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German, Danish Regulators Explain Dos And Don'ts Of Master Protocols

Executive Summary

Senior regulators from Germany's Federal Institute for Drugs and Medical Devices and the Danish Medicines Agency explain how sponsors can keep documentation and governance manageable for complex trials.

Master protocols are a popular choice in oncology and haematology related clinical trials, but top regulators in Germany and Denmark feel their use should be restricted to instances when they are "unavoidable for scientifically sound methodological reasons."

While master protocols are intended to accelerate drug development and reduce futility, they should not be used as a simplified authorization vehicle, to reduce regulatory contacts or to shorten the review timelines of regulators and ethics committees, the regulators write in a recent article in The Lancet Oncology. In their view, using master protocols for such purposes "must be considered unethical and inappropriate."

Weakened Regulatory And Ethical Reviews

Although the use of integrated protocols is increasing, the article points out that the drug development process still consists of a series of consecutive trials that are planned and carried out based on previously gained preclinical and clinical knowledge.

The BfArM and DMA regulators are concerned that using an "all-in-one protocol" – that contains the complete drug development process for a new compound in a single trial protocol – could weaken the regulatory and ethical review system, which is intended as a third-party institutional patient protection system by the European legislation.

Many master protocols, they explain, are not aimed at the development of a single new agent, but at new treatment concepts, including the early detection of promising candidates or at the early proof of futility stage. "We generally acknowledge the usefulness of these concepts but do not see their strengths in the developmental programme of unapproved new drugs," the regulators state.

Although they believe that master protocols present a "good opportunity" for identifying new treatment options, they are concerned by the fact that in the EU, most master protocols – particularly basket trials – are submitted as single clinical trial applications with several sub-protocols.

Such applications contain protocols running into several hundred pages, sometimes with several approved and unapproved investigational medicinal products. These protocols "can hardly be read linearly" as they are structured into various appendices and attachments that are then cross-referenced, resulting in reduced readability for regulators and ethics committees who evaluate these to short deadlines, the article states.

Problems can also arise due to the amount of information generated from sub-trials and the volume of changes and amendments made to the trial applications, which can cause issues during trial supervision, and during the analysis and review of a corresponding application for marketing authorization.

Platform trials, in particular, carry the risk of

becoming "functionally immortal" as new sub-studies are added without clear stopping rules for the master trial itself. The regulators point out that neither the current EU legal framework nor the upcoming Clinical Trials Regulation require reporting of terminated sub-studies, "but only the submission of a final report 12 months after termination of the overarching trial according to the overarching master protocol."

This poses serious concerns as the results of terminated sub-studies (positive and negative) could seriously impact the regulatory and ethical opinion on the ongoing trial. However, there are "no legal means to force sponsors to submit sub-trial reports in a timely fashion when a master protocol has been submitted as a single clinical trial application," the article states.

Split It Up

To overcome these issues, the regulators recommend that sponsors should split up protocols in an overarching master protocol describing master hypothesis, patient population, screening platform and patient allocation, while treatment sub-protocols should be submitted as distinct individual clinical trial applications.

As sub-protocols might refer to the overarching master protocol, "they can be designed as lean and smart protocols only specifying the sub-protocol relevant procedures and requirements and referring to the overarching master protocol for common procedures and requirements, as the European legislation allows references to already approved clinical trial application protocols," they explain.

Earlier this year, the EU Clinical Trials Facilitation Group issued guidance to help national competent authorities who have been increasingly facing issues when reviewing and authorizing master protocols. (Also see "EU Addresses Complex Clinical Trial Designs In New Guideline" - Pink Sheet, 11 Mar, 2019.)

The guideline generally asks for pre-specification of all relevant study parts and sub-protocols, which does not prohibit the use of dummy sub-protocols to be extended later on in the application process, but would require a multiple clinical trial application approach rather than a combined single application, the article explains.

Amgen's Elliott Levy On Adaptive Design And Real-World Evidence Strategies

Executive Summary
Levy, SVP of global development, notes that two years after launching an in-house Center for Design and Analysis, Amgen considers adaptive designs for most new studies and more than half include adaptive elements.

Amgen Inc.'s Elliott Levy, senior vice president of global development, notes that the company is focused on innovation in terms of both the molecules in its research and development pipeline and the R&D processes it employs to take novel therapies from preclinical studies through regulatory approval.

