D2.2. Clinical Operations Best Practices Report

853966 – EU-PEARL

EU Patient-cEntric clinical tRial pLatforms

WP2 - Scientific, Regulatory and Operational Methodology

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Abbreviations

Acronym/Abbreviation	Meaning
AE	Adverse Event
ALS	Amyotrophic Lateral Sclerosis
CAs	Competent Authorities
CCSC	Clinical Candidate Selection Committee
CONSORT	CONsolidated Standards fOr Reporting Trials
CRF	Case report form
CRO	Contract Research Organization
CTFG	Clinical Trials Facilitation Group of EMA
CTR	Clinical Trial Regulation
CTTI	Clinical Trials Transformation Initiative
D	Deliverable
DIAN-TU	Dominantly Inherited Alzheimer Network Trial
DMC	Data Monitoring Committee
DoA	Description of the Action
DSMB	Data and Safety Monitoring Committee
DSUR	Drug Safety Update Report
DSWPs	Disease-specific work packages
EEA	European Economic Area
EC	Ethics committee
EDC	Electronic Data Capture
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
EPAD	European Prevention of Alzheimer's Dementia
EU	European Union
EU-PEARL	EU Patient-cEntric clinical tRial pLatforms
FDA	Food and Drug Administration
GCP	Good clinical practice
HA	Health Authority
ICF	Informed Consent Form

Acronym/Abbreviation	Meaning
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Institutional Ethics Committee
IMI JU	Innovative Medicines Initiative Joint Undertaking
IMP	Investigational medical product
ISAs	Intervention Specific Appendices
IRB	Institutional Review Board
IRP	Integrated Research Platform
IWRS	Integrated Web Response System
MDD	Major Depressive Disorder
MPT	Master Protocol Template
MRCT	Multi-regional clinical trials
MRI	Magnetic Resonance Imaging
NA	Not applicable
NASH	Non-alcoholic steatohepatitis
NCI	National Cancer Institute
NCT	National Clinical Trial
NF	Neurofibromatosis
PMO	Project Management Office
PoC	Proof of Concept
SAE	Serious Adverse Event
SC	Steering Committee
SOPs	Standard Operating Procedures
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
TMF	Trial Master File
TMG	Trial Management Group
UK	United Kingdom
US	United States
WP	Work package

1. Publishable Summary

Clinical operations best practices for planning and conduct of clinical trials have been developed over decades, streamlining operational processes within the quality, ethical, GCP and regulatory frameworks that safeguard patient safety and data integrity. As new complex, innovative designs such as platform trials emerge, these best practices need to be extended to address the new challenges they bring.

In the case of a platform trial with a public-private collaboration and multi-company involvement, a considerable range of new challenges arises: communication/collaboration between stakeholders spanning across public and private sectors, ensuring on-time delivery of tasks, timely issue escalation, decision-making, resource planning, role and responsibility clarity. Along the traditional challenges but in a more complex environment: data collection, patient engagement, patient consent, ethical approval, site management, vendor selection and management, safety monitoring, and supply. These complexities are compounded by having to take into account different sponsor SOPs and processes, the evolving positions of regulatory bodies, and the fluidity of the business models that provide the funding to support the collaboration.

The EU-PEARL consortium aims to address these operational challenges through the creation of standardized frameworks and a clinical operations best practices guidance for the setup and conduct of an Integrated Research Platform (IRP). This early deliverable 'D2.2. Clinical Operations Best Practices Report' - developed within the activities of Work Package 2 'Scientific, Regulatory and Operational Methodology' - is a review of the current landscape to understand which challenges have the most complexity and impact. For this task the team conducted a literature search and website review, and found limited published information so an outreach to current trial teams was conducted.

A standardized way of collecting input was built, a checklist with 9 operational domains was created (see section 12.1 below). We express great gratitude for the trialist teams who were willing and able to take the time to share information. Information from 4 out of 10 approached external teams has been collected to date. We hope to update this document with information from other teams over the life of EU-PEARL.

The outcome indicates the following areas must be prioritized for special attention:

- roles and responsibilities,
- resource planning,
- governance structure,
- sponsorship identification
- vendor selection and management,
- tailored training for all key stakeholders.

Clear communication, transparency and collaboration are important attributes within each of these key areas for successful IRP planning, setup, implementation, oversight and execution.

The EU-PEARL operational best practices framework will be developed iteratively in collaboration with the Disease Specific Work Packages and continued interactions with other trialists. In parallel with the best practice guide, EU-PEARL will also develop a master protocol template that may include aspects of the operational good practices.

2. Introduction

The objectives of EU-PEARL are to enable a transformation of drug development through multi-sponsor, multi-compound, Integrated Research Platforms (IRPs). An IRP is a novel clinical development concept centered around a master protocol trial that can accommodate multi-sourced interventions, using an existing infrastructure of hospitals and federated patient data, and an agreed, optimized regulatory pathway.

A major goal of EU-PEARL is to design a master protocol template for the platform trials in these IRPs, along with operational standards and a set of best practices for planning, implementing, conducting, executing, and reporting on IRPs. For more background around the terminology and definition of master protocols, platform trials, umbrella trials and basket trial designs please refer to the EU-PEARL glossary in EU-PEARL deliverable D2.1.

One of the challenges of IRPs is to create a collaboration amongst stakeholders including sponsor companies, researchers, patients and regulators that is capable of both being adaptive and working effectively in a highly regulated environment.

While platform trials offer the potential to accelerate drug development they do introduce many operational challenges. The operational challenges exist across the entire clinical operational spectrum of trial planning, setup, implementation, oversight and execution. Such challenges include:

- communication and collaboration between stakeholders that span across public and private sectors,
- ensuring on-time delivery of tasks,
- data collection strategy and tools,
- timely issue escalation,
- decision-making,
- resource planning,
- role and responsibility clarity,
- patient engagement,
- and vendor selection, setup, and management.

Furthermore, these complexities are compounded by different sponsor SOPs and processes, interactions with regulatory bodies, and the sometimes fluid funding model for the IRP.

There are many successful platform trials running, but to date, there is limited literature on the operational aspects of these trials. For that reason, work package 2 (WP2, see further detail on this WP in Section 12.3) established a working group to reach out to other platform trial teams to make inventory of the operational hurdles they had to overcome in setting up and running their platform trials.

This document is a summary of the current results of that outreach.

In the next phase of the project this work package will learn from the efforts of the EU-PEARL disease specific work packages (DSWPs), the problems they encounter, the solutions they consider and the solutions they finally adopt. In addition, it will continue to reach out to other ongoing initiatives and trialists to learn from their experiences too. The final deliverable will be a Clinical Operations Best Practices Report for creating IRPs for use by sponsors, research centers, universities, and health

agencies across the public and private sectors for any disease area and hence contribute to the EU-PEARL goal of lowering the threshold to the establishment of IRPs and platform trials (Fig 1).

