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## European Federation of Pharmaceutical Industries and Associations

✳ **Position Paper**

# Innovation in Clinical Trial Design:  A review of The Clinical Trial Design Landscape

A white paper by the EFPIA Clinical Trial Design Taskforce

on behalf of the EFPIA Clinical Research Expert Group

**EFPIA Brussels Office**
Leopold Plaza Building ✳ Rue du Trône 108
B-1050 Brussels ✳ Belgium
Tel: + 32 (0)2 626 25 55 ✳
www.efpia.eu ✳ info@efpia.eu

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**Authors**

Simon Bennett, Biogen

Nicky Best, GlaxoSmithKline

Susan Bhatti, Merck Healthcare KGaA

Solange Corriol-Rohou, AstraZeneca

Marielle Eerdekens, Grunenthal

Christine Fletcher, GlaxoSmithKline (lead)

Rod Junor, Pfizer

Mireille Muller, Novartis

Tom Parke, Berry Consultants

Susan Sandler, Janssen Pharmaceutical Companies of Johnson & Johnson

Stefan Schwoch, Eli Lilly

**EFPIA Brussels Office**
**Leopold Plaza Building ✳ Rue du Trône 108**
**B-1050 Brussels ✳ Belgium**
**Tel: + 32 (0)2 626 25 55 ✳**
**www.efpia.eu ✳ info@efpia.eu**

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## Glossary

| Term | Detailed definition |
|---|---|
| Adaptive designs | An adaptive design is defined as a design that allows modifications to the trial and/or statistical procedures of the trial after its initiation without undermining its validity and integrity. The purpose is to make clinical trials more flexible, efficient and fast. |
| Enrichment designs | Enrichment designs are intended to increase the efficiency of drug development and support precision medicine by tailoring treatments to those patients who will benefit based on clinical, laboratory, genomic, and proteomic factors. |
| Master protocol | A master protocol is an overarching protocol designed to answer multiple questions. Master protocols may involve one or more interventions in multiple diseases or a single disease, as defined by current disease classification, with multiple interventions, each targeting a biomarker-defined population or disease subtype. |
| Umbrella trial | An Umbrella studies multiple investigational drugs administered as single drug combinations in a single disease population. [Ref FDA Guidance on master Protocols].<br>The trial may include patient sub-grouping and sub-group specific treatments but that is not an essential aspect of an umbrella trial. |
| Basket trial | A basket trial studies a single therapy in multiple diseases or disease subtypes (such as disease age, histology's, genetic or other biomarkers) [Ref FDA Guidance on Master Protocols]. |
| Platform trial | A platform trial studies multiple therapies in a single disease in a perpetual and open-ended manner, with treatments leaving the trial when complete and new ones entering the trial when they become available and there is room in the trial to accommodate them. |
| Historical control | Old data is used to compare with new data from new trials. Information is essentially "borrowed" from historical data. |

**EFPIA Brussels Office**
**Leopold Plaza Building ✳ Rue du Trône 108**
**B-1050 Brussels ✳ Belgium**
**Tel: + 32 (0)2 626 25 55 ✳**
**www.efpia.eu ✳ info@efpia.eu**

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## Commonly used Acronyms

| | |
|---|---|
| CER | Comparative Effectiveness Research |
| CREG | Clinical Research Expert Group |
| CHMP | Committee for Medicinal Products for Human Use |
| CRM | Continuous Re-Assessment Method |
| CTA | Clinical Trial Application |
| CTFG | Clinical Trials Facilitation Group |
| DIA | Drug Information Association |
| DMC | Data Monitoring Committee |
| EFPIA | European Federation of Pharmaceutical Industries and Associations |
| EMA | European Medicines Agency |
| EU | European |
| EUnetHTA | European network for Health Technology Assessment |
| FDA | Food and Drug Association |
| HTA | Health Technology Assessment |
| IMI | Innovative Medicines Initiative |
| IMP | Investigational Medicinal Product |
| IMPD | Investigational Medicinal Product Dossier |
| MAMS | Multi-Arm Multi-Stage |
| PDUFA | Prescription Drug User Fee Act |
| PhRMA | Pharmaceutical Research and Manufacturers of America |
| PSoC | Placebo Standard of Care |
| RAR | Response Adaptive Randomisation |
| RCT | Randomised Controlled Trial |
| USA | United States of America |

**EFPIA Brussels Office**
**Leopold Plaza Building ✱ Rue du Trône 108**
**B-1050 Brussels ✱ Belgium**
**Tel: + 32 (0)2 626 25 55 ✱**
**www.efpia.eu ✱ info@efpia.eu**

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**EFPIA Brussels Office**
**Leopold Plaza Building ✳ Rue du Trône 108**
**B-1050 Brussels ✳ Belgium**
**Tel: + 32 (0)2 626 25 55 ✳**
**www.efpia.eu ✳ info@efpia.eu**

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## Executive Summary

In recent years there has been significant focus on using innovative and more complex clinical trials with the aim of increasing the effectiveness and efficiency of clinical trials to provide high quality data to support regulatory and reimbursement decision making. Regulatory agencies are increasingly supporting the use of complex trials with a number of guidelines and/or reflection papers emerging. This white paper is a landscape review of innovation in clinical trial design, on behalf of the European Federation of Pharmaceutical Industries and Associations (EFPIA) Clinical Research Expert Group (CREG). The primary focus is on enrichment designs, adaptive designs, master protocols and the use of historical controls in clinical trials. Key findings include:

**Enrichment designs** Using enrichment designs for drug approval and/or companion diagnostics approvals is very attractive but challenging and success will depend on how much prior knowledge and biological rationale are available before starting pivotal trials. Key uncertainties include whether the proposed enrichment will yield positive outcomes (e.g. have we enriched for the right thing) and screening test performance (e.g. can the test be implemented in routine clinical practice), and regulatory/Health Technology Assessment (HTA) agencies' acceptance of the enrichment strategy.

**Adaptive designs** Adaptations can play a key role in the success of clinical trials if properly pre-planned. Interim analyses can also enable stopping of trials for futility and efficacy. Key advantages include statistical efficiency, improved treatment for the subjects in the trial, and improved understanding of new drug effects. Key uncertainties include Type I error rate control, trial integrity, and acceptability to all stakeholders of the evidence generated. Engaging in early dialogue with regulators and HTA agencies can help to reduce some uncertainties and align on evidence generation requirements.

**Master protocols** A master protocol incorporates efficient approaches in clinical trial design enabling multiple questions on different treatment options to be answered in a single study and thus accelerate clinical development. The high complexity of these trial designs requires sophisticated statistical methods to ensure proper randomization, interim analysis and robust criteria for success/futility assessment of each trial arm. Early involvement of regulators, HTA agencies, ethics committees, investigators and patients is essential to ensure any concerns on the design can be addressed. In Europe, an opportunity for multi-national Pre-CTA consultations would be advantageous to explain the master protocol rationale prior to submission. Describing the proposed design in a cover letter for the trial application will aid the understanding of the clinical trial design.

**Use of historical controls** The use of previous control data to support pre and/or post-licensing strategy should be identified early in the clinical development plan and revisited regularly. Where historical data will be used in a clinical trial its use needs to be justified, in particular, how the data were selected, taking into account the disease, population, regulatory and scientific considerations.

Wider stakeholder engagement, in particular regulators and HTA agencies, is needed to understand if data generated from innovative and more complex trial designs will be acceptable for both regulatory and reimbursement decision making. In the future the opportunity to develop an improved process for discussing complex designs with multiple stakeholders prior to the initiation of a study would be advantageous.

**EFPIA Brussels Office**
**Leopold Plaza Building ✳ Rue du Trône 108**
**B-1050 Brussels ✳ Belgium**
**Tel: + 32 (0)2 626 25 55 ✳**
**www.efpia.eu ✳ info@efpia.eu**

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# 1. Introduction

In the Pharmaceutical Industry, clinical trials form an essential part of a drug development program for a new medicine.  Given the burden for patients participating in clinical trials, the time and number of patients required to complete all the phases of drug development, and the high risks and costs of failure at each phase, there has been a focus in recent years to use novel and innovative clinical trial designs throughout all phases of drug development.  The aim of this is to accelerate patient access to new medicines and improve the efficiency and the success rate of clinical trials.

The Clinical Development Expert Group within the European Federation of Pharmaceutical Industries and Associations (EFPIA) established a Clinical Trial Design taskforce with the aim of exploring the current and future landscape of innovation in clinical trial design, and to promote the awareness, understanding and acceptance of these designs amongst stakeholders.  Core to the mission of the taskforce is promoting an ongoing evolution in drug development programs and clinical trials driven by the needs of patients that focus on value-added treatments.

The EFPIA clinical trial design taskforce reviewed the emerging types of clinical trial designs of interest for further research.  An initial range of clinical trial designs were prioritised as it was recognised it would not be feasible to research all possible novel and emerging approaches to clinical trials.  However, it was considered feasible to focus on clinical trial designs identified by regulatory agencies as being of significant interest, such as the FDA and the Complex Innovative Design pilot programme [1] and the EMA draft 'Regulatory Science to 2025' strategy [2], and where there has been some experience of these designs in marketing authorisation applications or subsequent post-authorisation applications.  A literature review was conducted, and relevant information has been included.

Clinical trial innovation also extends to other areas intended to drive efficiency such as usage of common protocol, statistical analysis plan and study report templates and therapeutic area specific data standards across industry as, for example, being developed by TransCelerate [3].  Innovation also includes direct incorporation of patient data from electronic health records into study CRFs, and patient-centric measures, such as patient advisory boards, electronic informed consent, activity monitors and other smartphone enabled technology solutions for measuring patient benefit and replacing study site visits with home visits.  However, these important areas of clinical trial innovation are beyond the scope of this white paper which focuses on the following categories of innovative and novel clinical trial designs:

- ❖ Enrichment designs
- ❖ Adaptive designs
- ❖ Master protocols
- ❖ Use of historical controls in clinical trials

These categories of trials are interlinked.  This white paper is a landscape review of innovation in clinical trial design.  Some aspects are less well understood than others, as such additional papers may follow allowing for a more in-depth discussion and review on specific topics as applicable.

**EFPIA Brussels Office**
**Leopold Plaza Building ✳ Rue du Trône 108**
**B-1050 Brussels ✳ Belgium**
**Tel: + 32 (0)2 626 25 55 ✳**
**www.efpia.eu ✳ info@efpia.eu**

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Every clinical trial features some form of enrichment, as is reflected in the inclusion and exclusion criteria. Such criteria are intended to optimize assay sensitivity and benefit-risk, by defining how patients with the target disease/condition should be selected in terms of diagnosis and severity, which potentially confounding comorbidities, concomitant treatments and other patient characteristics that could affect efficacy assessments should be excluded and which co-morbidities and concomitant treatments should be excluded for reasons of patient safety. There are a multitude of disease specific clinical and regulatory guidelines which cover many of these aspects, especially patient identification.

This approach generally reflects a relatively broad patient population e.g. patients with mild/moderate/severe disease/condition X/Y/Z etc. Studies designed in this (traditional) way may be successful, but in the case of an unsuccessful outcome or when the treatment difference is much smaller than anticipated, interrogation of the data may reveal some patients responded to study drug and others did not. This raises a question of whether those responders are different in some way, whether they can be prospectively identified (e.g. with a specific phenotype or biomarker etc.) and -crucially- whether if a trial were restricted only to that specific subpopulation, the probability of a successful outcome would be increased. This prospective identification of a subpopulation in which assay sensitivity is expected to be increased, is the type enrichment considered herein. As above, it may be a strategy which is implemented after an unsuccessful trial or preferably it is done based upon a thorough understanding of the disease state and the pharmacology of a drug to drive successful outcomes from initial studies in man through to approval.

Clinical trials using adaptive designs have been used for more than a decade and they were introduced with the aim of increasing the probability of a trial achieving a successful outcome. These trials can improve how doses are selected in early phase studies, allow ineffective doses to be dropped in later phase studies and can reduce the time between phases of drug development with seamless designs for example phase 2/3 designs. More recently, complex adaptive designs have emerged where the probability of which treatment group to assign the next patient depends on the responses of previous patients enrolled in the trial using adaptive randomisation schemes.

Whilst adaptive designs have been available for many years, their use was limited. Key factors that have reduced the uptake of more complex designs include a lack of understanding of adaptive design strategies and methodologies, lack of validated software, concerns by industry on the acceptability by regulators and HTA agencies of the evidence generated, logistical burden of conducting more complex designs, and limited expertise to design and implement these types of trials. However, due to the creation of expert groups such as the Drug Information Association (DIA) Adaptive Design Working Group, the increased availability and use of software solutions such as FACTS, emerging FDA regulatory guidance on Adaptive Designs for Clinical Trials of Drugs and Biologics [4], and increase in the number of publications of case studies sharing experiences of alternative trial designs, adaptive designs are now more common place. Despite this, the widespread use of adaptive designs, especially the more complex designs where randomisation schema and treatments to be tested during a trial are modified after a trial starts, is still to be realised.

Another type of clinical trial gaining significant momentum in a range of disease settings, especially oncology, are master protocols. Umbrella, basket and platform trials fall into this category. The paper by Woodcock et al [5] has provided much needed alignment and recommendations for

**EFPIA Brussels Office**
**Leopold Plaza Building ✳ Rue du Trône 108**
**B-1050 Brussels ✳ Belgium**
**Tel: + 32 (0)2 626 25 55 ✳**
**www.efpia.eu ✳ info@efpia.eu**

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terminology, allowing clear definitions and descriptions of these designs and recently a draft guidance on "Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics" [6] has been published by the FDA. Master protocols provide a novel approach for studying a number of new treatments in the same disease (umbrella), for studying a new treatment in a number of related diseases (basket), or for studying multiple therapies in a single disease in a perpetual and open-ended manner (platform). These designs are complex for a variety of reasons: the set of treatments to be studied in a trial can change during the trial, the patient populations to be included in a trial can change over time, and the data to be collected could evolve after a trial has started. Compared to a traditional clinical trial design where these aspects are fixed at the start of a trial, platform trials are complex in terms of their design, how trials are operationalised and how trials are analysed.

In addition to more complex clinical trial designs, there has been an explosion in recent years on the availability of data, in particular, access to existing data sources, Big Data and real-world data. In clinical settings where patient recruitment can be difficult, for example in rare disease populations with limited number of patients, or in more common disease areas where patient recruitment is increasingly difficult due to logistical and patient burden issues, using historical control data to augment or replace a control arm in a randomised control trial is of great interest. The advantages of this approach are the ability to run a clinical trial (that may previously have been considered impractical) effectively and efficiently thereby reducing patient burden as well as time and resources needed for the study. However, there are many challenges, including; when is it appropriate to consider using historical control data; whether the historical control data available contain the specific information of interest; which historical control is most appropriate; what are the potential biases and limitations of the historical controls in terms of their clinical characteristics and treatment strategies that were previously available relative to how current patients are being treated: and which patients are eligible for a treatment. The use of a historical control, whether to partially or completely replace a concurrent control group or to augment a control group, will require more complex statistical methods in both the design and analysis of the clinical trial.

The EFPIA CREG taskforce conducted a series of literature reviews in each of the above listed categories of trial designs. In sections 2-5, the findings from each literature review are summarised including describing the variety of trial designs under each category, highlighting useful reference materials for further reading, identifying published case studies, available regulatory guidance documents, and providing a series of recommendations. The current knowledge, understanding and experience of each of these types of designs varies and this is reflected in the white paper. A great deal of attention is focussed on adaptive designs, in particular understanding what has been learnt from the application of these designs over the last decade. Challenges of each design are discussed, and potential risks and limitations are highlighted. Future considerations highlight key areas of focus to further advance innovation in clinical trial design. The conclusion summarises key points and recommends all stakeholders embrace novel and complex designs where possible in their drug development programs.

## 2.  Enrichment Strategies

### 2.1 Definitions

An enrichment design is defined as "The prospective use of any patient characteristic to select a study population in which detection of a drug effect (if one in fact is present) is more likely than it would be in an unselected population" [7].

**EFPIA Brussels Office**
**Leopold Plaza Building ✳ Rue du Trône 108**
**B-1050 Brussels ✳ Belgium**
**Tel: + 32 (0)2 626 25 55 ✳**
**www.efpia.eu ✳ info@efpia.eu**

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In the wider sense, all clinical trials are enriched in some way through selection criteria. The purpose of selection can be to decrease heterogeneity, to enrich from the prognostic standpoint (for example patients most likely to relapse or to have specific events of interest such as major adverse cardiovascular events), or to use predictive enrichment strategies (recruit only those patients most likely to respond to a drug).

## 2.2 Pre-randomization run in periods

When studies are conducted in conditions in which subjective endpoints are necessary (e.g. pain, depression, anxiety, human abuse liability studies etc.) the pre-randomization period may be utilized to try to avoid recruiting patients with baseline score inflation/deflation, excessive placebo response or identify those refractory to or unable to discriminate treatment benefits. For example, blinded placebo run-in may be incorporated as part of a trial in order to randomize only patients who remain symptomatic under placebo i.e. to exclude patients who respond to placebo (by a pre-defined criterion) who may compromise the opportunity to see a true drug effect if they were randomized. An alternative is the blinded active withdrawal run-in, where only patients whose symptoms get worse on washout of active drug are randomized (i.e. a flare up of symptoms on withdrawal). A third strategy is active run-in which can be used to identify patients who can accurately discriminate active drug effects from placebo, and who can tolerate the active drug.

