D2.1. Report on Terminology, References and Scenarios for Platform Trials and Master Protocols

853966 – EU-PEARL

EU Patient-cEntric clinical tRial pLatforms

WP2 – Scientific, Regulatory and Operational Methodology

Lead contributor	Tom Parke (14, Berry Consultants LLP)
	tom@berryconsultants.com
Other contributors	Juan M. Pericàs (1, VHIR)
	Martin Posch (4, MUW)
	Natalie Heimbach, Hans-Peter Dauben (18, EUROSCAN)
	Cecile Spiertz, Christopher Zizzamia, Molli Sandor (24, JANSSEN)
	Peter Mesenbrink (25, NOVARTIS)
	Catherine Dubanchet (32, SERVIER)

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Acronyms and Abbreviations

Acronym / Abbreviation	Meaning
ANDAs	Abbreviated new drug applications
BEST	Biomarkers EndpointS and other Tools resource
CHMP	Committee for Medicinal Products for Human Use
CTFG	Clinical Trials Facilitation Group
D	Deliverable
DMCs	Data Monitoring Committees
EHR	Electronic Health Records
EMEA	European Medicines Agency (sic)
EU-PEARL	EU Patient-cEntric clinical tRial pLatforms
EWP	Efficacy Working Party
FDA	Food and Drug Administration
GDPR	General Data Protection Regulation
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IMI	Innovative Medicines Initiative
IMP	Investigational Medicinal Product
IRP	Integrated Research Platform
ISA	Intervention Specific Appendix
LNHS	Longitudinal Natural History Study
MAMS	Multi-Arm Multi-Stage
NDA	New drug application
OS	Overall Survival
PFS	Progression Free Survival
PoC	Proof of Concept
Q&A	Question and Answer
RAR	Response Adaptive Randomization
RWD	Real World Data
SAP	Statistical Analysis Plan
SME	Small and Medium Enterprise
SoC	Standard of Care
WP	Work Package

1 Publishable Summary

This EU-PEARL deliverable is published as a resource to the EU-PEARL project. It contains a selective glossary of terms for complex trials, and platform trials in particular, that we hope will inform and promote consistent usage. The domain of EU-PEARL's research, Integrated Research Platforms and Platform Trials is relatively new and consequently the vocabulary is fluid.

Several comprehensive clinical trial terminology lists are already available in literature (in particular ADAPT SMART and the Eurordis glossary). The glossary presented here aims to minimize how much it duplicates from these references, selecting just the key terms relevant to the EU-PEARL project and the domain of Platform Trials. The aim is to ensure consistent use across the consortium as well across all external stakeholders involved. We have tried as much as possible to draw on external definitions from authoritative sources and to avoid creating a potential EU-PEARL specific vocabulary that might form a barrier to communication with the wider world.

This document also lists the current published platform trials and tabulates their key design features.

Lastly, drawing on recent publication surveys, this document contains a curated and rated set of publication references for Platform Trials.

2 EU-PEARL Glossary

This glossary of terms relevant to the EU-PEARL project has - where possible - been drawn on existing definitions.

References for glossary terms:

[ADAPT-SMART] http://adaptsmart.eu/wp-content/uploads/2016/04/D2-02-ADAPT-SMART-Glossary-first-edition.pdf

[Berry] www.berryconsultants.com

[BEST] Biomarkers EndpointS and other Tools Resource. https://www.ncbi.nlm.nih.gov/books/NBK326791/

[Cambridge] The Cambridge Dictionary of Statistics, 4th Edition, B.S. Everitt, A. Skrondal.

[Carauna] "Longitudinal studies" Edward Joseph Caruana, Marius Roman, Jules Hernández-Sánchez, Piergiorgio Solli, J Thorac Dis. 2015 Nov; 7(11): E537–E540. doi: 10.3978/j.issn.2072-1439.2015.10.63

[CTFG] Recommendation paper on the initiation and conduct of complex clinical trials. https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2019_02_CTFG_Recommendation_paper_on_Complex_Clinical_Trials.pdf

[EHR] https://ec.europa.eu/health/ehealth/overview_en

[EMA] https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/conditional-marketing-authorisation

[EU-GDPR] https://gdpr.eu

[Eurordis] The Eurordis clinical trials glossary:

https://www.eurordis.org/IMG/pdf/CT_GLOSSARY_FINAL.pdf

[FDA] Master Protocols: Efficient Clinical Trial Strategies to Expedite Development of Oncology Drugs and Biologics: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/master-protocols-efficient-clinical-trial-design-strategies-expedite-development-oncology-drugs-and

[FDA2] https://www.fda.gov/drugs/development-resources/surrogate-endpoint-resources-drug-and-biologic-development

[FDA3] https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure

[Hughes] Nigel Hughes, EFPIA Co-ordinator "The European Health Data and Evidence Network, What is it?". https://www.miracum.org/wp-content/uploads/2018/09/What-is-IMI-EHDEN-NH050618.pdf

[ICH E9] Statistical Principles for Clinical Trials: https://www.ema.europa.eu/en/ich-e9-statistical-principles-clinical-trials

[ICH E10] Choice of Control Group in Clinical Trials: https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-10-choice-control-group-clinical-trials-step-5_en.pdf

[IMI call] IMI2 Call15-01: https://ec.europa.eu/info/funding-tenders/opportunities/portal/screen/opportunities/topic-details/imi2-2018-15-01

[MAMS] "Some recommendations for multi-arm multi-stage trials", James Wason,

Dominic Magirr, Martin Law, Thomas Jaki, Statistical Methods in Medical research, Volume: 25 issue: 2, page(s): 716-727

[Park et al] "Systematic review of basket trials, umbrella trials, and platform trials: a landscape of master protocols", Park et al, Trials 20, Article number 572 (2019)

[Woodcock] "Master protocols to study multiple therapies, multiple diseases, or both." Woodcock J, LaVange LM. N Engl J Med. 2017;377:62-70

Term	Definition	Reference
Electronic Health Records (EHR)	EHRs refer to the comprehensive medical records of an individual that are accessible in electronic form.	[new EU-PEARL]
EMA marketing authorisation	The approval to market a medicine in one, several or all European Union Member States.	[EMA]
EMA conditional marketing authorisation	The EMA may grant a conditional marketing authorisation for one year renewable annually where: • "the benefit-risk balance of the product is positive; • it is likely that the applicant will be able to provide comprehensive data; • unmet medical needs will be fulfilled; • the benefit to public health of the medicinal product's immediate availability on the market outweighs the risks due to need for further data." Also commonly used to gain approval on a surrogate outcome where the final outcome is not easily obtainable. For example: Because of the complexity and novelty of a Platform Trial, possibly using a Bayesian Analysis, its Regulatory Pathway may be to a potential conditional marketing authorisation, leading to full marketing authorisation on completion of a further, subsequent study.	[EMA] [EU-PEARL]
EU-GDPR	The European General Data Protection Regulation was drafted and passed by the European Union (EU). It imposes obligations for organizations, regardless of location, that target or collect data related to people in the EU.	[EU-GDPR]
Federated Data Network	A federated data network uses a common platform to facilitate bi-directional data flow, data harmonisation (from diverse sources) and connectivity for research reuse; supported by a harmonisation fund and	[Nigel Hughes]

	certified/qualified SME network. A federated data network retains local provenance and governance while facilitating remote connectivity with RWD for research reuse.	
Integrated Research Platform (IRP)	An Integrated Research Platform is a novel clinical development concept centered on a master trial protocol which can accommodate multi-sourced interventions using the existing infrastructure of hospitals and federated patient data in design, planning and execution, while an optimized regulatory pathway for these novel treatments has been assured.	[EU-PEARL]
Longitudinal Natural History Study (LNHS)	An observational study in which subjects are followed for the same variable(s) over a period of time. “This study type is particularly useful for evaluating the relationship between risk factors and the development of disease, and the outcomes of treatments over different lengths of time”.	[ADAPT SMART], [Caruana]
Regulatory Pathway	The route used to assess the regulatory aspects of a marketing authorization. All medicines must be authorized before they can be marketed and made available to patients. For the European Union (EU) this relates to the procedures to obtain approval for a medicinal product in an EU country or European Union. For the USA, drugs are approved by the FDA by three main regulatory pathways: (i) 505(b)(1) new drug applications (NDAs); (ii) 505(b)(2) NDAs; and (iii) 505(j) abbreviated NDAs (ANDAs).	[new EU-PEARL]
Stakeholders	In the context of EU-PEARL there are many stakeholders. The principal ones identified in the EU-PEARL proposal are: “pharma, patients, clinicians, regulators and reimbursement agencies”.	EU-PEARL proposal, Part B.

