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Current perspective

Convergence of science, regulations and society in cancer clinical research: A perspective based on the EORTC DE-ESCALATE Study

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ABSTRACT

Recent or upcoming regulations are significantly shaping the European clinical research landscape. Assessing their impact is crucial to ensure pragmatic implementation and identify areas requiring legislative refinement. The DE-ESCALATE trial, addressing treatment optimisation for prostate cancer, highlights key challenges in applying current regulatory frameworks, particularly regarding their suitability for pragmatic, patient-centred clinical research. Advancing clinical research to facilitate access to treatment in the EU demands urgent engagement from policymakers to implement risk-based and proportionate regulations, enabling all types of clinical trials.

1. To which clinical context the DE-ESCALATE study belongs?

The introduction of androgen receptor pathway inhibitors (ARPI) – abiraterone acetate, apalutamide, darolutamide and enzalutamide - has profoundly reshaped the management of metastatic hormone naïve prostate cancer (mHNPC). Results from seven trials demonstrated that combining an ARPI with standard androgen deprivation therapy (ADT), also referred to as continuous maximum androgen blockade (cMAB), reduces the risk of death by 20–40 %, delays subsequent treatment, and improves health-related quality of life (HRQoL) [1–7].

Despite demonstrated benefits, uncertainties remain regarding optimal treatment duration, long-term complications, and patient selection. In clinical practice, treatment is generally continued until biochemical, radiological, or clinical progression occurs. This approach exposes patients to sustained adverse effects and potentially to inferior quality of life, as shown in recent real-world studies and preliminary data from a meta-analysis, with a significant increase of hypertension, cardiovascular disease, cognitive decline, fatigue and falls [8–12]. Furthermore, pivotal clinical trials have included patients not representative of the real-world. Addressing how patients benefit most from ARPIs reinforces the importance of post-licensing clinical research [13].

Hence, the question of interrupting treatment in responders has emerged, aiming to reduce side effects and improve quality of life. In patients reaching a Prostate-Specific Antigen (PSA) level $\leq$0.2 ng/ml after 6–12 months of cMAB, prolonged survival is expected, and historically, intermittent therapy (iMAB) was recommended without compromising survival. Already consensus meetings advocate treatment interruption in selected patients with a deep PSA response [14]. Determining whether iMAB can be safely administered in this context, compared to cMAB, is clinically relevant for patients seeking reduced side effects and improved quality of life, and has important public health implications. This rationale sustains the design of the DE-ESCALATE study, a pragmatic, interventional Investigator-Initiated Trial (IIT) led by the European Organisation and Research of Cancer (EORTC) in collaboration with other international academic research groups worldwide, indicating that this clinical question represents a global clinical concern. DE-ESCALATE is a non-inferiority trial randomising 1600 patients. The co-primary endpoints are (1) the proportion of patients who do not resume their hormonal therapy within one year following the interruption of MAB and (2) overall survival. The sample size calculation of this study is primarily driven by the expected overall survival rate at 3 years, expected to be 85 % in the cMAB arm, with a non-inferiority margin set at a 4 % absolute difference [15].

DE-ESCALATE exemplifies efforts in addressing over-utilisation of therapeutic interventions in oncology. While the development of robust datasets to inform patients, clinicians and society is warranted, treatment optimisation research comes with regulatory and feasibility challenges despite its public health importance [16,17]. Drug costs, resource utilisation, and management of side effects, exacerbated by over-utilisation, substantially impact healthcare systems [18,19].

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Alongside, pivotal trials tend to become smaller, relying on surrogate endpoints, consequently limiting their clinical applicability. This contributes to a growing gap between regulatory science and healthcare decision-making regarding access. Hence, the economic evaluation for metastatic castration sensitive prostate cancer has been a point of great attention [20].

Treatment optimisation approaches, specifically de-escalation strategies, convey new opportunities aligned with public health priorities. As a result, key questions emerge: i) what types of clinical trials are best suited to efficiently inform patients, clinicians, and society in a more patient-centric ecosystem? and ii) how to efficiently conduct public health trials addressing clinically relevant questions in routine care practice? In response, the European Organisation for Research and Treatment of Cancer (EORTC) is focusing on pragmatic trials [17,21,22]. A key consideration is whether trials aimed at documenting optimal use of well-established therapeutic interventions should be regulated and conducted similarly to trials for innovative interventions for which little is known.

