Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Harmonised but not more attractive? The EU Clinical Trials Regulation and the site allocation of multinational drug trials

Can Apaydın

can.apaydin@omu.edu.tr

Ondokuz Mayıs University

Research Article

Keywords: Clinical trials, Pharmaceutical regulation, Research and development location, European Union, Difference-in-differences

Posted Date: November 3rd, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11260307/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Harmonised but not more attractive? The EU Clinical Trials Regulation and the site allocation of multinational drug trials

Can Apaydın

can.apaydin@omu.edu.tr

Abstract

Europe's share of industry-sponsored clinical trials has fallen for a decade. The Commission's 2025 Biotech Act proposal seeks to reverse this by amending the Clinical Trials Regulation (CTR), which in 2022–2023 replaced national authorisation with a single coordinated procedure. I evaluate the CTR's effect on where trials are run, using 12,955 multinational industry trials started in 2013–2025, linked to national decision dates from the EU Clinical Trials Register and the Clinical Trials Information System, and compare the EU/EEA with other world regions within the same trial. The CTR nearly eliminated cross-country differences in authorisation times, reducing the dispersion of national decision times by about 85 per cent around a common median of roughly four months. Yet after the CTR became mandatory, the probability that a multinational trial included any EU/EEA site fell relative to other regions, by 3.9–11.5 percentage points from a base of 78 per cent depending on how the pre-existing EU trend is modelled. A triple difference with region × year fixed effects, which absorbs EU-wide shocks, shows a further 14.3-point decline for phase 1 relative to phase 3 trials, with flat pre-trends. Trials remaining in Europe used more member states, but selection may account for this increase. Member states whose authorisation had been slowest gained no share. Harmonisation thus did not make Europe more attractive for trials. The results are consistent with a higher fixed cost of entering Europe, a cost that further harmonisation alone does not address.

Keywords Clinical trials · Pharmaceutical regulation · Research and development location · European Union · Difference-in-differences

JEL classification I18 · L65 · O31 · O38

Introduction

Clinical trials are the largest single component of pharmaceutical research and development (R&D) spending and the stage at which regulation most directly shapes where innovation takes place (DiMasi et al. 2016; Wouters et al. 2020). Each multinational trial requires the sponsor to decide which countries will host its sites. That choice affects which patients gain early access to new medicines, which health systems build research capacity, and which regulators shape evidence that later supports reimbursement (Thiers et al. 2008; Glickman et al. 2009; Alsan et al. 2024). Europe has been losing in this competition. The European Economic Area's share of commercially sponsored trials fell from 22 per cent in 2013 to 12 per cent in 2023, while China's rose sharply (EFPIA et al. 2024; Li et al. 2019). The decline features prominently in the debate on European competitiveness (Draghi 2024).

The main EU policy response so far has been regulatory harmonisation. Under Directive 2001/20/EC each member state authorised trials separately through its competent authority and ethics committees, and sponsors running a trial in ten countries filed ten dossiers on ten timetables (European Parliament and Council of the European Union 2001). Regulation (EU) No 536/2014, the Clinical Trials Regulation (CTR), replaced this system with a single application through the Clinical Trials Information System (CTIS), a coordinated assessment led by a reporting member state, statutory timelines, and extensive transparency obligations (European Parliament and Council of the European Union 2014). The CTR applied from 31 January 2022

and became mandatory for all new applications from 31 January 2023. In December 2025, the Commission proposed amending it again through the European Biotech Act, shortening authorisation timelines, strengthening the reporting member state and tying a supplementary protection certificate extension, among other conditions, to trials run in more than two member states (European Commission 2025). These amendments are being negotiated without ex-post evidence on how the CTR itself changed trial location.

This paper provides that evidence. I assemble trial-level data on 12,955 multinational industry trials that started between 2013 and 2025 from ClinicalTrials.gov and link them with national authorisation records from the EU Clinical Trials Register (Directive era) and CTIS (CTR era). The identifying variation comes from comparing, within the same trial, the EU/EEA with other world regions before and after the CTR became mandatory. Trial fixed effects absorb everything about a trial that determines its overall footprint, including the disease, the sponsor, the phase and the planned enrolment. I study three margins. The first is presence, whether a trial includes any EU/EEA site. The second is breadth, how many member states a trial with an EU footprint uses. The third is the reallocation of trials across member states according to how slow their authorisation had been before the CTR.

A simple site-choice framework guides the analysis. Harmonisation has two opposing effects. It lowers the marginal cost of adding a member state to a trial already in Europe, because one dossier now covers all of them. It can also raise the fixed cost of entering Europe at all, through a new IT system, longer harmonised timetables for some sponsors, and transparency rules that expose protocols and commercially sensitive documents. If the second effect dominates for trials with small European footprints, the CTR should reduce presence while increasing breadth.

