A summary of the key messages of ICH E9, an introduction to Estimands and the Addendum to ICH E9

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David Wright

- **Worked at UK Drug Regulatory Agency (originally the Medicines Control Agency (MCA) and then the Medicines and Healthcare products Regulatory Agency (MHRA) from 1999-2016**
- **Co-authored “Assessing the impact of ICH E9” Pharmaceutical Statistics, 2008, 7; 77-87 with David Brown Simon Day and Rob Hemmings**
- **Co-authored the 2011 CHMP guideline on missing data in confirmatory clinical trials**

David Wright

- **Became an Expert Statistical Assessor and Chair of the Biostatistics Working Party for CHMP at the European Medicines Agency (EMA)**

- **Currently interested in Estimands and the impact the Addendum to ICH E9 will have on the design and analysis of clinical trials in the future**

Introduction to ICH E9

- **Came into effect in 1998**
- **Key document that outlines the statistical principles for the design and analysis of clinical trials that will form part of a submission to a regulatory agency**
- **Very well respected throughout the pharmaceutical industry and has largely stood the test of time (more on this later)**

ICH E9 – who is it for?

- **Advice for Sponsors on the design, conduct, analysis and EVALUATION of clinical trials of an investigational product in the context of its overall clinical development**
- **Also assists assessors (Medical/Clinical and Statistical) at regulatory agencies who prepare summaries of applications and ASSESS EVIDENCE of efficacy and safety provided by clinical trials in later phases of clinical development**

Key Messages/Sections in ICH E9

- **Pre-specification of Analysis**
- **Analysis of Multicentre trials**
- **Subgroup Analyses**
- **Evaluation of safety and tolerability**

Pre-specification of analyses

- **Pre-specify the confirmatory analysis of the primary variable in the study protocol. More technical details should be provided in the Statistical Analysis Plan.**
- **Both documents have to be finalised before breaking the blind (in a double blind study).**
- **Analysis needs to be precisely defined to avoid concerns about *post hoc* choices that can lead to concerns about multiplicity.**

Pre-specification of analyses

- **One of the successes of ICH E9**
- **Today primary analysis is routinely predefined**
- **However even now there can sometimes be uncertainty over the exact details of the analysis that will be conducted and also why this analysis has been specified (this relates to one of the reasons the Addendum to E9 has been written)**

Analysis of Multicentre trials

- **In the late 1990s there was considerable debate over how to analysis multicentre trials**
- **E9 explains why multicentre trials are necessary**
    - Speed up recruitment
    - Provide a better basis for generalising the results from the study to the intended patient population
- **Explains what terms should be included in the primary analysis for a multicentre study.**

Subgroup Analyses

- **Stratify for factors expected to have an important influence on the primary variable**
- **Account for these factors in the analysis**
- **In most cases subgroup analyses are exploratory and should be clearly identified as such and hence the analyses should be interpreted with caution and any conclusions of treatment efficacy (or lack thereof) or safety based solely on exploratory subgroup analyses are unlikely to be accepted.**

Subgroup Analyses

Also see:

- **ICH E17 on General principles for planning and design of multi-regional clinical trials (2018) https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-e17-general-principles-planning-design-multi-regional-clinical-trials-step-5-first_en.pdf**
- **CHMP guideline on the investigation of subgroups in confirmatory clinical trials (2019) https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-subgroups-confirmatory-clinical-trials_en.pdf**

Evaluation of safety and tolerability

- **General advice on the collection of safety data**
- **Advise on how to report incidence of adverse events**
- **Most safety analyses will be descriptive but not always e.g. diabetes trials and cardiovascular risk**
- **No advice on meta-analysis of safety data – see CIOMS X (Evidence Synthesis and Meta-Analysis for Drug Safety) for advice**
- **Relevant to later discussion on Estimands**

ICH E9 20 years on – What has changed?

- **Missing data**
- **Estimands and Sensitivity Analyses – Addendum to ICH E9**
- **Analysis sets**
- **Non-inferiority studies**

Missing data

- **The frequency and type of protocol violations, missing values, and other problems should be documented in the clinical study report and their potential influence on the trial results should be described.**
- **Methods for handling missing data should be prespecified in the protocol. But the investigation will depend on the pattern and timing of the missing data and hence can only be fully determined retrospectively.**

Missing data

- **Area inadequately addressed in many regulatory submissions (quote from 2008)**
- **This led to CHMP guideline on Missing Data in confirmatory clinical trials being revised in 2011 https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-missing-data-confirmatory-clinical-trials_en.pdf**
- **And led to the FDA convening an Expert panel in 2010 which produced The Prevention and Treatment of Missing Data in Clinical Trials (National Research Council) report.**