The company also has streamlined operational costs in anticipation of multiple blockbuster products facing generic and biosimilar competition with the goal of bringing new products to market at a faster pace.

Anticipation of multiple blockbuster products facing generic and biosimilar competition has also spurred the company to streamline operational costs to help bring new products to market at a faster pace. (Also see "Lower-Cost Competitors Hit Amgen's Blockbusters" - Scrip, 30 Apr, 2019.) Cost cuts began in 2014 with a double-digit reduction in head count as Amgen sought to reallocate resources to its later-stage R&D pipeline and near-term commercial opportunities. (Also see "2Q EARNINGS: Amgen cutting up to 2,900 jobs to reinvest in pipeline" - Scrip, 30 Jul, 2014.) Further streamlining in R&D and manufacturing was announced later that year. (Also see "Amgen hits new high on investor-friendly growth plan" - Scrip, 29 Oct, 2014.)

Levy said in a recent interview that Amgen has taken about three years out of its development cycle time in the past few years, mostly in the preclinical space.

"For the KRAS G12C inhibitor we applied everything we learned about shortening preclinical cycle times and as a result were able to come to the clinic faster than anyone expected, and I believe we're ahead of the competition," he said.

Indeed, Amgen was the first drug maker to report positive clinical trial results for a cancer therapy targeting G12C mutations in the KRAS oncogene when early Phase I results for its drug AMG 510 were presented at the American Society of Clinical Oncology earlier this month. (Also see "Amgen's KRAS Inhibitor AMG 510 Leans Toward Tumor-Dependent, Not Agnostic, Approach" - Scrip, 3 Jun, 2019.)

The Pink Sheet spoke with Levy at Amgen's headquarters in Thousands Oaks, CA about the company's use of adaptive designs in clinical trials and real-world evidence to support its studies and its regulatory submissions. [The interview below has been edited for length and clarity.]

Pink Sheet: How are you using adaptive designs and other methodologies to run more efficient clinical trials?

Elliott Levy: We see adaptive methodologies as a unique opportunity to simultaneously increase probability of success, shorten trial durations and cut costs. Usually in trials we can only optimize on one of those three dimensions. If we want to increase the probability of success, we need to run a larger, longer trial at greater cost. If we

want to go faster, we have to reduce the level of experimental precision and [increase] the chance of either a false negative or a false positive result.

But adaptive designs, particularly the response-adaptive designs where patients are reallocated from under-performing study arms to high-performing study arms, those can involve fewer subjects than a conventional fixed study design, they can give us more precise estimates of the treatment effects of doses of interest, and they can result in meaningful reductions in overall trial size and cost.

We decided about two years ago that we really wanted to fully embrace adaptive methodologies and other innovative methodologies. We combined various quantitative sciences groups within the company to form a Center for Design and Analysis. That center includes our traditional biostatistics function, but it also includes a Design and Innovation Center that's staffed by experts in innovative methodologies. They act as expert consultants to project teams and they essentially walk them through the process of evaluating adaptive methodologies. They can provide support for modeling and simulation, if that's appropriate, as it often is. And then we have a separate data analytics center that relies on both real-world data and repurposed clinical trial data to help us optimize study design and execution.

Since we've launched this center, in two short years we've reached the point where virtually every study that we launch seriously considers an adaptive design and over half of the studies are incorporating adaptive elements, so we're very excited. We've got a trial moving forward in lupus [for AMG 570 targeting B-cell activating factor (BAFF) and inducible co-stimulator ligand (ICOSL/B7RP1)] that, to my knowledge, might be the first adaptive trial in lupus and perhaps the first that's conducted under an [investigational new drug (IND) application] with the Division of Rheumatology at the [US Food and Drug Administration].

Pink Sheet: In terms of the US FDA, are you finding that they're really receptive to those ideas? The agency has spent a lot of time looking at adaptive design and talking to companies about what's useful.

Levy: We find them to be quite interested. In fact, we've sent staff down there to lecture FDA staff on adaptive methodology. They, of course, will appropriately scrutinize each protocol to ensure that the information it provides is interpretable, and there may be cases where they feel adaptive methodology is not appropriate, but both in principle and in practice we are finding them to be receptive to adaptive designs.

Pink Sheet: What kind of things are you trying to do to use real-world evidence to your advantage?

