Tips on a) What questions to ask regulators and HTAs, b) Interpreting the answers given and c) What to do when different authorities give conflicting advice

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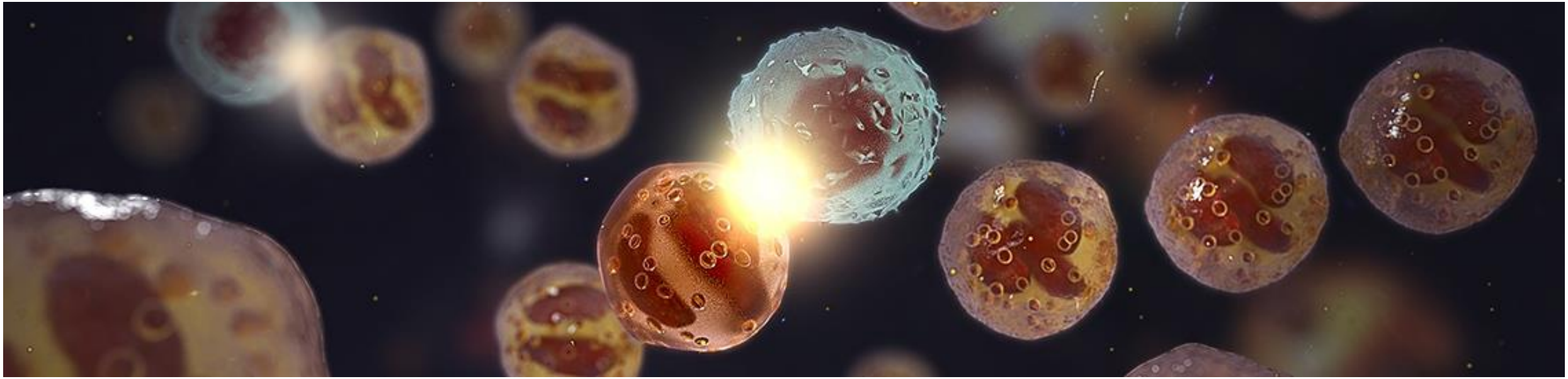
14th September 2023



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Introduction to my career in regulatory statistics

- **Worked at MHRA from 1999-2016 as a Statistical Assessor**
- **Chair of Biostats Working Party**
- **Alternate Member of Scientific Advice Working Party**
- **Lead of MHRA scientific advice review committee**
- **Involved in setting up parallel scientific advice process between MHRA and NICE**

Time for a change in Mindset?

Avoid being pigeon-holed

Don’t work in silos

What questions to ask regulators and HTAs

Be part of the Team

- **Make sure you are involved in thinking about all the clinical questions being asked not just the “statistical” ones – the estimand framework should help here.**
- **Make sure you understand the detailed clinical objective and hence understand why the primary estimand has been chosen.**

Be Precise

- **Questions need to be precise. If you ask a vague question you might get a vague answer.**

Be Concise

- **Do you really need to ask 25 questions? Probably not, so be focused on the key issues that you want scientific advice on and limit the number of questions accordingly.**
- **Asking too many questions creates a problem for the assessors (the time they have to work on each advice is finite!) and they may spend more energy answering some of the minor questions and then you won't get a such a comprehensive answer to the major ones.**

What statistical questions to ask regulators

- **Avoid more speculative questions related to unpublished methods. These sort of questions are better suited to qualification opinion or informal discussions at conferences with regulators.**
- **Focus on the main issues with connected with the primary estimand.**

HTAs

- **Are you a regulatory project statistician or a HTA statistician! [back to silo culture again!] – do you fully understand the regulatory strategy/detailed clinical objective/primary estimand? Can the proposed pivotal study be used to investigate the detailed clinical objective for a HTA submission? If not, what tweaks to the design would be needed for the study to fulfill both requirements? Or is a separate study needed?**
- **What is your strategy for important subgroups? Do you understand the estimand of primary interest to HTAs and why they consider it primary.**

Interpreting the answers given

Form your own opinion on what the advice means

- **Don’t accept a summary of the advice/key messages from someone else – read all of the answers given yourself and form your own view first.**
- **Only then have a meeting with others in the Team and see if you have a common understanding of the meaning of the advice given. If not, take time to narrow down on the areas where you have a different interpretation.**
- **Don’t rush this stage – many disagreements come from rushing this part.**

Interpreting the answers given

Don’t over interpret answers or lack of answers or make it fit what you want to see!

- **Seeing things that aren’t there! - Absence and evidence isn’t evidence of absence – i.e. just because they didn’t comment on something it doesn’t mean they agree with it unless you specifically asked about/mentioned it. This goes back to asking the key questions to get key issues addressed in the advice.**
- **Don’t make it fit what you want to see. Sometimes the advice is very clear but teams refuse to see it because they don’t want the advice to suggest a change to the programme.**

What to do when different authorities give different advice

1. Don’t panic
2. Establish if the different authorities have really given different advice.
3. Are the differences of nice to have issues or are their fundamental differences that impact on choice of study design (e.g. different primary endpoints, study duration, strategies for intercurrent events, summary measures, patient population) or choice of suite of clinical trials required?
4. Can you put a feasible development plan together that meets both authorities concerns?
5. If not, quantify the risk to not going with the advice from one authority.

Conclusion

- **Regulators have a hard job – don’t make it even harder by the way you ask questions in scientific advice – be fully up front and transparent.**
- **Make sure you fully understand the strategy and reasons for conducting the clinical trials proposed – use the estimand framework to explore any areas you are unclear on.**
- **Work together with the rest of the clinical project team on the scientific advice questions and the briefing book.**
- **Don’t panic if the answers from different regulatory agencies give differing opinions. Sometimes with greater scrutiny the pieces of advice can be close to each other than they first appear or may have been driven by different questions being asked to different regulatory authorities**