Proceedings from the PCSIG Workshop on Incorporating Patient Centric Sampling into Multicentre Clinical Trials

The Patient Centric Sampling Interest Group (PCSIG) convened a two-day workshop on 'Incorporating Patient Centric Sampling (PCS) into Multicentre Clinical Trials' at Roche's facilities in Welwyn Garden City, UK on 11 and 12 June 2024. The event was hosted by Neil Spooner (Chair, PCSIG) and attended by 48 individuals from organisations representing patient engagement, pharmaceutical and biotech companies, contract research organisations, technology and solutions vendors, publishing and consulting sectors.

The purpose of the workshop was to:

- Outline the key stages associated with the implementation of PCS for multicentre clinical trials
- Define the challenges to implementation of PCS for multicentre clinical trials
- Identify how we can overcome these challenges

The workshop started with a presentation from Jenny Royle and Chi Pakarinen (MediPaCe) on 'Patients in patient-centric sampling – How broader expectations have changed' to ensure that the patient perspective was considered throughout the discussions and integrated into the outputs from the workshop. The PCSIG noted it is actively working on creation of a 'PCSIG Patient Advisory Group' with the vision of direct patient involvement in its future activities and outputs. The day then focused on defining the challenges of implementing PCS in multicentre clinical trials, concentrating on the key stages along the clinical trial pathway, through separate discussions attended in rotation by all participants: requirements and concerns of patients; study planning; logistics; study conduct; and regulatory interactions (Figure 1). The facilitators of the workshops closed Day 1 by summarising the discussions and with all participants agreeing on ten challenges arising from the discussions, which would be addressed on Day 2 of the workshop.

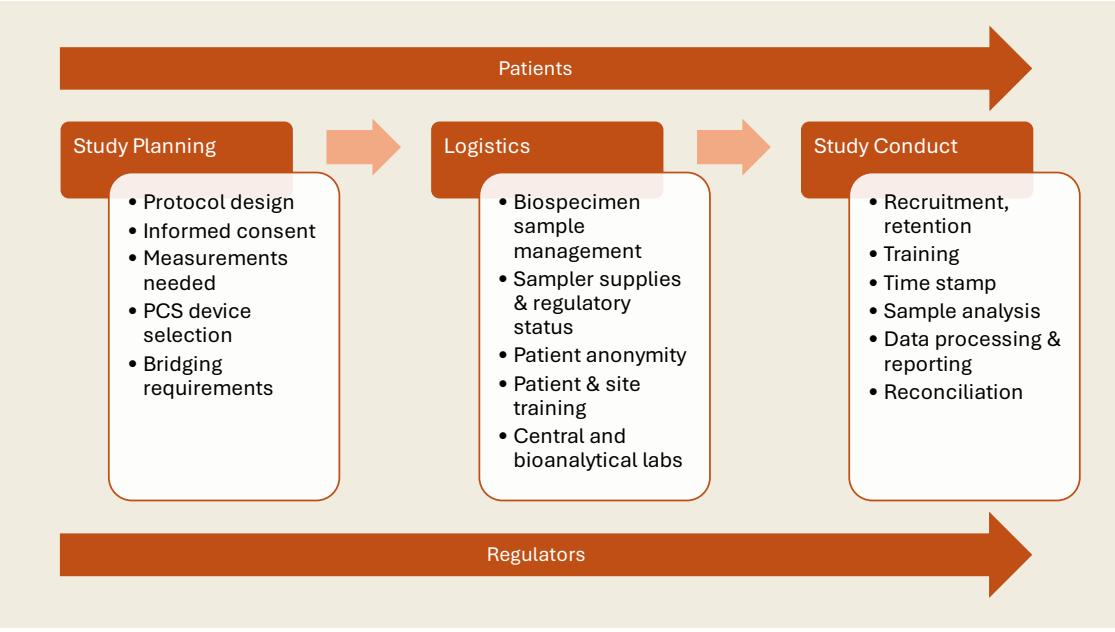

Figure 1: Pathway outlining considerations for the incorporation of PCS into multicentre clinical trials.