Levy: We have a number of successes using real-world data. We secured initial marketing authorization for Blincyto – our bispecific T-cell engager therapy for acute lymphoblastic leukemia – using real-world evidence as benchmark data for a single-arm registrational trial. (Also see " A behind-the-scenes look at fastest BLA review in US " - Pink Sheet, 26 May, 2016.) Interestingly, we were required by the FDA to conduct a confirmatory randomized trial in the same population. When that was completed, it demonstrated exactly the same effect size on response that we had shown comparing our single-arm trial to our real-world evidence study. To me, that points to the growing maturity of the methodologies that are being used to create real high-quality real-world evidence. (Also see "Real-World Evidence At US FDA: Bavencio, Blincyto Approvals Point Way Toward Broader Use " - Pink Sheet, 7 Aug, 2018.)

We subsequently obtained an approval for

Blincyto as a treatment of minimal residual disease in patients with acute lymphoblastic leukemia. This approval was, like the initial approval, based on the results of a single-arm trial supported by real-world evidence providing referencing or benchmarking information. Interestingly, this was the first approval ever for a drug for treatment of minimal residual disease. (Also see "FDA Grants Blincyto Accelerated Approval Based On MRD Response Endpoint" - Pink Sheet, 30 Mar, 2018.) That gives you some idea of the confidence the FDA had in using real-world evidence to infer the presence of a meaningful therapeutic benefit.

The agency [recently] issued guidance on the identification of real-world evidence within regulatory submissions. They clearly would like to begin cataloging the number of cases in which real-world evidence is used in registrational dossiers and essentially to be able to categorize the manner in which it's being used, so they identified four cases in which real-world evidence would be used. One of them is as supplemental information support and efficacy supplements for a product and that's exactly the context in which we have used it. I think at this point they probably need to understand the data better – its gaps and limitations as well as its promise – before they can begin to routinely consider its use as the sole basis for approval of an indication. But in a supportive setting, I think they're quite interested in receiving it.

I think that another important use of real-world data is in evaluation of product safety. Of course, the FDA has been using real-world data for years through Sentinel to conduct post-marketing safety surveillance, but we believe we've really only begun to scratch the surface in the use of real-world evidence in safety surveillance.

I'll give you a recent example: We recently received approval for Evenity (romosozumab), which is a sclerostin inhibitor for the treatment of patients with post-menopausal osteoporosis at high risk of fracture. (Also see "Amgen Launches Evenity For High-Risk Osteoporosis At $21,900 List Price" - Scrip, 15 Apr, 2019.) In the second of the large Phase III studies we conducted, there was a cardiovascular safety signal. We assembled an extensive body of evidence from numerous sources in order to support the evaluation of that safety signal. One of the sources was our deCODE genetics database, which among other things is a superb real-world data resource. It is a data set that includes the health care records of the entire population of Iceland, in addition of course, to the genotypes to a substantial part of that population. (Also see '"Beautiful baton pass' as Amgen picks up deCODE to validate drug targets " - Scrip, 11 Dec, 2012.)

Through deCODE we were able to identify sclerostin variants that were associated with decreased expression of sclerostin and then evaluate whether those variants were themselves associated with any alterations in cardiovascular risk. You would expect that if treatment with a pharmacologic inhibitor of sclerostin increased cardiovascular risk, the genetic variants which reduce sclerostin activity would themselves be associated with increase cardiovascular risk. That was not observed in the deCODE real-world data set. That was not the only piece of information that we provided in support of evaluation of the cardiovascular safety signal, but it was a particularly interesting use of real-world evidence that, right now, I think we're in the best position to do because of our access to the Icelandic data.

Real-World Evidence: Replication of Controlled Trials Expected To Fail Sometimes, US FDA Says

Executive Summary
Agency study deliberately not weighting RWE populations the same as RCTs it aims to duplicate. "We learn the most when we don't replicate," Harvard Medical School's Jessica Franklin tells the DIA annual meeting.

SAN DIEGO – The US Food and Drug Administration expects that its study to reproduce the results of randomized controlled trials using real-world evidence will fail to replicate in some instances – a result that could drive a better understanding of how to use claims and other real-world data.

Asked during a 25 June session of the DIA annual meeting, Center for Drug Evaluation and Research's David Martin acknowledged that the agency is not expecting complete replications.

