The Science Huddle

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SMALL DATA, BIG OUTCOMES

Strategies for Achieving Statistical Significance when Global Patient Populations are Limited

Highlights from a timely panel debate on emerging approaches to clinical research and data collection for advanced, novel and personalized therapies, especially linked to rare diseases.

With the reach and impact of biopharma growing exponentially, experts in biotech and the evolving regulatory environment came together in November 2022 to discuss the critical next steps for the industry. As well as highlighting the enormous potential for breakthrough treatments for rare diseases, the panel's subject matter experts discussed the ways the industry must continue to adapt its regulatory approaches if promising new therapies are to be brought to market swiftly and efficiently, without compromising patient safety.

This first **Science Huddle** session considered the necessary evolution of clinical trials, and new means of eliciting critical safety data, when available patient populations are small - and when successful outcomes may not be immediately tangible or measurable in traditional ways.

Participants in this first Science Huddle event were:

Moderated by **Dr. Christian K. Schneider, Head of Biopharma Excellence** and a world expert in adapting existing regulatory frameworks for biopharmaceuticals.

Nick Sireau, CEO and Chair of Trustees, AKU Society

Rachelle Jacques, President and CEO, Akari Therapeutics

Daniel O'Connor, Deputy Director, Innovation Accelerator and Regulatory Science, MHRA

Panelist bios:

Christian Schneider, head of biopharma excellence and Chief Medical Officer for biopharma at PharmaLex, is a former regulator, having worked for the British MHRA and the Danish Medicines Agency, among other leading roles. He is passionate about the potential of orphan medicines.

Nick Sireau is CEO and Chair of Trustees for the AKU Society which is dedicated to improving the lives of Alkaptonuria (AKU) patients through patient support, community building, and medical research. His two sons have the condition. The AKU Society and Nick personally won the EURORDIS (Rare Diseases Europe) 2021 members award for successfully developing a new treatment for AKU.

Rachelle Jacques is President and CEO of Akari Therapeutics, a late-stage biotechnology company developing advanced therapies for auto-inflammatory and orphan diseases.

Daniel O'Connor is Deputy Director with responsibility for the Innovation Accelerator and Regulatory Science at UK healthcare agency, the MHRA. He has a strong background in cancer research, and completed his PhD in the specialist area of tumor suppressor genes. Today he has a special interest in rare diseases, drug repurposing, and early access.

What keeps the panel awake at night?

Moderator Christian Schneider opened the discission by describing his own passion for orphan medicines, acquired across a long career in regulatory authorities and their regulatory environment, and noting the many practical challenges that remain for innovative drug developers striving to bring groundbreaking new treatments to market.

Clarifying that all opinions expressed during the debate would be each participant's own personal views, he asked each of the panelists what kept them awake at night in the context of cutting-edge medicine.

The scale of the work ahead

Having worked in rare diseases for a decade or more, **Rachelle Jacques of Akari** Therapeutics said she had had the opportunity to meet a lot of patients who are battling for their lives, along with their families, which has given her a strong perspective on both the opportunity and the associated urgency.

"When I think about all those experiences and stories, one thing is clear - that we have a lot more work to do," she said. "We've made a lot of progress, but when you're talking about 7,000 rare diseases and only 5% of them having therapeutic options today, that leaves 95% without therapeutic options. But I believe that we are going to get to that 95%, the same way that we that we were able to address the first 5%."

For Rachelle, one of the barriers to progress to date has been the complex stakeholder ecosystem involved in approving drugs and bringing them to market – an environment that can be difficult for developers to navigate on their own. "This panel debate is very representative of the kinds of discussions we need to have to make progress," she commented. "We've got to work together if we want to have a greater impact."

Access to funding

Nick Sireau, of AKU Society, said it was funding that concerned him the most. He runs a specialist patient group which he created because his two sons both suffer from the ultra-rare disease, Alkaptonuria (abbreviated to AKU). It relies heavily on grant funding and donations. Over the last two decades, Nick has been working with a team of scientists at the University of Liverpool and the Royal Liverpool University Hospital, to advance research and development targeted treatments.