2.1 Types of Master Protocol

Term	Definition	Reference
Basket Trial	To study a single targeted therapy in the context of multiple diseases or disease subtypes. A Master Protocol designed to test a single investigational drug or drug combination in different populations defined by disease stage, histology, number of prior therapies, genetic or other biomarkers, or demographic characteristics. *An alternative definition of Basket Trial exists whereby each disease subtype is given a therapy targeted to that sub-type (e.g. [Renfro & Sargent]).* CTFG define Basket trials as trials that investigate the safety/efficacy/effects of an IMP or combination of IMPs across a variety of populations or sub-populations.	[Woodcock], [FDA]
Platform Trial	To study multiple targeted therapies in the context of a single disease in a perpetual manner, with therapies allowed to enter or leave the platform on the basis of a decision algorithm. *A Platform Trial is by definition an extension of an "Umbrella Trial", it may or may not include elements of a "Basket Trial" as well. –I-SPY 2 (see section: 4.3.3) and GBM-Agile (see section 4.3.9) include Basket Trial elements.*	[Woodcock], [FDA]
Umbrella Trial	To study multiple therapies in the context of a single disease. A Master Protocol designed to evaluate multiple investigational drugs administered as single drugs or as drug combinations in a single disease population. CTFG define Umbrella trials as trials that investigate the safety/efficacy/effects of several IMPs in a single population.	[Woodcock], [FDA]
Matrix Trial	This term describes a trial that is **both** an Umbrella Trial (testing multiple therapies) and a Basket Trial, including analyses in multiple disease sub-types. Many Platform Trials are Matrix Trials with the additional feature that as the trial progresses and treatments leave the trial, new treatments may enter, and the trial does not have an initially fixed duration or sample size.	[new EU-PEARL]

Multi-Arm Multi-Stage (MAMS) design	A Multi-Arm Multi-Stage trial using the designs described by Thomas Jaki and Dominic Magirr and implemented in their MAMS R-package (a software package that can be used in the free "R" statistical programming system). These analyse the trial results in a Group Sequential framework and control overall Type-1 Error, making them potentially attractive for Umbrella or Platform Trials intended for regulatory submission. This framework avoids features that are more problematic for regulatory submission such as response adaptive randomization, sub-group analysis, and Longitudinal Modelling.	[MAMS]

2.2 Master Protocol

Term	Definition	Reference
Master Protocol	"The term "master protocol" refers to a single overarching design developed to evaluate multiple Hypothesis, and the general goals are to improve efficiency and establish uniformity through standardization of procedures in the development and evaluation of different interventions. Under a common infrastructure, the master protocol may be differentiated into multiple parallel sub-studies to include standardized trial operational structures, patient recruitment and selection, data collection, analysis, and management." "In contrast to traditional trial designs, where a single drug is tested in a single disease population in one clinical trial, master protocols use a single infrastructure, trial design, and protocol to simultaneously evaluate multiple drugs and/or disease populations in multiple sub-studies, allowing for efficient and accelerated drug development." In a Platform Trial the protocol will have the infrastructure to drop interventions and allow new interventions or combinations of interventions to enter the study based on decision rules in the Master Protocol. Master protocols are used to describe study designs such as basket, umbrella, matrix, or platform designs. CTFG define master protocol as describing the overall clinical trial design applicable to all related sub-protocols such as the clinical trial rationale, objectives, Endpoints, benefit-risk assessment, shared procedures regarding safety monitoring and reporting, and a common screening platform dictating trial subject eligibility and/or treatment allocation.	[Park et al] [FDA]
Intervention Specific	Master Protocols for Platform Trials have an extensible set of appendices, one for each intervention. The	ref [IMI call]

Appendix (ISA)	appendix describes the specific features of the intervention and treatment of patients randomized to that intervention. A major aspect of a Platform Trial's design is what design features are common across the trial and hence in the main body of the protocol and what features will be described in the ISAs and hence can vary from intervention to intervention. Synonyms are: "Domain Specific Appendices" and "Comparison Protocols" and "sub-protocols". CTFG define 'sub-protocols' to be the separate parts of a complex clinical trial design that will be described by sponsors in separate protocols or within a common protocol as study cohorts or arms depending on the context.

2.3 Statistical Terms for Platform Trials

Term	Definition	Reference
Adaptive Design	An adaptive design allows the pre-specification of flexible components to the major aspects of the trial, like the treatment arms used (dose, frequency, duration, combinations, etc.), the allocation to the different treatment arms, the eligible patient population, and the sample size. An adaptive design can learn from the accruing data what the most therapeutic doses or arms are, allowing for example, the design to home in on the best arms.	[Berry]
Bayesian Analysis	The Bayesian approach provides a mathematically rigorous and principled methodology for making decisions under arbitrarily complex scenarios. It provides a powerful framework for determining optimal behaviour in the face of uncertainty. The Bayesian approach is ideal for many adaptive designs because it provides a naturally sequential learning framework and allows the efficient and transparent integration of complex clinical trial and external data and natural prediction of future events (e.g. clinical trial results).	[Berry]
Interim Analysis	A pre-planned analysis during a clinical trial that looks at the accumulating data in order to make an early decision or adaptation. An intrinsic element of an adaptive trial.	[new EU-PEARL]
Longitudinal Model	An optional part of the analysis of the patient outcome when the patients' final outcomes are a significant time after their randomization. A longitudinal model allows partial information from patients in the trial who have not yet reached their final outcome at an interim	[new EU-PEARL]

	analysis, to be included in that analysis. Longitudinal models can also be used to impute data that may not be available from missed assessments or subjects dropping out from the trial prior to the final assessment.	
Disease Progression Model	A model used to characterize patient clinical outcome(s) that takes into account their disease state and other baseline patient characteristics upon their entry into the trial or that emerge during the course of their participation in the trial. This allows the analysis of the patient outcome to have greater power than a conventional analysis when a broader population of patients is included in the trial.	[new EU-PEARL]
Common/Shared Control	In an Umbrella Trial/Platform Trial, in which multiple treatments are being tested, instead of each treatment having its own control arm within the Intervention Specific Appendix (ISA), there is one shared Common Control arm. This greatly increases the efficiency of the trial and improves the probability of patients who participate receiving a new treatment rather than an agreed “Standard of Care”.	[new EU-PEARL]
Contemporaneous Control	When using a Common/Shared Control in a Platform Trial, in which there are concerns that the “Standard of Care” received by patients on the Control Arm may change over time, or the profile of the patients enrolled on the trial may change over time, the comparison of a treatment’s effects may be restricted to a comparison with those subjects on the Control arm who were enrolled/randomized into the trial in the same time period as subjects who were allocated to the treatment. These are the “Contemporaneous Control” subjects.	[new EU-PEARL]
Historical Control	A group of individuals treated in the past and used as a comparison group when one is not available in the existing trial or sub-study or at the same time but in a different setting.	[ICH E10]
Response Adaptive Randomization (RAR)	This is when the Randomization Ratios are updated after an interim analysis based on the relative responses to the treatment that have been observed.	[new EU-PEARL]
Early Stopping	When a clinical trial or a trial arm is stopped before the planned ending point due to pre-defined decisions rules due to 1) superior efficacy, 2) insufficient efficacy, or 3) unacceptable safety risk.	[new EU-PEAL]