Slides that Martin had prepared state that "probability of regulatory agreement in the absence of bias should be in the 80-90% range" for a real-world evidence (RWE) study aiming to duplicate a randomized controlled trial (RCT) that showed "significant effects." The presentation was less clear about how much replication the agency is expecting for RCTs without significant effects.

"All I would say that's premature for me at FDA to talk about that in more detail than that," Martin said. "But I think the general message that is clear is, obviously in the in the absence of bias, there is a statistical expectation that it would still not be 100% duplication. And I'm comfortable saying that."

Martin, the associate director for RWE analytics in CDER's Office of Medical Policy, did reveal that FDA has still not settled on the terminology to describe the replication effort. "By the way, my first disclaimer is we haven't really decided," he said, referring to the ubiquitous disclaimer slide that makes up the second screen of every presentation at the four-day meeting.

"Some believe that duplication is perhaps a better term than replication since there's some inherent differences," Martin said. "We don't have a strong opinion, I don't think. Feel free to call it whatever when you wish."

FDA is funding a study with the goal of creating approximately 30 retrospective trial replications by March 2020 as part of a requirement of the 21st Century Cures Act. (Also see "Real-World Data Could Get Boost From Trial Replication Project" - Pink Sheet, 26 Apr, 2018.)

The study's lead investigator, Harvard Medical School's Jessica Franklin, told the DIA session that complete replication wouldn't even be the best outcome. "We learn the most when we don't replicate, because then we really have to dig in and figure out why," she said.

"We certainly will for all of the clinical trial replications be doing lots of sensitivity analyses, whether we replicate or not. Because if we did replicate, how robust is that finding? Does it fall apart when you change one little thing? But then if we don't replicate, can we figure out why?"

For the primary analyses of the RWE studies, the project is using the same inclusion/exclusion criteria as the RCTs did, "but we're not actually weighting to the trial population," Franklin noted. "And then with sensitivity analyses, we will do that

to try and explore if these smaller differences between our population and the trial population could explain the differences."

The study will also consider other sensitivity analyses like changing follow-up time and different definitions of inclusion and exclusion criteria, because "in all of our attempts to replicate, we're having to make hundreds of choices that are as clinically and epidemiologically informed as possible, but certainly another set of investigators would likely make many different decisions than us," Franklin said.

"My hope is that anybody else who's interested … if they want to look at our documentation that's available on clinicaltrials.gov and go and implement their own replication, that would make me extremely happy. And if they're able to replicate in places where we can't, that would be great, because we would all learn a lot from that."

Martin emphasized that not weighing the populations in the RWE studies was a deliberate effort to increase the validity of the findings and increase the value of such studies going forward.

"After applying the trial inclusion/exclusion criteria to the best of our ability using the real word data sources that we have, we are intentionally not weighting the population, because going forward in the future, were you to do this without a reference trial, you would have no population to weight your population to," he said.

US FDA Seeks Ways To Prevent Non-Responders From Sinking Tissue-Agnostic Indications

Executive Summary

Agency officials and oncologists debate considerations where a data package overwhelms non-responders in favor of a tissue-agnostic indication.

Sponsors may be able to obtain a tissue-agnostic indication despite failing to show a response in one tumor type as the US Food and Drug Administration intends to remain flexible with its approval requirements.

The FDA seems willing to look past a lack of response in one histology, if success is seen in several others among enough patients. Tatiana Prowell, scientific lead for breast cancer in the FDA's Office of Hematology and Oncology Products, as well as assistant professor of oncology in the Johns Hopkins Breast Cancer Program, said the agency many be willing to retain non-responding subgroups in the indication under certain circumstances.

"It gets to this issue of how big is the denominator. What's your fraction look like," Prowell said during a workshop on development of tissue-agnostic, biomarker-based indications sponsored by the FDA, Friends of Cancer Research and American Society of Clinical Oncology.

"I think if you have a histology where you don't see responses with a limited number of patients in that subgroup, but you have a large number of histologies represented, it gives you greater confidence that maybe we don't want to carve that out and have that as a limitation of use for example, or include language in the label suggesting that those patients don't benefit, recognizing that that has real implications for access and reimbursement," Prowell added.

The goal of the workshop, which solicited opinions from oncologists, regulators, patient advocates and others, was in part to gather input on the FDA's approaches to reviewing applications for products seeking tissue-agnostic indications.

