# The Final ICH E9(R1)

# E9 addendum

**Chrissie Fletcher, Amgen Ltd & EFPIA lead for ICH E9(R1)**

**BBS Causal Inference 1-day meeting, 21st August 2019**

International Council for Harmonisation of Technical Requirements
for Registration of Pharmaceuticals for Human Use

# Disclaimer (Chrissie Fletcher)

- **The views expressed herein represent those of the presenter and do not represent the views or practices of Amgen, the views of the other Industry representatives on the ICH E9 working group, or the views of the general Pharmaceutical Industry.**

# Acknowledgements

**E9 Working Group members**

# Agenda

- **Introducing the final ICH E9(R1)**
  - Focus on key changes
  - Emphasise key aspects of E9 addendum
- **Proposal for ICH E9 Implementation Working Group**
- **Update on TransCelerate and ICH M11**
- **EFPIA/EFSPI E9(R1) Implementation Working Group**
- **Conclusions**

# Final E9 addendum: New layout & title

**Estimands and Sensitivity Analysis in Clinical Trials**

**TABLE OF CONTENTS**

# Scope of E9 addendum

**"The principles outlined in this addendum are relevant whenever a treatment effect is estimated, or a hypothesis related to a treatment effect is tested, whether related to efficacy or safety. While the main focus is on randomised clinical trials, the principles are also applicable for single arm trials and observational studies. The framework applies to any data type, including longitudinal, time-to-first event, and recurrent event data. Regulatory interest in the application of the principles outlined will be greater for confirmatory clinical trials and, where used to generate confirmatory conclusions, for data integrated across trials."**

# Reminder: Key topics clarified in E9 addendum

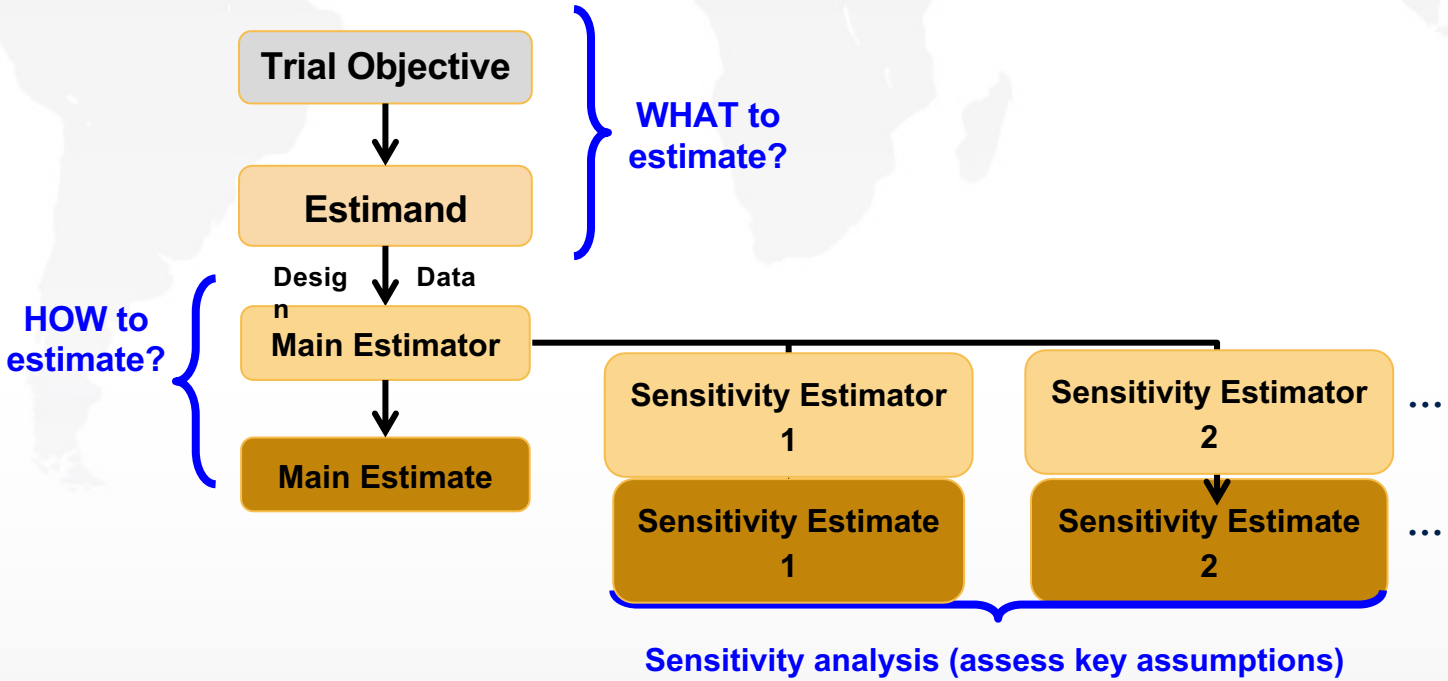
- **Intention to treat**
  - Discussing other treatment effects not aligned to the ITT principle
  - Points to consider for the design and analysis of trials to give estimates of these treatment effects that are reliable for decision making
- **Data handling and missing data**
  - Distinguishing discontinuation of randomised treatment from study withdrawal
  - Study withdrawal is not an intercurrent event
  - Establishing which data need to be collected and hence which data, when not collected, present a missing data problem