Motivation for ICH E9 Addendum

- **Lots of discussion about handling missing data. Then the following example highlighted that there can still be issues with a complete data set.**

Type II diabetes (HbA1c measured for 24 weeks patients randomised to treatment A or B) – for illustration

Different perspectives on the inclusion of data

- Sponsor: Remove data after initiation of rescue medication

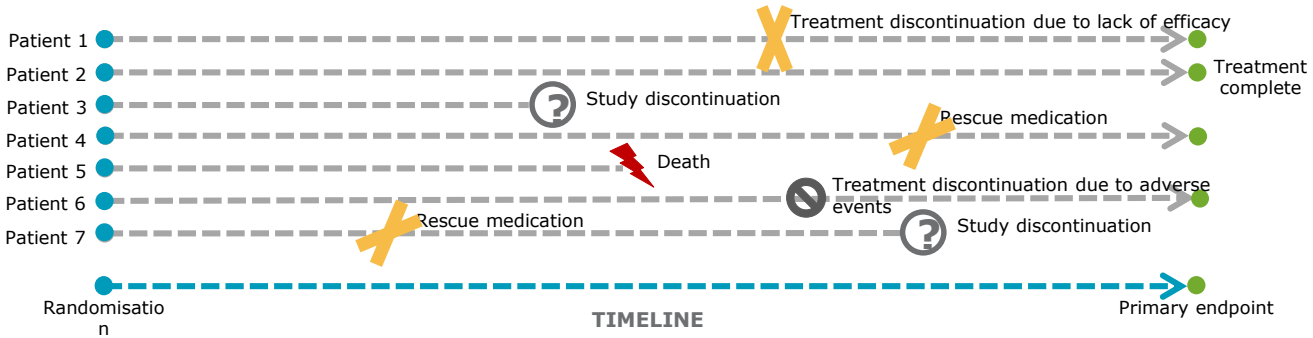
- FDA: Include all data regardless of initiation of rescue medication

Implied 'scientific questions of interest':

- Sponsor: Attempt to establish the treatment effect of the initially randomized treatments had no patient received rescue medication;
- FDA: Compare treatment policies 'A plus rescue' versus 'B plus rescue'.

Disagreement over what to estimate; the estimand.

Intercurrent events



- Events may occur that make the relevance, the definition, or even the existence of the primary variable questionable.
- Such events may include: death, treatment discontinuation due to adverse events or lack of efficacy, use of other medicines affecting the outcome, whether specified or prohibited by the protocol.

More generally…

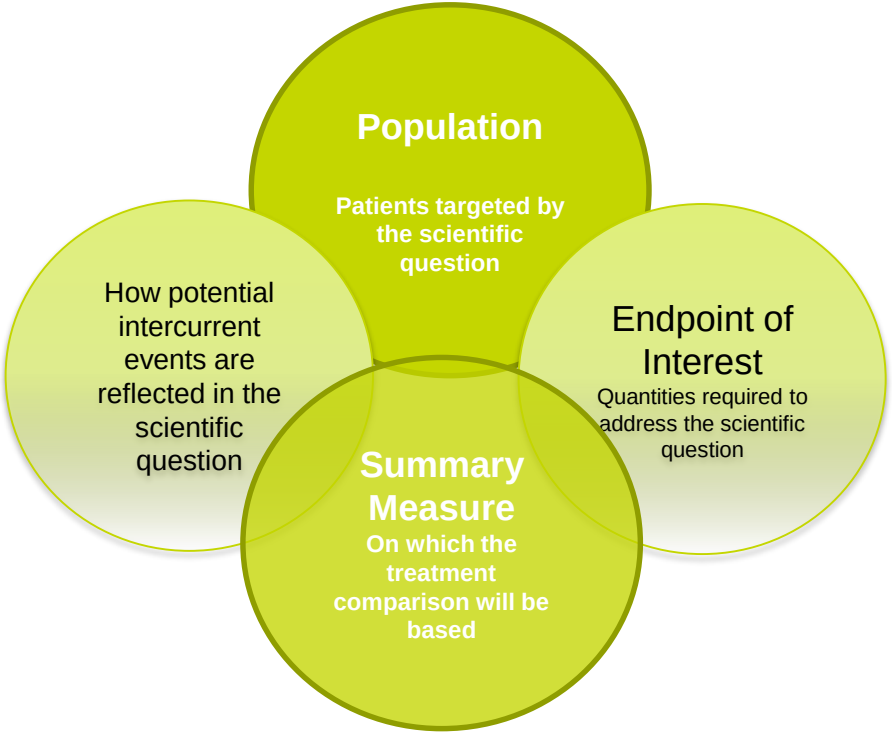
- Statisticians have long discussed ‘missing data’.
- Old methods were criticised; new methods introduced … then criticised.
- The conversation between sponsor and FDA was imprecise, but ultimately necessary.
  - Didn’t recognise that some of the ‘missing data’ were not in fact missing!
  - There was a focus on particular techniques and the assumptions required in order that they give reliable estimates.
  - The meaning of ‘intention to treat’ had become obscured.

