

# Robust decision making and precise estimation

Wolfgang Jacquet

3 November 2022

# Clinical trials: Two aims!!!

## Robust **decision making** and **precise estimation**

- Complex Designs
- Artificial Intelligence (AI)
- Real World Data (RWD)

How to move forward?

# Disclaimer

- What follows is not the position of the FAGG –AFMPS nor the EMA.
- It is solely intended as a basis for reflection on ethics, trials and decisions.

Two aims!!!

## **Robust decision making and precise estimation**

- ICH E9
- CTR
- ...

# Clinical Trial?

What is a complex (clinical) trial?

- CTR -> Clinical Trial
- Complex trial???

ROBUSTNESS - CTR

≠

ROBUST STATISTICS

Complexity

Urgency

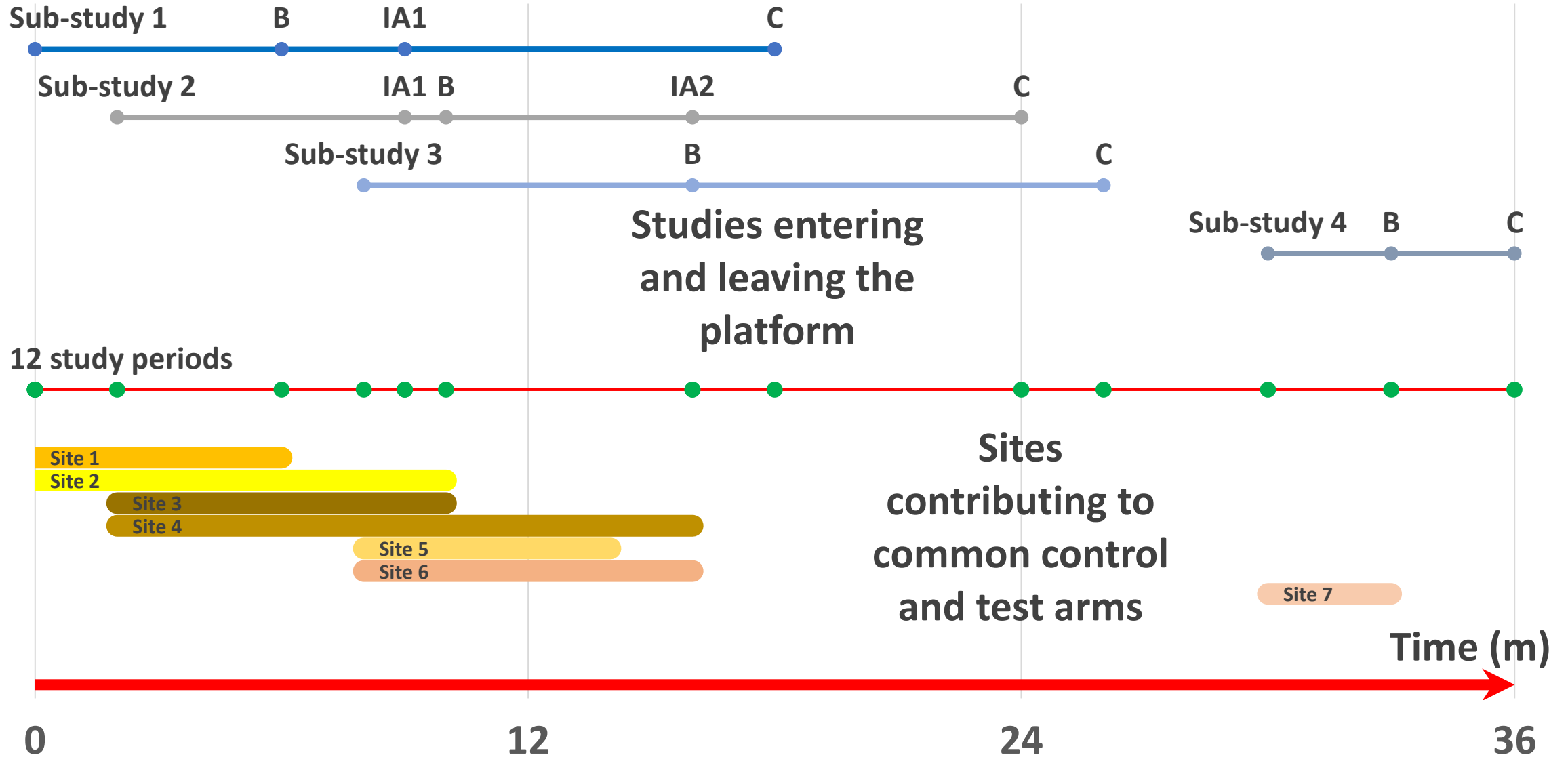
Complexity

Urgency

Complex Trials



# A platform example



# Causality

# Causality

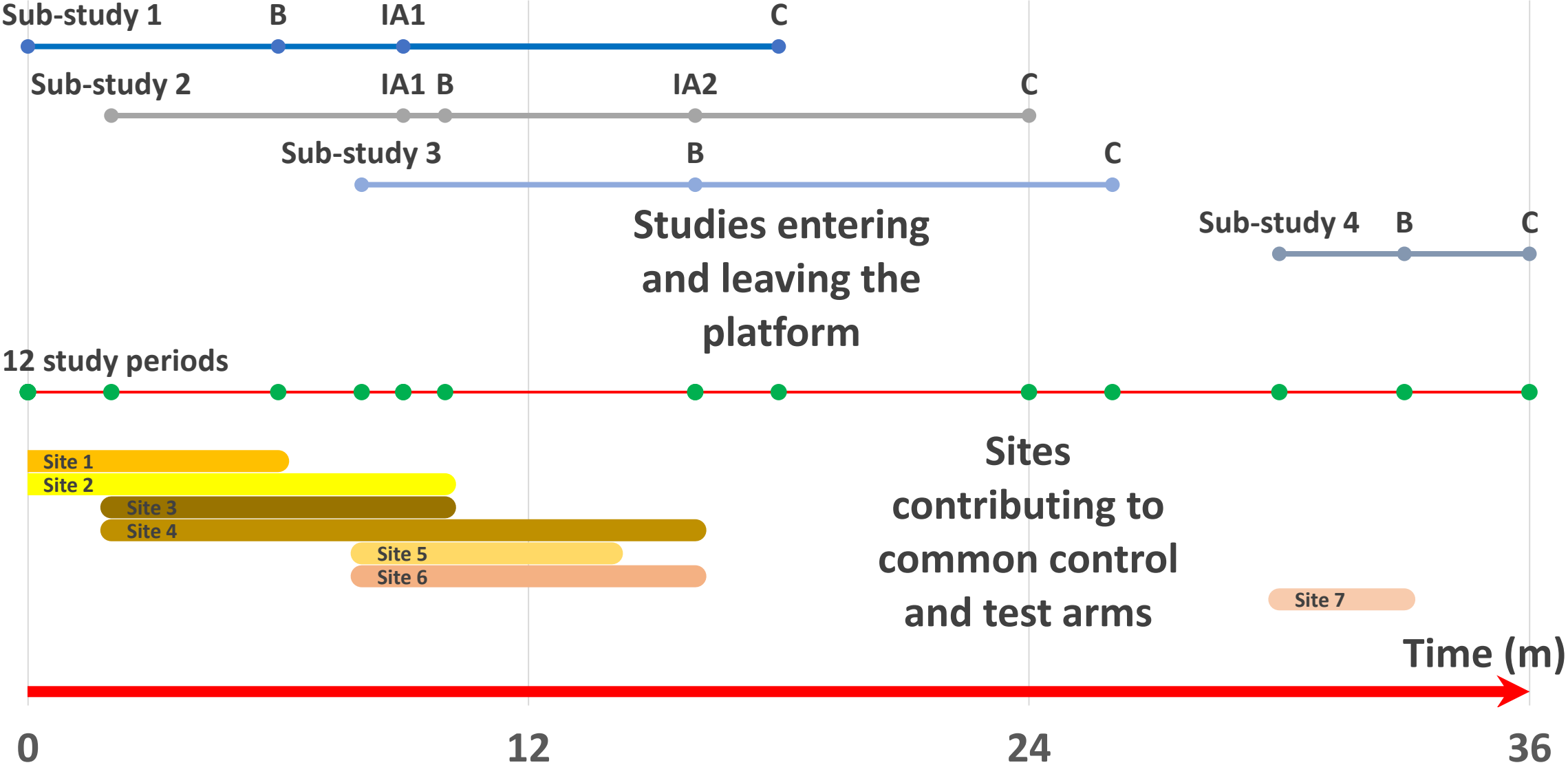
## Probability Experiment

Randomized Clinical Trials (RCT's) with an *internal concurrent control* arm are considered the standard in trial design where *appropriate and feasible*.

