



Innovative oncology trial designs: Time to act – A review with recommendations of the Cancer Drug Development Forum

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ABSTRACT

Introduction: Clinical oncology trial design constantly adapts and evolves to meet the needs of all stakeholders, from patients to regulators. This evolution has however also led to an increase in the complexity of clinical development, and investigators are expected to invest more time and money in planning and running their studies and overall clinical and regulatory pathway.

Methods: Here we review recent innovations in trial designs, study endpoints, and relevant regulatory guidelines, before making recommendations to enhance the clinical trial ecosystem in the EU.

Results: Innovative clinical study designs that go beyond traditional randomised, double-blinded, placebo-controlled trials often promise greater flexibility and efficiency in the conduct of oncology studies, but adoption has been slow. Furthermore, the increased complexity associated with innovative trials means that coordination between all relevant stakeholders is essential to every phase of clinical development. Despite recent advances, there is a risk that Europe is becoming seen as a less attractive location for clinical trials, and this article outlines initiatives and possible steps to improve patient access to medicines and processes across Europe.

Policy summary: Innovative trial designs promise more efficient, flexible, and inclusive clinical trials, but more needs to be done to encourage their adoption if the advantages outweigh the limitations. Partnership and coordination between all stakeholders, from patients to regulators, and at all phases, is more important than ever. Finally, effective action is needed to make Europe a more attractive destination for clinical research and to improve access to innovative medicines for patients.

1. Introduction

'Classical' clinical trials – typically randomised, double-blinded, and placebo-controlled – have been described as the gold standard for

determining the efficacy and safety of new treatments thanks to their robustness, the quality of evidence they generate, and the ease with which their results can be interpreted [1,2]. However, they are often limited by cost, duration, logistical challenges and recruitment

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constraints.

Clinical trial design constantly adapts and evolves to meet the needs of all stakeholders, including clinicians, patients, and sponsors, with the aim of making trials that are more efficient, adaptive, inclusive, and informative [3,4]. The need for innovative trial designs is particularly pronounced in the field of oncology: between 2012 and 2021, 159 novel active oncology substances were approved globally (30 in 2021 alone), including 68 for solid tumours [5]. With over 2000 products currently in development, there is the potential for the number of new market authorisations to continue accelerating in the future. If the increased throughput of authorisations is to be realised, the evolution of trial methodology and its implementation will need to keep pace with the expanding therapeutic opportunities. Innovative trial designs offer huge opportunities to ensure efficiency, whilst an improved focus on framing the optimal clinical question and choosing appropriate endpoints can ensure their relevance, allowing the most promising agents to be identified as early and accurately as possible. At the same time, the scientific validity of a design needs to be ensured to obtain reliable and interpretable results. The submission of multi-state trial applications is complicated by a fragmented clinical trial authorisation and ethics committee landscape in Europe. The upcoming reform of the EU pharmaceutical legislation aims to simplify the regulatory environment (i.e. by reducing assessment time, strengthening pre-authorisation support) and to provide more support and improved conditions for innovation [72], which may help, together with innovative designs complementing established trial concepts, to better streamline the development of new medicines.

Here we review recent innovations in trial designs, study endpoints, and relevant regulatory guidelines, before making recommendations to enhance the clinical trial ‘ecosystem’ in the EU.

2. Evolving trial designs

2.1. Master protocols

A master protocol is a single overarching protocol that allows simultaneous and continuing investigation of multiple research questions as part of one unified study design, thereby allowing logistic efficiency and potentially accelerated clinical development when compared with running separate studies [6]. Master protocols can be subdivided into basket, umbrella, and platform trials [7]. Basket trials test a single investigational drug or drug combination in multiple populations and can help investigators identify specific subpopulations or disease subtypes most responsive to the treatment while being more cost-effective and faster than running separate trials for each condition. Umbrella trials evaluate multiple targeted therapies in a single disease and are particularly useful for exploring personalised medicine approaches; their use can enhance recruitment as well as the cost-effectiveness and statistical power of a trial. Platform trials allow for the simultaneous study of multiple treatments in an ongoing manner, with repeated interim analyses for efficacy and futility, and with the option of adding or removing treatment arms [7,8].