Estimand

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
- Variable or Endpoint of interest
- Measure of intervention effect
- How potential intercurrent events are reflected



These attributes should be considered consciously and explicitly in relation to each other

Is that sufficient to fully define an estimand?

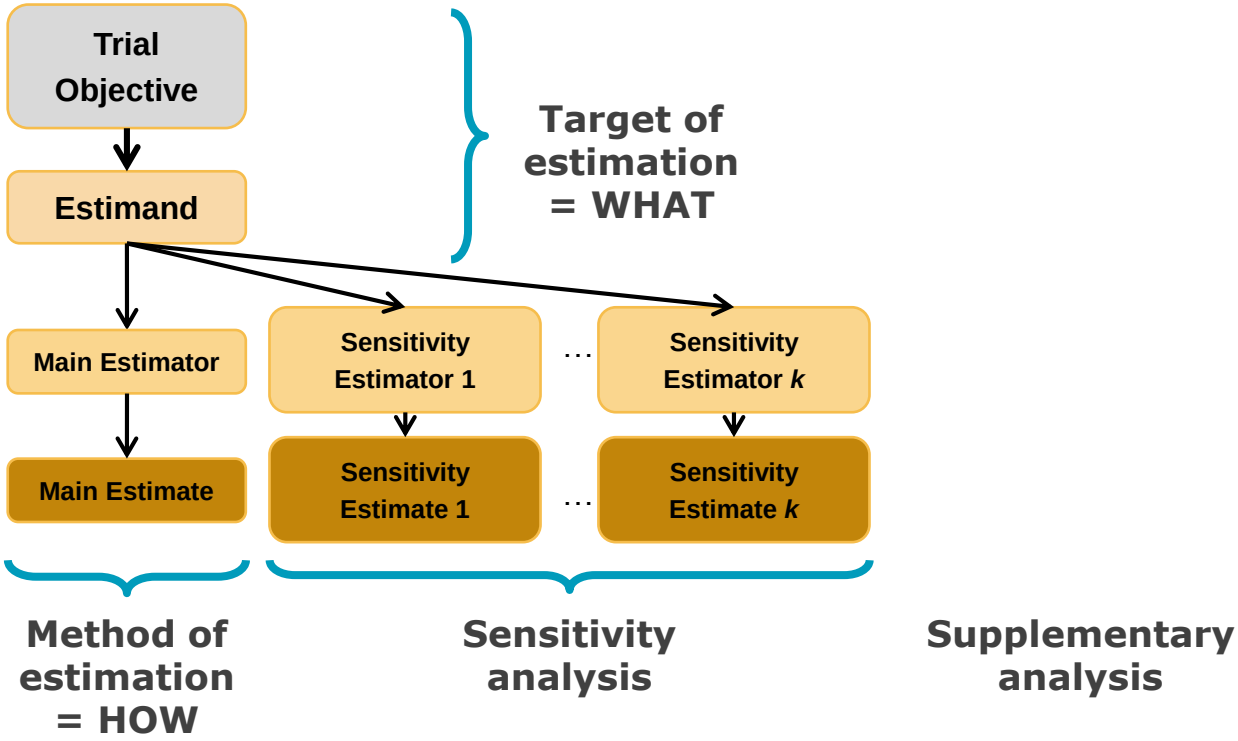
- Breaking news – final version of guidance will also include “treatment” as part of the estimand definition

Sensitivity Analyses

- How many analyses are really needed?
- Estimand Framework helps focus on the key analyses that are needed
- Also if other Estimands are of interest the framework helps provide clarity on which analyses are relevant to which question

Framework I

Choice of estimand may impact study design and conduct and needs to be discussed first.



Three potential estimands of interest
Differ only in their 'measure of intervention effect'

Attribute	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 from baseline to 24 weeks after randomisation in HbA1c level	Change from baseline to 24 weeks after randomisation in HbA1c level	Change from baseline to 24 weeks after randomisation in HbA1c level
Measure of intervention effect	Effect regardless of what treatment was actually received, i.e. • 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. • 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. • Effect assuming patients did not receive rescue medication

Three potential estimands of interest
Primary analyses

	Estimand 1	Estimand 2	Estimand 3
Analysis Variable	• Change from baseline to week 24 in HbA1c • All HbA1c values are used, regardless of treatment	• Change from baseline to week 24 in HbA1c • HbA1c values after intake of rescue medication are set to missing	• Change from baseline to week 24 in HbA1c • HbA1c values after intake of rescue medication are set to missing
Primary Statistical Model	Analysis of Covariance model (ANCOVA)	Missing data will be multiple imputed under a 'missing not at random' assumption: • Borrow information from placebo arm patients. For every completed data set fit an ANCOVA model. Overall inference is obtained by applying Rubin's rules on the estimates obtained from every imputed/completed data set.	Missing data will be multiple imputed under a 'missing at random' assumption: • Borrow information from patients in the same treatment arm. For every completed data set fit an ANCOVA model. Overall inference is obtained by applying Rubin's rules on the estimates obtained from every imputed/completed data set.

