“Real World Evidence”

Armin Schüler, Hans Ulrich Burger, EFSPI Statistical Leaders Meeting 2015 Brussel

2015-07-01

Structure of this session

- **Introduction (25’)**
- **Round Table discussion (30’)**
- **Joined discussion (20’)**
  - short summary per table
  - Overall summary and action items

Introduction

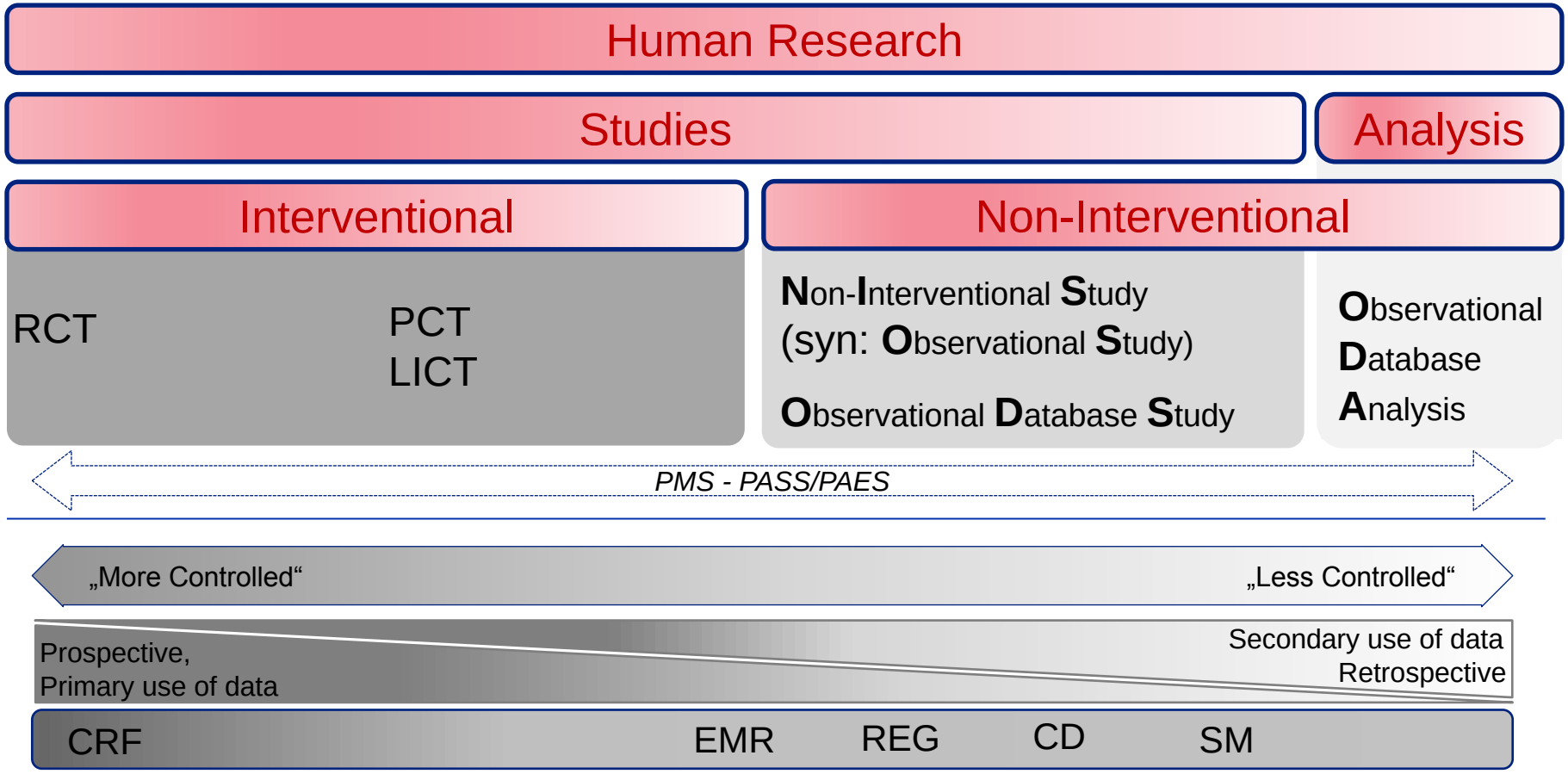
- "**Big data** is high volume, high velocity, and/or high variety information assets that require new forms of processing to enable enhanced decision making, insight discovery and process optimization."[1]

- "**Real World Data**" are observations of effects based on what happens after a prescriptive (treatment) decision is made where the researcher does not or cannot control who gets what treatment and does not or cannot control the medical management of the patient beyond observing outcomes