2.4 Biomarker Terms that are Particularly Relevant

Term	Definition	Reference
Biomarker	A biomarker is a defined characteristic that is objectively measured as an indicator of normal biological processes, pathologic processes, or responses to an exposure or intervention, including therapeutic interventions. In a drug development context, biomarkers may be used for several different purposes such as identifying patients for clinical trial enrolment, monitoring the safety of a therapy, or determining if a treatment is having the desired effect on the body.	[FDA2]
Diagnostic Biomarker	A Biomarker used to detect or confirm presence of a disease or condition of interest or to identify individuals with a subtype of the disease.	[BEST]
Monitoring Biomarker	A Biomarker measured serially for assessing status of a disease or medical condition or for evidence of exposure to (or effect of) a medical product or an environmental agent.	[BEST]
Pharmacodynamic / response Biomarker	A Biomarker used to show that a biological response has occurred in an individual who has been exposed to a medical product or an environmental agent.	[BEST]
Predictive Biomarker	A Biomarker used to identify individuals who are more likely than similar individuals without the biomarker to experience a favourable or unfavourable effect from exposure to a medical product or an environmental agent.	[BEST]
Prognostic Biomarker	A Biomarker used to identify likelihood of a clinical event, disease recurrence or progression in patients who have the disease or medical condition of interest.	[BEST]
Biomarker Qualification	A conclusion, based on a formal regulatory process, that within the stated context of use, a medical product development tool can be relied upon to have a specific interpretation and application in medical product development and regulatory review.	[BEST]
Safety Biomarker	A Biomarker measured before or after an exposure to a medical product or an environmental agent to indicate the likelihood, presence, or extent of toxicity as an adverse effect.	[BEST]
Surrogate Endpoint	An endpoint that is used in clinical trials as a substitute for a direct measure of how a patient feels, functions, or survives. A surrogate endpoint does not measure the clinical benefit of primary interest in and of itself, but rather is expected to predict that clinical benefit or harm based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence. The FDA distinguishes between “reasonably likely and	[BEST] [FDA3]

	"generally accepted" surrogate biomarkers. There is a list of accepted surrogate biomarkers on their website.	
Susceptibility / risk biomarker	A Biomarker that indicates the potential for developing a disease or medical condition in an individual who does not currently have clinically apparent disease or the medical condition.	[BEST]
Biomarker Validation	A process to establish that the performance of a test, tool, or instrument is acceptable for its intended purpose. Analytical validation is the validation of the test, tool or instrument's technical performance (such as sensitivity and specificity), but not a validation of its usefulness. Clinical validation is the process to establish that the test, tool, or instrument acceptably identifies, measures, or predicts the concept of interest.	[BEST]

2.5 Essential Statistical Terms

Following are terms that will be used by the Statisticians in WP2 and therefore require common understanding:

Term	Definition	Reference
Alternative Hypothesis	This usually refers to the proposal expressing the particular way the Null Hypothesis is held to be false. It usually reflects a difference the researcher hopes to demonstrate.	Eurordis
Clinical Endpoint	A characteristic or variable that reflects how a patient feels, functions, or survives. Clinical endpoints are distinct measurements or analyses of disease characteristics reflecting the effect of a therapeutic intervention in a clinical trial or study.	Eurordis
Covariate	A variable that may affect the outcome of a clinical trial, either because it has a direct causal relationship to the outcome or because it influences the outcome in a non-causal fashion. A Platform Trial may be flexible in the covariates collected in the trial, allowing new ones to be added that are relevant to a new incoming treatment.	Online medical dictionary.
Hypothesis	A supposition or assumption advanced as a basis for reasoning or argument, or as a guide to experimental investigation.	Eurordis
Inference	The reasoning involved in drawing a conclusion or making a logical judgment on the basis of circumstantial evidence and prior conclusions rather than on direct observation. In statistics, the use of information from a sample to draw conclusions about the population from which the sample was taken.	Eurordis

Multiplicity	A feature of certain inferential problems that arise in clinical trials with multiple objectives (e.g. the investigation of several treatments, subgroups or Clinical Endpoint), or if a series of hypotheses are tested. If not accounted for, multiplicity can increase the probability of making a Type-1 Error and confound the interpretation of statistical Inferences made.	ICHE9
Null Hypothesis	The proposal that no difference exists between groups or that there is no association between risk indicator and outcome variables. If the null hypothesis is true, then the findings from the study are the result of chance or random factors. In clinical trials, the null hypothesis is the prediction that there is no relationship between your treatment and your outcome.	Eurordis
Outcome	The impact of care provided to a patient as measured on the Clinical Endpoint. Outcomes can be positive, such as the ability to walk freely as a result of rehabilitation, or negative, such as the occurrence of bedsores as a result of lack of patient mobility.	Eurordis
Power	The probability of rejecting the null hypothesis when it is false. Power gives a method of discriminating between competing tests of the same hypothesis, the test with the higher power being preferred. It is also the basis of procedures for estimating the sample size needed to detect an effect of a particular magnitude.	[Cambridge]
Posterior Distribution	The posterior distribution $f(\theta\|x)$ expresses what is known about θ after observing the data x, given our prior distribution $f(\theta)$. Where θ is some value we wish to estimate, such as a treatment effect.	adapted from [Cambridge]
Treatment Modalities / Treatment Domains	Platform Trial such as REMAP-CAP (www.remapcap.org) are randomized to receive treatments in each of one or more categories (modalities / domains) such as antibiotic, antiviral and steroid.	[new EU-PEARL]
Type-1 Error	A rejection of a Null Hypothesis when it is true. An example of Type 1 Error is finding a substance effective when it is not. This is an error of "seeing too much in the data"	Eurordis
Type-2 Error	An acceptance of a Null Hypothesis when it is false. An example of Type II Error is not finding a substance effective when it is. This is an error of "not seeing enough in the data".	Eurordis

