23 February 2022
EMA/618265/2021

# Minutes – BSWP Stakeholders Meeting

9 February 2022

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Chairs: Jörg Zinserling – Frank Pétavy

| Item | Preliminary draft agenda | Presenter/Speaker | Time |
|---|---|---|---|
| **1.** | **Welcome and introduction** | | |
| | Jörg Zinserling / Frank Pétavy | | 10:00 - 10:05 |
| **2.** | **Raw data submission** | | |
| | EMA - BSWP | Eftychia Eirini Psarelli, EMA | 10:05 – 10:15 |
| | EFSPI | Uli Burger, Roche | 10:15 – 10:25 |
| | Discussion | | 10:25 – 11:00 |
| **3.** | **Use of external control data** | | |
| | EUROPABIO | Lisa Hampson, Novartis Pharma AG | 11:00 – 11:10 |
| | | Armin Schueler, Merck Healthcare KGaA | |
| | | John-Philip Lawo, CSL Behring | |
| | EUCOPE | May Mo, Amgen | 11:10 – 11:20 |
| | EFSPI | Christoph Gerlinger, Bayer | 11:20 – 11:30 |
| | Discussion | | 11:30 – 11:55 |
| **4.** | **Conclusions** | | |
| | Jörg Zinserling / Frank Pétavy | | 11:55 – 12:00 |
| **5.** | **List of Participants** | | |

**Official address** Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
**Address for visits and deliveries** Refer to www.ema.europa.eu/how-to-find-us
**Send us a question** Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

**2. Raw data submission -** Eftychia Eirini Psarelli, BSWP for EMA and Uli Burger, Roche for EFSPI

**John-Philip Lawo**, CLS Behring representing EUROPABIO

1st presentation: Data requirements to follow CDISC standards. Pilot to come.

2nd presentation: raw data analysis not only to verify collection and datasets (as FDA does) but also to be able to combine with other data sources (eg, registries). Connected to Big data analysis. Thus to allow to send in raw data and shiny apps for analysis. CDISC is seen as framework but not as data structure, which is desired here.

Discussion:
EAM is looking for combining data and draw conclusions from it as a long term goal.

EMA to provide the structure and framework?

EMAs approach to set a standard aside CDISC submission done to FDA and PMDA to also cover big data and registries? Trying to do the big shot? -> EMA will be requesting SDTM and ADaM and not deviate from FDA standard.

IMPORTANT NOTE ON EMAIL: One important point to me was the definition of 'raw data' and as May indicated there should be clarity on what is meant exactly and how much CDISC fits for purpose and where it does not in the view of EMA.

**May Mo**, AMGEN representing EUCOPE

I really appreciate the comprehensive systematic framework presented by Lisa, Armin and John, and the Pharmaceutical Statistics paper (Burger, et al) shared in the EFSPI presentation.

1st presentation (EMA BSWP):
- Raw data - defined as patient level data
- Raw data project – prepare for acceptance of raw data for future regulatory submissions; submission via eCTD; raw data to follow CDISC standards; FDA and PMDA experience
- Proof-of-concept pilot – kick off 2022

2nd presentation (EFSPI):
- Danish (DAC) initiative taken up by EMA
- Go beyond re-analysis - "also combining it with national registry data. This should provide more support for companies and intensify scientific advice process"
- Global requirements and process, ICH working group?
- Areas EFSPI can help (CDISC experience, R Shiny apps, etc.)

Discussion:
- "Raw data" has different interpretation in the industry and usually refers to source data prior to any manipulation. Derived individual patient data (SDTM and ADaM) are normally not considered raw data.
- Using consistent data standard (CDISC) globally helps improve data processing and analysis efficiency for both industry and regulatory agencies.

