Experiences with the Estimand
The regulatory view

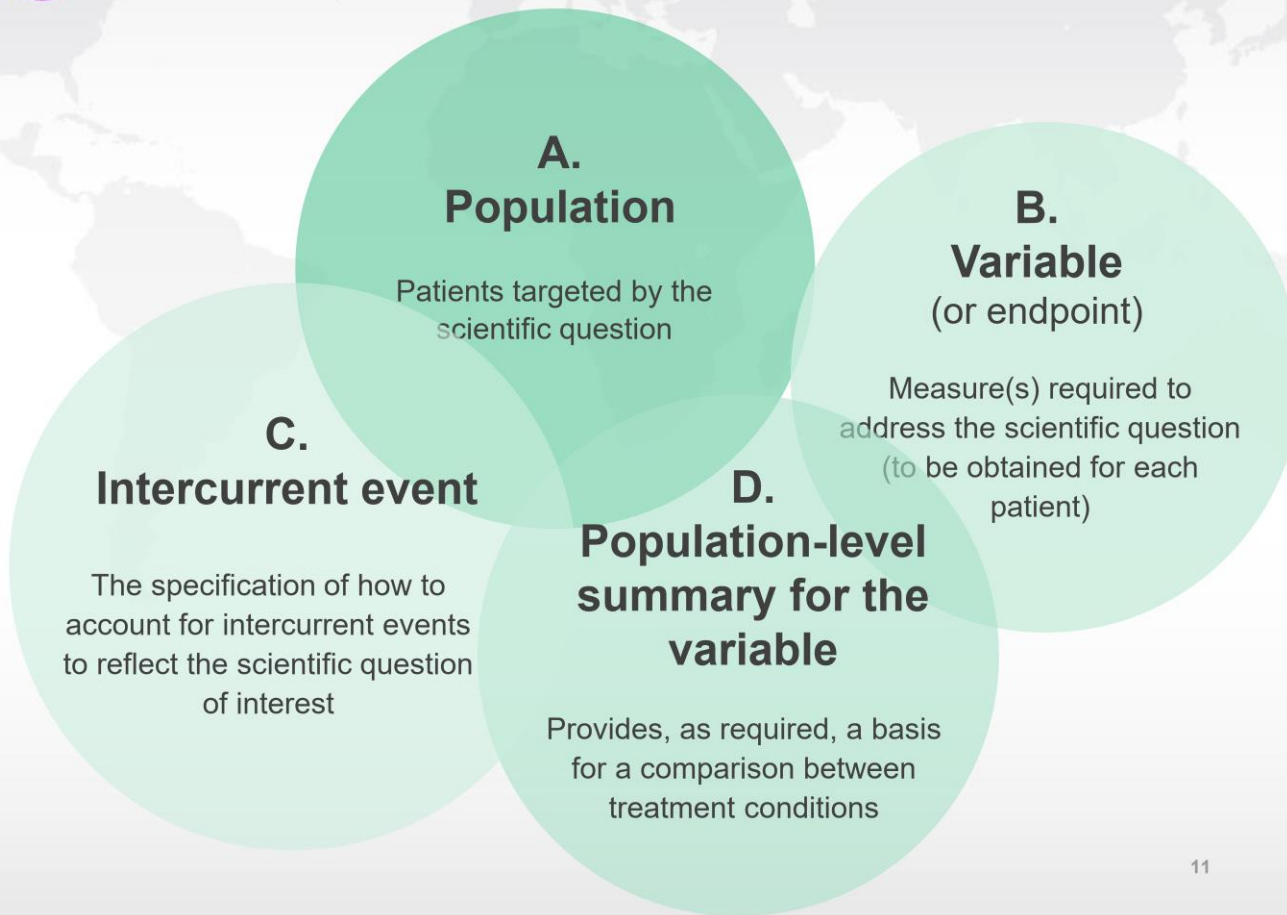**Anja Schiel, PhD, Lead methodologist/Statistician**
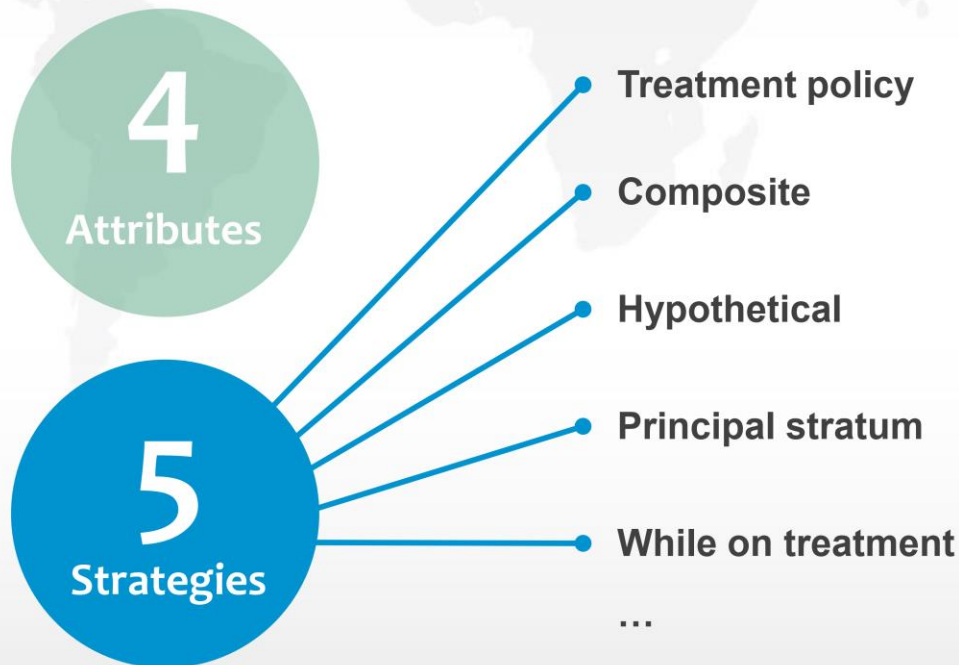
Norwegian Medicines Agency

