Meeting Regulatory SIG with MHRA statisticians on November 19th, 2020

The Regulatory SIG has met with the MHRA statisticians face to face for an informal exchange for many years, but unfortunately that (as many other personal meetings) was not possible in 2020. Instead we met virtually with MHRA statisticians on November 19th, 2020. Five statisticians from MHRA and 19 members of the SIG were present. A wide range of topics were covered during the two hours:

Follow-up of topics from the meeting in 2019

Estimands

The CHMP adopted the addendum in July 2020 after it became final and the MHRA have noticed a pleasing uptake in Sponsors. The expectation is that adoption of the principles becomes the norm, but without overcomplication (e.g. not necessary to use the precise terminology used in the addendum provided the principles are followed). It was felt that the framework was especially useful in the light of COVID-19. The MHRA have been running internal training for statisticians and clinicians, sharing concrete examples to help understanding, and have noticed Industry doing similarly.

The MHRA have seen a few issues in implementing the principles, including a mismatch between design/strategy and analysis performed (e.g. the use of MMRM with a Treatment Policy strategy for handling intercurrent events) and Sponsors proposing estimands not of primary interest to a Regulator. Within the agency, Khadija is a member of the estimands implementation working group, considering topics such as handling missing off-treatment data when the Treatment Policy strategy for handling intercurrent events is applied and development of a protocol template for incorporating the estimands framework. She has also provided comments on training material to help the implementation. An MHRA statistician and clinical assessor presented at a joint EFSPI/BBS workshop on estimands in neuroscience. The MHRA statisticians enjoyed the interaction with the Oncology SIG in September, where the group shared information about upcoming publications and would like more interactions like this in the future, both with the Oncology and other SIGs.

Chrissie Fletcher felt that there had been great progress in the year since the addendum was finalized, with the impact of COVID-19 helping to cement it, but noted there was still more to do at an EFPIA level, especially with clinicians, as well as with the Missing data group and in bridging the estimand framework with the evidence-based medicine framework that clinicians are more familiar with, e.g. PICO.

Real World Evidence (RWE)

An MHRA guidance has been written on points to consider when running RCTs using real world data and this is currently out for consultation. One objective was to counter the perception of regulatory reluctance to accept trials based on RWE, thus promote their use especially for broadening the labels of existing medications. The guidance is focused specifically on RCTs and also applies to trials that include both routinely collected data alongside data collected specifically for the study, but this particular guidance does not cover (non-randomised) observational studies. It was emphasized that the choice of estimand must come first, before considering potential data sources. Subsequent approaches, including analysis, should then follow the standard estimands framework. It was noted that, unlike the EMA guidance, the MHRA guidance doesn't cover the analysis aspects and this could be fed back as part of the consultation process. However, the focus was on where the data were coming from and the feeling was that the same principles would apply as normal RCTs (i.e. those without RWE), other than careful selection of endpoints.

Some other guidelines are planned for the future, with the next one likely to be on external controls (which will have more on statistical analysis). A publication is planned on complex designs/master protocols, though it has yet to be decided whether will lead to a guidance document. The MHRA would be interested in receiving suggestions for other (non-RWE) topics where guidance would be welcomed.

Can you give us an update on current statistical issues and potential regulatory statistical concerns of the future?

Biosimilars

Other than RWE, another main area of focus for the MHRA has been biosimilars. Again, an MHRA guideline is available for consultation, associated with a paper on streamlined approval. https://www.gov.uk/government/consultations/mhra-draft-guidance-on-the-licensing-of-biosimilar-products This is advocating that an efficacy/safety trial is NOT necessary in the majority of cases, based on experience that an efficacy trial was rarely the main factor in swaying the regulatory decision, even if the efficacy trial failed (i.e. focus more on PK/PD). The publication, which represents a change from current standard practice, seemed to have made an impact, given the media attention.

Guidance

It was noted that there was a possibility that we might see more MHRA-authored guidelines in future, now that the MHRA have more freedom to write their own and will not be contributing to EMA guidelines. The MHRA are reaching out to other bodies (e.g. NICE) and are looking to help create an integrated UK-wide approach.

Agency and patient focus

The MHRA as an agency is also adapting. Following the Cumberlege review , the MHRA is committed to becoming a more patient-focused Regulator and is increasing patient-engagement aspects. Perhaps patient reported outcomes (PROs) could be a focus area for EFSPI? The HTA

ESIG regularly discuss PROs but more in the context of how PROs are used to support HTA. The Regulatory ESIG will discuss options for how to increase the emphasis of PROs in EFSPI collaborating with other groups where applicable. The MHRA have their own SIG looking into this area, which was set up last year. It was felt that PROs are often at the end of a long list of endpoints and lack sufficient planning in the protocol and SAP (e.g. there is a major issue with missing data which needs to be addressed, while information about the validity and psychometric properties of the instrument is also often missing). It was also felt that RCT designs could incorporate patient-focused aspects to a greater extent, including studies in non-oncology indications. The MHRA have run an internal survey around PRO knowledge and awareness amongst staff and are preparing training and considering future guidance. It was noted that PROs are garnering more focus in Industry too, especially for Payer discussions. Lack of validation for PRO instruments (across countries) is also an important issue to address. In addition, patients can recalibrate their expectations over time, especially with chronic disease, and this can lead to difficulties in interpreting changes from baseline (this issue might be exacerbated if the RCT is not blinded). ePROs may have additional challenges and the MHRA Inspectorate have a joint publication with the FDA that covers some issues on trial integrity associated with electronic systems in general. See https://ascpt.onlinelibrary.wiley.com/doi/10.1002/cpt.1794

Are there any areas that you feel that PSI/EFSPI should be leading to improve quality and standards across the industry?