Indeed, some cancer treatments expected to be tissue-agnostic have run into problems with efficacy not equal across tumor location. Roche found during a trial that its BRAF inhibitor Zelboraf (vemurafenib) that tumor histology was important in determining the response in BRAF V600-mutated cancers. (Also see "Tissue-Agnostic Approach To Cancer Drug Development Takes A Hit" - Pink Sheet, 14 Sep, 2015.) A study of Puma Biotechnology Inc.'s pan-HER inhibitor neratinib also found efficacy only in some kinds of cancer with HER2-activating mutations. (Also see "Puma's Neratinib SUMMIT Study Shows Potential & Pitfalls Of Precision Medicine" - Pink Sheet, 2 Apr, 2017.)

We'll Never Understand All Non-Responders, Oncologist Says

Agency officials said throughout the workshop that they will consider the totality of evidence when determining whether to grant a tissue-agnostic indication. But the question of how or whether to approve a tissue-agnostic indication when some patients subgroups did not respond seemed vexing.

Theodore Laetsch, a pediatric oncologist at the University of Texas Southwestern Medical Center, said when there is enough data suggesting a tissue-agnostic response, the agency should need more than a few non-responders to dispute it. He also reminded the room that determining the

cause of the non-response will be difficult, if not impossible.

"It is important from a mechanistic standpoint to define why patients don't respond, but I don't believe there's ever been a drug that we've been able to define why every single patient that didn't respond didn't respond," Laetsch said. "That should be our goal as academicians to understand that better and to better enable patient selection, but I do think that's also not going to be really possible for every patient."

Vivek Subbiah, clinical medical director in the MD Anderson Cancer Center's Center for Targeted Therapy, said pre-clinical or early clinical work may help avoid non-responder problems.

"In the early studies that we see resistant tumors, we can exclude those tumors," Subbiah said.

The FDA also can use postmarket experience to police the validity of tissue-agnostic indications. Agency officials said during the workshop that real-world evidence could inform indication carve-outs or move products from tissue-specific to tissue-agnostic indications. (See sidebar.)

The agency has approved tissue-agnostic labeling for two products so far, which allow for the product to be used for a specific form of cancer no matter where it appears in the body. The first, Merck & Co. Inc.'s Keytruda (pembrolizumab), gained the distinction as a supplemental indication in 2017. (Also see "Biomarker-Led Claim Is Small Step For Merck's Keytruda, Giant Leap For Cancer Indications" - Pink Sheet, 23 May, 2017.)

Loxo Oncology Inc. and Bayer AG gained the second tissue-agnostic approval – the first of a novel product prospectively developed for that purpose – for Vitrakvi (larotrectinib) in 2018. (Also see "Vitrakvi, Daurismo Approvals Put US FDA On Brink Of Another Record " - Pink Sheet, 27 Nov, 2018.)

Is Four To Five Tumor Types Enough For A Tissue-Agnostic Indication?

Stakeholders also tried to narrow the FDA's broad case-by-case approach to the evidence necessary to obtain a tissue-agnostic indication. The debate seemed to narrow the total, but there still seemed to be concerns about the work that may be required.

Howard Burris, an oncologist at Sarah Cannon, the cancer institute of HCA Healthcare, said defining a number is difficult, but settled on four tumor types as symbolic of a potential tissue-agnostic response.

"It is hard to pin down to a number, but it feels like if you're not north of four or more unique and very different tumor types, there's some number there in the four, five range where it feels like it probably ought to be studied," Burris said. "And there needs to be some diversity in terms of those histologies not even being similar."

Subbiah said there likely is no answer because early studies are necessary to determine the tumor types that could be studied for a tissue-agnostic indication.

Joon Rhee, global clinical lead for Lynparza (olaparib) combinations and new opportunities at AstraZeneca PLC, also said the FDA must be careful in dictating the patient groups to prioritize for a tissue-agnostic indication study.

"I think the reality is it's very, very difficult to find these patients in rare populations," Rhee said. "The reality is we need to do what's feasible."

The FDA released draft guidance on molecularly-targeted drugs seeking indications across multiple patient subsets in 2017 that attempted to streamline the development process. The

agency wrote that broad labels could be allowed, but the agency indicated that labels may be narrowed or additional studies may be mandated if emerging data suggests a lack of efficacy in some subgroups. (Also see “US FDA Outlines Streamlined Development Path For Targeted Therapies” - Pink Sheet, 16 Dec, 2017.)