In addition, the output of the "requirements and concerns of patients" discussions was summarised into a checklist, which was used to guide the discussions on Day 2, to ensure that the patients' voice was heard at all stages of the process (Figure 2).

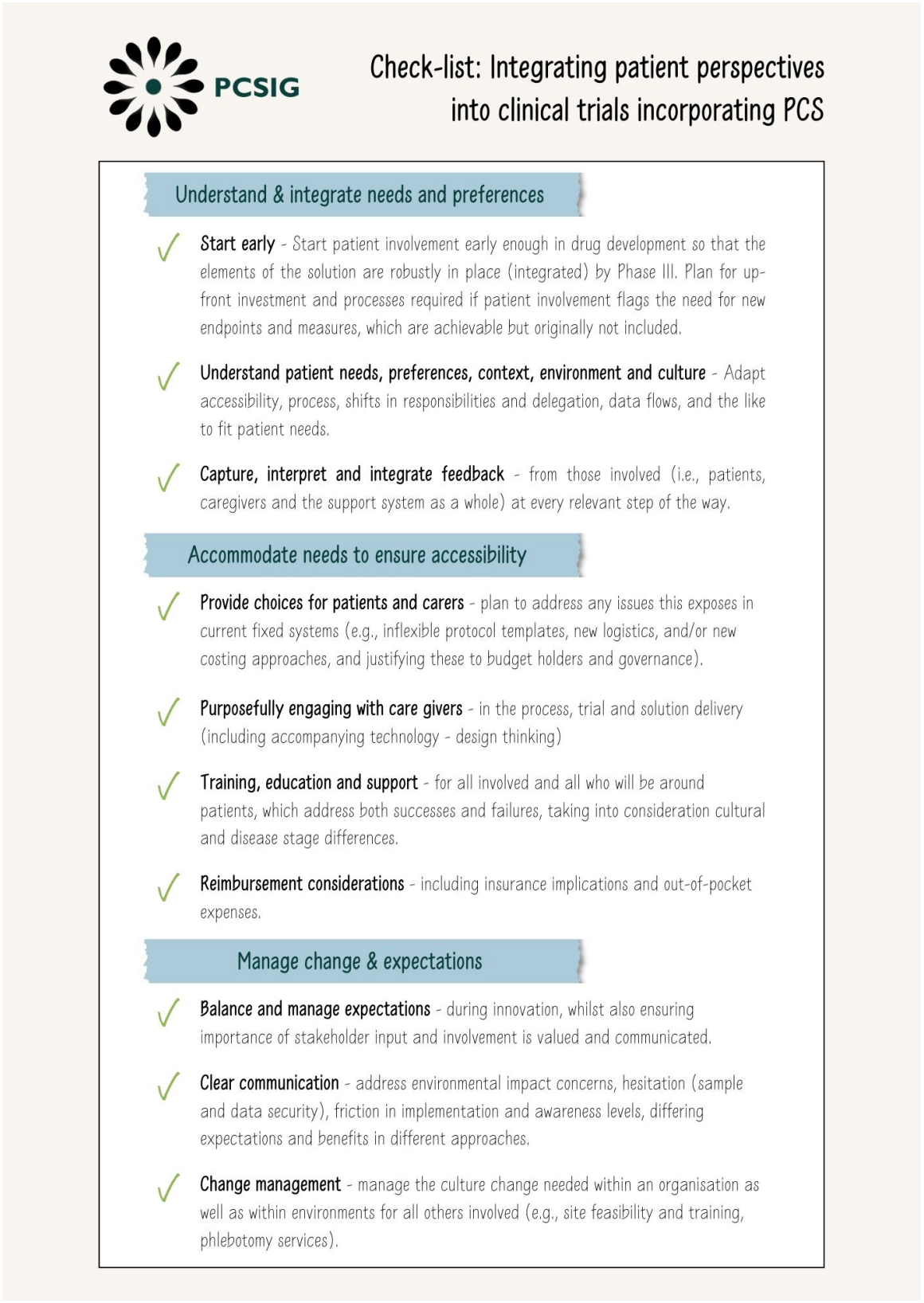

Figure 2: Checklist used as a reminder to ensure that the patient's perspective was considered in discussions around the incorporation of PCS approaches into multicentre clinical trials.

