Overview Of The ICH E9(R1) Addendum
&
The Estimand Framework

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Outline

- Illustrative example
- The estimand framework
- Considerations for intercurrent event strategies
- Impact on trial design, conduct and analysis
- Further examples

Acknowledgments

- Some slides include adapted training material available by ICH

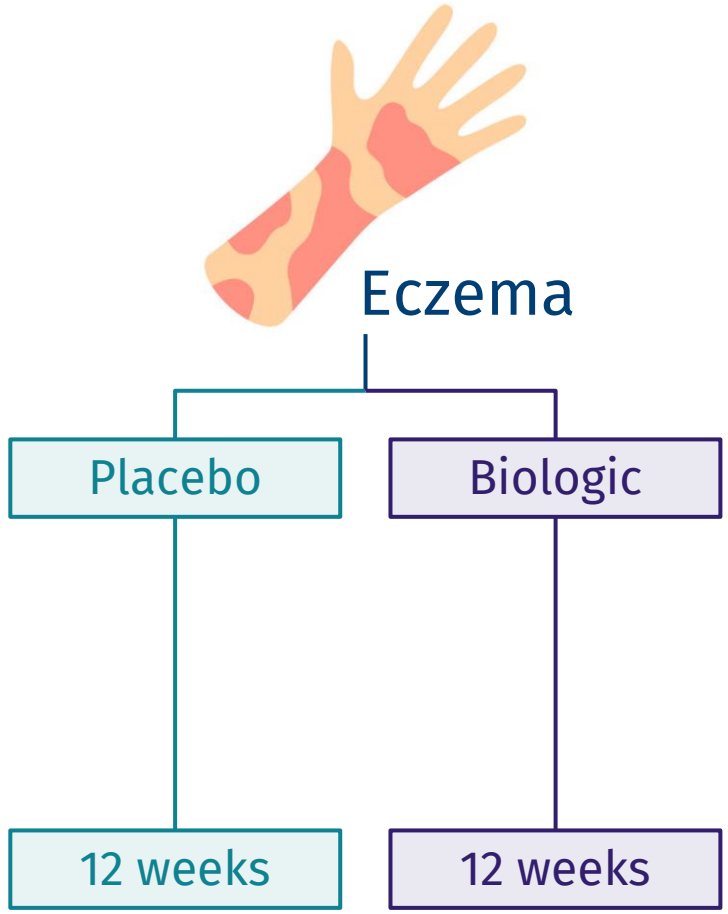
- The views expressed are those of the presenters and should not be understood or quoted as being made on behalf of the International Conference on Harmonisation (ICH) or reflecting the position of the ICH or the author's affiliated institutions/companies.

Example: Testing a new biologic in eczema

- **Objective:**

  To compare a 12-week course of a new biologic against placebo in routine practice

- Primary endpoint: EASI at 12 weeks



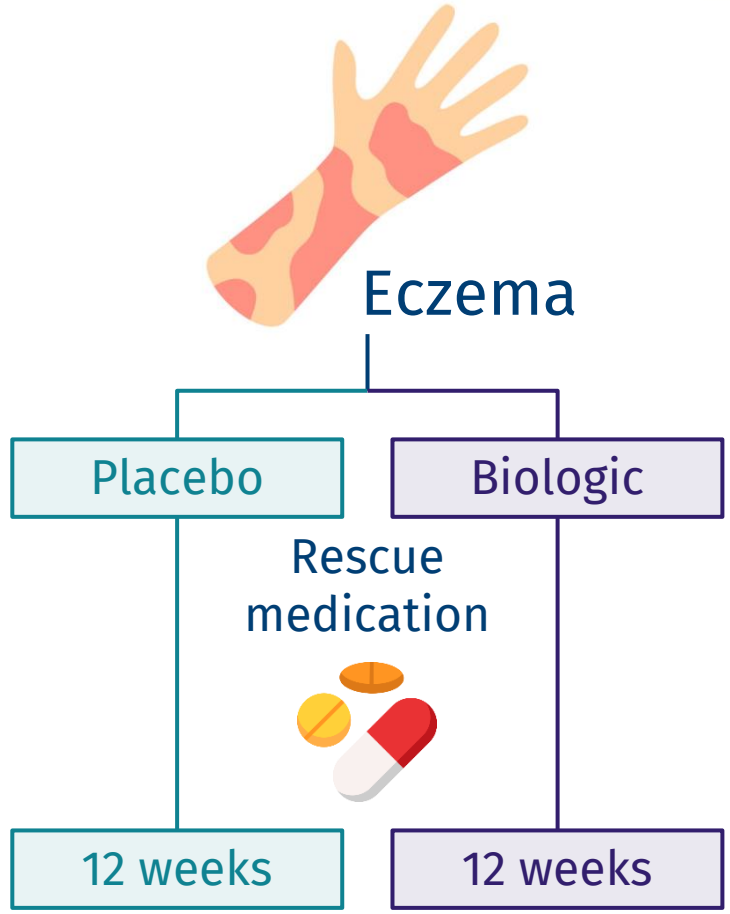
Example: Testing a new biologic in eczema

- **Objective:**

  To compare a 12-week course of a new biologic against placebo in routine practice

- Primary endpoint: EASI at 12 weeks

- Rescue medication available if needed (available in routine practise)

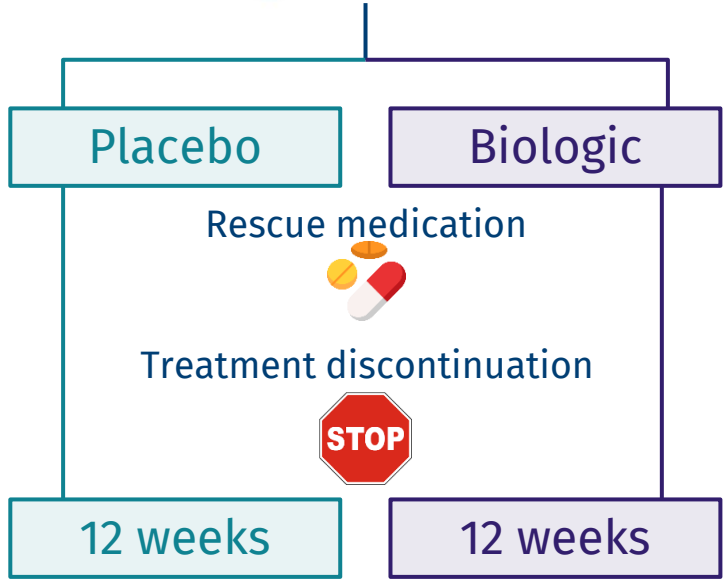


What exactly do we want to find out?

- If we specify *"the treatment difference between the biologic and placebo on eczema severity at Week 12"* there is ambiguity.