## 2.4 Predictive enrichment

This is the most promising category in terms of potential for innovative/adaptive design and precision medicine. Identifying patients more likely to respond to an intervention is not a new concept (traditional example: use of antibacterial drug in patients whose organism is sensitive to the antibacterial drug). This strategy is addressing an obvious need for more efficient trials and better benefit-risk for subjects.

For example, this strategy has been successfully implemented in the pain therapeutic area, where it has been recognized for many years that only a proportion of patients actually responds to drugs. Because of precedence and a regulatory preference, analgesic clinical trials have traditionally been conducted in specific patient populations which are based upon well-established clinical diagnoses (e.g. diabetic peripheral neuropathy, post herpetic neuralgia, complex regional pain syndrome etc.). However, it was elegantly established by the German Research Network on Neuropathic Pain in a large patient group that within single clinical diagnoses there is a considerable degree of heterogeneity based upon a number of quantitative sensory testing biomarkers [8]. This was postulated as an explanation for the observation that only a proportion of patients responds to treatment with a given analgesic. Across different pain diagnoses, a number of specific somatosensory profiles (determined by biomarkers) are conserved and this observation led to the idea that targeting a drug to a patient's specific pain phenotype (i.e. irrespective of clinical diagnosis) would lead to a greater treatment effect. This was subsequently demonstrated in a biomarker stratified clinical trial design [9] who showed that oxcarbazepine is more efficacious for relief of peripheral neuropathic pain in patients with the "irritable" vs the "non-irritable" nociceptor phenotype.

Enrichment strategies based on pathophysiological biomarkers are not restricted to academic research. Several have been successfully implemented in reaching the end goal of a drug approval as is apparent from the Summaries of Product Characteristics which can be reviewed at www.medicines.org.uk e.g. Trastuzumab in patients with overexpressed HER-2-neu receptor [10], Imatinib in c-kit positive GIST tumours [11], and Vemurafenib in melanoma with the BRAF mutation.

**EFPIA Brussels Office**
**Leopold Plaza Building ✳ Rue du Trône 108**
**B-1050 Brussels ✳ Belgium**
**Tel: + 32 (0)2 626 25 55 ✳**
**www.efpia.eu ✳ info@efpia.eu**

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[12].  However, with the development of more complex, "personalized" biomarkers, with less obvious mechanistic link to the drug effect, innovative approaches are called for.

## 2.5 Genomic biomarkers in oncology

In oncology, genomic material is frequently collected and analysed retrospectively for predictive value. In general, signals need to be confirmed in prospective trials, and this is where several approaches; adaptive or not, have been discussed [13, 14,15]. Key considerations include reducing time, and numbers of patients and control of type I error, by splitting the trials in 2 phases, retrospective and prospective.

The 2019 FDA guidance document on enrichment strategies provides general recommendations on study designs as well as numerous references, applying to different situations, including adaptive randomization designs, with strategies to control type 1 error rates.  The numerous references provided in the guidance document, as well as references from a literature search, provide technical and statistical methods to address those issues.

There are however few examples of those strategies having been used successfully for approval and the feasibility of this approach may be country-specific – certain countries require specific lists of genetic markers for informed consent forms at the beginning of the trial which may not be compatible with exploratory analyses during the conduct of an adaptive trial unless every conceivable molecular marker has been pre-specified.

## 2.6 Design issues

Several papers have described a theoretical framework for prospective predictive biomarker clinical validations.  Figure 1 summarises three types of design: biomarker stratified design (A), enrichment design (B), and biomarker-strategy design (C). Depending on the clinical setting and prior knowledge the recommendations for their respective use are summarized in Table 1 [16].  The FDA guidance includes recommendations consistent with the above.   In practice, those designs have been adopted for academic trials but have rarely been used in confirmatory trials for drug registration.

## 2.7 Biomarker qualification and companion diagnostic co-development

Prognostic and predictive enrichment are heavily dependent on the performance characteristics of the screening test and on whether or not the test can be utilized in the real world post-approval setting. If the test is not routinely already available in clinical usage, consideration to developing a companion diagnostic is necessary. The definition of a companion diagnostic is a test that provides information that is essential for safe and effective use or a corresponding drug or biological product.

In the context of drug development, FDA issued draft guidance on "Principles for Co-development of an In Vitro Companion Diagnostic Device with a Therapeutic Product" [17], "Biomarker Qualification: Evidentiary Framework Guidance for Industry and FDA Staff DRAFT GUIDANCE" [18] and "Developing and Labeling In Vitro Companion Diagnostic Devices for a Specific Group or Class of Oncology Therapeutic Product" (draft guidance, Dec 2018) [19].  While the EMA "Concept paper on the development and lifecycle of personalised medicines and companion diagnostics that measure predictive biomarkers which help to assess the most likely response to a particular treatment" [20] has not been followed by a complete guideline yet. While a process has been developed by FDA for collaboration between agencies for in vitro diagnostics and drug regulators, this has not been the case so far in Europe although EMA has published "letters of support" and guidance for obtaining scientific advice on biomarker qualification. A proposed process was described at a stakeholder meeting held in April 2017, and the general recommendation is to apply for CHMP qualification

**EFPIA Brussels Office**
**Leopold Plaza Building ✳ Rue du Trône 108**
**B-1050 Brussels ✳ Belgium**
**Tel: + 32 (0)2 626 25 55 ✳**
**www.efpia.eu ✳ info@efpia.eu**

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opinion "on the acceptability of a specific use of the proposed method (e.g. use of a biomarker) in a research and development (R&D) context (non-clinical or clinical studies), based on the assessment of submitted data". The letters of support issued so far from that process are involving disease related markers, potential prognostic markers (for Alzheimer, COPD, toxicity markers), but no companion diagnostic.
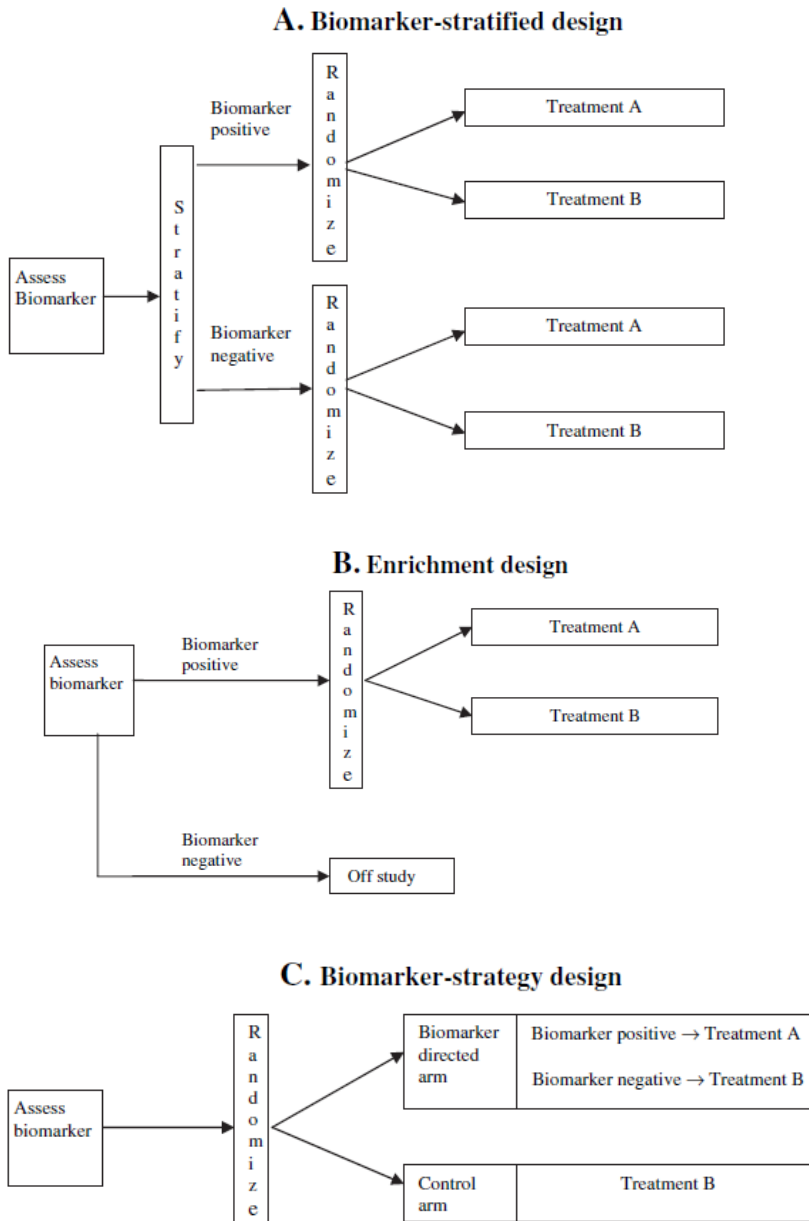
The new in vitro medical device directive [**Error! Reference source not found.**] is specifically addressing the companion diagnostic devices, which are to be treated as high risk device and require consultation with drug authorities. A process is being developed for approval of such devices, similar to what is needed for drug device combinations. It is not very clear how clinical trial applications for drug trials including a companion diagnostic device should be handled in the context of the new clinical trial regulation.

To facilitate parallel submissions of applications for drug biomarker qualification or clinical outcome assessment to EMA and to the United States Food and Drug Administration (FDA), the two agencies launched a joint letter of intent in December 2014 [**Error! Reference source not found.**].  The list of approved companion diagnostic devices is available of FDA website [23].

In conclusion, using enrichment designs for drug approval and/or companion diagnostics approvals is very attractive but challenging and success will depend on how much prior knowledge and biological rationale are available before starting pivotal trials.  Key uncertainties include whether the proposed enrichment will in fact yield positive outcomes (e.g. have we enriched for the right thing) and screening test performance (e.g. can the test be implemented in routine clinical practice), and regulatory/Health Technology Assessment (HTA) agencies' acceptance of the enrichment strategy.

**EFPIA Brussels Office**
**Leopold Plaza Building ✳ Rue du Trône 108**
**B-1050 Brussels ✳ Belgium**
**Tel: + 32 (0)2 626 25 55 ✳**
**www.efpia.eu ✳ info@efpia.eu**

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**Figure 1 Types of Enrichment Designs**



Source: Freidlin et al. 2010 [14]

Figure 1. Biomarker designs. A) Biomarker-stratified design. All patients are randomly assigned regardless of biomarker status with the random assignment and analysis plan stratified by the biomarker status. Sometimes, a standard (non-stratified) randomization can be used (with the analysis plan stratified by the biomarker) when post randomization biomarker evaluation is feasible. B) Enrichment design. The biomarker is evaluated on all patients, but random assignment is restricted to patients with specific biomarker values.  C) Biomarker- strategy design.  Patients are randomly assigned to an experimental treatment arm that uses the biomarker to direct therapy or to a control arm that does not.  Some biomarker-strategy designs evaluate bio-markers only in patients randomly assigned to the biomarker-directed arm.

## Table 1: Comparison of the key features of the biomarker designs

| Feature | Biomarker-stratified design | Enrichment design | Biomarker-strategy design, with biomarker assessment in the control arm | Biomarker-strategy design, without biomarker assessment in the control arm |
|---|---|---|---|---|
| Questions design can answer | What is the best treatment in each biomarker-defined subgroup? What is the best treatment in the overall study population? Is the biomarker-directed treatment strategy better than the control in the overall study population? (indirect assessment)  Is the biomarker prognostic? Predictive? | What is the best treatment in the biomarker-positive patients? | Is the biomarker-directed treatment strategy better than the control treatment in the overall study population? (direct assessment) What is the best treatment in the biomarker-positive subgroup? Is the biomarker prognostic? | Is the biomarker-directed treatment strategy better than the control treatment in the overall study population? (direct assessment) What is the best treatment in the biomarker-positive subgroup? (indirect assessment) Is the biomarker prognostic? (indirect assessment) |
| Questions design cannot answer | | What is the best treatment in the biomarker-negative subgroup? Is the biomarker prognostic? Predictive? | What is the best treatment in the biomarker-negative subgroup? Is the biomarker predictive? | What is the best treatment in the biomarker-negative subgroup? Is the biomarker predictive? |
| Advantages | Provides efficient assessment of relative treatment efficacy in each biomarker-defined subgroup and in the whole group | If the assumption that the biomarker reliably identifies the group likely to benefit from the experimental therapy is true, then the design provides an efficient test of efficacy of the experimental treatment in that subgroup, particularly if the biomarker positivity rate is low | Can be used for evaluation of complex biomarker-guided treatment strategies with a large number of treatment options or biomarker categories | Biomarker assessment is limited to the biomarker-directed arm (resource consideration) No issues associated with withholding the biomarker status from the control-arm patients Compliance not influenced by patient knowledge of the biomarker status in the control arm Can be used for evaluation of complex biomarker-guided treatment strategies with a large number of treatment options or biomarker categories |
| Disadvantages | The design is not feasible for evaluation of biomarker strategies with a large number of treatment options | If the experimental therapy is beneficial in a subgroup but the biomarker does not correctly identify this subgroup, a promising therapy may be missed  A positive trial does not prove the utility of the biomarker because the relative treatment efficacy may be the same in the unevaluated biomarker-negative patients | A positive trial does not prove the utility of the biomarker because the experimental treatment may be better than the control treatment for all patients regardless of biomarker status Inefficiency | A positive trial does not prove the utility of the biomarker because the experimental treatment may be better than the control treatment for all patients regardless of biomarker status Inefficiency |

Source:   Freidlin et al 2010 [14]

**EFPIA Brussels Office**
**Leopold Plaza Building** ✳ **Rue du Trône 108**
**B-1050 Brussels** ✳ **Belgium**
**Tel: + 32 (0)2 626 25 55** ✳
**www.efpia.eu** ✳ **info@efpia.eu**

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## 3. Adaptive Designs

The ideas for Adaptive Trial Designs date back to 1977 for Group Sequential (GS) designs for Phase III two arm trials, and 1990 for the Continuous Re-Assessment Method (CRM) for Phase I trials but use at that time was minimal. Adaptive Designs became, at least more discussed if not practiced in the late 1990s.  ICH E9 'Statistical Principles in Clinical Trials' [24] introduced the concept that trials could be modified as defined in Independent Data Monitoring Committees.  There was a huge literature promoting and extending the CRM, the first major Bayesian response adaptive randomisation trial (the ASTIN trial) was run and the first papers on more flexible frequentist approaches to adaptive designs were published. Adaptive Designs became of widespread interest in the early 2000s with the establishment of the Pharmaceutical Research and Manufacturers of America (PhRMA) Adaptive Designs Working Group in the US, as an element of the 2004 FDA Critical Path Initiative [25], and as the subject of numerous conferences. The EMA published a reflections paper in 2007 [26] and FDA published a draft guidance on adaptive designs in 2010 [27].

This is the appropriate time to conduct this review given that it is over 10 years since the publication of the EU reflection paper, and in the US, a new draft guidance on adaptive trial designs was published in September 2018 [4]. Furthermore, both Japan and Canada have Task Forces addressing the topic and, in the case of Canada, there are commitments to fund further research in this area (Innovative Clinical Trials Initiative [28]).

### 3.1 Definitions

The EMA reflection paper defines an 'adaptive' study design *in a confirmatory setting* as one in which statistical methodology allows the modification of a design element (e.g. sample size, randomization ratio, treatment arms) at an interim analysis with full control of the type I error.  It advises that such designs should only be used in trials with diseases, indications or populations where clinical trials will be difficult to perform e.g. where there are ethical constraints to experimentation.  The reflection paper does not discuss specific statistical methods but addresses opportunities for interim trial design modifications and considerations when flexibility is introduced into a confirmatory efficacy trial.

The FDA in the US provide a broader scope in their latest draft guidance.  Like the EMA, the FDA defines an 'adaptive design' as a clinical trial design that allows for prospectively planned modifications to one or more aspects of the design based on accumulating data from subjects in the trial. However, in contrast to the EU reflection paper, while the need for control of type I error in simulation and not analysis is explicitly highlighted.   This draft guidance addresses special considerations for adaptive trials as well as issues to consider in the evaluation of a completed study.

There appears to be an increase in the use of adaptive trial design in recent years [9, 13].  Most examples of the use of adaptive designs occur in the earlier stages of clinical development (predominantly phase II) with significantly fewer examples in confirmatory trials; of the various disease areas they have predominantly, but not exclusively, been used in oncology.  Table A1 in the appendix provides a number of examples of products that span a broad range of conditions, from HIV to psoriass,which have been approved by US and EU regulators and include some element of adaptive design in their clinical development.

**EFPIA Brussels Office**
**Leopold Plaza Building ✳ Rue du Trône 108**
**B-1050 Brussels ✳ Belgium**
**Tel: + 32 (0)2 626 25 55 ✳**
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## 3.2 Types of Adaptation

There are several different types of adaption that may be used in clinical development, many of which were highlighted in the literature search. These are summarised in Table 2. There are also elements that, whilst not in themselves types of adaptation, are often associated with adaptive designs. These are summarised in Table 3. Both tables include a consideration of their respective benefits and drawbacks.