Limitations of master protocols include the fact that investigators may have to deal with increased operational and logistical complexity from needing to manage the various treatment arms and patient populations in parallel [9]. Master protocols also require a significant investment in terms of costs and time to establish the necessary trial infrastructure and can also be challenging to manage from a logistical and regulatory perspective, particularly for international trials, so careful design and planning are essential, as is close co-operation and communication between all stakeholders. Recommendations, caveats and open issues are outlined in documents published by the EMA and FDA [10,11]

2.2. Adaptive trials

Adaptive trials are designed to increase trial flexibility by using scheduled reviews to allow pre-specified changes to an ongoing trial, such as adding or removing specific treatments or doses or changing the ratio in which patients are allocated to the treatment arms based on pre-specified reviews and adaptations [12]. Potential benefits include greater flexibility, more efficient allocation of patients, shorter trial duration, and lower sample size and costs. However, adaptive trials require more time for careful planning (with consultation with authorities being advised). Adaptive trials are also at increased risk of certain operational biases; for example, while patients may generally prefer to enrol later in a response-adaptive trial on the assumption that they are more likely to be assigned to superior treatments, sicker, later-line patients with fewer alternative options may be overrepresented in the early stages of the trial [13]. Challenges associated with adaptive trials include obtaining funding, communicating the trial design to participants, and reporting findings, amongst others [12]. More work needs to be done to ensure details of adaptive elements are reported consistently and to ensure adequate reporting of how biases introduced by adaptive study designs are accounted for [14]. In June 2025, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) released the ICH E20 guideline on adaptive designs for clinical trials as a draft for public consultation [15]. It provides principles for the planning, conduct, analysis, and interpretation of trials with an adaptive design to achieve greater harmonisation worldwide.

2.3. Pragmatic trials

Unlike traditional ‘explanatory’ clinical trials, which are typically designed to demonstrate the efficacy and safety of an intervention under highly controlled conditions – essentially asking whether an intervention could improve outcomes – pragmatic clinical trials evaluate the effectiveness of interventions in settings which more closely reflect routine clinical practice to determine whether an intervention really does improve outcomes in actual clinical practice [16]. For example, pragmatic trials may recruit patients who are likely to be candidates to receive the intervention under study if it was in routine use (whereas traditional oncology clinical trials may exclude patients with common comorbidities) [17,18]. Pragmatic trials are also often more patient-centric than traditional studies.

However, the focus on replicating real-world conditions can complicate the conduct of pragmatic trials [16] and this may be reflected in the somewhat limited rate of adoption historically: fewer than 2 % of randomised clinical trials (RCTs) conducted between 1990 and 2010 used pragmatic designs [19]. This also highlights a key challenge of pragmatic trials: the tendency to see them as either incompatible with explanatory trials or else as one of two extremes on a ‘pragmatic–explanatory’ continuum [20]. In practice, pragmatic trial elements can be integrated into traditional clinical trials, leading to trials with a mix of pragmatic and explanatory features, and trials are likely most useful when they feature both pragmatic and explanatory elements.

As with other innovative trial designs, early dialogue with regulators and HTA bodies is key if the results are to be suitable for regulatory decisions. Important points of discussion include the careful selection of endpoints, the validity and completeness of data, and how missing data are to be handled [21].

2.4. External control arm trials

External control arm (ECA) trials use a comparator arm built from data sources outside the trial itself (whether ‘real-world’ data or data from other clinical trials), using data from patients who share similar characteristics and who undergo similar clinical management to the patients recruited within the trial. Compared with a single-arm trial, the

use of ECAs can reduce false positive rates and allow for a comparator arm in specific settings [22,23]. As a result, ECAs are often considered by sponsors when RCTs are deemed unethical, unfeasible, or lack equipoise, as could happen in cases of rare indications or molecular subgroups, significant unmet medical needs, and/or limited treatment options; ECAs may be of particular utility in oncology, where all of these criteria are commonly met, perhaps especially in paediatric indications. From a regulatory perspective, the likely introduction of biases (i.e. use of time to event endpoints in this setting) and difficulties with

interpretation are the major considerations that prevents this approach from being used on a regular basis for pivotal trials. Nevertheless, ECAs can provide additional context and the field continues to evolve.