3 Summary of Features of Relevant Existing Trials

3.1 Summary of the Trials

Trial	Reference	Trial Description	Trial Type	Disease	Endpoint
LUNG-MAP	Herbst RS, et al. Lung master protocol (Lung-MAP)—a biomarker-driven protocol for accelerating development of therapies for squamous cell lung cancer: SWOG S1400. Clin Cancer Res 2015; 21: 1514–24	A screening and multi-sub-study randomized phase II/III trial with a hybrid master protocol	Umbrella	Metastatic squamous cell carcinoma of lung	Progression Free Survival (PFS) for phase II and PFS plus Overall Survival for phase III
BATTLE 1	Liu S, Lee JJ. An overview of the design and conduct of the BATTLE trials. Chin Clin Oncol 2015; 4: 33.	BATTLE was a prospective, phase II, biopsy- mandated, biomarker-based, adaptively randomized clinical study in patients with pre-treated, advanced lung cancer	Umbrella	Advanced non-small cell lung cancer	8 week disease control and Overall Survival
BATTLE 2	Gu X, et al. Bayesian Two-stage Biomarker-based Adaptive Design for Targeted Therapy Development. Stat Biosci 2016; 8: 99-128.	BATTLE-2 was a randomized, phase II, multicenter, open-label study in patients with advanced NSCLC refractory to prior platinum-based chemotherapy	Umbrella	Advanced non-small cell lung cancer	8 week disease control
N2M2	Wick W, et al. N2M2 (NOA-20) phase I/II trial of molecularly targeted therapies plus radiotherapy in patients with newly diagnosed non-MGMT hypermethylated glioblastoma. Neuro-Oncol 2019; 21: 95-105	The NCT Neuro Master Match (N2M2) trial is an open-label, multicenter, phase I/IIa umbrella trial	Umbrella	Newly diagnosed non-MGMT hypermethylated glioblastoma	PFS at 6 months

CLUSTER	De Benedetti F, et al. Canakinumab for the treatment of Autoinflammatory Recurrent Fever Syndromes. N Engl J Med 2018; 378:1908-1919.	A randomized, double-blind, placebo controlled study of Canakinumab in patients with hereditary periodic fevers	Basket	Familial Mediterranean Fever (FMF), Hyper-immunoglobulinemia (HIDS), Tumor-necrosis, factor receptor-associated period syndrome (TRAPS)	Complete response (resolution of the baseline disease flare and no new disease flares)
UPSTREAM	Galot R, et al. Personalized biomarker-based treatment strategy for patients with squamous cell carcinoma of the head and neck: EORTC position and approach. AnnOncol 2018; 29: 2313–2327	Non-randomized, open-label, phase II, pilot study of a personalized biomarker-based treatment strategy	Umbrella	SCC of head and neck	Objective response rate or PFS, depending on cohort
AMBITION	Lee JY, et al. An umbrella study of biomarker-driven targeted therapy in patients with platinum-resistant recurrent ovarian cancer: a Korean Oncology Group study (KCOG 3045), Ambition. Japan JClin Oncol 2019; 49: 789–792	This is a randomized, multi-center, open-label, phase II study for HRD+ patients and a biomarker-driven multiple-arm phase II study for HRD-patients	Umbrella	Platinum resistant recurrent ovarian cancer	Objective response rate
VIKTORY	Lee J, et al. Tumor Genomic Profiling Guides Patients with Metastatic Gastric Cancer to Targeted Treatment: The VIKTORY Umbrella Trial. Cancer Discov 2019 Oct;9(10):1388-1405	The VIKTORY trial classified metastatic GC patients on 8 biomarkers and where possible allocated patients to matched trials. The results for the matched patients were	Umbrella	Metastatic gastric cancer	Overall response rate or PFS

		compared to the results for the unmatched.			
FOCUS 4	Kaplan R, et al. Evaluating many treatments and biomarkers in oncology: a new design. J Clin Oncol 2013; 31: 4562–68.	A multi-arm, multi-stage phase II/III randomized trial in colorectal cancer	Platform	Colorectal cancer	PFS
STAMPEDE	Sydes MR,et al. Flexible trial design in practice—stopping arms for lack-of-benefit and adding research arms mid-trial in STAMPEDE: a multi-arm multi-stage randomized controlled trial. Trials 2012; 13: 168.	A multi-arm, multi-stage phase II/III randomized controlled trial in prostate cancer	Platform	Prostate cancer	Overall survival
I-SPY 2	Barker AD, Sigman CC, Kelloff GJ, Hylton NM, Berry DA, Esserman LJ. I-SPY 2: an adaptive breast cancer trial design in the setting of neoadjuvant chemotherapy." Clin Pharmacol Ther 2009; 86: 97–100.	A multi-arm open label, adaptively randomized, phase II study in neoadjuvant breast cancer	Platform	Neoadjuvant breast cancer	Pathological complete response
PREVAIL II	The PREVAIL II Writing Group. A Randomized, Controlled Trial of ZMapp for Ebola Virus Infection. N Engl J Med. 2016; 375: 1448-1456.	A two arm, adaptively randomized, open-label, phase I/II trial	Platform	Ebola virus disease	Mortality at 28 days
EPAD	Ritchie CW, et al. The European Prevention of Alzheimer's Dementia (EPAD) Longitudinal Cohort Study: Baseline Data Release V500.0. J Prev Alzheimers Dis. 2020;7:8-13.	A phase II, PoC randomized multi-arm, multi-site trial	Platform	Alzheimer's	Cognitive outcomes (RBANS)
DIAN-TU	Bateman RJ, et al.	A phase II/III randomized, double-blind, placebo controlled study	Platform	Alzheimer's	Cognitive composite

	The DIAN-TU Next Generation Alzheimer's prevention trial: adaptive design and disease progression model. Alzheimer's Dement. 2017; 13:8-19				
GBM-AGILE	Alexander BM,et al. Adaptive Global Innovative Learning Environment for Glioblastoma: GBM AGILE. Clin Cancer Res. 2018 ;24:737-743.	A phase II/III multi-arm, adaptively randomized open-label study	Platform	Glioblastoma	Overall survival
INSIGhT	Alexander BM, et al. Individualized Screening Trial of Innovative Glioblastoma Therapy (INSIGhT): A Bayesian Adaptive Platform Trial to Develop Precision Medicines for Patients With Glioblastoma. JCO Precision Oncology 2019 :3, 1-13	A phase II, randomized multi-arm open-label trial	Platform	Glioblastoma	Overall survival
ALIC4E	Protocol & SAP	A platform, response-adaptive, open randomized controlled pragmatic trial	Platform	Influenza-like illness	Time to return to usual daily activity
Intergroup LEAP	Walter RB, et al. Intergroup LEAP Trial (S1612): A Randomized Phase II/III Platform Trial to Test Novel Therapeutics in Medically Less Fit Older Adults with Acute Myeloid Leukemia. Am J Hematol. 201; 93: E49–E52	A randomized phase II/III trial, with subsequent groups of new arms grouped in "cassettes"	Platform	Acute Myeloid Leukemia	Overall survival

3.2 Description of features

Compare to a common control: A simple and common efficiency of Platform Trials is to just have a single control arm as a shared comparator for all investigational treatment arms. This can create some challenges. If the trial is long running, the response in the control arm may change, the Standard of Care may change, and may even evolve to include a successful treatment from earlier in the trial. The usual approach to overcome this is to only compare an arm to the control subjects enrolled at the same time – a "Contemporaneous Control". Another issue is the allocation ratio to Control as the number of treatments in the trial change. While there is only one treatment, allocation might be 1:1, when there are four treatments it might be 1:1:1:1:1. Randomization, supply and patient consent need to take this into account.

Sub-group analyses: In some trials, subjects are randomized across all treatments in all sub-groups (though possibly the randomization is "response adaptive" and not equal). In others, the treatment available depends on the patient's sub-group. In FOCUS 4, for example, a treatment is initially only available in its targeted sub-group, becoming available in the other sub-groups after it is successful in its targeted sub-group.

Borrowing control data across time: A more sophisticated solution to the problem of the response on the control arm changing over time, is to include that possibility in the model, and therefore enable comparison of a treatment to the whole (time-adjusted) control data. This may not be accepted by regulators except for rare diseases, but can be used in phase II platform trials.

Disease progression / Survival endpoint: These trials have typically long endpoints that can make adaptation difficult.