## 3.3 Debates in the literature about the use of adaptive trial designs

There have been two principle concerns expressed with adaptive designs, one is the issue of their ethics, the second is the statistical efficiency of the use of response adaptive randomization including trial and data integrity and operational difficulties.

**Ethical Considerations**

The principle ethical point debated is that for patients with serious diseases enrolled in clinical trials, the randomized allocation of their treatment by chance is only supportable where there is genuine uncertainty about the relative efficacy of the treatments being compared in the trial. Outcome-adaptive allocation schemes, or response adaptive randomization are cited by some as unethical given that they dynamically adjust the allocation ratio in favour of the better performing treatment arm. This seems a little peculiar as the typical adaptive allocation strategy is to reflect the probability that the treatment is better in the randomization. The 2018 draft FDA guidance on adaptive designs regards ethical considerations as a possible advantage of adaptive designs. "There are many ways in which an adaptive design can provide ethical advantages over a non-adaptive design. For example, the ability to stop a trial early if it becomes clear that the trial is unlikely to demonstrate effectiveness can reduce the number of patients exposed to the unnecessary risk of an ineffective investigational treatment and allow subjects the opportunity to explore more promising therapeutic alternatives."

**Statistical Considerations**

Arguments over response adaptive randomization have to be divided into two very distinct settings. The first is the two-arm setting of comparing a treatment against a control, and the second is when comparing multiple treatment arms against a control.

In the first case, of adaptive randomization between just two arms, it has been shown that statistically biasing the randomization by response inevitably loses some statistical power. The counter (non-statistical) argument becomes whether it is ethical to randomize in equipoise when our belief is no longer in equipoise, and whether in certain indications it will be possible to recruit subjects into a trial where they only have a 50% probability of being randomized to the new treatment. Lastly when balancing the treatment of subjects in the trial against the treatment of future patients, the greater the proportion of the potential treatment population that will be recruited in to the trial the greater the relative benefit of optimizing the treatment of subjects in the trial compared to completing the trial as efficiently as possible.

**EFPIA Brussels Office**
**Leopold Plaza Building ✳ Rue du Trône 108**
**B-1050 Brussels ✳ Belgium**
**Tel: + 32 (0)2 626 25 55 ✳**
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**Table 2: Types of Adaptation**

| Adaptation | Description | Benefits | Challenges |
|---|---|---|---|
| Stopping Early for Futility | The use of a statistical measure such as a test statistic, conditional power, a Bayesian posterior probability or a Bayesian predictive probability, to make the decision to stop a trial for futility at an interim analysis point.<br><br>This adaptation is one part of a conventional Group Sequential trial (the other part is stopping for efficacy – see below) It is also frequently used along with other adaptations. | Stopping for early futility (when the results are clear that the trial is futile) allows patients and resources to be more quickly allocated to new trials. It is also only ethical to stop a trial if the early data is so overwhelmingly negative that there is almost no chance of the trial being ultimately successful.<br><br>Early stopping for futility has the advantage of not being statistically contentious, since it does not inflate type-1 error and there is no need to adjust the significance threshold in the final analysis.<br><br>Early stopping for futility does reduce the type-1 error and when used in combination with early stopping for efficacy it allows the significance threshold for early efficacy stopping to be lowered slightly. However, latest FDA Guidance on Adaptive Trials: "if a trial continues despite meeting prespecified futility rules, the Agency will likely consider the trial to have failed …" | The designers must decide how many interims to include in the trial, at what points in the trial and what the futility stopping bounds should be.<br><br>Stopping early for futility does introduce a risk of stopping for futility when there is in truth an effect and hence a drop in the "power" of the trial. This can be mitigated by setting the stopping boundaries conservatively, but it is up to the trial designers to make the trade-off between the loss of power and the ability to detect futility early.<br><br>Finally, if the drop-in power is not too great it can be recovered by a corresponding increase in the overall trial sample size, which can be done whilst still having a smaller expected *average* sample size compared to the fixed design. This will however have potential time and cost implications that will need to be weighed, again using simulations to estimate the trade-off. |

**Table 2: Types of Adaptation (continued)**

| Adaptation | Description | Benefits | Challenges |
|---|---|---|---|
| Early stopping for efficacy | Early stopping for efficacy is the second most common form of adaptation, normally used in combination with early stopping for futility in a group sequential design.<br><br>Early stopping for success does introduce the need for a statistical correction – the additional opportunities to stop for success create additional opportunities to make a type-1 error and the significance level of the statistical test needs to be adjusted to counter act this. This is the purpose of the "group sequential' design process, and it achieves this as efficiently as possible. However, note that the majority of the group sequential design literature only concerns itself with comparing a *single* treatment arm against a control arm. For trials testing multiple treatment arms the more limited literature and recent literature on MAMS (Multi-Arm Multi-Stage) designs should be consulted. | The design can take into account the amount of information required to make other determinations after the trial, over and above the detection of a treatment effect, and insure that the earliest check for stopping for success is not until these requirements have been met.<br><br>As long as the design ensures that the first interim is not until this minimum required information has been collected, then it is clear that there is both an ethical and commercial advantage to stopping early for efficacy – an effective treatment will become available to patients earlier. | Issues to be decided around early stopping designs include: when to start checking for stopping; how often to check; and how aggressive to be. Typically, one thinks of apportioning the possible "type-1 error" between the various interims and the final analysis. A more aggressive design allows greater chance of error at early interims – increasing the chance of early stopping, at the price of greater adjustment of the significance level at the final analysis to reduce the probability of errors at that point.<br><br>A problem with conventional early stopping rules is that they only consider the information available at the interim – and in many cases there will have been subjects recruited into the trial but not yet complete. The issue then arises regarding how to manage any less favourable subsequent analysis after all subjects complete, a problem known as overrun.<br><br>Early work on Group Sequential trials tended to ignore this time to final endpoint issue reporting sample size savings as though the endpoint was instantaneous. Bayesian versions of Group Sequential allow longitudinal models to be used to incorporate the data on the incomplete patients and predictive probabilities to be used to make stopping decisions based on the final expected outcomes. |

**Table 2: Types of Adaptation (continued)**

| Adaptation | Description | Benefits | Challenges |
|---|---|---|---|
| Sample Size Re-assessment | A Sample Size re-assessment can either be "blinded" or "un-blinded". At an interim the current study data is analyzed and the further sample size required to complete the study is computed – usually with both minimum and a maximum amount by which it will be increased. The aim of the increase is to protect the planned power of the trial. | Blinded re-assessments are used to adjust the sample size incase "nuisance" factors such as the variability of the endpoint are worse than expected, they provide an insurance against some of the possible incorrect assumptions that have to be made when designing a trial. Blinded sample size re-assessments can be done so they do not inflate type-1 error and so no adjustment to the required significance is required and they are looked on favourably by regulators.<br><br>Unblinded re-assessments are used to adjust the sample size in-case the observed treatment effect at the interim is worse than hoped for, but still sufficient to be useful. It can be used as an investment decision point. | In designing a sample size re-assessment, like other adaptations, one has to balance early adaptation (allowing greater saving) against adaptation too early that is misled into making a wring adaptation by random variation in a small data set. The risk is of not expanding the sample size when that is actually required to maintain power, or of expanding it unnecessarily. Most sample size re-assessment designs use frequentist techniques to give guaranteed control of type-1 error, but simulations are necessary to estimate the other operating characteristics of the design.<br><br>The time to endpoint needs to be considered, relative to the time to accrue the subjects. If it is significant it will limit the amount of sample-size adjustment possible, if it is too great a sample size re-assessment will be impossible.<br><br>Bayesian sample size estimate techniques can be used with a frequentist final analysis, these techniques can use prior information and longitudinal models to make more informed predictions of future data, and Bayesian predictive power calculations to more conservatively calculate the required sample size. |

**Table 2: Types of Adaptation (continued)**

| Adaptation | Description | Benefits | Challenges |
|---|---|---|---|
| Arm dropping | Arm dropping is like early stopping for futility but in a multi-arm trial. If the response on a particular treatment arm is sufficiently poor at an interim then that treatment arm is dropped from the trial, but the trial continues.<br><br>As the setting is a multi-arm trial, if the objective is to select the best efficacious dose (not test each treatment arm independently for success/futility) then the dropping rules can be based on "the probability that the arm has the maximum response" – so that arms that have some observed treatment effect, but are clearly not the best, can be dropped. | The advantage of arm dropping during a trial is that it allows either the trial to complete sooner (the overall sample size is shrunk by the future subjects that are not now recruited for that arm) or more data to be collected on the remaining arms (by re-allocating those future subjects between them).<br><br>Arm dropping can make a trial more ethical, by reducing the allocation of subjects to ineffective treatments and possibly increasing the allocation to effective treatments.<br><br>Compared to response adaptive randomization (see below), arm dropping is considered to be easier to implement in terms of managing the randomization and the supply.<br><br>There is a frequentist form of arm dropping design, that is an extension of group sequential designs called "MAMS" designs (Multi-Arm Multi-Stage) which can provide analytical control of type-1 error – but these tend to be limited to dropping arms simply on the basis of that arms response rate relative to control, not its response rate relative to the best arm. | Like response adaptive randomization (see below) it is important not to allow the adaptation until there has been a reasonable initial amount of data (the "burn-in") collected.<br><br>However due to the irreversible nature of the decision, arm dropping normally needs to be more conservative than response adaptive randomization where there is an opportunity to correct from giving an arm a very low allocation at one interim at a subsequent one if the balance of the data changes. |

**Table 2: Types of Adaptation (continued)**

| Adaptation | Description | Benefits | Challenges |
|---|---|---|---|
| Response Adaptive Randomisation (RAR) | In a RAR design, after an initial period, over a series of interims the randomization ratios are adjusted to give preference to arms that have a higher probability of meeting some criteria, typically predicted to have a greater probability of success (but it can be more complex than that when taking a number of different endpoints into consideration) | Trials with multiple arms response adaptive randomization (RAR) can assign more patients to the arm most likely to be selected at the end of the trial. This increases the power of the comparison of that arm with the control arm, and provides more data on the selected arm than a fixed allocation would.<br><br>Response Adaptive Randomisation can make a trial more ethical, by reducing the allocation of subjects to ineffective treatments and possibly increasing the allocation to effective treatments. | There are many options in an RAR trial design – when to start adapting, what to 'target' in the adaptation, how frequently to adapt and what proportion to allocate to the control arm. These need to be explored and optimized using simulations.<br><br>In trials with only two-arms (a novel treatment and control) the use of RAR is contentious, and generally it is agreed that the loss of power in this setting means it should not be used. There are some circumstances when RAR could be beneficial in a two-arm setting – better treatment of the subjects in the trial, for instance when the study population is effectively the whole patient population.<br><br>In the multi-arm setting, "response adaptive techniques can in some circumstances minimize the variance of test statistics, leading to shorter trials, smaller samples sizes and/or greater statistical power" [FDA 2018 draft guidance]. When data is available early enough to be able to adapt on, simulations show that a response adaptive design on average preforms better than a fixed or arm dropping design [paper in review] as long as adaptations do not start too soon, nor reduce the allocation to the control arm. Simulations of the design will be necessary to ensure that adaptations aren't started until there is sufficient data to adapt to. |

**EFPIA Brussels Office**
**Leopold Plaza Building** ✳ **Rue du Trône 108**
**B-1050 Brussels** ✳ **Belgium**
**Tel: + 32 (0)2 626 25 55** ✳
**www.efpia.eu** ✳ **info@efpia.eu**

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**Table 2: Types of Adaptation (continued)**

| Adaptation | Description | Benefits | Challenges |
|---|---|---|---|
| Seamless designs | A "seamless" trial design is one that combines two phases of drug development in one trial. Thus, possible trials a are Seamless Phase 1/2, Phase 2a/2b and Phase 2/3. The design of the phases can themselves be fixed or adaptive, in a seamless design, the decision's usually taken between the two phases are instead taken in a pre-specified fashion and with control of blinding. | There are two principal benefits of a seamless design:<br><br>• Saving in time, the usual 6-12 month gap between phases is avoided.<br><br>• Inclusion of data from the first stage in the analysis in the second stage. This can result in a reduction in the required sample size for the second stage. Such a design is said to be "inferentially seamless", a seamless trial that uses a final analysis based just on the second stage data is referred to as "operationally seamless". | The draft 2018 FDA guidance makes no specific mention of seamless trials, previously FDA comments on seamless Phase 2/3 trials had been cautious, warning of the "loss of thinking time". The concern was that there were many potential learnings from a Phase 2 trial over and above a go/no-go decision, dose selection and effect size estimation. These are still valid concerns and it is likely that seamless phase 2/3 trials will predominantly be in well understood diseases with well understood endpoints, such as Diabetes, and the risk of "unknown unknowns" is felt to be small, or in rare diseases where it will be difficult to recruit of a standard size phase 3 trial in a reasonable time.<br><br>A seamless design will typically take longer to design and require larger upfront investment (particularly in manufacturing capacity) and this needs to be taken into account in deciding to embark on a seamless design.<br><br>If the final endpoint is not relatively soon after enrolment, then there a number of challenges:<br><br>• What to do with subject's accrued but not complete at the time of the between stage interim.<br><br>• What to do with enrolment while transitioning from the first stage to the second stage, if it is paused or slowed, how easy will it be to re-start it?<br><br>There may be significant operation steps between the stages (manufacturing, open more sites etc.), if the design aims to be inferentially seamless considerable care will need to be taken to maintain the blinding. |

**Table 3 Developments that are not specific to adaptive designs but are particularly relevant to them**

| Feature | Description | Benefits | Challenges |
|---|---|---|---|
| Clinical Trial Simulation | Writing computer code that simulates the random sampling of subject responses from a number of assumed 'true' distributions ("scenarios") and applying the planned trial design to it to see how the design performs. | Simulations have a number of significant advantages over the design by sample size calculation/analytical method:<br><br>• rather than using single fixed assumptions for the unknown elements the simulations can incorporate all the significant unknowns (e.g. accrual rate, dropouts, time to data),<br><br>• the simulations can simulate data coming from more complex distributions (e.g. joint distributions, truncated distributions, hazard rates that vary over time) than sample size calculations allow for,<br><br>• the trial designs can include features which would preclude a sample size calculation,<br><br>• the simulation results allow the estimation of additional features of the trial that may be important (or even critical) to correct decision making after the trial – such as the likelihood of selecting the correct dose or selecting the correct patient sub-groups. | The drawback is the time and resources required to write and test the required computer code. In particular as it is usual to have to modify the design and the code (due to changing external circumstances and to what is learnt from the simulations) and repeat the simulations several times.<br><br>Typically, simulations are run over a range of specific scenarios, each scenario being simulated 1,000-10,000 times in order to provide a reasonable estimate of the design's performance in that setting. The definition of each scenario will have many aspects to it and it is highly unlikely that any one scenario exactly matches what eventually transpires in the real trial. Thus, the aim should be for the scenarios to 'bracket' what is likely to occur in practice and rely on the fact that operating characteristics in almost all settings change smoothly (and often monotonically) as each parameter in the scenario is changed. Thus, the performance in the actual trial could be inferred from the scenarios that were close to it.<br><br>Sometimes simulation may use a distribution of scenarios sampled from estimates of the range of the likely values of the different parameters that make up the scenarios (such as: dose response, safety/side effects, endpoint variability, rates on the control arm, endpoint correlation, accrual rate, dropouts) but this is usually to estimate the likely outcome of the trial rather than characterize the design. |

**Table 3 Developments that are not specific to adaptive designs but are particularly relevant to them (continued)**

| Feature | Description | Benefits | Challenges |
|---|---|---|---|
| Dose Response Modelling | Simultaneous evaluation of multiple doses of a treatment within a unified statistical model, | Response modelling across doses increases the power of the trial to detect an effect in circumstances where normally power has been lost due to adjusting for multiplicity of testing multiple doses.<br><br>Dose response modelling also allows the treatment effect to be inferred for intermediate doses that have not been tested. | The problem is that the response modelling may make assumptions about the shape of the dose response that may not be borne out by the data collected. But approaches such as model averaging (MCP-Mod) or Bayesian smoothing models (such as NDLM) can be used to avoid assumptions about the shape of the data.<br><br>Dose Response modelling is not used in Phase 3 trials, as testing enough doses to make dose response modelling worthwhile normally has to be completed before Phase 3 starts. |
| Bayesian Statistics | As an alternative to conventional frequentist statistics that calculate a p-value, Bayesian statistics can be used, either just for interim decision making or also for the final analysis. | Using Bayesian statics to analyze the trial data allows more complex models to be deployed, prior data to be incorporated, and more natural statistical conclusions to be drawn. The American Statistical Association published a statement on p-values [ref] urging that their role be reduced and their unsuitability for inference.<br><br>Bayesian statistics allow data to be borrowed in a flexible fashion using hierarchical models, predictive probabilities to be calculated and evidence for or against conclusions to be weighed.<br><br>For instance Designs using Bayesian stopping rules allow rules that can be stated more naturally ("if this trial were to run to its completion what is the probability the final analysis would be successful?" and "if we were to stop accrual now and follow-up the current subjects to completion, what is the probability the final analysis would be successful?"). | The principle challenges of the use of Bayesian statistics are firstly the need to specify "prior" beliefs about the parameters and secondly that the type-1 error of a planned analysis under a Null hypothesis is no longer analytically controlled but needs to be shown by simulation.<br><br>The setting up of the "priors" is important as these priors can have an impact on the calculated final values (the "posterior" estimates) it is important that these priors reflect the beliefs of those who need to be convinced, not those aiming to do the convincing. But these may be diverse and difficult to elicit.<br><br>In order to set decision thresholds on the posterior estimates that control type-1 error to the required degree, the trial design has to be simulated over a range of "null hypotheses". While the 2010 draft FDA guidance said that this process was "controversial", the 2018 draft FDA guidance lays out a process for implementing it. |

