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Regulatory Issues of Platform Trials: Learnings from EU-PEARL

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Although platform trials have many benefits, the complexity of these designs may result not only in increased methodological but also regulatory and ethical challenges. These aspects were addressed as part of the IMI project EU Patient-Centric Clinical Trial Platforms (EU-PEARL). We reviewed the available guidelines on platform trials in the European Union and the United States. This is supported and complemented by feedback received from regulatory interactions with the European Medicines Agency and the US Food and Drug Administration. Throughout the project we collected the needs of all relevant stakeholders including ethics committees, regulators, and health technology assessment bodies through active dialog and dedicated stakeholder workshops. Furthermore, we focused on methodological aspects and where applicable identified the corresponding guidance. Learnings from the guideline review, regulatory interactions, and workshops are provided. Based on these, a master protocol template was developed. Issues that still need harmonization or clarification in guidelines or where further methodological research is needed are also presented. These include questions around clinical trial submissions in Europe, the need for multiplicity control across the whole master protocol, the use of non-concurrent controls, and the impact of different randomization schemes. Master protocols are an efficient and patient-centered clinical trial design that can expedite drug development. However, they can also introduce additional operational and regulatory complexities. It is important to understand the different requirements of stakeholders upfront and address them in the trial. While relevant guidance is increasing, early dialog with relevant stakeholders can help to further support such designs.

The EU Patient-Centric Clinical Trial Platforms (EU-PEARL) was a public-private partnership funded by the Innovative Medicines Initiative with around 36 organizations representing patients, clinicians, researchers, authorities, and industry. EU-PEARL had the ambition of transforming the current approach of conducting single-compound clinical trials into the use of cross-company integrated research platforms (IRPs) designed as a framework to conduct platform trials, taking into consideration both patients' interests and the opportunities from novel treatments for addressing medical needs.[1,2] In a platform trial, multiple treatments can be studied in a perpetual manner, with treatments allowed to enter or leave the platform during the ongoing trial.[3] Patient-centric data and knowledge sharing have the potential to accelerate the development of new treatments and to reduce the operational costs of clinical trials. It was the aim of EU-PEARL to create a general framework for IRPs, such as templates, guidance documents, and other resources, but also to develop specific frameworks for platform trials ready to operate in four disease areas still facing unmet medical need: major depressive disorder, tuberculosis, non-alcoholic steatohepatitis, and neurofibromatosis.

The complexity of the IRPs (e.g., increased complexity of study design, multiple study arms, adaptive features, and issues due to their cross-company and collaborative nature) poses challenges for regulatory and ethical assessment. One of the main objectives of EU-PEARL was to understand and address these challenges.

The aim of this paper is to summarize relevant aspects and potential gaps in the approval and the assessment of IRPs for clinical trial applications or marketing authorization applications, which have been discussed in EU-PEARL. A glossary of important regulatory terms is provided in **Table 1**. Furthermore, the requirements of health technology assessments (HTAs) for IRPs are discussed. Throughout the entire project, interactions with regulators, ethics committee members, and HTA experts occurred in specific workshops and

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Table 1 Glossary of important regulatory terms

Term	Meaning
Complex innovative trial design	Trial designs that have rarely or never been used to provide evidence of effectiveness in new drug applicants or biologics license applications, or applications of complex trial features to a given indication even when these features have been used in other indications. Examples are for studies that borrow external information, sequential multiple assignment randomized trials or master protocols.[4]
Critical Path Innovation Meeting (CPIM)	Forum for FDA and stakeholder to discuss potential advancements in drug development which includes for example biomarkers in early phase of development or innovative conceptual approaches to clinical trial design and analysis.[5]
Clinical Trial Application (CTA)	Clinical trial sponsors that want to run a clinical trial in Europe must submit a request for authorization; often abbreviated as CTA.[6]
Clinical Trials Coordination Group (CTCG)	Working group that contributes to harmonizing and optimizing the regulatory environment for clinical trials in the European Union; often abbreviated as CTCG.[7]
Clinical Trials Facilitation and Coordination Group (CTFG)	Working group that acts as a forum for discussion to agree on common principles and processes throughout the European Medicines Regulatory Network.[8]
Clinical Trials Information System (CTIS)	System for clinical trial sponsors to apply for authorization to run a clinical trial in Europe via a single online application.[9]
Electronic Common Technical Document	Standard electronic format for submitting applications to regulatory authorities; also known as eCTD.[10]
European Medicines Agency (EMA)	Agency of the European Union which is responsible for the scientific evaluation, supervision and safety monitoring of medicines.[11]
US Food and Drug Administration (FDA)	Responsible for ensuring the safety, efficacy, and security of human and veterinary drugs, biological products and medical devices in the United States.[12]
Investigational new drug (IND)	Clinical trial sponsors that want to run a clinical trial overseen by the FDA must submit an Investigational New Drug application, also known as IND.[13]
Integrated Research Platforms (IRP)	Novel clinical development concept centered on a master protocol, which includes multiple interventions using existing infrastructure of hospitals and federated patient data in design, planning, and execution, whereas an optimized regulatory pathway for these novel treatments has been assured.[3]
Innovation Task Force (ITF)	Multidisciplinary group that includes scientific, regulatory and legal competences set up by the EMA.[14]
Marketing authorization application (MAA)	Application for the approval to market a medicine in Europe; often abbreviated as MAA.[3]
Substantial modification	Modifications to clinical trials that have a substantial impact on the safety or rights of the trial participants or on the reliability and robustness of the data generated in the clinical trial are subject to an authorization procedure similar to the initial authorization procedure.[6]

panel discussions. This paper reflects the current regulatory status, discussions with regulatory experts, and regulatory documents that have recently been released or were available before the inception of EU-PEARL.