Output from the discussions for each of the challenges

Day 2 of the workshop consisted of participants working in rotation through five roundtable discussions, each focusing on how to overcome two of the ten challenges to implementation of PCS for multicentre clinical trials, which were identified during the previous day. The outcomes of these discussions are summarized below.

Study Planning - Stakeholder engagement

Facilitated.by.Graeme.Clark.(Parexel).and.Phil.Garner.(Becaris.Publishing)

The need for education and influence, alongside involvement of cross-functional internal teams, and potentially external expertise, was considered critical to increase senior stakeholder engagement and buy-in for the use of PCS in clinical trials. The use of a decision tree or infographic was discussed as a potential approach for facilitating this, with each step in the process outlined (e.g., cost, experience, logistics) including FAQs, and links to resources, clinical trials and publications, focused on overcoming the perceived barriers. A challenge noted with this approach was that those individuals who were likely to engage with the decision tree are already likely to be engaged with PCS.

A consistent theme of the discussions was that resistance to implementation of PCS sat with individuals who had to operationally deliver the approach and the general feeling of the workshop participants was that the technique was considered too complex for delivery by clinical operations. To lower this barrier, the wider role of the PCSIG to lobby on behalf of PCS was considered, through continued presence at appropriate conferences (e.g., SCOPE) and publishing relevant insight, by curating experiences from across the community; for example, case studies on what worked, what regulators ask for, and how to respond. It was also considered important that project teams engage with clinicians, as they have the ability to influence operations to enable implementation of PCS when the clinician sees value in this approach.

Study Planning - Protocol and informed consent form (ICF) templates

Facilitated.by.Graeme.Clark.(Parexel).and.Phil.Garner.(Becaris.Publishing)

Discussions around solutions to challenges associated with standardised wording for study protocol and ICF templates, where PCS approaches are used, rapidly expanded to the idea of a decision tree (potentially hosted on the PCSIG website), which would take the user through a series of questions, such as: is your device approved?; what is the data being used for?; geographical considerations – are devices available/approved in all countries?; and on-site/clinic vs decentralized vs hybrid study design. Once the user had worked through the decision tree and reached a final point, relevant templated documentation would be available to insert/download into study plans, ICFs or lab manuals, as well as supporting information, such as device training and legal information. This quickly led to a realization that the decision tree will be complex, naturally overlapping with some of the output from the other key challenges discussed in the workshop, such as logistics, regulatory, and bioanalysis methodology. Due to this complexity, it was considered that an interactive website would be a more productive format than a simple ‘print and keep’. However, it was recognised that this would require resource and time, and a more immediate solution would need to be addressed first.

A first step could be a series of more focused decision trees to help stakeholders get to key documentation and templates needed to implement PCS, such as FAQs for patients, internal stakeholders, physicians, nurses; training material; list of potential risks/specific issues to be mindful of; and links to relevant published research and ongoing clinical trials.

Study Planning - Selection of best device and biological matrix

Facilitated.by.Alex.Georgiou.(Roche).and.Navdeep.Kalia.(Roche)

To aid device and matrix selection, it was suggested that PCSIG create a Wikipedia-like resource and incorporate a FAQ section. Access to scientists, stakeholders, sites, patients, and caregivers should be ensured as a resource benefit, and to as many relevant groups as possible with layperson language used where possible and appropriate. A decision tree or similar tool could be developed to aid matrix and device selection, considering variables such as volume, matrix, patient choice, patient population, therapy area, and the end use of/need for the data. Feasibility scoring, complexity scoring, and risk factors could also be included.