  - ISPOR task force

[1] Laney, Douglase of 'Big Data': A Definition". Gartner. Retrieved 21 June 2012 via Wikipedia (2015-05-20)
ISPOR = *International Society For Pharmacoeconomics and Outcomes Research*

Scientific Human Research



RCT: Randomized clinical/controlled trials
PCT: Pragmatic clinical trials
LICT: Low-interventional clinical trials
SM: Social Media

ODS: Observational database studies
ODA: Oberservational database analyses
PMS: Post marketing surveillance
PASS/PAES: Post approval safety/effectiveness study

CRF: Case Report Form
REG: Registries
CD: Claims Databases
EMR: Electronic Medical Record

EU directive 536/2014

2. For the purposes of this Regulation, the following definitions also apply:

(1) 'Clinical study' means any investigation in relation to humans intended:

(a) to discover or verify the clinical, pharmacological or other pharmacodynamic effects of one or more medicinal products;

(b) to identify any adverse reactions to one or more medicinal products; or

(c) to study the absorption, distribution, metabolism and excretion of one or more medicinal products;

with the objective of ascertaining the safety and/or efficacy of those medicinal products;

(2) 'Clinical trial' means a clinical study which fulfils any of the following conditions:

(a) the assignment of the subject to a particular therapeutic strategy is decided in advance and does not fall within normal clinical practice of the Member State concerned;

(b) the decision to prescribe the investigational medicinal products is taken together with the decision to include the subject in the clinical study; or

(c) diagnostic or monitoring procedures in addition to normal clinical practice are applied to the subjects.

(3) 'Low-intervention clinical trial' means a clinical trial which fulfils all of the following conditions:

(4) 'Non-interventional study' means a clinical study other than a clinical trial;

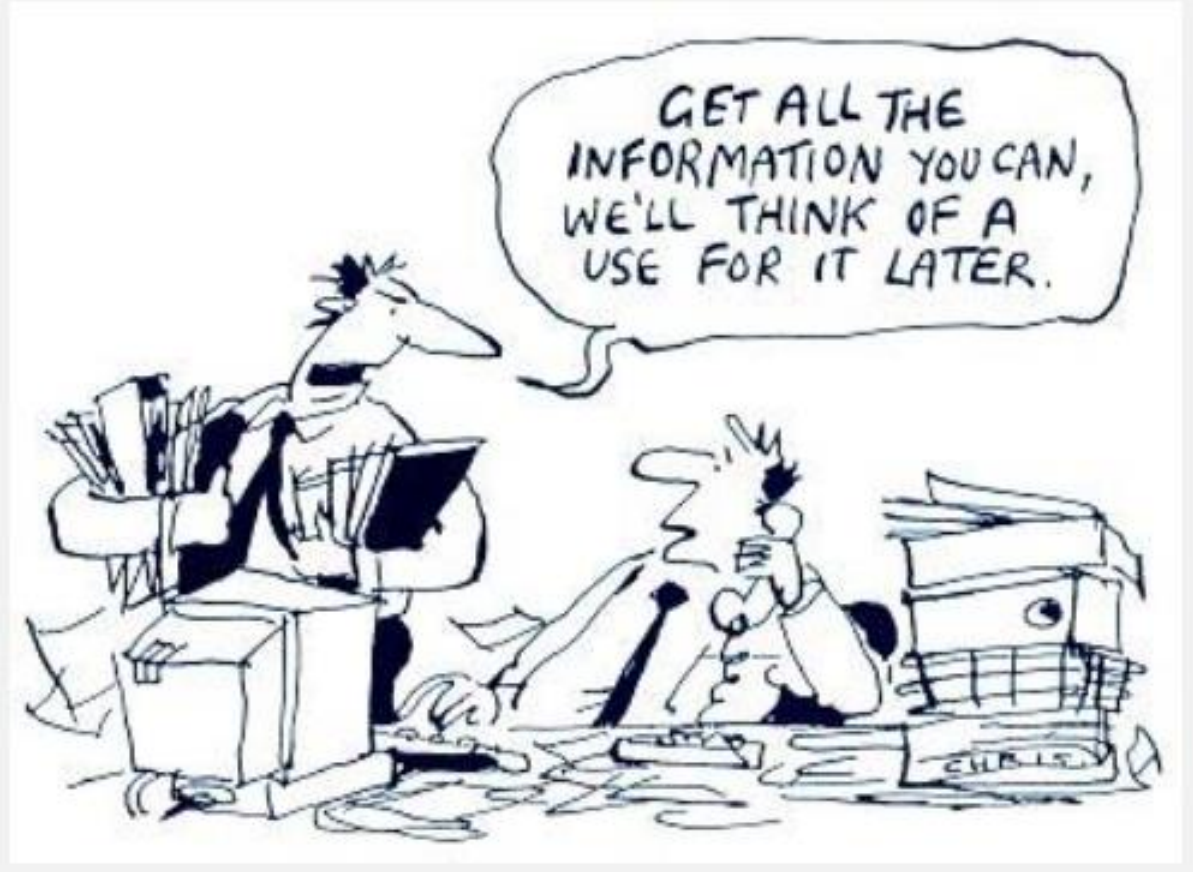
(5) 'Investigational medicinal product' means a medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial;

