ICH
harmonisation for better health

# Estimands

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**EFSPI Statistics Leaders 2015**

International Conference on 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 necessarily 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.**

# Agenda

- **Introduce the ICH E9 working group**
- **Estimand definition and framework**
- **Example**
- **Case study exercise – hypothetical diabetes trial**
- **Questions and feedback**

# E9 WG - goals

- **Develop an addendum (Revision 1) for E9**
- **Acknowledge this is a new topic and new framework for improved clinical trial planning, conduct, analysis and interpretation. Not only a missing data problem.**
- **'Estimand'**
  - Need to clarify what measure of treatment effect is being estimated in a clinical trial. Failure to do so results in inconsistencies in conduct and analysis and confusion in interpretation.
- **'Sensitivity analysis'**
  - Current practice may lead to misaligned and uninformative analyses and confusion for decision makers. Build on existing E9 principles to introduce an improved framework.

# E9 WG Objectives

- **Improved framework for clinical trial planning, conduct, analysis and interpretation.**
  - **Trial Objective**
    ↓
  - **(Consequent) Estimand**
    ↓
  - **(Choice of) Analysis methodology**
    ↓
  - **(Consequent) Sensitivity Analyses**
- **Current practice is often not aligned with this proposed framework.**

# E9 WG - membership

- **Rapporteur: Rob Hemmings, EU**
- **Regulatory chair: Estelle Russek-Cohen, FDA**
- **Represented: EU, EFPIA, MHLW/PMDA, JPMA, FDA, PhRMA, HC, DoH China, DRA Australia, DRA Brazil**
  - EU: Rob Hemmings (Rappourteur), Frank Petavy
  - FDA: Estelle Russek-Cohen (Regulatory Chair), Tom Permutt
  - EFPIA: Chrissie Fletcher (Amgen), Frank Bretz (Novartis)
  - MHLW/PMDA: Yuki Ando, Hirofumi Minami
  - JPMA: Satoru Tsuchiya, Satoru Fukinbara
  - PhRMA: Devan Mehrotra, Vladamir Dragalin
  - HC: Catherine Njue
- **First meeting Nov 2014**

# Work Plan

| Completion Date | Deliverable |
|---|---|
| November 2014 to June 2015 | Work towards *Step 1 Technical Document*: |
| ICH Meeting<br>6-11 June 2015 | *Step 1 Technical Document*:<br>Aim to resolve any disagreements identified and to finalise the *Step 1* document.<br>Aim for *Step 2a:* Seek agreement of the SC members that there is sufficient scientific consensus on the technical issues for the technical document to proceed to *Step 2b*. Alternatively, if a finalized Step I document cannot be reached, reach agreement on actions needed to resolve divergent positions. |
| July 2015 to November 2015 | Work towards for *Step 2b:* Continue discussion of methodological issues identified in the technical document and start drafting the draft Addendum based on the *Step 1* technical document.<br>Draft the outline of a technical appendix. Identify actions that will be undertaken until the ICH meeting in November 2015, and that will contribute to the creation of the Addendum. |
| ICH Meeting November 2015 | Finalise *Step 2b*: Finalise the draft Addendum and the technical appendix, to be ready for public consultation. Seek endorsement by the SC. *Step 2b* is reached when the six Regulatory Parties sign off the draft Addendum. |
| November 2015 to June 2016 | *Step 3 Stage I*: Publish the *Step 2* document for regional regulatory consultation after the November 2015 ICH Meeting. The duration of public consultation, either 3 or 6 months, is subject to approval by each ICH region.<br>Initiate *Step 3 Stage II*: Depending on the duration of the public consultation in each region, start discussion of regional consultation comments. |
| ICH Meeting June 2016 | Deliverables set for this period will depend on the duration of the public consultation in each region and may be delayed.<br>Aim for *Step 3 Stage II*: Discussion of regional consultation comments.<br>Finalise *Step 3 Stage II*: Address the comments received and reach consensus on the *Step 3* Experts Draft Addendum. |
| June to November 2016 | Deliverables set for this period will depend on the duration of the public consultation in each region and may be delayed.<br>Aim for *Step 3 Stage III*: finalisation of the *Step 3* Experts Draft Addendum.<br>Aim for *Step 4*: adoption of the Addendum by the SC. |

