**EFSPI Regulatory SIG Meeting with MHRA Statisticians on 17th November 2021**

As was the case in 2020, the annual meeting with the MHRA statisticians took place virtually. Five statisticians from the MHRA and 19 members of the SIG attended the meeting. As usual, it was an open and interesting exchange of information and ideas.

**Post-Brexit Regulatory World**

The MHRA statisticians introduced the SIG to **the Innovative Licensing and Access Pathway (ILAP)**. This is a collaboration with NICE, the Scottish Medicines Consortium and the All Wales Therapeutics and Toxicology Centre, which gives the opportunity for sponsors to meet regulators and Health Technology Assessment (HTA) bodies in the same room. There are a number of criteria to enter the process, including that this must be an actual drug development programme for a specific product; it is not a general scientific/regulatory advice process.

As part of the ILAP, a target development profile (TDP) is created and is made up of a selection of toolkits which can include: adaptive inspections, certifications, continuous benefit-risk assessment supplemented with real world evidence, assistance with patient recruitment and patient management, novel methodology and trial design, rapid dossier pre-assessment and innovative licensing routes. The licensing routes include accelerated assessment (a 150 day process), rolling review, conditional approval and full approval but with conditions.

The novel methodology toolkit includes opportunities for qualification of new methodologies, agreement on novel approaches to evidence generation, use of AI or virtual tools. This differs from the service of the Innovation Office which can be used for more general topics and does not need a specific drug product to be attached to the proposal.

More information here:

<https://www.gov.uk/guidance/innovative-licensing-and-access-pathway>

Other new regulatory pathways include Project ORBIS, a collaboration that includes the FDA and focuses on innovative oncology drugs, as well as the Access Consortium, a regulatory collaboration between UK, Australia, Canada, Singapore and Switzerland.

More information here:

<https://www.gov.uk/guidance/guidance-on-project-orbis>

https://www.gov.uk/guidance/access-consortium

**Major Restructure of the MHRA**

The MHRA statisticians discussed the ongoing restructure of the MHRA. Chief Officers have been appointed to head up new areas which include Science Research and Innovation, Safety and Surveillance, Healthcare Quality and Access (which will include the statisticians). There will be more matrix working across these areas. The hope is that the new structure will add value by enabling innovation, bringing/incorporating patients’ views and perspectives more into decision making, accelerating access to medications and bolstering safety. The downside is that the workforce at the MHRA has seen a large reduction.

**Will MHRA be developing new guidelines?**

Currently the MHRA is still following existing EMA guidelines. There is no intention for the MHRA to diverge greatly from the EMA guidelines as the MHRA were involved in developing and writing them, so are in agreement with the principles outlined in these. New guidelines might be created by MHRA which are additive to existing EMA guidelines, for example, the MHRA has just published one on the use of real world data in randomized clinical trials, included in a Real World Data guidance series. This includes some discussion of non-inferiority trials and there is mention of estimands.

https://www.gov.uk/government/publications/mhra-guidance-on-the-use-of-real-world-data-in-clinical-studies-to-support-regulatory-decisions

The MHRA ambition is to start on a guideline for external controls, but this will not be published imminently.

New guidelines might also be created where there is divergence in advice compared to the EMA, for example MHRA has released a guideline on licensing of biosimilars where MHRA’s guideline indicates that there is not always the need to have a comparative efficacy trial for approval.

There has been some divergence between MHRA and the EMA in opinions for some applications (this is not a surprise or a divergence from guidance as the votes from the national authorities at CHMP are often not unanimous). One statistical aspect that may sometimes see a divergence in approach is in the insistence on Type I error control where available regulatory guidance can be interpreted differently.

**Data Analytics Centre**

The MHRA are not planning to set up a data analytics centre similar to the one set up by the Danish Medicines Agency, although they do have the ability to perform analyses of data.

**SIG on Patient Related Outcomes**

A special interest group has been set up to work on and promote Patient Reported Outcomes (PROs). They aim to meet with patient interest groups to work on the PROs.

**New CTA Approval Process for CTIMPs**

From 1 January 2022, all Clinical Trials of Investigational Medicinal Products (CTIMPs) in the UK will benefit from a more streamlined and efficient CTA approval process, *via* a new service that combines regulatory and research ethics committee review. See the link here for more information - [Health Research Authority](https://hra.nhs.uk/cwow)

**Medical Devices**

MHRA statisticians have a lot of involvement with Medical Device trials and it was noted that EFSPI doesn’t include many statisticians working in this area. Consultation is open on the future regulation of devices and how to move forwards. The MHRA have also produced statistical guidance for trials for medical devices (see https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment\_data/file/989415/Statistical\_considerations\_clinical\_investigations\_-\_May\_2021.pdf).

**Decentralised Clinical Trials**

The MHRA statistics group have not been keeping track of the number of decentralised trials being carried out. There is guidance allowing flexibility to be built into trials. Processes such as eConsent, eMonitoring and risk-based monitoring facilitate this. This was already in place before the COVID-19 pandemic but has been adopted further at this time. Increased adoption of decentralised concepts may lead to a broader patient population participating in trials for certain disease areas such as Alzheimer’s and Parkinson’s. The requirement for data integrity and quality is still important in decentralised trials. It is particularly important that there is consistency in evaluation of outcomes carried out at the study site and those performed remotely. Therefore, consideration should be given to how remote data can be validated. The guidance on remote access to medical records has relevant advice as linkage to the medical records of patients in the clinical trials is one way to implement decentralisation and to augment on-site assessments with those electronic records. Decentralising assessments in clinical trials may not be appropriate for all therapeutic areas and outcomes, and sponsors need to justify why this approach is preferred relative to on-site assessments. Patient safety is paramount, but this approach can provide an advantage by facilitating greater representation.