Disclaimer

- The views and opinions expressed in the following PowerPoint slides are those of me

- The opinions neither represent the views of the Norwegian Medicines Agency nor the European Medicines Agency

- I shamelessly borrowed the majority of slides from ICH

- It is there you find the training material we all need to rehearse every couple of month maybe?
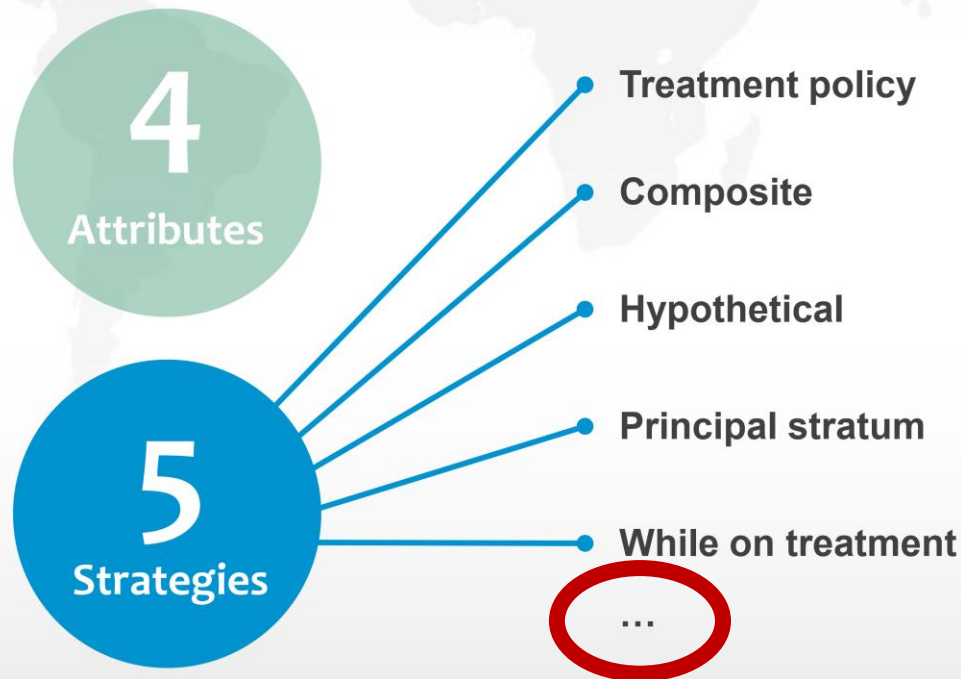
➢ https://www.ich.org/