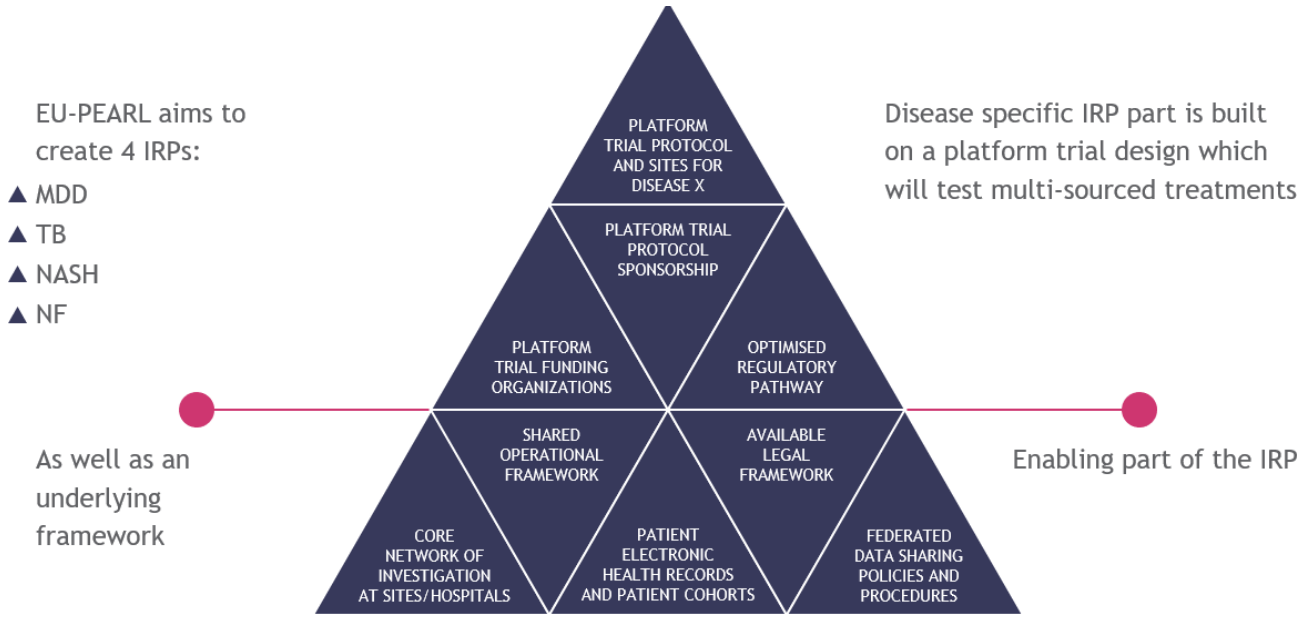

Fig 1 . *Conceptual representation of the IRP and current thinking depicting the place of the operational standards and tools as an enabler to more rapidly and efficiently setup multi-company IRP.*

2.1. Literature review

The results of a thorough literature review for platform trials can be found in EU-PEARL D2.1 Glossary and Scenarios. That review drew upon: "The evolution of master Protocol Clinical Trial Designs - A Systematic Literature Review" by Koenig F. et al., Clinical Therapeutics, 2020 which can be used as an even larger set of references **[1]**.

Of particular relevance to this document were three papers on the experiences of running the STAMPEDE (a multi-arm, multi-stage phase II/III randomized controlled trial in prostate cancer) and FOCUS4 (a multi-arm, multi-stage phase II/III randomized trial in colorectal cancer) platform trials:

- "This is a platform alteration: a trial management perspective on the operational aspects of adaptive and platform and umbrella protocols." by Shiavone F et al., Trials 2019; 20:264 **[2]**
- "Changing platforms without stopping the train: experiences of data management and data management systems when adapting platform protocols by adding and closing comparisons." by Hague D et al., Trials 2019;20:294 **[3]**

- "Mind the gap? The platform trial as a working environment." by Morell L et al., Trials 2019; 20:297 **[4]**

More references for these studies can be found in D2.1.

Topics highlighted by Schiavone et al. include the governing structures for clinical decision making for adding new treatment arms (comparisons), protocol development and review, continuous biomarker development, funding, budgeting, contracting out, and drug supply.

Recommendations with regards to the database setup and case report form and their change management is described in detail by Hague et al. The authors cautioned about the volume of data and the complexity of the adaptive nature and longevity of these platform trials.

Resource demands were highlighted by Morrel et al. **[4]**, pointing out the need to appropriately account for the challenges operational staff encounter when running a platform trial, over and above those encountered on a conventional trial.

Ethics and regulatory assessment implications of the protocol and appendices structure have also been highlighted in the upcoming European Clinical Trial Regulation (CTR) **[5]** and the "CTFG Recommendation paper" **[6]**. There are two regulatory models available in EEA: complex clinical trials with sub-protocols can be submitted either as one trial or as separate trials. It is anticipated that the rollout of the Clinical Trial Regulation with the implementation of the Clinical Trials Information System will only allow a substantial amendment to be submitted when the previous substantial amendment has been approved.

A parallel initiative on master protocols was launched in the US last year. The Clinical Trials Transformation Initiative (CTTI), a public-private partnership co-founded by Duke University and the Food and Drug Administration (FDA). An expert meeting on Master Protocols was held in April 2020 and the materials are available on the CTTI website, but they have not at the time of writing published any recommendations on Master Protocol trials. The CTTI is also working on other areas relevant to EU-PEARL, such as patient centricity in trials. EU-PEARL will leverage key insights and recommendations from CTTI.

2.2. Websites review

The established websites and published data for the following platform trials were reviewed as a source of possible supplementary information for the contents of this report:

- DIAN-TU
- EPAD
- STAMPEDE / FOCUS4
- I-SPY 2
- LUNG-MAP
- HEALEY-ALS

A summary of the relevant highlights from them is presented below.

2.3. Outreach to Trialists

In order to supplement the available data from literature and web, we reached out to the global community of clinical trialists with experience in the start-up and conduct of platform trials. A structured approach was created to capture the experiences of the various groups in a systematic way (as detailed in Section 5). Trialists were asked to share their experience of the operational differences between a platform trial and a conventional standalone trial, and provide a ranking of complexity. Since 'clinical operations' cover a wide range of topics, we were interested in learning which were particularly important for platform trials and master protocols.

3. Summary of Platform Trial Literature on Clinical Operations

The literature review is limited to the 3 papers describing the lessons learned from 2 early platform trials in the UK: STAMPEDE and FOCUS4 **[2]**, **[3]**, **[4]**. They find that the primary novel challenge for platform trials is handling the addition of new interventions [2] both in the structure of the protocol and the operational issues surrounding it.

Both STAMPEDE and FOCUS4 agreed to a process for assessing new interventions and whether they should be considered for the trial. This was based on a "new interventions" group responsible for encouraging, vetting and facilitating new interventions for the trial with documented criteria for assessing new comparisons **[2]**:

1. Requires sound scientific rationale
2. Preliminary evidence for mechanism of action or activity
3. Different from the other therapies in trial
4. Clear path for trial results to translate into improved care or impact on public health
5. Investigator enthusiasm
6. Sufficient sites can participate in administering the comparison
7. Successful independent peer review

[Note that depending on the trial's circumstances this group's activities can lie anywhere on the spectrum between "gate keepers" for the trial – ensuring that new interventions are of sufficient worth to be included – to "a salesforce" for the trial – trying to locate and convince potential providers of a new intervention to participate in the trial.]

The candidate interventions were presented to the Trial Steering Committee group to agree the prioritization of new interventions and decide on the timing of the interventions' introduction into the trial. To ensure timely introduction of a new intervention, it is necessary to hold early discussions of new interventions with funders, regulators, sites and the Trial Management Group.

There are intrinsic operational challenges whenever a new intervention is added: firstly, possible change in risks in the trial, secondly procurement, manufacturing and packaging and finally operational changes to accommodate it.

In STAMPEDE and FOCUS4, each new intervention was scientifically peer reviewed for its suitability

and impact on the current trial. A group from the Steering Committee and funders assessed the financial viability of adding the new intervention.

It is recommended that standard templates for contract negotiation are developed to avoid delays in introducing new interventions, particularly novel agents (IMPs). Packaging, labelling and supplies to sites need to be agreed, and if this process is too lengthy, current interventions in the trial may have the required number of randomized patients complete their participation in the trial before the new intervention can be added to the trial and the randomization adapted accordingly to include the new treatment. A trial team needs to decide whether to establish a central supply system that all interventions use, or for each intervention to have its own supply system. Both choices have their potential difficulties, a central approach may have to adapt to a new supply arrangement for a new intervention (e.g. provide cold storage), whereas a per intervention approach has more players, will be more work to coordinate, and has the potential overhead of adding a new supplier every time a new intervention is added.

There should be a Trial Management Group (TMG) responsible for day-to-day running of the trial – this should include an overall chief investigator and a per intervention arm chief investigator. The TMG charter will need updating for each new intervention – though using standard templates **[2]**. In addition to these, the TMG should include patient and public representatives "to represent the patients voice" **[2]**. In STAMPEDE as well as the intervention chief investigator, they introduced the role of Co-chief investigator for an intervention "responsible for leading a dedicated subgroup developing the research question underpinning a new comparison, facilitating its introduction and championing it across the clinical community". In summary "A strong, diverse and collaborative TMG is recognized as an important asset for these protocols [STAMPEDE & FOCUS4]".