For matrix selection, it is advised to start early during nonclinical development and to preferably maintain the same matrix throughout, to minimise the need for bridging studies. Further, it is important to consider the patient's perspective (where patient groups are known) and the nature of the disease and patient population when choosing the appropriate matrix and sampling technology. In this respect, training and resources should be provided to project teams to understand the reasons behind matrix selection, such as volumes and the bioanalytical strategy. Creating a process map or roadmap for covering the drug development pathway can aid decision-making and contribute towards increased standardisation and greater opportunity for PCS. Developing an industry standard for performing and interpreting bridging data, including the necessary number of data points, and how to handle correlations, can also be beneficial. A best-practice document for assay validation experiments, specifically for PCS, should be created, considering additional stability, and options for matrix selection.

Engaging with blood sampler and analytical platform manufacturers to ensure analysers are aligned with future needs and expanding the selection of available anticoagulants and stabilizers compatible with the device can enhance device selection. It was considered that promoting existing materials on the PCSIG website about devices and enhancing the understanding of the regulatory approval status in different countries is crucial. It was observed that Study Sponsors need to allocate resources to understand the equivalence of different PCS devices and address potential issues if a device becomes discontinued or rejected by patients during the study. Furthermore, device considerations should be included in assay validation experiments, such as on-device stability. It was considered important that patient advisory groups should be involved in device selection by the Study Sponsor. Furthermore, to further consider patient-centricity, where possible analysis could be bundled, fewer labs could be selected, and one sample could be used for multiple purposes, thus reducing the need for multiple samples.

Study conduct - Meta data capture

Facilitated.by.Alex.Georgiou.(Roche).and.Navdeep.Kalia.(Roche)

To improve metadata capture, a digital solution aiming to minimize the risk of errors should be implemented, e.g. incorrect capture of collection date and time, and storing or processing the sample incorrectly. Existing technologies (for example as used by the likes of Amazon.com Inc. and Tasso+) could be utilized, but there should be one unified solution for all sites and patients. Barcodes and pre-filled information should be utilized to reduce errors. Secure systems should be in place to protect patient data and metadata. Options for recording errors and alerts/alarms for dosing and sample collection should be included. Technical at-hand telephone or home visit support should be provided for those without access to technology, allowing site staff to assist with data entry or perform the entry on behalf of the patient or caregiver. Additional metadata information required for home collection, collection by a caregiver, and site collection should be

clarified, along with the minimum requirements for sample assay and data reporting. Non-essential queries could be left open for longer, avoiding unnecessary pre-analysis problem-solving. These solutions aim to address the challenges associated with patient-centric sampling and improve the overall process in clinical trials.

Study conduct - Chain of custody

Facilitated by Jasbinder Bajwa (Roche) and Jennifer Russell (Roche)

The biggest challenge with chain of custody was considered to be, ensuring that the kits and samples are fully traceable, whilst all patient details remain anonymous. Various global strategies will be needed to provide a truly patient-centric supply, such as home delivery, clinical site or alternative center (e.g. local pharmacist) collections.

If we focus on the patient-centric supply chain of custody, we should consider digital solutions for accurate metadata capture, to make the process as simple as possible for patients. This needs to include the following steps:

- Kit ordered;
- Kit shipped;
- Kit in transit;
- Kit received by patient;
- Sample collected or missed or past the window (step-by-step instructions);
- Kit shipped back (if postal), or kit collected by courier;
- Kit in transit;
- Kit received at lab;
- Chain of custody within the lab.

There should be a mechanism of feedback to the patient that their kit was received, and sample quality met, to support engagement and compliance.

To find optimal solutions now, we need to consider:

- Relationships with global couriers;
- Relationships with patient - trust and verify legitimacy of sample collection;
- Leverage what other industries have already achieved - do to not reinvent;
- Consider intermediary locations to provide support with distribution, compliance and patient assistance, in addition to clinical sites. These could include:
    - Pharmacist network;
    - Phlebotomy clinics;
    - Home nursing.

Longer-term considerations include:

- Standardization at an Industry level of metadata naming conventions, specifically for labelling; collection types; barcode/QR code, that allows 'real-time' traceability;
- Automation for device and tube handling at the lab, to allow digital chain of custody;
- Recommendation for standardized room temperature (ambient) storage - location and monitoring conditions for sample integrity and if the data forms part of the chain of custody.