The document is structured as follows:

The section "Regulatory guidance, HTA, and regulatory interactions" provides an overview of the current available guidelines specific to platform studies from the European Medicines Agency (EMA), the European Heads of Medicines Agencies, the US Food and Drug Administration (FDA), and HTA-related requirements regarding IRPs. Furthermore, a summary of the regulatory interactions with the EMA and the FDA during EU-PEARL disease-specific discussions is presented, and a brief introduction of the master protocol templates developed by EU-PEARL. The section "Statistical challenges" describes the most important statistical challenges in the context of platform trials that can lead to substantial regulatory discussions: multiplicity, non-concurrent controls (NCCs), patient allocation in platform trials, and the use of simulation studies, and refers to the existing guidelines, where possible and applicable, or points out gaps that still exist.

The conclusion summarizes what challenges have been solved and provides an outlook on what challenges remain to be solved in the context of platform trials from an academic, industry, and regulatory perspective in the future.

REGULATORY GUIDANCE, HTA, AND REGULATORY INTERACTIONS

In this section, we discuss relevant US and EU guidance structured along the relevant topics. We start with discussing study design, conduct, and statistical aspects covered in guidelines in the section "Regulatory guidance on study design, study conduct, and statistical aspects," and cover guidance on regulatory submission aspects and communication around the approval of complex clinical trials in the section "Considerations for the submission of clinical trials and communication." In the section "Regulatory interactions" general learnings from regulatory interactions during EU-PEARL are shared. Additionally, an overview of the key content of each available guideline is provided in **Supplementary File S1**.

The section "Health technology assessment" provides aspects from an HTA perspective.

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Regulatory guidance on study design, study conduct and statistical aspects

The Clinical Trials Facilitation and Coordination Group (CTFG) Recommendation paper on the Initiation and Conduct of Complex Clinical Trials (CCTs) was the first European regulatory document that specifically addressed CCTs and provides key recommendations for the initiation and conduct of complex trials as well as regulatory considerations and communication.[15] According to the recommendation paper, the most common features of CCTs are subprotocols, extensive adaptations, such as the addition of new treatments and/or populations, and the use of a master protocol. In addition, a Questions and Answers document (Q&A)[16] on CCTs published by the Accelerating Clinical Trials in the EU (ACT EU) expands and supplements the recommendation paper[15] with guidance on scientific aspects for the conduct, reporting, analysis, and interpretation of results. The FDA's first guideline on master protocols for the treatment of cancer[17] and the FDA's newest draft guideline on master protocols for drug and biological products[18] (distributed for comment purposes only) defined a master protocol as "a protocol designed with multiple substudies, which may have different objectives and involve coordinated efforts to evaluate one or more investigational drugs in one or more disease subtypes within the overall trial structure." Whereas the first guideline is applicable for master protocols in oncology, the latter applies to a range of therapeutic areas and focusses mainly on umbrella and platform trials.[18] The FDA issued another guideline on master protocols for the treatment or prevention of coronavirus disease 2019 (COVID-19),[19] which is strongly based on the FDA's guideline on master protocols in oncology.[17]

The increased flexibility and efficiency in drug development[17] due to shared protocol elements or infrastructure[18] and opportunities for biomarker-driven development[15] are recognized, whereas also the challenges with the increased complexities are mentioned. Flexibility can be obtained by starting and stopping of substudies or arms. A clear description of closed, current, and future arms, and all conditions leading to trial adaptations should be described in the protocol.[15,17] Furthermore, changes in the randomization ratio[18] due to starting and stopping of arms should be accounted for in the analyses. The use of shared controls is recommended to increase the efficiency,[17,18] however, only concurrently enrolled subjects should be used for comparative analyses[15–19] as changes over time, such as changes in the patient population,[18,19] the standard of care,[15,16] or biomarker testing[15,16,18] may occur. Further aspects on the potential use of NCCs and attributes that must be considered when choosing an appropriate control is provided in the ACT EU's Q&A[16] and the FDA's guideline on master protocols.[18] With regard to biomarker-driven developments, clear criteria or conditions for subject allocation need to be predefined[15–17] – especially when populations overlap.[15] Furthermore, the biomarker assay must be analytically validated[17] and/or compliant with the diagnostics regulations.[16]

Patient safety is of particularly high priority and therefore discussed in all guidelines.[15–19] The use of an independent data monitoring committee,[15–19] appropriate risk mitigation strategies, and adequate oversight[15,16,18] are expected in that regard.

Whereas the FDA's guideline on master protocols in COVID-19[19] and on master protocols for drug and biological products[18] do not call for a multiplicity adjustment for multiple comparisons of different treatments to the comparator in umbrella or platform trials, sponsors should be aware of the increased chance of multiple false-positive findings. Additional considerations, such as the meaningfulness of the estimated effect,[19] need to be discussed in this light or the trial design elements can be implemented to reduce this issue (e.g., increased allocation of subjects to controls).[18,19] The risk of multiplicity issues is also mentioned in the CTFG's recommendation paper without further details.[15]

The FDA's newest guideline on master protocols additionally discusses the issue of information dissemination in platform trials and the potential risk to trial integrity.[18] Multiple aspects in platform trials can lead to dissemination of information, such as sample size re-estimation based on blinded pooled data when using shared controls and treatments entered into the trial at the same time. This could lead to partial unblinding of comparative results for treatments still on the trial. Thus, access to pooled data should be restricted.[18]

Although the CTFG recommendation paper and the Q&A on CCTs touch on statistical aspects, further guidance on statistical issues will be provided by the EMA.[20] The upcoming reflection paper on platform trials is planning to address terminology and key concepts, describe key methodological topics in platform trials, and discuss these in the light of increased complexity and uncertainty in decision making. This discussion will cover topics such as the requirements for type I error control (including multiplicity), the use of NCCs and the change in patient populations over time.