- Rescue medication use will affect the interpretation of outcomes

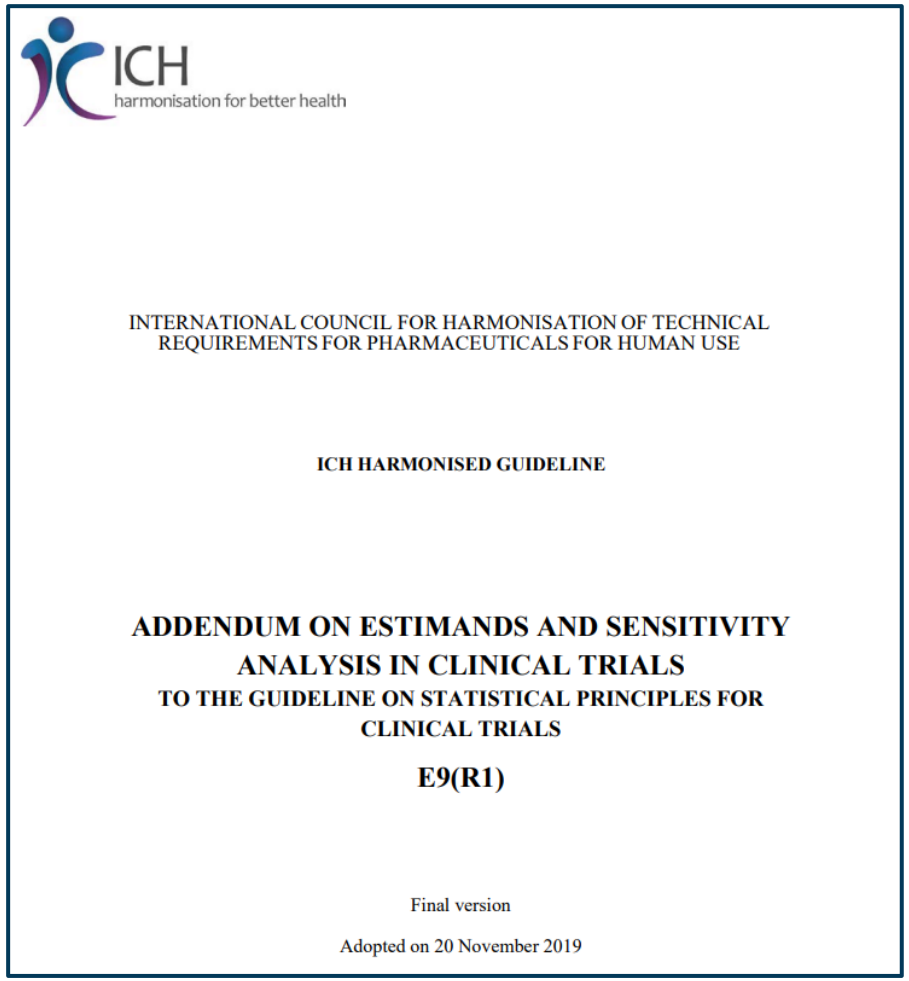
- As will early treatment discontinuation



Purpose of ICH E9 (R1) & estimand framework

- Highlights and addresses issues surrounding such ambiguity:
  - Recognition that the treatment effect is not always precisely defined
  - Lack of transparency as to how intercurrent events handled
  - Historically the data collection and analysis methods would inform which treatment effect is being estimated
  - Shift in view: the estimand of interest should inform the data collection and analysis approach

ICH E9 (R1) addendum



ICH
harmonisation for better health

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

ADDENDUM ON ESTIMANDS AND SENSITIVITY ANALYSIS IN CLINICAL TRIALS
TO THE GUIDELINE ON STATISTICAL PRINCIPLES FOR CLINICAL TRIALS

E9(R1)

Final version

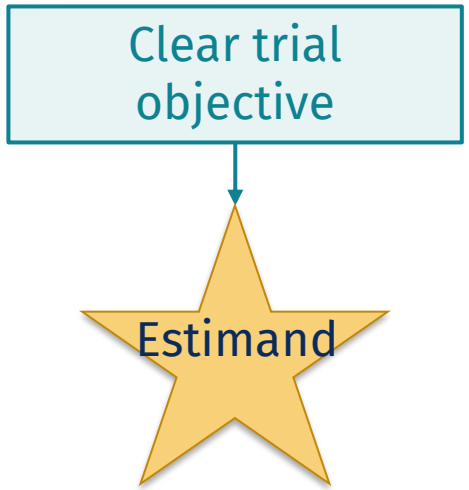
Adopted on 20 November 2019

- Applicable whenever treatment effects are to be estimated and tested:

  - all phases of clinical development
  - clinical trials and observational studies
  - regardless of therapeutic area