(6) 'Normal clinical practice' means the treatment regime typically followed to treat, prevent, or diagnose a disease or a disorder;

Types of Real-World Databases

- **Administrative (claims) data**
  - Medicare, Humana, MarketScan, Pharmetrics, Optum
  - German Sickness Funds
- **Hospital data**
- **Electronic health (medical) records**
- **Surveys of patients and providers**
- **Patient/drug registries**

Status


GET ALL THE INFORMATION YOU CAN, WE'LL THINK OF A USE FOR IT LATER.

Example 1

- Development in a rare disease
- Application of RWE
  - Understanding unmet medical need (may not be clear)
  - Understanding endpoints
  - Handling limited size of studies by adding in additional RWE data.
    - Need for controlling selection bias depend on size of observed treatment effect
    - A number of methods available for replacing control arm and for enriching control
  - Safety may be ensured partly through post-marketing activities using RWE

Example 2

- Rare disease setting with high unmet medical need in patients, different proposals for treatment of disease, none proven to be efficacious/superior due to rarity of disease
  - Approach of a single arm study was chosen to examine new drug
  - Direct control arm not available
  - Literature research revealed wide range of observed response to treatment
  - Knowledge on prognostic factors very limited or only known as risk factor for development of disease

➔ Need for reference/control to bring observed results of single arm trial into perspective

➔ Making use of existing data to generate control in the frame of an observational study

➔ Deserves same attention for planning and time for conduct like RCT

Example 2 cont'd

Combination of database search (patient identification) and EMR (further detail on patient characteristics, treatment and outcome) according to pre-specified protocol for extracting data from EMR firewalling from outcome

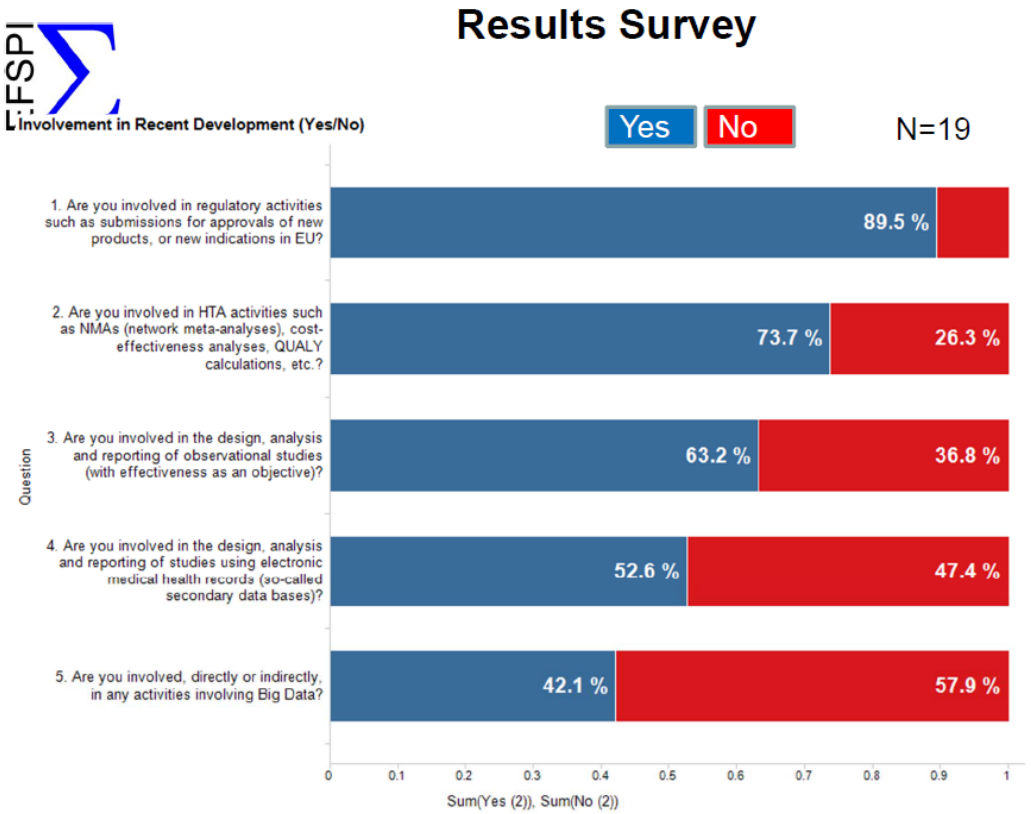
- Matching selected prognostic factors to the single arm study
  - Very limited or no knowledge over prognostic factors can introduce severe bias in study results
- Propensity score matching to baseline characteristics of single arm trial population
  - Needs larger amount of data to be able to find cohort with good overlap regards baseline characteristics
  - Finding suitable control patients in rare disease setting with evolving diagnostic/treatment possibilities over time could be very problematic, worst case when no overlap exists
  - Comes closest to mitigate lack of control arm when well-conducted (Yue, 2012; Yue et al. 2014) and could be acceptable for designing premarket comparative studies using existing data as control