**Table 3 Developments that are not specific to adaptive designs but are particularly relevant to them (continued)**

| Feature | Description | Benefits | Challenges |
|---|---|---|---|
| Endpoint adaptation | If a trial has multiple primary endpoints (such as a more desirable one versus one where it may be easier to show a treatment effect) but testing them carries a statistical penalty for "multiplicity".<br><br>It might be possible to reduce the statistical penalty by select between the endpoints at an interim, fixing which will be tested first before gathering and testing the remaining data. | This can reduce the risk of mis pre-selecting the order in testing the endpoints, or reduce the cost of testing a number of endpoints in parallel. | The adaptation of endpoint runs the risk of mis-selection if made on too little data, but the less data collected after the selection the less the benefit of the adaptation. Like other adaptations it will be necessary to sun simulations in order to evaluate the trad-offs. |
| Utility Function | A utility function can be used to combine the results on different endpoint such as efficacy and safety or primary and secondary efficacy endpoints. | A utility function allows dose selection and adaptive decisions to be made on the basis of benefit risk or total benefit. | It can be hard to get consensus on the endpoints to include and to the relative weights to be given to the various endpoints in the overall utility function. Whether they need to be accepted by the regulator depends on the use made of the utility function – it can just be used for internal decision making such as for dose selection rather than to support regulatory approval. |

**Table 3 Developments that are not specific to adaptive designs but are particularly relevant to them (continued)**

| Feature | Description | Benefits | Challenges |
|---|---|---|---|
| Disease Modelling | This method has been introduced for degenerative diseases, where the subject's stage of the disease affects either the likely degree of further degeneration that might be seen over the observation period of the trial (e.g. Alzheimer's Disease) or the appropriate endpoint measure to use (e.g. Duchenne Muscular Dystrophy). | This approach ensures that all subject data are informative about the degree of treatment effect. Without it, subjects may fail to contribute to the estimate either because the change in endpoint is small relative to that of other subjects (e.g. Alzheimer's Disease patients with only moderate cognitive impairment will only show a slight decline in cognitive measures over two years compared to those more advanced in the disease), or the endpoint is inappropriate to the subject's current condition (e.g. 6 minute walk for patients with wasting diseases such as Duchenne Muscular Dystrophy, Progressive Multiple Sclerosis and GNE Myopathy.   In such wasting conditions early in the disease patients may have no impairment in their walk over the period of the trial while later in the disease patients may be unable to walk at all). | The use of disease modelling shares the problems of potentially introducing a new endpoint. This will require regulatory endorsement supported by a clinical rationale. Input from patient groups could be valuable in the selection of a new endpoint. This is compounded by the additional complexity of a disease model as an endpoint and concern over the comparability in changes in the score at one of the scales compared to changes at the other. |
| Improved Endpoints | Standard outcome measures may not be equally informative for all patients or may be crude and not reflect patient priorities. Improving endpoint measures can increase the power of a trial and /or increase the evaluable patient population. | For progressive diseases, such as Alzheimer's Disease and Multiple Sclerosis patients expected progression is highly dependent on a patient's state when entering the trial. An endpoint that uses a progressive disease model (e.g. the EPAD trial in Alzheimer's disease) allows a trial to have greater power or broader inclusion criteria [29].

Dichotomous or simple ranked outcomes can be replaced by scoring schemes that properly reflect the impact of the different outcomes on the patient population (e.g. the DAWN trial) and provide greater statistical power. | The introduction of new endpoints will require regulatory endorsement supported by a clinical rationale, and can be challenging. There is also a risk that the results of new trials are not comparable to those of previous trials. There will be the concern that the new endpoint may be less stringent and may not correspond to meaningful clinical improvement. |

In the second case, comparing multiple arms against control, in the normal setting where the aim is to demonstrate efficacy and select *a* treatment then response adaptive randomization is more efficient than fixed randomization – as long as sufficient allocation to control is maintained.

**General Considerations**

Additionally, the DIA conducted a recent survey to investigate potential barriers to implementing adaptive designs. Respondents to the survey highlighted some of the persistent barriers to implementing adaptive designs as very practical issues including: education of teams on methodology; lack of validated software available; team preference; lack of time to conduct clinical trial simulations; negative experience; and perceived regulatory risk.

Regarding patient Involvement in relation to adaptive designs, the European Patients' Academy (EUPATI) advises that patient input into adaptive design can help researches identify the most appropriate design by helping to define and understand the needs and requirements of the patient population. Patients can also be involved in the Data Monitoring Committee. Its website [30] provides educational material on adaptive designs.

## 3.4 Regulatory authority recommendations when considering the use of adaptive designs in clinical trials

In 2014, EMA published a short paper summarizing their scientific advice experience of adaptive design (Adaptive clinical trial designs for European marketing authorization: a survey of scientific advice letters from the EMA from 2014) [31]. Among the observations that were highlighted in the paper around potential adaptive designs included continuing concerns over the ability to control for type 1 errors. The paper also included several other points for medicine developers to consider when planning to employ an adaptive study design including the need to provide sound justifications of the adaptive design proposed; inclusion of (extensive) simulation studies, where the operating characteristics of the adaptive design are compared to more classical approaches as fixed sample trials or several trials in sequence; and concerns that the extent of reflection and adaptation required at the end of phase II will be too extensive to make a phase II/III 'seamless' trial practical.

Following a subsequent analysis of completed confirmatory studies published by EMA authors, they conclude more positively that "if properly pre-planned, adaptations can play a key role in the success of some of these trials, for example to help successfully select the most promising dose regimens for phase II/III trials. Interim analyses can also enable stopping of trials for futility when they do not hold their promises'. The authors go on to state that Type I error rate and bias control, trial integrity and results consistency between the different stages of the analyses are fundamental aspects to be discussed thoroughly. They also recommend engaging in early dialogue with regulators and implementing the scientific advice received [32].

The 2018 FDA draft guidance on adaptive designs has a more positive approach than its predecessor. It notes that "adaptive designs can provide a variety of advantages over non-adaptive designs. These advantages arise from the fundamental property of clinical trials with an adaptive design: they allow the trial to adjust to information that was not available when the trial began. The specific nature of the advantages depends on the scientific context and type or types of adaptation considered.

**EFPIA Brussels Office**
**Leopold Plaza Building ✳ Rue du Trône 108**
**B-1050 Brussels ✳ Belgium**
**Tel: + 32 (0)2 626 25 55 ✳**
**www.efpia.eu ✳ info@efpia.eu**

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Advantages cited by FDA are statistical efficiency, ethical considerations, generalisability and improved understanding of drug effects as well as acceptability to stakeholders.

The perspectives of both regulatory authorities support the notion that over the last ten years their positions have moved from initial reservations to a more encouraging attitude towards the use of adaptive designs in clinical trials.

# 4. Master Protocols

The use of biomarkers to identify small genetic sub-populations within a disease has resulted in increasing limited numbers of patients being eligible for a specific treatment regimen. This has led to the need for trial designs which encompass several treatment options depending on the genetic subtype of patient entering the trial. Such master protocols are particularly useful in the field of oncology [33], where using biomarkers to identify those patients likely to respond to a therapy is now standard practice. However, master protocols can also be useful in other therapeutic areas where there are several treatment options to be tested or where a given disease can be differentiated in multiple sub-categories. Recent examples of the uptake of these designs outside oncology include clinical trials for Alzheimer's Disease [34,35,36] and infective diseases [37,38]. In all cases the complexity of these trials can be challenging and there is a need for guidance and best practice sharing among industry and other stakeholders.

In addition to the FDA guidance on master protocols, the Clinical Trials Facilitation and Coordination Group (CTFG) recently published a recommendation paper on the Initiation and conduct of complex clinical trials [39].

By conducting a literature and database search, as well as gathering information shared at various meetings with Health Authority, HTA, and other stakeholder representatives, the authors of this paper have complied a summary of current stakeholder perspectives on master protocols, which encompass umbrella, basket and platform trial designs. This chapter discusses the advantages and disadvantages of these novel trial designs and provides suggestions on how better alignment can be reached amongst stakeholders on the use of these novel designs to support drug development, approval and rapid patient access to innovative medicines.

## 4.1 Definitions

Master protocols are defined in a recent review paper [5] as overarching protocols designed to answer multiple questions. Included under this broad definition of a master protocol are three types of designs: umbrella, basket, and platform trials.

Master protocols can bring multiple benefits:

- Allow to quickly test hypotheses and answer scientific questions
- Evaluate and compare treatments and combinations thereof, maximizing trial opportunities for patients
- Access to complex disease areas and/or rare indications (small populations)
- Collaborative set-up, allows for better efficiency

**EFPIA Brussels Office**
**Leopold Plaza Building ✳ Rue du Trône 108**
**B-1050 Brussels ✳ Belgium**
**Tel: + 32 (0)2 626 25 55 ✳**
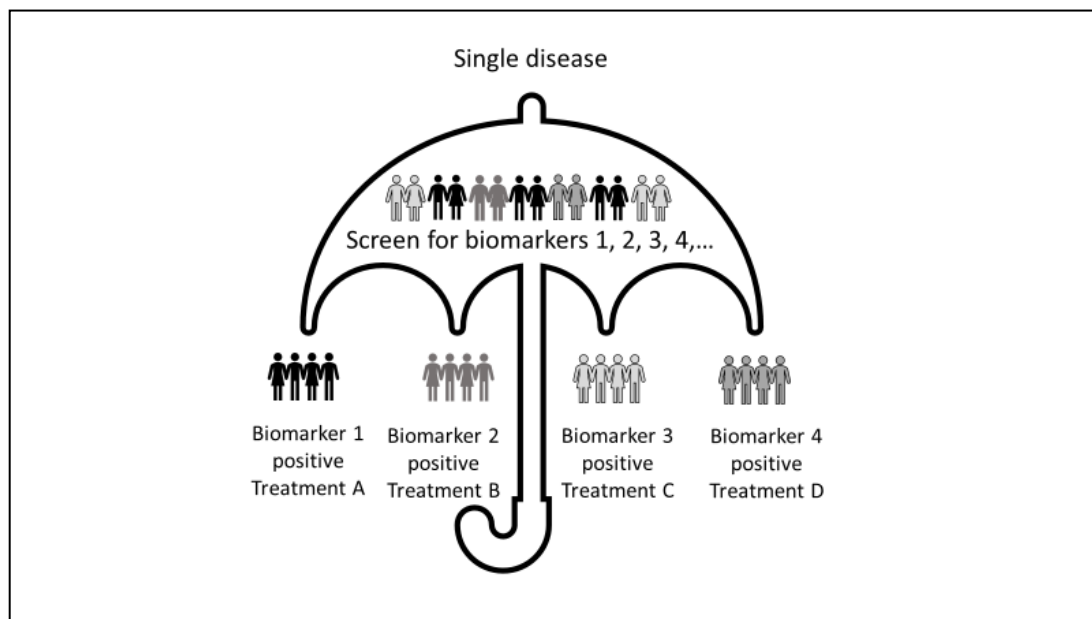**www.efpia.eu ✳ info@efpia.eu**

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- Faster time to activation of additional study arms to investigate new sub-populations or study drugs
- Faster clinical development and patient access to transformative drugs

However, there are also potential drawbacks associated with the intrinsic complexity of master protocols, which are set out below for the different study designs.

## 4.2 Umbrella Trials

Umbrella trial designs are useful e.g. when there are different genetic mutations of one disease or when several promising drugs and treatment options are being investigated for the same disease. Umbrella trials can have a single protocol encompassing multiple treatment arms or one overarching screening protocol and several separate protocols for each individual treatment option. In oncology umbrella trials the patients are screened on entry and assigned to one of several possible drug treatment arms, usually based on results of biomarker tests (Figure 2). Umbrella trials often have adaptive elements which enable the opening and closing of study arms depending on the effect of the test drugs on a specific molecular target. Such trials also enable new and more specific biomarkers to be added during the course of the study to ensure all patients receive a therapy that is optimally targeted at their disease: However, this design also has limitations as shown in Table 4.

**Figure 2: Schematic Representation of a Master Protocol with *Umbrella Trial* Design**

**Table 4: Benefits and Limitations of Umbrella Trials**

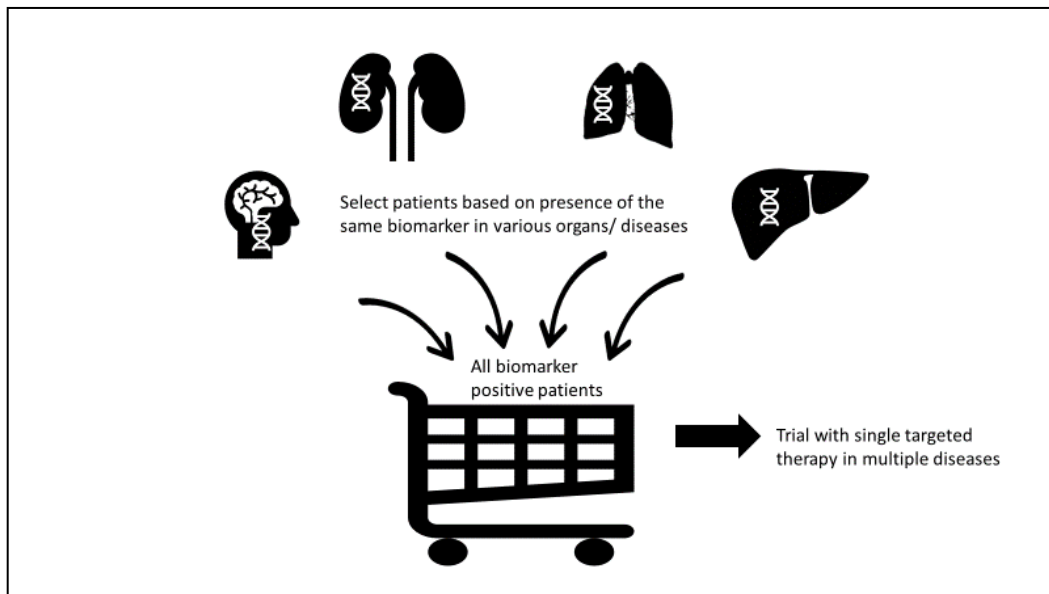| UMBRELLA TRIALS | |
| --- | --- |
| **BENEFITS** | **LIMITATIONS** |
| • A single control arm can be used with a standard comparator treatment for the disease being investigated<br><br>• Clustering different biomarkers under a single trial will help to reduce the screen failure rate, avoid multiple screening of patients, and increase the likelihood of a patient being eligible to participate in a study<br><br>• Enables a direct comparison of several treatment options for a disease<br><br>• Due to the multi-pronged approach, umbrella trials can accelerate the speed of development, save costs and support rapid approval of new drugs (however, regulatory acceptance varies in the different regions).<br><br>• Operational efficiencies due to familiar trial procedures for the different arms. | • There are statistical challenges for introducing new treatment arms after a study has started regarding potential introduction of bias compared to treatments and control in place at the start of the trial<br><br>• Treatment assignment/stratification is often based on molecular biomarkers so centralized screening tests are required for multiple biomarkers, as locally performed genotyping can lead to less reproducible results<br><br>• Each new diagnostic biomarker needs to be validated and will be subject to a regulatory approval pathway<br><br>• Standard of care for a disease may change during the course of lengthy trials as new treatments become available, potentially requiring changes to the control arm treatment, which could have implications for statistical inferences (see also section on use of historical controls and changes in standard of care) |

**EFPIA Brussels Office**
**Leopold Plaza Building ✳ Rue du Trône 108**
**B-1050 Brussels ✳ Belgium**
**Tel: + 32 (0)2 626 25 55 ✳**
**www.efpia.eu ✳ info@efpia.eu**

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## 4.3 Basket Trials

In basket trials the effect of a drug is tested on patients who are selected using a single type of biological marker or have an overarching condition (e.g. pain) which occurs in a variety of diseases or organs (Figure 3).  The benefits and limitations of basket trials are summarised in Table 5.