The STAMPEDE and FOCUS4 protocols were different in structure. STAMPEDE had a single protocol with amendments while FOCUS4 learned from the STAMPEDE experience, using the modular "master protocol" and intervention specific appendices (ISAs). Their difficulties encountered with the master protocol approach: when intervention specific changes were introduced it could be difficult to maintain overall consistency when different parts were updated at different times, and when Ethics Committees (ECs) and Competent Authorities (CAs) failed to understand that it was a single protocol. This latter problem should abate as these stakeholders become more accustomed to seeing protocols with a Master Protocol structure.

Due to the novelty of master protocols at the time, there were major re-writes of the FOCUS4 protocol before it was accepted because ECs and CAs did not recognize the master protocol and its appendices as a single protocol. Terminology was important here, it is noted that new interventions should not be referred to as "new trials" or "sub-trials" **[2]** – FOCUS4 settled on the term "comparison", whereas EU-PEARL is using the term "intervention".

Site activation is discussed in detail **[2]** and not summarized here, once STAMPEDE was running, having taken 5 years for 80 sites to have each site randomize at least 1 patient, when new interventions were added that milestone was reached in 3-4 months.

As these were ground breaking trials, it was challenging to adapt some important tools to provide the additional flexibility required for a platform trial. In particular, **[3]** discusses the difficulties of accommodating new treatments in the Central Database and updating the Clinical Report Forms (CRFs). It needs to be possible to add or drop an intervention while continuing data collection on the other interventions as normal **[3]**. New interventions may have different biomarkers, different tests

and different AE monitoring requiring database updates to accommodate new fields and tables. It is difficult to pre-plan for these and both STAMPEDE and FOCUS4 resorted to database splitting to ease problems with accommodating changes and increasing data volumes, at the cost of a more complex process required to extract data reports.

The third paper from the STAMPEDE and FOCUS4 trials **[4]** focused on the adaptive trial as a working environment. A simple theme (corroborated by EU-PEARLs trialist outreach) was that the central resources required to achieve the practical efficiencies were greater than expected. This led to a high workload, and a sense of not being in control.

In these non-profit, multi-company settings, promised contributions of drugs and distribution facilities from commercial partners were always contingent on commercial realities. This made the timing of their availability hard to predict and hence plan for.

Those working on the trial believed that it offered good career opportunities, with fast paced challenging work, and the opportunity to experience all stages of a trial much more quickly than in a conventional trial. There were problems. There was a conflict between day-to-day tasks and 'high profile' work such as performing interim analyses and introducing or closing interventions. The continuing nature of the trial implied that the pace was steady, not providing usual periods when normal work could pause and teams could celebrate successes. The longevity and scale of the trial meant that there was a continuous demand to train new staff.

When staffing the senior roles in the trial, it needs to be recognized that the head of the trial will have a role equivalent to that of the CEO of a medium-sized company, and that the trial is likely to be high profile – resulting in high loyalty, high stress and jealousy from those not involved.

Biomarker driven trials (personalized medicine) can lead to a closer relationship between patients and trialists. Having patients in groups for which there is no effective therapy can be stressful for staff, and care for researchers well-being needs to be planned, e.g. twice-yearly meetings with presentations by nurses of patient journeys **[4]**.

4. Summary Website Review

DIAN-TU: As described by Mills S.M., Mallmann J. et al. **[7],** the DIAN-TU trial has academics (Washington University) serving as a sponsor for a platform trial with multiple drugs and multiple pharmaceutical partners. It is a Phase II/III randomized, placebo-controlled study into Alzheimer's. The trial addresses a widely distributed rare population (genetically pre-disposed to get Alzheimer's) with intensive safety and biomarker assessments. Significant aspects of the trial management were home health research delivery, safety magnetic resonance imaging (MRIs) at remote locations, monitoring clinical and cognitive measures, and regulatory management involving multiple pharmaceutical sponsors. DIAN-TU required diverse and committed collaborations between academia, patient advocacy groups, participant populations, pharmaceutical companies and regulatory agencies.

EPAD: The EPAD Platform utilises the power of adaptive design and Bayesian statistics to efficiently deliver early, accurate, results in a phase II, PoC, randomized multi-arm, multi-site trial into pre-clinical and prodromal Alzheimer's. A single academic entity (University of Edinburgh) is the sponsor of the EPAD PoC trial, and takes full responsibility for ensuring compliance across the project, with accountability for auditing/quality control, site training and coordination (which was outsourced to a CRO), and medical governance of the study. The Clinical Candidate Selection Committee (CCSC) evaluates all nominated therapies for the trial, novel small molecules, repurposed molecules, biologics, vaccines and combinations of these can be considered.

STAMPEDE/FOCUS 4: The STAMPEDE trial has added, closed and adapted new research comparisons during the course of the study and completed recruitment into six of them. FOCUS4 has closed one research comparison following pre-planned interim analysis (lack of benefit) and added one new research comparison, with a number of further comparisons in the pipeline. See section 2.1 and 3 above for literature covering operational aspects from these trials, and D2.1 for other references.

I-SPY 2: The I-SPY 2 study was one of the first platform trial. It is a multi-arm open label, adaptively randomized, phase II study into neo-adjuvant breast cancer. I-SPY 2 is a collaborative effort among academic investigators, the National Cancer Institute (NCI), the US FDA, and the pharmaceutical and biotechnology industries under the auspices of the Foundation for the National Institutes of Health Biomarkers Consortium. It has been noted **[8]** that a) variability across Informed Consent Form (ICFs) resulted in variability in the time to approval by Institutional review boards (IRBs), b) delays also resulted from the lack of a centralized IRB, c) it would have been better to separate data required for interim analyses from the rest so its collection and cleaning could have been prioritised.

LUNG-MAP: The Lung-MAP trial is a multi-drug, multi-sub-study, biomarker-driven randomised phase II/III trial in squamous cell lung cancer. Subjects are tested only once according to a "master protocol". They are then assigned to one of multiple trial sub-studies (each testing a different drug). The trial involves a private-public partnership with multiple stakeholders and therefore inherently very complex. A link to an investigator blog indicated that the setup of the original study required a great deal of planning and organization with selection of the platform for biomarker testing, negotiation of the trial design with the NCI and FDA, negotiation of the trial design with the 5 involved pharma companies, and budgets and contracts with all participating organizations.

HEALEY ALS: The HEALEY ALS Platform Trial is a collaborative effort between a research hospital (Massachusetts General), philanthropic donations (Sean M. Healey & AMG, TackleALS, ALS Association, ALS Finding a Cure and ALS One) and pharmaceutical companies. This is the first Amyotrophic Lateral Sclerosis (ALS) platform trial, accelerating the path to new ALS therapies by testing multiple treatments at once, intending to reduce the cost of research by 30%, decrease the trial time by 50%, and increase patient participation by 67%. These efficiencies will come from shared infrastructure, common data and sample collection processes, and central governance within the platform trial.

5. Method Used in Outreach to Trialists

Platform trials and associated stakeholders were collected via literature search and from knowledge within the EU-PEARL project. In total 10 trialist have been contacted and 4 responded.

The overall strategy was to prepare a detailed questionnaire and request key stakeholders to complete the questionnaire with the option to conduct an interview if deemed necessary. The questionnaire (ANNEX I. Questionnaire) was developed by the cross-functional WP2 team and covered key categories across the operational spectrum. The questionnaire had the following three parts:

1. **Mandatory Questions:** focused on critical topics such as sponsorship and delegation of responsibilities
    - Sponsorship in particular is a complex focus area for platform trials considering the plethora of regulatory responsibilities as defined in ICH GCP and Health Authority (HA), Institutional Review Boards (IRB) and Ethics Committee (EC) regulations and requirements.
2. **Tiering exercise:** Ranking categories from 10 (most important/challenging) to 1 (least important/challenging) when considering platform trials setup, design, implementation and execution in comparison to a standalone trial. The following categories were provided to questionnaire participants:
    - Protocol Development & Medical Writing
    - Regulatory & Ethics
    - Study Start Up
    - Legal
    - Clinical Supplies/Ancillary Supplies
    - Team Structure/Contingency Planning
    - Interactive Web Response System (IWRS)/Data Management/Programming/ Statistics/Safety
    - Clinical Monitoring/Quality Management
    - Study Closeout
    - Organizational/Systems
3. **Top 3 Categories – sub questions:** Additional detailed questions for the top 3 rated categories to allow respondents to take a deeper dive into the areas they deemed most important.