One armed trial

a most complex trial

# Back to the platform example

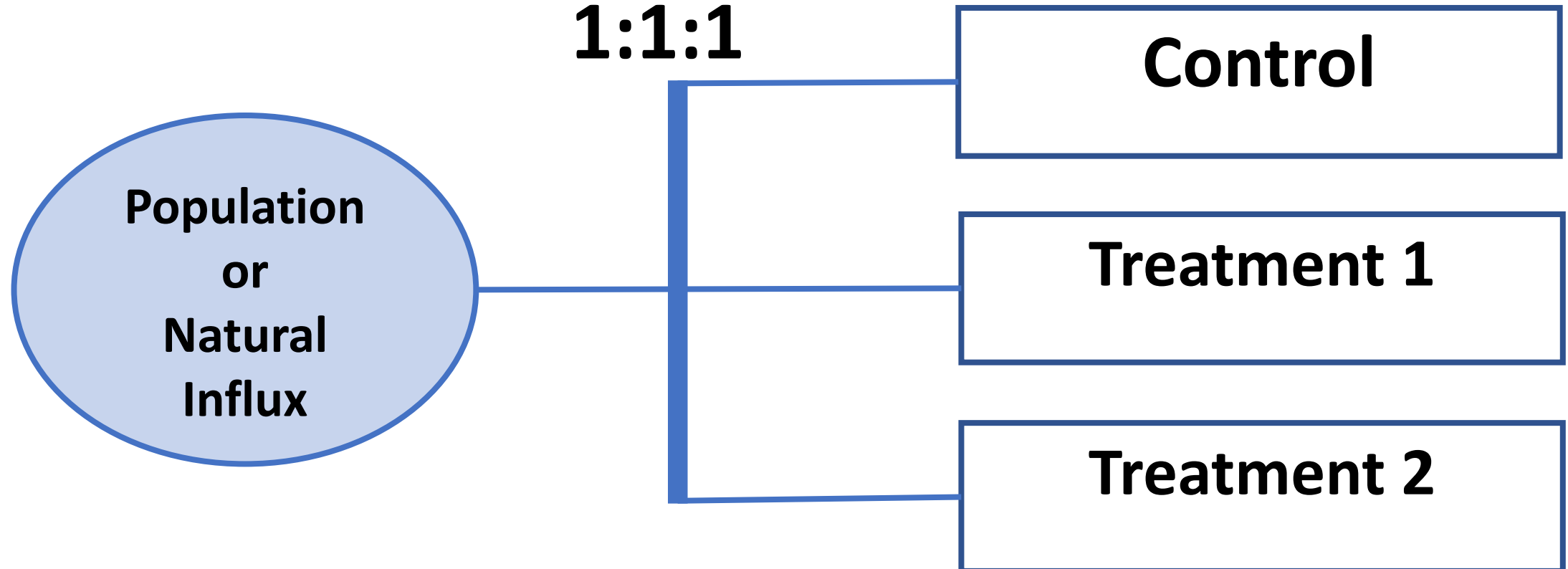


# « Reculer pour mieux sauter »

One indication – a proposed trial

## Randomization

**1:1:1**

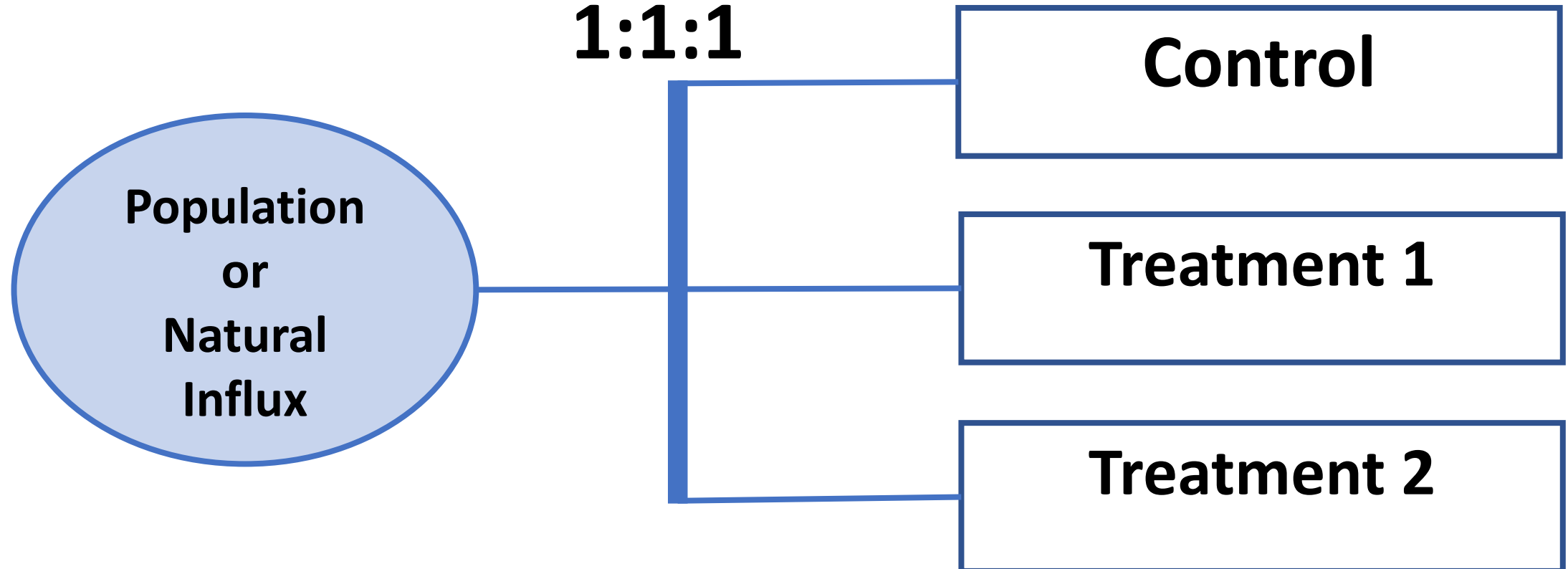


# Is the test dependency a problem?

One indication – a proposed trial

## Randomization

**1:1:1**





Type I<sub>r</sub> error  
regulator significance level

$\alpha_r$

Back to the three-arm platform example

The Type  $I_r$   
is controlled at  $\alpha_r = 0.05$

Are there remaining problems?

Back to

## Robust **decision making** and **precise estimation**

- Complex Designs
- Artificial Intelligence (AI)
- Real World Data (RWD)

How to move forward?

Slow? Not really but certainly thorough!!!

