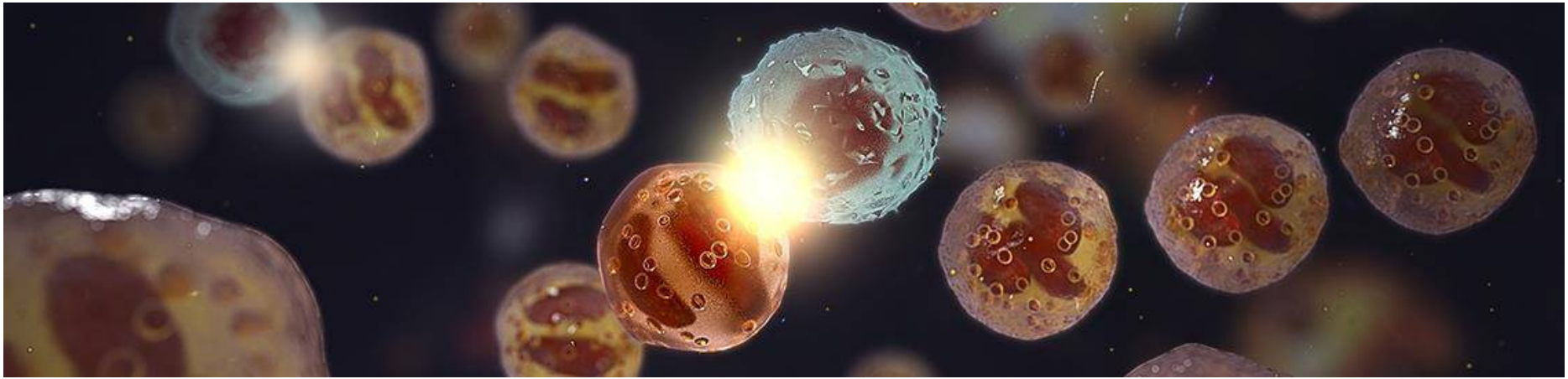
Choosing Estimands in a Clinical trial
Introduction

Rosa Lamarca

38th Annual Conference International Society for Clinical Biostatistics

13th of July 2017



Disclosure statement

- The views and opinions expressed in the following slides are those of the individual presenter and should not be attributed to Astra Zeneca

Program

Time	Title	Speaker
9:30 – 13:00	Session 1: New scientific and regulatory environment ICH E9 Addendum	Chair R. Lamarca
9:30 – 9:45	Introduction	R. Lamarca
9:45 – 12:30 (break 11:00)	ICH E9 addendum on 'Estimands and Sensitivity Analysis'	R. Hemmings / M. Akacha
12:30 - 13:00	Clinical perspective	E. García
13:00 – 13:30	Panel discussion	Moderator F. Bretz R. Hemmings / M. Akacha/ E. García
13:30 - 14:30	*Lunch*	
14:30 -15:30	Session 2: Methodological perspectives on the estimand framework	Chair R. Lamarca
14:30 - 15:00	Statistical perspective	J. Roger
15:00 - 15:30	Causal inference perspective perspective	R. Daniel
15:30 - 16:00	Session 3: The new era in clinical research	Moderator F. Bretz
15:30 -16:00	Panel discussion and Q&A	M. Akacha, F. Bretz, R. Daniel, E. García, R. Hemmings and J. Roger

Background

- Around 2008, it was further discussed the impact of MISSING DATA on clinical trials research

A review of the handling of missing data in clinical trials

- Powney et al. Trials 2014, 15:237
  - Database: MEDLINE (Ovid interface)
  - Keywords: longitudinal randomi$ed controlled trial$ or repeated measure$ randomi$ed controlled trial$ or longitudinal RCT$ or the same searches with ‘controlled’ replaced by ‘control’
  - published between 2005 to 2012
  - written in English
  - Exclusion: papers with only binary outcomes and nonhuman participants
- 100 papers were selected at random due to time constraints

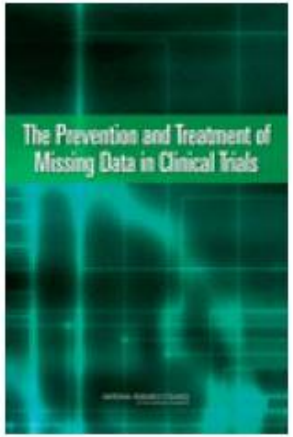
A review of the handling of missing data in clinical trials

Primary approach to analysis	Papers
Complete case analysis	**32**
Mixed models	**18**
Simple imputation	**14**[1]
LOCF/FOCF/BOCF	9
Average value either side Imputed	1
Simple algorithmic-based imputation	1
Mean of other patients values imputed	1
Median values imputed	1
Multiple imputation methods	**4**
Other non-imputation-based methods[2]	**14**
Exclusion based on amounts/reason of missingness	**7**
No missing data	**9**
Unclear	**3**

32% of papers failed to provide any reasons for patients dropping out

[1] One paper which used a complete case analysis also used simple imputation as a secondary analysis
[2] Comparison of means, for example, t-test, RMANOVA.