Once the questionnaire was completed, the WP2 team members had the option to request and conduct a semi-structured interview with key stakeholders to obtain additional information. Interview guidance as well as an interview tool (ANNEX II. Interview guide) were provided to ensure a consistent approach to conduct the interview including a core team member as a scribe. The following guidance was provided:

- Overall completeness of the questionnaire
- Responses to mandatory or categorical questions
- Anticipated benefit of additional 1:1 time with trial contact, etc.

The WP2 data collection instruments were the completed questionnaires and interview tool (where applicable), with electronic notes transcribed by the recorder during the interview.

6. Results of the Outreach to Trialists

Ten trial teams were contacted in early February 2020.

The Survey Questionnaire (Section 12.1) was created by the team of public and private trial management experts within EU-PEARL WP2. It enlists 96 critical domains of expertise and decision-making required when setting up a clinical trial, and can be used as a check list by the EU-PEARL and trialist community as a point of reference. New insights following the roll out of the CTTI initiative output will be taken into consideration as well.

For the purpose of issuing this first report on operational best practices on time, the timeframe for response was short, only 4 weeks. Of these, four trial teams completed the questionnaire. All trials are multi-company platform trials, except for Platform Trial 3, which is a single company platform trial.

6.1. Summary of Mandatory Questions

Recipients were asked to answer and comment on these following mandatory questions. Note here we use the term “sponsor” to refer to the organization initiating and running the platform trial. Below each question in this section is a summary of respondent data:

1. ***Platform Trial sponsorship*** *- what entity is the formal sponsor and why was this entity chosen? (e.g. a hospital, a non-profit entity, a pharma company etc.)?*
    - The sponsor of the platform trial ranged from the public and private sectors including universities, foundations, and pharmaceutical companies. Several main determining factors in trial sponsorship included: experience, resources, infrastructure, access to sites and to the desired patient population.

2. *Additionally, describe* ***overall platform governance****? Did any company take a lead position and/or how were decisions made?*
    - In general, the platform trials had an established leadership team or executive core team serving in a governance capacity with overall responsibility, accountability and oversight. In collaboration with the governance team, and reporting in to them, are work package teams (WP) and per treatment (”appendix”) steering committees (SC) which have clear role and responsibilities for delivery of platform trials or treatment specific tasks. Each WP and SC had decision-making abilities and would escalate issues or key items that required governance input or support.

3. ***Delegations of responsibilities*** *(what was delegated to and from the formal sponsor, to whom and why).*
    - Medical writing/protocol development was managed by the sponsor in all these trials, as well as site payments. In some cases, monitoring and safety pharmacovigilance

activities were managed by the sponsor and in others they were delegated to other vendors (and/or participating biopharma companies). Activities such as submission to Health Authorities (HA) and Ethics Committees (EC), contracting/clinical trial agreement and data management were either managed by sponsor only or by sponsor and other vendors.

4. *How was the **trial funding** organized for setup? And how was funding organized when the platform was ongoing? And when products leave and enter the platform trial?*
    - In some trials, funding and financing was a complex process where the initial contract took almost 2 years to execute due to legal issues and the need for granular breakdown of the proposed budget. There are different processes for the funding and financing setup. Either the platform trials are fully covered by the pharma company related budget, or by industry partners that participated in the trial, while their product is in the platform (covering the costs for overall trial management and operations and providing their investigational product at no cost), or by a funding body such as IMI or a charity.

5. *What feedback was provided from the **participating companies** on **what interested/ motivated them to join the platform**? What were the anticipated or **actual benefits** that were realized?*
    - In most cases, the participating sites or pharma/industry partners have shown the enthusiasm and willingness to participate in the program where they have an ongoing drug development program in the respective disease area. Using the platform trial to test their investigational products in a specific disease area might lower the cost burden. In one trial, during start-up phase, sites were very eager and motivated to participate, however long IRB/IEC and Health Authority approval/rejection process and questions were experienced/received. In general, no formal feedback has been received yet from the industry partners about anticipated or actual benefits.

6.2. Ranking categories

Ranking categories from 10 (most important/challenging) to 1 (least important/challenging) when considering platform trials setup/design, implementation and execution in comparison to a standalone trial. Recipients could rate the top 3 categories.

The summary of key responses under **Top 3 Categories** by category including interview details is provided:

6.2.1. Platform Trial 1

Setup summary: A University was the sponsor of this trial. Governance was organized by internal and executive committees along with 8 work packages tasked to conduct platform work.

A Platform Study Working Group was established as sub-team to the work package designed to plan, implement and monitor all aspects of the studies including the platform trial. It included members from trial sponsor, pharmaceutical partners, plus the CRO responsible for study start-up and monitoring. A Platform Trial Planning Committee was established from the beginning, where sponsor,

pharmaceutical entities, CROs and vendors were present. Vendors reported to the study sponsor with collaboration of the pharmaceutical companies.

An external project management team collaborated with platform project executive teams, work packages, and IMI JU.

Key differences between a platform and standalone trial: Platform trials are more complex because the participating companies' SOPs differ, and vendors selected for the platform might not be preferred partners to all the participating sponsors. Overall the sponsor SOPs were used, but for the appendices where the IMP is to be provided by pharmaceutical companies, their SOPs are to be followed. The huge number of stakeholders delayed the decision-making processes.

Best practices, lessons learned: From each entity, appropriate persons with same level of decision-making authority must be assigned and they should attend the appropriate meetings. Ensure that the sponsor can meet timelines and has adequate resources/infrastructure to conduct the study as planned. Resources (at the sponsor side) to setup the trial have been underestimated, due to the complexity of a platform study, the resource need is more demanding than for a standalone study. There should be a sufficiently empowered core decision-making body, and it should escalate the key decisions to all stakeholders in a timely manner. Collaboration and flexibility are critical. Harmonization of processes needs to be done early when setting up the trial to support smooth implementation.

6.2.2. Platform Trial 2

Setup summary: A University was the sponsor and responsible for vendor and CRO selection and management and oversight. The setup took much longer than for a standalone study.

Key differences between a platform and standalone trial: The length of the process is a significant difference. Contract negotiation and external funding made it even more difficult. Flow of communication was challenging due to multiple vendors and internal/external stakeholders. It took more time to get updates and metrics in real time, there was a lack of clarity in signature processes, and delay experienced in uploading documents to the Trial Master File (TMF).

Best practices, lessons learned: There should be adequate resources available for design and setup, as platform setup is more demanding than a standalone study. Clear roles and responsibilities are key for the delivery and smooth collaboration. At the kick-off meeting, or even before, a core team should be established to drive the study. The participating companies should have SOPs on how to work in a platform trial setting. The site and vendor contracts should be negotiated at a platform level using platform level templates. Frequent meetings are needed to ensure consistent expectations, monitor progress, and address issues. Involving the appropriate parties in reviews and decision making is critical for compliance purposes as well. Templates used for communications should be prepared and all external communications should be reviewed by appropriate stakeholders before release. Alignment on the expectations at the beginning is key.

6.2.3. Platform Trial 3

Setup summary: A Pharma company was the sponsor and responsible for all setup activities, including the funding/budget related ones. Splitting of the protocol into two parts (master and

appendices) facilitated future changes of the platform protocol structure. The study included 4 arms and 6 different investigational products (indication: breast cancer, Phase Ib study). Producing one single master Informed Consent Form (ICF) for all study arms did not take much longer than the usual process. Guidelines released by the FDA on platform trials (available on www.FDA.gov) were reviewed and discussed by the study team.