A.
Population

Patients targeted by the scientific question

B.
Variable
(or endpoint)

Measure(s) required to address the scientific question (to be obtained for each patient)

C.
Intercurrent event

The specification of how to account for intercurrent events to reflect the scientific question of interest

D.
Population-level summary for the variable

Provides, as required, a basis for a comparison between treatment conditions

How are potential intercurrent events reflected in the scientific question of interest?

4 Attributes

5 Strategies

- Treatment policy
- Composite
- Hypothetical
- Principal stratum
- While on treatment
- …

How are potential intercurrent events reflected in the scientific question of interest?

4 Attributes

5 Strategies

- Treatment policy
- Composite
- Hypothetical
- Principal stratum
- While on treatment
- …

A 'new' framework

Clear trial objectives should be translated into key scientific questions of interest by defining suitable estimands.
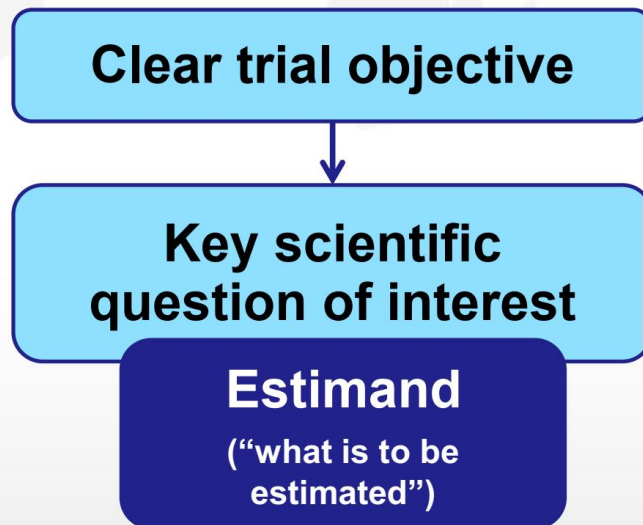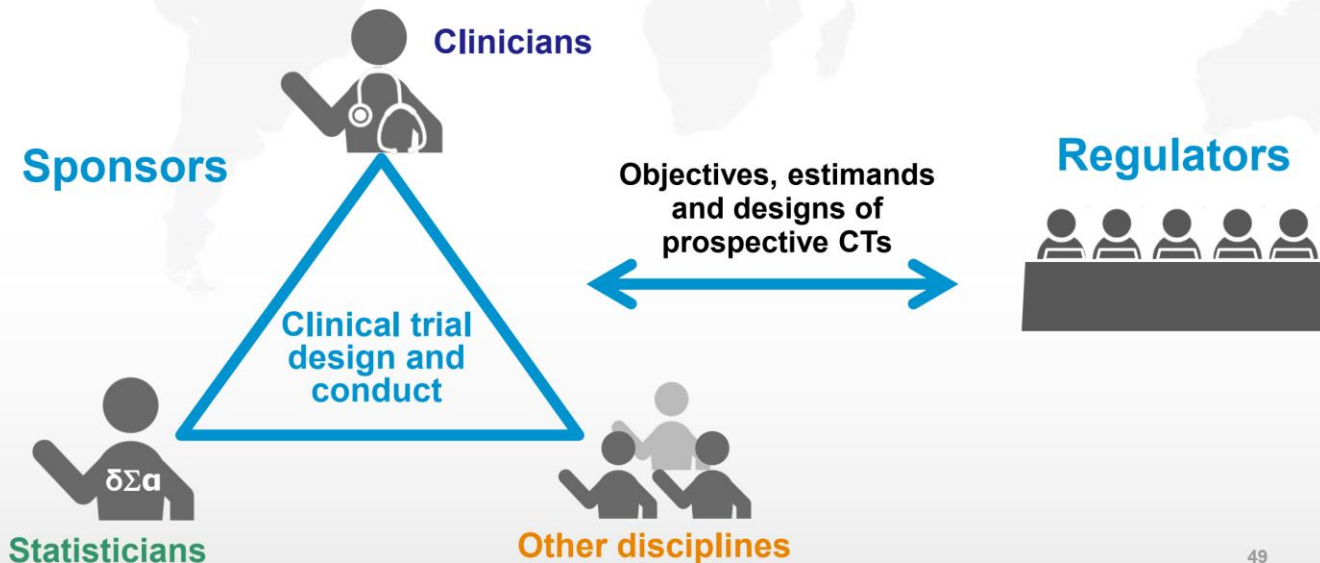
The objective, a matter of language