Considerations for the submission of clinical trials and communication

Initial submission of complex clinical trials. With increasing complexity, communication with regulators becomes even more important.[4,15,18] The guidelines in general recommend early interaction with regulators to discuss the proposed trial designs. The FDA issued a guideline specifically for interactions with the FDA on complex innovative trial designs.[4] The guidance emphasizes that "novel clinical trial designs call for clear communication between sponsors and FDA on aspects of the design, including the purpose, execution, and operating characteristics (such as the chance of producing erroneous conclusions) of the design." The guidance provides recommendations regarding common elements that should be provided for FDA feedback. This includes descriptions of possible design adaptations, interim analyses, and statistical considerations. Furthermore, it addresses the issue of simulations, which are often needed to estimate the operating characteristics of different trial design components (overall trial duration, average type I error and type II error, number of arms evaluated, etc.). It also includes guidance on the protocol components for a CCT, such as the master protocol and subprotocols, the description of the statistical methods for the level of the platform and each subprotocol,[16] and the expected electronic common technical document structure.[17] An example

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of a structure for a master protocol with multiple substudies is provided in the FDA's guideline on master protocols for drug and biological products.[18] Additionally, description of relevant governance and oversight committees for monitoring of subject safety should be included.[16–18]

To support the design, submission, and conduct of platform trials, EU-PEARL developed templates for the master protocol, intervention-specific appendices, the statistical analysis plan, and the Data Monitoring Committee Charter. Additionally, guidance for supplementary information on platform trials in the cover letter for submission in the Clinical Trials Information System (CTIS) is available.[21] Regulatory feedback was obtained from the clinical trials coordination group as part of a formal review of the master protocol and intervention-specific appendix templates, and the guidance document for supplementary information to the cover letter.[22]

In addition, in most countries, an ethic's review and approval are required before the initiation of a trial. Ethics committee members emphasized during an EU-PEARL Stakeholder Workshop[23] and at a European Federation of Pharmaceutical Industries and Associations (EFPIA) workshop[22,24] the need for training and for the availability of relevant statistical expertise due to the increasing complexity of the designs. The importance of the involvement of ethics committees in the discussion of novel concepts at the earliest possible stage was raised. It was mentioned during both events, that the higher complexity of platform studies poses challenges in informing patients via informed consent forms due to the need for very long or sometimes multiple consent forms (e.g., a master consent form and intervention-specific ones). Furthermore, the assessment of the CCTs is challenging because of the large number and length of documents and the involvement of several interventions. Yet, the time established, as per the regulation, to review a CCT is the same as for a standard (two-arm) clinical trial application.

Substantial modifications. Substantial modifications, or substantial amendments, need to be submitted for regulatory and ethics approval. They are triggered by changes that affect the safety of patients or scope of the trial,[5] including the addition or closing of sub-protocols and arms.[25] Naturally, these are expected more frequently in complex clinical trials.

Information which is required in the submission of amendments when adding or closing subprotocols are provided in the CTFG's recommendation paper[15] and the FDA's guidance on master protocols.[17,18] Required documents to be submitted for an amendment are an updated informed consent document, a clean and tracked changes version of the amended master protocol, and a list of changes in tabular format with the rationale for each change.[17] Furthermore, an update on the status of each treatment in the master protocol is recommended.[18]

In Europe, amendments can only be submitted in the CTIS "after a decision on an initial application or an application for [substantial modification] or addition of a Member State concern[ed] is taken.[26]" Hence, the number of submissions per calendar year is limited considering the approval timelines. This is highly relevant for platform trials where new subprotocols are potentially submitted as substantial modifications to an ongoing trial. With this limitation of submitting amendments in a timely manner, the timing of amendments requires careful planning, considering also unforeseeable events.

The SolidAct platform trial was one of the first platform trials to submit in the CTIS.[27] The study team encountered problems in complying with disparate member state-specific requirements and in structuring the study data in CTIS given the trial's complex design. Furthermore, in their experience, the CTIS "wasn't designed to take care of platform trials," because "the way CTIS is set up means that each upcoming study arm in the shared framework has to be entered as a brand new trial"[27] (i.e., re-submitting all the documents every time they started a new arm, a lack of clarity on when and where the master protocol must be submitted, and paying the full fees for every arm they added).

No such issues with submissions of amendments in the United States were reported so far, as the Investigational New Drug structure is better suited for the submission of master protocols. General considerations on the Investigational New Drug structure for master protocols are provided in the FDA's guideline on master protocols for drug and biological products.[18]

Regulatory interactions

Many stakeholders are aware of the standard options for obtaining feedback for a development program such as the EMA Scientific Advice,[28] National Scientific Advice in the European Union,[29] or formal meetings, such as type B meetings with the FDA.[30] Opportunities for early and product-agnostic engagement are also available from the EMA and the FDA via the Innovation Task Force (ITF) meeting[14] and the Critical Path Innovation meeting (CPIM),[5] respectively. These venues are perfectly tailored for an early discussion around (platform) trial design and methodology, and clinical aspects of the targeted disease. These meetings facilitate informal exchange of information and provide guidance in the development process. They do not substitute for a formal scientific advice, regulatory meeting with the FDA or for a plan to submit the trial under the FDA complex innovative design initiative.[31]

Within EU-PEARL, two ITF meetings with the EMA were granted to discuss two disease specific platform trial plans, and one CPIM with the FDA was granted. The objective of these meetings was to discuss the platform trial design and draft master protocols. These draft protocols were based on the templates created within EU-PEARL (see the section "Considerations for the submission of clinical trials and communication"). Although disease-specific aspects were discussed in the meetings as well, the meeting focus was on general methodological and regulatory learnings. Nonetheless, the clinical background is important to understand the design choices and recommendations. For more details, see the dedicated reports cited below.