ECAs have the same requirements for rigor in the external control population as for an internal control arm, and every aspect of the identification of data sources, identification of a suitable patient population, and statistical methods used to limit the extent of possible bias must be prespecified in the study protocol and statistical analysis plan [24]. In particular, the understanding, discussion, and elimination of

DEFINE AIMS		PERFORM TRIAL		IMPLEMENT FINDINGS		POST-REGISTRATION			
Targets /Questions	Estimands	Design	Delivery	Surrogate Endpoints	Final Endpoints	Phase 4	Future		
	Define meaningful patient benefit	Acceptability	Patient groups	Immediate outcomes (ORR)	Correlative PROMs				
	Estimand acceptability	Accessibility	Engagement	Ongoing participation for longterm outcomes	Correlative QoL	Support groups	New areas of need		
	Treatment acceptability	Patient practicalities	Participation	Education / outreach	Education / outreach	Real world experience	Individualised treatment decisions		
Patients & Communities	Areas of need	Define meaningful clinical benefit	Clinical practicalities	Disease networks	Provisional treatment guidelines	Treatment guidelines	Real world evidence	Individualised treatment discussions	Patients & Communities
	Patient groups	Population & eligibility considerations	Validated PROM tools	Education	Disease networks	Disease networks	Safety reporting	Tolerability optimisation	
	Gap analysis	Treatment deliverability	System practicalities	Academic networks	Robust peer review	Robust peer review	Real world eligibility	Expand eligibility	
↕	Healthcare and big data research	Identify current comparators & benchmarks	Clinical population	Patient identification / referral	Clinical service development	Clinical service development	Clinical service evaluation	Clinical service refinement	↕
Clinicians & Academics	Clinical questions	Define meaningful healthcare benefit	Clinical expertise	Individualised trial discussion	Interim & crossover decisions	Real world evidence from early access	Treatment sequencing	Treatment algorithms	Clinicians & Academics
	Clinical research	Inclusion & exclusion criteria	Academic trials	Clinical oversight	Data interpretation	Data interpretation	Expand indications	Trials in other populations	
↕	Target discovery	Formal endpoints and summary measures	Additional science & biomarkers	Infrastructure, treatment & data	Data presentation	Data presentation	Potential to improve other treatments	Combination trials	↕
Industry	Biomarker discovery	Define treatment	Statistical innovations	Adaptive insights	Data release (ORR, DoR, early PFS)	Data release (mature PFS, DFS, OS)	Refine populations (biomarkers)	Personalised medicine trials	Industry
	Drug discovery	Anticipate intercurrent / censoring events	Trial design	Manufacture	Approval submission	Approval submission	Identify resistance	Resistance mechanisms	
Regulatory Authorities	Preclinical evaluation & optimisation	Statistical powering	Documents & submissions	Strategic oversight	Early access schemes	Global access	Access	Next generation agents	Regulatory Authorities
	National priorities & strategies	How to handle intercurrent events	Strategy	Regulatory maintenance	Parallel confirmatory studies	Sequential confirmatory studies	Marketing	Novel agents	
		Estimand guidance	Funding	Regulatory standards	Accelerated approval schemes	Full licensing	Post-marketing surveillance	Evolution of regulatory environment	
	Define meaningful approval benefit	Regulatory guidance	Regulatory oversight	Provisional reimbursement	Ongoing reimbursement				
				Approval guidance	Application guidance				

Fig. 1. Involvement of stakeholders throughout the design and conduct of clinical trials.

biases, as well as the value of data quality, are crucial [25]. Limitations of ECA trials include the impossibility of direct management of the control population, and the need for access to suitably large databases of the necessary quality to identify suitable patients with the required data documentation. ECAs are also less able to detect small to moderate differences, as only differences larger than any possible bias can be convincingly demonstrated in this type of study. ECAs also involve complex statistical methods and additional interactions with regulators.

Elements of the ECA concept may also be incorporated into hybrid randomised trial designs, where only a proportion of the internal control arm is replaced by external data. This approach offers additional opportunities to verify that external controls are similar to the internal trial patient population [26]. Such hybrid randomised phase III trials may offer a potential middle-ground to support drug development, regulatory evaluation, market approval and reimbursement decisions, while avoiding some of the limitations of full ECA designs. Currently, there is limited experience with hybrid designs and it may be challenging to mitigate concerns (i.e. similarity of patient populations, possibly of increased type I error rate, lack of randomisation and possibly blinding, or other biases); therefore it remains to be seen whether this approach will become more widely accepted by regulators.