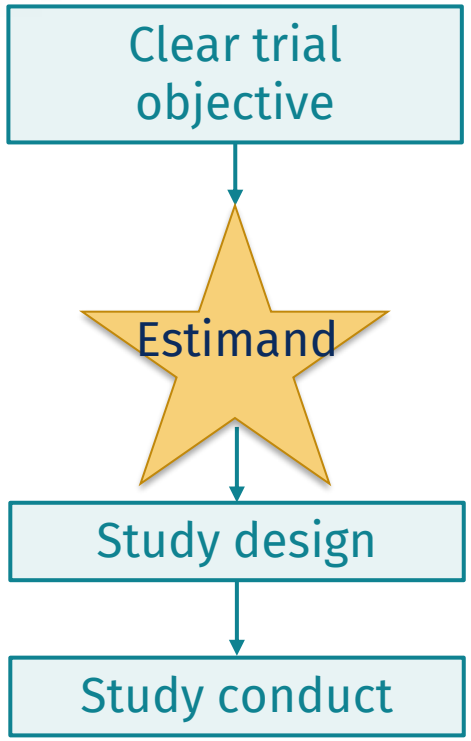
The Estimand Framework

The estimand framework



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

The estimand framework



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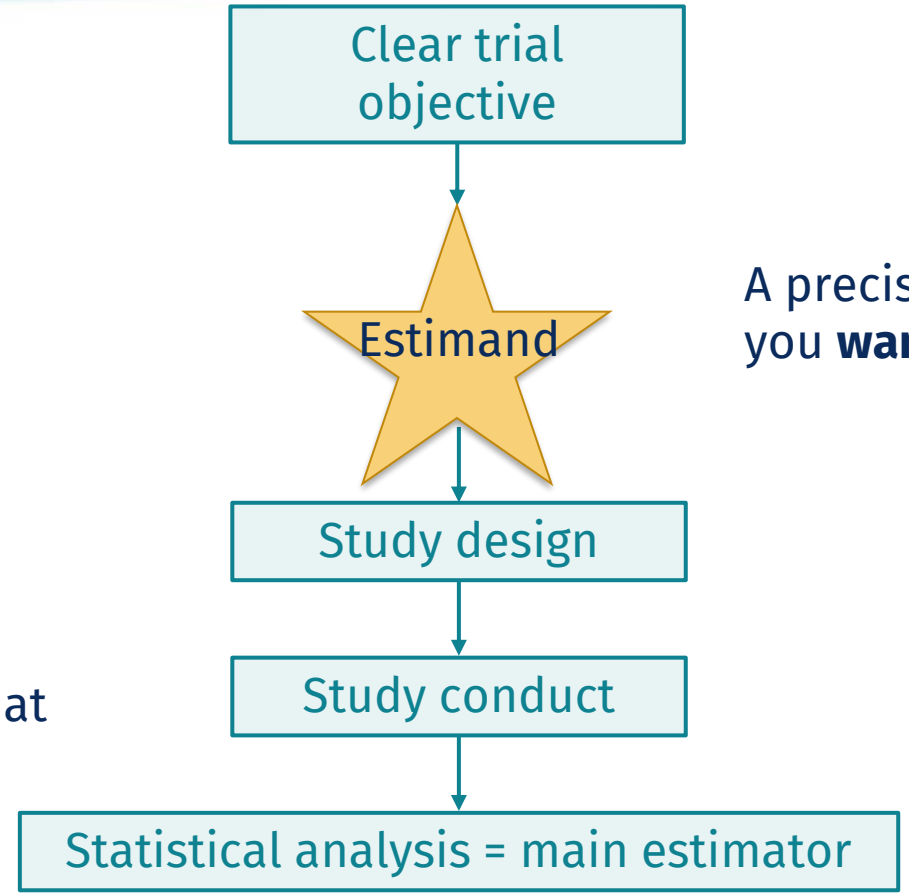
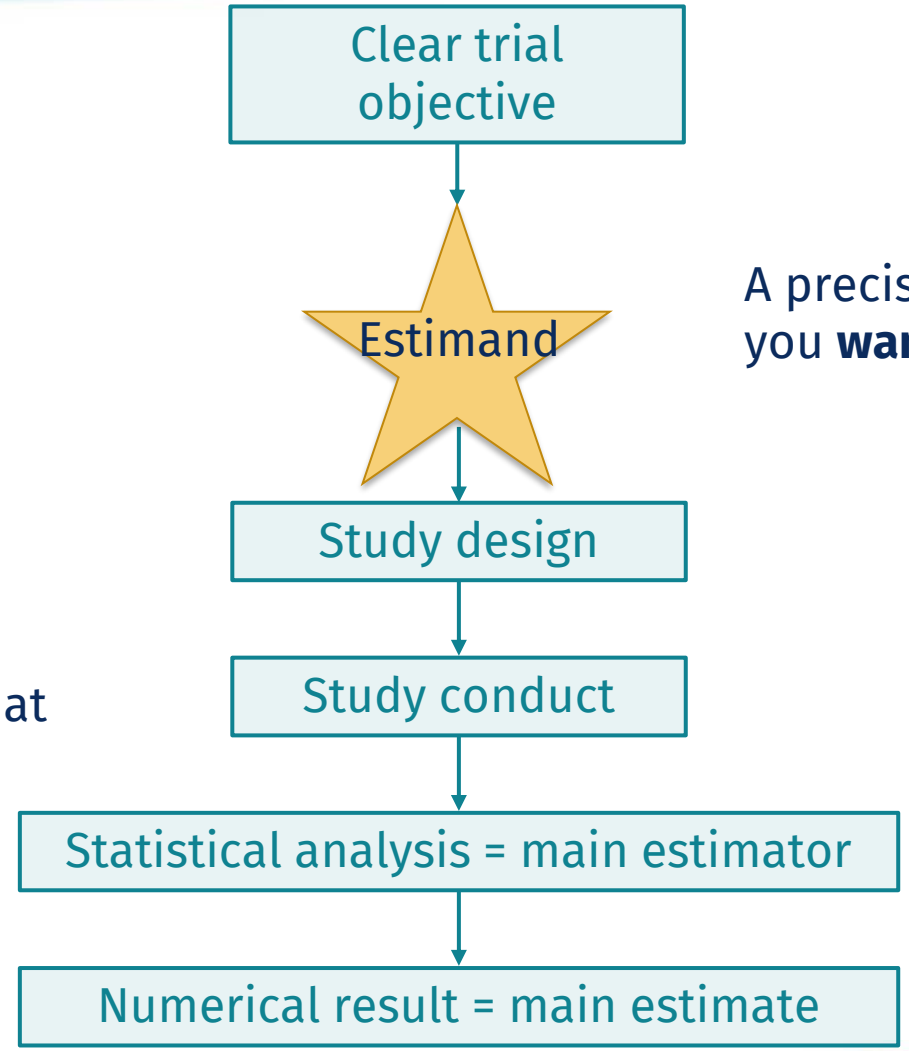


A precise description of exactly ***what*** you **want (or *demand)*** to find out

The machinery that gets you to what you want to know e.g. linear regression model

The estimand framework



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

The machinery that gets you to what you want to know e.g. linear regression model

What you want to know e.g. = 7 EASI points

The estimand framework

The estimand framework

Recipe

Ingredients

- 150g unsalted butter, plus extra for greasing
- 150g plain chocolate, broken into pieces
- 150g plain flour
- ½ tsp baking powder
- ½ tsp bicarbonate of soda
- 200g light muscovado sugar
- 2 large eggs

Method

1. Heat the oven to 160C/140C fan/gas 3. Grease and base line a 1 litre heatproof glass pudding basin and a 450g loaf tin with baking parchment.