Three potential estimands of interest
Sensitivity analyses

	Estimand 1	Estimand 2	Estimand 3
Sensitivity Analyses	• Include/exclude covariates • Include/exclude outliers • Relax the normality assumption	• Include/exclude covariates • Include/exclude outliers • Relax the normality assumption • Modify the 'missing not at random' assumption	• Include/exclude covariates • Include/exclude outliers • Relax the normality assumption • Modify the 'missing at random' assumption

Some strategies to address a given intercurrent event

- **Treatment policy**: Treatment effect regardless of intercurrent event; comes close to the traditional “ITT principle” (Estimand 1)
- **Composite**: Treatment effect based on a composite endpoint where the intercurrent event is part of the endpoint, *e.g.* patients with early discontinuation of treatment are non-responders
- **Hypothetical**: Treatment effect if the intercurrent event had not occurred (Estimands 2 and 3 are examples of types of Hypothetical estimands)
- **Principal stratum**: Treatment effect in subgroup of patients that would not experience the intercurrent event
- **While on treatment**: Treatment effect while the intercurrent event did not occur *e.g.* while patients did not take any rescue medication

Other reflections

- List of possible estimand strategies was not exhaustive, other strategies are possible
- The proposed strategy for **EACH** intercurrent event needs to be specified
- Hence the overall primary estimand may have **DIFFERENT** strategies to handle **DIFFERENT** intercurrent events.

Construction of an estimand

- Should be:
  - A consequence of the trial objectives and should precede choices relating to data collection and analytic approaches.
  - clinically interpretable, in terms of the population and endpoint, but also in terms of the intervention effect of interest and, finally, the summary measure.

Construction of an estimand

- Should be:
  - duly justified considering the therapeutic setting and the treatment goals of the intervention, from which the key scientific questions of interest can be derived.
  - a **multi-disciplinary undertaking** and should be the subject of discussion between sponsors and regulators.

What about Non-inferiority studies?

Since E9 was written excellent guidance has been provided:

- CHMP guideline on the choice of non-inferiority margin https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-choice-non-inferiority-margin_en.pdf (2006)
- FDA guidance on Non-inferiority clinical trials to establish effectiveness (2016) https://www.fda.gov/media/78504/download

What about non-inferiority studies?

- Estimand framework still applies
- Exposes some flaws in specifying a per protocol population as the primary analysis population for non-inferiority studies
    - This approach doesn't provide enough detail (e.g. imagine a subject who misses 1 dose in a 3 year study, have they failed to take the medicine as instructed and therefore should they be
    1. Completely excluded from the analysis
    2. Data completed before they missed the dose included then rest ignored?
    3. Data collected before the missed dose included and data collected once dosing restarted included? Etc

- Estimand framework can address issues above in a transparent way.

Is this just about long term studies with a continuous endpoint?

- No, all trials have intercurrent events and hence can benefit from going through the process outlined in the Addendum

Final reflections

- Even after 21 years, ICH E9 remains an excellent document for statisticians and clinicians in the pharmaceutical industry to understand key areas to take into account when designing, analysing and interpreting the results of clinical trials intended to be included as part of a regulatory submission.
- Not surprisingly some areas have developed since 1998, *e.g.* subgroup analysis, missing data, non-inferiority trials, adaptive designs, meta-analyses of safety data and Estimands.

Final reflections

- The Addendum to E9 offers a fantastic framework to assist in the design of a clinical trial to answer a particular question of interest. Using the framework in dialogue between different experts in sponsor companies can aid improvement in the design and analysis of a confirmatory clinical trial. The same framework can be used to assist in conversations with other stakeholders such as patients, regulators and reimbursement agencies so they can make an informed decision on which estimands are most relevant to them and so they can understand whether the analyses provided are suitable to estimate the estimands of interest to them.

Final reflections

- Still much to do however:
  - Ensuring clear communication of estimand strategies in regulatory labels/public assessment reports
  - If different companies use different strategies again this needs to be made clear to avoid false assertions being made by stakeholders
  - Process is not just statistical and is a multi-disciplinary undertaking and should also involve discussions between the Sponsor and regulators.

THANK YOU

Any questions?

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