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Belgium as an innovative clinical trial location in Europe

May 2022

MAKING AN IMPACT THAT MATTERS since 1845

Introduction

Preface

Preface by
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500 new authorised clinical trials each year make Belgium one of the top leaders in Europe in terms of clinical research per capita.

Belgium has a unique ecosystem enabling to map itself as a clinical trials hub. With over 70 hospitals among which 7 academic hospitals, 12 universities with internationally renowned life sciences departments and research teams, and more than 50 companies member of pharma.be active in clinical research & development, Belgium is a cluster of excellence at the heart of Europe. Belgium boosts several trendsetting companies and world class centres of research in therapeutic areas such as oncology, vaccination and gene- and cell therapies.

The country's many biopharma clusters are a key driver of the Belgian economy and competitiveness. Moreover, the fact that Belgium is an attractive country for starting-up clinical trials offers benefits to the health of its population. Besides providing rapid access to innovative treatments in development, the trials can also generate valuable insights in to treatments for other conditions.

The clinical trials landscape is in constant evolution and novel trial protocol designs are emerging and offering a different approach for clinical development. These novel designed trials allow to evaluate and compare treatment combinations, to generate real-world evidence. Patients gain timely access to multiple therapy trials with an increased chance of being enrolled in one of the groups receiving an active treatment. Moreover, new technologies and digital tools offer new opportunities for conducting trials and facilitating patient participation.

Belgium is committed to keep its position of preferred location for conducting clinical trials in Europe. We have to be innovative and pro-active to allow and facilitate the conduct of complex novel design trials in our country, and have the Belgian stakeholders internationally recognized for their expertise in complex protocol design, as well as to pave the way to digitalisation in the conduct of clinical trials. This will bring new or improved treatments that will help providing patients with a better quality of life.

Preface

Preface by
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Well-designed clinical trials are of paramount importance in providing patients with fast access to new treatments. In recent years, efforts have been made to transform the traditional clinical trial into more flexible, innovative designs, leveraging advancing insights in genomics and digital technology. New, innovative clinical trial designs such as umbrella, basket, and platform trials have the potential to decrease the time from bench to bedside and ensure that patients get access to innovative treatments even faster. At the same time, digital technologies have enabled the emergence of a new type of clinical trial that allows participants to receive treatment and monitoring from the comfort of their home. Next to improving efficiency, these technology-enabled decentralized trials can address some of the challenges faced in traditional clinical trials regarding patient recruitment and enrollment, patient monitoring, adherence and retention, and clinical-trial diversity. Increasing diversity in clinical trials will ensure that the study population is more representative of the intended patient population. This is important for the development of safe and effective treatments. Decentralized clinical trials fully or partially remove the necessity for patients to travel to the clinical trial site, making participating in clinical trials more accessible to underrepresented or vulnerable populations, for example people who live more remote or people with reduced mobility. Improving access for vulnerable populations to clinical trials by decentralization and the use of digital technologies can also improve health equity. After all, clinical trials are often the main route through which patients receive unapproved but potentially lifesaving treatments that would otherwise be unavailable. For the new clinical trial designs to achieve their potential in speeding up and improving patient access to innovative treatments, a collective understanding of the pros and cons of these designs and practical considerations for all stakeholders is of foremost importance. Our hope is that this whitepaper will help to keep the conversation flowing so that an environment can be created in Belgium in which these innovative clinical trials can become reality and improve patient lives.

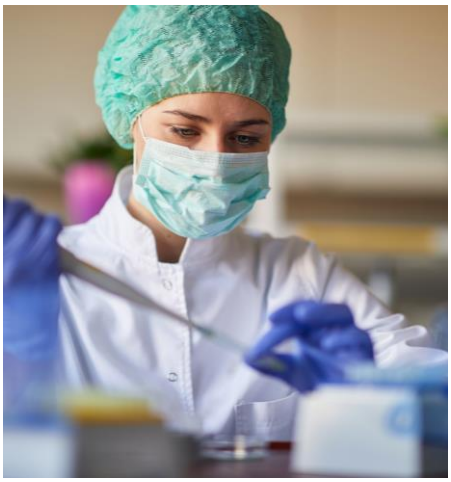
Executive summary

A traditional clinical trial typically tests one drug, one target at the time, in one trial. While useful in many cases, the use of this traditional clinical trial design is associated with long drug development cycles, high costs, and unnecessary delays in patient access for some treatments and diseases.

Innovative trials designs such as umbrella, basket, and platform trials (collectively known as Master Protocols) address these challenges by allowing the study of multiple diseases, multiple treatments, or both, in one trial. The parallel characteristics of these trial designs mean that fewer patient receive a placebo. In addition, Master Protocols are highly adaptable. Therefore, they have the potential to accelerate clinical trials and thereby decreasing the time from bench to bedside in diverse disease areas. Innovative clinical trial designs have proven to be especially relevant in oncology, neurology, rare diseases, and paediatric diseases, where time is even more valuable and populations are small and diverse.

The recent COVID-19 pandemic has also accelerated the uptake of other innovative clinical trial designs. These includes seamless trials, with overlapping phases, and decentralised trials that test a treatment in the patient's own environment, enabled by digital technology.

The aim of this whitepaper is to provide an overview of innovative clinical trial designs and their associated opportunities and challenges from a scientific, practical, and regulatory perspective. This whitepaper also includes a set of recommendations on the implementation of these innovative clinical trial designs in Belgium, in order for the country to maintain its position as the ambitious frontrunner for clinical trials in Europe in the light of recent EU regulations.



Apart from the overall cost and time benefits, each of the clinical trial designs presented in this whitepaper offers its unique way to drive innovation. In addition, the designs can be combined, leading to endless possibilities in innovative clinical trial designs. Understanding the benefits and attention points for each of the designs helps to identify when to use them, which type or combination of types is most beneficial given the specific goals of a trial, and how to apply these designs successfully.

Increased understanding of these new trial designs on a country level would allow that meaningful steps forward can be made to create an advanced ecosystem (e.g., improved data infrastructure, patient recruitment) that facilitates innovation in how clinical trials are carried out.