# Reminder: Key topics clarified in E9 addendum (cont.)

- **Role of analysis sets**
  - The definition of the treatment effect of interest determines inclusion in the analysis of both the subjects and the values from each subject, considering the occurrence of intercurrent events
  - The meaning and role of an analysis of the per-protocol set is strongly questioned
- **Concept of robustness and sensitivity analysis**
  - Clarifies the meaning of robustness
  - Sensitivity of inference to the assumptions of a chosen method of analysis and sensitivity to the choice of analytic approach more broadly.
  - Clarifies selecting sensitivity analysis

# A Structured Framework

**For a given clinical question of interest: aligning trial objective, target of estimation, design, method of estimation and sensitivity analysis**




10

# Estimand - definition

**Estimand** A precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarises at a population-level what the outcomes would be in the same patients under different treatment conditions being compared.

# Intercurrent event - definition

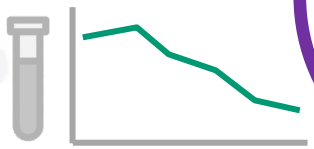
**Intercurrent event** Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest. It is necessary to address intercurrent events when describing the clinical question of interest in order to precisely define the treatment effect that is to be estimated.

New

# Inputs for Constructing an Estimand

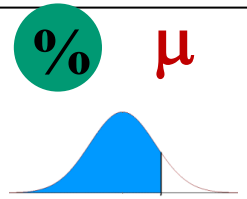
**Target Population**

**Variable (Endpoint)**

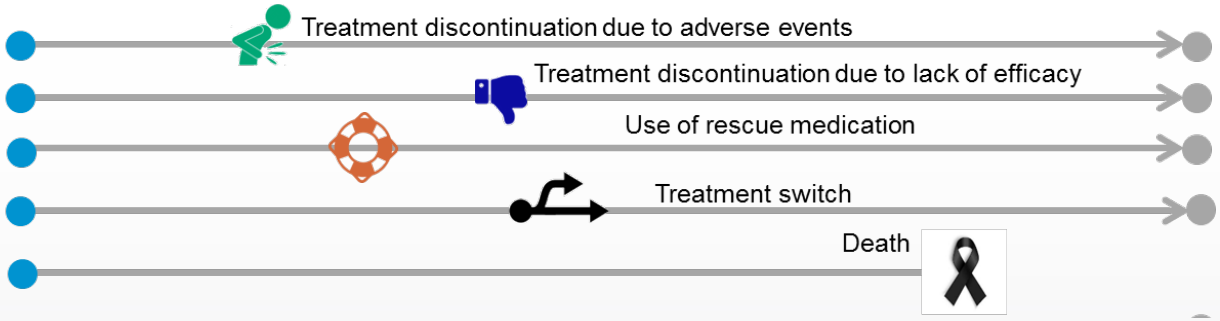


**Treatments being compared**

**Population-level Endpoint Summary**




***Intercurrent Event(s)* that can impact the above input(s)**






11

# A3.3 Estimand attributes

- ***"The treatment condition of interest and, as appropriate, the alternative treatment condition to which comparison will be made"***
  - *"These might be individual interventions, combinations of interventions administered concurrently, e.g. as add-on to standard of care, or might consist of an overall regimen involving a complex sequence of interventions."*
- "*Precise **specifications of treatment, population and variable** are likely to address many of the intercurrent events considered*"
- "*The clinical question of interest in respect of any **other intercurrent events** will usually be reflected using the strategies introduced as treatment policy, hypothetical or while on treatment*."