Key differences between platform and standalone trial: The main difference was to balance specific requirements for each arm, with ensuring consistency across all of them and to anticipate potential operational challenges while writing the protocol. Since the study involved 6 different investigational products, more resources were required for protocol development and more review cycles were needed. But overall the timelines for protocol writing were similar to a 'normal' study. It was a challenge to make the ICF specific and complete enough without overloading the patient with repetitive information.

Best practices, lessons learned: During protocol and ICF development, feedback was frequently requested from several sponsor's country representatives and this was more important than in usual protocol setup activities. It is necessary to consider the potential impact of each protocol section on site or vendor management. A well-defined protocol structure was very important to the study team and was discussed several times before the actual protocol writing. Taking time to design a proper protocol structure from the beginning will help in an operational point of view when amendments come. There is no HA feedback that can be shared at the moment.

6.2.4. Platform Trial 4

Setup summary: A research center was established with a philanthropic donation with the individual physicians as leaders and regulatory sponsor for the trial. The leadership team consisted of physicians, scientists, clinical research professionals and patient representatives. The "Therapy Evaluation Committee" reviewed applications from potential collaborators and recommended which IMPs should be considered for inclusion. The team developed an in-house IWRS system that interfaced with the central pharmacy to manage drug supply. A vendor was contracted to convene and manage their data and safety monitoring committee (DSMB). Outside consultants were contracted to manage interim analysis and lead the Independent Statistical Analysis Committee that advises the DSMB. A package of standard CRF was developed for the master protocol with unique additional forms developed for each regimen. Developing safety reporting process required discussions and involvement of many individuals (medical monitor, industry partner representatives, trial managers) and different steps required for SAE/SUSAR/DSUR reporting.

Key differences between platform and standalone trial: The complexity of the setup phase and involvement/need for collaboration with many partners.

Best practices, lessons learned: It is critical to engage with all stakeholders from the initial stages of project development and maintain an open and ongoing dialogue with all parties including industry, regulators, and patients. In diseases where an established clinical trial network and strong patient advocacy already exist, these partnerships can facilitate the rapid and efficient establishment of the platform.

6.3. Summary of the results

From the feedback there is a clear pattern in the responses from representatives of existing platform trials. Whilst individual trial processes such as data management, site management and drug supply will be more complex in a platform trial than in a single sponsor single investigational treatment trial, none of the respondents described this as unexpectedly challenging.

The significant challenges instead all come from the increased scale of the operation and the larger number of stakeholders. In particular, these following topics were markedly more complex and time and other resource consuming:

- **Study setup:**
  - Complexity of many procedures in the setup phase: key documents development, study systems organization, vendor selection.
  - Length of the process and resources required
  - Contract negotiations
  - External funding procedures
- **Definition of roles and responsibilities:**
  - Involvement of many different parties
  - Governance organisation
- **Project communication and management of communication:** challenging due to multiple vendors and internal/external stakeholders involved

7. Discussion

Ten trialists were contacted for interviews and questionnaires and responses received from four of them.

The analysis of the survey responses and interviews and the literature review highlighted the following key clinical operations areas:

- roles and responsibilities in the platform trial setup,
- resource planning and adaptation,
- platform trial governance including decision making and oversight,
- vendor selection, management and oversight,
- training.

This is consistent with what has been made available in the few reports which have been published **[1], [2], [3]** about the planning and conduct of master protocols and platform trials.

The main highlights for each key area, and other relevant items identified by the team, are described below area by area.

7.1. Roles and responsibilities in the platform trial

The need for clear roles and responsibilities was highlighted by several trialists. Even in the single company platform trial, it was significantly more time consuming to align with the different program teams that contributed to the protocol. In Platform Trial 2, which was a multi-company platform trial with 40 vendors, it was described as having “too many cooks in the kitchen”. As a result, more time needs to be factored in for platform trial setup and protocol writing. This would also apply to other trial-related documents, such as the informed consent form.

The planned EU-PEARL template for the master protocol, aims to shorten the time needed for inter-company alignment.

The interviewees recommended creating work packages with clear missions and responsibilities and escalation processes to the governance bodies. A core team in charge of oversight, communication and issue escalation/decision-making was recommended as well. Clarity of task delegation is important, especially when partner entities are less experienced in clinical operations.

To address these issues the EU-PEARL deliverable Clinical Operations Best Practices (D2.10) will need to contain advice on:

- the flow of communication,
- the organization of the core team and work packages,
- the writing of the master protocol based on the EU-PEARL Master Protocol template
- running the trial efficiently despite the number of stakeholders.

7.2. Resource planning and adaptation

The resources required for setting up and running platform trials were underestimated in all multi-company platform trials. Recommendations on planning and managing the resources will be integrated in the Final Report on Clinical Operations Best Practices (D2.10).

This finding is supported by the report from Hague et al. **[3]** where they specifically pointed out the challenges for data management related to adaptive designs and platform protocols. They highlight the resourcing peak the data management team will face when opening new comparison arms, while continuing to safeguard patient safety and the data integrity of the ongoing trial. Some of the challenges reported are shared with other large trials that run for a long time, but the size and longevity of the platform trials might be even harder to predict.

The EU-PEARL deliverable Clinical Operations Best Practices (D2.10) will need to contain advice on the ensuring sufficient resources for platform trial setup and ongoing support – in particular around opening up new arms.

7.3. Platform trial governance, decision-making and oversight

Trialists identified governance as a key area for platform trials. For example, the Platform Trial 1 involved 36 partners including academia and pharmaceutical industry (EFPIA). Platform Trial 1 stressed that it was necessary to ensure that appropriate representatives were present from each entity, with appropriate decision-making authority, and that an effective governance structure is

imperative to ensure successful collaboration, decision-making, escalation and oversight.

Governance structures are very important for platform trials and therefore should be addressed within EU-PEARL, either in WP1 or in the Clinical Operations Best Practices (D2.10).

7.4. Vendor selection, management and oversight

Vendor qualification and oversight is mandatory in the current GCP requirements and in the applicable quality standards, to ensure patient safety and data integrity. One trialist mentioned that vendor setup is more complex in platform trials, considering that selected vendors may not be preferred/qualified vendors for all participating pharmaceutical companies. In Platform Trial 2, 40 vendors had to be contracted, which is significantly more than in standalone trials. Also, the Platform Trial 1 mentioned the complexity of vendor selection and aligning between different sponsor SOPs (particularly pharmacovigilance).

The additional time required for vendor setup needs to be factored in during study setup. However, it was also mentioned that a big gain is the time saving when new arms are added, as the infrastructure is already setup.

The EU-PEARL deliverable Clinical Operations Best Practices (D2.10) will need to contain advice on vendor selection, leveraging from available best practices reports. One possibility will be to develop a decision tree template to be implemented and approved by the core team/appropriate governance body for the selection of the vendors.

7.5. Training

Although training was not mentioned during the interviews its importance and role is discussed in **[2]** for sites, trial management and staff. A recent round table discussion on ‘Ethical challenges in adaptive and platform trials,’ coordinated by the MRCT Center of Brigham and Women’s Hospital and Harvard University, also identified the need to timely consider training of Ethics Committees as they will be requested to review and approve these novel master protocol, appendices and ICFs.

The EU-PEARL deliverable Clinical Operations Best Practices (D2.10) will need to contain advice on the specific platform trial training needs.

7.6. Limitations

The scope of this clinical operations survey also included areas such as Pharmacovigilance, Data Management and Clinical Supplies. However, our principle contacts with existing trials was with the trial management. So, the depth of information received related to these technical areas was limited.

These will need to be explored for the final version of the EU-PEARL deliverable Clinical Operations Best Practices (D2.10).

8. Conclusion

Overall, the input prioritizes the following areas for the WP2 team working on the clinical operations best practices:

- clarity on roles and responsibilities,
- effective resource planning,
- a sound governance structure,
- strategic approach to vendor management and
- robust training for all key stakeholders.

When writing the EU-PEARL Description of the Action (DoA), these topics had not been identified at all, let alone as priorities, they will be added to the proposed list of contents.