The following recommendations are formulated:

1. Agree on common understanding of innovative trials, their definition and intended use
2. Stay up to date with the latest developments in the science and technology of innovative clinical trials and offer data sharing guidance; e.g., by means of a knowledge sharing platform bringing relevant stakeholders together and organized by a neutral party
3. Invest in statistical know-how
4. Advance understanding of biology and biomarkers
5. Support the use and acceptability of data collected using digital health technologies in clinical trials
6. Support data sharing between hospitals and between the patient and the trial site by ensuring interoperability of digital data and building data infrastructure
7. Ensure clarity and understandability of the informed consent

The five types of innovative clinical trial designs discussed in this whitepaper:

Master protocol clinical trial designs

01 Basket trials

Trials studying a single treatment for multiple diseases or disease subtypes based on patient screening (e.g., mutation or biomarker).

Case study: Six-year phase II cancer study using biomarker-based treatment for multiple disease cohorts.

02 Umbrella trials

Trials studying multiple treatments for a single disease or single disease subtype, in which each treatment is assigned based on patient screening (e.g., mutation or biomarker).

Case study: Phase II trial for identifying new and improved treatments for advanced breast cancer. Six drugs moved from phase II to III in the trial.

03 Platform trials

Open-ended trials studying multiple treatments, assigned based on patient screening (e.g., mutation or biomarker), in which treatments can be added or withdrawn and patients can be switched between treatments.

Case study: Trial testing multiple treatments for Alzheimer's disease in parallel to enable trial efficiencies (e.g., pooled placebo groups).

Innovative trial designs accelerated by COVID-19

04 Seamless clinical development

Trials combining two or more phases into one adaptive design study. Decisions on how to 'adapt' the study are made after taking planned interim views of the data.

Case study: Seamless phase I/II trials and phase II/III trials for the rapid development of COVID-19 vaccines.

05 Decentralized clinical trials

Trials where the treatment is brought to the patients in their environment rather than being provided at a central location.

Case study: REMOTE was the first entirely web-based trial, without any in-person site visits.

Methodology

Information gathering

Information on innovative clinical trial designs was gathered by searching the scientific and gray literature and through interviews with key opinion leaders.

Targeted literature review

A targeted literature review was performed through a search in PubMed, a leading database for life science and biomedical sciences literature, using the search terms 'platform trial', 'adaptive trial', and 'basket trial' and filtering for review articles published since 2018 (the last 5 years).

To identify key gray literature publications, the webpages of organizations including the European Federation of Pharmaceutical Industries and Associations (EFPIA), the European Medicines Agency (EMA), the U.S. Food and Drug Administration (FDA), and the World Health Organization (WHO) were searched using Google Advanced Search and the search term 'clinical trial design' (e.g., "clinical trial design" site:who.int).

Key Opinion Leader interviews

To complement the targeted literature review, a series of semi-structured interviews were held with Key Opinion Leaders (KOLs) from the life science and pharmaceutical industry, regulatory bodies, ethical committees, and patient organizations. The interviews were adapted based on new insights gained from previous interviews, as well as the interviewee's field of expertise.

Other sources of information

Other sources of information were publications recommended by the KOLs in the interviews, as well as insights gathered during the virtual EFPIA workshop of October 2021.

Scope

The aim of this whitepaper is to provide an overview of innovative clinical trial designs and their associated opportunities and challenges from a scientific, practical, and regulatory perspective.

The focus is on Master Protocols (umbrella, basket, and platform trials) as well as two specific types of clinical trials which saw an increased uptake as a result of the COVID-19 pandemic (seamless and decentralized clinical trials).

This whitepaper also includes a set of recommendations on the implementation of these innovative clinical trial designs in Belgium, in order for the country to maintain its position as the ambitious frontrunner for clinical trials in Europe in the light of recent EU regulations.

The need for innovative trial design

A traditional clinical trial typically tests one drug, one target at the time, in one trial [1]. While useful, this traditional model may no longer be suitable in an era of precision-medicine, where biomarkers are used to identify small genetic subpopulations of patients who are likely to respond to a certain treatment [2]. For these types of treatments, using a traditional clinical trial may lead to a long drug development cycle, high costs, and unnecessary delays in patient access. In addition, for drug developers, it can be hard to find the right patient to participate in a trial if there are many trials in a disease area. From a patient perspective, it can be difficult to find a trial that fit one's specific needs, and when enrolled in a traditional trial, the chances of being assigned to a placebo group are roughly 1 in 2 [3].

Accelerating clinical development and patient access to innovation

Innovative trials designs such as umbrella, basket, and platform trials (collectively known as Master Protocols) address these challenges by allowing the study of multiple diseases, multiple treatments, or both, in one trial. This means that multiple questions on different treatment options can be answered at the same time, thus speeding up clinical development and patient access to new treatments while also saving R&D costs. Innovative trials also facilitate patient recruitment, and increase the likelihood for patients of being assigned to a treatment arm instead of a placebo [3].

The recent COVID-19 pandemic came with its own unique challenges for conducting clinical trials, such as travel restrictions and site closures due to lockdowns. This has accelerated the uptake of innovative trial designs such as trials designed to increase speed by overlapping phases (seamless trials) and trials conducted remotely or through local healthcare providers, making optimal use of digital technology (decentralized clinical trials). To illustrate, pre-COVID-19, decentralized clinical trials had a compound annual growth rate (CAGR) of about 7%, the CAGR between the second halves of 2019 and 2020 was as high as 77% [4].

The need for innovative clinical trials is recognized by key players in the drug development field in Europe and elsewhere. In the United States, the U.S. Food and Drug Administration (FDA) set up the Complex Innovative Trial Design Pilot Meeting Program in 2018, to support the goal of facilitating and advancing the use of complex adaptive, Bayesian, and other novel clinical trial designs [5]. The European Medicines Agency's (EMA) 'Regulatory Science to 2025' strategy explicitly mentions fostering innovation in clinical trials, including the promotion and facilitation of the conduct of complex clinical trials and other innovative clinical trials, as a key focus area [6].