# Strategies for Addressing Intercurrent Events

- **Treatment Policy**

The occurrence of the intercurrent event is considered irrelevant. The value(s) is used regardless of whether or not the intercurrent event occurs. [Impacts treatment]

- **Hypothetical strategies**

A scenario is envisaged in which the intercurrent event would not occur: the value of the variable to reflect the clinical question of interest is the value which the variable would have taken. [Impacts treatment]

Caution: clinically relevant scenarios

- **Composite variable strategies**

The intercurrent event is incorporated into the definition of the variable. [Impacts variable]

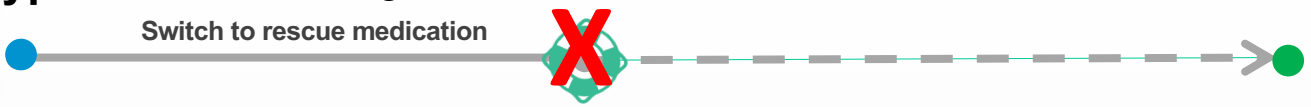
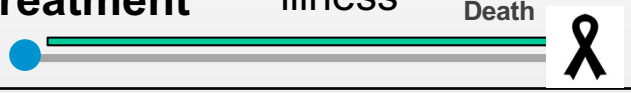
- **While on treatment strategies**

Response to treatment prior to the occurrence of the intercurrent event is of interest. [Impacts variable]

- **Principal stratum strategies**

The clinical question of interest relates to the treatment effect only within the stratum of interest. [Impacts population]

# Strategies for Addressing Intercurrent Events

| Strategy | *Example of Treatment Effect of Interest* |
|---|---|
| **Treatment Policy** | Overall survival regardless of whether or when **treatment switching** happens   |
| **Composite** | Heart attack **or** **treatment discontinuation due to AE**   |
| **Hypothetical** | Change in HbA1c if **rescue medication** is not used   |
| **Principal Stratum** | Infection severity in subpopulation that will **become infected** despite preventive treatment  |
| **While on Treatment** | QoL under palliative treatment until **death** in terminal illness   |

# Attributes of an estimand description

**Population**

Patients targeted by the scientific question

**Variable**
**(or endpoint)**

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

**Treatment**

The treatment of interest, and if appropriate, the alternative treatment to which comparison will be made

**Remaining Intercurrent events**

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

**Population-level summary for the variable**

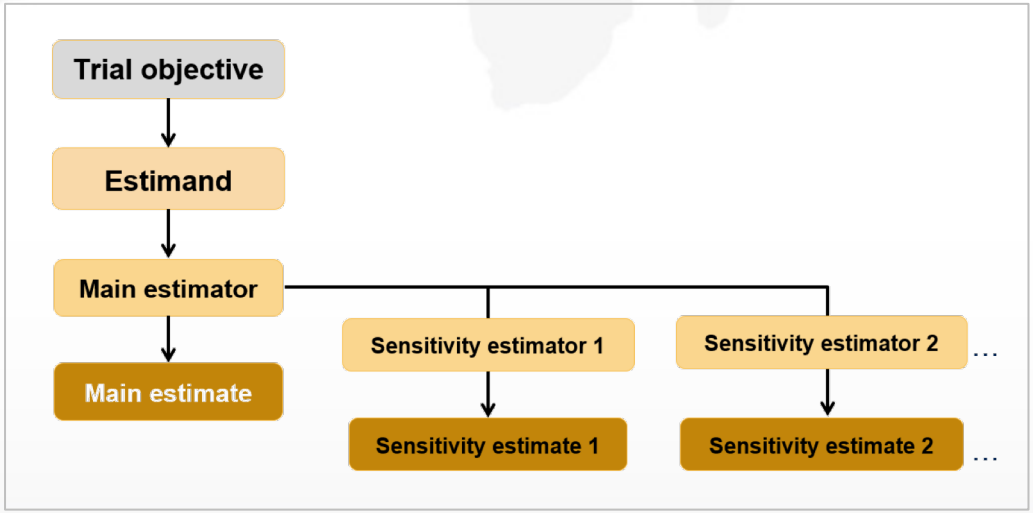
Provides, as required, a basis for a comparison between treatment conditions

# Impact on Trial Design and Data Collection

- The **design of a trial** needs to be **aligned to the choice of the estimand** or estimands that reflect the **primary trial objectives** and which will form the basis to establish whether those objectives have been met.
- The agreed **estimand dictates the data that need to be collected** during the trial.
- **Different estimands** might have **different requirements** regarding data collection.
- Each trial is likely to have **multiple estimands**, which means that data collection should be determined by the **need to address them all.**

# Trial Analysis: Main estimation

Any **assumptions made should be explicitly stated**, and **sensitivity analysis** should be used to assess the robustness of the results to the underlying assumptions.