The following links were shared:

<https://sites.google.com/nihr.ac.uk/remotetrialdelivery/home/remote-trial-delivery-preliminary-guidance-from-the-nihr-remote-trial-deli>

[Access to Electronic Health Records by Sponsor representatives in clinical trials - GOV.UK (www.gov.uk)](https://www.gov.uk/guidance/on-site-access-to-electronic-health-records-by-sponsor-representatives-in-clinical-trials)

[ACRO-QbD-Manual-FINAL-for-WEBSITE-UPLOAD-1.pdf (acrohealth.org)](https://www.acrohealth.org/wp-content/uploads/2020/08/ACRO-QbD-Manual-FINAL-for-WEBSITE-UPLOAD-1.pdf)

**Use of External Controls**The next guideline to be developed in the Real World Data series will focus on comparisons with external controls. Thinking is still evolving in this area and the guidance is likely to provide points to consider rather than definitive solutions, which would not be possible to generate.

Some general thoughts were discussed on the use of external controls (not specific to RWD), some of which are summarised below, but none of this should be taken as a formal MHRA position.

Randomisation is always preferred in clinical trials but if this is not possible then the baseline characteristics and background care should be as similar as possible in the treatments being compared. If the control data are already available, it might be possible to run a trial with a single arm that includes a threshold for success. If the two arms are running at the same time or the control data are being collected after the trial has ended, then matching on important characteristics should be attempted. Depending on the situation, propensity scores might be useful. Ideally, factors used for matching should be identified a priori. Sensitivity analyses using different methods for matching are recommended. Black box approaches producing p-values are not necessarily helpful. If Bayesian approaches are used it is important to avoid double counting when considering the overall body of evidence.

If the strategy is to combine a small control arm with an external control arm, there are open questions that need to be thought through. For example, how different can the external control group be compared to the randomized control before it is discarded? What happens with the Type I error? If the control arms are good fits for the primary endpoint, does that also hold for the secondary endpoints? There is a need to ensure that external control data for secondary endpoints are as balanced as that for the primary endpoint. Concern was expressed about making decisions purely based on statistical inference on small datasets in rare diseases; biological and medical information is needed.

**Non-Inferiority Trials**

In principle, it was felt that the estimand should not change based on the hypothesis test being employed (superiority or non-inferiority). However, in a non-inferiority trial there is still a necessity to ensure that any results that indicate no difference between the treatment arms are not caused by poor trial conduct – but this can be addressed by means other than the primary estimand. The UK will join ICH in development of the guidelines. There has been no suggestion heard by MHRA that the ICH E9 addendum will be revisited to address this topic.

**Estimands**

There has been a mix of experiences in the application of estimands. More larger companies have been including estimands in their protocols along with good discussions of intercurrent events. Some smaller companies do not understand the concept at all. But there is a mixed response in general, regardless of company size. More sponsors are coming to the MHRA with protocols that do not include estimands than that do. There is a long way to go before the concept is fully adopted. MHRA sees examples where there is a mismatch between the stated estimand and the approach of estimation, confusion between sensitivity and supportive analyses, and a mix-up between intercurrent events and missing data. In the specification of estimands, the terminology (the 5 attributes) is not of great concern, more important are the strategies for dealing with intercurrent events. The MHRA does not impose the use of estimand terminology if the approach to the analysis outlined is clear and acceptable. But if the approach is not acceptable, or there is a complex setting involving several intercurrent events, the use of the estimand framework has helped discussion of the issues. The MHRA statisticians find it difficult to discuss estimands if there is no statistician from the company in the room, although they seem to be seeing more statisticians at meetings since they have gone virtual. The handling of terminal events is a particularly challenging issue, with no consensus on the best approach so far.

The estimand implementation working group (EIWG) has carried out a survey to identify barriers to uptake, and they are contacting journal editors to determine when estimands are described incorrectly in scientific papers. The survey highlighted that there is very low uptake of estimands in academic trials. There will be a publication to celebrate two years of estimand uptake. The EIWG has developed a Transcelerate protocol template that includes estimands. The EIWG has drafted a paper on the impact of missing data on estimation when a treatment-policy strategy is being used for handling intercurrent events. The EIWG are working on other topics such as use of estimands in early phase trials and for PROs. The estimand framework has helped discussions in recent issues, such as the impact of covid-19-related events on clinical trials.

The MHRA has incorporated the estimands concept in its guidance on minimising disruptions to the conduct and integrity of clinical trials of medicines during COVID-19

https://www.gov.uk/guidance/guidance-on-minimising-disruptions-to-the-conduct-and-integrity-of-clinical-trials-of-medicines-during-covid-19

 Frances Lynn (Orchard Therapeutics) on behalf of the European Regulatory Special Interest Group