Belgium as a clinical trial location in Europe

Belgium is and has been an attractive location for clinical trials, ranking second in Europe in terms of the number of clinical trials per habitant in 2017. Though clinical trials in Belgium are evenly distributed over the three main phases (Phase I, Phase II, Phase III), the country is especially strong in the area of Phase I trials, with one-third of Phase I trials being “first-in-human” trials as part of early clinical drug development, a key strategic focus area of the competent authorities [7]. The reasons for Belgium’s attractiveness as a clinical trial location are manifold. However, the main drivers of selecting Belgium as a trial location in a 2018 survey were the expertise of the authorities, the quality of the research centres, investigator expertise, access to scientific advice, and start-up timelines (with a 15-day approval time for Phase I clinical trials) [7].

On the 31st of January, 2022, the EU Clinical Trials Regulation entered into application and the Clinical Trials Information System (CTIS) went live (https://euclinicaltrials.eu/home). The Regulation harmonizes the submission, assessment and supervision processes for clinical trials in the European Union. The main change brought about by the Regulation is that from 2023 onward, all clinical trial applications have to be submitted through CTIS. A related initiative from the European Commission, the Heads of Medicines Agencies and the European Medicines Agency (EMA) launched in January 2022 called Accelerating Clinical Trials in the EU (ACT EU) was also launched in January 2022. The initiative aims to further strengthen Europe’s position as a clinical trial location, with “enabling innovative trial methods” as one of the ten top priority actions for 2022/2023 [8].

The entering into application of the new EU legislation is levelling the playing field in Europe when it comes to attractiveness of different Member States as a clinical trial location. Therefore, if one country wants to differentiate themselves, they will need to make some strategic choices to maintain a prominent position at the forefront of clinical research and innovation in Europe. For Belgium, offering strong expertise on innovative clinical trial designs represents an opportunity to achieve this goal. In 2019, 31% of clinical trials in Belgium were in oncology and it is mainly in therapeutic areas such as oncology - where there are several treatment options to be tested or where a given disease can be differentiated in multiple sub-categories - that innovative trials designs like Master Protocols have the most added value.

Understanding innovative trial design: benefits and attention points

Traditional clinical trials (figure 1) are used in an isolated study of one drug within one disease. It consists of three or more sequential phases. This process, and the need for a population consisting of hundreds to thousands of people, results in a clinical development program with several trials that can take years to complete [9].

Innovative clinical trial designs are increasingly being used to decrease the time from bench to bedside. Innovative clinical trial designs allow multiple treatments and/or diseases to be studied in one single trial. Both because of this parallel aspect (which means fewer patients receive a placebo) and because of the ability to use adaptive elements, the process accelerates and the right treatment gets to the patient faster. Innovative clinical trial designs are therefore very interesting for time-sensitive diseases, neurological diseases, rare diseases and paediatric diseases where a great value is added.

In this paper, five types of innovative clinical trial design are described and discussed:

- Three master protocol clinical trial designs (or simply master protocols): umbrella trials, basket trials, platform trials
- Two innovative designs that have been used more frequently because of COVID-19: decentralised trials and seamless clinical trials.

The most important added value of innovative clinical trials is how it benefits the patient indirectly. Innovative clinical trials allow a trial study to be conducted more quickly and efficiently, getting scientific answers more quickly, allowing the treatment to reach the market and therefore the patient more rapidly. This has the effect of helping patients faster and genetically more specified/personalised to strive for a healthier society.

In a master protocol, patients only need to go through the screening process once and are automatically randomized to the most appropriate treatment arm in the trial allowing them to access multiple targeted therapy tests fairly quickly, with an increased likelihood of being included in an active treatment arm [1].

They allow the evaluation and comparison of treatment combinations or competing drugs. It reduces cost, lead time and time to activation. Also, master protocols encourage partnerships to share risks and costs.

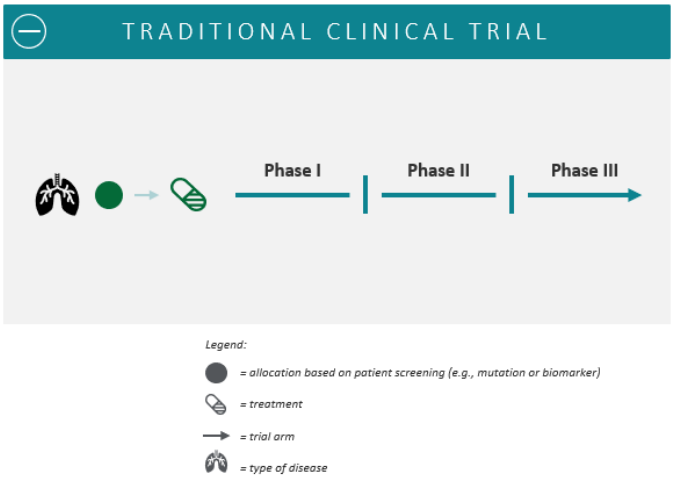


Figure 1: Schematic representation of traditional clinical trial design

With access to the latest and best ideas on complex disease areas, the ability to test hypotheses and answer scientific questions quicker, learning is continuously ongoing during studies. Master protocols have more flexibility compared to traditional clinical trials and hence enable the generation of real-world evidence such as generating evidence that a particular therapy is as effective as or more effective than other therapies that are currently under development. Real-world evidence is defined as evidence derived from the analysis, synthesis, or both, of real-world data. Real-world data is an umbrella term for data generated outside highly-controlled RCTs (e.g., research data collected on the use of an intervention in routine clinical practice, or research data from routinely collected data) [10].The observational data generated by long-term master protocol trials can act as a continuous learning system [1].

Master protocol clinical trial designs

As introduced above, there are three types of master protocols: umbrella trials, basket trials and platform trials (figure 2). Master protocol designs enable multiple questions to be answered in one study [11]. Rather than pursuing a one-treatment, one-purpose approach, master protocols allow studies to test (multiple) treatments for multiple purposes, disease subtypes and patient populations.

Master protocols are mainly used in cancer trials where patient screening (e.g. mutation or biomarker) is used to assign patients to a certain trial arm.