Regulatory actions - 2010



The Prevention and Treatment of Missing Data in Clinical Trials

Panel on Handling Missing Data in Clinical Trials; National Research Council

ISBN: 0-309-15815-X, 162 pages, 6 x 9, (2010)

Panel of experts:
RJA Little, R D'Agostino, K Dickersin, SS Emerson, JT Farrar, C Frangakis, JW Hogan, G Molenberghs, SA Murphy, JD Neaton A Rotnitzky, D Scharfstein, W Shih, JP Siegel, H Stern, M Cohen, and A Gaskin (assistant)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Guideline on missing data reviewed

2 July 2010
EMA/CPMP/EWP/1776/99 Rev. 1
Committee for Medicinal Products for Human Use (CHMP)

Guideline on missing data in confirmatory clinical trials

Regulatory actions - 2010

- Proportion and timing of withdrawals
- Causes of discontinuation (non-compliance, AE, lack of efficacy, …)
- Collection of data after discontinuation
- Carry-out different analytical models assuming different withdrawal mechanisms, dissertation about the plausibility of each model
- Differential pattern as per cause of discontinuation, including a discussion about the hypothesised treatment effect by cause
- 18 recommendations on missing data from the National Academy of Science

Regulatory actions - 2010

Respiratory area: COPD exacerbations

"…stopped patient follow-up at the time they discontinued the study drug. Thus, any outcome information after the patients were withdrawn, but before the planned end of study follow-up, was not collected. As such, **the fundamental intent-to-treat analysis for such trials was not possible, since the data were truncated at the time of drug discontinuation**."

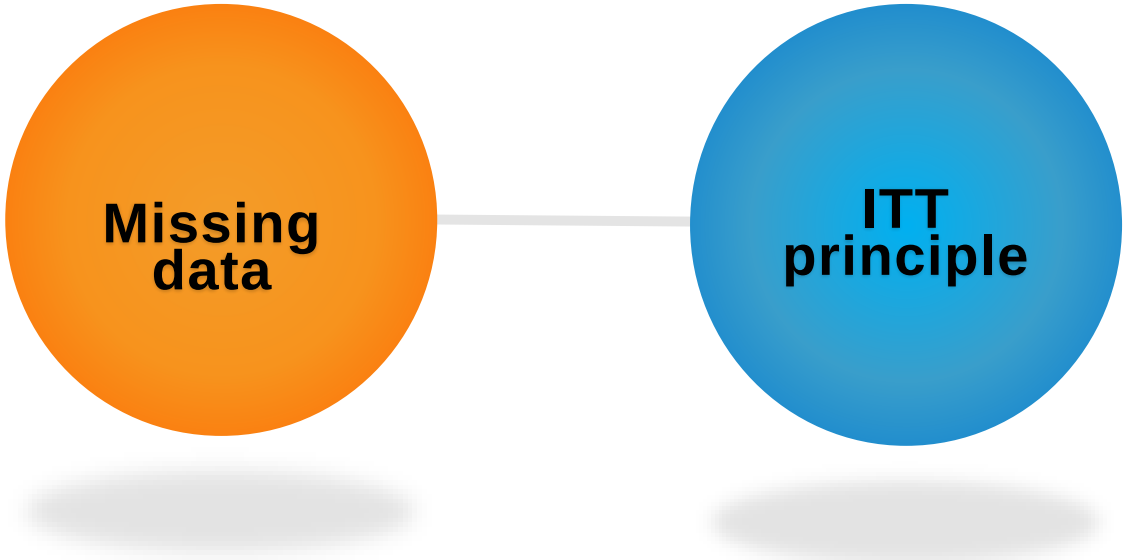
Methodological issues in therapeutic trials of COPD. Suissa S, Ernst P, Vandemheen KL, et al. Eur Respir J **2008**; 31: 927–933

Respiratory area: COPD exacerbations

"… **patients who prematurely stop a study medication should not be considered "drop-outs**" unless they absolutely refuse permission for the study to continue to follow them. Ideally, these patients **should be retained in the study** for its duration and any **subsequent COPD exacerbations should be attributed to their randomised group**"

Aaron SD, Fergusson D, Marks GB, et al. Counting, analysing and reporting exacerbations of COPD in randomised controlled trials. Thorax **2008**;63:122-128.

