Breakout Session #4
Trials incorporating historical controls or with adaptive features

EFPIA European Federation of Pharmaceutical Industries and Associations

PPD

Norwegian Medicines Agency

Day 2
6 October 2021

Breakout session 4

Trials incorporating historical controls or with adaptive features

Multi-stakeholder workshop
5 - 6 October 2021

Chairs:
Christine Fletcher (GSK, EFPIA)
Frank Bretz (Novartis, EFPIA)

This session highlights two case studies of complex innovative clinical trials that incorporate historical control data or have adaptive features. The first case study illustrates the borrowing of information from external data sources in a randomized pediatric trial in multiple sclerosis. The second case study uses a complex Bayesian adaptive design to explore dose ranging and generate safety and efficacy evidence. The discussion focuses on key questions allowing different stakeholder views to be shared, with the objective to foster the use of such clinical trials designs.

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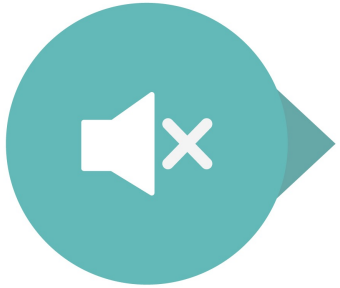
(For active participants in the Zoom call)



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- Introduce yourself (name, company, role) when taking the floor

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Agenda

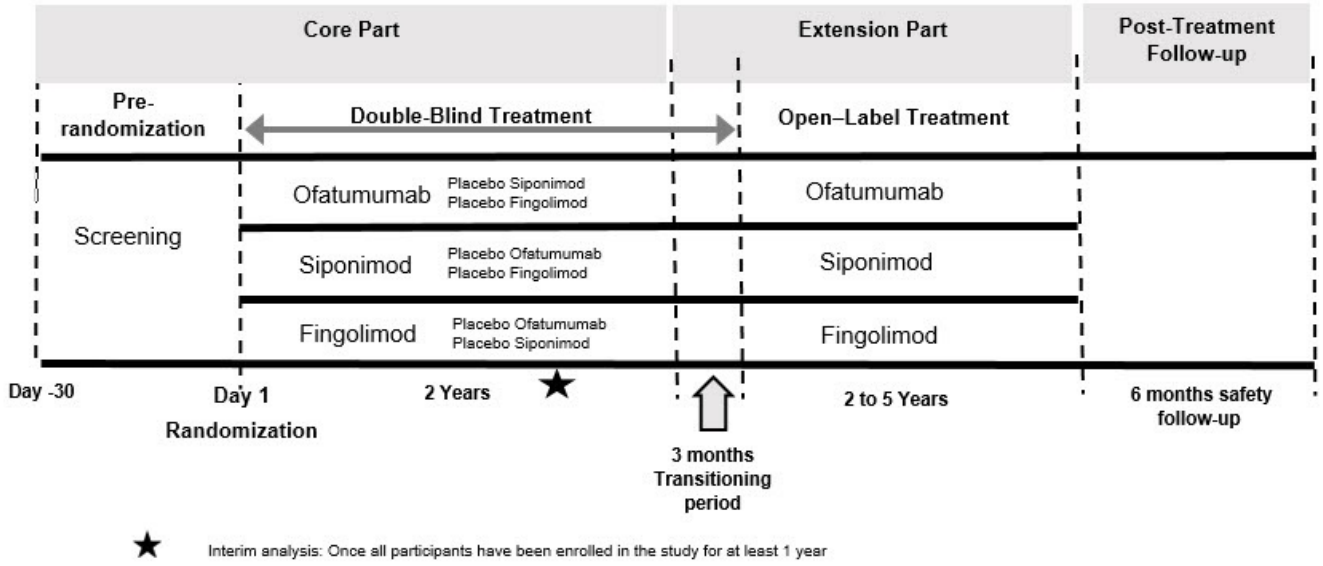
- **Welcome (5 min)**
  - Aims and objectives
  - Stakeholders present today
  - Rules of engagement
- **Introduction to case studies (10 mins)**
  - NEOS
  - SLE Phase 2b study
- **Discussion (1h 40 min)**
  - Experience, robustness and stakeholder views
  - Key design challenges
  - New frontiers
  - Call for action: future for trials incorporating historical information or with adaptive features including Bayesian methods
- **Wrap up discussion and key messages (5 mins)**