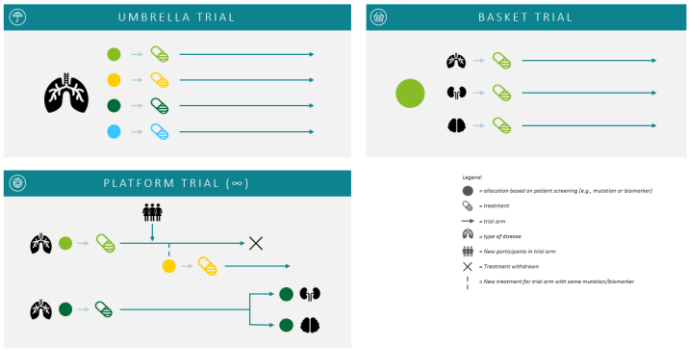


Figure 2: Visualisation of the master protocols

These new types of clinical trial designs have increased rapidly in recent years (figure 3) and were mostly applied in the US in experimental drug research in oncology. Basket and umbrella trial designs are mostly used in the early stages of a clinical trial (phase I/II) and platform trial design more commonly in phase II/III [12].

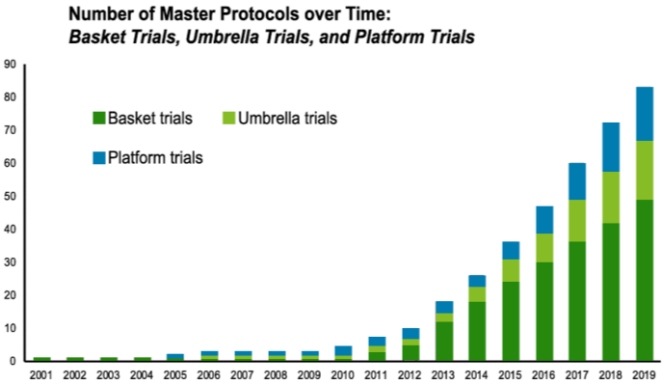


Figure 3: Master protocol trend over the last 20 years: basket (dark green), umbrella (light green), and platform (teal) trials [12] .

The analysis of Deloitte Insight 1 shows that biopharmaceutical companies can potentially save costs (12-15%) and study duration (13-18%) by using master protocols in a phase II oncology studies due to among other things shared control arms and infrastructure [1].

Basket trial design

Basket trials can be defined as trials studying a single treatment for multiple diseases or disease subtypes based on patient screening (e.g., mutation or biomarker). Patients recruited in a basket study can have the same genetic mutation, but they can have different types of cancer such as lung, liver or prostate.

In basket trial designs the patient population is chosen based on a common element (e.g., a genetic mutation) regardless of the patient's disease. It is that common marker that is indicative that a particular treatment should work for these patients. Basket trials are mostly used in oncology and they become more useful when genetic screening increases. These trials can also determine if a treatment may be effective in a cancer located in other locations in the body where a same genetic mutation is found. The exposure in multiple locations can provide an additional understanding of sensitivity and resistance of the treatment.

Case study 1: In the B2225 study of Michael C. Heinrich, Heikki Joensuu et. al. a basket innovative clinical trial was used in a six-year phase II, open-label, single arm cancer study using biomarker-based treatment (imatinib treatment) for multiple disease cohorts. This study was conducted in response to a previous study with imatinib treatment in which the results indicated the importance of molecular characterization of tumors to identify patients likely to benefit from the imatinib treatment [13].

Case study 2: Signature is a programme with a set of 8 phase 2, agent-specific basket protocols. It uses a rapid approach to initiate clinical trials. Each basket protocol evaluated one drug in patients with solid or haematological malignancies and an actionable mutation. The clinical benefit rate after 16 weeks was the primary endpoint of each study (stable disease, complete response or partial response) [14].

Case study 3: The AcSé-Crizotinib trial is a non-randomised phase II study. Patients with advanced lung cancer and cancers of the thymus are divided into several targeted therapy arms based on their tumour molecular profiling (tumour biopsy examination). There are a total of 23 cohorts with the targeted therapy crizotinib for ALK-, MET-, or ROS1-alterations [15].

Umbrella trial design

Umbrella trials are trials studying multiple treatments for a single disease or single disease subtype, in which each treatment is assigned based on patient screening (e.g., mutation or biomarker). In an umbrella trial in oncology, for example, patients may have the same type of cancer with a different type of underlying genetic mutation identified in the screening process.

The patient population of umbrella trial designs is chosen based on the type of disease (e.g., a specific type of cancer) regardless of the patient's genetic mutation. As with basket trials, umbrella trials are used mainly in cancer studies where patients with a same cancer receive targeting treatments depending on their molecular features [16]. In distinction to basket trials, umbrella trials can draw meaningful conclusions that are specific to a particular type of disease (e.g. tumour) and thus less sensitive to heterogeneity present within a given study cohort [17].

Case study 1: I-SPY 2 is a randomized, controlled, multi-centre trial for women with newly diagnosed, locally advanced breast cancer. The phase II trial identifies new and improved treatments. Those treatments are assigned to specific patient subgroups based on molecular characteristics (biomarker signatures) where the treatment are most effective in. Six drugs moved from phase II to III in the trial [18].

Case study 2: Lung-MAP case study is a multi-sub-study randomised phase II/III umbrella trial for patients with advanced squamous cell carcinoma (SCC) of the lung. Lung SCC is a complex disease of which 60% of patients have genetic defects that can be addressed with therapy. Depending on specific genetic abnormalities, patients were divided into sub studies (methodology was predefined) using a common infrastructure to test patients for multiple biomarkers [19].

Case study 3: Beat AML is a study consisting of multiple, single-arm, two-stage phase II designs. It is a biomarker-based treatment of Acute Myeloid Leukaemia (AML). Patients were screened for biomarkers and assigned to a sub study according to a hierarchical algorithm depending on the presence of somatic mutations of a dominant clone identified via NGS. For patients without a useful biomarker, allocation to a marker-negative group was possible, allowing evaluation of new therapies with broad activity [20].

Platform trial design

Platform trials are open-ended trials studying multiple treatments, assigned based on patient screening (e.g., mutation or biomarker), in which treatments can be added or withdrawn and patients can be switched between treatments. This makes the platform trials the most complicated of the three master protocol designs but it is also the design with the most flexibility and possibilities.

Platform trials generate answers faster and are potentially more cost-effective than a series of traditionally trial designs. Platform trials allow new treatment arms, new patient populations or new types of diseases to be added or excluded during a study. For example, if a drug gives good results for lung cancer with a specific biomarker, it is possible to start a new treatment arm with that drug, used in a different disease with that same biomarker. This flexibility allows for an efficient transition to a confirmatory clinical trial, but can also result in trials that never end. The high complexity of these trials requires sophisticated statistical methods to ensure proper randomisation and robust criteria for assessing the utility of each trial arm. Intermediate analyses are needed to stop a trial arm in time or set up a new one [2].

