**PSI/EFSPI Regulatory SIG Meeting with MHRA Statisticians on 23rd November 2022**

Over the last two years we realised that our annual meeting with the MHRA statisticians could be held very effectively using MS Teams, so we opted to do that again in 2022 even though there were no travel restrictions in place anymore. Four statisticians from the MHRA and 15 members of the Regulatory SIG attended the meeting. As usual, it was an open and interesting exchange of information and ideas.

**What is on your agenda?**

The MHRA statisticians started with an update on current statistical issues and potential regulatory statistical concerns of the future.

The MHRA statistics team does not currently seek out research topics independently. Instead, it collaborates with researchers and other agencies to investigate relevant/current issues. Post-Brexit, the collaboration with EMA is less frequent, but on the other hand the collaboration with the FDA through project ORBIS and other initiatives, and ACCESS consortium partners (Australia, Canada, Singapore and Switzerland) is more frequent. Work is still ongoing on the MHRA real world data guidelines, with the guideline on external control arms being drafted.

The MHRA statistics team is also actively supporting the following project: Dose Finding Extensions for early phase dose finding studies to improve the reporting of early phase studies (to be released in Q1 2023). The project is being undertaken by an international group of early phase trials specialists and methodologists led by Professor Christina Yap. Other MHRA plans for future guidelines includes patient reported outcomes, decentralised trials and quality at the point of care and for topical products (for both manufacturing and product).

It was clarified that, despite some divergences (eg biosimilar guidance, where the MHRA position offers some benefits for companies), there’s no intent to create discrepancies across regulatory agencies.

In addition, the MHRA recently became a member of ICH, with increasing involvement of their statisticians. EFSPI/PSI asked about ICH E20 on adaptive designs and MHRA clarified that the MHRA’s role in it is yet to be defined. MHRA added that MHRA actively provides feedback on the ICH guidance that are available for public consultation as well.

**Planning for safety assessments – what does good look like in clinical studies?**

EFSPI/PSI initiated the discussion by providing an introduction on the topic and on the SAVVY project (see above for more details - also please refer to [https://numbersman77.github.io/savvy/](https://nam02.safelinks.protection.outlook.com/?url=https%3A%2F%2Fnumbersman77.github.io%2Fsavvy%2F&data=05%7C01%7CAlessandro.Previtali%40bms.com%7Cb1908141f2104bbaab3808dad14ed9b4%7C71e34cb83a564fd5a2594acadab6e4ac%7C0%7C0%7C638052433863408018%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C3000%7C%7C%7C&sdata=Ix%2FLxGajta%2FxSiXjdM3nbO%2FSqdPQeGpjUp2D33mhDxI%3D&reserved=0)). EFSPI/PSI further complemented the introduction underlying the importance of framing the safety questions using estimand, in order to clearly determine the safety question of interest and concluded the intro by questioning the role of the treatment policy for safety.

MHRA addressed the last comment first, suggesting that the safety population was the most appropriate set to analyse safety data. The MHRA statistics team usually focus on efficacy objectives rather than safety, unless a safety endpoint is being formally analysed statistically or they are specifically asked to look at safety. Otherwise clinical safety data are mainly reviewed by medical assessors.

It was noted that in general the main design focus for clinical trials tends to be efficacy and not safety, hence some aspects can be difficult to tackle. A complex adaptive design particularly targeting efficacy may make a clear interpretation of some aspects the safety data difficult (for example the difference in drug exposure across arms, and its impact to safety). The SmPC reports generally qualitative information rather than exact estimates of safety risks.

MHRA added that in some cases Cox proportional-hazard models are used for safety unless the proportional hazard assumption is clearly violated. MHRA supports further discussions on this topic and is open to ideas/suggestions to improve the safety reports. Proposals can be submitted to MHRA’s Innovation Office.

EFSPI/PSI asked about the role of the safety division within MHRA. MHRA explained that it includes epidemiologists, they would review pharmacovigilance plans and that they are involved in post-marketing assessments and safety reviews.

EFSPI/PSI thanked MHRA for the discussion and commented about the importance of data collection for safety and its impact on study designs.

**Dose optimisation in oncology**

EFSPI/PSI initiated the discussion by referring to the Project Optimus ([Project Optimus | FDA](https://www.fda.gov/about-fda/oncology-center-excellence/project-optimus)) recently launched by the FDA, which recognises that for many decades the paradigm for oncology drugs was that higher doses were always more efficacious, but that no longer necessarily the case for novel therapeutics.

MHRA highlighted that the rationale for identifying the maximum tolerated dose (MTD) and for pushing the dose as high as possible, is likely linked to the assumption that the higher the dose the better its efficacy, and the fear that potential additional efficacy could be lost if the highest tolerated dose isn’t used. The traditional 3+3 designs are still common, however, an increase is seen in the use of alternative designs, including Bayesian designs aiming at narrowing in on an optimal dose. The MHRA sees such designs positively.

It was acknowledged that there is an awareness that the MTD might be suboptimal, and that there may be value in considering additional data to optimize dose selection, including PK, PD, and long-term safety (PROs were also mentioned). One additional complication is that the dose selection commonly is based on a single cycle, and that data from the following cycles is not incorporated in the decision. Value can be seen in spending more time in the early clinical development stages to optimize the dose selection which might lead to benefits for patients in the long-run – however value can also be seen in getting medicines to patients who need them quickly.

Important note is that it is difficult to object to an application where the benefit-risk profile is deemed acceptable even when you may suspect that there might be another dose with a better benefit-risk profile.