A decade ago, AKU Society applied for EC funding via FP7, a process which Nick describes as difficult but successful. This has given rise to multiple new projects. "We want to launch a gene therapy, mRNA therapies, all kinds of things," he said.

"But generally, funding is limited. There are all sorts of brilliant projects, on all kinds of rare diseases, that are trying to get off the ground. The key challenge is trying to increase the funding and access to it - particularly for patient groups and for the teams that they work with."

Accelerating patient access to critical new treatments

Regulators appreciate many of these issues. **Daniel O'Connor**, whose remit at MHRA is Innovation Acceleration within a regulatory context, reflected on the delicate balancing act that's needed as the authorities continue to uphold the highest standards of patient safety, yet without standing in the way of bringing life-changing new therapies to market.

"We absolutely appreciate the scale of the unmet medical needs that exist today, yet we must also consider the overall picture of 'small population' research," he noted. "What keeps me up at night is thinking about how we capture the right data - when we're talking about rare conditions, and also personalized medicine. It's about trying to determine what makes pragmatic sense - being both feasible but also robust - in our decision-making as regulators, i.e. what is the **data** we need to be able to support marketing authorization and licensing?"

The panel welcomed this direction. **Nick** noted that AKU Society encountered its own challenges navigating the regulatory requirements as it sought to bring new therapies to those affected by AKU, despite forming a European consortium with other interested stakeholders.

"It was a **lot** of work to get all the different ethics approvals, regulatory approvals, and so on," he recalled. "If things could be more streamlined, it would definitely accelerate the process and make it much cheaper."

Elaborating, he said: "The other issue when you're talking about ultra-rare diseases *(AKU affects roughly one person in half a million)* is in actually identifying patients in the general population and then recruiting them, bringing them into clinical trials - and then retaining them. That was difficult, but we managed by helping to set up AKU Societies in all the different countries across Europe to find and pool patients. If there was some kind of Europe-wide database to help bring these patients together, that would be a significant help."

These observations led into the heart of the debate.

The 'statistical significance' paradox in studies of orphan diseases

Summarizing the numbers challenge, Christian noted that while small-scale clinical studies can appear to yield findings of clinical significance, the numbers may not be sufficient to ensure statistical significance.

Daniel noted that this was an age-old issue, and not just in the context of rare diseases. "I think you've always got to start with the patient, and the clinical significance. That's always got to be your bottom line," he said. "And, of course, what we want to see as regulators are robust data; studies that are well designed and which have a strong statistical methodology."

Seeing a result that's both clinically meaningful and statistically significant is the ideal, he continued. If that's by way of a randomized study, so much the better.

"But equally, as regulators, we know it's not always possible to run randomized trials - for a variety of reasons – particularly with very rare, very rare conditions," he conceded.

The key, he suggested, was for drug developers to seek scientific advice – rather than to look for workarounds which may satisfy the health authorities.

"With the right plan, you might be able to demonstrate real clinical relevance in terms of the outcome measures, particularly if you've got patients involvement in the design of that study, and the endpoints are truly representative of that particular condition," he said. "But don't make those trade-offs on your own: have those discussions with the regulators and other decision-makers."

With a late-stage development perspective, Christian asked **Rachelle** about her experience in getting from *clinical* to *statistical* significance.

"That's a really tough question, and it comes back to what we're ultimately trying to do here – e.g. if you're looking at this from the perspective of someone not involved in drug development or the regulatory pathways. You might start with the definition of statistics and the concept of collecting and analyzing data in large quantities. But then we're talking about rare diseases. So how is it that we even got to this point where these concepts must live together?

"I think this is just one example of areas where we need to rethink what we've been doing," she continued. "Coming back to what Nick said about funding - one of the challenges here is the length of the runways. If we're going to power a study in a rare disease area which involves hunting for one patient at a time around the world, trying to find them trying to bring them into a study, that process is many years in the making. And almost all biotech companies have no revenue. Which means we are relying entirely on our investors to fund that work."