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The estimand framework

Estimand

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Estimator

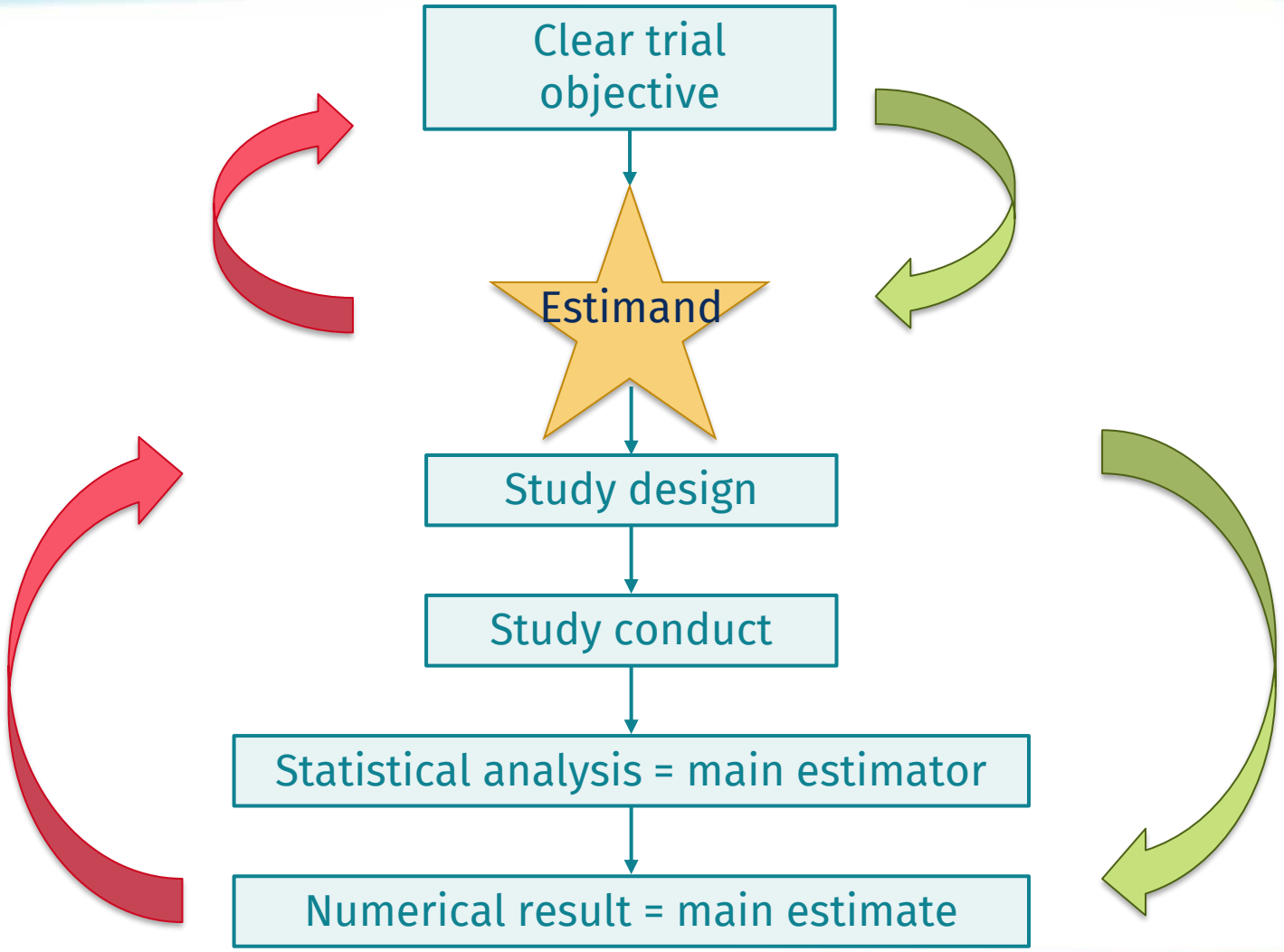
Estimate

The estimand framework

The estimand framework

Where significant issues exist to derive a reliable estimate for a particular estimand, the trial objectives need to be reconsidered from top-down to main estimator (green arrows).

The main estimator should never define the trial objective from bottom up (red arrows).



Estimands

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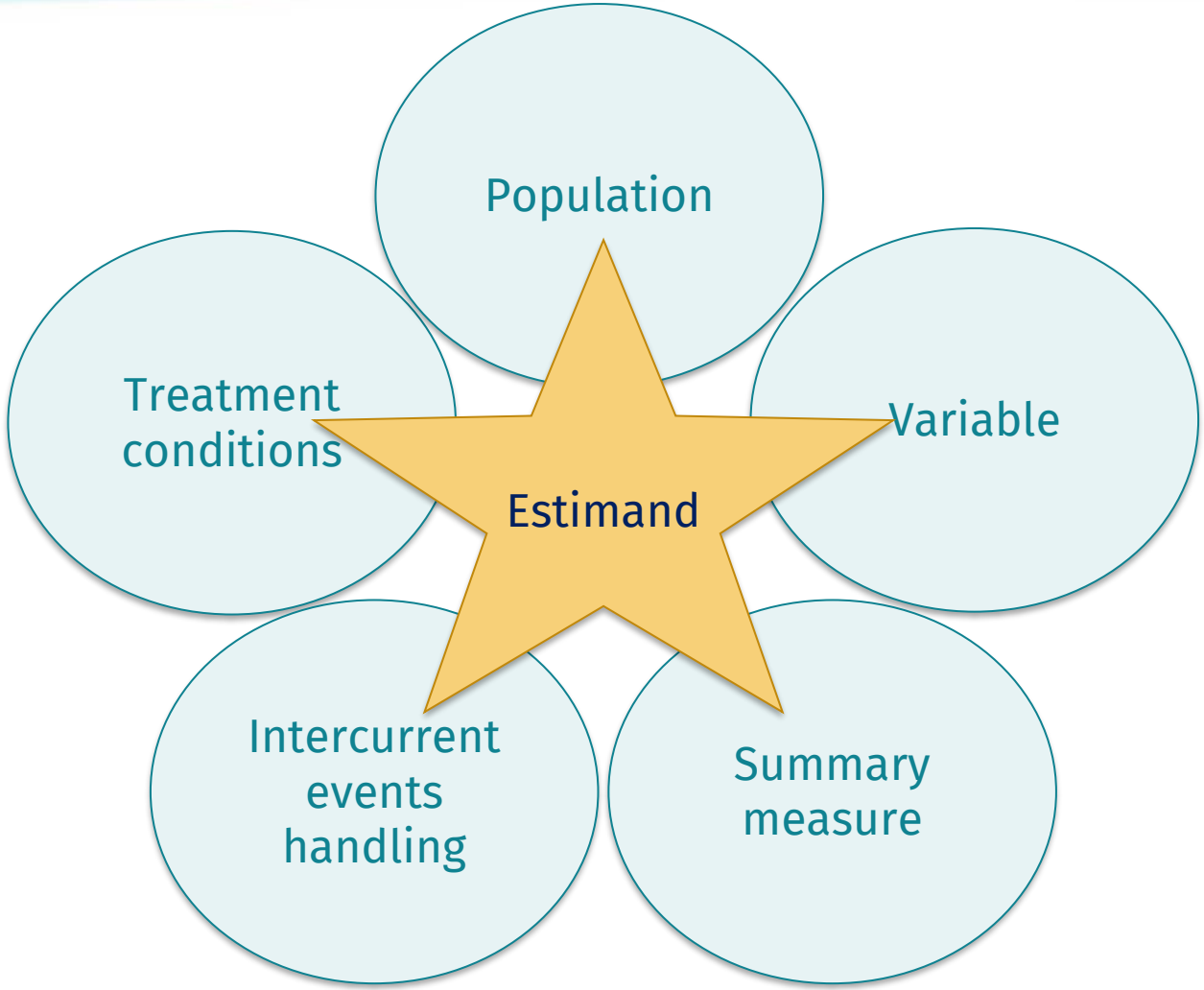