- We would like to get away from:

- *We explore the effectiveness and safety of drug X in indication Y*

- We want to see the objective explaining in real words

  - Which drug do you want to investigate
  - In which population and which setting
  - What do you want to show, what do you expect your drug to really do

➤ This should not be hidden in the SAP (see later)

➤ We are running trials for patients, not Statisticians

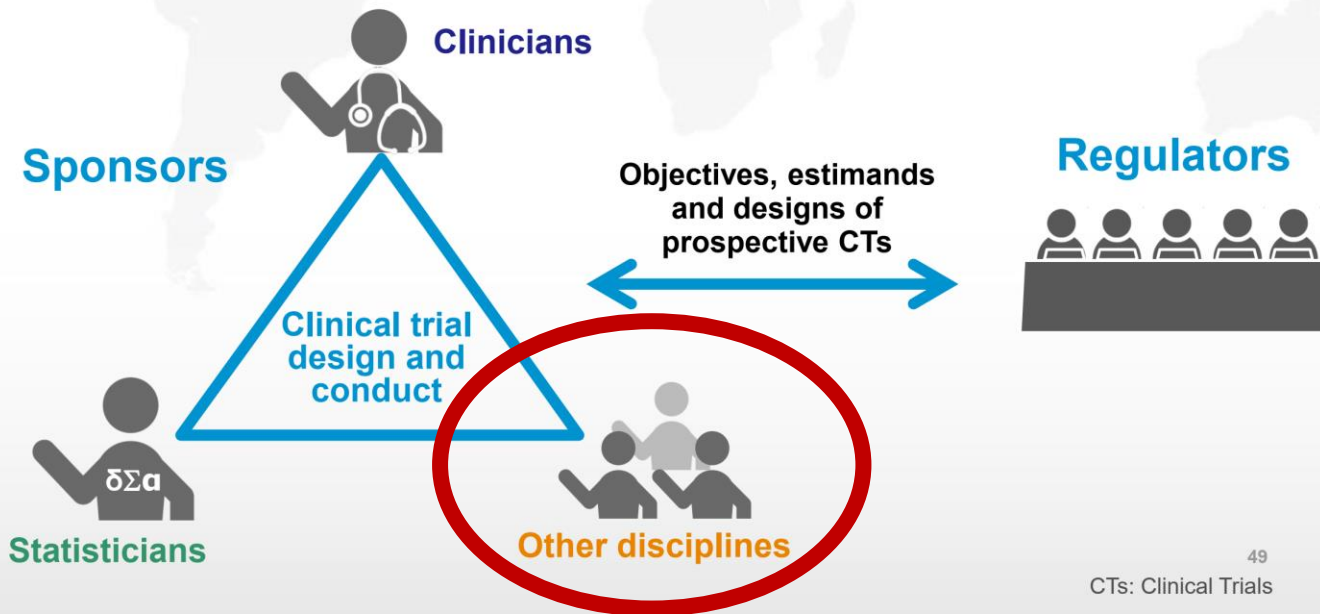# Construction of an estimand

It is a **multi-disciplinary undertaking** and should be the subject of discussion between sponsors and regulators.
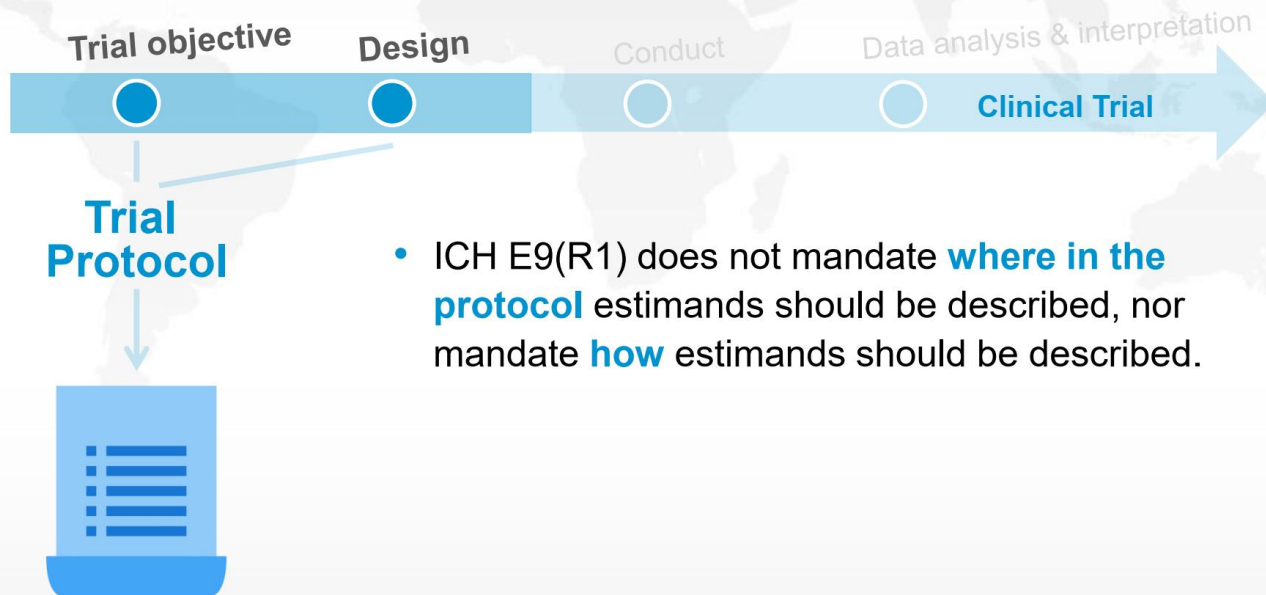