Uses a safety / efficacy trade-off: These trials are designed to make decisions based on the balance of efficacy and safety. Different stakeholders may place a higher emphasis on one over the other. For example, patients may be more willing to tolerate safety issues in favour of efficacy than other stakeholders.

Interim analyses / early decision making: These trials have interim analyses either at fixed points in the accrual of an arm or at regular intervals of the whole trial – and then at these interims

Types of early decision: Based on estimates of efficacy or safety.

Decision made for: Typically, the early decisions are for early stopping for success or futility.

Adaptive Randomization: The modification of randomization probabilities to favour the treatment arms with what cumulative data show as having the best treatment effect, or the best treatment effect for a patient's particular sub-group. Often combined with a fixed allocation to control and a fix-allocation "burn-in" period before adaptive randomization starts.

Flexible, extensible analysis model: Not used in any of these trials, but a design appropriate for future outbreaks of influenza or antibiotic resistant disease, structured to easily add new covariates or modalities of treatment used in combination with other modalities.

Prediction of subject final outcome: Using some form of longitudinal model incorporating early observations of the same measure that will be taken at the patient's final assessment, or some early measurement, to predict a patient's final outcome (e.g. I SPY-2's use of tumour imaging to predict PCR) to increase the amount of information available for interim decision making.

3.3 Table of Trial Features

Trial	Compared to a single control	Sub-group analyses	Borrowing control data across time	Disease progression/ Survival endpoint	Trial uses safety / efficacy trade-off	Interim Analyses – Early Decision making	Types of early decision	Decision made for	Adaptive Randomization	Flexible, extensible, analysis model	Prediction of subject final outcome
LUNG-MAP	No	Yes	No	Yes	No	Yes – Yes	Efficacy	Futility	No	N/A	No
BATTLE 1	No	Yes	No	Yes	No	No – Yes	Efficacy	Futility	Yes, in second step	N/A	Yes
BATTLE 2	No	Yes	No	Yes	No	Yes – Yes	Efficacy	Futility	Yes	N/A	Yes
N2M2	No	No	No	Yes	Yes	Yes – Yes	Efficacy / Safety	Futility	No	N/A	No
CLUSTER	No	Yes	No	No	No	No – No	N/A	N/A	No	N/A	Yes (non-responder)
UPSTREAM	No	No	No	No	No	No – No	N/A	N/A	No	N/A	No
AMBITION	No	Yes	No	Yes	No	No – No	N/A	N/A	No	N/A	No
VIKTORY	No		No	Yes	No	Yes – Yes	Safety	Toxicity	No	N/A	No
FOCUS 4	Yes	Yes	No	Yes	No	Yes – Yes	Efficacy	Futility	No	N/A	No
STAMPEDE	Yes	No	No	Yes	No	Yes – Yes	Efficacy / Safety	Futility	No	N/A	No
I SPY-2	Yes	Yes	Yes	No	No	Yes – Yes	Efficacy	Success & Futility	Yes	No	Yes
PREVAIL II	Yes	Yes	No	Yes	No	Yes – No	No	Superiority	Yes		Yes
EPAD	Yes	Yes	No	Yes	No	Yes – Yes	Efficacy	Futility	No	N/A	Yes
DIAN-TU	No	No	No	Yes	No	Yes – Yes	Efficacy	Futility	Yes	N/A	N/A
GBM-AGILE	Yes	Yes	Yes	Yes	N/A	Yes – Yes	Efficacy	Futility	Yes	N/A	Yes
ALIC4E	Yes	Yes	Yes	No	No	Yes – Yes	Efficacy	Success & Futility	Yes	No	No

4 EU-PEARL References and recommended reading

4.1 General Overviews (Terminology)

We use a **3 categories rating**:

●●● Most relevant papers for EU-PEARL

●● Papers relevant to EU-PEARL on a specific topic (see the description for what that topic is) – read if that topic is relevant

● Papers included because of their likely visibility, but of less relevance to EU-PEARL (see the description for why).

Reference	Rating	Description
Woodcock J, LaVange LM. Master protocols to study multiple therapies, multiple diseases, or both. N Engl J Med. 2017;377:62-70	●●●	Probably the definitive introduction to Master Protocol trials (Umbrella, Basket, Platform).
FDA Master Protocols: efficient clinical trial design strategies to expedite development of oncology drugs and biologics - guidance for industry.	●●●	The FDA's guidance on Master Protocol trials. It is also a good introduction to the topic.
Lesser N, Naaz B. [in EU-PEARL Consortium shared repository] Master Protocols, Shifting the drug development paradigm. Deloitte Insights	●●	Another introduction to Master Protocol trails – an executive level summary. However, the expected savings seem to be on the low side and the assumptions behind them are not described.
The Adaptive Platform Trials Coalition Adaptive platform trials: definition, design conduct and reporting considerations. Nat Rev Drug Discov. 2019;18:797-807.	●●●	A good introduction concentrating on platform trials, adaptation and embedding in clinical practice, providing a different emphasis from the other introductions.
The Clinical Trials Facilitation and	●	This document may well form the basis for an EMA position paper on Master Protocol trials., Our perception is

Coordination Group (CTFG) "Recommendation Paper on the Initiation and Conduct of Complex Clinical Trials"		that it is currently at an early stage and still requires substantial re-drafting.
London AJ, Kimmelman J. Clinical Trial Portfolios: A Critical Oversight in Human Research Ethics, Drug Regulation, and Policy. Hastings Cent Rep. 2019;49:31-41.	●●	Mainly about the ethics of clinical trials from a portfolio perspective rather than that of a single trial, with mention of platform trial benefits. The authors point out that they allow some control of the pacing and coordination of trials (as separate trials are now different arms in the same trial) and this has ethical advantages.
Sudhop T, Brun NC, Riedel C, Rosso A, Broich K, Senderovitz T. Master protocols in clinical trials: a universal swiss army knife? Lancet Oncol2019; 20:e336-e342	●●	Interesting because unlike the other introductions it has a stronger emphasis on challenges of platform trials. This publication highlights problems of consenting patients into a changing trial and possible issues with the number of protocol amendments. The paper also raises the concern that the European legal framework may have issues with the multi-treatment and flexible nature of platform trials. Note that this publication has a different definition of what an Umbrella trial is compared to our EU-PEARL definition.
Berry SM, Connor JT, Lewis R. The Platform Trial: An efficient strategy for evaluating multiple treatments. JAMA. 2015;313:1619-1620.	●●	Very brief (2 pages) introductory piece.
Saville BR, Berry SM. Efficiencies of platform trials: A vision of the future. Clin Trials 2016;13: 358-366	●●●	A simulation exploration of a simplified treatment development example showing how the compound effects of platform trials and adaptive elements could transform the speed and efficiency of the discovery of a treatment for a disease.
Renfro LA, Sargent DJ. Statistical controversies in clinical research: basket trials, umbrella trials, and other master protocols: a review and examples. AnnOncol 2017; 28: 34–43,	●	An early document describing basket and umbrella trials with concentration on the genetic biomarker driven designs such as SHIVA, NCI-MATCH and NCI-INSIGHT. The definitions given in the paper of Basket, and Umbrella trials are very oncology-centric.

Koenig F, et al. The evolution of master Protocol Clinical Trial Designs - A Systematic Literature Review. submitted to Clin Ther	●●	An excellent list of references that was used as a basis for the list of references here. Because the most relevant references have been incorporated in this document – this publication may be of interest only if you are seeking a wider set of references.
Collignon O, et al. Current statistical considerations and regulatory perspectives on the planning of confirmatory basket, umbrella and platform trials. Am Soc Clin Pharmacol Therap 2020 Feb 4. doi: 10.1002/cpt.1804.	●●●	A strong paper, particularly on the multiplicity issues of the potentially large number of sub-studies within a master protocol.