Noteworthy, DE-ESCALATE has received funding from the European Union's HORIZON-MISS-CANCER-2022–01 initiative, which supports pragmatic trials designed to examine effectiveness of therapies in routine healthcare practice.

2. Which are the regulatory observations raised by DE-ESCALATE?

- In DE-ESCALATE, all therapeutic interventions are part of practice, and the protocol questions the schedule of administration rather than the interventions themselves. It was initially submitted for authorisation in 2024 in accordance with the provisions of the Clinical Trials Regulation (EU) (CTR) No 536/2014 [23]. The experience with this trial highlights the misalignment between the CTR framework and the specific needs of pragmatic clinical trials. Regarding Investigational Medicinal Products (IMPs), the CTR does not distinguish trials addressing well-documented therapeutic interventions that, from the medical perspective, are no longer investigational. Such trials do not address IMPs but rather Investigational Medical Strategies. The true investigational question is the schedule of administration, specifically whether intermittent use is as effective as continuous treatment. Although the addressed therapeutic agents are well-established and commonly used in daily practice, they are considered IMPs under the CTR. This highlights a challenge in applying the CTR framework to pragmatic clinical trials addressing optimisation (e.g., schedule, dosing frequency). The CTR may not be sufficiently flexible to accommodate low-risk, high-relevance optimisation studies, despite their importance for patients and public health.
- **Low-Intervention Clinical Trial (LICT):** an attempt was made to classify DE-ESCALATE as LICT by referencing existing publications that supported intermittent administration of ADT [24–27]. However, these studies were conducted with previous generations of agents, prior to the implementation of ARPI. As a result, the request for LICT status was not accepted, as the intermittent schedule was not validated based on the current generation of therapies. This outcome appears relatively counterintuitive, as this was indeed the rationale sustaining the trial.
- **Adhering to standard practice:** the pragmatic protocol for DE-ESCALATE mandated that PSA testing follows routine clinical practice for ensuring high external validity. However, it was requested that additional PSA measurements are recommended, hence rejecting a core pragmatic element of this trial design. In response, the protocol was revised in its second submission to introduce more frequent PSA monitoring.
- **Request for information (RFI):** the initial submission of DE-ESCALATE generated 72 RFIs during protocol review. These were provided in an unstructured manner, were often duplicative or even contradictory. A significant number challenged the whole concept and rationale of the trial. Although the statistical design was questioned, and additional interim analysis were suggested, these modifications did not impact the sample size. The added interim analysis for closer monitoring of patient's safety was potentially a valid point, actually supporting the urgence of the trial requested by investigators who are routinely confronted with balancing disease control and patient wellbeing. Furthermore, under CTR, applicants must respond to assessment RFIs within a 12-days timeframe. For DE-ESCALATE, this timeline did not consider that a revised protocol would trigger additional RFIs, rendering it practically impossible to meet the deadline. This ultimately led to the withdrawal of the application and necessitated a full resubmission of the trial.

3. What is the DE-ESCALATE protocol teaching us?

The experience with DE-ESCALATE highlights critical insights on the suitability of the CTR for pragmatic, patient-centred clinical research. It is first important to dichotomise between the CTR itself and its implementation. One must acknowledge that once a regulation is adopted, assessors and civil servants are responsible to enforce its provisions.

Another critical observation is that the CTR does not distinguish between regulatory trials, aimed at registering new agents, and public health oriented clinical trials. While the former may need high internal validity, the latter aim for high external validity. Unfortunately, the CTR applies a uniform regulatory framework to all trials, hence forcing clinical trials addressing documented therapeutic interventions to follow the same requirements as trials on novel drugs. By retaining the IMP definition from the Clinical Trials Directive (CTD)[28] and applying it uniformly and rigidly, the CTR neglects the nuanced objectives of such pragmatic studies. Furthermore, the restrictive definition of LICT, limiting this designation to trials involving fully documented interventions or to those used as per marketing authorisation, is a major limitation. It is therefore critical that proportionate risk-based approaches are developed to enable these trials which historically have demonstrated to substantially contribute to therapeutic progress with impact on survival and quality of life [29].