# Sensitivity analysis - definition

**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

# Missing data - definition

**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 definition, ICH E9(R1) Draft addendum*

# Role of sensitivity analysis

- Sensitivity analysis is used to evaluate the **robustness of inferences** made on a particular estimand to **limitations in the data** and **deviations from the assumptions** used in the statistical model for the main estimator.
- With an agreed estimand, and a pre-specified statistical analysis that is aligned to that estimand, sensitivity analysis can focus on sensitivity to deviations from assumptions in respect of a particular analysis rather than sensitivity to the choice of analytic approach.

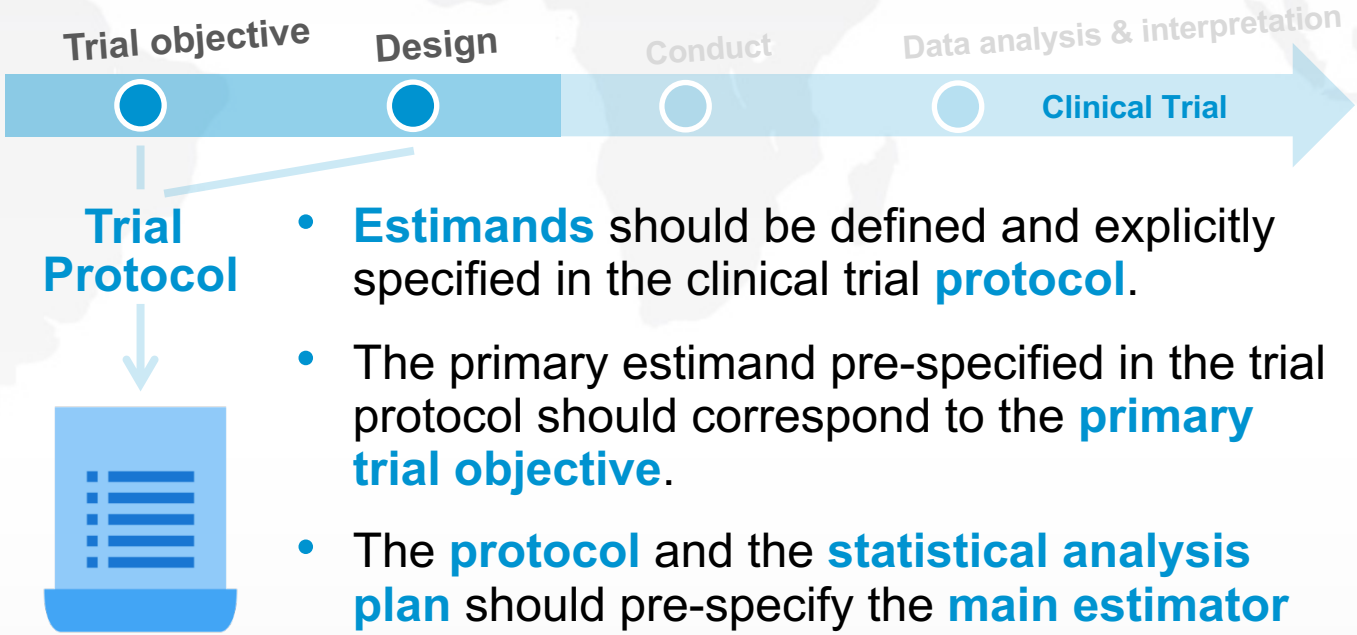
# Supplementary analysis - definition

**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

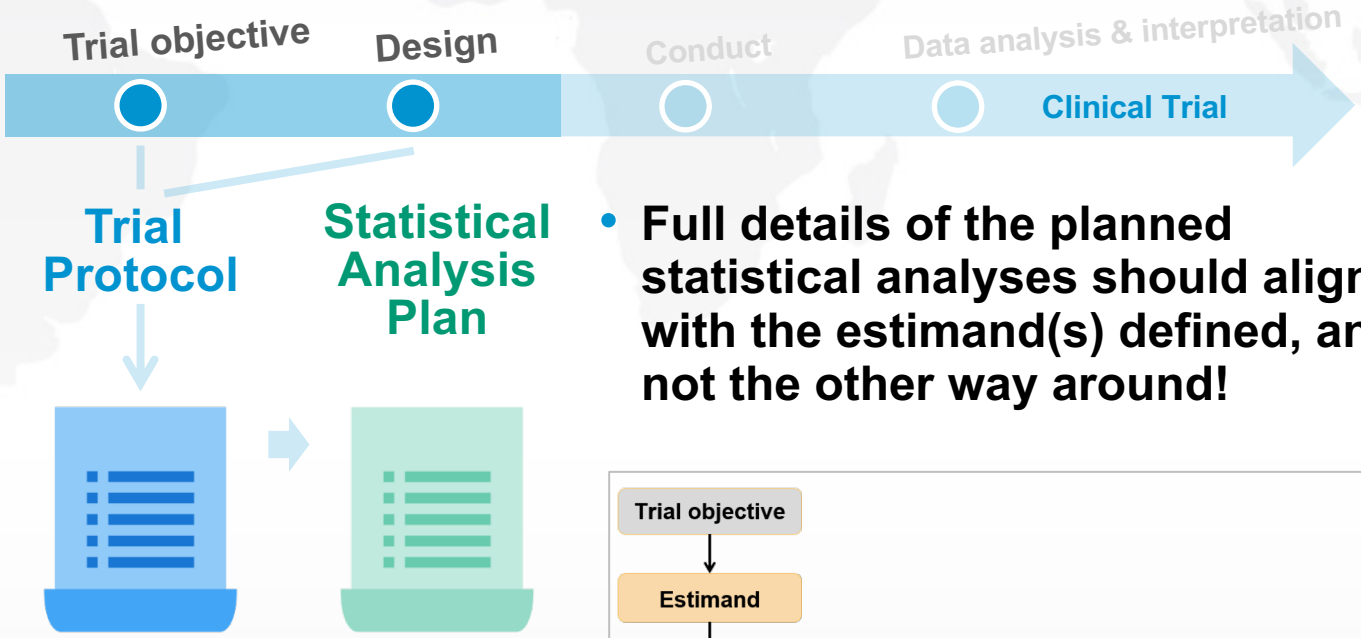
- If the **estimate** corresponding to a given estimator, and associated inference, is shown to be **robust** through sensitivity analysis, then the **interpretation of trial results** should focus on the main estimator for each selected estimand.