Case study 1: A study sponsored by the Washington University School of Medicine, saw an opportunity in the use of platform trials to prevent dementia. The “Dominantly Inherited Alzheimer Network Trial” is testing multiple treatments for Alzheimer’s disease in parallel to enable trial efficiencies (e.g., pooled placebo groups). The study’s subjects are known to have an Alzheimer's disease-causing mutation. The purpose of this study is to assess the safety, tolerability, biomarker and cognitive efficacy of investigational products by determining if treatment with the study drug slows the rate of progression of cognitive impairment and improves disease-related biomarkers. The first results will be available in July 2022 [21].

Case study 2: STAMPEDE is a study for men with prostate cancer using the multi-arm multi-phase trial (MAMS). It is an open-label, 5-stage, 6-arm randomised controlled trial [22].

Benefits and attention points for master protocol clinical trial designs

Impact on patient recruitment	Operational impact	Impact on patient outcome	Scientific impact	Financial impact	Regulatory impact
✓ More patients with the correct treatment faster ✓ Reduced start-up time, less screening, patient faster in trial ✓ Easier patient recruitment, especially beneficial for time-sensitive diseases, neurological diseases, rare diseases and pediatric diseases ✓ Patients faster enrolled in correct study	✓ Faster completion of studies ✓ Reducing time cycle ✓ Continuous learning	✓ Faster access to working treatment ✓ Less risk for participants due to screening process and less placebo ✓ Bigger chance on best working treatment/more patients with a correct treatment faster	✓ Real-world evidence ✓ Additional understanding of the mechanism of sensitivity and resistance ✓ More clinical insights, easier to add and investigate new therapies real-time	✓ A revenue impact due to faster go to market ✓ Longer benefit from patents ✓ Save costs by taking less time	✓ Governmental support can stimulate data sharing ✓ Supported by EMA strategy for "Regulatory science up to 2025" and ACT EU, among others, can strengthen Europe's position as a clinical trial location and stimulate the use of innovative clinical trial designs
! Difficult to find study population in rare diseases ! Time is needed to find sufficient study population	! Time lost due to need for approval ! It takes a lot of time to explain to the patient how an innovative clinical trial study works. Informed consent is important but it is currently not clear how (and by whom) it can be efficiently explained to the patient	! Protecting patient safety comes first when designing the trial ! Timing for when results can be shared may depend on not compromising study and data integrity	! Trial design may have many objectives to address multiple scientific questions of interest	! Some clinical divisions and administrative infrastructure are not ideal for innovative clinical trials which causes investigators/coordinators to work together or to work across departments	! All clinical trial applications must be submitted through Clinical Trials Information System (CTIS) ! Deeper expertise on master protocols required within the regulatory bodies, e.g., amendments streamlined through adapted process

Innovative trial designs accelerated by COVID-19

The COVID-19 pandemic has had a major impact on the medical research industry and its clinical trials. The industry faced new challenges caused by the pandemic measurements such as self-isolation, site closures, travel restrictions, supply chain interruptions for the research product, staff or subjects becoming infected with COVID-19 and many more [23].

The industry and its researchers were challenged to be inventive in order to allow the clinical trials to continue. In addition, they wanted to speed up clinical trials in order to avoid infection in the patient population of the study as this may impact results. This section discusses two innovative clinical trial designs that have become more used as a result of the pandemic: seamless clinical trials and decentralized clinical trials.

Seamless clinical trial design

A first innovative trial design that has accelerated due to COVID-19 is seamless clinical trial design, which are trials combining two or more phases into one adaptive design study. Decisions on how to 'adapt' the study are made after taking planned interim views of the data. This design brings phases together (figure 4).

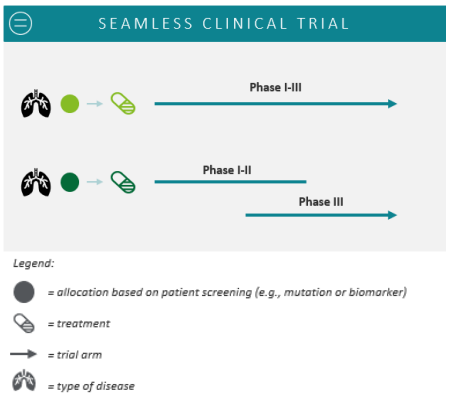


Figure 4: Visualisation seamless clinical trial design

A seamless clinical trial design that merges the traditional three phases of trials into one continuous trial is called an expansion cohort trial and can be used when testing new oncology drugs and biologics in humans for the first time [24].

Seamless studies require rigorous preparation and pre-specified statistical analysis plans and sample sizes. Objective decision thresholds must be specified in advance in the study protocol to guide intermediate design changes. When seamless studies are used, clear efficacy endpoints should also be established when designing the study. Certain factors determine the extent to which a study provides reliable statistical estimates, including variation arising in study subpopulations, molecular heterogeneity within the disease, clinical prognostic heterogeneity, comorbidity and outcome assessment [25].

Seamless clinical trials should include one or more interim safety studies as necessary to protect patients before a conventional dose escalation study. In addition, large seamless trials designed to evaluate measures of efficacy and clinical endpoints require intermediate futility analyses to limit patient enrolment in ineffective regimens, combinations or dosage levels [25].

Case study 1: Seamless phase I/II trials and phase II/III trials for the rapid development of COVID-19 vaccines

Benefits and attention points for seamless clinical trial design

Impact on patient recruitment	Operational impact	Impact on patient outcome	Impact on data	Financial impact	Regulatory impact
✓ Reduction in trial population	✓ Faster completion of studies	✓ Earlier readout of data for fast decision making to progress to next phase	✓ Real-world evidence	✓ Reduction in trial population	✓ Governmental support can stimulate the use of seamless clinical trial design
! Possibility to refine regimens/ regulations for future study	! Clinical trial systems need to accommodate multi-phase trials	! Trial results may not be available until the end of the trial to protect study and data integrity	! Risk for wrong assessment and interpretation (due to less time available for interpretation)	! Possibility to refine regimens/ regulations for future study	! All clinical trial applications must be submitted through CTIS

Decentralised clinical trial design (DCT)

Decentralised clinical trials (DCT) are trials where the treatment is brought to the patients in their environment rather than being provided at a central location. This can be done by involving local healthcare providers or, going one step further, by using digital technologies (e.g., telemedicine) and hence moving the trial to the patient's home (remote DCT) (figure 5).

