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Estimands Workshop

PSI New Starters SIG, 28MAR2019

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+ Why is this topic important for us?
+ Framework – estimand definition and attributes
+ Intercurrent events and strategies
+ Examples
+ Discussion

Why is this topic important for us?

Estimands implemented into ICH guidance*

- Increased focus in the area of clearly defining trial objective and how the endpoints and analyses reflect this
  - NRC report (2010)
  - Papers published by the FDA and industry statisticians

- New addendum to Statistical Principles for Clinical Trials (ICH E9)
  - Draft guidance on Estimands and Sensitivity Analysis in Clinical Trials – 30th Aug 2017
  - More than 1000 comments received during consultation period
  - Planned ICH meeting June 2019 to finalise addendum – expect final by end of 2019
  - Deceptive being in E9, impact far beyond the statistical considerations of a trial
  - **Regulators expecting us to follow the spirit of the addendum already**

- Quote from draft guidance

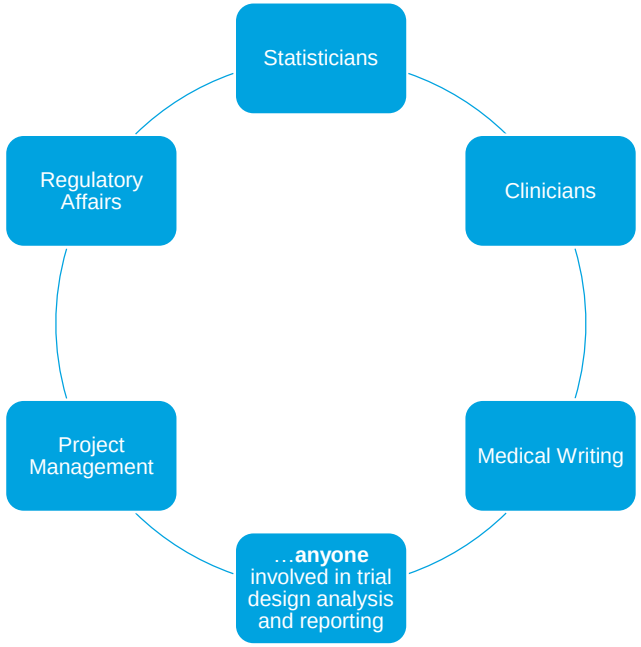
The construction of the estimand(s) in any given clinical trial is a multidisciplinary undertaking including clinicians, statisticians and other disciplines involved in clinical trial design and conduct

* International Council for Harmonisation

Why is this topic important for us?

Profound change in clinical development

- Statisticians need to collaborate closely with neighbouring functions from an early stage in these discussions



- Discussions from objectives to analyses more in depth at protocol stage, more scientific advice?
- Documentation requirements from protocol to study report → Template updates (protocol, analysis plan, study report)

Framework*

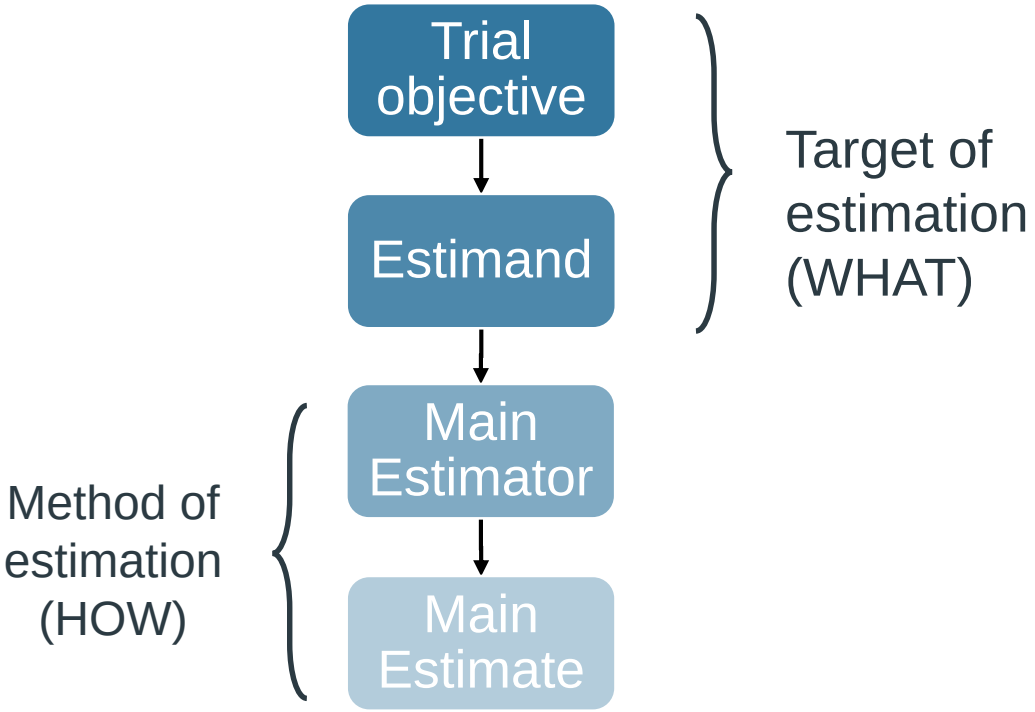
A framework and language are introduced to:

- Promote **alignment between trial objectives, design (data collection), conduct, analysis and inference**
- Promote understanding that trial objectives cannot be translated into estimands without reflecting how potential **intercurrent events** are addressed in the scientific question of interest
- Promote discussion of different **strategies** to handle **intercurrent events** in order to identify and describe the treatment effects that reflect the scientific questions of interest
- Define a treatment effect of interest – **before a trial is designed and conducted** – that is relevant to use of a medicine in clinical practice
- Highlight the importance of considering whether a main analysis will derive an estimate which is reliable for inference
- Redefine **missing data**
- Redefine **sensitivity analysis** and the regulatory assessment of robustness
- Introduce **supplementary analysis** as any other analysis conducted fully to investigate and understand the trial data

* ICH E9 (R1) Training material, Module 2.1 - Introduction

What is the question?

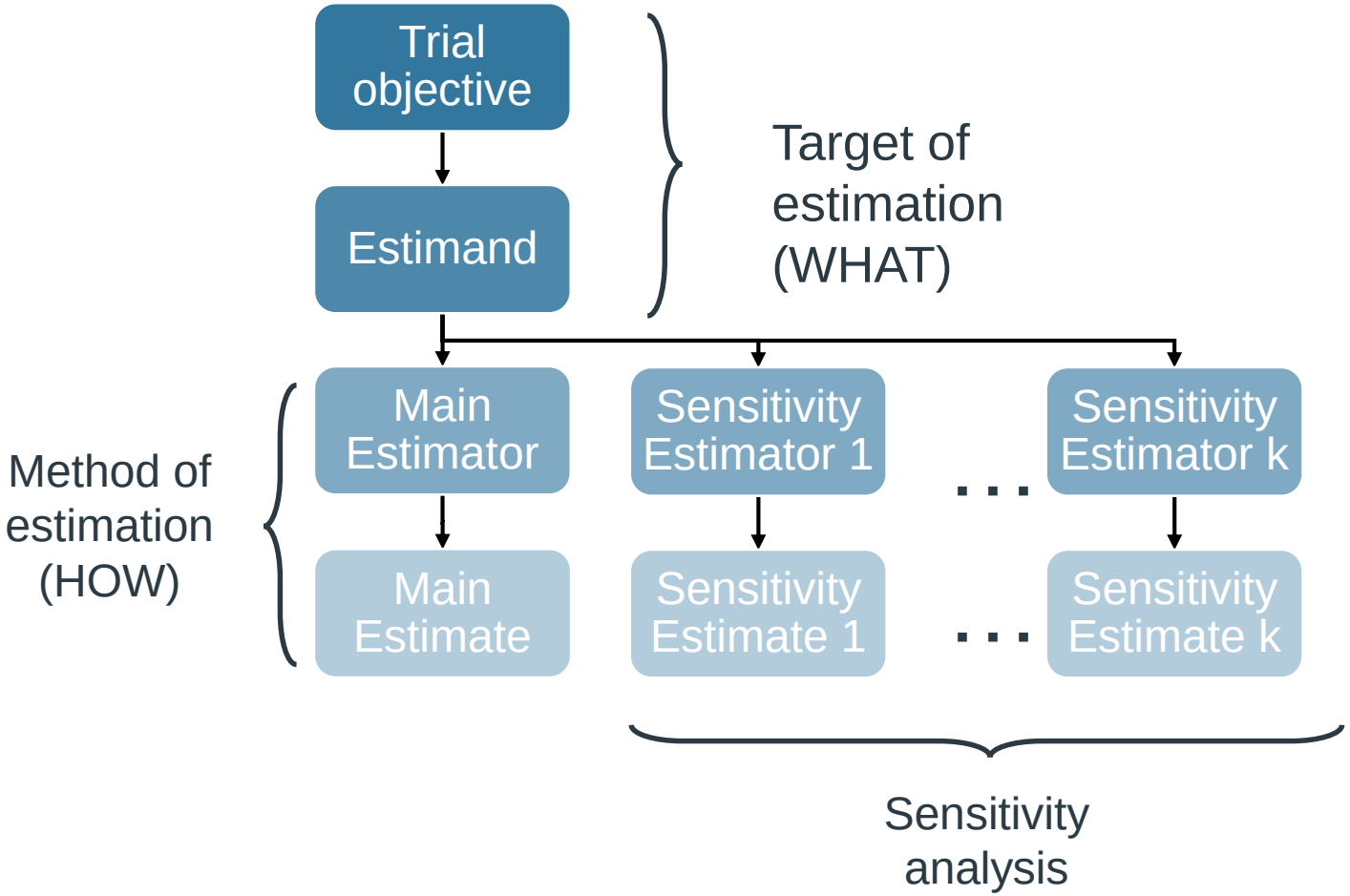
Objective of the trial



Scientific question should drive design, conduct and analysis (has been known to be done in reverse)

What is the question?

Objective of the trial



Scientific question should drive design, conduct and analysis (has been known to be done in reverse)

You have the question, what is the estimand?

How have we been forming the question?

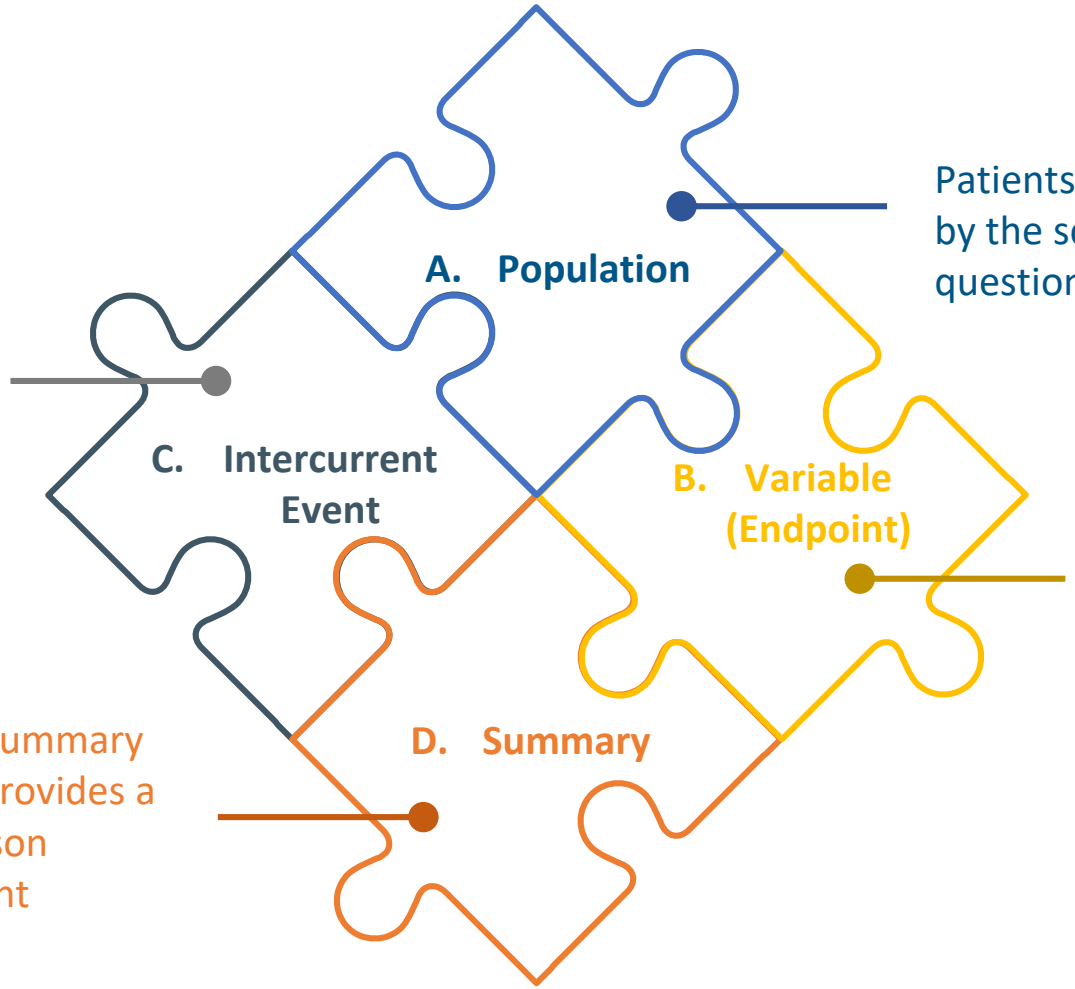
- Prior to the introduction of the estimands framework protocols have addressed:
  - The primary objective
  - The primary endpoint
  - Analysis of the primary endpoint (including analysis sets)