It needs to be a primary aim of EU-PEARL as it plans the IRP framework and the EU-PEARL proposed entity, which will eventually host the operational framework, that the lessons learned in the process can be captured, and some best practices identified, so that the complexity associated with the setup, start up and conduct of platform trials can be mitigated.

If all of the above is successfully done, it will enable the future teams which need to setup a new platform trial or IRP to focus on the trial protocol specific content, and will help these teams to avoid losing valuable time and reinvention of enabling infrastructure for multi-sourced, multi-company platform trials.

9. Next Steps

The main deliverables of EU-PEARL will be reusable standards and frameworks for teams planning to setup IRPs using master protocols. Advice created in a vacuum is likely to be of little long-term worth. The value of the deliverables will depend on being able to collect best practices from existing trials as their experience grows.

This activity will be largely dependent on the willingness of other trial teams to share and of the EU-PEARL team to establish the contacts at the expert's level required. The current thinking is to prioritize the domains according to outcome of this first inventory (D2.2).

There is a need to vet this priority ranking with the EU-PEARL DSWPs (WP4, 5, 6, 7) to ensure the relevance of the deliverables within EU-PEARL, and to collect input on the best practices from DSWPs. In addition, practices on site selection and qualification will need to be discussed with WP3.

A very important deliverable for WP2 is the creation of a Master Protocol Template and guidance on the associated Appendices (D2.6). The way in which a protocol is setup has major implications for critical drivers of clinical operations and trial management complexities. It is recognized that the new EU-CTR will have a profound impact on the choices to be made for the protocol setup and hence significant impact on operations. EU-PEARL will work under the assumption that the EU-CTR will be in effect at the end of the project.

The determination of a trial's sponsorship has a significant impact on operational planning and setup. The sponsorship concepts will be further worked out in WP1 as part of the creation of the EU-PEARL

entity, which is expected to be a great enabler for the DSWPs and future trialists. Eventually a Master Protocol Template document will host a number of purely operational paragraphs. Although these paragraphs will be summarizing guidance at a higher level, we will need to ensure close collaboration between the groups working to summarize best practices and the master protocol template.

In summary, to complete D2.10, the final Clinical Operations Best Practices Report, the team will:

- Continue with the survey and structured interviews and approach the collection of experience and best practices in a structured manner.
- Actively share outside EU-PEARL's activities on (clinical) operational framework even if incomplete, to engage in productive collaborations (e.g. CTTI) to avoid duplication of efforts and obtain more input.
- Break up into smaller teams working on very specific operational fields of expertise (domains).
- Prioritize the domains and ensure the interdependencies are transparent and appropriate for the internal EU-PEARL stakeholders.
- Need to make decisions on the desired format of the clinical operations best practice guide.

10. References

[1] Koenig F, et al.: “The evolution of master Protocol Clinical Trial Designs - A Systematic Literature Review”. Clinical Therapeutics (In Press) 2020.

[2] Shiavone F et al.: “This is a platform alteration: a trial management perspective on the operational aspects of adaptive and platform and umbrella protocols.” Trials 2019; 20:264

[3] Hague D et al.: “Changing platforms without stopping the train: experiences of data management and data management systems when adapting platform protocols by adding and closing comparisons.” Trials 2019; 20:294

[4] Morell L et al.: “Mind the gap? The platform trial as a working environment.” Trials 2019; 20:297

[5] CTR: REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC

[6] CTFG “Recommendation paper on the initiation and conduct of complex clinical trials” 12 Feb 2019”

[7] Mills S.M., Mallmann J. et al.: “Preclinical trials in autosomal dominant AD: Implementation of the DIAN-TU trial”, Rev Neurol (Paris). 2013 Oct; 169(10): 10.1016/j.neurol.2013.07.017.

[8] Laura Esserman “If I had to start the I-SPY-2 Trial over again, what would I do differently” Available on-line here.

11. Definitions

- **Participants** of the EU-PEARL Consortium are referred to herein according to the following codes:
  1. VHIR. Fundació Hospital Universitari Vall d´Hebron – Institut de Recerca
  2. EATRIS. EATRIS ERIC
  3. SYNAPSE. Synapse Research Management Partners S.L. Termination on May 31st, 2020 (Month 7 of the project).
  4. MUW. Medizinische Universitaet Wien
  5. KU Leuven. Katholieke Universiteit Leuven
  6. KCL. King's College London
  7. USR. Università Vita-Salute San Raffaele
  8. EMC. Erasmus Universitair Medisch Centrum Rotterdam
  9. LMU. Ludwig-Maximilians-Universitaet Muenchen,
  10. Charité. Charité - Universitaetsmedizin Berlin
  11. AP-HP. Assistance Publique - Hôpitaux de Paris
  12. CUSTODIX. Custodix NV
  13. i~HD. The European Institute for Innovation through Health Data
  14. BERRY. Berry Consultants LLP
  15. ECRIN. European Clinical Research Infrastructure Network
  16. EPF. Forum Européen des Patients
  17. UNEW. University of Newcastle upon Tyne
  18. EUROSCAN. EUROSCAN International Network e.V.
  19. PEI. Bundesinstitut für Impfstoffe und biomedizinische Arzneimittel, Paul-Ehrlich-Institut
  20. UOXF. The Chancellor, Masters and Scholars of the University of Oxford
  21. UMIL. Università degli Studi di Milano
  22. DocuMental. DocuMental OU
  23. UOM. The University of Manchester
  24. Janssen. Janssen Pharmaceutica NV
  25. Novartis. Novartis Pharma AG
  26. Allergan. Allergan Limited
  27. AZ. Astra Zeneca AB
  28. Novo Nordisk. Novo Nordisk A/S
  29. Otsuka. Otsuka Novel Products GmbH
  30. Pfizer. Pfizer Limited
  31. Sanofi. Sanofi-Aventis Recherche & Developpement
  32. Servier. Institut de Recherches Internationales Servier
  33. Teva. Teva Pharmaceutical Industries Limited
  34. CTF. Children's Tumor Foundation
  35. SpringWorks. SpringWorks Therapeutics INC
  36. TB Alliance. Global Alliance for TB Drug Development Non-Profit Organisation
  37. TEAM-IT. TEAM - IT RESEARCH SL (Start date: May 01st, 2020).

- **Grant Agreement**. (Including its annexes and any amendments) The agreement signed between the beneficiaries of the action and the IMI2 JU for the undertaking of the EU-PEARL project (Grant Agreement No. 853966).
- **Project**. The sum of all activities carried out in the framework of the Grant Agreement.
- **Work plan**. Schedule of tasks, deliverables, efforts, dates and responsibilities corresponding to the work to be carried out, as specified in Part B; 3.1 to the Grant Agreement.
- **Consortium**. The EU-PEARL Consortium, comprising the above-mentioned legal entities.
- **Consortium Agreement**. Agreement concluded amongst EU-PEARL participants for the implementation of the Grant Agreement. The agreement shall not affect the parties' obligations to the Community and/or to one another arising from the Grant Agreement.

12. ANNEXES

12.1. ANNEX I. Questionnaire

Participants to be routed to first complete mandatory questions and then complete questions for only top 3 based on tiering.

Instructions: You will be requested to complete five questions that will be requested of all participants followed by questions for your top 3 categories based on an exercise. We thank you in advance for your time, effort and support.