4.2 Example Umbrella Trials

4.2.1 BATTLE

Reference	Rating	Description
Kim ES, et al. The BATTLE trial: personalizing therapy for lung cancer. Cancer Discov 2011; 1: 44–53.	●	Randomization according to Bayesian adaptive algorithm – precision medicine-multidrug. Methodology in line with IRP but lack of practical details. Methodology is from 2005 – Might be more appropriate to focus on BATTLE 2
Liu S, Lee JJ. An overview of the design and conduct of the BATTLE trials. Chin Clin Oncol 2015; 4: 33.	●●●	Overview of the BATTLE 1 and BATTLE2 trials with an interesting description of the statistical methodology, lessons learnt from BATTLE 1, methodology of a 2 stage – biomarker based adaptive randomization design.

4.2.2 LUNGMAP

Reference	Rating	Description
Herbst RS, et al. Lung master protocol (Lung-MAP)—a biomarker-driven protocol for accelerating development of therapies	●●●	Public private collaboration that groups several biomarker targeted trials into a single trial to reduce screen failure. The operational and protocol development are consistent across all sub-studies (it uses a master protocol framework). A regulatory approval pathway is provided for drugs and companion diagnostic biomarkers.

for squamous cell lung cancer: SWOG S1400. Clin Cancer Res 2015; 21: 1514–24		Shared infrastructure for screening, database, enrollment, site management. Should increase efficiency of drug development (earlier access of efficient drugs for patients, cheaper development). No operational details.
Steuer CE, et al. Innovative clinical trials: the LUNG-MAP study. Clin Pharmacol Ther 2015;97: 488-91	●	Less detailed than Herbst paper above.
Ferrarotto R, et al. Lung-MAP—framework, overview, and design principles. Chin Clin Oncol 2015; 4: 36–41.	●●●	Information about trial framework: screening procedure, statistical design, adaptability of the framework.
LUNG-MAP. A ground breaking collaborative approach to clinical trials. http://www.lung-map.org	●●	Website for patients and investigators. Interesting for patient centric approach. The website includes information on the location of sites and on the progress of the study.

4.2.3 ALCHEMIST

Reference	Rating	Description
Govindan R, et al. ALCHEMIST trials: a golden opportunity to transform outcomes in early-stage non-small cell lung cancer. Clin Cancer Res 2015; 21: 5439–44.	●	Platform trial in a sense that 4 trials are linked. A screening trial to centrally genotype patients. 3 therapeutic trials to which patients are randomized to a drug treatment versus placebo depending on their genotyping. Note that this is not an adaptive design
Gerber DE, Oxnard GR, Govindan R. ALCHEMIST: bringing genomic discovery and targeted therapies to early-stage lung cancer. Clin Pharmacol Ther 2015; 97: 447–450.	●	Similar information to Govindan paper above, but less detailed.

4.2.4 BATTLE-2

Reference	Rating	Description
Gu X, et al. Bayesian Two-stage Biomarker-based Adaptive Design for Targeted Therapy Development. Stat Biosci 2016; 8: 99-128.	●●●	Bayesian two-stage biomarker-based adaptive randomization for the development of targeted agents. Clearly outlines Bayesian decision rules at each stage and provides simulation results to justify decision rules that have been defined for Stage 1 and Stage 2 along with the trial implementation plans.
Papadimitrakopolou V, et al. The BATTLE-2 Study: A Biomarker-Integrated Targeted Therapy Study in Previously Treated Patients With Advanced Non-Small-Cell Lung Cancer. JClin Oncol 2016; 34:3638-3647	●●	Strong clinical paper to accompany Gu et. al. that describes the results of Stage 1 of the study that was trying to identify predictive biomarkers of overall response for the 4 treatment arms studied. Unfortunately, the overall response rates are very low and prevent the identification of such biomarkers. The setup of the paper is helpful in explaining why the study was a failure (very difficult, refractory patient population). Based on the underlying assumptions, if the study observed the response rates that were planned for, the study had a chance to be successful.

4.2.5 N2M2

Reference	Rating	Description
Pfaff E, et al. Feasibility of real-time molecular profiling for patients with newly diagnosed glioblastoma without MGMT promoter hypermethylation- the NCT Neuro Master Match (N2M2) pilot study. Neuro-Oncol 2018; 20: 826-837	●	Paper focuses exclusively on the molecular profiling process that occurs and the categorization of the different biomarker matches that a subject may have from the medicines being studied. Information is explained in more detail as part of the Wick et al. (2018) paper below.
Wick W, et al. N2M2 (NOA-20) phase I/II trial of molecularly targeted therapies plus radiotherapy in patients with newly diagnosed non-MGMT hypermethylated glioblastoma.	●●	Two-part design with first part dedicated to identifying new biomarkers and new disease targets. Patients who are matching receiving the target therapy for which they are match in combination with radiotherapy. Two treatments in the design were reserved for subjects without matching biomarkers (asinercept and atezolizumab) with radiotherapy. The paper describes how it is determined if a subject meets the criteria for a specific targeted therapy and how a therapy will be stopped for dose-limiting

Neuro-Oncol 2019; 21: 95-105.		toxicities based on a Bayesian decision rule. The trial's Phase IIa part is exploratory and the paper does not describe how success will be determined for moving a combination therapy to the next stage of development.

4.2.6 CLUSTER

Reference	Rating	Description
De Benedetti F, et. al. Canakinumab for the treatment of Autoinflammatory Recurrent Fever Syndromes. N Engl J Med 2018; 378:1908-1919.	●●●	An umbrella trial that evaluated three rare autoimmune conditions that could be evaluated by the same endpoint at 16 weeks (complete response defined as resolution of the baseline disease flare and no new disease flares) and had similar inclusion/exclusion criteria with the exception of the genetic variation between the disease phenotypes. Each condition was evaluated independently, and the Type I error rate controlled within each cohort. The only big difference across cohorts was that the patients in the familial Mediterranean fever cohort were receiving canakinumab primarily as add-on treatment to colchicine in addition to the NSAIDs and corticosteroids being used as background therapy to manage disease flares. Full study protocol available in the supplementary materials.

4.2.7 UPSTREAM

Reference	Rating	Description
Galot R, et al. "Personalized biomarker-based treatment strategy for patients with squamous cell carcinoma of the head and neck: EORTC position and approach." AnnOnco 2018; 29: 2313–2327	●●	Review paper of the study design used to evaluate SCC of the head and neck. Detailed description given of the design and how patients are assigned to immunotherapy and biomarker-driven cohorts. Describes how the protocol has been designed with IRPs in mind, with a core protocol and addendum for each of the cohorts. It also describes the prioritization algorithm if a patient is genetically positive and has other pre-existing conditions (able/unable to swallow).
Saada- Bouzid E, Le Tourneau C, Beyond EGFR Targeting in SCCHN: Angiogenesis, PI3K and Other Molecular Targets. Front Oncol. 2019: 13;9:74	●	Review article on the use of EGFR targeted therapy in SCCHN and UPSTREAM is mentioned for its evaluation in p16-negative EGFR amplified, HER3-low and PTEN-high tumors.