CTs: Clinical Trials

# Incorporating estimands in protocol writing

Trial objective   **Design**   Conduct   Data analysis & interpretation

Clinical Trial

Trial Protocol

- ICH E9(R1) does not mandate **where in the protocol** estimands should be described, nor mandate **how** estimands should be described.

Incorporating estimands in the SAP

- Full details of the planned statistical analyses should align with the estimand(s) defined, and not the other way around!

SAP: Statistical Analysis Plan

13
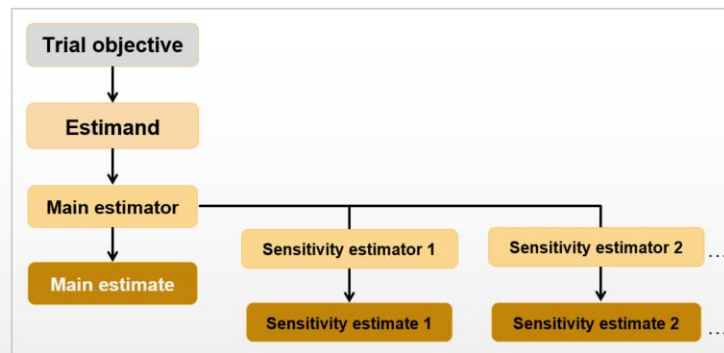
Aligning target of estimation, method of estimation, and sensitivity analysis, for a given trial objective