UK Explores Feasibility Of 100% Trial Registration Rates In Major Transparency Push

Executive Summary
By the end of this year, the UK's Health Research Authority plans to have developed a strategy to drive improvements in research transparency, particularly when it comes to the registration of clinical trials and making results public.

The UK's Health Research Authority is stepping up efforts to achieve "full clinical trial transparency" and has begun work on developing a detailed strategy to explain how it will go about doing this.

The HRA plans to submit its final transparency strategy – including clear deadlines and milestones – to the House of Commons Select Committee on Science and Technology by the end of this year. The committee had criticized the HRA in its October 2018 report for not doing enough to resolve the problem of un-registered, non-reported and mis-reported clinical trials, even though research transparency is one of its statutory objectives.

The HRA wants to ensure that its strategy is "robust, impactful and realistic" and, as part of this exercise, it is looking at, among other things, whether it would be realistic to push for 100% registration of clinical trials. "We think it is," Sir Jonathan Montgomery, HRA chair, told delegates at a conference in London on 6 June.

"We recognize that this is a challenge for us" and also "that we need to move from being reactive to proactive [on the issue of transparency] if we are really going to deliver on the expectations," Sir Jonathan said at the Westminster Health Forum policy conference, entitled "Regulation of medicines, clinical trials and medical devices in the UK."

In response to the select committee's recommendation that the HRA should introduce a system of sanctions to drive improvements in clinical trial transparency, Sir Jonathan said feedback would be collected on how fair and realistic it would be for the HRA to look at whether trial sponsors have previously met their transparency obligations before they can be allowed to commit to further research in the future. "This is likely to be controversial… but it might be a key lever that pulls the debate forward," he said.

Sir Jonathan believes that efforts to improve research transparency will require a holistic approach. From the work that the HRA has done so far on this topic, "we have seen that the industry responds to regulatory pressures quite effectively, but the academia does not. The academia has a culture where it continues to think about what it's doing as proprietary and [tends to be] defensive and competitive. So we are going to need to address both the cultural issues and also the regulatory ones," he said.

Last year, a major EU study found that drug companies were outstripping academics when it came to complying with EU rules on reporting clinical trial results. Specifically, it found that around 68% of commercially sponsored trials were reported on the EU Clinical Trials Register (EUCTR) versus 11% of non-commercially sponsored trials.

The HRA is looking at how improvements can be made on this front and plans to discuss "what

we should be aiming to achieve overall and what would be our job in dealing with that," Sir Jonathan said. He believes that much of the HRA's work on improving transparency can be broadly divided into four categories, of which ensuring trial registration and reporting of trials results are two categories that the HRA intends to actively "pursue and monitor."

The third category deals with the importance of providing feedback to trial participants, although Sir Jonathan acknowledged that there can be practical issues with this. The final category involves addressing the challenges associated with sharing clinical trial data. Sir Jonathan said that the HRA would probably "ease back a little" on this issue for now, with the aim of tackling it at a later phase.

The new transparency strategy is being shaped by the authority's Research Transparency Strategy Group, which at its meeting on 8 May, agreed that the HRA should first decide on a transparency "vision" that was clear and concise. The group said that the HRA should also focus on creating an accessible public record of health and social care research. For this, the authority is exploring whether it should set up its own registry.

"First of all, we need to be really clear about what's expected [of us] and then we can help deliver this [vision] through learning and training," said Sir Jonathan. For example, he explained, that the HRA can "do a lot to flag up what sponsors are missing [in terms of compliance] through automated reminders and we could provide feedback to them on their performance."

To support this, the HRA has stated in its 2019/2020 business plan that by the end of this year it would "develop a costed model for an effective post-approval compliance monitoring function to gather performance data and track progress."

To create the strategy, the Research Transparency Strategy Group is looking at several policy options to address the four work categories of transparency where improvement is required. The draft strategy, when ready, will be issued for consultation. It will also receive input from HRA partners, existing groups such as the Transparency Forum (a group of funders, sponsors, registries and journals working together to identify and share best practice in research transparency) and the wider research community. After the consultation period, the HRA will finalize the strategy and deliver it to the Science and Technology Committee by December 2019.