurrent events~~	4. What is being done about expected/unexpected events that happen to patients in the trial e.g. stopping prescribed medication early, taking other (non-trial) medications
~~Summary measure~~	5. What statistical measure are we using

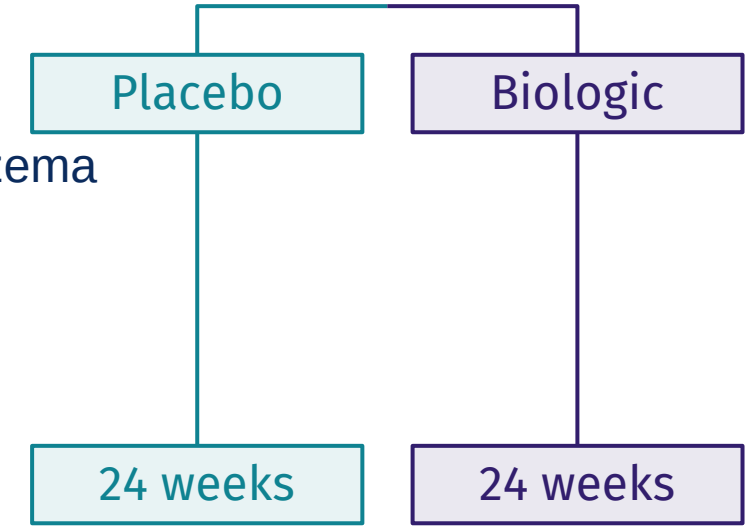
Results – 2nd in person meeting

- Updated proposal:

4 Pillars of the research question (estimand)
What is the trial testing
What people/condition are we trying to help
What is being measured
How are researchers handling unplanned participant related events e.g. stopping prescribed medication early, taking other (non-trial) medications

Application of proposal: Eczema trial

children with chronic eczema



Measured change in eczema severity [0 to 30]:
0 = no change
-5 = got better by 5
+5 = got worse by 5

Taken every 2 weeks via injection

Application of proposal: Eczema trial

- It is anticipated that not all the children will take the treatment as prescribed

- Exploring the research question/estimand with updated language

Application of proposal: Eczema trial

- When seeking public partner input on estimands during trial planning:

1. Discuss trial setting – obtain initial general thoughts on trial

2. Introduce what an estimand is and why its important

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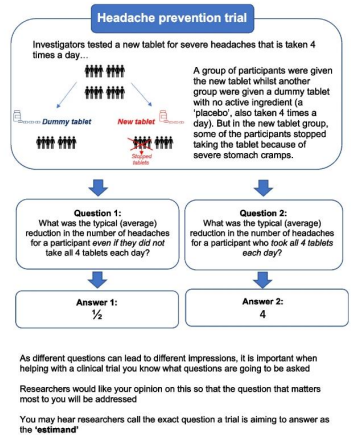

Headache prevention trial

Investigators tested a new tablet for severe headaches that is taken 4 times a day…

A group of participants were given the new tablet whilst another group were given a dummy tablet with no active ingredient (a 'placebo', also taken 4 times a day). But in the new tablet group, some of the participants stopped taking the tablet because of severe stomach cramps.

Question 1: What was the typical (average) reduction in the number of headaches for a participant *even if they did not* take all 4 tablets each day?

Question 2: What was the typical (average) reduction in the number of headaches for a participant who *took all 4 tablets each day?*

Answer 1: ½

Answer 2: 4

As different questions can lead to different impressions, it is important when helping with a clinical trial you know what questions are going to be asked

Researchers would like your opinion on this so that the question that matters most to you will be addressed

You may hear researchers call the exact question a trial is aiming to answer as the **'estimand'**

3. Discuss potential estimands researchers are considering using 4 pillars of the research question
   -obtain feedback on estimands

Application of proposal: Eczema trial

- Potential research question/estimand 1:

- How does biologic compare against placebo, even if not all of the biologic/placebo is received, for children with chronic eczema on the average change in eczema severity score?

4 Pillars of the research question (estimand)	Description
What is the trial testing	Biologic versus placebo
What people/condition are we trying to help	Children with chronic eczema
What is being measured	Change in eczema severity score
How are researchers handling unplanned participant related events e.g. stopping prescribed medication early, taking other (non-trial) medications	*Unplanned event* = Stopping biologic/placebo early *Solution* = *H*ow biologic/placebo performs ignoring stopping treatment early

Application of proposal: Eczema trial

- Potential research question/estimand 2:

- How does biologic compare against placebo, for children with chronic eczema who take all doses as prescribed on the average change in eczema severity score?

4 Pillars of the research question (estimand)	Description
What is the trial testing	Biologic versus placebo
What people/condition are we trying to help	Children with chronic eczema
What is being measured	Change in eczema severity score
How are researchers handling unplanned participant related events e.g. stopping prescribed medication early, taking other (non-trial) medications	*Unplanned event* = Stopping biologic/placebo early *Solution* = only interested in taking all doses as prescribed

Results – 2nd in person meeting

- For public partners involved in trial design all 4 pillars important to know

- For trial participants first 3 naturally already in PIS

  -don't want to make more confusing/unload with unnecessary information that might impact patient behaviour

4 Pillars of the research question
What is the trial testing
What people/condition are we trying to help
What is being measured
How are researchers handling unplanned participant related events e.g. stopping prescribed medication early, taking other (non-trial) medications

Results – 2nd in person meeting

- For patient/public using trial results want to know all 4 pillars

  -especially the last as may affect their behaviour i.e. influence how they take the treatment/encourage adherence

4 Pillars of the research question
What is the trial testing
What people/condition are we trying to help
What is being measured
How are researchers handling unplanned participant related events e.g. stopping prescribed medication early, taking other (non-trial) medications

Summary & next steps: public partners

- Support to involve public partners in choosing estimands
- 2-page leaflet available as a tool to start a conversation about what an estimand is and why matters
- Developed a simpler estimand language acceptable for public partners
- Next steps:
  -A third page will be added to co-developed estimand explainer tool to explain 4 pillars of research question that important for public partners to discuss with researchers
  -Will be shared & discussed with different groups of public partners to collect feedback

Future work: patients and public

- Ideally journals would have lay summaries communicating results to patients – with clear communication of underlying estimand

- Tackling this is an important area for future research highlighted by HEALTHY STATS public partners

  - “People see what they want to see – lay summaries need to be factual and clear without space to misinterpret”

References

- Initial work on how to start a conversation about estimands including co-developed 2-page tool available for use:

Cro, S., Kahan, B.C., Patel, A. Henley A, C J, Hellyer P, Kumar M, Rahman Y, Goulao. Starting a conversation about estimands with public partners involved in clinical trials: a co-developed tool. *Trials* **24**, 443 (2023). https://doi.org/10.1186/s13063-023-07469-9

- For researchers:

- Recordings of videos on estimand workshop: https://www.youtube.com/playlist?list=PLLNbbg2Y8KW6swbVHSO_IWo1lak_FvjgJ
- Coming Jan 23rd 2024...The ICH E9 estimands framework: a primer, BMJ (accepted Nov 2023), Kahan, Hindley Edwards, Cro†, Morris†

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