In general, it is **important to proceed sequentially**. The trial objective should determine the choice of estimands and the estimands should determine the choice of estimators, not the reverse.
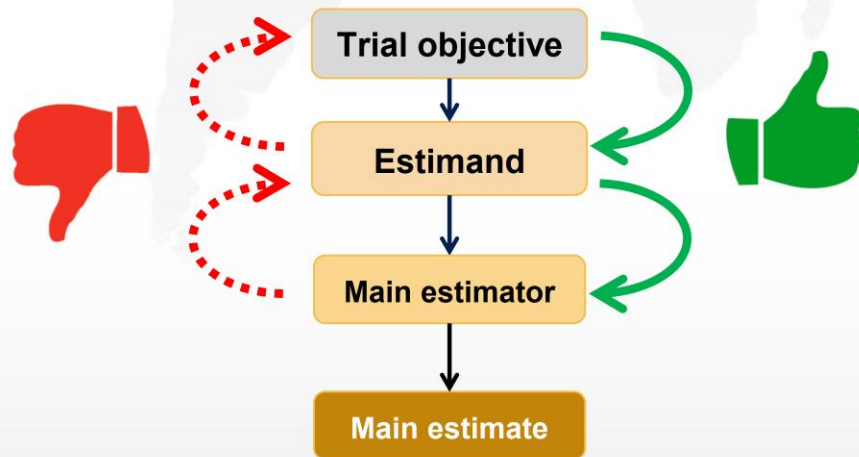
Where significant issues exist to derive a reliable estimate for a particular estimand, the trial objectives need to be re-considered from top-down to main estimator (**green** arrows). The main estimator should never define the trial objective from bottom-up (**red** arrows).

12

Are we there?

- No, we still see the bottom up argumentation

- For regulators it is not always clear

  - ➤ If there had been a thorough discussion but the conclusion was that the Estimand framework didn't make a difference or…
  - ➤ …there never was a discussion

- Also the regulators might have such an internal discussion and decide that there is nothing gained by demanding an Estimand discussion. (KISS)

A new framework

A common language and common understanding of this framework will help sponsors planning trials and regulators in their reviews, enhancing the interactions between these parties when discussing the suitability of designs, and the interpretation of results, to support drug licensing.
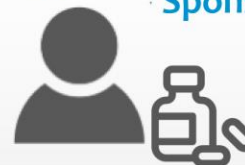
Regulators

ESTIMAND

ESTIMAND

Sponsor

Are we there?

- No

- Different stakeholder catch up at different speeds

- We see increasing numbers of submissions for Scientific advice with varying degrees of complexity on the Estimand use

- The number of products reaching the CHMP is less, increasing, but driven by 'need'.

- But downstream from CHMP, some of the stakeholders are living in blissful ignorance

A thinking process…

① **Therapeutic setting** and **intent of treatment** determining a **trial objective**

② Identify **intercurrent events**

③ **Discuss strategies** to address intercurrent events

④ **Construct** the estimand(s)

⑤ **Align** choices on **trial design, data collection** and method of **estimation**

⑥ Identify **assumptions** for the main analysis and suitable **sensitivity analyses** to investigate these assumptions

⑦ **Document** the chosen estimands

How the discussions really goes…….

- Step 1 possibly starts with the finished product and the placement in the market in mind already (wishful thinking or prospective thinking however you want to see it)

- If we assemble the right team including all disciplines and we use the Estimand framework likely Step 1 is out of the window and Step 2 jumps starts a lively discussion

A thinking process…

1 Therapeutic setting and intent of treatment determining a trial objective

2 Identify intercurrent events

3 Discuss strategies to address intercurrent events

4 Construct the estimand(s)

5 Align choices on trial design, data collection and method of estimation

6 Identify assumptions for the main analysis and suitable sensitivity analyses to investigate these assumptions

7 Document the chosen estimands

How the discussions really goes…….