4.2.8 AMBITION

Reference	Rating	Description
Lee JY, et al. An umbrella study of biomarker-driven targeted therapy in patients with platinum-resistant recurrent ovarian cancer: a Korean Oncology Group study (KCOG 3045), Ambition. Japan JClinOncol 2019;49: 789–792	●	A pilot study for biomarker-driven targeted therapy in patients with platinum-resistant recurrent ovarian cancer. Treatment allocation performed based HRD and PD-L1 status (positive or negative) to one of four arms to evaluate objective response rate (ORR) along with PFS and OS. HRD+ patients were randomized while the HRD- patients were assigned based on PD-L1 expression. Study is useful for defining a process for mixing randomization to treatment and assigning treatment based on gene expression.

4.2.9 VIKTORY

Reference	Rating	Description
Lee J, et al. Tumor Genomic Profiling Guides Patients with Metastatic Gastric Cancer to Targeted Treatment: The VIKTORY Umbrella Trial. Cancer Discov 2019;9:1388–405	●●	Targeted trial in metastatic gastric cancer. Capivasertib (AKT inhibitor), savolitinib (MET inhibitor), selumetinib (MEK inhibitor), adavosertib (WEE1 inhibitor), and vistusertib (TORC inhibitor) were tested with or without chemotherapy. Used tumor profiling to select treatment most suitable for that patient and assessed how profiling to determine which trial a patient enters could improve survival for the patient. Clinical sequencing program was conducted with 8 pre-specified genomic biomarkers and 10 independent biomarker associated clinical trials in patients with metastatic gastric cancer. Clearly described the process were assigned treatment based on the molecular profiling results. More details are provided in the supplementary materials.

4.3 Example Platform Trials

4.3.1 FOCUS4

Reference	Rating	Description
Kaplan R. The FOCUS4 design for biomarker stratified trials. Chin Clin Oncol 2015; 4: 35.	●●●	Provides overview of FOCUS4 design and puts it into perspective by comparing it to STAMPEDE and MAMS.
Kaplan R, et al.	●●●	Adds more detail for FOCUS4. The protocol randomizes novel agents against placebo in colorectal

Evaluating many treatments and biomarkers in oncology: a new design. J Clin Oncol 2013; 31: 4562–68.		cancer across a number of different biomarker defined population-enriched cohorts. Within each population, the trial uses a multi-staged approach with flexibility to adapt in response to planned interim analyses for lack of activity.
Medical Research Council (MRC) Clinical Trials Unit. "FOCUS4: molecular selection of therapy in metastatic colorectal cancer: a molecularly stratified randomized controlled trial programme. http://www.focus4trial.org	●●●	Provides overview about the programme. Useful for sites and patients as well. Web page contains contact information, status details, protocols and other useful information.

4.3.2 STAMPEDE

Reference	Rating	Description
Sydes MR, et al. Flexible trial design in practice—stopping arms for lack-of-benefit and adding research arms mid-trial in STAMPEDE: a multi-arm multi-stage randomized controlled trial. Trials 2012; 13: 168.	●●●	Provides a study overview: five research and one control arms, each undergoing a pilot stage (focus: safety, feasibility), three intermediate 'activity' stages (focus: failure-free survival), and a final 'efficacy' stage (focus: overall survival). Lack-of-sufficient-activity guidelines support the pairwise interim comparisons of each research arm against the control arm. Result: recruitment to a MAMS trial and mid-flow changes its design are achievable with good planning.

4.3.3 I-SPY 2

Reference	Rating	Description
Barker AD, Sigman CC, Kelloff GJ, Hylton NM, Berry DA, Esserman LJ. I-SPY 2: an adaptive breast cancer trial design in the setting of neoadjuvant chemotherapy. Clin Pharmacol Ther 2009; 86: 97–100.	●●●	Provides an overview and discussion of the trial design. For the assignment of drugs to patients, Bayesian methods of adaptive randomization are used to achieve a higher probability of efficacy. The adaptive design approach provides a model for rapid assessment of novel phase II drugs and identification of effective drugs and drug combinations.
Berry DA. The brave new world of clinical cancer research: adaptive biomarker-driven trials	●●	One author provides an overview of adaptive design trials and different setups. .

integrating clinical practice with clinical research. Mol Oncol 2015;9:951-9.		
Catenacci DVT. Next-generation clinical trials: novel strategies to address the challenge of tumor molecular heterogeneity. Mol Oncol 2015;9:967-96	●●●	Overview of complex trial designs (next generation clinical trial designs) in light of challenges of tumor molecular heterogeneity.
Park JW, et al for the I-SPY-2 investigators. Adaptive Randomization of Neratinib in Early Breast Cancer. N Engl J Med 2016; 375:11-22	●●	An account of the results of Neratinib from I-SPY 2.
Rugo HS, et al. for the I-SPY 2 investigators. Adaptive Randomization of Veliparib-Carboplatin Treatment in Breast Cancer N Engl J Med 2016; 375:23-34	●●●	An account of the results of Veliparib-Carboplatin from I-SPY 2.

4.3.4 EBOLA

Reference	Rating	Description
Berry SM, et al. A response adaptive randomization platform trial for efficient evaluation of Ebola virus treatments: A model for pandemic response. Clin Trials 2016; 13:22-30.	●●	Adaptive platform design. Multiple agents and combinations will be investigated simultaneously. New agents may enter the trial as they become available and failing agents may be removed. A critical feature of this design is the use of response adaptive randomization to assign treatment regimens. As the trial progresses, the randomization ratio evolves to favor the arms that are performing better, making the design also suitable for all-cause pandemic preparedness planning. The West African Ebola outbreak became controlled before the trial could be initiated.

4.3.5 PREVAIL II

Reference	Rating	Description
The PREVAIL II Writing Group A Randomized, Controlled Trial of ZMapp for Ebola Virus Infection. N Engl J Med. 2016; 375: 1448-1456.	●●	Adaptive design which allowed an investigational agent subsequently shown to have activity against Ebola could then be incorporated into an evolving standard of care and provided as the backbone therapy in each trial group and against which newer agents could be tested.

4.3.6 REMAP-CAP

Reference	Rating	Description
The REMAP-CAP Trial. Randomised, Embedded, Multifactorial Adaptive Platform trial for Community- Acquired Pneumonia. January 2018. https://www.remapcap.org/	●●●	A lot of detail now available on this website – the design is notable for the statistical approach that applies Bayesian adaptive methods.

4.3.7 EPAD

Reference	Rating	Description
Ritchie CW et al. The European Prevention of Alzheimer's Dementia (EPAD) Longitudinal Cohort Study: Baseline Data Release V500.0. J Prev Alzheimers Dis. 2020;7:8-13.	●●	Overview of a clinical trial very relevant to EU-PEARL. However, it has not yet been initiated due to lack of sponsors coming forward with treatments to test.

4.3.8 DIAN-TU

Reference	Rating	Description
Bateman RJ, et al. The DIAN-TU Next Generation Alzheimer's prevention trial: adaptive design and disease progression model Alzheimer's Dement. 2017; 13:8-19.	●●●	Detailed account of a clinical study very relevant to EU-PEARL.

4.3.9 GBM Agile

Reference	Rating	Description
Alexander BM, et al. Adaptive Global Innovative Learning Environment for Glioblastoma: GBM AGILE. Clin Cancer Res. 2018;24:737-743.	●●●	Provides a detailed account of a trial very relevant to EU-PEARL.