**Minutes of the 2nd Stakeholder Meeting held on 29 October 2021**

**2. Raw data submission -** Eftychia Eirini Psarelli, BSWP for EMA and Uli Burger, Roche for EFSPI

**Armin Schueler**, Merck Healthcare representing EUROPABIO

Raw Data Submission - Discussion:

- CDISC is a frame not a real format
- phuse is an important stakeholder for the question how to maximise the data by submissions.
- Presentations showed the importance of interactions
- It was clarified that if data would be shared all countries would have access.
- Pure re-analysis should not be the end of the exercise. What is the more tbd
- Subgroup analyses and sensitivity analyses were regarded as the analyses which would create the most value. In addition having access to the data would reduce the number of requests by the agency for simple analyses. This would speed up the process.
- It was noted that Stand alone pros submitted to FDA might be different to the ones used for analysis to allow easy rerun
- "ready to use" systems is what would be preferable
- Data could inform scientific advise meetings
- Policy P70 should be of help in this context

**Christopher Gerlinger**, Bayer representing EFSPI

Eftychia Eirini Psarelli and Uli Burger presented overviews on the topic on behalf of BSWP and EFSPI, respectively. There was a high interest from BSWP in raw data submission and they are keen to collaborate with stakeholders on this topic. It was clarified that by raw data submission this refers to standardised patient level data and the expectation that global standards can be adopted e.g. CDISC. The primary focus and value is expected to be additional exploration and analyses of the data rather than reproducing the analyses performed by the Sponsor.

**3. Use of external control data** Lisa Hampson, Novartis Pharma AG, Armin Schueler, Merck Healthcare KgaA, John-Philip Lawo, CSL Behring for EUROPABIO, May Mo, Amgen for EUROCOPE and Christoph Gerlinger, Bayer for EFSPI

**John-Philip Lawo**, CLS Behring representing EUROPABIO

1st presentation (ours): RCT gold standard but not always possible, leading to single arm trial (SAT). to increase its value consider external data. Use target trial framework to design that trial, also consider adaptive decision if external data can be used or RCT would be needed
2nd presentation: RCT not always possible, SAT possible but limited information, external data to provide better evidence. 1year discussion with FDA and EMA leading to alignment RCT not feasible, and SAT+RWD may be usable. Focus on data collection, consistency and objectivity as well as covariates needed for matching (by Propensity score), integrity and sensitivity analyses
3rd presentation: RWD is more widely available. There is some hype in using RWD, but key methodological issues (blinding, randomization, quality, bias [selection, time, regional, assessment, endpoint,…]) not finally solved. RWD is collected for a different reason, discuss types of bias.
Discussion:
There is more than RCT or SAT, especially in between that need to be consider. Consider bias and discuss openly with agency, not just starting 'RCT is infeasible thus have to do SAT'. No objection from EMA, instead the target trial framework seems useful.

**May Mo**, AMGEN representing EUCOPE

1st presentation (EUROPABIO):
• Systematic approach for leveraging ECD using the target trial & estimand framework to clarify the study question and using simulation to compare design options
• Design options overview of RCT, ATD, hybrid trials, RCTwEC_Walk and SATwECA
2nd presentation (Eucope):
• A real but anonymized case study in relapse or refractory, rare disease, pediatric oncology setting with a design of SAT + RWD ECA.
• Extensive discussion with FDA and EMA over a year leading to agreement that RCT not feasible, and SAT + RWD ECA design was accepted. The focus was on patient inclusion / exclusion, data relevance, consistency and objectivity as well as covariates needed for matching (by propensity score methods), trial conduct and sensitivity analyses.
3rd presentation (EFSPI):
• External controls are promoted as benefit to patients (speed to access new therapies; reduced exposure to potentially suboptimal treatment)
• Industry motivation includes speed and cost reduction of drug development
• External control studies increase risk for biased estimation of treatment effects
• Statisticians have a unique set of skills and understanding of data and methodology and should be fully engaged in the use of external controls to ensure the quality of data, analysis methods and result interpretation.
Discussion:
• There are alternative design options beyond RCT and SAT that may be appropriate for the specific settings
• Engage, discuss early and openly with agencies
• The target trial framework seems to be a good approach to select appropriate trial design
• Statistician engagement is key to ensure proper trial design to generate high quality evidence.