Introduction to case studies

NEOS: Combined study design for ofatumumab and siponimod (Heinz Schmidli, Novartis)

NEOS: Combined study design for ofatumumab and siponimod

- 180 patients randomized 1:1:1
- Control treatment: Fingolimod (only approved therapy in US and EU)
- 2- year double-blind, triple-dummy core, up to 5 years open-label extension
- Primary endpoint annualized relapse rate
- Interim analysis after last patients has reached 1 year of exposure to allow for early stopping for efficacy



Key innovative design elements

Non-inferiority design to compare versus de-facto standard of care Gilenya (fingolimod):

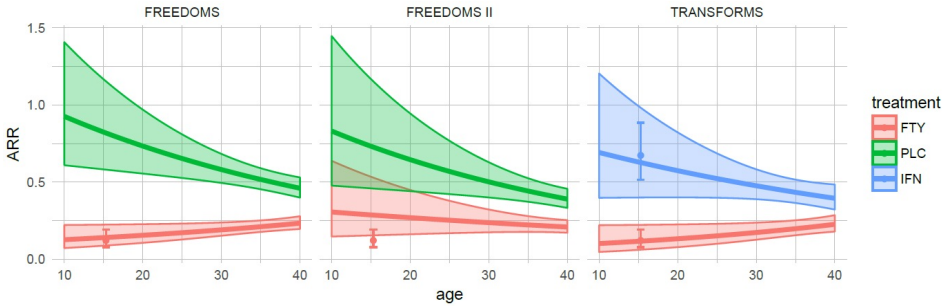
- Alternative superiority trial versus interferons or placebo considered unethical
- Non-inferiority margin can be chosen so that non-inferiority versus Gilenya guarantees superiority over interferons/placebo

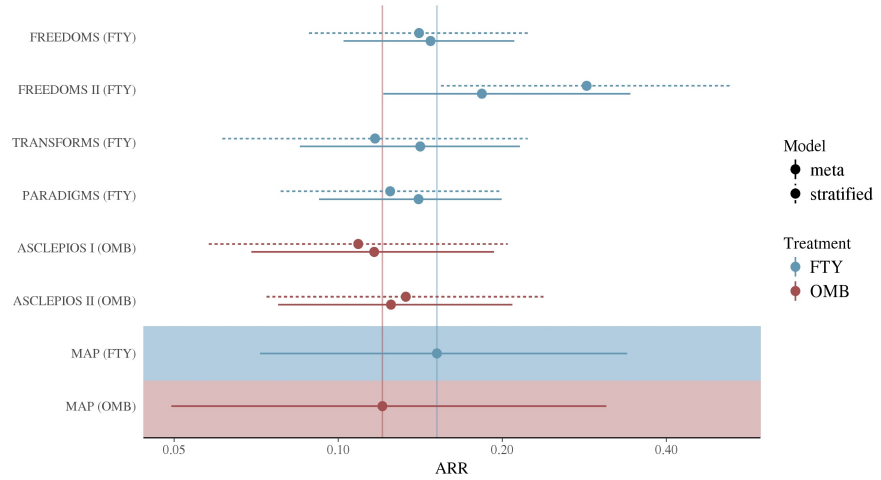
Extrapolation from adult studies:

- Extrapolation from adults to children (pediatric study population 10-17 years) is possible in MS with high accuracy
- Allows information from large Phase 3 studies to be leveraged

Bayesian design:

Meta-analytic-predictive priors (Neuenschwander 2010, Schmidli 2014) are used to robustly incorporate historical information on relapse rates from adult studies (extrapolated to children) and pediatric studies