Major depressive disorder. A phase II platform trial in patients with major depressive disorder was proposed to the EMA's ITF to investigate multiple drugs in different domains defined by different routes of administration (oral, intranasal, or intravenous).[32–34]

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A separate control arm was suggested per domain. The EMA was supportive of many of the proposed features of the study design, including:

- The two-step randomization process, where participants are first randomized to one of the domains and then to one of the arms (experimental or control) within that domain. Participants can opt-out of specific domains.
- Intra-domain blinding.
- Primary analysis based on concurrent controls.
- Square root allocation (see the section "Allocation in platform trials") to the placebo arm within each domain with a lower limit of 35% to reduce the risk of inflating the placebo response. To further reduce the placebo effect, only the possible range of placebo allocation shall be communicated in the intervention-specific informed consent. Whereas understood, this might be challenged during the ethics review.

More details on the clinical trial simulation were considered important and additional scenarios were requested by the ITF to better understand the trial characteristics in relevant situations, which resulted in exploring further scenarios afterward.[35] On the topic of whether to permit re-entry and re-randomization of participants into a platform trial, the EMA highlighted that further consideration needs to be given to the potential for changes in the patient population over time as this may lead to an increasing rate of resistant participants. The option for a participant re-entering within the same domain should be avoided.

Overall, this interaction shows that many design elements of the proposed platform trial were considered acceptable by the ITF experts for this phase II study. The design was, in general, supported.

Non-alcoholic steatohepatitis. A phase IIb master protocol was proposed to the EMA's ITF to investigate multiple intervention cohorts (either an investigational treatment or combination therapy of one or more investigational treatments compared with control) simultaneously or sequentially in patients with non-alcoholic steatohepatitis.[36] Patients are planned to be randomized to a study intervention cohort and then randomly assigned to investigational treatment(s) or matching placebo. The control patients used for comparison to a treatment can be either the control patients within a cohort only, or all concurrent control patients across all cohorts that meet the eligibility criteria for the specific intervention cohort regardless of whether the patient was randomized to that cohort or not.

The EMA was supportive of many of the proposed features of the study design including:

- A randomization process that accounts for patient choice with respect to which cohorts they would be willing to participate in.
- The Bayesian decision criteria based on clinically meaningful effect sizes for futility and efficacy.[37]
- The use of shared concurrent controls across cohorts who meet the eligibility criteria if the accrual rate across cohorts allows overlap of the recruitment periods.

EU-PEARL representatives acknowledged that strong control of the family-wise error rate (FWER) is needed for phase III studies. As the proposed study is a phase II study, the representatives argued that there was no need for strong control of the FWER because results are not planned for registration. However, there were concerns raised by some EMA experts with respect to the controlling of the type I error even in a phase II setting if dependence exists between treatment arms (multiple doses of the same investigational treatment or investigational treatments with similar mechanisms of action). In addition, the EMA experts raised the point that there is an increased risk of multiple false-positive results when a shared control arm is used. Concerns were also raised about the use of NCCs and not being able to fully characterize time trends. However, it was noted that, if necessary, the range of potential time trends could be simulated to understand how such trends would impact decision making.

The interaction with the EMA showed that the overall trial design was endorsed. However, stronger type 1 error control may be imperative in some scenarios, even in phase II trials, but may not be required in other situations if well justified.

Slightly in contrast, in the CPIM granted by the FDA,[36] regulators shared the view that multiplicity control is not required for a phase II design across all of the cohorts in a platform trial. Standard multiplicity control (e.g., across end points) is needed within each cohort.

In the situation where the sharing of control data across cohorts within a platform trial is being proposed, the FDA recommended consideration of the following topics:

- Potential differences in outcomes across cohorts need to be taken into account, separately for each end point.
- The comparison between an investigational drug and the shared control arm should include only concurrent control participants who consented to that cohort and that could have been randomized to that drug (i.e., met inclusion/exclusion criteria and the cohort was open at the patient's site at that time).
- The potential bias created by participant selection to participate in a specific intervention cohort should be considered.

The FDA endorsed the study design and agreed that type I error control across cohorts of the platform was not necessarily needed in this phase II design. The FDA suggested more considerations to support the sharing of control arms and was not in favor of using NCCs.

Health technology assessment

HTA supports the decision whether a technology can and should be implemented. By this, the primary HTA approach is a supportive methodology to the decision process within general reimbursement decisions and to decide whether the technology will have a benefit for the clinical service provider and for the system in general as well as it will support the added value assessment for deciding and negotiating the final price of the technology/service within a given jurisdiction. HTA's definition of a technology includes more than just a technology, such

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as robots or computer tomography. Technology also includes pharmaceuticals, medical products, healthcare procedures, and public health interventions.[38]

Platform trials offer the possibility to improve the comparability of clinical values of health technologies by comparing multiple interventions and using a shared, uniform, "clinical gold standard" control group (if planned). This can reduce the risk of bias in the description of observed effects of a health technology, which improves the reliability of evidence-based support of health decision makers through HTA.