Example 2 cont'd

When knowledge on population is limited, a 2-step approach could be useful

- Step 1 - starting off with an observational study with restriction on population I/E and decide upon feasibility for more appropriate study
  - Objective to learn more about population, treatment and potential prognostic factors in a first step and feasibility to undertake additional study including matching
- Step 2 – Take learnings from step 1 and conduct study matching clinical characteristics with single arm trial
  - 1:1 or 1:2 (1:4 best ratio) for limited number of known prognostic characteristics
  - Propensity score matching (also 1 to many)

From last year's survey



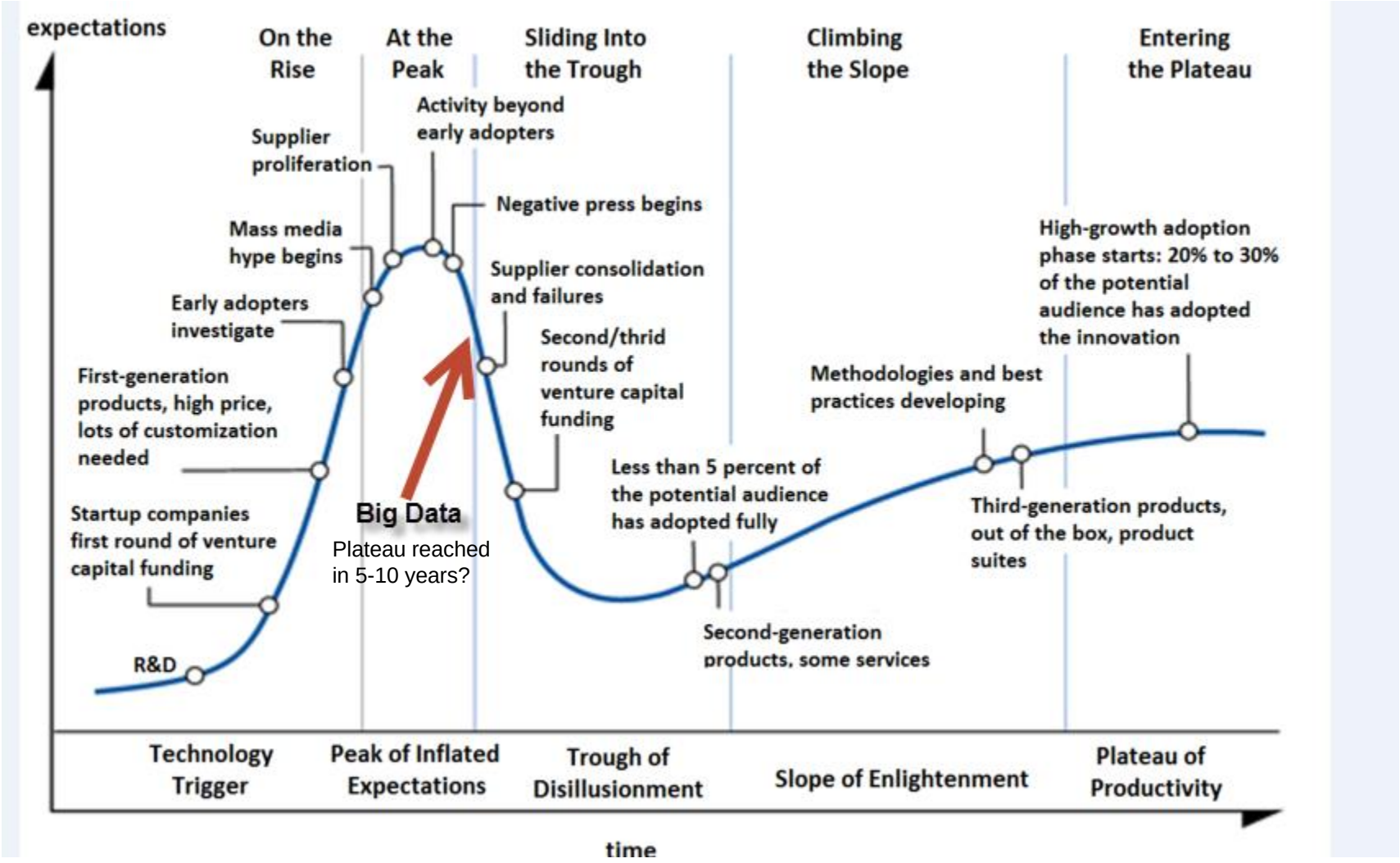
Involvement in Recent Developments

34

Quick pool on Q 5 "Are you involved directly or indirectly in any activities involving Big Data"

What's today's status within your organisation?

The hype cycle – were do we stand



Update from https://en.wikipedia.org/wiki/Hype_cycle, accessed 2015-06-15

What does RWE mean for us?

- RWE often used as a buzz word today (not sexy for statisticians)
- RWE often with marketing departments used for payer strategies but value could go much beyond
  - Indirect control for single arm trials
  - Understanding the disease (e.g. rare diseases)
  - Understanding relevant endpoints and their variability
  - Searching / validating surrogate endpoints before start of a study
- RWE may help gaining a more patient centric development view (beyond clinical trials) in line with a shift we see from regulatory approval to patient access

What does RWE mean for us?

- RWE often technically more complex than our bread and butter RCTs
  - Methodologically challenging and different to our world (confounding, data driven vs hypothesis driven research…). RWE may require specific expertise statistically closer to Epidemiology
  - Interpretation often complex and cannot be left over to other functions
  - Processes could be different
- RWE is a huge opportunity for statisticians in the industry with its own challenges

What can we do as statistics leader?

We should not shy away from it!

- There is meaningful usage of RWE. Provides additional information on how treatments behave in real life
  - Additional information on the treatment behavior in different settings (other combinations or back ground treatments etc)
  - Pharmacovigilance
  - Basic understanding of a disease (rare diseases)
  - Basic information for study planning