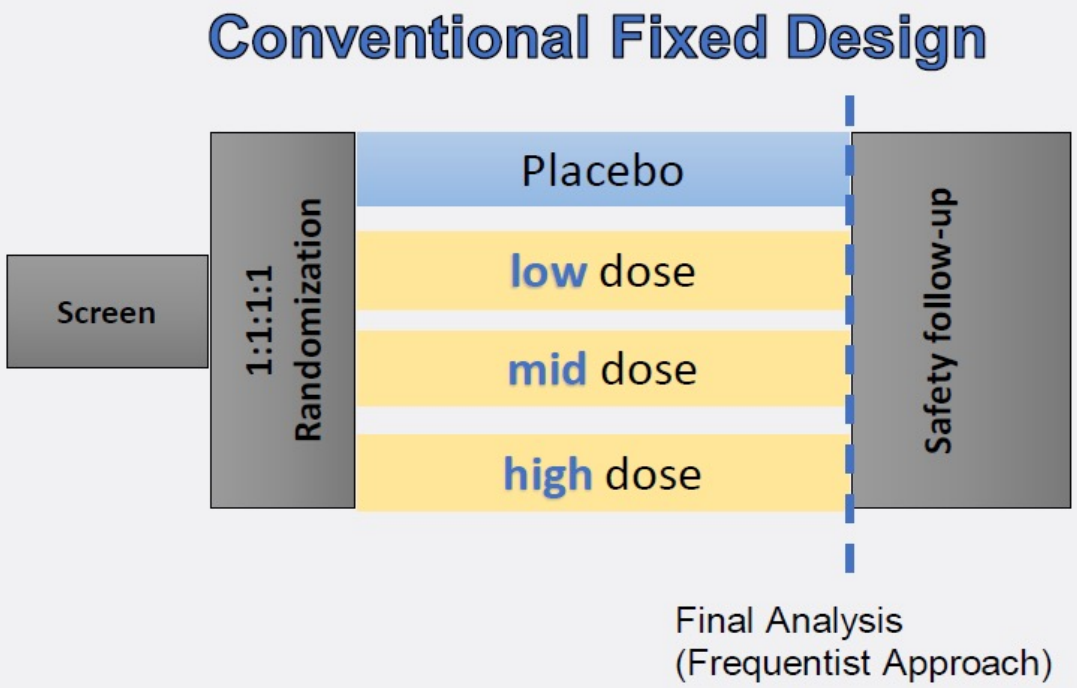
Bayesian design details

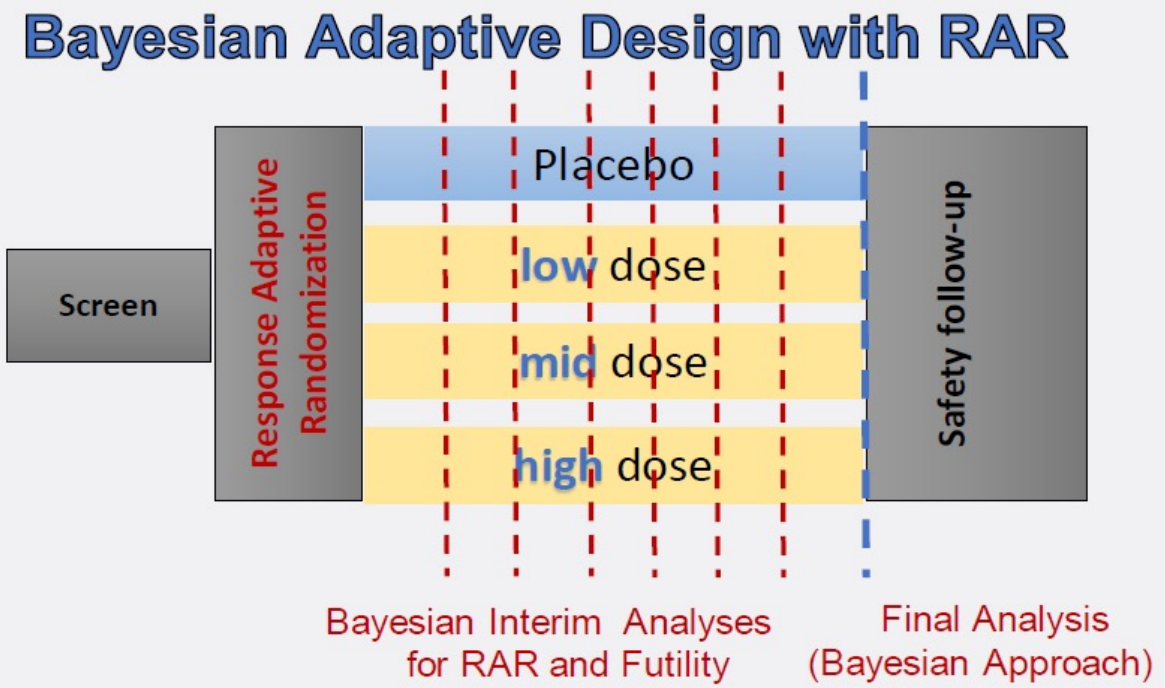
Robust meta-analytic-predictive (MAP) approach