# Estimand – Definition

**An estimand reflects what is to be estimated to address the scientific question of interest posed by a trial.**

**The choice of an estimand involves:**

- **Population of interest**
- **Endpoint of interest**
- **Measure of intervention effect**

# Estimand – Definition (cont.)

### (A) Population of interest

This is the population of subjects for which we are assessing the scientific question of interest. The population of interest will inform the study population used for a particular clinical study to answer the scientific question of interest. The study population is defined through the inclusion/exclusion criteria of the study.

### (B) Endpoint of interest

This is the measurable quantity directly related to the scientific question of interest. The endpoint of interest is characterized through measurements or observations at a specific time point or within a time period of interest.

### (C) Measure of intervention effect

This is the effect attributed to an intervention that should take into account potential confounding due to post-randomization events, such as non-compliance, discontinuation of intervention, treatment switching, or use of rescue medication.

# Estimand illustrations

NRC report:

1. (Difference in) outcome improvement for all randomized participants.
2. (Difference in) outcome improvement in those who adhere to treatment.
3. (Difference in) outcome improvement if all participants had adhered.
4. (Difference in) areas under the outcome curve during adherence to treatment.
5. (Difference in) outcome improvement during adherence to treatment

*Mallinckrodt et al*, give a further illustration:

6. For all randomized participants at the planned endpoint of the trial attributable to the initially randomized treatment

**Table II.** Proposed estimands and their key attributes.

| Estimand | Hypothesis | Inference | Population | Endpoint | Use of data after withdrawal of randomized study medication |
|---|---|---|---|---|---|
| 1 | *de facto* (effectiveness) | Treatment policy | All patients | Planned endpoint | Included in primary analysis |
| 2 | *de jure* (efficacy) | Initially randomized medication | Tolerators | Planned endpoint | Not included in primary analysis |
| 3 | *de jure* (efficacy) | Initially randomized medication | All patients | Planned endpoint | Not included in primary analysis |
| 4 | *de facto* (effectiveness) | Initially randomized medication | All patients | Undefined | Not included in primary analysis |
| 5 | *de facto* (effectiveness) | Initially randomized medication | All patients | Undefined | Not included in primary analysis |
| 6 | *de facto* (effectiveness) | Initially randomized medication | All patients | Planned endpoint | Likely imputed |

# The Role of Sensitivity Analyses

- **All sensitivity analyses should address the same primary estimand, i.e.**
  - same population,
  - same outcome and
  - same measure of intervention effect.
- **All model assumptions that are varied in the sensitivity analysis should be in line with the estimand of interest.**
- **If additional estimands are of interest, these could be considered as secondary or exploratory estimands.**
- **Sensitivity analyses can also be planned for secondary / exploratory estimands and aligned accordingly**

# Example


## Dapagliflozin (Bristol-Myers Squibb / AstraZeneca)

- Anti-diabetic therapy to treat hyperglycemia
- New drug application discussed in 2011 in a public advisory committee

# Dapagliflozin – Primary Endpoint and Statistical Analyses

- **Primary endpoint: Change in HbA1c from baseline to 24 weeks**
- **Analysis set: modified intention to treat (all randomized patients + at least one dose + baseline value + at least one post-baseline value)**
- **Data after initiation of rescue medication was considered as missing**
  - Interested in the effect of the initially randomized treatment
  - Rescue medication can mask or exaggerate effects of the initially randomized treatments
- **Primary analysis: ANCOVA using LOCF**
- **Sensitivity analyses:**
  - ANCOVA using only complete cases
  - Mixed-effects model for repeated measures (MMRM) of HbA1c values