Inherent in the discussion



bias, power

- Retain patients on-treatment

preservation of randomisation to secure the statistical inference

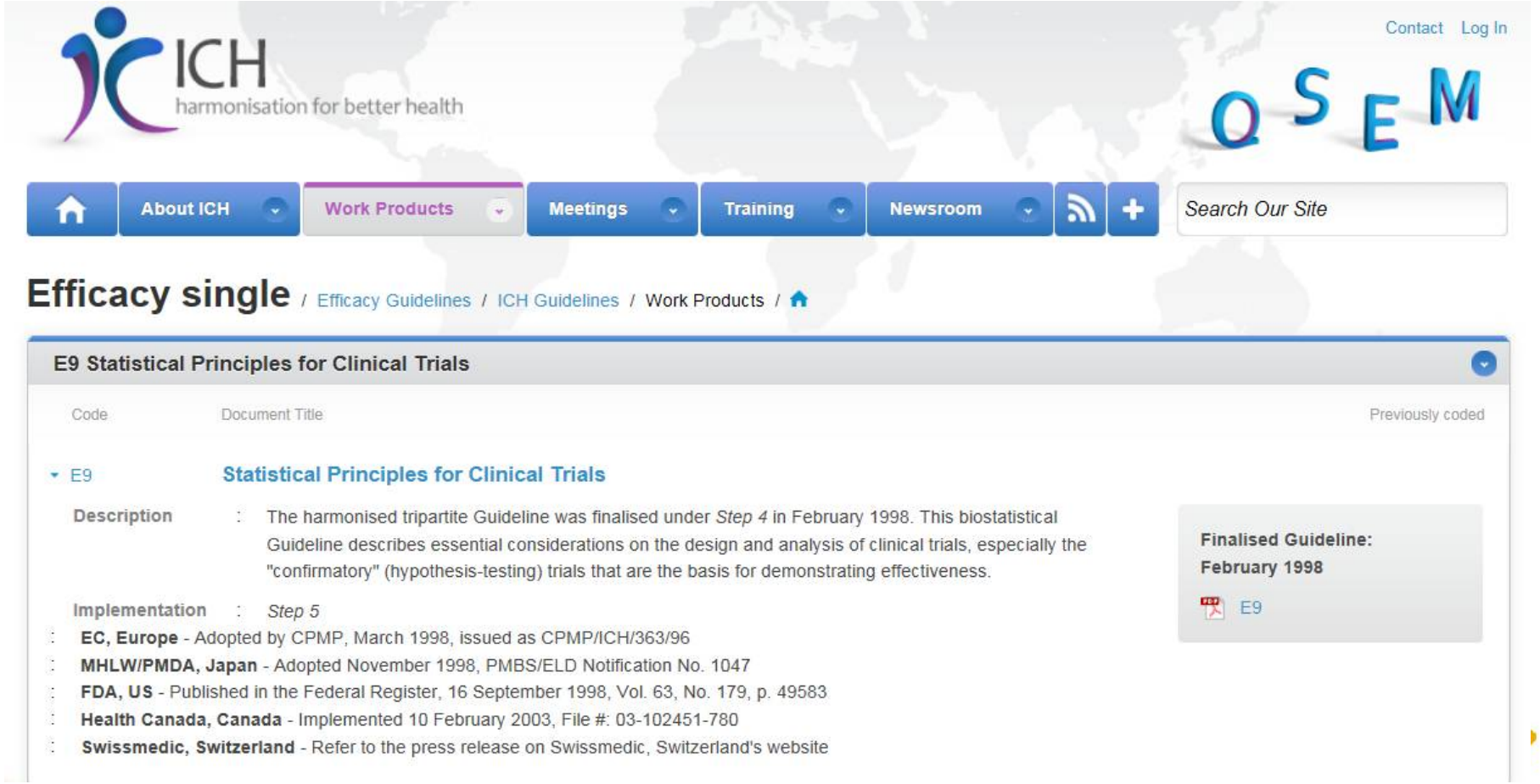
- to keep all randomised subjects in the trial regardless of intercurrent events

(i.e discontinuation of IP, rescue medication intake, treatment switching, non compliance)

A new era for clinical trials

- A joint global effort
  - all regions
  - all parties involved (regulators, academia, pharmaceutical industry, ….)
- Aiming to:
  - come back to the scientific question of interest
  - re-think about the clinical trial framework to reflect clinical practice and behavior of target population

ICH-E9 Statistical principles for Clinical trials



Addendum to ICH-E9 (R) Statistical principles for Clinical trials

- Endorsed by the ICH Steering Committee in October 2014
- provide clarification on E9 and an update on the choice of estimand in clinical trials to describe an agreed framework for planning, conducting and interpreting sensitivity analyses of clinical trial data.
- focus on statistical principles related to estimands and sensitivity analysis, not on the use or acceptability of specific statistical procedures or methods.
- primary focus on confirmatory clinical trials.