By integrating the concept of HTA into the master protocols researchers can ensure that the evidence generated in platform trials is relevant and useful for healthcare-related decision making, including reimbursement and clinical practice requirements. These are two out of seven so-called HTA domains.[39]

Platform trials can provide similar certainty of results as traditional trials. However, due to the flexibility the following should be considered[40]:

- The comparability of control patients recruited over a long period to the different interventions should be discussed.
- Blinding when multiple treatments are evaluated simultaneously can be difficult.
- A risk of a type 1 error inflation due to multiple interim analyses or comparisons exists if not controlled for.
- Rules for continuing or adding interventions should be defined and justified.

Considering HTA methodology in the analysis of a pharmaceutical product in platform trials thus not only leads to clarity of evidence required beyond regulation, it enables the parallelization of evidence generation in the platform trial and accompanying studies that are necessary to highlight the full added value of a product related to patient- and healthcare-relevant benefits compared with the standard of care.

STATISTICAL CHALLENGES

The use of CCT results not only in operational but also in statistical challenges can lead to substantial regulatory discussions. Statistical challenges specific to platform trials include but are not limited to multiplicity issues due to multiple treatment arms and a common control, the use of NCCs, patient allocation approaches, and the use of simulations for trial planning.

In the following sections, these challenges are described in more detail with a focus on the current scientific and regulatory aspects.

Multiplicity

Clinical trials, which aim to answer more than one research question, will have multiple chances of declaring false-positive findings (multiplicity). Statistical methods are typically implemented to control the impact on the rate of false-positive findings.

Sources of multiplicity are, for example, interim analyses, multiple end points, or multiple treatment arms. Guidelines from the EMA (on multiplicity issues[41] and on adaptive designs[42]) and the FDA (on multiple end points[43] and adaptive designs[44]) discuss situations in which multiplicity adjustments are necessary and provide guidance on the use of multiplicity adjustment methods. The guidelines consider multiplicity due to multiple end points or multiple treatment arms and provide guidance for adaptive designs, including interim analyses. However, these do not specifically address the issue of multiplicity in a platform trial.

An important feature of platform trials is the use of a shared control arm. Shared controls can increase the efficiency of clinical trials and reduce the number of control group patients required. Multiplicity issues arise if multiple arms are compared with a shared control in a single trial. Several research paper were published in recent years discussing the need for multiplicity control when using a shared control. It has been demonstrated that due to correlated test statistics, the FWER in a multi-armed trial with unadjusted tests is lower compared with the FWER of trials with separate controls. However, if a type I error is made, the probability to make several type I errors simultaneously is increased with the shared control arm.[45–47] Analogously, when the control is on a random high, multiple simultaneous type II errors pose a danger especially when the purpose of the platform trial is not to identify all effective treatments, but at least one (as might be the case in a pandemic).[48] There might be situations where a study-wise strong control of the type I error rate might not be required.[46,49–51] In particular, Collignon *et al.*[46] point out that the need for multiplicity adjustment depends on the inferential independence of the hypotheses in the master protocol. When hypotheses are considered inferentially independent (i.e., if the truth or falsehood of one hypothesis is unrelated to the truth and falsehood of the other hypotheses concerned), such as for hypotheses related to the efficacy of two different drugs with different mechanisms of action, no multiplicity adjustment might be required. On the other hand, when some treatment arms are different dose levels or different modes of administration of a single drug, the hypotheses are clearly related and a strict type I error control for this family of related hypotheses is required.

Furthermore, the number of treatment arms on the platform trial is not necessarily defined at the start of a trial as new arms can be added or dropped during the conduct of the trial. Thus, standard adjustment methods, such as Bonferroni or Dunnett, cannot be applied directly. As a simple solution, one could fix a maximum number of hypotheses being tested, but this would mean that if this number is reached, no further arm could be added which may contradict the principle of perpetual platform trials. Therefore, online control methods have been proposed in which the number of arms does not need to be known at the beginning of the trial.[52–54]

It should be noted that all the discussions of multiplicity concerns in platform trials to date tend to focus mainly on situations where there are multiple, concurrent treatment arms. Other situations, such as multiple arms that may only partially overlap in time, or arms that may be completely separate in time are not that well-covered. Multiplicity adjustment is usually not conceived to be necessary in the latter case, that is, if only concurrent controls are used in the analysis and arms are inferentially independent. To add another layer of complexity, different possible approaches to the use of the control arm exist (see the

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section "The use of non-concurrent controls") which further impact the type I error.

Recently, also Bayesian methods, like false discovery rate control with e-values,[55] have been suggested, but there is no practical and regulatory experience with these approaches in platform trials yet.

These situations are not discussed extensively in the existing guidelines mentioned above, however, these guidelines were not meant to provide recommendations to every situation of clinical trials where multiplicity may arise but rather to provide a general high-level guidance. It has to be further acknowledged that older guidance documents have been developed envisaging a trial with a single drug and objective. With the increased use of platform trials,[56] the need for further guidance became apparent and specific recommendations for CCTs were provided by the ACT EU,[16] the CTFG,[15] or the FDA,[17–19] as discussed in the section "Regulatory guidance, HTA, and regulatory interactions." In the latter guidelines,[18,19] it is mentioned that no multiplicity adjustments are needed for multiple comparisons of different drugs to a control, although exceptions exist (e.g., when evaluating multiple doses, or administrations of the same drug). In the European guidelines, multiplicity issues are mentioned as aspects that need to be addressed. The EMA published a concept paper on the need for a reflection paper focusing on methodological issues in platform trials, especially the requirement for type I error control.[20]

To allow an appropriate interpretation of trial results originating from a (potentially perpetual) platform trial, a discussion on the type of error control(s) implemented on platform and substudy level should be included in the overarching master protocol. If some hypotheses are considered inferentially independent, a framework should be given to (i) decide based on which criteria hypotheses are related and unrelated, (ii) how to define the families within the platform for which error rates, such as FWER, should be controlled, and (iii) whether changes of the testing strategy are needed when adding new arms in an ongoing trial. These aspects would aid planning and interpreting platform trials.