The data support the first prediction and reject the third, while the evidence on the second is mixed. I first document a strong first stage. By the second half of 2023, three quarters of new trials with an EU registry number were authorised under the CTR. The within-trial dispersion of national decision times fell from 0.63 to 0.23 log points, and cross-country differences in mean decision times almost disappeared. Harmonisation, however, converged on a median of about 118 days from submission to national decision. After the CTR became mandatory, the probability that a multinational industry trial included any EU/EEA site fell by 11.5 percentage points relative to other regions, from a pre-period mean of 78 per cent. The estimate is 3.9 points when I allow for an EU-specific linear trend and ranges from 3.9 to 15.3 points across all specifications and comparison regions. The decline is largest in phase 1 (17.5 points) and oncology (14.7 points) trials. A triple difference that compares phase 1 with phase 3 trials within each region and start year, and therefore absorbs any EU-wide shock that affects all phases alike, including the 2023 pharmaceutical package, gives a 14.3-point larger decline for phase 1 trials, with pre-period coefficients jointly indistinguishable from zero ($p = 0.90$). Against the United Kingdom and Switzerland, which share European patient pools and investigator networks but never applied the CTR, EU presence fell by 6.3 points. Trials that stayed in Europe used more member states, about 0.3 more per trial relative to other regions in the baseline regression (0.6 net of trend), and the raw count in the European registries rose from 5.0–5.3 to 6.0–6.3. A trimming bound shows, however, that this increase could be explained by the exit of trials with small European footprints. EU country-trial participation relative to high-income comparators fell by 3.2 points in my preferred specification, although this estimate is not robust to an EU-specific trend. Member states whose authorisation had been slowest did not attract more trials once the CTR equalised

timelines, which suggests that national delays were not the binding constraint on the allocation of trials within the EU.

The paper contributes to three literatures. First, it adds to work on how regulation affects the international diffusion of pharmaceutical innovation. That literature has focused on price regulation, reference pricing and health technology assessment as determinants of launch timing (Kyle 2007; Danzon et al. 2005; Cockburn et al. 2016; Maini and Pammolli 2023; Büssgen and Stargardt 2023; Righetti 2026). I move the question upstream to the location of clinical development, where regulation determines access before marketing authorisation. Second, it contributes to the literature on the costs and organisation of clinical trials (Sertkaya et al. 2016; Martin et al. 2017; Moore et al. 2018; Getz and Campo 2017; Budish et al. 2015) by showing that harmonising authorisation procedures can coexist with a decline on the extensive margin of site allocation, and that cross-country differences in authorisation speed did not drive within-EU allocation. Third, it complements evidence on European clinical trial regulation, which so far rests on descriptive trends and implementation experience (Hartmann 2012; Hearn and Sullivan 2007; Patrick-Brown et al. 2024; De Paola et al. 2025; European Medicines Agency 2025), and on the effects of the General Data Protection Regulation on European research and investment (Yom-Tov and Ofran 2022; Jia et al. 2021). Within this journal, the paper extends recent causal evaluations of European pharmaceutical policy on access, prices, shortages and generic entry (Büssgen and Stargardt 2023; Panhuysen et al. 2026; Dhingra et al. 2026; Yao and Liu 2025) and studies of pricing and R&D gaps for innovative medicines (Muniz et al. 2026; Fabbro et al. 2025) by turning to the regulation of evidence generation itself.

Institutional background

Under Directive 2001/20/EC, a sponsor wishing to run a trial in several member states submitted a clinical trial application to each national competent authority and obtained an opinion from one or more ethics committees in each country (European Parliament and Council of the European Union 2001). Requirements, fees and timetables differed across countries. Early evaluations found that the Directive raised the administrative cost of trials, particularly for academic sponsors, and that application volumes fell in several large member states (Hearn and Sullivan 2007; Hartmann 2012). Voluntary coordination through the Voluntary Harmonisation Procedure reduced, but did not remove, this fragmentation.

The CTR replaced national applications with a single dossier submitted through CTIS (European Parliament and Council of the European Union 2014). Part I of the dossier, covering the scientific and clinical assessment, is evaluated jointly under the lead of a reporting member state. Part II, covering informed consent, recruitment and site suitability, remains national. Each member state concerned issues a single decision that combines regulatory and ethical review. The Regulation sets statutory timelines for validation, assessment and decision, and it requires most trial documents, including protocols and assessment reports, to be published in CTIS. The transparency rules were revised in 2024 after sponsors raised concerns about commercially confidential information.