# **Restructuring the supporting layer**

- **EMA**
- **CHMP**

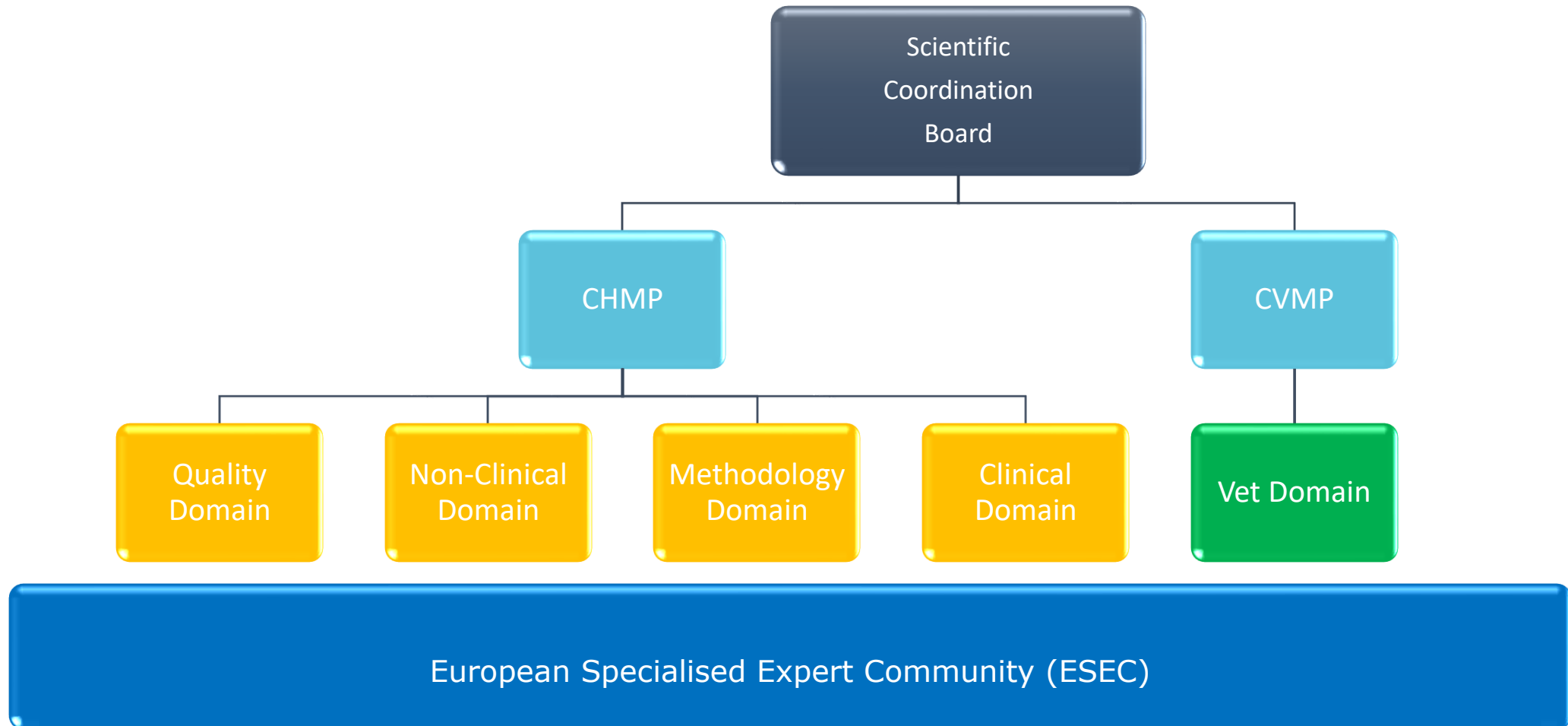
# Raw data project

## **EMA as a data driven organization**

Migration from “**data**” seen from a regulatory perspective as the *reports of studies* provided to support a MAA towards “**data**” seen as the raw data from *individual patient's* basis for the substantiation and *reinterpretation* of reports provided and *more in depth inquiry*.