EFSPI/PSI highlighted that one key difference between oncology and many other therapeutic areas is that early studies in oncology are carried out in patients and not healthy volunteers, implying that there is a value in limiting the number of patients exposed to suboptimal doses. There has been some exploratory work done in industry to further explore the impact of alternative study designs which incorporate efficacy data to the dose escalation, but difficult to evaluate impact of different design options as data don’t exist to fully evaluate what would have happened if another strategy had been used. The MHRA team mentioned that MHRA remains open to proposals from sponsors on this topic.

MHRA added that for medicines with a curative effect risk might be thought of differently and a high dose might be acceptable, compared to for treatments that do not have a curative effect. They concluded with highlighting the importance in keeping the patients at the centre when evaluating these designs and invited sponsors to carefully think about the right balance between the importance of a well-designed study to select the best dose (which would require more time) and the urgency of these patients to have new treatments available. For a curative treatment there may be more tolerance on the safety profile, while for non-curative treatments safety is more important.

EFSPI/PSI thanked MHRA for the discussion and highlighted that further work is needed in this area.

**Statistical methods for small populations**

EFSPI/PSI introduced the topic and highlighted that EFSPI is interested in specific questions and in general thoughts around the topic from the MHRA team.

The MHRA team started by highlighting that there are always case-by-case considerations, but that there is a common understanding that the burden of evidence can’t be the same for programs in these smaller populations as in larger populations, and that limitations in the data packages need to be accepted. The key is to do the best you can in the specific situation. If the answer to the question ‘Is it reasonable to think that more could have been done to inform the decision?’ is ‘No’, then what is done and the data available need to be enough to inform a decision. If the benefit is dramatic enough, then very limited data might be acceptable – what’s enough is dependent on the situation.

Randomization is not an absolute requirement, however, some randomized concurrent control is better than none. There is no guidance on what size of randomised control is ’s enough, but really low numbers might not be helpful. At times randomized control arms can be enhanced with an external control, and there is evidence that enhancing a randomised control arm is preferable to an entirely external control arm. A prospective control is preferable over a retrospective. The RWD guidance includes points to consider while accessing the quality of an external control / a database used to create an external control. This includes the reliability of the endpoint, frequency of data capture, missing data, appropriate patient population, and so forth. Note that quality needs to be assessed for the specific situation. The point was also made that the estimand framework could be helpful in assessing the quality of an external control group.

The MHRA team made the comment that it is not uncommon to see a Bayesian assessment as the primary assessment, and with a frequentist analysis as supportive (not only for rare disease). In most of these cases Bayesian and frequentist analyses are relatively well calibrated, and simulations are performed supporting a well-controlled Type I error. This makes sense as the same data should lead to the same conclusions – we should not draw different conclusions on the same overall evidence. However, it should be noted that transparency is critical, it needs to be clear about how much information there is and what strength the new evidence brings. We also need to be careful and transparent with the assumptions. It can be challenged if it is really sensible to consider a gradual value (eg via Bayesian dynamic borrowing methods) of the borrowed data or if it is more an ‘all or nothing’-decision. If the observed and borrowed data are close, then should the prior data be given full weight? And if the data is different, should the borrowed data then be disregarded completely? The importance of raising these questions in advance and to seek scientific advice, if needed, was highlighted.

Regarding the question on adapting the significance level, the MHRA made the point that for rare diseases a single p-value might be of less importance, and decisions are primarily made more broadly based on the totality of data. Data listings might help in these small populations. An example where approval was granted with great influence from video recordings of individual patients was shared.

The MHRA is preparing a guideline on how to use external data, with focus on prospective controls, relevant endpoints, completeness of data and missing data issues. In this context, estimands can help in formalising the question of interest.

Sponsors are invited to think about the problems of using a single-arm trial with lack of justification for the external data and the choice of endpoint (ie when is it right to use surrogate endpoints?). It is important to explore all opportunities to optimise the design. Patients need to remain at the centre of our assessments, hence the importance of including PRO. On this last point, MHRA highlighted the point of getting feedback on what is important for patients when evaluating the study design/endpoint.

MHRA finished by providing some general reflections: scientific advice is valuable as it is crucial to have the discussions upfront. Patient input is extremely helpful as they can shed light on what is important for them; apparently small impact on clinical endpoints can be transformational to patient’s quality of life. Engagement with patients and patient representatives is key. Statistics is a helpful tool to evaluate the strength of the evidence and it helps rationalize the decision making. It is important to explore how the study design can be optimized.

EFSPI/PSI thanked MHRA for the discussion and for the advice shared, highlighting the role we as statisticians play in this space where we can help to pressure test and explore study designs and optimize data collection.

**Closing**

MHRA asked if EFSPI was meeting with other agencies, and the EFSPI/PSI SIG explained that they used to meet with EMA but since 2020 meetings have only been held with all industry organisations together. EFSPI/PSI offered to provide a forum where MHRA could interact not only with EFSPI (as professional organisation) but also with other regulatory agencies during the EFSPI Regulatory Statistics Workshop.

MHRA asked about other relevant topics and EFSPI/PSI explained the role of the EFSPI Regulatory SIG in having them discussed as selected - this was done in the regular monthly meetings scheduled for the Regulatory SIG.

MHRA asked the EFSPI/PSI SIG about the role of data scientists in pharmaceutical research. EFSPI/PSI acknowledged the intent of their role in trying to speed-up the discovering/approval process, however he also mentioned the limitations of this new role, not being well defined, and that AI should be explainable. EFSPI/PSI mentioned the importance of remaining open for future developments of this role. Potentially, this could be a topic for the meeting next year. MHRA agreed on the fact that the role of data scientists, as well as its accountability, are currently not that well defined.

Jürgen Hummel (PPD, part of Thermo Fisher Scientific), Anna Berglind (AstraZeneca) and Alessandro Previtali (BMS) on behalf of the European Regulatory Special Interest Group