It is time to rethink what's meaningful for patients, Rachelle suggested. "Of course, we don't want to increase the risk," she noted. "But as long as we aren't sacrificing patient safety, I think we need to break the model and do something that's fit for purpose, which delivers on what patients need and which - with the available financing - we can actually achieve."

Supplementing trial data

The discussion moved on to the potential for supplementary data sets – such as pharmacodynamic read-outs, histological evidence, and so on – which can help enable regulators to reach robust decisions. Options also include use of historical controls, where old data is compared with new data from new trials.

Nick talked in more depth about his early experiences of trying to get new drugs approved for AKU. Fifteen years ago, 40 patients were recruited to an AKU drug trial that lasted three years and focused on a single hip rotation. *(AKU can cause significant damage to the bones.)*

"The trouble is, that AKU affects patients very differently," Nick noted. "It can affect *any* of the joints. So to just look at 40 patients with a single endpoint proved futile." Although patients were reporting that they could walk further, that their pain had reduced, that they were feeling better since joining the trial, the study itself failed. "It significantly delayed the development of a treatment for AKU."

It was this blow that led AKU Society to form a consortium, and a composite endpointa proposition which was well received in the EU. "They really seem to understand what we're up against with AKU," Nick said. "EMA told us they wanted us to have as a primary endpoint the metabolic/homogentisic acid/culprit molecule, reducing that to nearly zero; but also clinical or secondary endpoints as a positive trend - even if we didn't reach statistical significance.

"That changed everything. In the end we met the primary endpoint, and the secondary endpoints reached statistical significance - and we did a study on 140 patients, which was the largest ever study of an inborn error of metabolism. But that's how far it had to go to really manage to prove something."

Had requirements been more agile 15 years ago, AKU treatments might have been authorized much sooner, offering patients a real lifeline.

A progressive regulatory agenda

Christian recalled a time when 'historical control' was almost a no-go for regulators, who generally insisted on a randomized control trial even for very small indications, even if this was completely unfeasible. He asked Daniel whether that situation was changing now.

"We're definitely seeing an evolution in regulatory thinking, and that position of 15 years ago has changed a lot now," **Daniel** said. "What we're seeing now hopefully is a much more proportionate approach in terms of looking at the disease condition, based on how much is already known. We're getting into a really good position now - not just thinking about either a randomized study or a single-arm study.

"In many cases, oncology has really moved this position forward," he explained. "We've got the opportunity for basket studies which are increasingly being seen in the oncology setting," he explained. "But there is also a lot of work now looking at shared molecular entities in rare diseases. This is something that International Rare Diseases Research Consortium (IRDiRC) is moving on quite quickly now. So I think the toolbox, in terms of how we get the data that we need, is definitely expanding."

Daniel suggested that next steps ideally need to come from a collaborative discussion and feasibility conversation - with patients; with researchers; with the regulators – about what's viable with a clinical development program.

"We need to think about timelines, too," he added. "Three years is a long time to run a study. With 6,000-8,000 rare diseases to address, it will take centuries if we only use the tried and tested models to fulfil all of those unmet medical needs. Certainly we need to push the boundaries in terms of how we get data."

Reimbursement: identifying & aligning endpoints

Throughout the discussion, audience members were invited to submit questions and the topic of reimbursement soon surfaced.

Christian noted that, when there is no treatment, the endpoint isn't always clear. "You don't know what to measure because this is uncharted territory. As developers and regulators we're thinking about patient risk/benefit, but obviously the payers are thinking about cost/benefit," he said. So how can we account for that?"

Daniel ssuggested the industry as a whole must think more broadly in terms of endpoints that really matter, particularly when it comes to very rare diseases for which there have previously been no real treatment options. "To some degree, we can use patient-reported outcome measures, or clinical outcome measures that are applicable across multiple different groups of patients - to help to understand better a product's efficacy and safety, in terms of alignment for regulators and health technology assessment (HTA) bodies," he suggested.