The use of non-concurrent controls

For treatment arms entering later in a platform trial using a shared control, this will lead to NCC and concurrent control groups. NCCs refer to trial participants allocated to the control group, who were recruited in periods of time where the newly added experimental treatment was not yet part of the available treatment options. Using NCCs, the variability of treatment effect estimator shall be reduced, what may allow for earlier internal decision making (e.g., futility) and could increase statistical power. The later an arm enters the trial, the larger is the potential gain in power by including NCC data. However, a major concern is bias in the estimates introduced by time trends that can lead to a change in the response. Examples are temporal changes in the patient population, the disease, the standard of care, or end point assessment. Another concern arises when intervention owners decide to add an intervention due to potential awareness of negative control data. Model-based approaches have been recently suggested to utilize NCC data in the analyses while adjusting for time trends.[57,58] For fixed sample trials, such approaches can lead to an increase in power and unbiased estimates while maintaining the type I error rate control if time trends affect equally all arms and if the time effect is additive on the model scale.

Bofill *et al*.[59] performed two scoping reviews on the use of NCCs in platform trials. First, the authors identified currently available methods to incorporate NCCs in treatment-control comparisons, outlined the key concepts and assumptions, and described the main characteristics of each method. Second, a systematic search of regulatory guidelines regarding the use of NCCs was performed. The most relevant arguments and recommended methods were summarized. The authors highlighted that regulatory guidance for NCCs in platform trials are currently still limited. Hence the authors decided to broaden the review and extracted guidance for the use of external and historical controls and to discuss the relevance and transferability of the results to NCCs. However, the authors noticed the advent of guidelines with a focus on platform trials wherein the use of NCCs was vaguely discussed.

In the FDA's recent draft guideline on master protocols,[18] the use of concurrent controls is preferred. However, circumstances where the use of NCCs may be justified are also discussed.

Allocation in platform trials

Fixed allocation. The classical approach to clinical trials and also to platform trials is to use fixed allocation rules to assign patients to intervention or control arms based on allocation probabilities. Allocation ratios then generally only depend on the number of treatment arms currently in the trial and are not meant to depend on observed unblinded trial outcomes.

Equal allocation (1:...:1) will assert a fixed allocation ratio for any treatment-control comparison. Still, the total randomization ratio to control over the course of a platform trial will vary and depend on the number of arms in the study at any given time. If there are 3 investigational treatment arms, the allocation probability to control is 25%, whereas it drops to 20% if there is an additional fourth arm opened. Equal allocation is inefficient from a statistical perspective in situations where multiple arms are compared with a concurrent common control. The square root allocation rule (i.e., 1:1: ...: $\sqrt{k}$, where k is the total number of concurrent treatment arms) decreases the standard-error for all treatment-control comparisons and is considered optimal.[60] However, the rule is defined based on the number of active study arms. As such, it does not lead to a constant control group allocation over the platform trial. A third alternative is to use a fixed randomization probability for the common control arm, irrespective of the number of treatment arms. Although the total probability of receiving the control treatment would be fixed, this approach would result in a variable allocation ratio between any treatment arm and the control group whenever the number of treatment arms changes. A fixed randomization to the control arm was, for example, implemented in the major depressive disorder protocol (see the section "Regulatory interactions") to control placebo response rates.

None of those allocation rules is completely fixed over time in a platform trial. All allocation probabilities will change with the number of study arms open for randomization. In case of further non-intended changes over time, such as drifts in the patient population or the response to treatments, this induces bias in the effect

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estimate, if analyses do not adjust for time trends.[61] Note that these changes in allocation ratio will to some extend depend on unblinded data as they might be induced by (interim) analyses which led to the termination of an arm.

Optimal allocation strategies were investigated in Bofill Roig *et al*.[62] for platform trials with shared controls, showing that the optimal allocations depend on the entry and exit times of treatment arms and also demonstrating that the square root allocation, optimal in multi-arm trials, is not always optimal in platform trials.

Potential variation in the randomization ratio was flagged in the FDA's guideline on master protocols for drug and biological products[18] and in the Q&A on CCTs,[16] which recommend addressing this issue during the analysis, for example, by analyzing the data for each time period with a different allocation ratio separately. The latter refers furthermore to the guideline on adjustment for baseline covariates in clinical trials.[63]

Response-adaptive randomization. A platform study with many interventions for evaluation with equal priority may result in a relatively slow accrual of patients to all arms. Response-adaptive randomization (RAR) allows to skew allocation to arms which are deemed more promising based on unblinded interim data. The required data reviews may be conducted at formal interim analyses, or periodically at special allocation adjustment meetings. Prospectively defined allocation rules are used to update allocation ratios at data reviews. A variety of allocation rules could be considered, including optimal design theory and multi-armed bandit problems.