<table>
<tr><th>Question</th><th>Answer</th><th>NA</th></tr>
<tr><td colspan="3">Mandatory questions</td></tr>
<tr><td>1. Platform Trial Sponsorship - what entity is the formal Sponsor and why was this entity chosen? (eg a hospital, a non-profit entity, a pharma company etc.)?</td><td></td><td></td></tr>
<tr><td>2. Additionally, describe overall Platform governance? Did any company take a lead position and/or how were decisions made?</td><td></td><td></td></tr>
<tr><td>3. Delegations of Responsibilities (what was delegated to and from the formal Sponsor, to whom and why).</td><td>Tickboxes (multiple ticks possible for each row)
<table>
<tr><th></th><th>Sponsor</th><th>Participating biopharmaceutical companies</th><th>Other vendors</th></tr>
<tr><td>Protocol Development & Medical Writing</td><td></td><td>x</td><td></td></tr>
<tr><td>Monitoring</td><td></td><td></td><td>x</td></tr>
<tr><td>Safety & Pharmacovigilance</td><td>x</td><td>x</td><td>x</td></tr>
<tr><td>Clinical Trial supplies</td><td>x</td><td></td><td></td></tr>
<tr><td>Submissions to Health Authorities</td><td>x</td><td>x</td><td></td></tr>
<tr><td>Submissions to Ethics Committees / Institutional Review Boards</td><td>x</td><td>x</td><td></td></tr>
<tr><td>Site Contracting / Clinical Trial Agreements</td><td></td><td></td><td>x</td></tr>
<tr><td>Site Payments</td><td></td><td></td><td>x</td></tr>
<tr><td>Data Management</td><td></td><td>x</td><td></td></tr>
</table></td><td></td></tr>
</table>

4. How was the trial funding organized for setup? And how was funding organized when the platform was ongoing? And when products leave and enter the platform trial?		
5. What feedback was provided from the participating companies on what interested/motivated them to join the platform? What were the anticipated or actual benefits that were realized?		

Instructions: Please tier/rank the below categories from 1 (most important / challenging) to 10 (least important /challenging) when considering Platform trials setup/design, implementation and execution and the particularities in comparison to a standalone trial. Below each category are key points for reflection; and provide further context to the category focus area. You will be requested to answer additional questions for the top 3 rated categories. We thank you in advance for your time, effort and support.

Protocol Development & Medical Writing ( )
• Authoring of Master Protocol – including protocol structure and key sections such as Table of Events / Schedule of Events, eligibility, appendices, etc. • (Scientific) advice from Food and Drug Administration (FDA); (Scientific) advice from European Medicines Agency (EMA) • Communicating the design to trial stakeholders (organizations, participating companies, external service providers, patients, etc.) • Master Informed Consent development & adaptation to country and site requirements • Development of Clinical Study Report (CSR) and Reporting trial results
Regulatory & Ethics ( )
• Development of Core Health Authority (HA) Package, • HA, Ethics Committee (EC) / Independent Review Board (IRB) submissions and queries responses
Study Start Up ( )
• Site feasibility, site selection and non-selection; • Site Confidentiality agreements • Site Contracting & Site Payments • Patient Recruitment Tools: Professional Materials for use by investigators / site staff; Patient-facing tools
Legal ( )
• Liability, Intellectual Property, clinical trial insurance • (Scientific) advice from Food and Drug Administration (FDA); (Scientific) advice from European Medicines Agency (EMA) • Communicating the design to trial stakeholders (organizations, participating companies, external service providers, patients, etc.) • Vendor selection and setup
Clinical Supplies/Ancillary Supplies ( )
• Provision / distribution of clinical supplies when multiple companies are involved

• Import licenses for clinical and ancillary supplies • Export licenses (e.g. biological samples) • Investigational Product (IP) Labeling
Team Structure/Contingency Planning ( )
• Setup of teams within Sponsor Entity and participating companies/team(s) setup (i.e. trial contact list) • External service provider (vendors) team(s) organization or provisions; handover and/or transition management
Interactive Web Response System (IWRS)/Data Management/Programming/Statistics/Safety ( )
• WRS transactions (i.e. Platform screening, Intervention Specific Appendices (ISA) screening/randomization, and randomization/assignment to ISAs) • Safety reporting (EDC, suspected unexpected serious adverse reaction (SUSARs), Drug Safety Update Reports (DSUR))
Clinical Monitoring/Quality Management ( )
• Clinical Monitoring Plan (including Pre-trial Assessment Visit (PTAV), Site Initiation Visit (SIV), Interim Monitoring Visit (IMV), Unblinded Monitoring Visits (UMV, if applicable) Site Closeout Visit (SCOV) • Risk-based Monitoring/Central Monitoring • Protocol Deviation Management
Study Closeout ( )
• Filing and Data archiving • Preparation of appendices for Clinical Study Report, or marketing applications; publications
Organizational/Systems ( )
• Organizational setup about: Clinical Trial Management System and planning systems; Electronic Data Capture system (EDC) / electronic Case Report Form, Trial Master File • Decision making process on interventions / treatment arms / Intervention Specific Appendices (ISA) that enter and leave Platform

The participants received the following questions with the request to fill for each questions the following aspects:

Briefly describe how setup was completed for the Platform trial?

Highlight key difference(s) in Platform setup compared to to a standalone trial?

Share best practices/lessons learned identified throughout Platform setup?

Question
6. Authoring of Master Protocol – including protocol structure and key sections such as Table of Events / Schedule of Events (ToE), eligibility, appendices, etc.
7. (Scientific) advice from Food and Drug Administration (FDA)
8. (Scientific) advice from European Medicines Agency (EMA)
9. Master Informed Consent development
10. Country-level Informed Consent development (from Master)
11. Site-level Informed Consent development (from Country-level)
12. Strategy with appendices to the Master protocol (i.e. appendix adding an intervention)
13. Amendment management

14. Who led communication and messaging regarding the platform trial design to trial stakeholders (organizations, participating companies, external service providers, regulators, etc.)
15. How are (interim) outcomes/results reported on sites like clinicaltrials.gov and to IRBs/ECs?
16. Development of Clinical Study Report (CSR)
17. Development of Core Health Authority (HA) Package
18. Obtaining approval from Health Authorities for the initial submission of the trial
19. Obtaining approval from Ethics Committee (EC) / Independent Review Board (IRB) for the initial submission of the trial
20. Obtaining approval from Health Authorities for the addition and/or removal of an arm of the trial
21. Obtaining approval from Ethics Committee (EC) / Independent Review Board (IRB) for the addition and/or removal of an arm of the trial
22. Management of HA/EC/IRB queries/responses
23. ICF adaptations per HA/EC/IRB request
24. Confidentiality Disclosure Agreements
25. Country/Site feasibility planning/process
26. Site feasibility questionnaires
27. Site selection and non-selection
28. Sponsor training
29. Vendor training
30. Site training
31. Site and Subject numbering
32. Central Laboratory (primary)
33. Referral Labs (i.e. setup, contracting entity)
34. Site Contracts (contract negotiations approach, contract templates, budget)
35. Site payments organization
36. Process for obtaining informed consent: i.e. how often are patients consented; once for the study plus again for an intervention appendix, etc.
37. Investigator and site engagement (particularly prior to and between study appendices -ISAs)
38. Process for listing and maintaining on public registries (e.g. clinicaltrials.gov, EU trials registry, local registries)
39. How was Intellectual Property ownership/disclosure regarding the compounds organized across/between the participating companies? Where there any special arrangements for / with the Sponsor Entity around Intellectual property?
40. How was liability organized across the participating companies? As well as with the Sponsor Entity –
41. How was vendor selection and vendor contracting arranged? (eg External service providers (i.e. electrocardiogram (ECG), imaging, Electronic Clinical Outcome Assessment (eCOA), etc.))
42. How was clinical trial insurance arranged?
43. IWRS setup: drug accountability, supply strategy
44. How did you setup the supply / distribution of investigational drug if multiple companies were involved in the trial?
45. Import licenses for clinical and ancillary supplies (eg centrally arranged, or does every participating pharma arrange?)