- Allows us to borrow strength from trial-external sources
  - Informative priors are derived from relevant trial-external sources (historical MS trials in adults extrapolated to children, and historical trials in children)
  - These priors are robustified and then used in the primary Bayesian analysis of the target trial (NEOS study)
- Takes into account between-trial heterogeneity by using random-effects meta-analytic models to synthesize the evidence from historical sources
- Uses robustified priors to mitigate the risk of a conflict between the information from the source data and the data from the target trial
  - A robustified prior is a mixture of the prior derived from the trial-external sources and a vague prior
  - The mixture weight reflects the scepticism on the relevance of the trial-external sources
  - Robust priors imply that the prior information is discarded in case of prior-data conflict

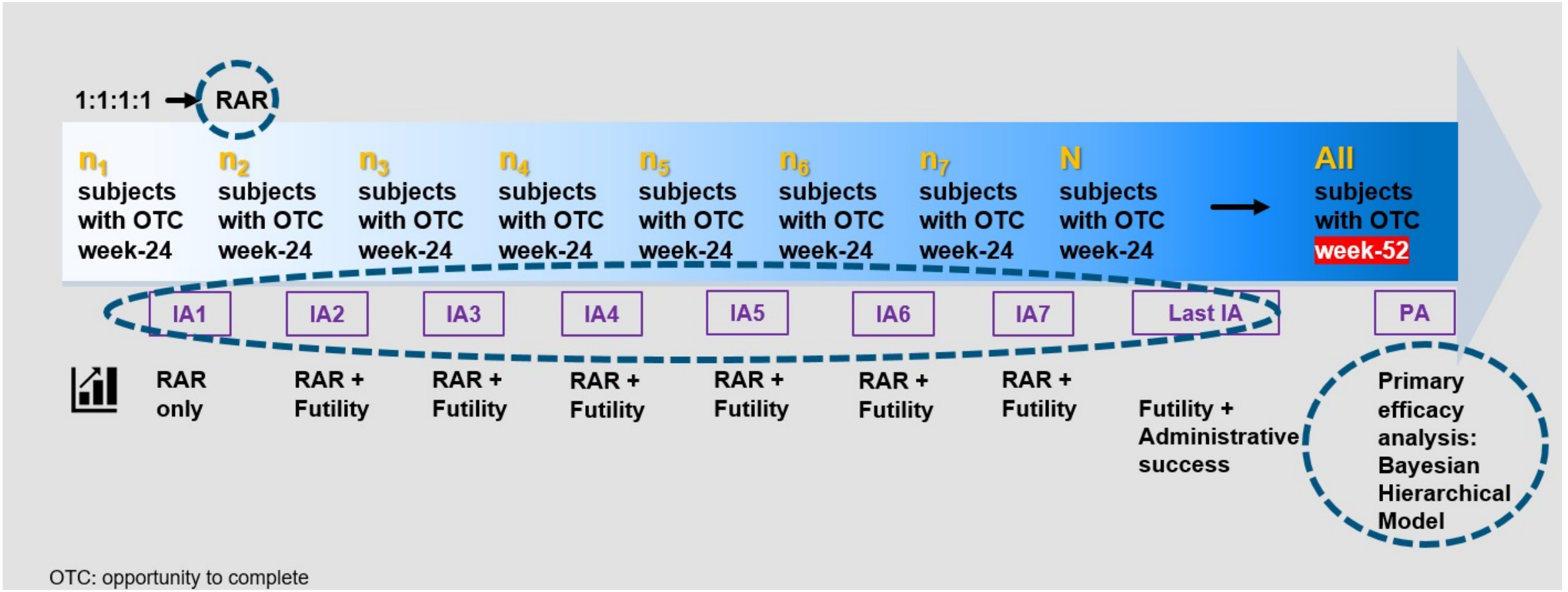
SLE Bayesian Adaptive Design (May Mo, Amgen)