The transition followed a fixed timetable. From 31 January 2022, sponsors could choose either regime for new trials. From 31 January 2023, all new applications had to use CTIS. Ongoing trials authorised under the Directive had to be transitioned to CTIS by 30 January 2025. During the three-year transition, 10,608 initial applications were submitted through CTIS, about half of

them by commercial sponsors (European Medicines Agency 2025). Because trials typically start several months after authorisation, I treat trials starting from July 2023 onward as exposed to the CTR, those starting between January 2022 and June 2023 as a transition cohort, and earlier trials as unexposed. The first-stage evidence in the "Results" section confirms this classification.

Several other policy changes overlap with the CTR period. The Commission's April 2023 pharmaceutical package proposed to modulate regulatory data protection (European Commission 2023a, 2023b). The joint clinical assessments of the Health Technology Assessment Regulation began in January 2025 for oncology medicines and advanced therapies. The December 2025 Biotech Act proposal would shorten CTR timelines from 75 to 47 days when no additional information is requested, remove the extra 50 days for advanced therapies, and condition a 12-month supplementary protection certificate extension on trials that test efficacy in more than two member states (European Commission 2025). The empirical design below addresses these overlapping changes directly.

Conceptual framework

Consider a sponsor allocating a trial across countries to reach a recruitment target at minimum cost and delay (Lakdawalla 2018). Let the value of including a set of countries depend on their patient pools and investigator networks. Including any EU/EEA country requires a fixed regional cost F, covering dossier preparation, regulatory interaction and compliance with transparency rules. Each additional member state k adds a marginal cost c_k and an expected authorisation delay d_k, which matters because the trial cannot start enrolling there until it is authorised.

Under the Directive, F was moderate but c_k was high, since each additional member state required a separate national submission, and d_k varied widely across countries. The CTR changes

all three parameters. It lowers c_k because one Part I assessment covers every member state concerned. It replaces heterogeneous d_k with a common harmonised timeline $\bar{d}$. It may raise F through CTIS learning costs, a longer coordinated timetable relative to the fastest national systems, and the disclosure of trial documents. Three predictions follow.

Prediction 1 (presence). If F rises, fewer trials include any EU/EEA site. The effect should be largest for trials whose expected European footprint is small, which in practice means early-phase trials that use few countries and for which speed and confidentiality matter most.

Prediction 2 (breadth). Because c_k falls, trials that do include Europe should spread across more member states. The effect should be largest for sponsors without established national regulatory teams, for whom separate national submissions were most costly. A higher F produces a similar pattern through selection, because the trials that leave Europe are those with the smallest expected European footprint, so the breadth margin alone cannot identify a fall in c_k.

Prediction 3 (reallocation). Because the CTR equalises d_k, countries whose authorisation had been slow should gain relative to previously fast countries, provided that delays shaped site choice before the CTR.

The net effect on the number of EU country-trial slots is ambiguous. It depends on whether the loss of trials on the extensive margin is offset by more member states per remaining trial.

Data

Trial registry data

My main source is ClinicalTrials.gov, which registers interventional trials worldwide and is the standard source for studying the global distribution of industry trials (Thiers et al. 2008; Alsan et

al. 2024). I downloaded through the public API, on 3 October 2026, all interventional studies with a drug or biological intervention and a start date between 2013 and 2025, which yields 131,440 trials. For each trial I record the start date and whether it is actual or anticipated, the phase, the lead sponsor and its class, conditions, the country of every listed site, and secondary identifiers. The secondary identifiers include EudraCT numbers (Directive era) and CTIS numbers (CTR era), which allow us to measure which regime authorised each trial in Europe.

The analysis sample comprises multinational trials, meaning trials with sites in at least two countries, that have an industry lead sponsor and are in phase 1, 2 or 3. It contains 12,955 trials run by 2,150 sponsors. I group countries into five regions, the EU/EEA (the 27 member states plus Norway, Iceland and Liechtenstein), Latin America, Asia-Pacific, other Europe and North America. I exclude Russia, Ukraine and Belarus from other Europe because the 2022 war removed trial activity there for reasons unrelated to EU regulation. The United Kingdom belongs to other Europe in all years, because it never applied the CTR. I classify oncology trials by condition keywords and define large sponsors as the 25 industry sponsors with the most registered trials in 2013–2019. Table 1 describes the sample by start year, and Appendix Table A1 defines all variables.