# Dapagliflozin – Comments by FDA Reviewer

**"While FDA has implicitly endorsed LOCF imputation for diabetes trials in the past, there is now more awareness in the statistical community of the limitations of this approach.**

**Instead I have included a sensitivity analysis in which the primary HbA1c outcomes are used regardless of rescue treatment, and no statistical adjustment is made for rescue.**

**This approach is also imperfect, but it comes closer to being a true intent-to-treat (ITT) analysis because it disregards the non-randomized rescue treatment."**

# Dapagliflozin – Sponsor's Interest versus Regulatory Interest

## Sponsor:

### What was done?

- Remove data after initiation of rescue medication

### Implied 'scientific questions of interest':

- Attempt to establish the treatment effect of the initially randomized treatments had no patient received rescue medication

## FDA:

- Include all data regardless of initiation of rescue medication

- Compare treatment policies 'dapagliflozin plus rescue' versus 'control plus rescue'

# Dapagliflozin – Sponsor's Interest versus Regulatory Interest

**Implied objectives / scientific questions of interest differ for both parties.**

**This is hidden behind the method of estimation / handling of 'missing data'.**

**Need to avoid such 'miscommunications'.**

# Case study exercise: hypothetical diabetes trial

- **Randomized, 2-arm (drug A and drug B) diabetes trial in patients with type 2 diabetes mellitus (T2DM)**
- **Endpoint is the change of HbA1c levels to baseline after 24 weeks of randomization**
- **HbA1c levels are measured at baseline and at 4, 8, 12, 16, 24 weeks**
- **For ethical reasons, patients are switched to rescue medication once their HbA1c values are above a certain threshold**
- **Regardless of switching to rescue medication all (!) patients are followed up for the whole study duration, i.e.**
  - there are no missing observations in this study
  - patients never discontinue their study medication, unless they start rescue medication

# Potential Estimands of Interest

## Differ only in their 'measure of intervention effect'

| | Estimand 1 | Estimand 2 | Estimand 3 |
|---|---|---|---|
| **Population** | Intended post-approval population of T2DM patients | Intended post-approval population of T2DM patients | Intended post-approval population of T2DM patients |
| **Endpoint** | Change of HbA1c level to baseline after 24 weeks of randomization | Change of HbA1c level to baseline after 24 weeks of randomization | Change of HbA1c level to baseline after 24 weeks of randomization |
| **Measure of intervention effect** | | | |

# Questions

- **What would you propose as the estimand?**

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| **Measure of intervention effect** | Effect regardless of what treatment was actually received, i.e.<br>• effect of **treatment policies** 'drug A until start of rescue followed by rescue' versus 'drug B until start of rescue followed by rescue'. | | |

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| **Measure of intervention effect** | Effect regardless of what treatment was actually received, i.e.<br>• effect of **treatment policies** 'drug A until start of rescue followed by rescue' versus 'drug B until start of rescue followed by rescue'. | Effect of the initially randomized treatments assuming that the treatment effect disappears and no rescue effect occurs after meeting rescue criteria, i.e.<br>• effect of 'drug A until intake of rescue followed by a disappearing drug A effect' versus 'drug B until intake of rescue followed by a disappearing drug B effect'. | |

# Potential Estimands of Interest

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| **Measure of intervention effect** | Effect regardless of what treatment was actually received, i.e.<br>• effect of **treatment policies** 'drug A until start of rescue followed by rescue' versus 'drug B until start of rescue followed by rescue'. | Effect of the initially randomized treatments assuming that the treatment effect disappears and no rescue effect occurs after meeting rescue criteria, i.e.<br>• effect of 'drug A until intake of rescue followed by a disappearing drug A effect' versus 'drug B until intake of rescue followed by a disappearing drug B effect'. | Effect of the initially randomized treatments had all patients remained on their randomized treatment throughout the study, i.e.<br>• effect assuming patients did not receive rescue medication. |

# Questions

- **What would you propose as the (consequent) analysis methodology?**
  - What would be your chosen primary analysis?