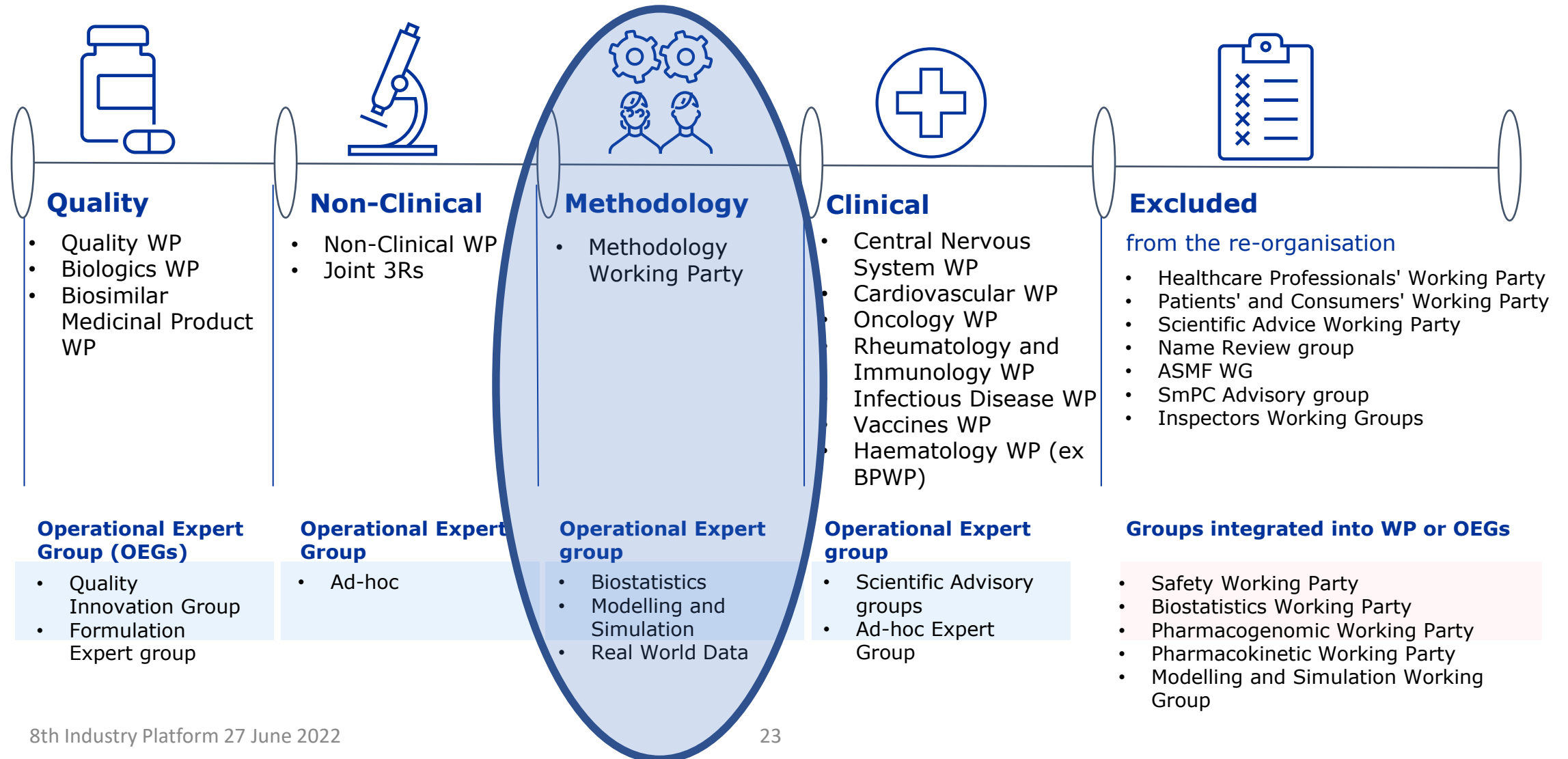
# Restructuring the supporting layer

## Five Domains

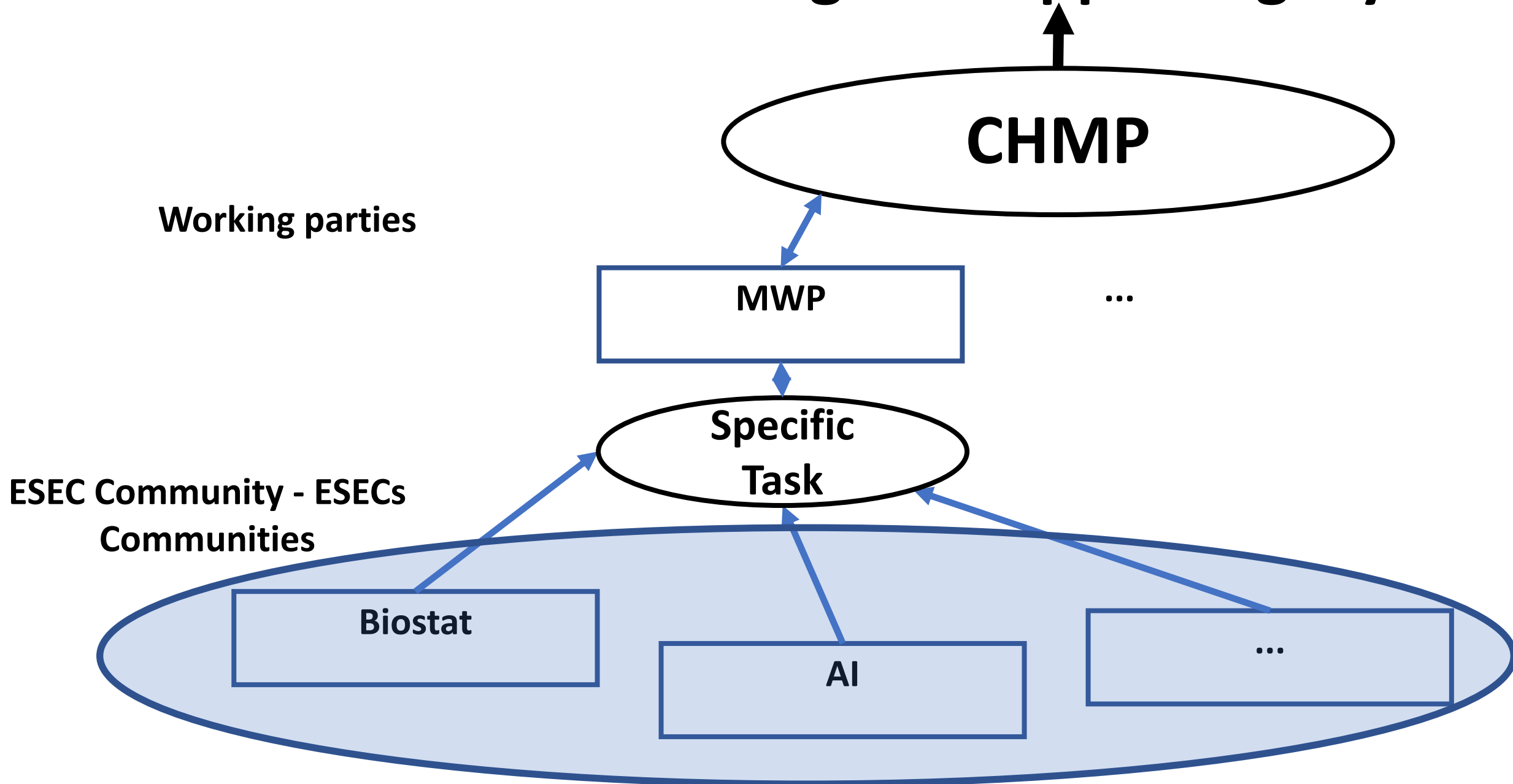


# Restructuring the supporting layer

## New