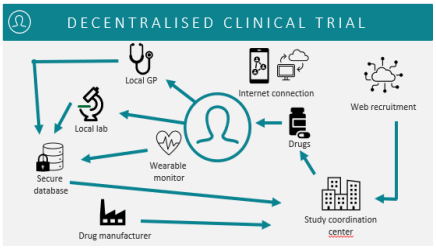


Figure 5: Visualisation decentralised clinical trial design based on [26]

The extent of decentralisation can vary, where the ideal configuration depends on the disease, site, study and patient characteristics. Its use can be further enhanced by advancements in and adoption of digital technologies (e.g., digital endpoints and telemedicine). Ongoing projects funded by the Innovative Medicines Initiative (IMI) 2 such as Mobilise-D (digital mobility assessment in five diseases) and IDEA-FAST (digital endpoints in neurodegenerative and immune-mediated diseases) are examples of initiatives aimed at enhancing the acceptance of digital endpoints for clinical research and practice by, inter alia, health authorities and regulators. COVID-19 has been an accelerator for (remote) decentralised clinical trials as hospitals were overwhelmed and patients felt more safe at home [27].

DCTs drastically reshape the patient journey and hence overcome typical hurdles found in traditional clinical trials, including but not limited to, patient recruitment, access, retention, and diversity [27].

Case study 1: Research on Electronic Monitoring of Overactive Bladder Treatment Experience (REMOTE) (2011) was the first entirely web-based trial, without any in-person site visits. Instead, researchers used online recruitment, questionnaires, and diaries, and drugs were delivered at the patient's home [26,28].

Case study 2: The Treatment In Morning versus Evening (TIME) study is a decentralised randomised remote clinical trial with one central site and remote participation. The study investigated whether home blood pressure monitors (HBPMs) from clinical trial participants were validated models. Patients were recruited by advertising to eligible patients after which they were invited to complete an online questionnaire. Communication took place by e-mail. Results were monitored using an information technology-based methodology [29].

Benefits and attention points for decentralised clinical trial design

Impact on patient recruitment	Operational impact	Impact on patient outcome	Impact on data	Financial impact	Regulatory impact
✓ Due to digitalisation: faster trial participant recruitment (especially for rare diseases that are highly geographically dispersed) ✓ More patients have access to trials (higher participation) ✓ Increased participant diversity ✓ More comfortable for patients due to less traveling to traditional locations	✓ Faster completion of studies ✓ Faster and more efficient trials	✓ Accelerate trial participant access to important medical interventions ✓ Greater control, convenience, and comfort for trial participants by offering at home or local patient care	✓ Real-world evidence ✓ Provision of more representative results (due to collecting data in the participant's everyday context) ✓ More diverse data collection methods ✓ improve data interpretability	✓ Reduced overall trial costs	✓ Governmental support can stimulate data sharing ✓ Supported by EMA's strategy for "Regulatory science up to 2025" and ACT EU, among others, can strengthen Europe's position as a clinical trial location and stimulate the use of innovative clinical trial designs
✓ Protecting patient privacy for data stored on connected devices & transmitted through connection services can be challenging [26]	✓ Choosing technological providers that will not only provide the best technology/service but also protect the patient's privacy while providing data in the right format at the right time ✓ Drug distribution and management is more challenging compared to a centralized trial [26] ✓ Operation of digital health technology depends on the availability of technical support and troubleshooting, batteries, transmission methods, and internet infrastructure [26] ✓ Some devices (e.g., wearables) require clinical validation before data generated by them is widely accepted by regulators [26]	✓ Less interaction between patient and principal investigator ✓ Ensuring consistency in how patient outcomes are being assessed when different approaches are being use e.g., hybrid models	✓ Acceptability of data collected using different methods	✓ May require investment in new tools for data collection	✓ All clinical trial applications must be submitted through CTIS ✓ Practical organisation of medical oversight

Leveraging a deep understanding of innovative trial design

Apart from the overall cost and time benefits, each clinical trial design offers its unique way to drive innovation. The goal of understanding the benefits and attention points is not to assess one against the other on an overall scale but rather to help identify when to apply which (one or more) of these trial designs and how to apply it in a successful way.

All master protocols can be combined with each other for the benefit of the trial and study design possibilities within an innovative clinical trial are endless.

On a country level, meaningful steps forward can be made when different levels of the clinical trial ecosystem (e.g., government, regulator, clinical trial site, principal investigator (PI), …) understand the benefits and attention points that were discussed in this section with regard to different impacted areas; patient recruitment, operations, patient outcomes, data, financial situation.

Recommendations for implementing innovative clinical trial designs in Belgium

Common Understanding

- Recommendation 1 : Agree on a common understanding of innovative trials, their definition and intended use
  - For the different types of innovative trial designs, multiple terminologies, definitions, and interpretations are circulating and may cause confusion. A common terminology and understanding across stakeholders is key to grow capabilities at different levels of the clinical trial ecosystem.