2.5. Evolving trial designs: what needs to be done?

Innovative trial designs represent a promising response to the advent of novel therapies and the focus on personalised care. The use of master protocols and adaptive trial designs for example means investigators can conduct more complex and flexible studies, while adopting features of pragmatic trial design allows for both greater efficiency and greater translatability of findings. However, a common challenge associated with innovative trial designs is the increased need for planning and coordination, particularly at the early stages of trial design. Crucial points from a regulatory perspective are ensuring that complex designs and novel methodological approaches maintain evidentiary standards. A better understanding of these challenges will help to reduce uncertainties in a benefit/risk assessment. This will require the cooperation of and communication between all stakeholders, from sponsors and regulators to physicians and patients, who each have important contributions at all stages of trial design and conduct (Fig. 1).

3. Evolving endpoints

3.1. Surrogate endpoints

Evidence for the effectiveness of cancer treatments usually comes from RCTs that assess objective and clinically meaningful outcomes. The gold standard of outcomes in oncology trials is overall survival (OS), defined as the time from randomisation to death from any cause. This reflects the key goal of cancer treatment: prolonging survival [27]. The use of OS as a primary endpoint necessitates a large patient population and sufficient time to accumulate a predefined number of events; it is thus of limited use in rare diseases or in diseases that progress slowly and where expected survival is relatively long. Other, 'surrogate' endpoints may be less intrinsically meaningful to patients but generally require less time to measure, allowing for shorter, smaller, less costly trials that can reasonably be expected to predict longer-term definitive outcome measures [28–30].

The use of surrogate endpoints is widespread; between 2009 and 2014, 55 of 83 (66 %) of oncology drugs approved by the FDA were approved based on surrogate outcomes like response rate and progression-free survival [28,31]. Commonly used surrogate endpoints in oncology trials include time-to-event endpoints like progression-free survival (PFS), disease-free survival (DFS), sometimes termed relapse-free survival or RFS), or event-free survival (EFS). While endpoints like PFS are widely used surrogate endpoint in advanced cancers, validation remains essential via subsequent assessment of OS whenever

possible (e.g. as a post-approval measure). In the adjuvant setting, registration decisions may be made on the basis of DFS so long as data is mature enough to observe a trend in OS (ruling out detrimental survival) and subsequent OS is eventually documented. Response rates (the proportion of patients whose tumour shrinks or disappears after treatment) are not considered a surrogate endpoint by European regulators; they are frequently seen in single-arm trials for establishing activity of a treatment in early phase trials and have been used for conditional approvals but would not be accepted as a primary endpoint for establishing efficacy in a confirmatory RCT.

Examples of newer surrogate endpoints under consideration include early metabolic response (EMR), circulating tumour DNA (ctDNA) levels, and complete response (CR) rates (including clinical complete response for 12 months, CCR12, such as in neoadjuvant rectal cancer treatment). RECIST is the most well-established framework for response assessment. However, while regulatory authorities may be considering these endpoints, they have not yet accepted their validity as acceptable surrogates. This does not mean that they will not be accepted; in April 2024, the FDA voted unanimously that data support the use of minimal residual disease (MRD) as an endpoint to support accelerated approval of treatments in multiple myeloma.

Nevertheless, surrogate endpoints may be less clinically meaningful for patients than more traditional endpoints, and concerns have been raised that there is insufficient evidence of a correlation between surrogate endpoints and OS [28,30,31]. This is particularly worrisome given the increasing use of surrogate endpoints to support drug approvals, with one study suggesting that only 10 % of approvals based on surrogate endpoints used endpoints that were highly correlated with survival [28]. On the other hand, patients may not have an improved survival but instead experience a clinically meaningful reduction in side effects or a better quality of life. Although, in any case, a detrimental effect on survival needs to be excluded. Formal validation of a surrogate endpoint through confirmatory studies can be challenging, however, and a considerable number of individual trials may be required to validate a surrogate endpoint.