**Figure 3: Schematic Representation of a Master Protocol with *Basket Trial* Design**

**EFPIA Brussels Office**
**Leopold Plaza Building ✳ Rue du Trône 108**
**B-1050 Brussels ✳ Belgium**
**Tel: + 32 (0)2 626 25 55 ✳**
**www.efpia.eu ✳ info@efpia.eu**

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**Table 5:  Benefits and Limitations of Basket Trials**

| BASKET TRIALS | |
|---|---|
| **BENEFITS** | **LIMITATIONS** |
| • Quick identification of several possible therapeutic indications<br><br>• Quick termination possible for those arms where patients are showing low responses<br><br>• Possible to investigate several rare diseases where patients' numbers are limited and collect more safety data than with individual trials<br><br>• Exposure in multiple contexts can provide additional understanding of mechanism of sensitivity and resistance of target<br><br>• Each trial requires the development / approval of only a single biomarker assay and this can often be tested locally at the sites<br><br>• These trials can reach statistical power with fewer subjects in less time. If the treatment has already been approved for one disease, this design can rapidly verify if efficacy converts to other indications.<br><br>• Use of basket designs in areas where certain phenotypes are found across disease populations (e.g. patients with different types of pain) can increase the probability of technical success for a drug with a specific mechanism of action.<br><br>• Basket trials take less time than performing individual trials per indication, which can accelerate the speed of development, save costs and support rapid approval of new therapies. | • Dose and/ or safety of the drug may be different in the various indications<br><br>• Potential issue of heterogeneity being introduced by the basket design<br><br>• Challenges from a technical perspective in using the same trial endpoints across different diseases sharing the same biomarker.<br><br>• Different types of standard of care and comparator treatments may be established for the various diseases, requiring multiple control arms to assess benefit of therapy<br><br>• Some arms within a basket trial may have small sample sizes and be difficult to evaluate. High treatment efficacy is a prerequisite to correctly determine the trial arms which should be continued or discontinued and avoid a selection bias based on chance findings in a few patients<br><br>• Many patients must be tested to find the few who fit the disease profile targeted by the treatment. It is frustrating for patients who agree to be screened when they are told they are not eligible to be treated because their disease profile does not match the drug target.<br><br>• Complexity of basket trials can lead to very lengthy protocols (> 500 pages) which present problems for ECs and investigators<br><br>• Basket trials require several individual patient information leaflets and different informed consent forms for the various indications<br><br>• Suitable principle investigators and facilities are required at each trial site to cover each of the indications in a basket trial, which is often difficult to realize |

## 4.4 Platform trials

In platform trials, patients' samples are tested for various predefined biomarkers according to a "screening protocol" and then based on these results they are assigned to a treatment arm within the Master Protocol [40,41] (Figure 4). The master protocol prospectively defines the criteria for adding and closing the different treatment arms as the trial progresses, as well as for switching patients between arms.  An example of such a trial is the NCI-MATCH trial [42] which is mentioned in the FDA draft guidance on "Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics" [6].
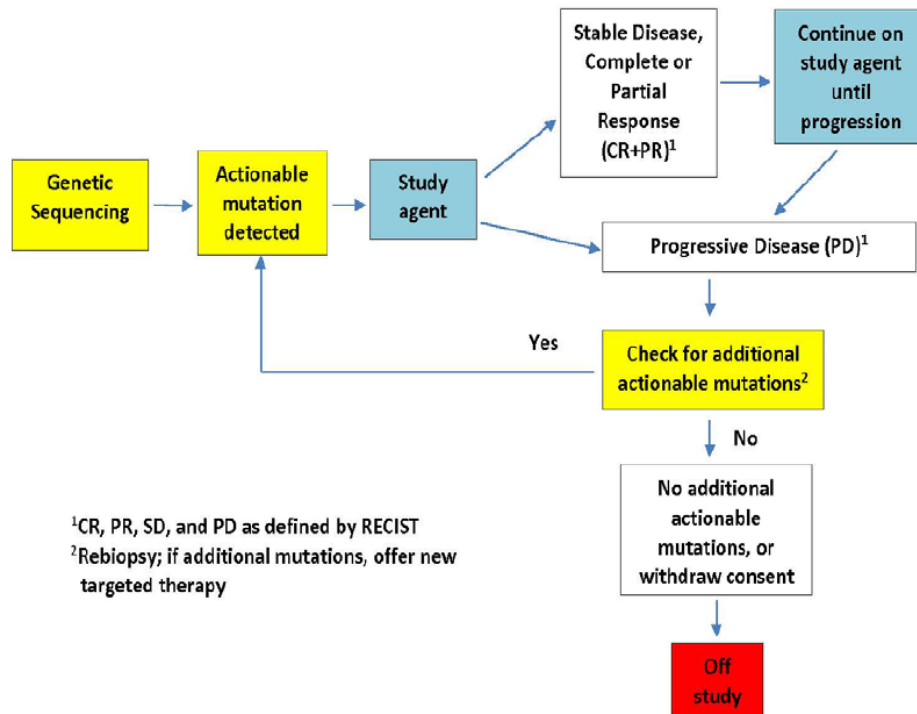
The high complexity of platform trial designs requires sophisticated statistical methods to ensure proper randomization, interim analysis and robust criteria for success/futility assessment of each

**EFPIA Brussels Office**
**Leopold Plaza Building ✳ Rue du Trône 108**
**B-1050 Brussels ✳ Belgium**
**Tel: + 32 (0)2 626 25 55 ✳**
**www.efpia.eu ✳ info@efpia.eu**

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trial arm. The advantage for patients is that they receive a tailored therapy at an earlier time point and are less likely to have prolonged exposure to an ineffective treatment.

A major concern of Health Authorities and Ethics Committees with platform trials is that, in theory, additional arms to explore new treatment options can be added indefinitely and potentially result in "never-ending" trials. So, it is important that in the master protocol and any sub-protocols the end of the clinical trial is defined, including how it will comply with legal obligations on reporting and trial transparency.

**Figure 4: Example of a Master Protocol with a Platform Trial Design**



¹CR, PR, SD, and PD as defined by RECIST
²Rebiopsy; if additional mutations, offer new targeted therapy

\* RECIST = response evaluation criteria in solid tumors.

Source: FDA draft guidance on Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics, Sept 2018 - Adapted from Abrams J et al., 2014, National Cancer Institute's Precision Medicine Initiatives for the New National Clinical Trials Network, Am Soc Clin Oncol Educ Book: 71-6,

## 4.5 Approvals based on data generated via master protocols

Despite the potential advantage of a master protocol in its flexibility and efficiency in drug development, to date only a small number of drugs have been approved and made available to patients based solely on pivotal data from umbrella, basket or platform trials. A master protocol provides an opportunity to incorporate efficient approaches, such as a shared control arm and/or the use of centralized data capture systems to enhance efficiency.

The potential of complex innovative clinical trial designs to support the approval of new treatments in an accelerated way is demonstrated by a handful of trials which have led to either the registration of new products or an extension of the product label (see Table A2 in Appendix). Although data

**EFPIA Brussels Office**
**Leopold Plaza Building ✳ Rue du Trône 108**
**B-1050 Brussels ✳ Belgium**
**Tel: + 32 (0)2 626 25 55 ✳**
**www.efpia.eu ✳ info@efpia.eu**

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collected in a platform trial may not be considered sufficient by itself to support drug approval [43] this approach allows identification of the most promising therapies in an efficient way that can ultimately lead to the registration of new indications more rapidly than using a standard approach. Most of the therapies listed below benefited from breakthrough or similar designation and eventually also benefited from accelerated assessment.

In short, there is currently no broad regulatory acceptance of the use of master protocols to generate results that will be accepted as pivotal data to support drug approvals. However, the FDA seems to be more familiar with these types of designs and shows a greater acceptance of these novel designs to support new submissions.

Input received from EU regulators during recent stakeholder meetings (BfArM dialogue meeting on complex study designs, 22 Nov 2017; CTFG workshop Complex Clinical Trial Designs, 22 March 2018; vfa meeting on personalised medicine, 26 April 2018; CTFG stakeholder meeting 24 Oct 2018) seems to indicate that the Health Authorities in Europe are beginning to look at how best to support clinical trials with umbrella/ basket and platform designs. The recently published CTFG recommendation paper as well as an article in Lancet Oncology [44] provides an insight into concerns that regulators may raise when assessing complex trial designs, some of which are shared by other stakeholders (Table 6). For this reason, it is important that certain criteria are fulfilled when designing and conducting umbrella, basket or platform trials (Table 7).

## 4.6 Regulatory considerations for conducting master protocol trials

Recent meetings with Regulators and Ethics Committees have confirmed that they would like to be involved in the discussion of complex protocols with sponsors at an early time point. During the CTFG Stakeholder meetings held in Rome in March 2018 and in Bonn in October 2018, there was a discussion on how such early engagement with regulators can take place. Currently some Health Authorities offer national scientific advice and there is the option to seek protocol advice from the EMA. However, given the multinational scope of many clinical trials, it would be desirable for a sponsor to have an EU-wide interaction with the Health Authorities in the countries foreseen for the conduct of a particular trial, which could potentially also involve the coordinating Ethics Committees. Multi-national Pre-CTA consultations for complex/innovative trials is especially important to:

- Discuss the protocol and clearly define endpoints and goals of the trial

- Clarify the ethical, scientific and methodological justification for conducting the trial under a master protocol
- Provide opportunity to address questions – helps to understand the national competent authority concerns
- Explain decision rules to stop, expand or add an arm, agree on procedure for early termination of one arm
- Explain choice of comparators/background therapy
- Discuss the role of DMCs (or other alternative bodies) with all the concerned member states
- Anticipate any major review roadblocks

**EFPIA Brussels Office**
**Leopold Plaza Building ✳ Rue du Trône 108**
**B-1050 Brussels ✳ Belgium**
**Tel: + 32 (0)2 626 25 55 ✳**
**www.efpia.eu ✳ info@efpia.eu**

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**Table 6 – Examples of concerns regarding Master Protocols raised by Regulatory Authorities, Ethics Committees and HTA bodies**

| Trial design aspect | Regulatory Authority and HTA Concerns | Ethics Committee Concerns |
|---|---|---|
| Preclinical development | • Proposed trial design must be supported by robust scientific evidence from preclinical studies on drug mechanism of action and selectivity for targets | • Preclinical development is not in the remit of Ethics Committees therefore this aspect was not commented on in the meetings |
| Protocol Design | **Regulatory Authority Concerns:**<br>• Master protocols<br>  – Different in-/ exclusion criteria in sub-protocols<br>  – Different visits and procedures in sub-protocols<br>  – Different end of trial in sub-protocols<br>  These factors challenge the definition of a clinical trial<br>• Protocols consisting of several hundred pages and cross references to various appendices/attachments are not reader friendly and do not facilitate quick review by regulators<br>• Master protocols can result in a larger number of substantial amendments to the trial, the evaluation of which have a markedly shorter deadlines for competent authorities. The high volume of amendments might jeopardize the quality of review of new sub-trials.<br>• What are the risks and risk-mitigations at investigator site regarding operational challenges due to increased complexity? How to ensure investigator oversight of the trial?<br>• CTFG considers a clinical trial to be defined by the initially defined hypothesis. The hypothesis must be scientifically sound and maintained throughout the trial.<br>• Switches from exploratory to confirmatory designed objectives during trial conduct without pre-specification cannot be considered as good science<br>• As clinical trial authorization is assessed on a case by case basis there needs to be a sound justification for each trial and each substantial amendment<br>**HTA Concerns:**<br>• Assessment of a medicine's additional benefit by HTA and Payers requires data on an appropriate comparator therapy. Therefore, it is difficult to perform this assessment if there is no approved comparator or any epidemiological or historical data e.g. for therapies based on biomarkers.<br>• The dynamic development of disease therapy means that new biomarkers (e.g. ALK, BRAFV600, EGFR, PDL1) allow identification of new patient sub-populations even as trials are ongoing. However, there may not be data to show if the normal standard therapy is relevant for these genetic subgroups and can therefore be used as a comparator to assess additional benefit. | • Protocols for complex trials can be extremely complex and long and are a serious problem for investigators and ECs when faced with short review timelines.<br>• Master protocols can require many individual patient leaflets for the different indications or treatments included in the trial<br>• Patients need to be closely involved and well-informed during these trials e.g. all changes impacting risk/ benefit (e.g. in case of outcome adapted randomization to new study arms). Re-consent will always be required on allocation of patients to a different study arm. |

**EFPIA Brussels Office**
**Leopold Plaza Building ✳ Rue du Trône 108**
**B-1050 Brussels ✳ Belgium**
**Tel: + 32 (0)2 626 25 55 ✳**
**www.efpia.eu ✳ info@efpia.eu**

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**Table 6 – Examples of concerns regarding Master Protocols raised by Regulatory Authorities, Ethics Committees and HTA bodies (continued)**

| Trial design aspect | Regulatory Authority and HTA Concerns | Ethics Committee Concerns |
|---|---|---|
| Pharmacology / biomarkers | **Regulatory Authority Concerns:**<br>• Validation of companion diagnostics, marker positivity and clinical relevance<br>• Many IMP profiles increase complexity and reporting responsibilities and procedures for safety oversight with multiple IMP suppliers are challenging.<br>• Biomarker hierarchy and patient allocation in case of more than one positive biomarker in a patient<br>**HTA Concerns:**<br>• Cancer site independent biomarker-based approvals (e.g. for pembrolizumab) would currently be very difficult to support from an HTA/ payer perspective due to a lack of any comparator therapy to support additional benefit. | • Master protocols ask for a central competent and powerful infrastructure is required at the sites, e.g. for the molecular. screening, administration, and organization |
| Statistics | • How to ensure statistical integrity of a trial e.g. control of Type I error probability (false positive) and effect on estimates<br>• Need to ensure confidentiality of interim data if knowledge of data can affect behavior of sponsor, investigators, and/or trial subjects<br>• Master protocols involve advanced statistics. Regulators find it difficult to evaluate studies from a statistical point of view without a fixed sample size.<br>• Sample size calculations depend on established clinical effects and their variability. Valid point estimators are hard to collect in small phase 2 studies. Therefore, it remains questionable whether master protocols should be applied before the optimal dosage and frequency of drug administration are established<br>• Statistical power might be lost when master algorithms react to results from sub-studies, thereby accepting or rejecting the underlying hypotheses and resulting in the closing or opening of study arms when no adjustments were prespecified in the protocol.<br>• The interaction between the master protocol and the subprotocol is often so complex that one might doubt whether it is possible for a non-specialized statistician to fully understand the study design.<br>• Physicians/investigators without appropriate statistical training might not be able to explain the benefit and risk for the individual patient adequately, particularly in trials where the chance of success might be changing as the trial progresses | • All master protocols are typically combined with adaptive design elements i.e. prospectively planned modifications of the trial protocol based on first results, which can increase the risk of bias<br>• Investigators may be able to draw conclusions from the type of adaptation performed during the trial on the efficacy/ safety of the IND, which can endanger the integrity of the trial conduct and data. |

**EFPIA Brussels Office**
**Leopold Plaza Building** ✳ **Rue du Trône 108**
**B-1050 Brussels** ✳ **Belgium**
**Tel: + 32 (0)2 626 25 55** ✳
**www.efpia.eu** ✳ **info@efpia.eu**

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**Table 6 – Examples of concerns regarding Master Protocols raised by Regulatory Authorities, Ethics Committees and HTA bodies (continued)**

| Trial design aspect | Regulatory Authority and HTA Concerns | Ethics Committee Concerns |
|---|---|---|
| Efficacy | • There are also concerns regarding the scientific value or outcome of complex clinical trials due to the parallel testing of several IMPs in small numbers of trial subjects, difficulties to control type I error, and challenges created by shared control arms, which need to be thoroughly addressed. In addition, complex trial designs raise concerns regarding data integrity as emerging data from closed sub-protocols may affect the conduct of the ones that are still ongoing<br>• An issue with high numbers of clinical trial amendments is that investigators might be able to anticipate which treatment could have better outcomes, and which will not. This might influence the investigator's behavior and their recruitment strategy, which in turn might jeopardise the informative value of the trial.<br>• Expansion of one large (mega) trial could prevent patient access to other, perhaps better trials | • Umbrella trials have potential advantages for patient care and combinable control groups. The advantages of basket trial are less obvious given that they are highly complex and have challenges regarding logistics, coordination etc. Single trials are easier in these respects. |
| Safety/Data Monitoring Committee (DMC) | • Considerations on wash-out periods when trial subjects are reallocated to another IMP sub-protocol/arm<br>• How to ensure quick detection of safety issues and actions for relevant stakeholders<br>• Impact analysis of requests for substantial changes (e.g. new IMP, new indication) on risk benefit of the trial<br>• Complex trial designs also mean increased operational complexity due to the presence of several IMPs, populations, trial sites, multiple manufacturers and contract research organisations (CROs). Therefore, adaptations may cause challenges at both investigator and sponsor level and could jeopardise the safety oversight of the trials thus affecting the safety of trial subjects or the benefit-risk balance of the clinical trial<br>• Clinical trials investigating an IMP in several study populations or several IMPs in one or more populations can be associated with an increased likelihood of mistakes due to the sheer complexity of the design. Adequate oversight together with early detection and immediate communication of safety signals are therefore crucial to protect the safety of the trial subjects in complex clinical trials with many IMPs, populations, and/or trial sites.<br>• Trial results and safety reports could be negatively affected by increased trial complexity as they typically result in extensive documents that are hardly readable for investigators, scientific assessors, or lay people | • Very complex and long protocols are problematic for the practical implementation and oversight of the trial<br>• Impact of changes in risk/benefit must be described in revised patient information materials and Ethics Committees need to be able to assess and agree to these changes before patients are assigned to treatment. Legal requirement on adequate patient information are difficult to meet.<br>• How to guarantee that the risk-benefit assessment is kept up to date and that decisions regarding continuation or stopping of the study are properly performed given the considerable time pressure<br>• Seamless designs shorten the time available for the analysis and interpretation of the data with a risk for wrong assessment and interpretation |