Most frequently, Bayesian rules are implemented, which update the allocation proportional to the probability of arms being superior to control or superior to any other arm within the trial. In general, the aim is to increase allocation over time to better performing arms. Eventually, all arms will run to completion unless they are stopped early for efficacy or futility, hence RAR only impacts the time to full accrual. RAR is not a novel design element specifically developed for platform studies. The ASTIN trial was an early complex RAR dose-finding design for stroke implementing frequent analyses using Bayesian modeling.[64] Meyer *et al*.[56] observed that 50% of the identified platform trials implemented RAR, including examples such as I-SPY 2,[65] GBM-Agile,[66] INSIGhT,[67] and ALICE.[68]

There is, so far, no regulatory guidance available on the acceptability of RAR for regulatory decision making. Thus, the use of RAR should be well-justified. There are situations where RAR may be well-motivated, such as early phase, exploratory clinical trials, or in rare diseases. Recruitment may be challenging and lengthy in those situations, such that harmonization of research under one master protocol, as well as prioritization of evaluation through RAR to the most promising interventions may be particularly interesting to address the unmet medical need as quickly as possible. Although intuitively appealing, RAR may pose significant challenges to the operations of clinical trials and validity of statistical analyses. Operational concerns include timely data entry and cleaning (which is of high relevance to adequately assess the response and hence to adapt the randomization ratios), the ability to run the analysis frequently, the ability of the randomization system to be frequently updated with new allocation ratios, and the ability of the drug supply to cope with the changing allocation rates. Concerning the credibility of results, concerns on bias due to time trends and selection bias have been raised in the scientific literature.[59] In addition, RAR does typically not result in the most efficient allocation ratio. The level of inefficiency of the achieved randomization ratio will depend on the exact design definition. To address this concern, some RAR approaches fix control group allocation probability to the allocation probability of the best treatment arm, thereby ensuring high statistical efficiency through a targeted 1:1 allocation for the best treatment arm vs. control.

Last, the consideration of RAR as a feature of patient centricity may not be obvious for all platform trials, as the window of opportunity for adapting randomization ratios to achieve a relevant impact on the overall response for the in-trial population may be relatively small. A notable impact on overall response may not be reached, if the targeted effect size is modest, or if there is a relatively small prior chance only for any of the new interventions to be efficacious or if efficacy of all arms is likely to be rather equal. To improve expected outcomes for participants in situations where biomarkers affect treatment response, RAR may be utilized to enrich patient populations, by favoring allocation to subgroups where the treatments appear to be working best, as done in I-SPY 2 and GBM-Agile. RAR is applied in this situation by subgroup, instead of applying it in the same proportion across the full study population. This approach may address the lack of differentiation between treatment arms and could therefore be beneficial for the patients.

The principal benefit of RAR in situations with low chance of treatment success, may be a quicker decision on the effectiveness of an investigational treatment, which may by itself be a worthwhile target to consider, as this may allow subsequent research to commence and ultimately reach market approval and thus benefit the patients outside of the trial earlier.

However, even the target of earlier completion may be at risk, if the gap between randomization of a patient and the availability of the patient's data is large compared with the rate of enrollment and the number of concurrent treatments. The targeted sample size for a comparison, or a substantial amount of it, might in this situation be reached prior to any adaptation update analysis. Statistical modeling strategies may reduce this concern through the integration of other sources of information into the allocation update analysis, including biomarkers or surrogate end points. Those approaches may address some of the concerns, but will generally also introduce new concerns, as the additional sources of information could also mislead the adaptation decision.

Simulations

Platform trials often include multiple design features which introduce complex dependencies between analyses, such that analytic solutions to evaluate trial performance or operating characteristics may be infeasible. Special design features in platform trials include but are not limited to the addition and removal of trial arms, the respective time of addition and removal, the use of a common control, or the allocation procedure.

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Furthermore, common considerations such as the recruiting speed or interim analyses and stopping rules are important. Not only the type I error or power need to be evaluated, but also outcomes such as expected trial duration, time to primary analysis of a specific treatment arm, or success probability are of interest. Tools to aid simulation of platform trials and the exploration of the simulation results have been developed within EU-PEARL.[69,70]

In the Q&As on CCTs,[16] complex clinical trials require interactions between clinicians, methodology experts such as statisticians, biometricians, modeling and simulation experts, and project teams. Simulations are requested to evaluate the operating characteristics, including the type I error, when using Bayesian statistics. The simulations should be documented in advance of a clinical trial application or marketing authorization application.

The FDA guidelines on interacting with the FDA on complex innovative designs[4] and on COVID-19 master protocols[19] address the fact that a common feature of many CCTs is the need for simulations rather than mathematical formulae to estimate trial operating characteristics. They point out that "for studies intended to provide substantial evidence of effectiveness, it can be advantageous to discuss plans for trial simulations at meetings with the FDA." For further detailed recommendations regarding the content and format of simulation reports it is referred to the FDA guideline on adaptive designs.[44] Besides general recommendations regarding simulation studies, it furthermore provides guidance on what to include in a simulation report, which should be submitted prior to initiation of an adaptive design trial.

CONCLUSION AND NEXT STEPS

The complexity of the IRPs due to their cross-company and collaborative nature poses regulatory and ethical challenges. One aim of EU-PEARL was to understand and address these challenges through discussions with regulatory experts from the EU regulatory network and ethic committee members. In addition, representatives from the EMA were involved throughout the project, for example, as members of the external advisory board. Not only did the project benefit from the regulatory involvement but also vice versa. Saesen *et al*.[71] recently published a review of the EMA's involvement in external research projects, including EU-PEARL. They stated that by participating in relevant external research projects, the EMA can gain "awareness of innovative research and of its hurdles and opportunities."[71] Furthermore, gaps in regulatory science can be identified. It also became evident that the open and trusted discussion among all relevant stakeholders was crucial for the success of the project.