# Potential Estimands of Interest

## Primary Analyses

| | Estimand 1 | Estimand 2 | Estimand 3 |
|---|---|---|---|
| **Analysis Variable** | • Change from baseline to week 24 in HbA1c<br>• All HbA1c values are used, regardless of treatment | • Change from baseline to week 24 in HbA1c<br>• HbA1c values after intake of rescue medication are set to missing | • Change from baseline to week 24 in HbA1c<br>• HbA1c values after intake of rescue medication are set to missing |
| **Primary Statistical Model** | **ANCOVA** model<br>• treatment group and region will be fitted as factors<br>• baseline HbA1c will be fitted as a continuous covariate. | | |

# Potential Estimands of Interest

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| **Primary Statistical Model** | **ANCOVA** model<br>• treatment group and region will be fitted as factors<br>• baseline HbA1c will be fitted as a continuous covariate. | Missing data will be multiply imputed based on a **'Copy Placebo'** controlled **imputation** approach.<br><br>For every completed data set fit an **ANCOVA** model,<br>• treatment group and region will be fitted as factors<br>• baseline HbA1c will be fitted as a continuous covariate.<br><br>Overall inference is obtained by applying **Rubin's rules** on the estimates obtained from every imputed/completed data set. | |

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| **Primary Statistical Model** | **ANCOVA** model<br>• treatment group and region will be fitted as factors<br>• baseline HbA1c will be fitted as a continuous covariate. | Missing data will be multiply imputed based on a **'Copy Placebo'** controlled **imputation** approach.<br><br>For every completed data set fit an **ANCOVA** model,<br>• treatment group and region will be fitted as factors<br>• baseline HbA1c will be fitted as a continuous covariate.<br><br>Overall inference is obtained by applying **Rubin's rules** on the estimates obtained from every imputed/completed data set. | The change from baseline HbA1c values for Weeks 4, 8, 12, 16 and 24 will be analyzed using a Mixed Model of Repeated Measurements (**MMRM**)<br><br>• Treatment group, visit and region will be fitted as factors<br>• Baseline HbA1c will be fitted as a continuous covariate<br>• Treatment group by visit and visit by baseline will be included as interaction terms<br>• Unstructured covariance structure |

# Questions

- **What would you propose as the (consequent) analysis methodology?**
  - What would be your chosen sensitivity analyses?

# Potential Estimands of Interest
## Sensitivity Analyses

| | Estimand 1 | Estimand 2 | Estimand 3 |
|---|---|---|---|
| **Analysis Variable** | • Change from baseline to week 24 in HbA1c<br>• All HbA1c values are used, regardless of treatment | • Change from baseline to week 24 in HbA1c<br>• HbA1c values after intake of rescue medication are set to missing | • Change from baseline to week 24 in HbA1c<br>• HbA1c values after intake of rescue medication are set to missing |
| **Sensitivity analyses** | Add/remove covariates and/or interactions. | Use 'Jump to Placebo' instead of the 'Copy Placebo' approach. | Use multiple imputation instead of MMRM |

# Review of hypothetical example

- **Was your estimand clear in terms of the measure of treatment effect?**
- **Was your analysis methodology aligned to your estimand?**
- **Were your sensitivity analyses aligned to your estimand?**

# Questions & Feedback

1. **Does the definition of an estimand make sense?**
2. **Does the proposed framework in the E9 addendum make sense?**
3. **Do you have any concerns with the framework?**
4. **How much of a difference is the proposed framework compared to what statisticians currently use for designing clinical trials?**
5. **What do you see as key challenges for introducing the framework?**
6. **How do you think clinicians will view estimands and the proposed framework?**
7. **Is the ITT (strict) estimand (#1) in the hypothetical example reasonable?**

# References


- ICH concept paper (2014) E9(R1): Addendum to Statistical Principles for Clinical Trials on Choosing Appropriate Estimands and Defining Sensitivity Analyses in Clinical Trials
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