Table 1 Multinational industry trials by start year

Start year	Trials	Share with an EU/EEA site	EU/EEA member states per trial with an EU site	Share with a China site	Share by top-25 sponsors
2013.0	463	0.806	6.33	0.108	0.719
2014.0	590	0.822	5.87	0.071	0.664
2015.0	737	0.829	5.60	0.069	0.662
2016.0	742	0.823	5.14	0.069	0.582
2017.0	1,082	0.795	5.14	0.093	0.475
2018.0	1,142	0.786	5.05	0.113	0.446
2019.0	1,152	0.783	5.11	0.141	0.425
2020.0	1,184	0.738	4.98	0.156	0.419

Start year	Trials	Share with an EU/EEA site	EU/EEA member states per trial with an EU site	Share with a China site	Share by top-25 sponsors
2021.0	1,403	0.738	5.07	0.180	0.410
2022.0	1,179	0.769	5.16	0.193	0.396
2023.0	1,073	0.742	5.37	0.229	0.434
2024.0	1,078	0.719	5.86	0.232	0.406
2025.0	1,130	0.710	5.72	0.296	0.451

Notes Multinational industry-sponsored phase 1–3 trials with a drug or biological intervention registered on ClinicalTrials.gov. EU/EEA comprises the 27 EU member states, Norway, Iceland and Liechtenstein. Top-25 sponsors are the 25 industry sponsors with the most trials starting in 2013–2019.

The descriptive pattern anticipates the main results. The share of multinational industry trials with an EU/EEA site was 0.82 in 2014–2016, fell to 0.74 during the pandemic, recovered to 0.77 in 2022 and then fell to 0.71 by 2025. Over the same period, the number of member states used by trials with an EU site rose from about 5.1 in 2018–2022 to 5.7–5.9 in 2024–2025. The share of multinational trials with a site in China rose from 7 per cent in 2015 to 30 per cent in 2025, which motivates the controls for China-linked trials described below.

National authorisation records

To measure authorisation delays, I use two European registries. For the Directive era, I drew a systematic sample of the EU Clinical Trials Register. The register's download interface returns trials in pages of 20, so I downloaded the first page of results for each of 288 four-day windows starting on the 1st, 8th, 15th and 22nd of every month in 2016–2021. Because windows are fixed in calendar time and cover all sponsors and phases, the sample is spread evenly over the period and is not selected on trial characteristics. Each record reports, by member state, the date the protocol was entered and the dates of the competent authority decision and the ethics committee

opinion. I define the national delay as the number of days from entry to the later of the two decisions, keeping authorised protocols with delays between 1 and 730 days in trials with at least two member states. This yields 7,091 national decisions in 1,615 trials. For the CTR era, I downloaded all 12,549 trials published in CTIS and retrieved the full records of 4,846 multinational trials with a pharmaceutical company sponsor. For the 3,015 trials that were initially authorised under the CTR rather than transitioned from the Directive, I compute the number of days from submission to the first decision in each member state concerned, which gives 18,522 national decisions.

The two delay measures start from different events, the entry of a protocol in EudraCT and the submission of an application in CTIS, so their levels are not strictly comparable. I therefore focus on their dispersion. For each trial, I compute the deviation of each country's log delay from the trial mean and then average these within-trial deviations by country. This measure removes everything specific to a trial, such as its complexity, and isolates how much faster or slower a member state decided than other member states in the same trial.

Empirical strategy

Presence and breadth

I stack the data at the trial × region level. For trial i and region r, let D_{ir} indicate that the trial has at least one site in region r, and let n_{ir} be the number of countries of region r it uses. I estimate

$$Y_{ir} = \beta\,(\mathrm{EU}_r \times \mathrm{Post}_i) + \gamma\,(\mathrm{EU}_r \times \mathrm{Transition}_i) + \alpha_i + \mu_{r,\mathrm{phase}(i)} + \lambda_{r,\mathrm{CN}(s(i))} + \varepsilon_{ir},$$

where α_i are trial fixed effects, μ are region × phase fixed effects and λ are region × sponsor China-exposure fixed effects. Sponsor China exposure classifies the lead sponsor $s(i)$ by its

share of 2013–2019 trials with a site in China (zero, up to 10 per cent, above 10 per cent, or no trials before 2020). Post indicates trials starting from July 2023 onward, and Transition indicates starts between January 2022 and June 2023. For presence, $Y_{ir} = D_{ir}$. For breadth, $Y_{ir} = \ln n_{ir}$, estimated on trial-region pairs with $n_{ir} > 0$ for trials present in at least two regions.