The aim of this paper was to summarize methodological and design issues of platform trials from a regulatory, ethical, and HTA perspective, and to present the current regulatory status. Some of the issues have been clarified or are already becoming standard in the regulatory context, but some still need further discussion and guidance from regulatory authorities. Questions such as when and how to adjust for multiplicity, and whether and when NCCs may be used in the primary analysis, are still controversial topics, especially among regulators. Platform trials can be multi-company trials and also be subject to multi-national regulations. Dedicated guidelines, from health authorities, such as the EMA, are still limited. Therefore, close and early interactions with the authorities are recommended for the initiation and implementation of platform trials, but also for the development of trial design methodology.

Next steps for academics and industry to foster multi-stakeholder trials

Recently, Koenig *et al*.[2] summarized 10 learnings from EU-PEARL. The lack of sufficient regulatory guidance is considered as one obstacle. Yet, especially for multistakeholder platform trials, this is not the main blocking issue. Independent sponsors, for example, contract research organizations or, as Koenig *et al*.[2] suggest, academic hospitals, are needed to facilitate these trials. They state that additional efforts are needed to pave the route for such academic sponsors of (complex) clinical trials. They need to be adequately resourced and, even more importantly, well experienced in conducting CCTs to adequately fulfill regulatory and administrative duties.

Uncertainty in the regulatory acceptability of platform trial designs eventually slows down protocol design discussions for intervention owners and may thereby lead to delayed study execution. Due to the increased complexity, the lack of experience and the resulting uncertainty, the probability of technical and regulatory success of a platform trial may be viewed as decreased, compared with conventional clinical trials. As discussed during the ACT EU Methodology workshop,[72] an increased transparent sharing of positive and negative platform submission and execution experiences among stakeholders is required to reduce the uncertainty and accelerate the design process. Whereas acceptable from the health-authority side (e.g., as implemented in the FDA complex innovative design pilot project[31]), sharing of such information may not necessarily be desired from the intervention-owner perspective, as study design discussions will eventually reveal the drug development strategy and thereby lead to a competitive disadvantage. EU-PEARL provided a legal framework, in which such discussions could be held, while still respecting confidentiality agreements. Appropriate frameworks to maintain a sufficiently blinded exchange of lessons learned will need to be established to accelerate design discussions and further decrease uncertainty.

Sharing of data is identified as another issue.[2] The use of shared concurrent controls and especially shared NCCs leads to partial unblinding and information leakage once an arm is completed. This could lead to regulatory concerns.[18] Furthermore, commercial treatment owners might fear direct comparisons of different treatments, which is facilitated by platform trials with the need for data sharing also for active arms, for example, to model potential time trends.

The issue of partial unblinding could be tackled, for example, by restricting primary analyses to concurrent controls and by strict adherence to a well-designed protocol. To counteract the fear of commercial sponsors to disclose data to competitors, adequate data sharing agreements need to be in place. Analyses can then be conducted by an independent entity under a well-defined scope of analyses. This entity needs to be a trusted organization.

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Care needs to be taken that the data sharing agreement is also able to meet regulatory needs. This means that treatment owners need to be accountable for any regulatory submission, as also discussed at the ACT EU Methodology workshop.[72] Of note, comparisons of treatments might be of high interest to patients and payers.[2,18,73] Although this should be taken into consideration, this should not additionally hamper the uptake of platform trials. One should rather embrace the benefits which are there than asking for more.

Next steps from regulators to support platform trials

Following the public consultation, a final version of the FDA's draft guideline on master protocols[18] is expected and during the public consultation for the EMA concept paper on platform trials,[9] the EFPIA submitted several comments referring to the outputs and deliverables from EU-PEARL that could be used in drafting the reflection paper on platform trials.[64] Initially, the reflection paper was planned to be adopted by the end of 2024.[9] At the ACT EU Workshop on Methodology Guidance,[62] the multistakeholder discussion on platform trials was continued and the need for methodological guidance was reinforced. Hofner[65] shared the current plans for the reflection paper and clarified that finalization of the reflection paper might take longer than anticipated, but that the EMA remained ambitious.

Instead of relying on the usual and rather static scientific advice procedures, the need to continue an open and collaborative dialog on CCTs, as exemplified in EU-PEARL, was stressed during the workshop.[73] Consequently, regulators should try to implement an adequate exchange and learning format, potentially facilitated by the ACT EU or the EMA working parties, such as the Scientific Advice Working Party[74] or the Methodology Working Party.[75] The ACT EU initiative should also play an important role in overcoming obstacles in the procedural and administrative obstacles for the approval of platform trials, which were introduced with the EU Clinical Trials Regulation.

Learnings from EU-PEARL

It is obvious that complex platform trials may not be the appropriate solution for every research problem. Specifics of research problems differ and hence may make some design elements appropriate and efficient, while making others overly complex and harming interpretability. Many situations exist where coordinated research through platform trials is beneficial to expedite the identification and development of new treatments, and to enable timely decision making addressing patients' needs, for example, when it is hard to enroll patients, collect relevant end point data, or for indications with very poor prognosis.

During the EU-PEARL project it became evident that different stakeholders are faced with different obstacles when designing, conducting, and assessing such CCTs. Academics need more awareness, training, and resources to take an active role in the initiation and conduct of platform trials. Pharmaceutical industry needs to value the benefits of platform trials over the added complexities, and to overcome their hesitation to let others take a sponsor role. They also need to overcome their concerns against direct or indirect comparisons of treatments within the platform. On the other hand, patients, academics, and HTA experts might want to refrain from wanting too much by always requesting head-to-head comparisons of all treatments just because master protocols might make these possible. Regulators need to work on relevant guidelines and help overcoming regulatory and procedural hurdles. Finally, all need to come together in an open and trusted environment to make the best use of the common resources and to obtain the best possible results for patients in a patient-centric and timely manner.

SUPPORTING INFORMATION

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CONFLICTS OF INTEREST

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