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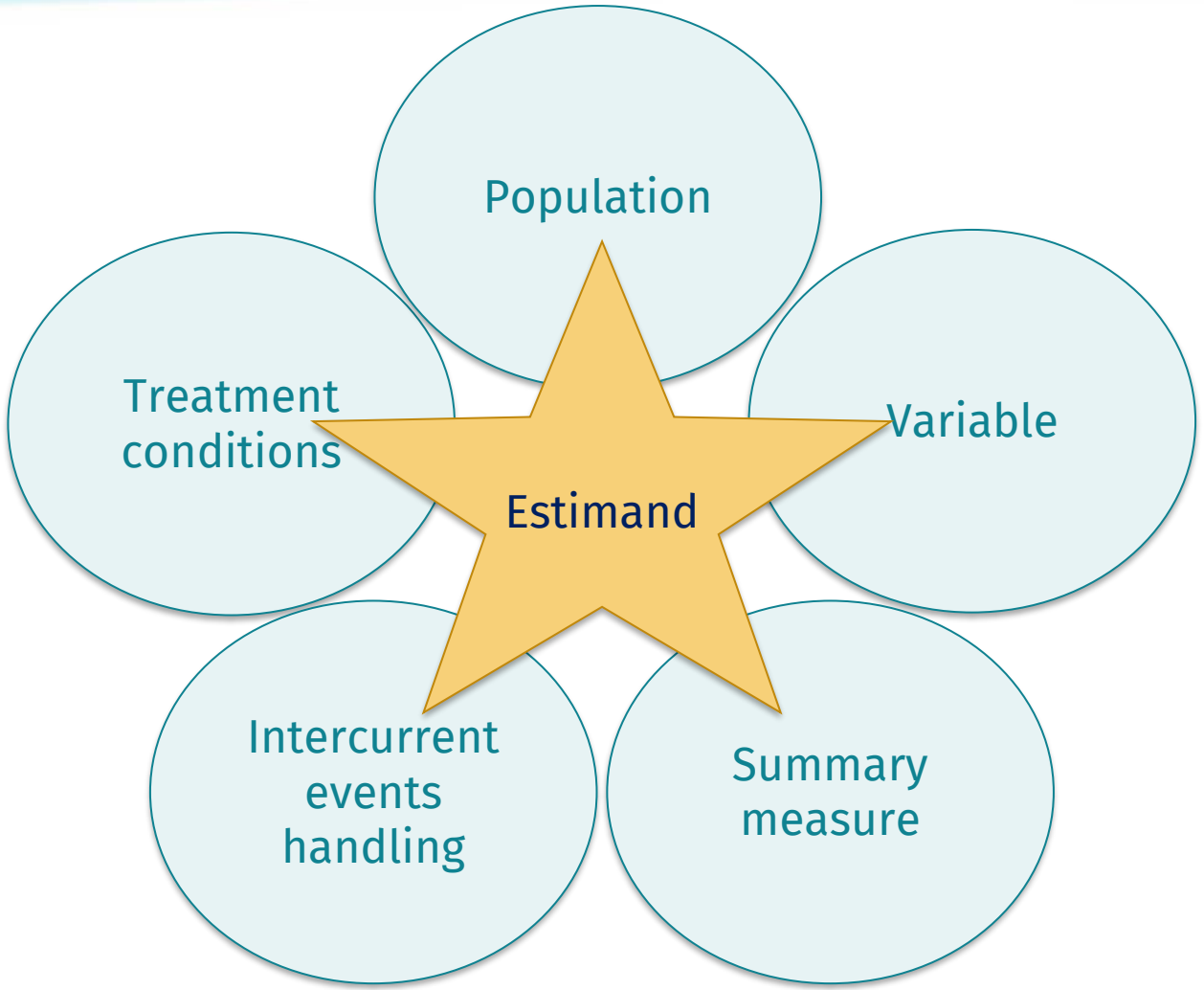

Intercurrent events may be incorporated into treatment, population and/or variable attributes

Treatment conditions

- The **treatment condition(s)** are the treatment strategies you want to compare, for example:

  - Intervention A versus intervention B
  - Intervention A plus rescue medication versus intervention B plus rescue medication

Population

- The **population** of patients who you want to know the treatment effect for:
  - wider population i.e. not only the patients recruited into trial
  - not the analysis population!

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  - not the analysis population!

- May be defined by inclusion/exclusion criteria in study protocol or,
  - further defined by a baseline characteristic
  - defined in terms of a *potential* intercurrent event (principal stratification), e.g. , patients who would adhere to treatment

Variable

- The outcome variable/endpoint to be measured for each patient

- May include whether the patient experience an intercurrent event:
  - Composite (e.g. need for rescue or poor clinical outcome)
  - While-on-treatment re-defines time point (e.g. quality of life up to 6 months or last time point on treatment)

Primary estimand for severe chronic eczema trial

Treatment conditions

Objective: To compare a 12-week course of a new biologic against placebo in routine practice

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IcEv1: Use of rescue medication

IcEv2: Treatment discontinuation

Treatment conditions

Objective: To compare a 12-week course of a new biologic against placebo in **routine practice**

IcEv1: Use of rescue medication

IcEv2: Treatment discontinuation

Estimand attribute	Description
Treatment condition(s)	12 weeks of treatment with new biologic compared to placebo (150 mg e.o.w) regardless of any treatment discontinuation or use of rescue medication

Population

Objective: To compare a 12-week course of a new biologic against placebo in **routine practice**

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Summary measure

Objective: To compare a 12-week course of a new biologic against placebo in **routine practice**

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Summary measure	Mean difference in outcome variable between treatment conditions

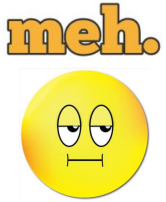
Intercurrent events

Objective: To compare a 12-week course of a new biologic against placebo in **routine practice**

Estimand attribute	Description	
Treatment condition(s)	12 weeks of treatment with new biologic compared to placebo (150 mg e.o.w) regardless of any treatment discontinuation or use of rescue medication	ICEv1 & IcEv2
Population	Patients with confirmed diagnosis of severe chronic eczema meeting trial eligibility criteria	
Variable (outcome)	Change in eczema severity as measured by the EASI score at week 12	
Summary measure	Mean difference in outcome variable between treatment conditions	

What about IcEv 3 - Use of Topical therapies?

Treatment policy

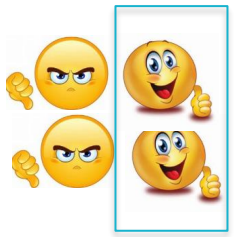


Hypothetical

Composite

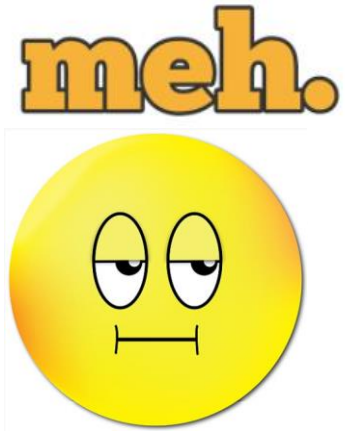
While-on-treatment/alive

Principal stratum



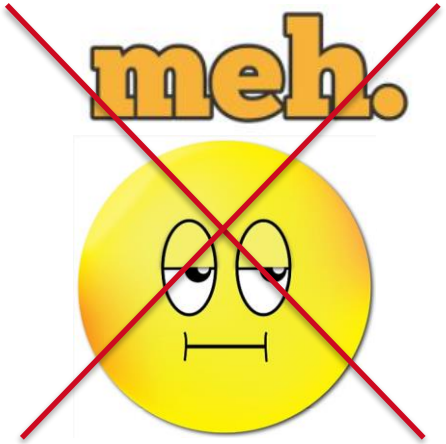
Considerations for **treatment policy strategy**

- Targets the treatment effect **regardless of/despite** the occurrence of intercurrent event (Intercurrent event considered as part of the treatment)
- Unconcerned/indifferent to the occurrence of intercurrent events
- Patient outcomes after intercurrent event of interest
  - Option 1: the treatment effect **despite** use of topical therapies



Considerations for **treatment policy strategy**

- *Cannot* be used when values for the variable after the intercurrent event do not exist for all subjects, e.g. generally cannot be used to deal with *death*!