The trial fixed effects mean that β is identified only from how a given trial distributes its sites across regions, compared with how trials did so before the CTR. Anything that raises or lowers a trial's overall footprint, such as larger enrolment targets in a therapeutic area or a sponsor's global strategy, is absorbed. The region × sponsor China-exposure fixed effects allow sponsors that were already active in China, whose trials increasingly include Chinese sites, to have systematically different regional patterns. I use a predetermined sponsor-level measure because whether a given trial has a Chinese site is itself part of the site-allocation decision, and I report trial-level China-site fixed effects and the exclusion of China-site trials as robustness checks. Standard errors are clustered by trial. Because the region-level contrast rests on five regions, I also cluster by region × start year and report randomisation inference that reassigns treatment to each region in turn. Since about a quarter of post-period EU trials were still authorised under the Directive, the estimates are intention-to-treat effects. I treat the phase triple difference described below as the primary causal estimate, because it absorbs EU-wide shocks and its inference relies on many trials within each region and year. The region-level estimates of presence, breadth and net participation are reported with the caveat that only five regions underlie them, so their conventional standard errors overstate precision relative to the randomisation-inference benchmark.

The key identifying assumption is that, absent the CTR, the EU's position relative to other regions would have evolved as before. Europe's share was already declining before 2022, so I

report event-study estimates relative to 2019, estimates with an EU-specific linear trend, and estimates that exclude the pandemic cohorts or restrict the sample to starts from 2019 onward (Roth et al. 2023; Rambachan and Roth 2023; Borusyak et al. 2024).

Triple difference by phase

The main threat to the presence estimates is an EU-wide shock coinciding with the CTR, such as the 2023 pharmaceutical package or a secular acceleration of Europe's decline. I therefore estimate a triple difference that compares phase 1 with phase 3 trials, adding region × start-year fixed effects,

$$D_{ir} = \delta\,(\mathrm{EU}_r \times \mathrm{Post}_i \times \mathrm{P1}_i) + \theta\,(\mathrm{EU}_r \times \mathrm{Transition}_i \times \mathrm{P1}_i) + \alpha_i + \mu_{r,\mathrm{phase}(i)} + \lambda_{r,\mathrm{CN}(s(i))} + \kappa_{r,\mathrm{year}(i)} + \varepsilon_{ir}.$$

The region × year fixed effects κ absorb every shock to the EU's position in a given start year that is common to phase 1 and phase 3 trials, including EU-wide regulatory uncertainty, the pandemic and secular trends. The coefficient δ is identified only from the differential change in EU presence of phase 1 trials. Prediction 1 implies $\delta < 0$, because early-phase trials use few countries and are most sensitive to the fixed cost of entry. Changes in regulatory data protection, by contrast, matter for products close to marketing authorisation and should, if anything, weigh more on phase 3 trials.

European comparators

The other world regions differ from the EU/EEA in patient pools, costs and the growth of Chinese research. I therefore also compare the EU/EEA with the United Kingdom and Switzerland, which are embedded in the same European investigator networks and contract

research organisations but never applied the CTR. The comparison has its own limitation. The United Kingdom left EU trial regulation in 2021 and from 2023 pursued reforms to shorten trial set-up, which would make it more attractive over the same period. A decline of EU presence relative to the United Kingdom could therefore partly reflect a pull toward the United Kingdom, so I also report Switzerland alone.

Country-level participation

To measure the net effect, I estimate an analogous model at the trial × country level. The comparison group consists of ten high-income countries outside the EU, namely the United Kingdom, Switzerland, the United States, Canada, Australia, Japan, South Korea, Israel, Taiwan and New Zealand. The outcome is an indicator that country c hosts a site in trial i, and the specification includes trial, country × phase and country × sponsor China-exposure fixed effects, with standard errors clustered by country and wild cluster bootstrap p-values. Because this outcome counts country-trial slots, it combines the presence and breadth margins.