3.2. Patient-meaningful endpoints

Data and endpoints that are meaningful to the patient population involved should be at the centre of every clinical trial. Nevertheless, patient involvement in trial designs is only a relatively recent trend, and progress in terms of patient involvement has been incremental [32]. For studies in advanced disease, symptom management or quality of life may have greater priority for patients than OS or PFS alone.

Primary and secondary endpoints should be defined together with patients, should be relevant to patients and relate to major life events, and should be objective and routinely collected. Since patient populations are diverse, there is no single set of rules to define what endpoints an individual may prioritise, but a consensus view can establish the key regulatory endpoints while ensuring other key patient-meaningful endpoints are collected.

Patient-reported outcomes (PROs) and patient preference data (PPD) provide a good way to ensure that the patient perspective is included in clinical research and to help measure the impact of benefit–risk trade-offs, while also potentially improving patient enrolment [33]. PROs/PPD can be grouped into a few key concepts: disease symptoms, physical functioning, emotional wellbeing, cognitive functioning, social wellbeing, symptomatic adverse events, and other contributors [34,35], and the importance of PROs and PPD in clinical trial design is reflected in regulatory guidelines in both Europe and the US [34,36].

The use of PROs and PPD can be considered for a wide range of decisions along a product's lifecycle, including endpoint selection (based on PPD), regulatory approval, access/reimbursement and individualised treatment decision-making. Recommendations from bodies like the consortium SISAQOL-IMI (Setting International Standards in Analysing Patient-Reported Outcomes and Quality of Life Endpoints in

Cancer Clinical Trials – IMI) can be used to standardise the use, analysis, and interpretation of PRO data in cancer clinical trials (see www.sisaqo-l-imi.org).

However, while patient-meaningful endpoints are considered key correlative data for quality and robustness by regulatory authorities, it should be recognised that analyses based on these data may not always be sufficiently statistically powered. As a result, the objectives and analysis methods used for patient-meaningful endpoints must be well specified. Stakeholders, including study sponsors, investigators, and patients, should work together to define, incorporate, collect and interpret PROs/PPD without duplicating efforts.

3.3. The estimand framework

Properly informed decision-making by various stakeholders and clear descriptions of benefits and risks of a treatment requires precise descriptions of the treatment effects of interest, reflecting clinical questions following from clearly understood trial objectives. However, evaluation of endpoints may be complicated by events occurring after the start of therapy, such as patients not taking the study drug as intended or other deviations from the intended course of treatment, known as ‘intercurrent events’ [37,38]. The ICH has developed an addendum to a statistical guideline and introduced the estimands framework which supports the formulation of clinical trial objectives, design, conduct, analysis and interpretation [39]. It should also strengthen the dialogue between sponsor and regulator regarding the treatment effect(s) of interest that a clinical trial should address [39].

Estimands use a structured approach and standardised terminology to ensure that all aspects of a treatment effect are described and can be easily understood, with a focus on the causal effects of treatment (i.e. describing how outcomes would differ in the same patients if exposed to different treatment strategies) [37,40]. There is increasing recognition of the need to incorporate estimands into clinical trial design (clearly defining the clinical question of interest and the estimand via five attributes: its endpoint, treatment condition, population, population-level summary, and handling of other intercurrent events like discontinuations) and to include descriptions of estimands in publications of clinical trial results to help readers understand the treatment effect being reported [40]. The framework also includes a set of five different strategies that may be used for addressing intercurrent events. Estimands provide a broader perspective compared to the limitations of intent-to-treat and per-protocol analysis and, given the focus on standardised terminology, should make it easier for physicians, patients, sponsors, and regulators to understand what trials reveal about the efficacy of a treatment, and to compare the results of different trials. Defining estimands benefits from a multidisciplinary approach, including clinical and statistical expertise, instead of a statistician working in isolation.

The estimands framework has not yet been broadly adopted outside of registrational trials, but this situation is expected to change. Implementation of the estimand framework is supported by regulators, e.g. via ACT EU, a multi-stakeholder platform to improve clinical trials in the EU (discussed below), and the Methodology Working Party (MWP) which was established by the Committee for Medicinal Products for Human Use (CHMP) to pool and use expertise in key areas such as artificial intelligence and data science, biostatistics, modelling and simulation, clinical pharmacology and pharmacokinetics, pharmacogenomics and diagnostics, and real-world evidence [41]. The estimand framework has also already been adopted in an early-phase extension to guidelines for the content of statistical analysis plans (SAPs) [42], and recent extensions to the CONSORT and SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines for factorial randomised trials [43,44]. Importantly, the concept is also referred to in the new revision 3 of ICH GCP E6 [45]. However, more work is needed to broaden the understanding of the framework's meaning, importance and impact.