4.3.10 INSIGhT

Reference	Rating	Description
Alexander BM, et al. Individualized Screening Trial of Innovative Glioblastoma Therapy (INSIGhT): A Bayesian Adaptive Platform Trial to Develop Precision Medicines for Patients With Glioblastoma. JCO Precision Oncology 2019 :3, 1-13	●●●	Provides a detailed account of a Bayesian adaptive platform trial design. Phase II, initially with 3 arms compared to common control, After burn-in randomization to arms is adaptive based on the probability of being better than control on the (earlier) PFS endpoint in the patient's subgroup. Analysis includes 3 binary biomarkers. Success/futility both early and final is based on the OS endpoint.
Alexander BM, Cloughesy TF. Platform trials arrive on time for glioblastoma. Neuro-Oncol *2018;*20: 723–725	●●●	Brief comparison of INSIGhT, N2M2 and GBL Agile, but a good discussion of the problems of assignment vs randomization in a biomarker driven trial.

4.3.11 ALIC4E

Reference	Rating	Description
Butler CC, et al. A trial like ALIC4E: why design a platform, response-adaptive, open, randomised controlled trial of antivirals for influenza-like illness? EERJ Open Res 2018; 4:pii 00046-2018	●●	Open label, pragmatic, platform trial, with response adaptive randomization. Provides rationale for the use of a response adaptive, pragmatic platform trial, but not a lot of detail on the design.
Practice B: Interventional trial influenza-like-illness in primary care – work package 4. https://www.prepare-europe.eu/About-us/Workpackages/Workpackage-4	●	ALIC4E is a trial designed as part of prepare-europe.eu. Additional information is likely to be added at a later date.
Bongard E, et al. Antivirals for influenza-like illness? A randomised controlled trial of clinical and cost effectiveness in primary care (ALIC4E): the ALIC4E protocol. BMJ Open 2018;8:e021032	●●	Contains protocol details, but lacks details of the proposed statistical analysis.

4.3.12 Intergroup LEAP

Reference	Rating	Description
Walter RB, et al. Intergroup LEAP Trial (S1612): A Randomized Phase II/III Platform Trial to Test Novel Therapeutics in Medically Less Fit Older Adults with Acute Myeloid Leukemia. Am J Hematol. 2018; 93: 49–52	●●	Provides unique approach in testing arms in ”cassettes”. Instead of arms entering when there is a “slot free” they enter in groups, and each group has its own control. Within a “cassette” arms can wait until a slot is free.

4.3.13 SHIVA

Reference	Rating	Description
Le Tourneau C, Paoletti X, Servant N et al. Randomised proof-of- concept phase II trial comparing targeted therapy based on tumour molecular profiling vs. conventional therapy in patients with refractory cancer: results of the feasibility part of the SHIVA trial. Br J Cancer 2014; 111: 17–24	●	Instructive as to how complex a precision medicine trial can be, and the attendant limitation of the interpretability of the results.
Le Tourneau C, Delord J-P, Goncalves A, et al. "Molecularly targeted therapy based on tumour molecular profiling versus conventional therapy for advanced cancer (SHIVA): a multicentre, open-label, proof-of-concept, randomized, controlled phase II trial." Lancet Oncol 2015; 16: 1324–1334	●	
Tsimberidou AM, Kurzrock R. Precision Medicine: lessons learned from the SHIVA trial Lancet Oncol 2015: 16 : 579-580	●	Criticisms of the SHIVA trial--not of platform trials per se, but of the design of this particular trial. Patients unlikely to respond to a monotherapy, the matching of everolimus with patients with RICTOR alterations, patients had hormone receptor abnormalities so response to hormone therapy was unlikely, other matches (of treatment to biomarker) were incorrect, patients on treatment were assigned treatment by

		algorithm, but patients on control were assigned therapy by physician.
Paoletti X, et al. Design and statistical principles of the SHIVA trial Chin Clin Oncol 2015: 4: 32 (3)	●	This article emphasizes that the trial is the complete treatment algorithm to SoC, not the treatments individually.

4.3.14 NCI-IMPACT

Reference	Rating	Description
"NCI-MPACT: molecular profiling-based assignment of cancer therapy for patients with advanced solid tumors." https://clinicaltrials.gov/ct2/show/NCT01827384	●	May be of limited relevance to EU PEARL.
Do K, O'Sullivan Coyne G, Chen AP. An overview of the NCI precision medicine trials NCI MATCH and MPACT. Chin Clin Oncol 2015; 4: 31.	●	"Both trials contain multiple arms with small number of patients designed not as definitive trials but more as exploratory trials in order to guide further exploration of both tumor and pathways."
Abrams J et al. National Cancer Institute's Precision Medicine Initiatives for the New National Clinical Trials Network. Am Soc Clin Oncol Educ Book. 2014:71-6	●	See comments above.

4.4 Platform Trial Operational Experiences

Reference	Rating	Description
Shiavone F, et al. [in EU-PEARL consortium shared repository] This is a platform alteration: a trial management perspective on the operational aspects of adaptive and platform and umbrella protocols. Trials 2019; 20:264	●●●	Provides insights into the operational aspects of Platform Trials.

Hague D, et al [in EU-PEARL consortium shared repository] 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	●●●	Provides insights into the data management aspects of Platform Trials.
Morell L, et al [in EU-PEARL consortium shared repository] Mind the gap? The platform trial as a working environment. Trials 2019; 20:297	●●●	Provides insights into the staffing aspects of Platform Trials.

4.5 Relevant Good Practice Guidance

Reference	Rating	Description
ICH E6 Good Clinical Practice (R2: Integrated Addendum to ICH E6 (R1) Guidance for Industry).	●●●	Authoritative and extensive guidance on designing, conducting, recording and reporting clinical trials.
EMA guideline on Data Monitoring Committees (EMEA/CHMP/EWP/5872/03 Corr).	●●●	An overview of the role of DMCs.
"Q&A document - Reference Safety Information (RSI)" published on the CTFG webpage in November 2017.	●●●	This is a set of authoritative answers to key questions concerning the Reference Safety Information section of an Investigator's Brochure for a clinical trial.
Duke Margolis Center for Health Policy. Pioneering statistical approaches to accelerate drug development through adaptive trial designs. June 30, 2016 https://healthpolicy.duke.edu/publications/pioneering-statistical-approaches-accelerate-drug-development-through-adaptive-trial	●●●	This is an article about an FDA sponsored workshop providing an introduction to the use of adaptive designs and Bayesian statistics in clinical trials.
Adaptive Designs for Clinical Trials of Drugs and Biologics. Draft Guidance for Industry	●●●	The FDA guidance for adaptive design clinical trials. Completely re-written in 2018 to replace the 2010 draft that in hindsight was felt to be too cautious and had

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/adaptive-design-clinical-trials-drugs-and-biologics-guidance-industry		resulted in dampening down enthusiasm for adaptive trials. Contains useful reference case studies, types of adaptation and main advantages.
Draft Guidance for Industry Master Protocols: Efficient Clinical Trial Design Strategies To Expedite Development of Oncology Drugs and Biologics Draft Guidance for Industry https://www.fda.gov/regulatory-information/search-fda-guidance-documents/master-protocols-efficient-clinical-trial-design-strategies-expedite-development-oncology-drugs-and	●●●	This document specifically addresses issues with master protocol designs, and though relatively short, covers the major areas.
CHMP: Reflection paper on methodological issues in confirmatory clinical trials planned with an adaptive design. https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-methodological-issues-confirmatory-clinical-trials-planned-adaptive-design_en.pdf	●●●	A thorough document on adaptive designs for confirmatory trials.
Effective delivery of Complex Innovative Design Cancer Trials—A consensus statement https://www.nature.com/articles/s41416-019-0653-9	●●	Provides recommendations based on I_SPY-2 experiences.

5 EU-PEARL PARTICIPANTS

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.**
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. Alliance. **Global Alliance for TB Drug Development Non-Profit Organisation**