Operational Model for Working Parties



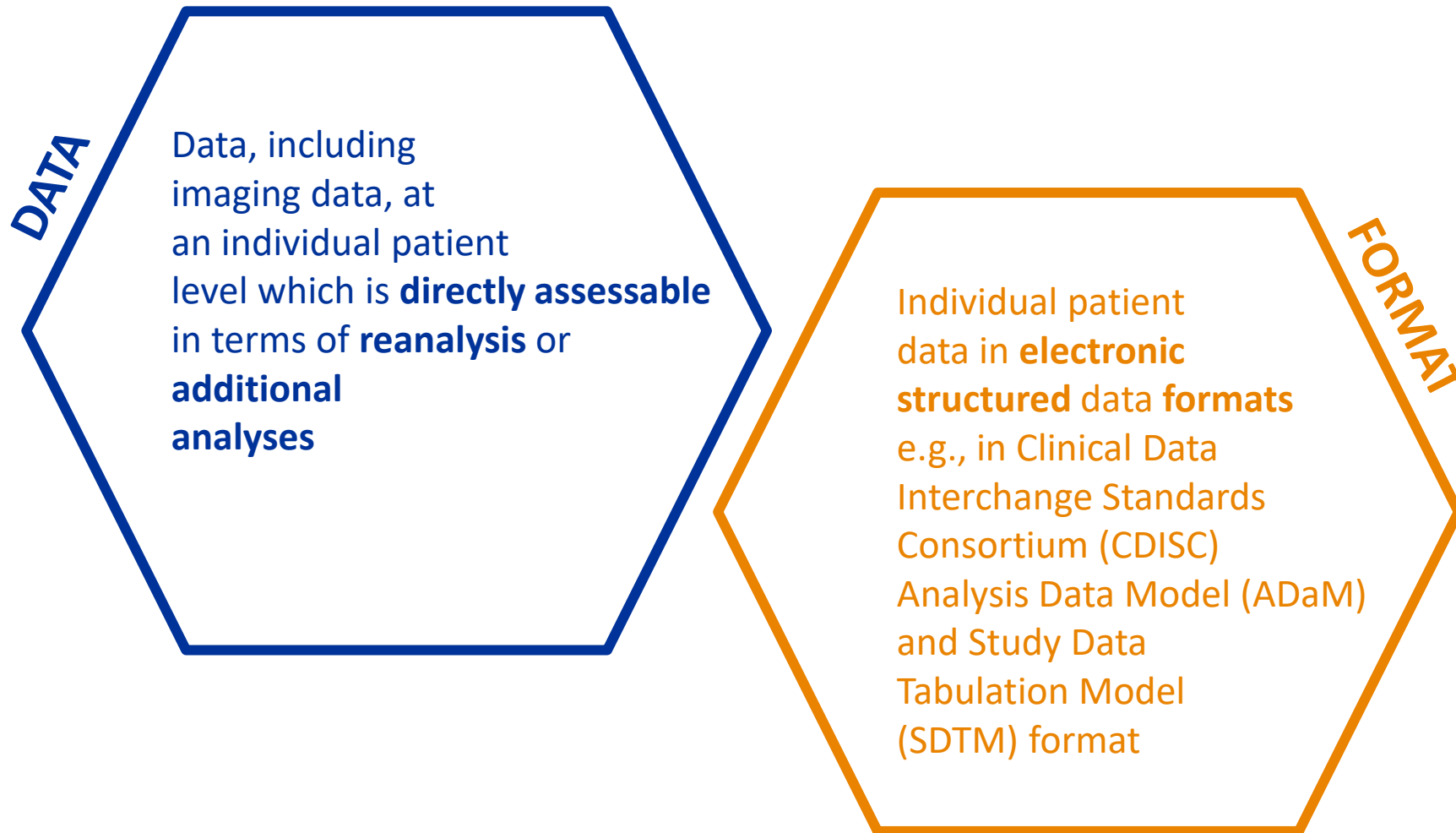
# Restructuring the supporting layer





# Raw data

- **Raw data** / Individual Patient Data (IPD) / Patient Level Data (PLD) / is **defined** as:



# Data scientists

- Bio-statisticians
- Data scientist
- AI community

Are all data scientists.

Current thinking is rapidly  
evolving!!!