Study conduct - Patient compliance monitoring & feedback

Facilitated.by.Chi.Pakarinen.(MediPaCe).and.Brenda.Yanak.(CT.Partners)

When clinical trial protocols are designed, samples are collected for a purpose, for example, to verify a patient's inclusion/exclusion from the trial; to investigate a primary/secondary endpoint, such as safety or efficacy; to investigate an exploratory endpoint, such as biomarker confirmation; or for unspecified future research use, to inform the next generation of clinical trials. As such, every sample collected is important, and correspondingly, patient compliance with the sampling regime - which sample is taken, at which timepoint, on which day ('visit'); how it is collected (device, amount); processed (e.g., inverted to mix reagents with the blood; or spun); stored (temperature); and shipped - is a key success factor to generate consistent, high quality data to ensure repeatable clinical trial results.

To improve patient compliance, several focus areas were discussed.

1) **Incentivizing the patient** - Educating the patient by conveying the rationale behind the sampling regime to the patient was deemed key. The assumption being that if the patient understands why the sample is important clinically, as well as how the process and handling can impact quality of the patient's data, then the patient would be more likely to comply with sampling instructions. Further incentivization to patients could be having sponsors return trial data, whether lay summaries or individual results, so that patients feel that they receive something tangible for their efforts. Returning data would further underscore the importance of sampling, as patients would be aware that the quality of what the data receive is directly related to their own input to sampling activities.

2) **Including patients in the design process** - Providing choice, while considering site burden and sponsor feasibility. Complementing the scientific aspects of sampling, plan study design with patients' input to gauge the burden of the required procedures – whether it be number of samples collected, timepoints, method – could help improve compliance to the proposed regimen. Further, allowing patients a choice of options, e.g., which device is preferred to be included in the kit, to the choice of sampling location (at home vs clinic) on a particular visit, could have a positive impact on adherence. Offering at home services was discussed, however this option may not be as realistic as others, as it may not be cost-effective for the sponsor and also, could relate to privacy issues, as not all patients may feel comfortable with someone coming into their home.

3) **Standardizing process & using technology to automate** - Other aspects of patient-centric process design worth considering, include providing a standardized schedule with reminders to sample. This could be through simple calendar templates and stickers (for the tech-averse), to offering an app to integrate into tech devices in the home (e.g., Alexa) to establish reminders to sample, at a frequency selected by the patient. Other technology / automation options discussed related to the device manufacturers and sponsors: including an automatic time/date stamp upon sample collection; including anti-degradation components within the collection tubes to ensure quality of sample can survive a broad range of handling scenarios; and considering the specifics of the disease population in the design of the device e.g. unique needs of arthritic, elderly, or pediatric patients.

4) **Design of training** - Patients' different learning styles and comfort levels with technology are considerations for successful self-sampling. Offering patient options to either, go to a site for training regarding collection, handling, storing, and shipping; to have someone come to the patient's home to train them; offering a paper insert in the kit with instructions; or

offering the ability to go to a website or use an app to view a training video for more independent learners, were all discussed as options.

Overall, the key theme to improve patient compliance was to offer options, allowing patients to choose. The number and types of options must be developed first and foremost within a range that does not risk the consistency or quality of the data produced. Within that frame of possibility, the sponsor must consider impact to trial budget; the balance between site and patient burden; and must be very clear as to what responsibilities lie with what party.

Communication pathways and feedback loops between the clinical site, sponsor, courier, logistics teams, and receiving labs and/or storage facilities must now be reconsidered and expanded to include the patient (and potentially the device manufacturer) to ensure that patient feedback is not only requested, but that it is clear who is responsible for acting on it.

A further aspect to consider, particularly for multi-centre clinical trials, is the buy-in of the Clinicians at the sites. If they see the value in including PCS approaches, they are more likely to encourage / enforce compliance with these sample types.