- Not always a clear link between these
  - Objective should inform endpoint and analysis

- Treatment effect should be defined first with the primary objective
  - Tolerability, adherence, additional medication
  - What events can occur during the trial need to be considered to avoid ambiguity in the analysis and interpretation of results

Definition of an estimand

The 4 attributes that together define an Estimand



Patients targeted by the scientific question

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

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

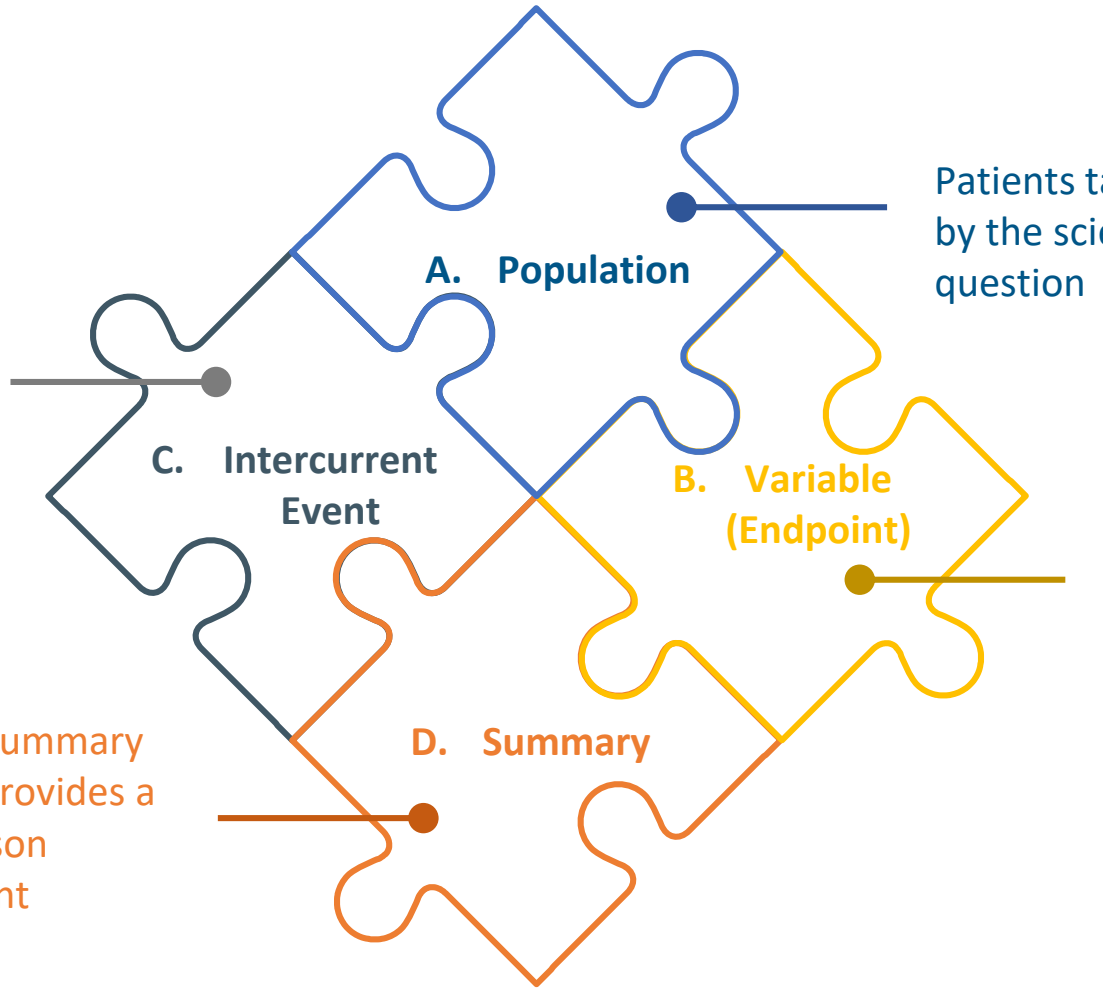
Population-level summary for the variable; provides a basis for comparison between treatment conditions

Definition of an estimand

The 4 attributes that together define an Estimand

NEW!