Considerations for **hypothetical strategy**

- The treatment effect in a hypothetical scenario is targeted,
  - Option 2: the treatment effect **if** topical therapies **were not available**
- Implicit or explicit predictions/imputations required for patients who experienced the event

Considerations for **hypothetical strategy**

- Some hypothetical scenarios might not always be informative/reasonable
  - e.g. **if** patients remained on treatment despite toxicities? ?

- Consider the plausibility of hypothetical scenario & clearly specify

Considerations for **composite strategy**

- The occurrence of the intercurrent event is included in the outcome variable by assigning it to a particular value of the outcome variable

- Simple binary responder/non-responder composite may be constructed:

  - Option 3: composite of no topical therapy and favourable clinical outcome (EASI-75)

Considerations for **composite strategy**

- May be an ordinal/categorical/numerical composite
  - less straight forward with numerical as requires assigning a particular value to an event
  - can assigning ranks to outcomes/intercurrent events (worse ranks) and analyse the ranks

- Complications if treatment has a different effect on components

Considerations for **while-on-treatment strategy**

- Response to treatment **prior to** the occurrence of the intercurrent event is of interest

- Option 4: assess EASI outcome at 12 week or at last time point prior to use of topical therapy

Considerations for **while-on-treatment strategy**

- Generally appropriate only when duration of treatment is not important;
  - because duration is truly not important or
  - because the rate of an event or outcome is constant

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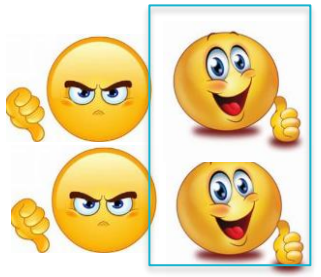
- Generally appropriate only when duration of treatment is not important;
  - because duration is truly not important or
  - because the rate of an event or outcome is constant

- When used to handle death, i.e. looking at response to treatment prior to the prior to occurrence of death
  - termed ***'while-alive'***

Considerations for **principal stratum strategy**

- The treatment effect only in the **subgroup** of the **population whose intercurrent event status would be identical**, irrespective of treatment group is targeted.

  - Option 5:treatment effect for the set patients who would not use topical therapies regardless of arm



Considerations for **principal stratum strategy**

- Modifies the **population** attribute – think about interpretation!
- Can identify the set who would not (or would) have the event in practice?

IcEv3 - Use of Topical therapies?

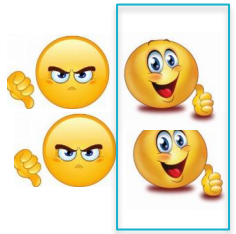
Objective: To compare a 12-week course of a new biologic against placebo in routine practice

Treatment policy strategy – regardless of topical therapy

Hypothetical strategy – if topical therapies **not available**

Composite strategy – include topical therapy **in definition of outcome**

While-on-treatment strategy – prior to use of topical therapy



Principal stratum strategy – subgroup of population who would not use topical therapy

Intercurrent events

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Population	Patients with confirmed diagnosis of severe chronic eczema meeting trial eligibility criteria
Variable (outcome)	Change in eczema severity as measured by the EASI score at week 12
Summary measure	Mean difference in outcome variable between treatment conditions
Handling Intercurrent events	IcEv1: Use of rescue medication – **treatment policy** (as part of treatment) IcEv2: Study treatment discontinuation – **treatment policy** (as part of treatment) IcEv3: **Use of other topical medication - treatment policy**

Missing data

- Anticipate ~15% loss to follow-up in the eczema trial
- Missing data are not Intercurrent events

> **Missing data** Data that would be meaningful for the analysis of a given estimand but were not collected. They should be distinguished from data that do not exist or data that are not considered meaningful because of an intercurrent event.

- Missing data are irrelevant to the construction of the estimand
- The handling of missing data should be addressed in the statistical methods – "How"

Missing data

- Collect informative reasons for why data are missing to distinguish intercurrent events from missing data
- For example, *"loss to follow-up"* may more accurately be recorded as *"treatment discontinuation due to lack of efficacy"*
- Where intercurrent event occurs, handle via the strategy chosen to account for that intercurrent event and not as missing data

Impact on trial design and conduct

- Trial design follows the specification of the estimand of interest & should align

- Alignment with estimand for:
  - The type of trial (e.g., double-blind placebo-controlled parallel design)
  - Duration of subject participation (12 weeks)
  - Discontinuation criteria for individual subjects, subject withdrawal criteria
  - Medications permitted before and during the trial (rescue and topical therapies)
  - Procedures for monitoring subject compliance
  - Measurements of efficacy parameters

Impact on trial design and conduct

- The estimand of interest should inform sample size calculation
- When referencing historical studies take account that might have reported estimated treatment effects or variability based on a different estimand
- The impact of the strategy to reflect intercurrent events is included in the effect size that is targeted and the expected variance (*Delta^2 guidance, Cook et al 2018*)

Estimand impact on data collection

- Eczema trial: Collect data post-treatment nonadherence and after use of rescue or any other topical therapies
- A composite strategy/while-on-treatment/principal stratum strategy would not require data collection after the intercurrent event
- For a hypothetical stratum strategy data after intercurrent is irrelevant
- Data collection should be appropriate to address all trial estimands where multiple are used

Impact on trial analysis – main estimation

- The analysis approach, the ‘estimator’ chosen to align with a given estimand
  - Eczema trial: linear mixed model for repeated measures fitting to all observed data