Study conduct - Training and education

Facilitated by Jasbinder Bajwa (Roche) and Jennifer Russell (Roche)

Training and education are key for patient uptake and compliance. Given the global nature of clinical trials, materials will need to be provided in various formats and languages. Furthermore, these need to be in layperson's language, with visuals, images, flowcharts and/or videos included. The manufacturer instructions for use should be integrated with the clinical trials documents and responsibility and support for training should be agreed between the Sponsor, PCS device manufacturer, Clinical Sites and Central Laboratories (where applicable).

Clinical sites will have a main role in the use of PCS devices within trials. As such, sponsors should ensure the rationale, benefits and all information pertaining to the device are clearly understood by site staff, and that they are in turn able to accurately relay the available options to their patients. As such, it is recommended to use a 'train the trainer' approach, with clinical site staff trained, to train the patients and to assess patient or caregiver proficiency with collection. Furthermore, it is recommended that all patients should complete their first collection with the PCS device at the clinical trial site. Verification of training and proficiency should be implemented for both clinical site staff and patients, with a post training site support model also considered.

Compliance with collection times and successful metadata completion by the patient can be increased by ensuring they understand what a good sample looks like and are provided with feedback when such samples are received. Missed or poor-quality collections should be followed up with the patient and retraining provided, or the option for home collection revoked as needed. It will be important to provide ongoing access to training or support, including real-time guidance if there are issues with their home collection.

Regulatory status of PCS technology

Facilitated by Chi Pakarinen (MediPaCe) and Brenda Yanak (CT Partners)

The solutions to the challenges experienced in 'understanding regulatory status of technology' related mainly to obtaining (and maintaining) the most up-to-date information on global and regional approvals. In addition to direct actions suggested (to collect and maintain this information), a broader strategy was agreed, to ensure this challenge can remain solved for the longer term. For example, through establishing ongoing intra-level interactions between subject-matter-experts

(SMEs) and other relevant cross-functional teams within pharmaceutical and medical device (MD) companies, and inter-level communications between companies. In addition, a co-created 'Risk Framework' was thought to be a useful tool for study planning phase to ensure the regulatory status, as well as data privacy concerns are considered early on. This framework could be developed by those involved in a particular study, but there could also be an opportunity for PCSIG to be involved in developing an outline risk framework for all to use. In short, this comprised the following:

1) Transparency on current regulatory status and global kit-device-innovation roadmap, where patient input is built in.
    - With ongoing dialogue with regulators;
    - Include kit/ technology/ application lifecycle management.
2) Ongoing interactions between internal SMEs and Regulatory Affairs / Legal / Patient Safety teams within pharmaceutical and MD companies, as well as between each other.
    - Establish a central repository of up-to-date regulatory information and regional approval status (MD companies could contribute this information), linking to the existing device listing on the PCSIG website
3) Stakeholders from the second point to co-create a 'risk-framework' for use in the study planning phase that includes device regulatory, safety and quality information.
    - Primary vs. secondary endpoints should be considered;
    - Interactions with regulatory agencies should be initiated as early as possible.
4) Privacy and related concerns:
    - Analysis of what data is linked to the patient through use of the device, and understanding what regulations apply, who the accountable party for managing it is, and how access is safe-guarded to only the appropriate parties
    - Understanding data flows and access, data- and sample transfer restrictions;
    - Data privacy considerations should also be linked to or considered as part of process and technology solutions in patient monitoring and feedback solutions (e.g., when considering digital/ /logistics infrastructures).

Who has burden of proof for the regulatory data?

Facilitated by Erwin Berthier (Tasso) and Dan Baker (AstraZeneca)

Discussions related to two different types of assays: those defended by Pharma (e.g., PK / biomarker assays) and those defended by external providers (e.g., companion diagnostics (cDx) / safety panels). There is uncertainty over who should be responsible for validating that a PCS assay generates suitable data. Questions primarily arose around cDx and safety panels (i.e., those where the burden of validation fell outside pharma). In this case, there was uncertainty as to whether a device manufacturer should be responsible for defending a PCS vs traditional capillary approach, or whether the burden of device validation would fall upon the lab performing analysis of the biological samples.