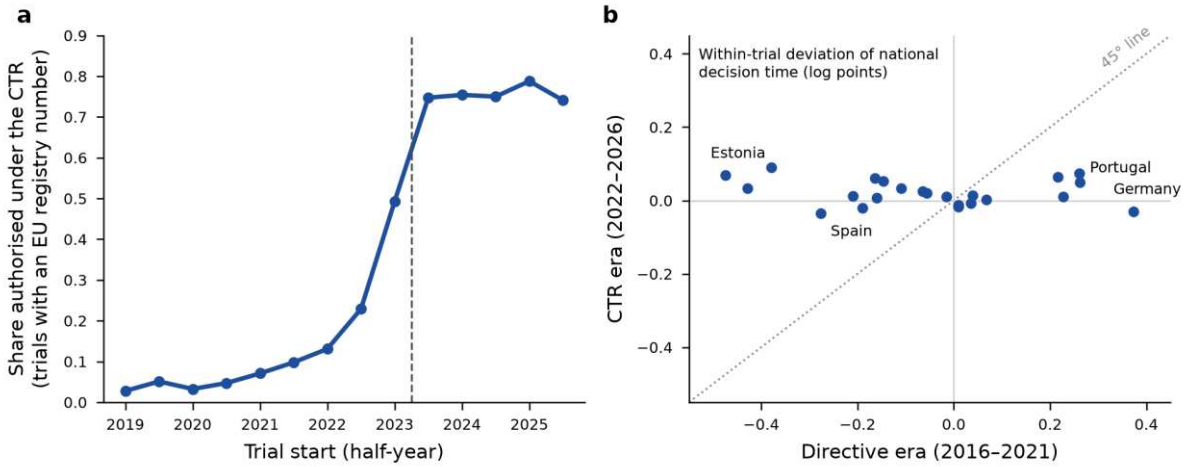
Reallocation within the EU

To test prediction 3, I restrict the country-level panel to the 23 EU/EEA member states with at least 30 Directive-era decisions and interact Post with the standardised pre-CTR within-trial delay deviation of each country. A positive coefficient means that previously slow member states gained trial participation after the CTR equalised timelines.

Results

First stage

Figure 1 shows that the CTR changed both the regime and the timing of authorisation. In panel a, the share of new trials with an EU registry number that were initially authorised under the CTR rose from below 10 per cent in 2021 to about 75 per cent from the second half of 2023. The remainder consists mostly of trials authorised under the Directive shortly before the deadline. My Post estimates are therefore intention-to-treat effects of the regime change, and dividing them by 0.75 gives the implied effect of full exposure. Panel b and Table 3 show that the CTR nearly removed cross-country differences in authorisation speed. Under the Directive, national decisions within the same trial differed widely. The standard deviation of within-trial log decision times was 0.632, and German, Portuguese, Irish and Dutch authorisations took 25–45 per cent longer than the trial average, while Estonian, Greek and Spanish authorisations were 24–38 per cent faster (Appendix Table A2). Under the CTR, the within-trial standard deviation fell to 0.232 and the standard deviation of country means from 0.226 to 0.035, a reduction of about 85 per cent. All member states now decide close to a common median of 118 days after submission. Both measures are calendar days and include any clock stops for requests for information. The CTR-era sample excludes trials transitioned from the Directive because those trials were authorised under national procedures.



311

312 **Fig. 1** CTR adoption and the convergence of national authorisation times. Panel a shows the
313 share of trials with an EU registry number that were initially authorised under the CTR, by start
314 half-year, among multinational industry trials with an EU/EEA site. The dashed line marks July
315 2023. Panel b plots each member state's mean within-trial deviation of log decision time under
316 the Directive (EU Clinical Trials Register, 2016–2021) against the same measure under the CTR
317 (CTIS). Countries with at least 30 decisions in both periods are shown, and the dotted line is the
318 45-degree line

319 **Table 3** National authorisation times and reallocation across member states

320 Panel A Dispersion of national decision times

Statistic	Directive era (EUCTR, entry to national decision)	CTR era (CTIS, submission to national decision)
Trials	1,615	3,015
National decisions	7,091	18,522
Median days to national decision	72	118
SD of within-trial log decision time	0.632	0.232
SD of country mean deviations	0.226	0.035

321 Panel B Reallocation toward previously slow member states

Specification	Pre-CTR delay (SD) × post	Countries

Specification	Pre-CTR delay (SD) × post	Countries
Baseline	−0.0038 (0.0068)	23
Dose-specific linear trend	0.0095 (0.0061)	23
Starts 2019 onward	0.0009 (0.0058)	23
Excluding Germany	−0.0063 (0.0075)	22
Trials with an EU site only	−0.0045 (0.0101)	23
Wild cluster bootstrap p-value, baseline	0.594	23
Pre-period mean participation	0.172	23
Minimum detectable effect (80 per cent power)	0.0190	23
Split-half reliability of delay measure	0.949	23

Notes Panel A uses authorised national decisions in multinational trials with delays between 1 and 730 calendar days. Directive-era delays run from protocol entry to the later of the competent authority decision and the ethics committee opinion. CTR-era delays run from submission to the first decision of the member state concerned, for trials initially authorised under the CTR. Within-trial deviations subtract the trial mean of log delay. The country-level standard deviation uses member states with at least 30 decisions. Panel B reports the coefficient on the interaction of the standardised pre-CTR delay deviation with Post in the trial × country panel restricted to 23 EU/EEA member states, with trial, country × phase and country × sponsor China-exposure fixed effects. Standard errors clustered by country in parentheses. The wild cluster bootstrap uses 1,999 replications with Webb weights. The minimum detectable effect is 2.8 standard errors. Reliability is the Spearman–Brown corrected correlation of country means across random halves of trials. * $p<0.10$, ** $p<0.05$, *** $p<0.01$.