3.4. Evolving endpoints: what needs to be done?

While surrogate endpoints allow researchers to design more efficient trials that require less time to read out, there is a lack of evidence to show correlation between some of these endpoints and OS. More confirmatory trials are needed to determine which surrogate endpoints are valid and worth using in clinical trials. More work also needs to be done to ensure that patient perspectives are included when defining endpoints for clinical trials. Progress is being made, but it remains incremental, despite the potential rewards (like improved patient enrolment) that are likely to accompany the use of patient-meaningful outcomes, PROs, and PPD. Finally, more work is needed to encourage incorporation of the estimands framework into all aspects of clinical trial design, conduct and analysis.

4. Evolving regulations

4.1. Regulatory responses to innovative trial designs and endpoints

Adoption of innovative trial designs will likely depend in some part on how readily regulators will accept the results of these types of trials. Although randomised clinical trials remain the gold standard [2], regulators are engaged with the need for innovative trial designs in the development of modern therapeutics.

The FDA's Oncology Center of Excellence has taken a particular interest in the design of dose-finding studies. While the choice of recommended dose and schedule for cytotoxic agents was historically largely driven by the identification of the maximum tolerated dose (MTD, i.e. the highest dose that does not cause significant toxicity), there has been increasing recognition that this needs to change, particularly due to the rise of modern targeted therapies and immunotherapies, where a higher dose may be associated with greater toxicity but not necessarily greater efficacy. The FDA's Project Optimus seeks to reform dose optimisation and dose selection by improving communication between drug developers and the FDA, setting expectations for dose-finding and dose optimisation, and developing new dose-selection strategies, with a principal goal of supporting a paradigm shift from MTD and towards demonstrating pharmacodynamic, dose–exposure, dose–toxicity, and dose–activity relationships, including early randomised evaluations for dose selection, prior to registration studies [46,47].

The FDA has also published guidance on the use of master protocols in the development of oncology drugs, including their content, safety considerations, and statistical considerations [48]. Meanwhile, the EMA, the European Commission (EC), and the Heads of Medicines Agencies (HMA) have published guidance on ‘complex clinical trials’, which includes guidance on the design and conduct of master protocols such as the additional information that needs to be included at the time of submission for clinical trial authorisation [49].

Furthermore, regulators have signalled a willingness to engage with adaptive trial designs for some time: in the US, guidance on how study sponsors can interact with the FDA when using adaptive trial designs was published in 2020, while in the European Union, a reflection paper on the use of adaptive trials was published in 2007 [50,51]. A guideline from the ICH on adaptive clinical trials, E20 Adaptive Clinical Trials, has been released for public consultation as of 2025 [15]. The FDA has also published draft guidance on the conduct of ECA trials [24]. Submission and regulatory acceptance of ECA trials has increased over the years, with oncology and haematology the most common therapeutic areas with the most ECA trial submissions to regulatory authorities [52,53]. Feedback from regulators and HTA bodies suggests that early engagement with and input from regulators is encouraged, while there are concerns about the interpretability of survival and other endpoints; the FDA is also more likely than the EMA to request additional analyses and may even at times request raw data to allow replication of analyses [52]. The EMA launched a proof-of-concept pilot on the submission and analysis of raw data on a voluntarily basis in September 2022 [73] and

the proposal for the upcoming regulation (COM/2023/193 final [74] foresees electronic submission of raw data.

For pragmatic trial designs, the FDA's Project Pragmatica, seeks to introduce functional efficiencies and enhance patient centricity through the appropriate use of pragmatic design elements. In Europe, groups like the European Organisation for Research and Treatment of Cancer (EORTC) and EU-funded ERA4Health Partnership are actively advocating for the use of pragmatic trials [54,55]. The European Federation of Pharmaceutical Industries and Associations (EFPIA) has published recommendations for pragmatic trials intended for regulatory decision-making, such as using a robust randomisation process [56].