**3. Use of external control data** Lisa Hampson, Novartis Pharma AG, Armin Schueler, Merck Healthcare KgaA, John-Philip Lawo, CSL Behring for EUROPABIO, May Mo, Amgen for EUROCOPE and Christoph Gerlinger, Bayer for EFSPI

**Armin Schueler**, Merck Healthcare representing EUROPABIO

Use of external control data - Discussion:
• External control data is not necessarily RWD. It could also be date from other clinical trials.
• Note, other trial data is also systematic recorded data compared to RWD
• In the on the possibility to run an RCT feasible and inconvenient are often mixed. It's sometimes argued "not feasible" while it is in reality "inconvenient".
• Clear justification and argumentation why an RCT is not possible is needed
• Pharma companies should start with a fresh eye. E.g. what has done within the paediatric setting
• Sometimes the concept is misunderstood – a example was given from a discussion where a failed randomised study was used to argue against running randomised trials while the example of an non-effective drug is rather an argument on the importance of RCT.
• External controls could be valuable for post-hoc question. On the other hand this could introduce bias which is difficult to control.
• Key is the transparency on choosing external control. It has to be clear what was used and what was not used. The lack of pre-specification was regards as a problem.
• Use of the Estimands Framework was regarded as good point to add to the workflow – what are the parameter of interest to answer the clinical question.
• Question was raised whether the target trial framework will achievable [note I am not that sure that I got the comment from A. Brandt correctly]
• When applying a target trial framework an qualification meeting or ITF meeting with EMA would be needed to discuss the plan in more detail.
• Challenge with RWD is to mimic the in- and exclusion criteria of the clinical tria
Closure: An interesting journey in the future. But not too optimistic where this could be applied.

**Christopher Gerlinger**, Bayer representing EFSPI

The EuropaBio representatives; Lisa Hampson (Novartis) and Armin Schüler (Merck Healthcare KGaA) presented a framework proposal. May Mo (Amgen) on behalf of EUCOPE – presented a case study on a single arm phase 2 trial paediatric in oncology. Christoph Gerlinger (Bayer) provided an overview on the topic on behalf of EFSPI.
The BSWP highlighted the challenge of truly assessing the viability/feasibility of a proposed randomised trial and the importance of considering a wide variety of trial designs before concluding that the only option may be the use of an external control. An additional concern is the potential to introduce additional biases as the historic external control data are known and lack of pre-specification is a key problem. It was recommended that the framework proposal be submitted to the EMA (via ITF?) for evaluation.

**5. List of participants:**

| | |
|---|---|
| **EFSPI** | Christoph Gerlinger (Bayer AG) - speaker |
| | Jürgen Hummel (PPD) |
| | Uli Burger (Roche) - speaker |
| | Dr. Florian Voß (Boehringer Ingelheim) - Silent Observer |
| | Anna Berglind (Astrazeneca) - Silent Observer |
| | Dan Evans (Pfizer) - Silent Observer |
| | Olivier Collignon (GSK) - Silent Observer |
| | Frances Lynn (Orchard Therapeutics) - Silent Observer |
| | Erika Daly (Cytel) – Silent Observer |
| **EFPIA** | Christine Fletcher (GSK) |
| **EGGVP** | Sandra Turk (KRKA) |
| **EUCOPE** | May Mo (Amgen) – speaker |
| **EUROPABIO** | Armin Schueler, Merck Healthcare KGaA - speaker |
| | Lisa Hampson (Novartis) - speaker |
| | John-Philip Lawo (CSL Behring) |
| **Medicines for Europe** | Márton Megyeri (Gedeon Richter) |
| | Martin Schiestl (Sandoz) |
| | Joseph Park (Samsung Bioepis) - Silent observer |
| | Marta Baldrighi (Medicines for Europe) – Silent Observer |
| **BSWP - EMA** | Eftychia Eirini Psarelli (TDA-MET) - speaker |