- This is our *recipe* to obtain an estimate of the estimand of interest

Ingredients

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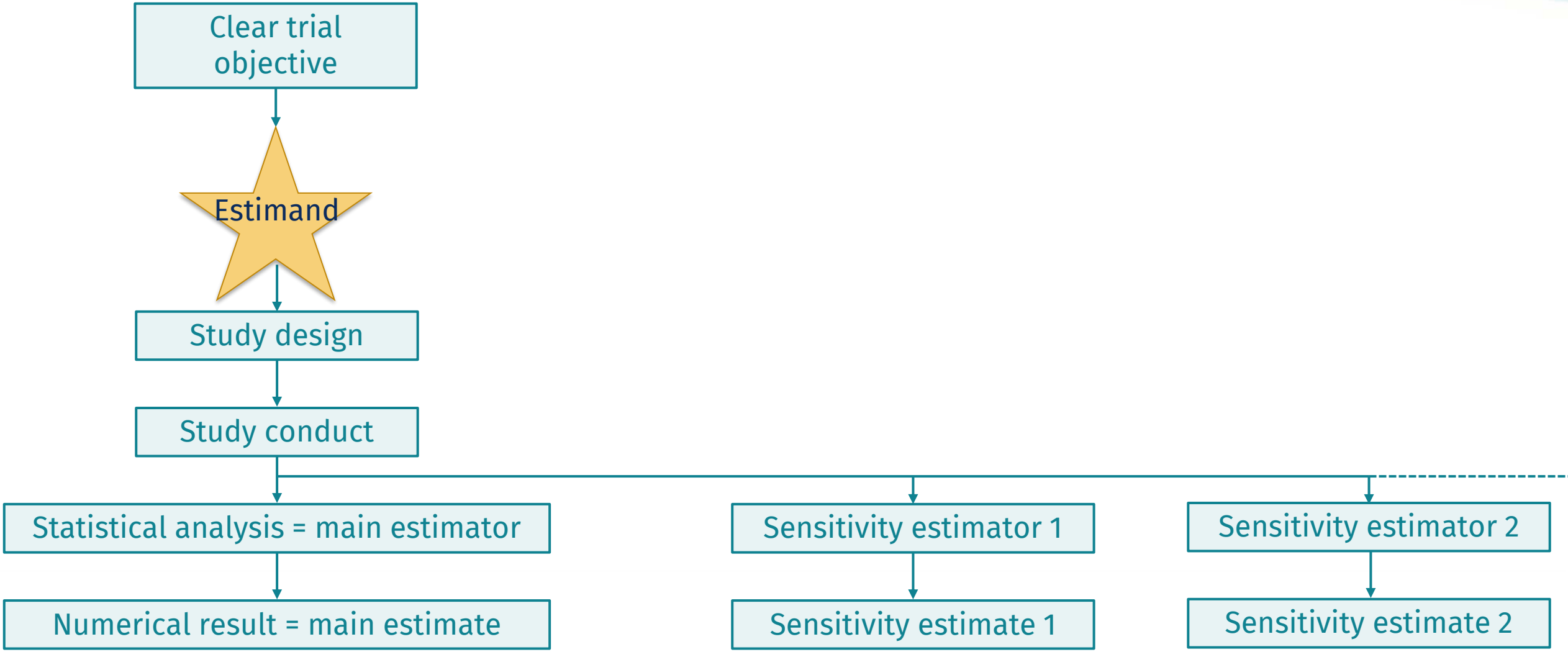
- The estimator selected should provide an estimate on which a reliable interpretation can be based

Sensitivity analysis

- Any assumptions made should be explicitly stated e.g. for missing data
- **Sensitivity analysis** should assess the robustness of results to the underlying assumptions

> **Sensitivity analysis:** A series of analyses conducted with the intent to explore the robustness of inferences from the main estimator to deviations from its underlying modelling assumptions and limitations in the data.

Sensitivity analysis



Sensitivity analysis

- ICH E9(R1) recommends investigating the impact of changing one assumption at a time
- Particular attention should be given to missing data in sensitivity analysis
- The estimand of interest defines what data is missing
- It also prescribes how missing data should be handled in the analysis/sensitivity analysis

Supplementary analysis

- Other planned analysis which targets a *different question*

Supplementary analysis: A general description for analyses that are conducted in addition to the main and sensitivity analysis with the intent to provide additional insights into the understanding of the treatment effect.

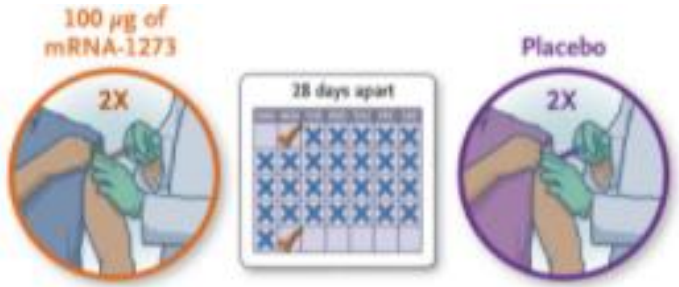
Supplementary analysis

Objective: To assess whether a 12-week course of biologic would improve disease severity for all patients if rescue not available, otherwise as used in routine practice.

Estimand attribute	Description
Population	Patients with confirmed diagnosis of severe chronic eczema meeting trial eligibility criteria
Treatment condition(s)	12 weeks of treatment with new biologic compared to placebo despite any treatment discontinuation **if rescue medication not available**
Variable (outcome)	Change in eczema severity as measured by the EASI score at week 12
Strategies used to handle Intercurrent events	Use of other topical medication - **treatment policy** Study treatment discontinuation – **treatment policy (as part of treatment)** **Use of rescue medication – hypothetical**
Summary measure	Mean difference in outcome variable between treatment conditions

Further examples – covid vaccine trial

Objective: To demonstrate the efficacy of mRNA-1273 to prevent COVID-19



Baden et al, NEJM, 2020

Further examples – covid vaccine trial

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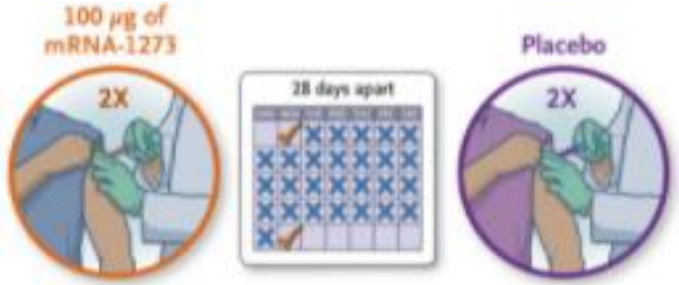

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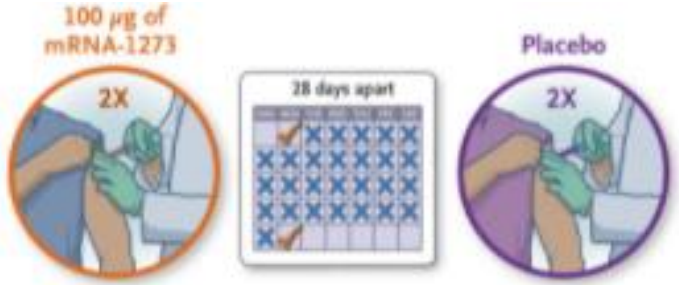
Target Population	Adults aged 18 years and older in circumstances at a high risk of SARS-CoV-2 infection but without medical conditions that pose additional risk of developing severe disease. The population excludes those previously infected or vaccinated for SARS-CoV-2 or with a medical condition, on treatment that poses additional risks (including those requiring immunosuppressants or immune-modifying drugs), or SARS-CoV-2 pre-positive.