  - Replacing a control arm in cases where treatment effect is large and control is consistent in showing little or no effect
- There will be also other usage of RWE
  - Providing evidence in an uncontrolled (e.g. non-randomized) setting
  - Replacing control arms in scenarios of small effects
  - Weakening general standard of evidence
  - …

What can we do as statistics leader?

There are things we cannot influence:

- No doubt there will be good applications, dirty stuff and generated hype
- No doubt there will also be over promising, over interpretation
- Most critical for us what we can influence:
  How to get to an adequate interpretation!

Risk of being overcautious:

- Someone else will do it (example Bio-informatics)

Alternative: Get engaged and influential

- Help making it a success
- Support adequate data analysis and interpretation
- This includes willingness to make hands dirty

Current environment

Overall situation:

- Companies are building up work forces
- Partly these are new departments partly within biometrics and statisticians engaged in, partly outside
- New departments frequently replace epidemiology
- We will be faced with in one or the other way anyhow!

Current environment

What can we do else?

- Need for good practise guidelines?
  - Applying good practice allows to reach full value.
  - Do we need ICH for RWE?
- Organizational:
  - Creating mixed role (Epi & Stat) or building around 2 different roles
  - How to develop or support Project Statistical Leads who need to acquire additional competences

Some Conclusions

- RWE is coming
- We should not shy away but be willing to take responsibilities, especially for adequate interpretation
- If we don’t take it, others will do
- We should get engaged more!
  - We need to discuss what this means in practise
  - We need to think about what else could be done to make RWE a success

Round table discussion

Round table discussions Questions:

- Do you think it is useful to invest in RWE?
- Should this be done within biometrics? Within biostatistics?
- What activities are ongoing in your company?
- Is there a change within your organization compared to last year's survey
- What can statisticians contribute in the area of RWE?
- In case statisticians get into RWE, is the span of activities becoming too large?
- What would success for statistics look like in RWE area?
- Where could an organization like EFSPI help?
  - Are there training needs?

Wrap-up summary from the round table

- ……
- ……
- ……