- **Any other analysis** that is planned, presented or requested in order to more fully investigate and understand the trial data and the effects of treatment is referred to as a **supplementary analysis**.
- Supplementary analysis might **target different estimands**, or target the **same estimand based on a different analytical approach**.

# Incorporating estimands in protocol writing

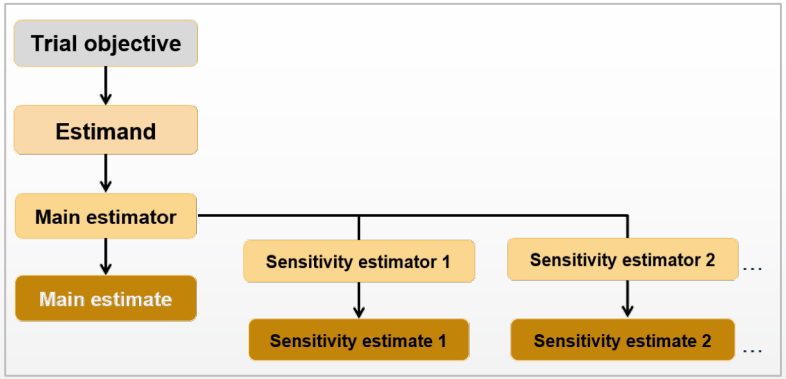



- **Estimands** should be defined and explicitly specified in the clinical trial **protocol**.
- The primary estimand pre-specified in the trial protocol should correspond to the **primary trial objective**.
- The **protocol** and the **statistical analysis plan** should pre-specify the **main estimator** that is **aligned with the primary estimand** and leads to the **primary analysis.** Suitable **sensitivity analysis** should be planned to explore the robustness under deviations from its assumptions.