Meanwhile, European policymakers have launched several initiatives such as ACT EU (Accelerating Clinical Trials in the European Union), COMBINE, and COLLABORATE to address operational challenges of the CTR as well as the interplay with other regulations, which also bring their levels of complexity for the performance of clinical trials [30,31].

4. What is the epilogue for the DE-ESCALATE protocol?

DE-ESCALATE was not approved during the initial submission due to the pragmatic nature of the trial design, unstructured RFIs, and limited time allocated for review. For the resubmission, the assessors' review was optimally used to adjust endpoint timing and the protocol was substantially rewritten documenting and justifying a pragmatic approach. It was ultimately approved in six EU member states in April 2025, a 9-month delay compared to the original timeline. Beyond the impact on study initiation, such regulatory delays have significant operational and financial consequences. The extended submission and resubmission process required multiple rounds of consultations with regulators, academic collaborators within the trial network, patient advocacy groups, and expert panels, all requiring considerable resources. These repeated interactions delayed patient enrolment, and ultimately the generation of clinical data. Financially, while the initial budget projected approximately €35,000 for protocol development and activation, the cumulative costs reached approximately €227,000, representing more than a sixfold increase.

A focused review on essential points could have addressed the core concerns earlier, which were initially overshadowed by technical details. Implementing pragmatism needs greater alignment between

relevant stakeholders to overcome the limitations of the CTR requesting a more flexible and pragmatic framework.

5. What are the observations on the EU regulations and processes for clinical trials?

In addition to the structural limitations of the CTR reducing all trials to the single model of drug development, interactions with other regulations governing the performance of clinical trials such as the *In Vitro Diagnostic Regulation* (IVDR) [32] or *Medical Device Regulation* (MDR) [33] do remain a point of attention but are beyond the challenges encountered while activating DE-ESCALATE.

The processes and decision-making levels have also proven to be somehow confusing. Clinical Trial Authorisation remains a Member State competence, and even though there are consensual approaches through the Clinical Trials Coordination Group (CTCG), expectations for an EU-collegial approach have not been materialised and are very much depending on the Reference Member State (RMS) with potential variability. The experience with DE-ESCALATE suggests that, despite lacking a formal mandate, the CTCG effectively holds a degree of regulatory authority, which can substantially impact clinical trial conduct.

These observations raise the need for a debate on how to address strategic research questions and clarify responsibilities at EU level. What is inferred with this example is that the societal value of clinical trials does not find an appropriate place for discussion yet in the EU.

Moreover, to date, the debate on internal versus external validity of clinical trials has yet to take place meaningfully at the EU level. While alternative designs such as cluster randomisation could have been considered, inherent baseline confounders would compromise the robustness required for addressing such a clinically oriented question. Society and regulators would potentially find equally beneficial trials which need substantial internal validity for regulatory purposes, and trials which priority is rather geared to external validity for public health purposes. The latter type needs the trial being evaluated in the global clinical context, especially when the questions addressed by the clinical trials focus on the optimal way to use these therapeutic interventions.

6. What could we recommend based on the learnings from DE-ESCALATE clinical trial?

Firstly, it is important to recognise that a one-size-fits-all approach does not reflect reality. A clear distinction between regulatory-driven and public health trials would position the EU as a leader in supporting diverse and innovative clinical trial approaches.

Secondly, public health-oriented trials must be contextualised within healthcare systems as they address therapeutic strategies, alongside patient pathways and the course of the disease. Failure to do so undermines patient centricity, a concept often emphasised by policymakers.

Thirdly, valuable regulatory expertise should be applied to facilitate clinical research in the EU, stimulating the conduct of trials addressing optimisation questions.

Lastly, we urge policymakers to rapidly engage relevant stakeholders, including institutions, investigators and patients with practical expertise, to revisit the regulatory environment, evaluating the impact of critical technical definitions, aiming for greater proportionality, consistency and genuine patient centricity, especially for trials with public health significance.

CRediT authorship contribution statement

Stephanie Kromar: Validation, Conceptualization. **Fabio Borges:** Writing – review & editing, Conceptualization. **Bertrand Tombal:** Writing – review & editing. **Denis Lacombe:** Writing – review & editing, Supervision, Conceptualization.

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Declaration of Competing Interest

The authors 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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