- Step 3 and 4 require that all involved are using the correct language -> the key is education and getting familiar with the way the discussions have to go

- Step 5 is where it get's likely more complicated again. If we did everything right from 1 to 4 then the trialists should be warned what will be expected. If we did it wrong they will explain to us that what we want to do is practically not feasible

- Back to Step 2!

A thinking process…

1 **Therapeutic setting** and **intent of treatment** determining a **trial objective**

2 Identify **intercurrent events**

3 **Discuss strategies** to address intercurrent events

4 **Construct** the estimand(s)

5 **Align** choices on **trial design**, **data collection** and method of **estimation**

6 Identify **assumptions** for the main analysis and suitable **sensitivity analyses** to investigate these assumptions

7 **Document** the chosen estimands

How the discussions really goes…….

- Ok, Step 6 would really require you to talk to the Statistician and make sure you had them on board all along!

- If you hadn't it's probably back to Step 2 (again)!

- If you manage to get to Step 7 straight away, congrats, you done this before

➢ The iteration isn't always done and this is reflected in the submissions we receive

Opportunities

Aligning drug developers and regulatory bodies' expectations for the target treatment effect in advance has the potential to give:

- More **meaningful descriptions of treatment effects** for licensing ✔
  and prescribing decisions;

- Clinical trials with designs that are **aligned to agreed objectives**; ✔

- **Increased transparency** with respect to data analysis and inference; ✔

- More **predictable** regulatory assessment **procedures**. ✔
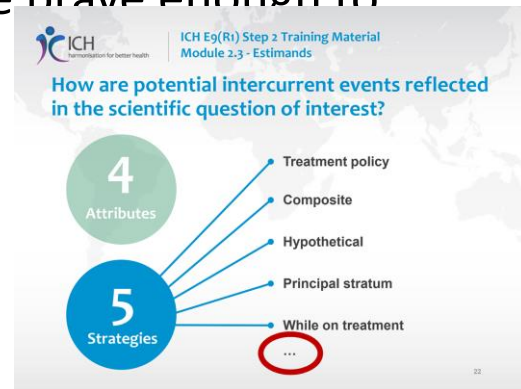
41

Does everyone see the opportunities?

- No, the uptake of the framework has not been comparable in all disease areas

- The main driver for the use of the framework are in fact the <u>intercurrent events</u>!

- In solid tumours, depending on the line we investigate, the advantage of the Estimand framework is not always clear
  - ➢ 'We have always done it that way….. '

- Mature discussions on all aspects of the framework are actually only seen in certain areas with a 'blank canvas'
  - ➢ Alzheimer's disease and Huntington's disease

The still open questions

- Had the authors mainly the RCT in mind when they were writing the Addendum?

  ➢ Is the framework applicable for single-arm trials

  ➢ What about the famous non-randomized comparisons

The still open questions

- Had the authors mainly the RCT in mind when they were writing the Addendum?

  - Is the framework applicable for single-arm trials

  - What about the famous non-randomized comparisons

- Are there only the famous 5 Estimands?

  - Are there no other Estimands or is just no one brave enough to propose additional ones?

The still open questions

- Had the authors mainly the RCT in mind when they were writing the Addendum?

  - ➢ Is the framework applicable for single-arm trials

  - ➢ What about the famous non-randomized comparisons

- Are there only the famous 5 Estimands?

  - ➢ Are there no other Estimands or is just no one brave enough to propose additional ones?

- How do we handle the concept of non-inferiority or equality designs?

The still open questions

- Had the authors mainly the RCT in mind when they were writing the Addendum?

  ➢ Is the framework applicable for single-arm trials

  ➢ What about the famous non-randomized comparisons

- Are there only the famous 5 Estimands?

  ➢ Are there no other Estimands or is just no one brave enough to propose additional ones?

- How do we handle the concept of non-inferiority or equality designs?

- How to handle the COVID 19 impact……………

Follow us

@legemiddelinfo   legemiddelverket   noma.no

Norwegian
Medicines Agency