For PK data, it was considered that the current ICH M10 guidance [1] provides enough information to give confidence from a bioanalytical perspective. However, for cDx assays, the situation is more complex;

- If the assay is within context-of-use and regulated by suitable external regulatory body, no additional assessment is required.
- If the assay is outside of context-of-use (e.g., therapy area or patient population), its use may require justification to regulator. This could be a collaborative opportunity between Pharma / CROs and the PCS technology manufacturer.

It was agreed that ultimately the burden of proof falls upon whomever certifies that the data is accurate.

Regulators - What, when & who do I need to interact with?

Facilitated.by.Erwin.Berthier.(Tasso).and.Dan.Baker.(AstraZeneca)

Focussing on PK assays, initial consensus was to engage early with regulators and to provide a data package to defend a PCS approach. Engaging early may require internal agreement for a PCS approach, with involvement of bioanalysts, operations, translational and clinical scientists. It was strongly suggested from experience, that feedback from clinicians and patients has substantial power to help encourage buy-in to the concept of a PCS approach both internally (i.e., project teams) and externally by regulatory bodies.

Regulatory engagement with a consistent strategy, and a clear and defined approach where possible, was deemed important. This would involve defining a strategy throughout clinical development (e.g., matrix to be used at each stage, bridging planned and benefits) leading from Phase I to Phase III. The need of engaging with regulators pre –Phase I vs Phase III must also be considered. There was some discussion around approaching regulators with the view to flagging up the use of a PCS approach. Some groups supported this early approach, whilst others supported using without prior notification, particularly if supported by ICH M10. The role of PCSIG as a potential lobbyist across industry in this regard was considered.

Discussion around data packages also took place. While some participants suggested a partial validation of an assay using ICH M10 as a framework, before approaching regulators with a PCS strategy, others suggested full validation should always be performed. From a bioanalytical perspective, attendees felt generally well covered in terms of regulatory expectations if a PCS strategy was decided upon. In this case, ICHM10 was deemed enough to provide guidance on technical BA validation that meets regulatory expectations. Issues arose when it came to GCP/clinical operations and uncertainty around collection and handling of these samples. Perhaps more support in defining the regulatory hurdles in this area is required.

It was suggested that PCSIG may be able to provide a template/decision tree to collectively engage with regulators in a unified manner, which could refer to programmes/studies where PCS has been applied previously as a use-case. The key is to avoid regulators thinking that this is something new / they have not seen before, and an industry-wide approach felt most appropriate to alleviate this risk.

The power of patient and clinician buy-in was recognised to be strongly persuasive and suggestions to engage with patient advocacy groups around this was made (could be PCSIG, company agnostic or company led).

Summary

The workshop concluded with agreed action points on next steps regarding activities arising out of the workshop discussions, and how to best communicate them with the wider community. This proceedings report is one of these actions, aimed to provide the wider audience with a snapshot of the discussions that took place during the workshop, and which will be used to help draw up a roadmap to guide the incorporation of PCS into multicentre clinical trials. This roadmap will provide a guide to be updated with advancements in processes, knowledge, regulations and trends in PCS. PCSIG is open to feedback and public comments on this initiative and welcomes the active involvement of individuals and organisations. Please write to contact@pcsig.org.

References

[1] European Medicines Agency. ICH.M76.on.bioanalytical.method.validation._Scientific.guideline. 2023. https://www.ema.europa.eu/en/ich-m10-bioanalytical-method-validation-scientific-guideline (accessed 26 June 2024).

About PCSIG

The Patient Centric Sampling Interest Group (PCSIG) is a not-for-profit Community Interest Company, incorporated in the UK. It is a global collaborative collective of individuals and organizations who have a shared interest in promoting patient centric sampling approaches. They are unified by their interest in facilitating the development and implementation of novel sample collection technologies for integration into standard of care.

The group is focused on fostering a broader understanding and future widespread implementation of these technologies and serves as a clearing-house for information that helps support this cause. Furthermore, the group's aim is to become the industry catalyst for innovation, technology transfer and the sharing of best practice between members, leading to better outcomes for these organizations and the end consumers of the technologies developed. This will be accomplished as a collaborative association, which is free to join for individuals and is funded by sponsorship.

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