Presence

Column 1 of Table 2 reports the effect on presence. In the baseline, the probability that a multinational industry trial includes any EU/EEA site falls by 11.5 percentage points relative to other regions after the CTR became mandatory. Relative to a pre-period mean of 0.783, this is a decline of about 15 per cent, or about 20 per cent when scaled by the 75 per cent compliance rate.

The estimate is negative and significant in every specification. It is larger when I exclude pandemic starts (14.7 points) or trials with a site in China (12.4 points), similar with region × China-site fixed effects (10.0 points), sponsor × region fixed effects (9.6 points) or a post window limited to the first year (10.4 points), and smaller when I restrict the sample to starts from 2019 onward (8.3 points) or allow for an EU-specific linear trend (3.9 points). Appendix Table A6 shows that it ranges from 6.9 to 15.3 points when the EU/EEA is compared with each other region separately, and that the EU/EEA has the most negative estimate of the five regions when treatment is reassigned to each in turn. With only five regions, the lowest attainable randomisation-inference p-value is 0.20.

The event study in Fig. 2a shows the timing. EU presence relative to other regions was stable or slightly higher between 2013 and 2017, with coefficients between −0.003 and 0.047 relative to 2019, and a joint test of the 2013–2018 coefficients does not reject zero at the 5 per cent level ($p = 0.097$). Presence fell during the pandemic years, to −0.054 in 2020 and −0.071 in 2021, and partly recovered in 2022. It then fell to −0.083 for the 2023 cohort, −0.123 for 2024 and −0.133 for 2025. Part of the decline therefore predates the CTR, and the post-CTR estimates should be read against that background. Following Rambachan and Roth (2023), I compute how large post-period departures from parallel trends would have to be to explain the decline. Relative to 2022, the average 2024–2025 decline remains significant unless the year-to-year deviation from parallel trends after 2022 is at least 80 per cent of the largest year-to-year change observed in 2013–2019 and always in the same direction. Relative to 2019, the breakdown value is 0.66. I therefore treat the trend-adjusted estimate of 3.9 points as a conservative lower bound. Under any of these specifications, the CTR did not halt Europe's declining presence in multinational trials.

Table 2 Effect of the CTR on EU presence and breadth in multinational trials

Panel A Trial × region estimates

Specification	EU presence (1)	Log EU member states (2)
Baseline	−0.115*** (0.010)	0.053*** (0.016)
EU-specific linear trend	−0.039** (0.016)	0.104*** (0.026)
Starts 2019 onward	−0.083*** (0.012)	0.066*** (0.018)
Excluding 2020–2021 starts	−0.147*** (0.011)	0.041** (0.017)
Region × China-site fixed effects	−0.100*** (0.010)	0.043*** (0.016)
Excluding trials with a China site	−0.124*** (0.012)	0.069*** (0.019)
Sponsor × region fixed effects	−0.096*** (0.010)	0.028* (0.017)
Post window limited to July 2023–June 2024 starts	−0.104*** (0.015)	0.035 (0.024)
Actual start dates only	−0.115*** (0.010)	0.052*** (0.016)
Clustered by region × start year	−0.115*** (0.019)	0.053* (0.032)
Observations (trial × region)	64,775	37,891
Trials	12,955	11,347
Pre-period EU mean	0.783	5.38 member states

Panel B Trial × country estimates (EU/EEA versus high-income comparators)

Specification	EU country inclusion
Baseline (country × sponsor China-exposure fixed effects)	−0.032** (0.014)
EU-specific linear trend	−0.007 (0.011)
Country × China-site fixed effects	−0.010 (0.010)
Excluding trials with a China site	−0.010 (0.009)
Dropping the United Kingdom	−0.033** (0.015)
Observations (trial × country)	492,290
Pre-period mean for EU/EEA countries	0.147

Notes Panel A uses a trial × region panel of trials and five world regions. EU presence is an indicator that the trial has at least one EU/EEA site. Log EU member states is the log number of countries the trial uses in each region, estimated on trial-region pairs with at least one country, for trials present in at least two regions. The baseline includes trial, region × phase and region × sponsor China-exposure fixed effects, where sponsor China exposure is the sponsor's share of 2013–2019 trials with a site in China (zero, up to 10 per cent, above 10 per cent, or no pre-2020 trials). Post covers trials starting from July 2023 onward, and every regression also includes an EU × transition indicator for starts between January 2022 and June 2023. Standard errors clustered by trial, or by region × start year where indicated, in parentheses. Significance stars

refer to these standard errors. With five regions, the randomisation-inference p-value for the baseline presence estimate is 0.20, the lowest attainable (Appendix Table A6). Panel B uses a trial × country panel of 38 countries (28 EU/EEA member states with registered sites and 10 high-income comparators) with trial, country × phase and country × sponsor China-exposure fixed effects, and standard errors clustered by country. * p<0.10, ** p<0.05, *** p<0.01.