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



Patients targeted by the scientific question

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

Population-level summary for the variable; provides a basis for comparison between treatment conditions

Common intercurrent events

- Premature treatment discontinuation due to adverse events
- Premature treatment discontinuation due to lack of efficacy
- Treatment switch
- Change in background therapy
- Use of rescue medications
- Use of prohibited concomitant medications
- Death
- Missing data from withdrawal of consent
- Etc.

Types of estimand

Variations based upon handling of intercurrent events

ICH E9 R1 draft guidance outlines 5 possible ways to take intercurrent events into account

- **Treatment Policy** – Actual values of the variable are used regardless of whether an intercurrent event has occurred
- **Composite** – Modification of the variable or the summary measure such that an intercurrent event becomes a component of the outcome
- **Hypothetical** – Values of the variable under some hypothetical conditions where an intercurrent event would not happen, or hypothetical results after an event had happened
- **Principal stratum** – Restrict the population of interest to the stratum of patients where the intercurrent event would not have happened
- **While on Treatment** – Values of the variable up to the time of the intercurrent event, rather than the planned assessment point.

Not an exhaustive list. You may have others or use a combination of the above

Diabetes + Hypercholesterolemia at high CV risk

Original protocol

- **Objective**
  - To demonstrate the superiority of Drug A in comparison with placebo in the reduction of **calculated** LDL-C after 24 weeks of treatment in patients with diabetes treated with insulin and with hypercholesterolemia at high cardiovascular risk not adequately controlled on maximally tolerated LDL-C lowering therapy
- **Endpoint (variable)**
  - Percent change in **calculated** LDL-C from baseline to week 24 using all LDL-C values regardless of adherence to treatment
- **Analysis**
  - **Primary:** Mixed-effect model with repeated measures (MMRM) approach. All post-baseline data available within Week 8 to Week 24 analysis windows will be used. Missing data accounted for by the MMRM model. Fixed effects: treatment, time point, treatment by time point interaction; baseline LDL-C and baseline LDL-C by time point interaction.
  - **Sensitivity:** A sensitivity analysis will be conducted using **measured** LDL-C to evaluate the robustness of the results regardless of the way to assess LDL-C*.

* calculated or measured

Diabetes + Hypercholesterolemia at high CV risk

Let's identify the elements of the estimand

- **Estimand (WHAT)**
  - **Population**: Patients with diabetes treated with insulin and with hypercholesterolemia at high cardiovascular risk not adequately controlled on maximally tolerated LDL-C lowering therapy (stated in the objective – see also I/E criteria)
  - **Endpoint (variable)**: Percent change in calculated LDL-C from baseline to week 24
  - **Intercurrent event(s)**: regardless of adherence to treatment
  - **Summary measure**: mean % change in calculated LDL-C from baseline to week 24
- **Analysis (HOW)**
  - Mixed-effect model with repeated measures (MMRM) approach. All post-baseline data available within Week 8 to Week 24 analysis windows will be used. Missing data accounted for by the MMRM model. Fixed effects: treatment, time point, treatment by time point interaction; baseline LDL-C regardless of adherence to treatment and baseline LDL-C by time point interaction.

- So this would be a **treatment policy** estimand; we use all data regardless of any intercurrent events.

Diabetes + Hypercholesterolemia at high CV risk

Sensitivity analysis and Supplementary analysis

- *A sensitivity analysis will be conducted using **measured** LDL-C to evaluate the robustness of the results regardless of the way to assess LDL-C.*

  - The variable here is not the same as in the primary estimand, so this analysis is not using a different method to estimate the same thing – it is using the same method of analysis to estimate something different
  - In the draft version of the addendum, this would be a **supplementary** analysis, rather than a sensitivity analysis
  - Sensitivity analysis would be, for instance, a non-parametric analysis of the % change in calculated LDL-C, instead of the parametric MMRM
  - However, this is one of the areas in which lots of comments were received, so we need to wait and see exactly how the addendum deals with this
  - Either way, the addendum accepts the need for multiple estimands / different ways of analysis, but the terminology is to be confirmed

Examples for group work

- Rheumatoid arthritis – ACR20 (binary)
- Asthma – Exacerbations (recurrent events – rate)
- Asthma - FEV1 (continuous)
- Melanoma – PFS (time to event)

How can we rewrite the examples in the estimands framework?