46. Final QP release procedures
47. Supply chain and product design (manufacturing sites, distribution network, devices)
48. Export licenses (e.g. biological samples)
49. IP Label design and Packaging & Labeling
50. Depot Management
51. IP destruction
52. How was placebo handled if products are very different (i.e. in case of non-matching placebo; in case several active products from different companies are involved
53. Sponsor Entity and participating companies/team(s) setup and tracking (i.e. trial contact list)
54. External service provider (vendors) team(s) organization or provisions?
55. Issue escalation and communication pathways across sponsor, partner organizations, different intervention appendix teams, etc.
56. Specific handover and/or transition management
57. Team engagement and contingency planning across sponsor, partner organizations, different intervention appendix teams, etc.
58. How was the project management of the trial setup at the Sponsor (i.e. cross-company team, outsource, project charter?
59. How was the project management of the trial setup at the participating companies?
60. Vendor Oversight Management including vendor audits
61. What was the feedback from investigative sites on working on a platform trial?
62. IWRS transactions (i.e. Platform screening, ISA screening/randomization, and randomization/assignment to ISAs)
63. Regarding IWRS specify drug supply parameters / system integration to external databases
64. IWRS Reporting
65. Independent Data Monitoring Committees
66. Data Review Committee
67. Adjudication Committee
68. Interim Analyses and how they were planned and organized
69. Database management and lock for a specific treatment arm / intervention when a treatment leaves the platform trial
70. Interpretation of trial results
71. CRF development – standard and unique pages
72. Maintaining the blind across ISAs
73. Data standards (i.e. Protected Health Information, data collection instruments and practices)
74. Safety reporting (EDC, suspected unexpected serious adverse reaction (SUSARs), Drug Safety Update Reports (DSUR))
75. Clinical Monitoring Plan (including Pre-trial Assessment Visit (PTAV), Site Initiation Visit (SIV), Interim Monitoring Visit (IMV), Unblinded Monitoring Visits (UMV, if applicable) Site Closeout Visit (SCOV)
76. Risk-based Monitoring/Central Monitoring
77. Protocol Deviation Management
78. Site Audit Plan

79. Risk Management
80. Site Closeout
81. External service providers (i.e. ECG, imaging, ECOA, etc.) Closeout
82. Equipment Retention/Return
83. TMF Filing and data archiving; post-trial data access
84. Preparation of appendices for CSR or marketing applications
85. Inspection readiness activities
86. Who is responsible for reporting and publication of results and describe the decision-making process (registries, papers, patient lay summary) – particularly on arms that leave the platform trial while the platform trial itself continues?
87. Post-trial Lesson Learned activities and training
88. In your organization's Clinical Trial Management System
89. In your organization's pharmacovigilance system
90. In your organization's financial systems and in managing the budget
91. In your organization's resources planning systems
92. In your organization's electronic filing system / Trial Master File
93. In your organization's Electronic Data Capture system (EDC) / electronic Case Report Form and the clinical database (i.e. backend database)
94. Standardization of data transfer agreements such as external laboratories or from vendor partners
95. In the Clinical Trials Supply system (or supply vendor's system)
96. Decision making process on interventions / Intervention Specific Appendices (ISA) that enter and leave Platform

12.2. ANNEX II. Interview guide

Interview Guide

Instructions: The following interview guide is intended to support in establishing a consistent procedure for the conduct of interviews of EU-PEARL trial outreach contacts.

Scheduling:

- Based on review of completed questionnaire determine if an interview is necessary considering:
  - Overall completeness of questionnaire
  - Responses to mandatory or categorical questions
  - Anticipated benefit of additional 1:1 time with trial contact, etc.
- If an interview is deemed necessary, it should be scheduled as soon as possible following receipt/ completed review of questionnaire
- Plan for interviews to be about 60 minutes
- Ensure two team members support interviews (1. Interviewer; 2. Minute/note taker)
- Add scheduled date and time of the interview to the tracker into the appropriate column located here
- In case interview is not applicable/rejected/etc. then add comment into the comment column

Preparation and Conduct:

- Review completed questionnaire in advance of interview and pre-identify key talking points and/or questions to obtain additional details
- Minute/note taker must use the questionnaire enclosed to take notes in the “Comment” section in alignment with actual questions.
- Following the interview notes should be reviewed and agreed upon between interviewer and minute/note taker

Deliverable:

- All notes must be provided electronically (in the following table) beside the corresponding questions. In case there is details provided not associated with a question a free text area is provided on the last page
- All interview guides with electronic notes are to by uploaded to the team SharePoint Site located here **by end of business Friday, 28Feb2020**

12.3. ANNEX III: EU-PEARL WP2

In the DoA the main objectives of WP2 are:

1. Quantitative Methods and Statistical Design: To assess and develop statistical methods for trial design and analysis;
2. Regulatory Aspects: To assess and further develop a regulatory framework meeting the needs of regulatory authorities, ethics committees and other relevant stakeholders;
3. Clinical Operations Best Practices: Firstly, to identify current practices and develop standardised and broadly applicable best practices for future IRPs, and secondly to provide tools for the design and implementation of platform trials and intervention selection, including safety reporting methods.

This deliverable and associated sub-task T2.3 contribute to goal 3. above.

The description of T2.3 in the DoA is:

- A systematic review of literature and other information will be performed to collect and assess the current experience on IRPs. This will cover methodological research (including quantitative methods identified in T2.1), ongoing and completed platform trials, relevant European, US and global regulatory guidance (identified in T2.2) and other relevant documents to identify the current state of the art, methodological gaps and major operational challenges. This review will inform a glossary of common terminology for IRPs to enable the communication of relevant concepts across stakeholders, and it will feed into Tasks T2.1 and T2.2 serving as the starting point for the development of guidance, methods and tools. This report (D2.1) will include a shared glossary, background and scope (types of IRPs to consider) for EU-PEARL.
  This deliverable has been submitted to IMI and published on the EU-PEARL website.

- The initial design of a set of generic tools, including a Master Protocol Template (MPT) with disease-specific appendices, will be addressed first in close collaboration with DSWPs. The protocol template from the non-profit TransCelerate organisation will be reviewed as a possible starting point along with existing master protocols such as IMI-EPAD and others. The principle deliverable of this sub-task will be a generic MPT (D2.3).
  The creation of this deliverable is under way.

- The principle deliverables preliminary and final reports on IRP Clinical Operations Best Practices (D2.2 and D2.10) will address the operational challenges of IRPs (see Table 3 for the major issues to be addressed).
  D2.2 is this deliverable, and D2.10 will be the updated and completed version of this deliverable at the end of EU-PEARL.

- *The final deliverable is summarized thus:* Best Practices, Templates and Operational Challenges:
  1. Structure of master protocols, intervention appendices, statistical analysis plans and data monitoring committee charters.

  2. Implementation of interim analyses, randomisation, patient allocation and blinding.

  3. Safety monitoring, evaluation and reporting of safety data, and safety monitoring committee charters.

  4. Data management, sharing, and protection, information management, data handling

processes along with maintaining the blinding if one arm's data is published and extensions to the CONSORT reporting standards.

5. Governance of platform trials, patient involvement, ethics approval and informed consent.
6. Identification, contracting, preparation, training, initiation, management, monitoring (QA and data integrity) and closure of clinical sites and vendors.

7. Clinical supplies issues, including blinding, sample numbering, distribution, recall, accountability and manufacturing/ CMC alignment with the protocol.

8. Addition and withdrawal of treatments (including handling of these events in CRFs, data storage, randomization, and DMC reports), and specification of whether (and how) the trial will allow new biomarkers, tests or ancillary procedures to be added.

9. Protocol deviation handling and issue escalation.

10. Planning for trial longevity (staff succession planning, long-term system maintenance, continuity of vendors and contractors).

11. Best practices on impact assessment with regard to intervention selection.

The next steps are described thus:

- Early drafts of the documents to be produced under the scope of this task, will be delivered to DSWPs, where they will be tested.
- The experiences and lessons learned from DSWPs will then feed back into WP2 so that the Best Practices report will be applicable to different disease areas and disseminated appropriately with relevant stakeholders.
- Close collaboration and sharing of information with DSWPs will be ensured through regularly scheduled meetings, and draft generic documents will be refined through continuous feedback from DSWPs, as well as external stakeholders.
- Based on disease-specific consent forms provided by the DSWPs, a generic template will be produced which will also address the main challenges and complexities of informing the patient about their participation in IRP trial.

The DoA emphasizes that T2.3 will not produce software solutions (e.g. for randomization, supply or data management), but it will describe the features required as an aid for evaluating potential external vendors of such solutions. Topics concerning the legal framework, IP, trial sponsorship, data protection, ethical and governance aspects will be covered by WP1, in conjunction with WP2. Topics covering the trial infrastructure will be covered by WP3, in conjunction with WP2.