# Incorporating estimands in the SAP

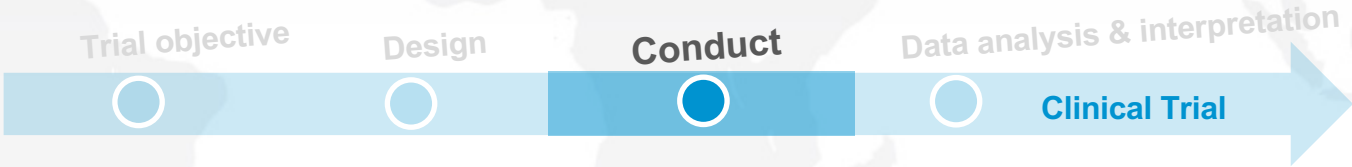



- **Full details of the planned statistical analyses should align with the estimand(s) defined, and not the other way around!**



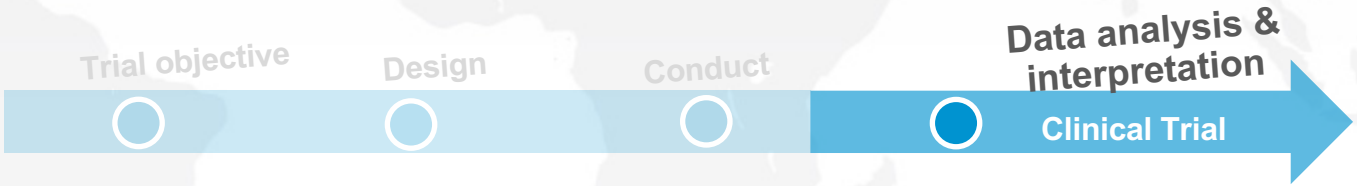

SAP: Statistical Analysis Plan

# Potential impact on study conduct




- The occurrence of anticipated intercurrent events should be **monitored during the study**.
- Estimands defined in the trial protocol could be subsequently **affected by issues arising during study conduct**.
- The impact of any **unanticipated intercurrent events** occurring and/or other study conduct issues possibly affecting the primary estimand should be evaluated.
- A **protocol amendment** could be considered depending on the nature and significance of such issues to the primary estimand.

# Data analysis and interpretation




- Results from the main, sensitivity and any supplementary analyses should be **reported systematically** in the clinical trial report, specifying whether each analysis was **pre-specified, introduced while the trial was still blinded, or performed post hoc**.

# 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

# The final E9(R1) will be released very soon….

# Proposal for ICH E9 Implementation WG

- **Help all stakeholders transition to adopting the new estimand framework**
- **Enable clinicians to be part of the IWG so they can help drive the update of the new framework**
- **Develop case studies**
- **Provide a point of contact to address questions**
- **Allow for potential face-to-face meeting(s) if needed**

# Proposed ICH E9 IWG Activities

- **The EWG will update the training materials and release animation and IWG could create additional materials to complement current modules**
- **Develop case studies**
- **Run, schedule and co-ordinate training sessions**
- **Develop additional materials as needed, e.g. FAQ**
- **Assess the impact of the estimand framework in other ICH guidelines**
- **Partner with the ICH M11 and provide input to new ICH protocol template**

# Update on TransCelerate and ICH M11

- **TransCelerate**
  - Common Protocol (CPT), Common SAP (CSAP) and Common Clinical Study Report (CSR) templates
  - E9 addendum will be incorporated into CPT, CSAP and CSR in 2020 – anticipated release Nov 2020
    - New release of CPT in Nov 2019 will correct description for ‘population’ attribute
- **ICH M11**
  - E9 WG presented the final E9(R1) in June 2019
  - Ongoing discussions to incorporate estimands and the new framework in the new ICH protocol template (in development)

# EFPIA/EFSPI E9(R1) Implementation WG

- **Bringing together statisticians and clinicians who are leading the implementation of E9(R1) in their organisations**
- **Enable statisticians and clinicians to share their experiences**
- **Identify best practices for implementing the new estimand framework**
- **Share feedback, lessons learned and any recommendations to the broader statistical and clinical communities**

Chair: Chrissie Fletcher (fletcher@amgen.com)

# Conclusions

- **The final ICH E9(R1) will be released very soon**
- **Follow and implement the new framework as soon as possible**
- **A new ICH E9 implementation working group is proposed to support all stakeholders in all regions to incorporate and follow the E9 addendum**
- **Within Europe, the EFPIA/EFSPI E9(R1) implementation working group will provide a forum to collaborate, share experiences and establish best practices**

# Estimand = A Mindset

(anagram)

- **Fundamentally change the way how we plan and design clinical trials**
- **Mutual understanding between clinicians and statisticians is crucial**
- **Established statistical approaches may need to be challenged**
  - No one-size-fits-all estimands are available (or even desirable)
  - Focus on causal estimands, hence the need to embrace “new” methodologies (e.g. causal inference)
    - What to do with established approaches that do not provide causal treatment effects (e.g. hazard ratios)?