Points to consider

- The objective of the trial – this has to guide everything else
- The 4 attributes of the estimand: population, variable (endpoint), intercurrent event(s), summary measure
- What are the intercurrent events that the protocol has considered and how are they dealt with (strategies)?
  - How do these translate into estimand terminology?
  - Implications on the trial conduct and data collection
- Analysis
  - Primary
  - Sensitivity
  - Supplementary
- Are there any other intercurrent events and strategies that we might we consider?
  - Would these address the same or a similar objective?
- Anything specific to each therapeutic area?

Rheumatoid Arthritis (RA)

Original protocol

- Objective:
  - The primary objective of this study is to evaluate the efficacy of Drug A (dose X) + MTX compared to Placebo + MTX in patients with active RA by assessment of the signs and symptoms of RA as measured by American College of Rheumatology 20% response criteria (ACR20) at Week 24.
- Variable
  - Proportion of patients with ACR20 at Week 24
    - › Withdrawal for any reason
    - › Increase of background MTX
    - › DMARD initiated

Non-responder for ACR20

- Analysis
  - Test of treatment difference in proportion of responders with a Mantel-Haenszel approach stratified by country (primary)
  - Logistic regression including terms for baseline DAS28 score, duration of disease and rheumatoid factor in addition to treatment and country
  - Subgroups will also be explored

Asthma study – Rate of exacerbations

Original protocol

- Primary objective
  - To determine the efficacy of Drug A (dose X) compared with placebo on the rate of severe asthma exacerbations* over 6 months in adults with uncontrolled persistent asthma, despite treatment with medium to high dose inhaled corticosteroids and long-acting β_2 agonists
- Primary variable
  - Number of severe exacerbations experienced by a patient over the 6 month treatment period
- Primary analysis
  - Poisson regression model taking overdispersion into account. Model will include treatment, oral corticosteroid use at baseline, geographical region and FEV_1 at baseline
- Sensitivity analysis
  - Negative Binomial regression using the same response variable and covariates as for the primary analysis

***Severe exacerbation** (defined by the American Thoracic Society / European Respiratory Society): A worsening in asthma symptoms requiring either the use of systemic corticosteroids for at least 3 consecutive days, or for patients on a stable maintenance dose an increase in the dose of oral corticosteroids for at least 3 consecutive days or an asthma specific emergency room visit/hospital admission requiring the use of single or multiple doses of systemic corticosteroids. Use of systemic corticosteroids is defined as tablets, suspension, injection or infusion. An injection of depot corticosteroids is considered equivalent to at least 3 consecutive days of systemic corticosteroids

Asthma – FEV_1

Original protocol

- Objective
  - Demonstrate the efficacy of Drug A (dose X) vs Drug C (active control) in children aged 6 to <12 years with asthma
- Variable
  - Change from baseline to Week 12 1-hour post-dose clinic FEV_1 (L)
- Analysis
  - MMRM assuming MAR. Model:
    - Change in FEV_1 = treatment + baseline FEV_1 + region + age + visit + treatment*visit
    - All collected 1-hour post-dose clinic FEV_1 data from baseline to week 12 will be included
  - Sensitivity:
    - include all data prior to termination of IP
    - Include all data up to start of alternative therapy

Melanoma

Original protocol

- Objective
  - To assess the efficacy of Drug A in combination with background therapy compared with placebo in combination with background therapy in terms of progression-free survival
- Variable
  - PFS using blinded independent central review (BICR) according to RECIST 1.1: time from randomisation until the date of objective disease progression or death regardless of whether the patient withdraws from randomised therapy or receives another anti-cancer therapy prior to progression
- Analysis
  - Stratified log-rank test
- Sensitivity analysis
  - Evaluation time bias: use the mid-point between the time of progression and RECIST 1.1 assessment of the previous evaluable scan
  - Attrition bias – include actual PFS time, rather than censor those who have missed two or more scans prior to progression; censor if subsequent anti-cancer therapy starts; censor if surgical resection of tumour prior to progression
  - Ascertainment bias – use investigator review, rather than BICR