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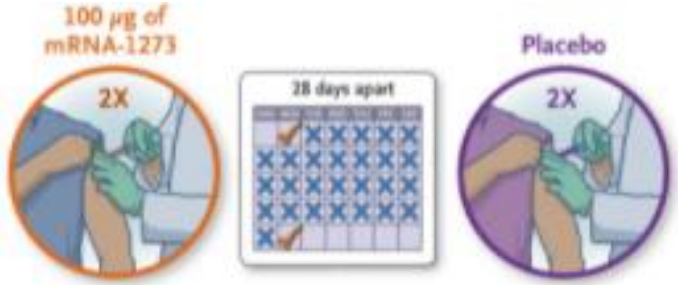
Target Population	Adults aged 18 years and older in circumstances at a high risk of SARS-CoV-2 infection but without medical conditions that pose additional risk of developing severe disease. The population excludes those previously infected or vaccinated for SARS-CoV-2 or with a medical condition, on treatment that poses additional risks (including those requiring immunosuppressants or immune-modifying drugs), or SARS-CoV-2 pre-positive.
Variable/Endpoint	Time to COVID-19 Disease, censoring at early discontinuation, early infection, or last assessment for an event not being observed, whichever comes earlier.



Baden et al, NEJM, 2020

Further examples – covid vaccine trial

Objective: To demonstrate the efficacy of mRNA-1273 to prevent COVID-19	
Estimand Description	Vaccine efficacy will be measured using 1 – HR (mRNA-1273/Placebo) of COVID-19 from 14 days after second dose of IP in adults. A while alive strategy will be used for deaths unrelated to COVID-19, and a treatment policy strategy for early infection. A principal stratum strategy is used to exclude participants missing a dose of IP or being SARS-CoV-2 positive at baseline.
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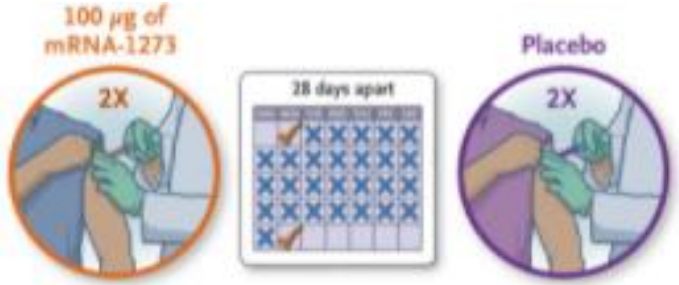
Treatment Condition(s)	**Test:** mRNA-1273 **Reference:** Placebo



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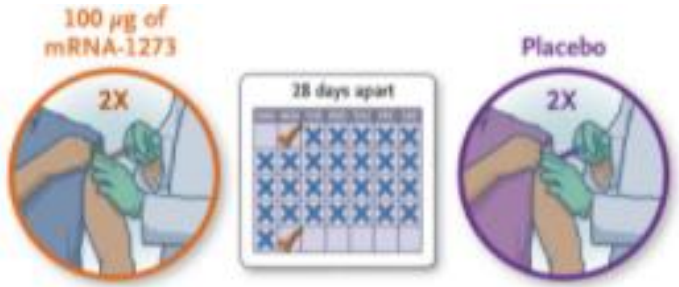
Population-Level Summary	Vaccine efficacy defined as 1 - HR of mRNA-1273/Placebo



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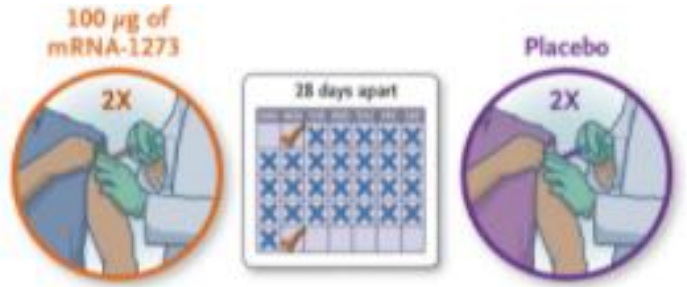
Population-Level Summary	Vaccine efficacy defined as 1 - HR of mRNA-1273/Placebo
Intercurrent Event Strategy	
IcEv1 (unrelated death):	While alive
IcEv2 (early infection):	Treatment policy
IcEv3 (Missed dose of IP):	Principal stratum
IcEv4 (SARS-CoV-2 positive at baseline):	Principal stratum



Emergency bowel surgery trial

FLOELA
FLuid Optimisation in Emergency LAparotomy

Primary Objective

To establish whether minimally invasive cardiac output monitoring to guide protocolised administration of intra-venous fluid during and for up to six hours after major emergency bowel surgery leads to an increase in the number of days alive and out of hospital within 90 days of randomisation.

Emergency bowel surgery trial

FLOELA
FLuid Optimisation in Emergency LAparotomy

Primary Estimand

The estimand for the primary outcome (DAOH90) is the ratio of means of days alive and out of hospital within 90 days of randomisation between protocolised cardiac output-guided haemodynamic therapy vs. usual care (intravenous fluid administered without use of cardiac output monitoring), regardless of adherence or use of cardiac monitoring in the control arm, in participants aged ≥50 years who undergo emergency bowel surgery

Emergency bowel surgery trial

FLOELA
FLuid Optimisation in Emergency LAparotomy

Aspect	Definition
Target population:	Patients ≥50 years old who undergo emergency bowel surgery
Variable/endpoint:	Days Alive and Out of Hospital within 90 Days of Randomisation (DAOH90 = count of days alive and out of hospital within 90 days of randomisation where DAOH90 = 0 if patient dies within 90 days and DAOH = 90 – (days in hospital within 90 days of randomisation) if patient alive 90 days after randomisation)
Treatment conditions:	**Intervention Group -** Protocolised cardiac output-guided haemodynamic therapy during surgery, and for six hours after in patients admitted to an area capable of delivering this intervention. **Usual Care Group -** Intravenous fluid administration without the use of cardiac output monitoring or protocol.
Population level summary measure	Ratio of means (Intervention v usual care group).

Emergency bowel surgery trial

FLOELA
FLuid Optimisation in Emergency LAparotomy

Aspect	Definition
Intercurrent events	**Strategy**
Surgery not received (applies to both treatment arms)	Principal stratum (of participants undergoing surgery)
Procedure modified after surgery begins such that no longer eligible for NELA (applies to both treatment arms)	Treatment policy
Receipt of cardiac output monitoring (control arm only)	Treatment policy
Failure to initiate cardiac output monitoring during/after surgery (intervention arm only)	Treatment policy
Cardiac output monitoring initiated but intervention algorithm not followed	Treatment policy

ICH E9(R1) Summary

- Introduced the estimand framework to align trial objectives, design (data collection), conduct, analysis and inference
- At initial planning stages translate trial objective(s) into estimands
- Consider intercurrent events and strategies relevant for clinical context
- Subsequently align design, conduct and analysis with estimand(s)
- Missing data is not an intercurrent event – estimation issue
- Conduct sensitivity analysis to explore the robustness of inferences to deviation from underlying assumptions (same estimand)
- Supplementary analysis are any other analysis conducted to fully investigate and understand the trial data (e.g. different estimand)