**EFPIA Brussels Office**
Leopold Plaza Building ✳ Rue du Trône 108
B-1050 Brussels ✳ Belgium
Tel: + 32 (0)2 626 25 55 ✳
www.efpia.eu ✳ info@efpia.eu

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**Table 6 – Examples of concerns regarding Master Protocols raised by Regulatory Authorities, Ethics Committees and HTA bodies (continued)**

| Trial design aspect | Regulatory Authority and HTA Concerns | Ethics Committee Concerns |
|---|---|---|
| Trial Transparency | • Platform trials bear the risk of becoming functionally immortal by adding new sub-studies without clear stopping rules for the master trial itself.<br>• Great concern for unpublished interim data from closed sub-protocols. According to the EU Directive 2001/20/EC, a clinical trial summary report will be made available to the competent authorities via the EudraCT database within one year of the end of the trial. A sub-set of the summary reports is made available to the public on the EU Clinical Trials Register. Data transparency is thus of great concern for complex clinical trials submitted as one clinical trial, since publication of sub-protocol results will be delayed until after the overall clinical trial is completed.<br>• Although results of terminated sub-studies (positive and negative) could seriously impact the regulatory and ethical opinion of the ongoing trial, there are no legal means to force sponsors to submit sub-trial reports in a timely fashion when a master protocol has been submitted as a single clinical trial application.<br>• Complex trial designs proposing extensive prospective adaptations such as the addition of new IMPs or populations also challenge the EU regulatory framework in terms of the definition of a clinical trial and data transparency, and they pose a challenge in terms of providing clear information particularly to the trial subjects | • A clear idea of the timeline horizon (end of study) is needed and a strategy to avoid "never-ending" trials with a lack of transparency on trial status and outcome. |

**Table 7 - Considerations to support the use of Master Protocols**

| Criteria | Points to consider |
|---|---|
| Preclinical development | • Master protocols require good preclinical models which provide the biological knowledge of the treatment mechanism of action on the selected targets. |
| Protocol Design and conduct | • Description of the overall design including the relationships and interactions between the overarching trial and sub-protocols and their respective inter-relation<br>• Design should be clearly described in protocol with overview of closed, ongoing, and suggested new sub-protocols/arms.<br>• The master protocol should clearly describe how trial subjects are allocated to the individual sub-protocols or arms and should describe decision criteria for opening and closing of sub-protocols/arms as well as for re-allocating trial subjects from one sub-protocol to another, if applicable.<br>• Assessment of the benefit–risk balance for overarching trial and each sub-protocol<br>• Specification of the expected end of trial date<br>• A visual representation of the trial would be helpful for all the stakeholders and reviewers of the trial in addition to a detailed description of the design<br>• Focus on clinical and practical feasibility when selecting investigators and trial sites with relevant experience and additional training. Ongoing dialogue with investigator sites on challenges also through trial planning (e.g. coordinating sites for larger trials)<br>• Appropriate two-way trial communication between sites and sponsor to ensure early detection of site issues and to guarantee that investigators are up to date with all relevant trial aspects<br>• The number of study arms or indications combined in one protocol needs to make scientific sense. The protocol should provide a rationale for the complex design and why it is more efficient and better for patients than performing several individual studies.<br>• Adaptive designs must always be prospectively planned in the trial protocol. Unplanned adaptations should be avoided as much as possible, because they could introduce substantial bias in the conclusions from the trial, even for exploratory trials conducted to generate new hypotheses. Retrospective protocol flexibilization is not usually supported by agencies except for safety reasons or changes in standard of care.<br>• Sub-protocol designs should be defined by an overarching hypothesis with related sub-protocol specific objectives. This also applies to amendments with addition of new sub-protocols.<br>• Interim analyses should be blinded and performed by an independent Data Monitoring Committee (considered mandatory for complex trials) and parameters may need to be set to determine "high" efficacy to create rules that can be used to include new arms in the trial or discontinue arms due to futility.<br>• Consultation with Regulators, Ethics Committees and HTA representatives to discuss and explain the proposed design of a master protocol is highly recommended. Scientific advice with regulators is available in some Member States and EMA scientific advice can be sought in parallel to HTA advice. |

**Table 7 - Considerations to support the use of Master Protocols (continued)**

| Criteria | Points to consider |
|---|---|
| Pharmacology / biomarkers | • It is crucial to have validated biomarker assays with strong analytic performance in a clinical setting, since an assay with low specificity will dilute the treatment effect in enrichment designs and an assay with low sensitivity for resistance variants also dilutes treatment effect<br>• Procedures for sample acquisition, handling and testing of biomarkers<br>• Description of biomarker assays used for treatment eligibility and allocation including validation, clinical relevance, cutoff values,<br>• Defined process for situation of patient allocation in the case of two or more positive biomarkers<br>• Clarify reporting responsibilities and procedures for safety oversight for trials with multiple IMP suppliers |
| Statistics | • Agencies are more likely to approve complex and innovative designs for exploratory trials as there is general concern that these studies can be susceptible to bias. For this reason, it is important to take measures to avoid bias and ensure estimates of treatment effect can be estimated with sufficient precision -especially if the number of subjects in each arm is small<br>• Description of type I error control in trial protocol<br>• Prospective planning of any adaptive design in the protocol is essential for Ethics Committee and Regulatory approval and to avoid bias and keep the trial integrity.<br>• Following adaptations are regarded as acceptable as long as these are based on prospectively planned blinded interim analyses and an independent DMC:<br>  – eligibility criteria<br>  – sample size<br>  – secondary endpoints without an association with efficacy parameters<br>  – group sequential plans and futility<br>  – data analysis plan<br>• Assessment of potential multiplicity issues deriving from complex trial design with each planned and new adaption and provision of mitigation strategies in the protocol (and amendments) to avoid multiplicity issues |
| Efficacy | • It is important to clearly define exploratory vs confirmatory trial phases and the hierarchy of endpoints in the study arms and in the overall trial must be clear.<br>• Patient stratification used in the pivotal clinical trials needs to be identical to that proposed for the marketing authorization and use in real life after authorization |

**Table 7 - Considerations to support the use of Master Protocols (continued)**

| Criteria | Points to consider |
|---|---|
| Safety/DMC | • Justification of complex design features in relation to identified risks, risk-mitigations and benefit-risk assessment.<br> – Identification of risks and risk-mitigations<br> – Reflection on impact of ongoing adaptations in design for risk-mitigations<br> – Risk-based monitoring and risk-mitigation plans on sub-protocol level<br> – Implementation of communication procedures for interim data<br>• Agencies and Ethics Committees have concerns they may not receive sufficient information on safety data for evaluation before next "phase" or arm of a trial is opened. Therefore, the DMC should be able to cooperate with Health Authorities and Ethics Committees to discuss any safety issues prior to decisions on whether additional arms or dosing schedules can be included / discontinued<br>• Provision of a communication plan for safety issues to ensure appropriate and timely information of all relevant stakeholders<br>• The definition of the DMC role in umbrella/ basket/ platform trials is essential as it has a critical function regarding treatment decisions that need to be during the trial e.g. closing treatment arms, changing dosing schedules, or reporting any safety or efficacy issues.<br> – Competences should be ensured to adequately monitor all indications.<br> – Define committee responsible for recommending implementation of adaptations from planned interim analyses<br>• A DMC charter should define roles and responsibilities as well as any cooperation with Health Authorities and Ethics Committees. The composition of a DMC should be according to guidelines which ensure they remain independent when making their assessments based on blinded interim data gathered during the trial.<br>• Provide Impact analysis of any substantial modification:<br> – Procedure for evaluation of effect in all sub-protocols/arms<br> – Reassessment of risk-benefit of entire trial and of each sub-protocol<br> – Reassessment of whether patient information and consent should be updated due to amendment/new information.<br> – Reevaluation of EOT and submission of supportive data from closed sub-protocols |
| Trial Transparency | • The protocol needs to define the milestones and how the reporting obligations will be fulfilled for each arm/ sub-trial to ensure transparency.<br>• Sponsor should declare "publication policy" for the trial with description of how and when interim data will be published.<br>• Suggest publication of interim data in IB update or clinical IMPD (if investigator confidentiality is necessary). |

It seems from the outcome of the stakeholder meetings that the national authorities also recognise the opportunity a multinational clinical trial advisory committee could offer when discussing master protocols in future.

For multinational trials with master protocols the use of the voluntary harmonisation procedure in EU countries is strongly recommended. It is important to clearly describe the proposed design in a cover letter, explaining any complex aspects of the trial, such as sub-protocol design, expansion cohorts and how these fit into the master protocol. The letter should also indicate whether all sub-protocols are intended to be open for recruitment in all countries involved the trial.

New complications with certain kinds of complex trial designs may arise after implementation of the EU Clinical Trial Regulation, as it will not be possible to submit several substantial amendments to a

**EFPIA Brussels Office**
**Leopold Plaza Building ✳ Rue du Trône 108**
**B-1050 Brussels ✳ Belgium**
**Tel: + 32 (0)2 626 25 55 ✳**
**www.efpia.eu ✳ info@efpia.eu**

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single protocol in parallel, to halt, stop or enlarge a specific trial arm. If several amendments were required to cover changes affecting different arms of a master protocol trial these would have to be submitted and approved sequentially, which could lead to practical problems in conducting the trial. To mitigate this concern, it would be helpful to identify where protocols could include appropriate decision criteria to reduce the need for substantial amendments, e.g. when transitioning from different study phases, expanding the study to increase the number of patients at a recommended dose following dose escalation etc.

Parallel discussions on complex trials are also needed with HTA bodies and decision makers on reimbursement aspects to ensure the design and any treatment comparators are also acceptable from this perspective. However, experience to-date with EMA/HTA parallel scientific advice has shown that scheduling such meetings requires considerable advanced notice and planning due to the limited number of HTA resources available to participate in such meetings. In the interest of study participants, it would be helpful to establish a less bureaucratic option for discussions with multiple stakeholders on acceptability of a proposed design prior to the initiation of a study.

## 5. Use of Historical Controls

### 5.1 How to optimise clinical trial design in a challenging environment?

Randomised controlled trials (RCTs) are considered the gold standard to demonstrate efficacy in the context of marketing authorisations and reimbursement decisions on drugs. Ideally, there is the wish to obtain an unbiased estimate of the effect of the treatment being investigated compared to placebo or to another active compound. The goal of obtaining an unbiased estimate of the size of effect is true in studies in small populations as well as large trials for common diseases. Thus, in developing any treatment, a comparative randomised trial will usually be *preferable* but may not always be *possible*.

RCTs have well known limitations however, and there are situations where a RCT may not be feasible or ethical; e.g. for a new drug with very strong biological rationale in a biomarker-selected population of patients; for new drug demonstrating an unprecedented objective response rate in a setting of high unmet need with no effective therapies; or for an already approved molecularly targeted agent when being tested in a rare tumour histology expressing the appropriate biomarker. In orphan diseases and areas of high unmet need, where subjects are scarce, or no effective standard of care is available, RCTs are not always feasible and health authorities have demonstrated willingness to accept evidence based on single arm trials, using historical control data to explicitly or implicitly define a benchmark efficacy threshold. However, significant challenges also exist in more common disease areas, such as Alzheimer's Disease, where recruiting subjects for clinical trials is increasingly difficult due to logistical and patient burden issues, resulting in increased clinical trial timelines. Paediatric clinical studies are often required to fulfil a Paediatric Investigation Plan agreement with HAs, but may present recruitment difficulties, especially when alternative treatments already exist. In therapeutic areas such as chronic kidney disease, where natural history of the disease and standard treatment options have remained stable for several years, there is an accumulating body of data from control arms of failed clinical development programmes which could be considered predictive of control responses in future clinical trials. In this context, the benefits of using existing control data are self-evident: fewer patients need to be enrolled in trials, the value of data gleaned from those who do will be multiplied, and the efficiency and speed of clinical trials are increased.

**EFPIA Brussels Office**
**Leopold Plaza Building ✱ Rue du Trône 108**
**B-1050 Brussels ✱ Belgium**
**Tel: + 32 (0)2 626 25 55 ✱**
**www.efpia.eu ✱ info@efpia.eu**

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This section discusses some of the opportunities and challenges for clinical trial designs utilizing historical control data, focusing particularly on recent developments in trial designs using a *combination* of historical and concurrent controls. Figure 5 summarises the types of designs considered, and Table 8 their benefits and limitations.

**Figure 5: Designs including non-randomised treatment comparisons**
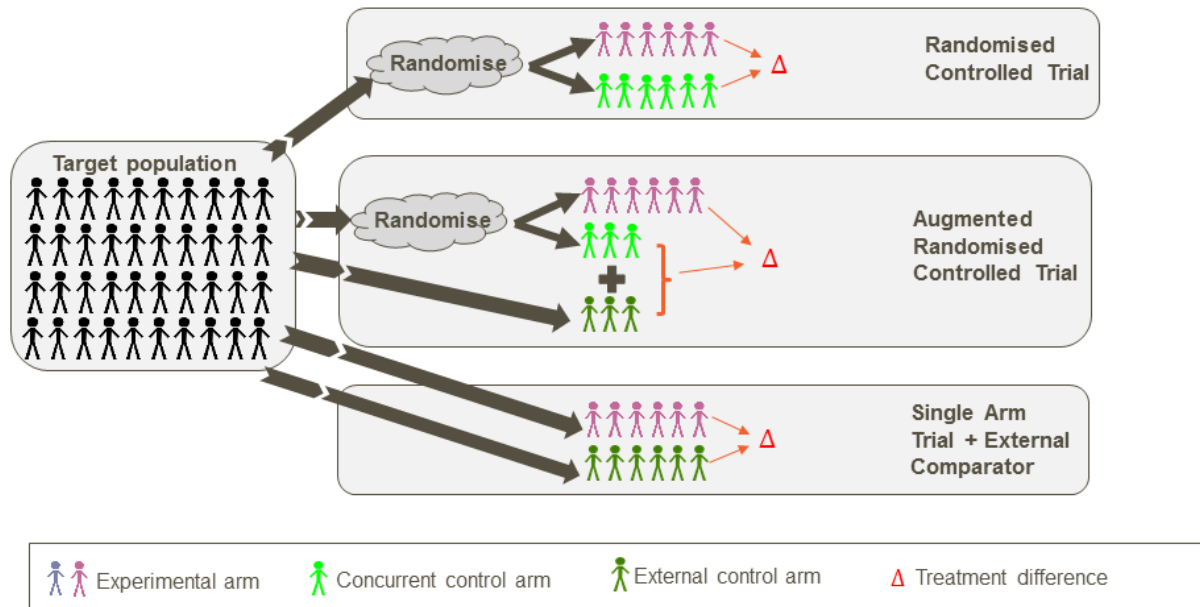
**Table 8: Benefits and limitations of CT designs**

| BENEFITS | LIMITATIONS |
|---|---|
| **Randomised Clinical Trials** | |
| • Randomisation ensures reasonable similarity of the test and control groups and protects against various imbalances and biases that could lead to erroneous conclusions<br>• Randomisation is ethical when there is equipoise | • RCTs are expensive and lengthy. Need alternative designs to speed up drug development to address recruitment challenges and minimise patient burden<br>• Equipoise is a useful principle, but it can break down when conventional care offers little benefit and mortality is extremely high, or where there are no currently available treatment options. |
| **Single arm studies** | |
| • Require fewer resources<br>• Take less time to complete<br>• Appropriate in refractory populations<br>• Easily understood by the target patient population | • Defined study population frequently not comparable to historic controls<br>• If response rate is marginal it may not reflect true clinical benefit<br>• Poor characterization of safety |
| **Augmented RCT using historical controls to supplement or partially replace concurrent controls** | |
| • Increased availability of high quality, curated, and trusted clinical data, e.g. through data-sharing initiatives (e.g. TransCelerate Placebo Standard of Care database, Project Data Sphere)<br>• Statistical methods for establishing causal treatment effects using non-randomised data are available, although typically require stronger assumptions than inference based on an RCT<br>• Potential for long run Type I error to be lower when using historical borrowing (Viele et al 2018)<br>• May be more appealing to participants who want a higher probability of being assigned to the experimental arm. | • If standard of care has improved over time, this tends to induce positive bias in favour of active treatment if using historical controls<br>• Challenge of assessing relevance of historical data, and risk of bias/type 1 error inflation if historical and current controls are not comparable |

## 5.2 Single arm studies – challenges & opportunities

A major goal of any clinical development programme is to implement the most efficient clinical trials that demonstrate the clinical benefit of a new drug, while limiting the number of patients who may be exposed to a treatment with limited effectiveness and/or tolerability.

Single arm studies have been often used by sponsors to support the registration of medicinal products in some specific circumstances, i.e. in areas of unmet medical need, when there is no other approved alternative, or no consensus on alternate salvage therapy, or in situations where a placebo control is not acceptable. In their 10-year report [45] of experience of Conditional Marketing Authorisations (CMA) published in September 2017, the EMA noted that '*Most studies (34/58) were randomised multiple arm studies, but just over a third of studies consisted of a single arm. There were relatively more singe arm studies in the oncology area (15/29) and relatively more randomised multiple arm studies in infectious diseases area (18/23).*' In 2016, the EMA explored further the use

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of single arm studies in oncology [46] as the basis for regulatory approval in order to identify whether a more systematic approach could be developed. With reference to the ICH E10 guideline [47], it was mentioned that the use of external control design should be '*restricted to situations in which the effect of treatment is dramatic and the usual course of the disease highly predictable*'.