Managing trials during COVID-19

The MHRA enquired as to how much involvement PSI/EFSPI have had in contributing to the COVID-19-related guidelines? It was noted that EU and US Biostatistics working groups had been working together to review guidelines as they came through. There is still much to learn and there is a plan to work with EFPIA to cover operational aspects (e.g. inadvertent unblinding during risk assessment). Some differences of opinion exist between the EMA and FDA e.g. regarding censoring, or the acceptability of a hypothetical strategy for handling pandemic-related intercurrent events. However, there is ongoing dialogue between the FDA and EFSPI oncology estimand SIG, trying to gather rationale/examples to convince internal stakeholders.

Bioequivalence

The MHRA has seen several instances of applying statistical tests in multi-dose studies with a conclusion that steady state has been reached if these tests were not significant – it is unclear if this is common practice. No-one from the PSI/EFSPI team were aware of such approaches, with the preferred approach being to try to address in design rather than analysis. It appears these examples are arising in applications from generic sponsors (who may lack the stats knowledge to drive this appropriately), however the bioequivalence community are very active in online forums.

Guideline on Statistical Analysis Plans

The MHRA are collaborating with academia to improve design, reporting and analysis of Early Phase clinical trials (both patient and healthy volunteer studies) and are hoping to publish early next year.

MHRA's Future Drug Regulation Strategy

There will be several different pathways for getting a UK license from the MHRA in future. The MHRA have recently hosted a series of webinars on this (although none had been attended by PSI/EFSPI members present). It was noted that the Northern Ireland (NI) protocol does cause a few challenges and things are still subject to change.

- New national licensing pathway for innovative solutions – pilots running at present.
- Rolling review procedure, a new modular assessment approach for new active and biosimilar products.
- Accelerated 150-day procedure for national applications (including conditional applications).

International collaboration options:

- Project Orbis for oncology, which is coordinated by the FDA with other countries contributing (the UK is an observer until January), sharing assessments if applications (per country) are done at a similar time (though ultimately, the decision would be country-independent).
- ACCESS Consortium – Australia, Canada, Switzerland, Singapore (and UK from January) – details yet to be fully communicated
- Reliance route – For a 2-year period, GB (so, not NI) will recognize EU decisions on centralised procedures, subject to a GB-specific review. Note that NI will remain part of the EMA decision framework as far as medicines are concerned, though the MHRA will continue to represent NI.

The UK will make its own decision on Orphan designation and have its own Paediatric Development Plans. There is no expectation that UK patients would be required in trials, assuming there is justification for the population enrolled and background care is close enough to the UK. Finally, it was noted that there has been no official collaboration with the EMA Biostatistics WP since last January when the implementation period came into force, and, though EU/UK negotiations are still ongoing, it is not expected that MHRA statisticians will be part of the group in the future.

For the most up-to-date information on these issues, you should consult the MHRA website: https://www.gov.uk/guidance/guidance-note-on-new-assessment-routes-from-1-january-2021

MHRA's experience with COVID-19

Experiences and concerns?

MHRA released a Guidance on minimising disruptions to the conduct and integrity of clinical trials of medicines during COVID-19. The primary focus is patient safety and MHRA have a dedicated assessment team for COVID-19 indications. Generally, there have been no concerns about adaptions if the original trial objectives and scientific question are preserved. Planning ahead is important and incorporating the estimand framework has been useful for undertaking risk assessment and data analysis. There have been a few requests for inappropriate amendments

e.g. unblinded interim analysis but not an expected adaption for COVID-19. Regulatory dialogue is encouraged for COVID-19 adaptations relating, for example, to the primary endpoint.

Considerations for vaccine evaluation?

MHRA have set up an expert advisory group looking into COVID-19 vaccines and treatments but cannot share further details at this stage.

Accelerated evaluation process?

Yes, there is a rolling review underway for some vaccines, as discussed in the media.

New guidance for decentralized clinical trials?

Nothing specific, beyond what was already discussed on RWE above. It was noted that the MHRA blog has some useful comments regarding decentralized trials

Complex Innovative Designs (CIDs)

Innovative designs have been most common in early phase trials and in oncology. Since 2007, 159 applications relating to novel trial designs have been assessed (92 initials; and 67 amendments). The numbers picked up during the last three years (27 initial applications in 2020 alone). In terms of design, the three most common designs were umbrella (37%), platform (26%) and basket (18%). Platform designs were more common in commercial initial applications and umbrella designs more common in non-commercial applications. In terms of therapeutic area, 75% were in oncology.

The MHRA collaborated on a recent publication on CID cancer trials, which resulted in 10 consensus recommendations: https://www.nature.com/articles/s41416-019-0653-9. These recommendations are also relevant to other disease settings. MHRA have recently run a workshop on novel trial designs and are keeping a log of these type of trials. MHRA are discussing emerging issues internally. It was noted that EFPIA had many collaborations ongoing, addressing technical, operational and agency challenges.

Any new/novel design can fall into the remit of the innovation office at the MHRA, including Bayesian and adaptive designs as well as RWE (e.g. CPRD control groups). The innovation office is consulted regularly and doesn't have a rigid process – sometimes, an email is the starting contact and then a meeting is arranged. Applicants can also request a broad scope meeting (part of scientific advice) e.g. for methodology issues. The MHRA will be sharing experiences with CIDs in the future, either through papers or guidelines. The following publication related to clinical pharmacology deficiencies in marketing applications was also thought likely to be of interest: https://www.sciencedirect.com/science/article/pii/S0273230020302300?dgcid=author.

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