Surrogate endpoints, including biomarkers, have been recognised by the FDA as important for the development of new therapies, and has published data on surrogate endpoints that have been used as the basis for drug approvals [57]. In Europe, the Heads of Health Technology Assessment Agencies Group (HAG) and the EMA have reviewed the benefits and limits to using "non-primary" confirmatory or complementary data. They have identified uncertain relevance as a key issue for decision-making. Therefore, surrogacy must first be established, and the importance of prospective planning at the time of study design is emphasised, including during scientific advice procedures [58].

4.2. Conditional marketing authorisation

To accelerate access to drugs for patients with unmet medical needs, conditional marketing authorisation (CMA) was put into effect in the European Union in 2006 [59,60]. Medicines that address unmet medical needs may be granted a CMA based on 'less comprehensive clinical data than normally required' if the benefit of the medicine being made immediately available outweighs the risk of doing so [59,60]. The EU's CMA is similar to the FDA's Accelerated Approval pathway, which allows for earlier approval of drugs that meet an unmet need, with approval based on evidence from surrogate endpoints [61].

Between 2006 and 2016, half of all CMAs concerned oncological indications [60]. Apart from fulfilling unmet medical needs, requirements for being granted CMA include a positive benefit-risk balance, likely submission of comprehensive data post-authorisation, and the benefit of immediate availability to outweigh the risk of data non-comprehensiveness [59,62]. Recent years have seen an increasing number of CMAs based on single arm trial (SAT) data as pivotal evidence, particularly for targeted oncology therapies [63].

Other trends in granting CMAs and other decision-making can be gleaned from the EMA's Committee for Medicinal Products for Human Use (CHMP). In the metastatic setting, improved OS in RCTs versus standard of care (SOC) is the gold standard for efficacy, but PFS with sufficient maturity and non-detrimental OS in RCTs is acceptable in specific circumstances. A rising number of CMAs are based on SATs with response-related outcomes as primary endpoint, but eventual provision of comprehensive data (usually from an RCT) must be agreed upfront. Sufficiently mature DFS and non-detrimental OS in RCTs in the adjuvant setting and EFS and non-detrimental OS in RCTs in the neoadjuvant setting may be accepted, but pathologic response endpoints (such as pCR or MPR) are not sufficiently validated across histologies. The CHMP tends towards favouring provisional endpoints with sufficient follow-up that would guarantee that data can mature for assessment. When deviations from the guidelines are considered, the CHMP recommends seeking scientific advice from the Scientific Advice Working Party (SAWP).

5. Optimising Europe as a clinical trials environment: time to act

The current situation for clinical trials in Europe presents a mixed picture. Despite challenges, there have been encouraging signs that Europe may become a more inviting place to conduct clinical studies.

The Accelerating Clinical Trials in the European Union (ACT EU)

initiative (<https://accelerating-clinical-trials.europa.eu>) aims to transform how clinical trials are designed, initiated, and run to further promote the development of high quality, safe and effective medicines, and to better integrate clinical research in the European health system. Proposed activities included implementation of the EU's Clinical Trials Regulation (which aims to harmonise and streamline the conduct of clinical trials) [64], supporting non-commercial sponsors of clinical trials, and providing a curriculum of clinical trials training that is informed by regulatory experience. Of particular importance is the ACT EU Multi-Stakeholder Platform (MSP), which aims to bring together all key stakeholders and enable pragmatic collaboration across differing viewpoints to improve clinical trials via the creation of an MSP advisory group comprised of representatives from key stakeholders (including patients, healthcare professionals, academics, industry sponsors, and funders) to provide strategic and operational advice for ACT EU initiatives, as well as via the organisation of events, consultations, and surveys to gather feedback.

The EU's Clinical Trials Regulation aims to harmonise and streamline the conduct of clinical trials, for example by allowing sponsors to submit a single application rather than separate applications to each national authority [64,65]. The Clinical Trials Regulation only came into full force in January 2025 after a three-year transition period, so it remains to be seen what its impact will be. However, there may be reasons to be hopeful: as the first country in Europe to successfully implement the Clinical Trials Regulation, Spain has seemingly gained a competitive advantage in clinical trials versus other EU member states: Spanish centres have participated in 3500 of 9045 (39 %) new clinical trials authorised in Europe via CTIS between 31 January 2022 and March 2025, the highest rate in the EU [66].