Once approved under conditions, on the basis of a single arm study, it is also not uncommon that additional supportive evidence is generated, which can help converting the marketing authorisation into a standard marketing authorisation, and successfully support pricing and reimbursement.

Prospective single-arm clinical trial(s) could be sufficient for the registration of molecularly targeted agents (MTAs) for rare tumours, provided that these agents show rapid, durable, and clinically meaningful activity, preferably together with positive exploratory health-related quality of life (HRQOL) and favourable (or at least acceptable) tolerability. As illustrated with crizotinib [48] or osimertinib [49], new MTAs will also need to demonstrate these findings in a prospective clinical trial of a properly selected patient population based on strong biological rationale, possibly with an appropriate companion diagnostic test for molecular patient selection in order to secure regulatory approval of the MTA. Of note, both crizotinib and osimertinib, while initially approved under conditions with a limited data package, were subsequently completed with additional evidence which has helped switching from a conditional marketing authorisation to a full marketing authorisation.

A key issue to support regulatory approval of single-arm trials is the identification and use of appropriate external evidence, e.g. historical controls or indirect comparisons.   While it is acknowledged that high unmet need and early (conditional) approval with high uncertainty are frequent in disease areas such as oncology, since it is often the only possible way forward, the contribution of single arm studies to health technology assessment (HTA) remains a challenge. Not all HTA bodies and payers accept single-arm studies as a basis for their relative effectiveness assessments. This might mean that regulatory approvals based on single-arm studies have less chance of receiving reimbursement in different countries, which is an essential step in facilitating patient access. As an example, in 2014 NICE published a review [50] of Appraisals using single arm trials, and concluded that drugs are unlikely to be approved by NICE on the basis of single-arm trial evidence (where used as the primary source of efficacy evidence) unless there is substantial supporting evidence from other sources (e.g., multiple single-arm trials) and/or unless there are other factors (e.g., high burden and unmet need). Indeed, for HTA bodies used to assessing the internal validity of non-randomised studies (NRS), there is the perception that "*the inclusion of NRS might mislead researchers into the false belief that RCTs are not worthwhile to perform*, while recognizing *they may play a greater role in the assessment of safety*. For EUnetHTA, the *decision to perform such studies should be made only after careful consideration of all advantages and disadvantages.*2 [51]  There are examples where a product was approved under conditions by the regulators based on a single arm study, and which was then rejected by HTA/payers, which had thus a noticeable impact on patients' access [52].

This position is also shared beyond Europe, as shown by the US Agency for Healthcare Research and Quality, which mentioned in their Research White Paper [53] that the reporting of inclusion or exclusion of single group studies in the comparative effectiveness review (CER) of the Effective Health Care Programme was sub-optimal. The review of published CERs indicated that single group studies were commonly included in CERs, but the rationale for including them was not consistently

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reported, and the methods relevant to their use not clearly defined. Clarity and transparency in the rationale for including or excluding single group studies in CERs should therefore be promoted.

More recently, the IMI ADAPT SMART consortium as part of their work on the Evidence Generation throughout the life cycle, identified 'single arm studies' as a topic [54] for a future EU research project,  to develop a methodological, structured framework and the necessary tools (guidelines, software, interactive online systems) that allows to decide whether it is appropriate to provide patient access to a novel treatment based on evidence generated by one (or multiple) single-arm studies.

## 5.3 Historical borrowing designs combining historical and concurrent controls

Much of the debate over the relative merits of randomized or historical controls has been predicated on the assumption that a trial can only have one or the other.  As far back as 1976, Pocock proposed a quantitative approach for the *combination* of historical and concurrently randomised control data, together with a set of operational criteria for determining the acceptability of historical controls, arguing that "this should lead to a more efficient use of patients in the execution of clinical trials". Pocock's idea of combining historical and randomised controls has gained relatively little traction until very recently. New statistical developments, particularly those using Bayesian methods, have facilitated the approach of combining the two sources of control data: these methods allow the information derived from the historical controls to be down-weighted in accord with the amount of "drift" (i.e. difference between the concurrent and historical control data, as well as enabling statistical covariate adjustments for differences between known baseline patient characteristics that may lead to different responses in historical and concurrent controls [55]. Use of such methods helps to minimise the risk of biased treatment effect estimates due to inappropriate borrowing, although potential for inflation of false positive rates remains a key challenge. Extensive clinical trial simulations are needed to inform the trial design and calculate the key risks and trade-offs between reduced sample size and timelines, gains in precision of treatment effect estimates and risks of bias and type 1 error.

A key driver for the renewed interest in designs combining historical and randomised controls is that sources of historical data (as well as computational resources to store, search and process such data) have become much more readily available over time. Most major pharmaceutical companies have an external data sharing initiative, and there are increasing efforts at data-sharing among various consortia: Project Data Sphere [56] for oncology trials and CAMD [57] for Alzheimer's trials are two such examples in specific disease areas, whilst in 2015, TransCelerate initiated the development of a database containing placebo and standard of care (PSoC) data from completed clinical trials across multiple disease areas, with the aim to enhance innovative drug product development by better informing clinical safety interpretation and trial design [58]. The PSoC database will enable pharmaceutical R&D companies to share clinical data in a non-competitive, collaborative environment to enhance the development of new medicines. Recent discussions with regulatory agencies also indicate an increased openness to consideration of supplementation with historical controls. As a result of the PSoC work, TransCelerate published a white paper [59] which provides guidance on the potential applications of this large historical PSoC database, and examples for the possible implementation of historic data in seven specific applications (use cases). TransCelerate also organised a workshop in 2018 which aimed to develop ongoing discussions with Health Authorities and other key stakeholders addressing the challenges of utilizing historical clinical data in confirmatory trials.

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Table 9 summarises the initial list of criteria and considerations that was developed for the workshop; TransCelerate are currently refining and developing these criteria to create a guidance document with examples which can support utilization of historical data to be acceptable for submission and to ensure that the use is appropriate and objective.

**Table 9: Considerations for historical borrowing**

| Criteria | Points to consider |
|---|---|
| **Disease-specific considerations** | • What factors would allow us to judge in advance whether the use of historical data is appropriate?<br>  ○ Would these factors change for a rare vs. a more common disease, and if so how?<br>• Are there disease areas/endpoints that are more/less appropriate for this approach?<br>• Unmet medical needs/ Time sensitive to find a treatment? |
| **Data availability and quality** | • What historical data are available?<br>  ○ What studies containing target clinical trial population are available? Is the data at the patient-level or is it published aggregate information?<br>• Consider similarity of trial population/conduct/design/visit timing, imbalance in covariates.<br>• Quality of the historical data<br>• Are similar assessments of endpoints or treatment evaluations available?<br>• Currency/recency<br>• Variability/drift |
| **Operational considerations** | • Does the context require reducing the length of patient recruitment and minimizing participant burden by using historical data supplementation?<br>• Are there a minimum number of concurrent controls that need to be maintained in a clinical trial?<br>• Change of standard of care? Do the historical data adequately reflect the current SoC?<br>• Who should pick the historical trials/data within trials? |
| **Risk-benefit assessments** | • What are the risks of using historical data?<br>• Does the benefit outweigh the risk? |
| **Methodology considerations** | • To ensure the historical control is relevant to the current trial one must clearly lay out prospective plan/rationale for the type of data chosen, how and why it will be incorporated, so as to:<br>  ○ Address potential issues of selection bias?<br>  ○ Ensure comparability of study populations?<br>• Having selected a set of historical trials, what methods can be used to account for any bias that may exist? (e.g., covariate adjustment)<br>• Can we model the difference between the historical and concurrent data if we know that there are factors that affect this in predictable way? |
| **Reporting** | • What needs to be shared with authorities [Have a look at FDA devices guidance] |

Disease registries can also be used as a source for historical controls. Registers used in this way should contain high quality data, and GCP inspection might be anticipated (EMA guideline on CTs in small populations [60]). Recently EMA qualified the European Cystic Fibrosis Society Patient Registry (ECFSPR) [61] as deemed by CHMP as an appropriate data source for post-authorisation studies to

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support regulatory decision making on medicines for the treatment of cystic fibrosis.  There are numerous issues relating to disease registries that are outside the remit of this paper.

## 5.4 Regulatory considerations for historical control borrowing designs

As yet, there is very limited information in the public domain about regulatory experience of historical borrowing designs combining historical and concurrent controls, although several examples of the use of such designs in early-phase development, and as part of ongoing late-phase development programs, have been shared publicly at recent scientific conferences. No guidance documents directly relating to such historical control borrowing designs for drug approvals are currently available in either Europe or USA, although the role of historical controls is mentioned in other guidance documents for medical device trials. These include the FDA's Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials (2010) [62], which states that Bayesian methods can be useful for combining historical controls with concurrent controls by using historical controls as prior information for the concurrent control. Another more recent FDA guidance (FDA, 2017 [63]) cites where Real World Evidence may potentially be applied to enhance understanding of medical device performance at different points in the total product life cycle, including as a historical control, a prior in a Bayesian trial, or as one source of data in a hierarchical model or a hybrid data synthesis.

# 6.  Future Considerations

While the EU and USA regulatory authorities are relatively mature in their consideration of adaptive designs, more work is being done in this field.  In the EU, two workshops on adaptive designs in confirmatory trials have taken place (2007, 2009) in which FDA participated, the first of which took place just after the EMEA published its reflection paper on the topic (2007) and the second, which focused on case studies and good practices, took place just prior to the publication of draft USA guidance (2010).  To promote and increase awareness and a common understanding across different stakeholders of the full range of innovation now possible in clinical trials, regulatory agencies could develop videos describing types of trial design.  In addition, additional workshops similar to the one led by FDA on complex innovative designs in other countries would be valuable to enable different stakeholders to debate the value, use and acceptability of these designs.

The output from the planned pilot programme of sponsor-FDA engagement, on proposed complex trial protocols, will inform the development of a single draft guidance on complex adaptive trial designs (due September 2019).  By September 2020, FDA is committed to updating relevant procedural documents to reflect the use of such designs in decision making.  Separately, draft guidance on model informed drug development is also scheduled (by September 2019).

The significant progress made in this field is such that development of a new ICH guideline on adaptive designs [64], reflecting the importance of this topic amongst a more international groups of regulatory authorities.  In a recent review of the methodological and data developments that have acted as enablers for historical control borrowing designs concluded that "the industry and regulatory science has matured to the point where high quality data exists to support these approaches; the statistical methods have evolved to provide a robust understanding of risk; and our evolution to a patient-centric model demands that we leverage these methods more broadly".

Getting direct patient input into study designs and modifying designs accordingly will likely become the new normal, particularly as the growing use of patient-facing digital technologies provides new

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ways to engage with patients, as well as changing the types of endpoints and ways in which data are collected in clinical trials [65].  Obtaining feedback from patients or patient advocacy groups on what procedures and how many procedures patients feel they can tolerate, and incorporating this feedback into study protocols reduces the number of procedures to those essential and could prevent and/or reduce drop outs and the extent of missing data to assess study outcomes. Patient insights to help understand reasons for recruitment challenges may support use of historical control data to reduce number of patients exposed to placebo in new trials. Patient input into informed consent forms can ensure these are user friendly with a trend for patients to provide their consent electronically.  Similarly, the need for patients to attend sites for assessments is reducing as data collection is being done remotely with technology such as e-dairies and activity monitors as examples.  This could also lead to increasing retention of patients in clinical trials. Levitan et al [66] have shown that such patient engagement activities have the potential to add considerable financial value for sponsors in terms of return on investment, as well as improving patient experience.

New digital technologies for data capture and sharing of both clinical trial and real-world data, combined with growing use of AI and machine learning tools to extract patterns from these data, offer the potential to build and continuously update predictive models of disease natural history or patient outcomes under existing treatment options. Such models could be used to generate synthetic control arm information to supplement or replace concurrent controls in RCTs; prototype examples of synthetic controls are already being developed for use in early phase oncology clinical trials [67].

Use of external/historical controls and Bayesian designs is one of the areas identified as of being of interest under the USA's PDUFA VI Complex Innovative Designs Pilot programme, and the recent stakeholder workshops and meetings of the TransCelerate PSoC working group with FDA and EMA reflect a willingness by regulatory authorities to consider greater use of historical borrowing designs. A fundamental consideration is whether the historical data are of sufficient quality and relevance to inform or support a particular regulatory decision. Decisions about quality and relevance of historical data must be made on a case by case basis, and sponsors need to engage early with regulatory authorities to discuss this.

## 7. Conclusions

Innovation in clinical trial design is transforming evidence generation in drug development.  Whilst adaptive designs and designs enabling the target population to be enriched have been available for many years, their use has substantially increased in recent years.  The use of master protocols to investigate either multiple treatments or multiple diseases in the same clinical trial is quickly growing, as are designs augmenting or replacing a control arm with historical data.

The regulators have recognised the need for more complex designs to increase the efficiency and effectiveness of clinical trials whilst maintaining high quality data for regulatory decision making. The acceptability of data from innovative or more complex clinical trials is essential to allow new medicines to be available as treatment options for patients with unmet medical needs.  Whilst there has been and there will be significant interactions between Industry and regulators on guidelines, recommendations and best practices for innovative clinical trial designs, there has been limited discussions with HTA agencies.  Additional focus is needed to ensure all key stakeholders align on the use of novel clinical trial designs.

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## Appendix

**EFPIA Brussels Office**
**Leopold Plaza Building ✳ Rue du Trône 108**
**B-1050 Brussels ✳ Belgium**
**Tel: + 32 (0)2 626 25 55 ✳**
**www.efpia.eu ✳ info@efpia.eu**

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Table A1: Regulatory-approved products that include some adaptive design element in their clinical development

| Compound | Adaptive design element | Key Results/ outcome | Indication in EU label | | Indication in US label |
|---|---|---|---|---|---|
| | | | at least partially supported by data generated via adaptive clinical designs | | |
| Symtuza (EU/USA) Janssen-Cilag International N.V. | Phase I, relative bioavailability, adaptive-design, randomised, open-label, multiple-dose, 3-part, multiple cohort. Compared three formulations of fixed dose combination (monolayer vs bilayer; 25 mg vs 10 mg of one active ingredient) repeated dosing. Aim was to select one formulation for Part 3 of the study and for further development, starting with a Phase 2 study. Part 3 evaluated possible interaction of certain combinations. n =102 | Formulation 3 was chosen for Part 3 of the study and for further development | Symtuza is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and adolescents (aged 12 years and older with body weight at least 40 kg). Genotypic testing should guide the use of Symtuza (see sections 4.2, 4.4, and 5.1). Symtuza : EPAR - Public assessment report https://www.ema.europa.eu/en/documents/product-information/symtuza-epar-product-information_en.pdf | | SYMTUZA is indicated as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults: <br>• who have no prior antiretroviral treatment history or <br>• who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen for at least 6 months and have no known substitutions associated with resistance to darunavir or tenofovir. SYMTUZA prescribing information |

Table A1 (cont.): Regulatory-approved products that include some adaptive design element in their clinical development

| Compound | Adaptive design element | Key Results/ outcome | Indication in EU label | | Indication in US label |
|---|---|---|---|---|---|
| | | | at least partially supported by data generated via adaptive clinical designs | | |
| Lucentis Ranibizumab Novartis Europharm Limited (extension of indication) | Phase II: Originally flexible design. Based on outcome of interim analysis, there were two parts for analysis of efficacy, a pilot/supportive part (n=42) and a confirmatory part (n=109) with the new primary efficacy endpoint 'mean average change in visual acuity from baseline from Month 1 to Month 12' | Sufficient data support the choice of dose, 0.5 mg, the flexible dosing frequency, the re-treatment and stopping criteria that are based on assessment of VA. A statistically convincing effect of ranibizumab in the treatment of visual impairment due to DME has been demonstrated | Lucentis is indicated in adults for:<br>• The treatment of neovascular (wet) age-related macular degeneration (AMD)<br>• The treatment of visual impairment due to diabetic macular oedema (DME)<br>• The treatment of proliferative diabetic retinopathy (PDR)<br>• The treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO)<br>• The treatment of visual impairment due to choroidal neovascularisation (CNV)<br><br>https://www.ema.europa.eu/en/documents/variation-report/lucentis-h-c-715-ii-0020-epar-assessment-report-variation_en.pdf<br>https://www.ema.europa.eu/en/documents/product-information/lucentis-epar-product-information_en.pdf | | LUCENTIS is indicated for the treatment of patients with:<br><br>1.1 Neovascular (Wet) Age-Related Macular Degeneration (AMD)<br><br>1.2 Macular Edema Following Retinal Vein Occlusion (RVO)<br><br>1.3 Diabetic Macular Edema (DME)<br><br>1.4 Diabetic Retinopathy (DR)<br><br>1.5 Myopic Choroidal Neovascularization (mCNV)<br><br><br>LUCENTIS prescribing information |

**EFPIA Brussels Office**
**Leopold Plaza Building ✳ Rue du Trône 108**
**B-1050 Brussels ✳ Belgium**
**Tel: + 32 (0)2 626 25 55 ✳**
**www.efpia.eu ✳ info@efpia.eu**

