EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Summary of Sessions and Way forward

FP7 Small Populations Research Methods Projects and Regulatory Application Workshop – 29, 30 March 2017
Asterix, IDeAl, InSPiRe

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Session 2: Evidence synthesis

- There are methods available now to deal with meta-analysis heterogeneity issues
- Can a meta-analysis help regulatory decision-making? When would regulators accept meta-analysis as pivotal evidence? If regulators accept one single pivotal trial, why not meta-analyses? (= does treatment work, what is estimate of benefit?)
- What do we include in the MA? Trials posing different questions (design, population)? Different types of experiment (interventional, observational)?
- In a Bayesian framework, potential that the posterior distribution is influenced too much by prior information? There exist methods to mitigate this problem, but more work needed to check posterior is robust.
- Heterogeneity remains important and needs to be understood. It's not only about statistical criteria: We need to involve subject matter aspects to understand.
- Methods available to analyse a set of n-of-1 trials in a pre-planned manner

Session 3: Extrapolation

- There are tools (dose-finding, scepticism factor, comparison of dose-response curves) that can utilise other data to inform paediatric development.
  - Can go beyond paediatric development (phases of drug dev., or across different diseases)
  - Can be frequentist, Bayesian or a mix of the two, but does it really matter for regulators
- Scepticism factor is in fact a good way to have a discussion in a structured way, to articulate and quantify the discussion.
- Present not only one scenario, but also alternatives. Intuitive for statisticians who want to stress their method.
- Knowledge models and continuous information addition to the knowledge base
- When extrapolation strategies are considered for paediatric development, start planning at the same time as for adults. Consider using other data.
- 2 Are there circumstances where no paediatric data is needed? -> legal implications…

Session 4: Level of evidence and decision theoretical aspects

- Alternative ways to approach benefit-risk, with an impact on the calculation of the sample size. Population size was mentioned several times and does matter
- Can evaluate the performance of randomisation on the level of evidence
- Different questions need to be answered at different levels (does treatment work, estimated B/R on average, for patient,…); with different levels of information and evidence needed. Alignment between EMA and payers – in progress, will take time.
- What is expected from regulators? At what level can we discuss a way forward?
- Utility function thinking could provide armamentarium to include patient perspective, but triggered a lot of discussion:
  - Patients feel excluded of the discussion on trial design
  - Some ways already exist : SAWP (EMA); PPI (UK)
  - Need to reach patients on the practical level

Session 5: Study endpoints and statistical analysis

- Methods can cope with smaller numbers of patients in clinical trials
  - Relatively simple, leading to computational advantage + transparency of what was done
  - Applications in different scenarios: repeated measures, subsamples, clusters (sites) of different size
- Goal attainment scale – sparked a lot of discussion…
  - When there are no alternatives; important for settings where disease manifestation is heterogeneous
  - Validation is sparse (only in geriatrics/rehabilitation, and non-drug experiments)
  - GAS already submitted in SA as a secondary endpoint. Primary endpoint?
  - Important issues remain, e.g. interpretation, understand trial treatment effect at the level of patients or patient subgroups
- Often multiple co-primary endpoints are relevant, especially in rare diseases; proposals allow substantial efficiency gain in small sample setting

Session 6: Innovative designs, pharmacometrics, modelling and optimal designs

- Historical controls (no randomisation so beware !); pre-specification; number of trials is important rather than number of patients
- Group sequential designs; possibility to stop early vs. larger maximal sample size; multi-arm, multi-stage – several comparison objectives can be set; limitations (or not) re: type of disease, recruitment, response time
- Non-linear mixed effect models; a range of benefits for small samples
- Tool to choose optimal FIM design
- Incorporating PK data in Phase I dose-finding; enriches dose-toxicity relationship
- Use pharmacometric data to inform efficacy trial design and sample size

Now what can we do?

- Continue involving patients; more often at the design stage; we may not have the exact means and language yet, but need to experiment and learn
- Use full information on disease and drug to help designing trials
- Select principles that can be discussed in the EMA Small Population Guideline
- Regulators need to see early (and well prepared) proposals to seriously consider new methods (and learn)
- In parallel to proposals assocatied with a particular new product, consortia can consider qualifying methodology (e.g. GAS as suggested); problem of fee
- Identify the right regulatory pathways for the right methods (product vs. method qualification)
  - Projects to feedback to EMA on the regulatory pathways considered for implementation; e.g. pros &cons for the submission of a qualification procedure