SLE Bayesian Adaptive Design





Pre-Specification of Interim Analysis, RAR Algorithm and Decision Rules



OTC: opportunity to complete

Response Adaptive Randomization (RAR) & Bayesian Hierarchical Model (BHM)

RAR

- The randomization ratio to each active treatment group is based on the posterior probability that each group has the highest response rate at week 52 among the three active treatment groups.

$$Allocation_d \propto \Pr\left(p_d = \max_c p_c \,|\text{interim data}\right) \; c, d \in \{low, medium, high\}$$

BHM

- The number of responders in each group is modeled using a binomial distribution:

$$X_d \sim Binomial(p_d, N_d)$$

  where p_d is the week 52 response rate in group d.

- Each response rate is modeled independently using a logistic model:

$$\log\left(\frac{p_d}{1-p_d}\right) = \alpha_d$$

- The log-odds of response in the treatment groups is modeled using a hierarchical prior:

$$\alpha_d \sim \mathcal{N}(\alpha_{treatment}, \sigma^2) \text{ for } d \in \{low, medium, high\}$$

- BHM is used in futility and primary efficacy analyses

Pre-specified Decision Rules

- ***Futility Stopping***

  Enrollment to the study may be stopped for futility if

  $$\max \Pr\left(p_d - p_{placebo} > \textbf{target treatment effect} \mid \text{Interim Data}\right) < \textbf{low value threshold}, d \in \{low, medium, high\}$$

- ***Administrative Success***

  BHM will be fit to compute the **predictive probability of success** in **a hypothetical, future phase 3 study**, with a frequentist final analysis tested at the 2.5% one-sided level. The threshold of administrative success is the predictive probability of success in this hypothetical future study is larger than **a cutoff value**.

- ***Primary Analysis Success***

  The null hypothesis will be rejected if the posterior probability of superiority in any group is above a threshold:

  $$\Pr(p_d > p_{placebo} \mid \text{Data}) > \textbf{high value threshold}, \text{ for } any\ d \in \{low, medium, high\}$$

Discussion

Experience, robustness and stakeholder views

1. What is the relevance of Type I error control when regulatory agencies and sponsor agree to use trial-external sources of information or Bayesian adaptive designs?

2. What views do stakeholders have on the acceptability of evidence generated from designs incorporating historical information or response adaptive randomization designs?

Key Design Challenges

1. Any preferences on sources of historical information, e.g. historical clinical trials or real-world data? For example, how can we ensure that data sources are fit for purpose balancing quality and relevance: Sometimes we may prefer historical clinical trial data for its quality and other times we may prefer contemporaneous real word data.

2. What are key concerns relating to statistical methodology that need addressing?

New frontiers

Based on the success FDA has had with the CID Pilot and considering the differences in the EU regulatory framework how could Europe/EMA go about establishing a collaborative CCT program?

Call for action

What is the future for trials incorporating historical information or with adaptive features including Bayesian methods?

Wrap-up & key messages

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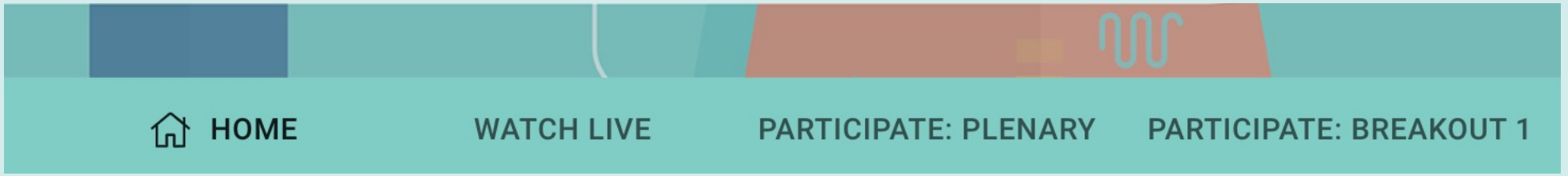

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