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Table A1 (cont.): Regulatory-approved products that include some adaptive design element in their clinical development

| Compound | Adaptive design element | Key Results/ outcome | Indication in EU label | Indication in US label |
|---|---|---|---|---|
| | | | at least partially supported by data generated via adaptive clinical designs | |
| Gardasil 9<br><br>human papillomavirus 9-valent vaccine (recombinant, adsorbed)<br><br>Sanofi Pasteur MSD | Phase IIb/III, adaptive with 3 sub-studies (n=1242). Based on interim analysis of immunogenicity data in the phase II dose selection part (Part A), one dose was selected for evaluation in the phase III part (Part B). | In women aged 16-26 years, vaccine protected against the composite clinical endpoint. | Gardasil 9 is indicated for active immunisation of individuals from the age of 9 years against the following HPV diseases: i) premalignant lesions and cancers affecting the cervix, vulva, vagina and anus caused by vaccine HPV types; ii) genital warts (Condyloma acuminata) caused by specific HPV types. See sections 4.4 and 5.1 for important information on the data that support these indications. The use of Gardasil 9 should be in accordance with official recommendations.<br><br>https://www.ema.europa.eu/en/documents/assessment-report/gardasil-9-epar-public-assessment-report_en.pdf<br><br>https://www.ema.europa.eu/en/documents/product-information/gardasil-9-epar-product-information_en.pdf | **1.1 Girls and Women**<br>GARDASIL®9 is a vaccine indicated in girls and women 9 through 45 years of age for the prevention of the following diseases:<br>• Cervical, vulvar, vaginal, and anal cancer caused by Human Papillomavirus (HPV) types 16, 18,31, 33, 45, 52, and 58<br>• Genital warts (condyloma acuminata) caused by HPV types 6 and 11<br>And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58:<br>• Cervical intraepithelial neoplasia (CIN) grade 2/3 and cervical adenocarcinoma *in situ*<br>• Cervical intraepithelial neoplasia (CIN) grade 1<br>• Vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3<br>• Vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3<br>• Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3<br>**1.2 Boys and Men**<br>GARDASIL 9 is indicated in boys and men 9 through 45 years of age for the prevention of the following diseases:<br>• Anal cancer caused by HPV types 16, 18, 31, 33, 45, 52, and 58<br>• Genital warts (condyloma acuminata) caused by HPV types 6 and 11<br>And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58:<br>• Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3<br>**1.3 Limitations of Use and Effectiveness -** See label<br><br>GARDASIL 9 prescribing information |

**EFPIA Brussels Office**
**Leopold Plaza Building** ✳ **Rue du Trône 108**
**B-1050 Brussels** ✳ **Belgium**
**Tel: + 32 (0)2 626 25 55** ✳
**www.efpia.eu** ✳ **info@efpia.eu**

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## Table A1 (cont.): Regulatory-approved products that include some adaptive design element in their clinical development

| Compound | Adaptive design element | Key Results/ outcome | Indication in EU label | Indication in US label |
|---|---|---|---|---|
| | | | at least partially supported by data generated via adaptive clinical designs | |
| Trulicity Dulaglutide Eli Lilly and Company | Phase 2/3, adaptive, inferentially seamless, multicenter, randomized, Placebo-controlled, double-blind, parallel-arm study (ITT= 1098) (One of 5 phase 3 studies completed). | 5 main studies involving over 4,500 patients with type 2 diabetes. Dulaglutide doses that were tested (1.5mg and 0.75mg) consistently showed a significant and clinically relevant mean reduction in HbA1c from baseline which was the primary efficacy endpoint. | Type 2 Diabetes Mellitus  Trulicity is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise • as monotherapy when metformin is considered inappropriate due to intolerance or contraindications • in addition to other medicinal products for the treatment of diabetes. For study results with respect to combinations, effects on glycaemic control and cardiovascular events, and the populations studied, see sections 4.4, 4.5 and 5.1.  https://www.ema.europa.eu/en/documents/assessment-report/trulicity-epar-public-assessment-report_en.pdf  https://www.ema.europa.eu/en/documents/product-information/trulicity-epar-product-information_en.pdf | TRULICITY® is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.  Limitations of Use: See label  https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125469s023lbl.pdf |

**EFPIA Brussels Office**
**Leopold Plaza Building** ✳ **Rue du Trône 108**
**B-1050 Brussels** ✳ **Belgium**
**Tel: + 32 (0)2 626 25 55** ✳
**www.efpia.eu** ✳ **info@efpia.eu**

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Table A1 (cont.): Regulatory-approved products that include some adaptive design element in their clinical development

| Compound | Adaptive design element | Key Results/ outcome | Indication in EU label | Indication in US label | |
|---|---|---|---|---|---|
| | | | at least partially supported by data generated via adaptive clinical designs | | |
| Kevzara sarilumab Sanofi-aventis Groupe | Operationally seamless Phase II (dose-ranging)/III double-blind, placebo-controlled study (one of two Phase III placebo-controlled studies). Part A: n=306). | Both sarilumab groups were statistically significant superior with regard to the 3 co-primary endpoints | Kevzara in combination with methotrexate (MTX) is indicated for the treatment of moderately to severely active rheumatoid arthritis (RA) in adult patients who have responded inadequately to, or who are intolerant to one or more disease modifying anti rheumatic drugs (DMARDs). Kevzara can be given as monotherapy in case of intolerance to MTX or when treatment with MTX is inappropriate (see section 5.1). https://www.ema.europa.eu/en/documents/assessment-report/kevzara-epar-public-assessment-report_en.pdf https://www.ema.europa.eu/en/documents/product-information/kevzara-epar-product-information_en.pdf | KEVZARA® is indicated for treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to one or more disease-modifying antirheumatic drugs (DMARDs). KEVZARA prescribing information | |
| Skilarence dimethyl fumarate Almirall S.A | Phase II, Randomised, DB, multi-centre, 3-arm, active, and placebo-controlled, adaptive two-stage design applying Bauer and Köhne method allowing for sample size adjustment after stage 1 (n=699) I.e. to increase sample size or stop for futility. | The DMC recommendation to increase sample size was not implemented however the threshold for statistical significance was penalised Overall demonstrate a convincing evidence of superior efficacy compared to placebo and a comparable efficacy to active comparator | Skilarence is indicated for the treatment of moderate to severe plaque psoriasis in adults in need of systemic medicinal therapy. https://www.ema.europa.eu/en/documents/assessment-report/skilarence-epar-public-assessment-report_en.pdf https://www.ema.europa.eu/en/documents/product-information/skilarence-epar-product-information_en.pdf | | |

Table A1 (cont.): Regulatory-approved products that include some adaptive design element in their clinical development

| Compound | Adaptive design element | Key Results/ outcome | Indication in EU label | Indication in US label |
|---|---|---|---|---|
| | | | at least partially supported by data generated via adaptive clinical designs | |
| Skilarence<br><br>dimethyl fumarate<br><br>Almirall S.A | Phase II, Randomised, DB, multi-centre, 3-arm, active, and placebo-controlled, adaptive two-stage design applying Bauer and Köhne method allowing for sample size adjustment after stage 1 (n=699) I.e. to increase sample size or stop for futility. | The DMC recommendation to increase sample size was not implemented however the threshold for statistical significance was penalised Overall demonstrate a convincing evidence of superior efficacy compared to placebo and a comparable efficacy to active comparator | Skilarence is indicated for the treatment of moderate to severe plaque psoriasis in adults in need of systemic medicinal therapy.<br><br>https://www.ema.europa.eu/en/documents/assessment-report/skilarence-epar-public-assessment-report_en.pdf<br><br>https://www.ema.europa.eu/en/documents/product-information/skilarence-epar-product-information_en.pdf | |

Table A1 (cont.): Regulatory-approved products that include some adaptive design element in their clinical development

| Compound | Adaptive design element | Key Results/ outcome | Indication in EU label | Indication in US label |
|---|---|---|---|---|
| | | | at least partially supported by data generated via adaptive clinical designs | |
| Zinplava<br><br>Bezlotoxumab<br><br>Merck Sharp & Dohme B.V. | Phase III. Study 1 and 2: Randomised, DB, placebo-controlled, multicentre study. Study 1: 4 arms, adaptive (one or both of the individual mAb groups (actoxumab and/or bezlotoxumab) could be dropped based on interim analysis if there was a significant difference in the reduction of CDI recurrence when compared to actoxumab + bezlotoxumab. (n=1452 randomised.)  Study 2: 3 arms, no interim analysis; however, an adaptation was permitted if bezlotoxumab alone arm was dropped in study 1 based on recommendations of the eDMC at the time of the interim analysis. (n=1203 randomised) | Study 1: Following the interim analysis further enrollment into actoxumab arm was stopped for safety reasons (this arm was not included in Study 2).  In each study a lower proportion of subjects had CDI recurrence for bezlotoxumab group compared to placebo group. | ZINPLAVA is indicated for the prevention of recurrence of *Clostridium difficile* infection (CDI) in adults at high risk for recurrence of CDI (see sections 4.2, 4.4 and 5.1).<br><br>https://www.ema.europa.eu/en/documents/assessment-report/zinplava-epar-public-assessment-report_en.pdf<br><br>https://www.ema.europa.eu/en/documents/product-information/zinplava-epar-product-information_en.pdf | ZINPLAVA™ is indicated to reduce recurrence of *Clostridium difficile* infection (CDI) in patients 18 years of age or older who are receiving antibacterial drug treatment of CDI and are at a high risk for CDI recurrence.<br><br>Limitations of Use and Effectiveness: See label<br><br>ZINPLAVA prescribing information |

**EFPIA Brussels Office**
**Leopold Plaza Building** ✳ **Rue du Trône 108**
**B-1050 Brussels** ✳ **Belgium**
**Tel: + 32 (0)2 626 25 55** ✳
**www.efpia.eu** ✳ **info@efpia.eu**

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Table A2 - Examples of Master Protocols supporting approval of new treatments

| Compound | Design | Key Results/ outcome | Indication in US label | Indication in EU label |
|---|---|---|---|---|
| | | | at least partially supported by data generated via master protocols | |
| *Imatinib – GLIVEC/ GLEEVEC®* Novartis | B2225 Basket trial 2001-2004 | 186 patients with 40 different pathologic diagnoses were enrolled (78.5% solid tumours, 21.5% hematologic malignancies). Notable activity of imatinib was observed in several tumour types | • Adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with PDGFR (platelet-derived growth factor receptor) gene re-arrangements as determined with an FDA-approved test<br>• **Adult patients with aggressive systemic mastocytosis (ASM) without the D816V c-Kit mutation as determined with an FDA-approved test or with c-Kit mutational status unknown**<br>• Adult patients with hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL) who have the FIP1L1-PDGFRα fusion kinase (mutational analysis or FISH demonstration of CHIC2 allele deletion) and for patients with HES and/or CEL who are FIP1L1-PDGFRα fusion kinase negative or unknown<br>• Adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP) | • adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) gene re-arrangements.<br>• adult patients with advanced hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukaemia (CEL) with FIP1L1-PDGFRα rearrangement.<br>• the treatment of adult patients with unresectable dermatofibrosarcoma protuberans (DFSP) and adult patients with recurrent and/or metastatic DFSP who are not eligible for surgery |

## Table A2 (cont.) - Examples of Master Protocols supporting approval of new treatments

| Compound | Design | Key Results/ outcome | Indication in US label | Indication in EU label |
|---|---|---|---|---|
| | | | at least partially supported by data generated via master protocols | |
| *Pembrolizumab – KEYTRUDA®* Merck Sharp & Dohme | Keynote 001 Basket trial 2012-2014 | 1235 patients in indication-specific cohorts.<br>• Melanoma (n=655): ORR 33%, 12-month PFS 35%, median OS 23m<br>• NSCLC (n=495): ORR 19.4%, median PFS 3.7m, median OS 12m | Melanoma<br>• treatment of patients with unresectable or metastatic melanoma.<br>• Non-Small Cell Lung Cancer (NSCLC)<br>• as a single agent for the first-line treatment of patients with metastatic NSCLC whose tumors have high PD-L1 expression [(Tumor Proportion Score (TPS) ≥50%)] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations.<br>• as a single agent for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with disease progression on or after Pt-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving KEYTRUDA.<br>• in combination with pemetrexed and carboplatin, as 1st-line treatment of patients with metastatic nonsquamous NSCLC. | • KEYTRUDA as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults.<br>• KEYTRUDA as monotherapy is indicated for the first-line treatment of metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 with a ≥ 50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations.<br>• KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic NSCLC in adults whose tumours express PD-L1 with a ≥ 1% TPS and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumour mutations should also have received targeted therapy before receiving KEYTRUDA. |

**EFPIA Brussels Office**
**Leopold Plaza Building ✳ Rue du Trône 108**
**B-1050 Brussels ✳ Belgium**
**Tel: + 32 (0)2 626 25 55 ✳**
**www.efpia.eu ✳ info@efpia.eu**

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## Table A2 (cont.) - Examples of Master Protocols supporting approval of new treatments

| Compound | Design | Key Results/ outcome | Indication in US label | Indication in EU label |
|---|---|---|---|---|
| | | | at least partially supported by data generated via master protocols | |
| *Vemurafenib – ZELBORAF®* Roche | VE-BASKET BRAF V600 Basket trial 2012-2016 | 26 pts <br> • confirmed ORR: 61.5% in overall cohort; 54.5% in patients w ECD. <br> • 2-yr PFS: 86%; 2-yr OS was 96%. | • ZELBORAF® is indicated for the treatment of patients with Erdheim-Chester Disease with BRAF V600 mutation. | Vemurafenib is indicated in monotherapy for the treatment of adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma |
| *Durvalumab – IMFINZI®* Astra-Zeneca | Lung-MAP, sub-trial SWOG S1400A Platform trial 2014-2017 | 116 pts <br> Of 68 eligible patients, 11 responders 16% ORR, median OS=11.5 m; med PFS=2.9 m. | • Locally advanced or metastatic urothelial carcinoma who: <br> • have disease progression during or following Pt-containing chemotherapy. <br> • have disease progression within 12 m of neoadjuvant or adjuvant treatment with Pt-containing chemotherapy. Unresectable, Stage III non-small cell lung cancer (NSCLC) whose disease has not progressed following concurrent Pt-based chemotherapy and radiation therapy. | Imfinzi as monotherapy is indicated for the treatment of locally advanced, unresectable non-small cell lung cancer (NSCLC) in adults whose tumours express PD-L1 on ≥ 1% of tumour cells and whose disease has not progressed following Pt-based chemoradiation therapy. |

**EFPIA Brussels Office**
**Leopold Plaza Building ✳ Rue du Trône 108**
**B-1050 Brussels ✳ Belgium**
**Tel: + 32 (0)2 626 25 55 ✳**
**www.efpia.eu ✳ info@efpia.eu**

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## Table A2 (cont.) - Examples of Master Protocols supporting approval of new treatments

| Compound | Design | Key Results/ outcome | Indication in US label | Indication in EU label |
|---|---|---|---|---|
| | | | at least partially supported by data generated via master protocols | |
| *Pertuzumab PERJETA* Genentech | I-SPY-2 Platform trial 2010-2016 | 52 patients and 31 patients (control) Allowed 94% POS identification for T-DM1 + pertuzumab | • Use in combination with trastuzumab and docetaxel for treatment of patients with HER2-positive metastatic breast cancer (MBC) who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease<br>• adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence | Perjeta is indicated for use in combination with trastuzumab and docetaxel in adult patients with HER2-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease. |
| *Neratinib NERLYNX Puma technology* | I-SPY-2 Platform trial 2010-2013 | 115 pts Allowed 80%POS identifcation in Ph3 | • NERLYNX is a kinase inhibitor indicated for the extended adjuvant treatment of adult patients with early stage HER2-overexpressed/amplified breast cancer, to follow adjuvant trastuzumab-based therapy | Nerlynx is indicated for the extended adjuvant treatment of adult patients with early-stage hormone receptor positive HER2-overexpressed/amplified breast cancer and who are less than one year from the completion of prior adjuvant trastuzumab based therapy |

## Table A2 (cont.) - Examples of Master Protocols supporting approval of new treatments

| Compound | Design | Key Results/ outcome | Indication in US label | Indication in EU label |
|---|---|---|---|---|
| | | | at least partially supported by data generated via master protocols | |
| *Larotrectinib* *VITRAKVI* Bayer | RECIST basket master protocol design with 12 tumour types 2015-2017 | objective response rate in 55 patients was 75%, with at least 39% of responses lasting for at least 1 year | VITRAKVI is a kinase inhibitor indicated for the treatment of adult and pediatric patients with solid tumors that: <br>• have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation, <br>• are metastatic or where surgical resection is likely to result in severe morbidity, and <br>• have no satisfactory alternative treatments or that have progressed following treatment. | Vitrakvi as monotherapy is indicated for the treatment of adult and paediatric patients with solid tumours that display a Neurotrophic Tyrosine Receptor Kinase (NTRK) gene fusion, <br>•who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and <br>•who have no satisfactory treatment options (see sections 4.4 and 5.1) <br>*It is of note that this is the first approval in the EU of a histology independent indication.* |