Knowledge and skills

- Recommendation 2 : Stay up to date with the latest developments in the science and technology of innovative clinical trials and offer data sharing guidance, e.g., by means of a knowledge sharing platform bringing relevant stakeholders together and organized by a neutral party
  - (Regulatory) authority and investigator expertise are key attributes that makes a country/region attractive for clinical trials. For innovative trial designs to be truly useful in bringing new drugs to patients, not just investigators and sponsors need to stay knowledgeable, but also regulators should be open to using evidence generated by innovative clinical trials, and know how to use them to support decision-making.
  - In addition, clear guidance on data sharing is important as innovative trial designs are often applied in therapeutic areas where patient pools are limited and patients need to be recruited across many different sites. Not only guidance on data sharing is needed, but also the availability of standardized, high quality, exchangeable data between clinical institutions and sponsors.
  - In this context, there could perhaps be a role for the to be established Health Data Authority, that may among other things develop a health(care) data strategy, function as a single point of contact for health data, and be in charge of GDPR-conform centralisation of databases (see also Recommendation 6 on digital data infrastructure).
    - ✓ Belgian authorities could encourage the use of these types of trials and real-world evidence in generating data for drug development, to support similar efforts at the European level [30].
    - ✓ A knowledge sharing platform could be organized by a neutral party (e.g., FAMHP) bringing together different stakeholders to share knowledge, best practices, identify where guidance is needed, etc.
- Recommendation 3 : Invest in statistical know-how
  - Master protocols (umbrella trials, basket trials, platform trials) are complex. Advanced statistical methods are needed to safeguard appropriate randomization and interim analysis, and proper criteria for success or futility in the trial arms [2]. It is therefore important for regulatory authorities, sponsors, and investigators to invest in the knowledge and skills needed to set up and analyze innovative trials. Adaptive designs (e.g., seamless trials) allow modifications to the trial and/or the key design elements after the trial has started (e.g., changes to eligibility criteria, subgroups, decision points, and end points).
- Recommendation 4 : Advance understanding of biology and biomarkers
  - Biomarkers play an important role in many Master protocols. With patients being coupled to a treatment based on the presence of a biomarker, understanding these biomarkers and understanding the implications of specific findings is key. For example, if a specific treatment arm is working in one tumour type, you cannot assume it will work in other types and it is important to understand the biology to make informed decisions.

- ✓ The suggested knowledge sharing platform could leverage specific knowledge of genomics which is key for designing trials with precisely defined biomarkers so that distinct patient groups can be targeted and genetic drivers of disease (e.g., cancer) can be further examined.
- ✓ Next to supporting the determination of biomarkers itself, another important aspect would be to provide best-practices and guidance around measuring methods and quality assurance (accuracy, repeatability).

Infrastructure

- Recommendation 5 : Support the use and acceptability of data collected using digital health technologies in clinical trials
  - Decentralised clinical trials are enabled by digital health technology.
  - ✓ With the launch of the National Institute for Health and Disability Insurance (INAMI-RIZIV)'s health app reimbursement scheme in January 2020 [31], Belgium made a significant step in the integration of digital technology in the healthcare system. To facilitate the uptake of innovative clinical trials, it is important to support and recognize the appropriate use of these digital health technologies, for example for measurement of clinical outcomes in these trials [32]. Creating awareness of digital health technology and digital endpoints and increasing the acceptance of their use in clinical research and practice can facilitate further uptake of decentralised clinical trial designs.
  - ✓ Authorities and other stakeholders should consider the implications of practical implementation of the new EU Clinical Trials Regulation where it relates to decentralized trials. Specifically, they should consider whether additional national guidance is needed.
  - ✓ Specific pilot projects involving pioneering sites, sponsors and governmental authorities could uncover areas of improvement, offer lessons learned and support capability building (acquiring skills and knowledge needed to carry out, understand, and assess complex clinical trials)
- Recommendation 6 : Support data sharing between hospitals and between the patient and the trial site by ensuring interoperability of digital data and building data infrastructure
  - Innovative clinical trials will likely include multiple trial sites and hospitals. Possibilities for efficient and safe sharing of data between these trials sites, hospitals, patients (e.g., data generated via wearable technology in the context of the trial) and investigators are therefore of great importance. Ensuring interoperability of digital data and having the necessary data infrastructure in place are key elements in enabling data sharing in the context of innovative clinical trials. Clinical trials may be run within a healthcare system, such as through a registry.
  - ✓ Innovative data brokers are well-placed support in the technology enablement of more efficient data sharing. Regulatory and ethical guidance is still needed on a nation-wide level, which may possibly be sped up by the future Health Data Authority and associated nation-wide ambitions related to digital transformation, e-health, and digital health data (see Recommendation 2 on knowledge sharing).

Patient engagement

- Recommendation 7 : Ensure clarity and understandability of the informed consent
  - ✓ The use of e-informed consent is being investigated in Belgium, which could be leveraged in the case of novel clinical trial designs and more specifically in decentralized trials. Important to note is that clear explanations and guidance needs to remain available to patients, especially since the more complex protocols might be harder to understand and may possibly raise concerns. Data privacy considerations must adhere to GDPR.
  - ✓ Next to clear informed consent, the new complex clinical trial protocols require additional efforts in terms of patient engagement in the early development of protocols. This is especially true in the case of decentralized trials, where design factors (e.g., preferred technology for off-site interactions with the investigators, preferred number of on-site interactions) are likely to have a big impact on patient experience.