Meanwhile, efforts to streamline clinical trial start-up and conduct have been facilitated by the Clinical Trials Information System, an online portal to streamline communications between sponsors and regulators, allowing for the submission of annual safety reports and trial results for example, thereby lowering the administrative burden for conducting clinical trials, at least in theory [67]. CTIS has also allowed some progress to be made in terms of patient access; as part of ACT EU, the EMA has launched a new clinical trial map that is accessible via CTIS, allowing patients and healthcare providers to see real-time information about clinical trials in their area [68].

There are also other encouraging signs. The EU's Precision Cancer Medicine Repurposing System Using Pragmatic Clinical Trials (PRIME-ROSE) project aims to use existing adaptive and pragmatic clinical trial platforms to facilitate the implementation of precision cancer medicine in Europe [69]. Meanwhile, projects like Personalised Response Monitoring in Oncology: Co-Creating Clinical Trials in Advanced Breast Cancer (PREMIO COLLAB) aim to modernise breast cancer response evaluation by taking a patient-centric approach [70]. These projects, along with many others, are funded by the EU Cancer Mission, a broader initiative to address the increasing burden of cancer in Europe.

However, challenges remain. The European Federation of Pharmaceutical Industries and Associations (EFPIA) have noted that 'regulatory fragmentation' and 'operational complexity' in the EU continue to make it a less attractive location for clinical trials, and suggest that greater investment, simplified policy implementation, and revised legislation are needed [71].

6. Conclusion

Improvements in our understanding of the pathology of cancer have led to the development of modern targeted therapies and the promise of personalised patient care. Corresponding advances have been made in the field of clinical trial design, but the increasing complexity of clinical trials means that investigators are expected to invest more time and money in planning and running their studies, which should be balanced against savings in other areas of a complex trial. Partnership and coordination between all relevant stakeholders, from patients to regulators,

and at all phases, is more important than ever. The long-term strategic plan for any clinical trial should incorporate flexibility, creativity and innovation from the start if studies are to be efficient, while a focused approach in both design and conduct remains important. Education is also vital if innovative trial designs are to be more widely adopted.

The co-operation of and communication between the various stakeholders in clinical trials is essential, particularly given the increasing complexity of trial design. Each stakeholder has important contributions to make, from defining the aims of the study through to post-registration activities (Fig. 1). This paper has brought together different views, perspectives and expertise from a multidisciplinary group of experts who represent different stakeholders, not necessarily implying consensus, but highlighting contemporary challenges in the clinical trial landscape, and possible ways forward towards a more favourable environment for innovation and for research.

Improving the conduct of clinical trials in Europe remains challenging. Initiatives such as ACT EU have the potential to underpin a fit-for-purpose evidence generation process, but more needs to be done to improve patient access to medicines and to harmonise regulations and processes across Europe. The European Commission, the Heads of Medicines and the EMA have recently published two new targets in the next five years: (i) an additional 500 multinational clinical trials are added to the current average of 900 that are already authorised each year (i.e. an estimated 100 per year) and (ii) two thirds (66 %) of clinical trials should begin recruiting patients within 200 calendar days or less from the date of application submission; this is in comparison to only 50 % of clinical trials today [75]. These ambitious aims can only be achieved collaboratively with all stakeholders involved and innovative designs will play an important role to support strengthening clinical research in Europe.

Disclaimer

The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the regulatory agencies or organisations with which the authors are employed/affiliated.

CRediT authorship contribution statement

Christina Yap: Validation. **Laurence Collette:** Validation. **Fergus Sweeney:** Validation. **Theodor Framke:** Validation. **Lada Leyens:** Validation. **Rosa Giuliani:** Conceptualization, Validation, Writing – review & editing. **Peter van de Ven:** Validation. **Jan Bogaerts:** Validation. **Aaron Sosa Mejia:** Validation. **Rachel Giles:** Validation. **Nafsika Kronidou-Horst:** Validation. **Symeonides Stefan:** Conceptualization, Validation, Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Rosa Giuliani reports financial support, administrative support, article publishing charges, travel, and writing assistance were provided by Cancer Drug Development Forum. Rosa Giuliani reports a relationship with Cancer Drug Development Forum that includes: board membership. None to disclose If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

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