In Europe, he noted, there have been some proactive moves to collaborate to ensure that the preferred endpoint works for both the medicines regulator and for the HTA body in terms of their respective decision-making. In the UK, the Innovative Licensing and Access Pathway (ILAP) looks to support certain discussions, while on the continent there are ongoing collaborations between the EMA and the HTA bodies. But patient input is critical too, Daniel warned. "You've got to bring them into the discussion - and you've got to bring them in early when you're considering new endpoints. That's so important," he said.

For **Rachelle**, trying to keep all parties happy during drug development and study design is a huge part of the challenge.

"Moving forward with a program, hoping that everybody's going to be okay with the totality of the data, the historical control arm, and the endpoints, is a major preoccupation. We have to figure out how to de-risk that a bit earlier. Sometimes these things work out brilliantly, but then others following the same pathway will hit roadblocks. Or you've been making significant progress and then you go into a discussion on reimbursement and suddenly the endpoints don't work. And then what? This is about how we can get those discussions to happen earlier."

Reflecting on her time at Enzyvant, an accelerator for transformative regenerative medicines where she worked previously, Rachelle said: "We had a very interesting tissue-based therapy, that had a lot of data generated over years. But, the authorities wanted to know, was it run as a controlled study? Were there particular endpoints that were captured?

"Across that experience there was a lot of data – in fact, when we went back afterward, we were able to leverage a lot of data generated in academia," she continued. "Ultimately, we were just trying to find the best path forward, because there was a lot of evidence that the therapeutic approach was potentially life-saving. And we wanted to find the fastest path, given that the patient population was very small. And it did work out brilliantly: we were able to achieve FDA approval. BUT this was such an outlier approach that it left me wondering why everything needs to follow approaches that are more suitable for larger studies and larger positions."

Asking patients what matters

On the criticality of the patient voice as part of endpoint discussions, Christian asked what Nick thought about possible approaches to bringing patient groups into the frame at a much earlier point.

Nick said he sensed from EMA that accommodating the patient perspective was something it had now built into its structures, whereas on the whole the big pharma companies were less proactive about patient engagement. One exception here has emerged in AKA Society's relationship with Swedish Orphan Biovitrum (Sobi).

"Most drug companies will start working on something and then get in touch with us right at the last minute when things have started to go wrong," he said. "There doesn't seem to be any systematic way that pharma companies engage with patient groups, particularly in the rare disease space. A lot of lip-service is paid to 'patient centricity', but I'm not sure how many companies really do it."

This oversight can lead to problems with clinical trials, Nick said. "They don't design them properly. They don't have an understanding of the patients."

Reducing trial timelines

The discussion then turned back to protracted trial times, and the inevitable expense involved – when funding can be hard to come by. Following the change in pace shaped by the Covid-19 pandemic, there has been a growing focus on "Phase 2 trials, with accelerated approval", the panel noted.

"From what we see in our work, that's basically what everyone wants now," Christian said. "So, is this the new default? Is there a risk that as an industry we could be departing from our gold standards by heading down this path; is it something we should be considering on a case-by-case basis; or might we be so bold as to say that if the data is done well, it might actually be fine?"

"It comes back to the flexibility of the approach, then the regulator, the patient group, and the condition involved," **Daniel** said. Ultimately the data has to mean the right things to the right people. "So really you need to start right from the very beginning, to map out what's feasible."

Involving patients at an earlier stage, and finding out what's most important to them, is a growing area of focus among those thinking about all of this more strategically. Where cures aren't possible or may still be a way off, for instance, factors such of quality of life can be hugely significant to patients.

Daniel referred to the Innovative Medicines Initiative (IMI), SISAQOL-IMI, which is working on recommendations about how to analyze and interpret data on health-related quality of life (HRQOL). It is led by the European Organisation for Research And Treatment Of Cancer and, although it is specific to oncology, some of its findings are likely to support the broader application of patient-reported outcomes.