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References

1. Lesser N, Naaz B, Deloitte Center for Health Solutions. Master protocols - Shifting the drug development paradigm. Deloitte Insights.
2. European Federation of Pharmaceutical Industries and Associations. *Innovation in Clinical Trial Design: A Review of The Clinical Trial Design Landscape*.; 2020.
3. Innovative Medicines Initiative. EU-PEARL. Accessed February 25, 2022. https://www.imi.europa.eu/projects-results/project-factsheets/eu-pearl
4. Gao F, Solomon. Maurice, Roy A, Chaplin W. Why Decentralized Clinical Trials Are the Way of the Future.
5. U.S. Food and Drug Administration. Complex Innovative Trial Design Pilot Meeting Program.
6. European Medicines Agency. EMA Regulatory Science to 2025 Strategic reflection. EMA/110706/2020.
7. Pharma.be. *Belgium, Leading the Way in Clinical Trials*.; 2019.
8. European Medicines Agency. Regulatory harmonisation of clinical trials in the EU: Clinical Trials Regulation to enter into application and new Clinical Trials Information System to be launched.January 25, 2020.
9. National Cancer Institute - Center for Cancer Research. Clinical Trial Design and Patient Outcomes. Accessed February 25, 2022. https://ccr.cancer.gov/news/horizons/article/clinical-trial-design-patient-outcomes
10. Mol P. Use of real world data pre-authorisation – what can it answer? European Medicines Agency. Accessed April 29, 2022. https://www.ema.europa.eu/en/documents/presentation/presentation-session-1-use-real-world-data-pre-authorisation-what-can-it-answer-peter-mol_en.pdf
11. McNair L. Basket Clinical Trial Designs: The Key to Testing Innovative Therapies is Innovation in Study Design and Conduct. Published February 11, 2020. Accessed February 25, 2022. https://acrpnet.org/2020/02/11/basket-clinical-trial-designs-the-key-to-testing-innovative-therapies-is-innovation-in-study-design-and-conduct/
12. Park JJH, Siden E, Zoratti MJ, et al. Systematic review of basket trials, umbrella trials, and platform trials: a landscape analysis of master protocols. *Trials*. 2019;20(1):572. doi:10.1186/s13063-019-3664-1
13. Heinrich MC, Joensuu H, Demetri GD, et al. Phase II, Open-Label Study Evaluating the Activity of Imatinib in Treating Life-Threatening Malignancies Known to Be Associated with Imatinib-Sensitive Tyrosine Kinases. *Clinical Cancer Research*. 2008;14(9):2717-2725. doi:10.1158/1078-0432.CCR-07-4575
14. Slosberg ED, Kang BP, Peguero J, et al. Signature program: a platform of basket trials. *Oncotarget*. 2018;9(30):21383-21395. doi:10.18632/oncotarget.25109
15. ClinicalTrials.gov. Molecular Profiling and Targeted Therapy for Advanced Non-Small Cell Lung Cancer, Small Cell Lung Cancer, and Thymic Malignancies. Published February 21, 2022. Accessed February 25, 2022. https://clinicaltrials.gov/ct2/show/NCT01306045
16. Trial Expert at Credevo.com. Clinical Trial Designs: Basket, Umbrella & Platform Trial Designs – Part II. Published 2021. Accessed February 25, 2022. https://credevo.com/articles/2020/09/15/clinical-trial-designs-basket-umbrella-platform-trial-designs/
17. Renfro LA, Sargent DJ. Statistical controversies in clinical research: basket trials, umbrella trials, and other master protocols: a review and examples. *Annals of Oncology*. 2017;28(1):34-43. doi:10.1093/annonc/mdw413
18. Quantum Leap Healthcare Collaborative. New Data From Phase 2 I-SPY 2 TRIAL Shows Improved Outcomes with Combination of Merck's KEYTRUDA® (pembrolizumab) Plus Standard Neoadjuvant Therapy in Patients with High-Risk Breast Cancer. Published 2019. Accessed February 25, 2022. https://www.ispytrials.org/newsitems/adipisci-quidem-eos-quisquam
19. ClinicalTrials.gov. Lung-MAP: A Master Screening Protocol for Previously-Treated Non-Small Cell Lung Cancer.
20. ClinicalTrials.gov. Study of Biomarker-Based Treatment of Acute Myeloid Leukemia. Published June 29, 2021. Accessed February 25, 2022. https://clinicaltrials.gov/ct2/show/NCT03013998

21. ClinicalTrials.gov. Dominantly Inherited Alzheimer Network Trial: An Opportunity to Prevent Dementia. A Study of Potential Disease Modifying Treatments in Individuals at Risk for or With a Type of Early Onset Alzheimer's Disease Caused by a Genetic Mutation. Master Protocol DIAN-TU001 (DIAN-TU). Published November 4, 2021. Accessed February 25, 2022. https://www.clinicaltrials.gov/ct2/show/NCT01760005
22. Sydes MR, Parmar MK, James ND, et al. Issues in applying multi-arm multi-stage methodology to a clinical trial in prostate cancer: the MRC STAMPEDE trial. *Trials*. 2009;10(1):39. doi:10.1186/1745-6215-10-39
23. U.S. Food and Drug Administration. Clinical Trial Conduct During the COVID-19 Pandemic. Published June 1, 2020. Accessed February 25, 2022. https://www.fda.gov/drugs/coronavirus-covid-19-drugs/clinical-trial-conduct-during-covid-19-pandemic
24. nQuery Team. New FDA Guidance on Seamless Clinical Trials. Published August 22, 2018. Accessed February 25, 2022. https://blog.statsols.com/new-fda-guidance-on-seamless-clinical-trials
25. Hobbs BP, Barata PC, Kanjanapan Y, et al. Seamless Designs: Current Practice and Considerations for Early-Phase Drug Development in Oncology. *JNCI: Journal of the National Cancer Institute*. 2019;111(2):118-128. doi:10.1093/jnci/djy196
26. van Norman GA. Decentralized Clinical Trials. *JACC: Basic to Translational Science*. 2021;6(4):384-387. doi:10.1016/j.jacbts.2021.01.011
27. Innovative Medicines Initiative. Topic: Centre Of Excellence – Remote Decentralised Clinical Trials. Published 2019. Accessed February 25, 2022. https://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/future-topics/IndicativeTopic_RemoteTrials.pdf
28. Orri M, Lipset CH, Jacobs BP, Costello AJ, Cummings SR. Web-based trial to evaluate the efficacy and safety of tolterodine ER 4mg in participants with overactive bladder: REMOTE trial. *Contemporary Clinical Trials*. 2014;38(2):190-197. doi:10.1016/j.cct.2014.04.009
29. Anbarasan T, Rogers A, Rorie DA, Kerr Grieve JW, MacDonald TM, Mackenzie IS. Home blood pressure monitors owned by participants in a large decentralised clinical trial in hypertension: the Treatment In Morning versus Evening (TIME) study. *Journal of Human Hypertension*. 2022;36(1):32-39. doi:10.1038/s41371-021-00496-6
30. European Federation of Pharmaceutical Industries and Associations. Make the regulatory system fit for the future of medical innovation. Published June 30, 2020. Accessed February 25, 2022. https://www.efpia.eu/news-events/the-efpia-view/blog-articles/make-the-regulatory-system-fit-for-the-future-of-medical-innovation/
31. Osborn Clarke. Breakthrough for digital healthcare in Belgium as scheme launches to reimburse mobile health apps. Published February 2, 2021. Accessed February 25, 2022. https://www.osborneclarke.com/insights/breakthrough-digital-healthcare-belgium-scheme-launches-reimburse-mobile-health-apps
32. de Brouwer W, Patel CJ, Manrai AK, Rodriguez-Chavez IR, Shah NR. Empowering clinical research in a decentralized world. *npj Digital Medicine*. 2021;4(1):102. doi:10.1038/s41746-021-00473-w

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