Addendum to ICH-E9 (R) Statistical principles for Clinical trials

- Step 1 to be moved to Step 2 shortly
- Work plan

Completion Date	Deliverable
2017	*Step 1 and Step 2a* Finalisation of the Technical Document (draft Addendum) and sign-off by all ICH Parties' members in the EWG and by the Assembly. *Step 2b* Draft Addendum and sign-off by the ICH Regulatory Parties.
2017	*Step 3 phase* Publish draft Addendum.
2018 - 2019	*Step 3 phase* Discuss comments received during the public consultation period and consolidate the Draft Addendum.
2018 - 2019	*Step 3 and Step 4* Finalisation of the Addendum and sign-off by topic leaders of the ICH Regulatory Parties and by the ICH Regulatory Parties.

ICH-E9 Survey

- e-survey conducted in May/June 2015

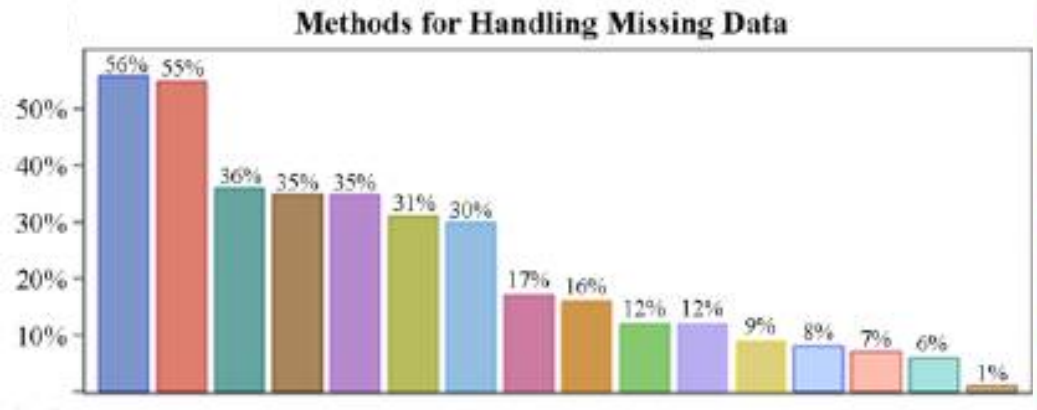
- Participants: pharmaceutical companies (56%), academia (21%), contract research organisations (11%), regulatory agencies (6%), medical device (1%) companies and others (4%)

- 23 questions:
  - 4 demographic
  - 4 estimands,
  - 9 handling of missing data in clinical trials
  - 5 sensitivity analyses
  - 1 general comments

Source: C. Fletcher, S. Tsuchiya, and D.V. Mehrotra, on behalf of the ICH E9(R1) Working Group . Current Practices in Choosing Estimands and Sensitivity Analyses in Clinical Trials: Results of the ICH E9 Survey. Therapeutic Innovation & Regulatory Science 2017, 51: 69-76

ICH-E9 Survey

71% collect data on patients after they stop taking study medication but who have not withdrawn from the trial



- Mixed-models repeated measures (MMRM)
- Last observation carried forward (LOCF)
- Responder analysis (dropout is treated as a nonresponder)
- Multiple imputation (using regression model)
- Analysis based on computers only (ie, exclude dropouts)
- Worst-case imputation
- Multiple imputation (using MCMC)
- Baseline observation carried forward (BOCF)
- Generalizing estimating equations (GEE)
- Single imputation (using time point or subject average)
- Inverse probability of censoring weighted method / weighted GEE
- Unable to answer / not applicable to job role
- Single imputation (using regression model)
- Other
- Slope/average using any response observed after initiating the assigned treatment
- Not disclosed

Source: C. Fletcher, S. Tsuchiya, and D.V. Mehrotra, on behalf of the ICH E9(R1) Working Group . Current Practices in Choosing Estimands and Sensitivity Analyses in Clinical Trials: Results of the ICH E9 Survey. Therapeutic Innovation & Regulatory Science 2017, 51: 69-76

Confidentiality Notice