"That's not only in clinical studies, which is really important for the decision-makers such as regulators and payers, but also in a real-world setting - to be able to truly monitor how patients are doing across their journey with a particular medicine after authorization. It's something the MHRA is really keen on," he noted. "We're working very hard to try to embed patient-reported outcomes as much as we possibly can in the clinical input that we give to those developing medicines."

Post-authorization challenges

Post-authorization, there are challenges to be overcome too, the panel agreed. Negotiating reimbursement for specialist therapies can trip up developers, even once a drug has been approved, frustrating patients as well as drug developers and their investors. The case of Bluebird serves as a cautionary tale here: the company exited the EU following difficulties negotiating reimbursement for a particular gene therapy.

Again, the consensus was that greater stakeholder collaboration was needed at a much earlier stage, so that all priorities are aligned and reflected in the action plan.

As **Rachelle** put it, "Conceptually, parties have agreed on all kinds of interesting models and you see them all over the headlines. But if you look in detail, they aren't actually being implemented. And the reason is down in the details, in the administrative pieces of what needs to be done. If you're negotiating with a government payer in the US, in practice this means taking on an entire state budgeting and legal challenge which isn't practical. And it's not easy for individuals and small companies trying to solve these problems. But the details really do matter. And we're going to need to solve some of these at a macro level.

The panel highlighted the need for harmonization across the whole system, as in Europe too differences between EU member states as well as the UK can lead to problems in getting new therapies to patients. Where knowledge about rare diseases and the latest treatments is scant, regulators like MHRA are working closely with payers to bring them up to speed.

"Having a visible platform for very early dialogue is really important," **Daniel** said, referring to MHRA's Innovative Licensing and Access Pathway (ILAP). "If you want to do something novel, or if you want to try to push the boundaries or the acceptability of the data, or think about different managed access approach, having those early discussions with both the medicines regulator and also the HTA bodies is key."

ILAP is a collaboration between the MHRA, NICE, the Scottish Medicines Consortium (SMC) and the All Wales Medicines Strategy Group (AWMSG), and paves the way for the creation of products that are both regulatory approval and access ready. "It doesn't automatically mean that there's a Yes at the end of it, but ILAP's existence means that this kind of alignment is more likely," Daniel suggested.

A wish-list for change

Drawing the discussion to a close, Christian asked the panelists to say what would be at the top of their wish-list for change, if barriers didn't apply.

For **Rachelle**, the catalyst for positive progress will be multi-stakeholder approaches to overcoming practical barriers at a macro level. That's rather than one company at a time; one patient advocacy organization at a time; one regulatory body at a time – so that the 95% of remaining unmet needs can be addressed sooner rather than later.

Daniel felt that electronic health records would enhance development programs in future, with improved access to the rich real-world data they contain.

Speaking for patients, **Nick** said his wish would be finding a funding model that really works particularly for ultra-rare diseases, to fund studies which are otherwise just not commercially viable.

"The US is very fortunate to have the Chan Zuckerberg Initiative, which is doing really good things in building patient groups with significant funding," he noted. "If we could have something along those lines in the UK or the EU, potentially funded by the pharma industry, that could be huge."

The recording of the full Science Huddle panel debate is available to watch or download on the Biopharma Excellence web site. Future Science Huddle events will take place quarterly.

The Science Huddle, Sparked by Biopharma Excellence, are thought leadership panel discussions featuring key stakeholders from across the life sciences ecosystem, focusing on the complex challenges in the race to bring critical, cutting-edge treatments to patients.

Upcoming sessions will address:

- Proposed approaches to the practical problem and associated risks of empty capsids in gene therapy trials.
- The fallout of poor global product development planning, and the advantages of starting a dialogue with regulators much earlier in the cycle.
- The difference a more aggressive strategy can make in biosimilar delivery and market success.

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