Breadth

Column 2 of Table 2 shows that trials that include Europe use more member states relative to how they use other regions. The baseline increase is 5.3 per cent, which corresponds to about 0.3 member states at the pre-period mean of 5.4. Registry data independent of ClinicalTrials.gov show a larger increase (Appendix Table A3). Multinational commercial trials in the EU Clinical Trials Register used 5.0–5.3 member states in 2016–2020, and commercial multinational trials initially authorised through CTIS used 6.0–6.3 member states in 2023–2025.

This evidence is less robust than the presence result, for three reasons. First, it depends on the comparison region. The increase is 11.1 per cent relative to North America and 6.1 per cent relative to other Europe, but the EU/EEA becomes narrower relative to Asia-Pacific, where trials with Chinese sites increasingly spread across several Asian countries (Appendix Table A6). Asia-Pacific has the largest breadth increase of the five regions when treatment is reassigned (Fig. 3c). Second, the increase is concentrated in the 2024 cohort (Fig. 2b). It is not significant when the post window is limited to July 2023–June 2024 starts or when standard errors are clustered by region × start year at the 5 per cent level, and pre-period coefficients show a downward drift (joint p = 0.072). Third, and most importantly, the breadth increase may reflect selection. If the trials that left Europe were those that would have used the fewest member states, the remaining

trials are broader even if no trial changed its European footprint. When I drop from the pre-period the EU trials with the smallest footprints, in proportion to the baseline presence loss, the breadth effect becomes −0.102. With a proportion matching the trend-adjusted loss, it is 0.006. I therefore cannot distinguish a lower marginal cost of adding member states from the exit of small-footprint trials, and both interpretations are consistent with the presence result.

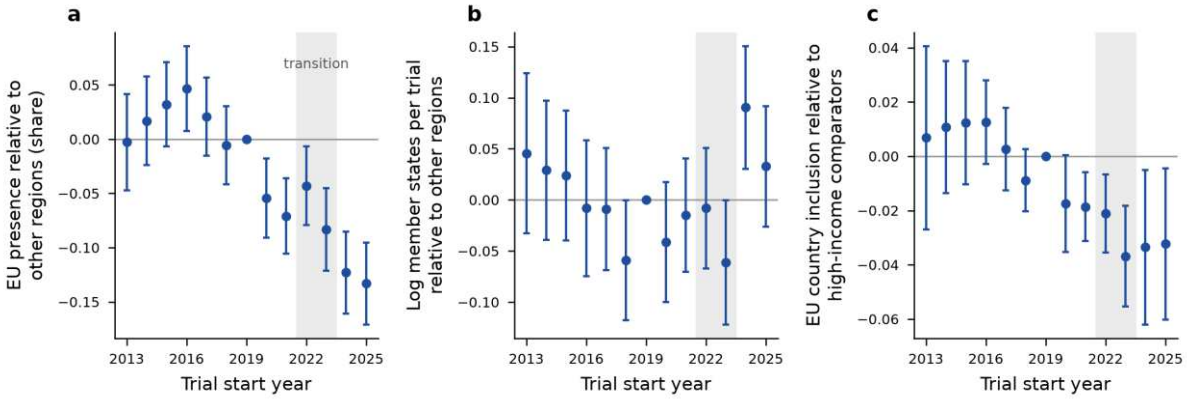


Fig. 2 Event-study estimates. Each panel plots coefficients on EU × start year relative to 2019, with 95 per cent confidence intervals. Panel a shows EU presence relative to other regions, panel b the log number of member states relative to other regions, and panel c the inclusion of each EU/EEA country relative to ten high-income comparators. The shaded band marks the 2022–2023 transition cohorts. Specifications follow the baselines in Table 2. Standard errors are clustered by trial in panels a and b and by country in panel c

Net participation

Panel B of Table 2 combines the two margins. In the preferred specification, the probability that a given EU/EEA country hosts a site in a multinational trial falls by 3.2 percentage points relative to the ten high-income comparators, from a pre-period mean of 0.147. The wild cluster bootstrap p-value is 0.039, and the estimate is unchanged without the United Kingdom. The event study in

Fig. 2c shows, however, that EU participation had been drifting down since 2018, and the estimate falls to −0.007 with an EU-specific trend. When I condition on trial-level China sites instead of sponsor-level China exposure, or exclude China-site trials, the estimate is −0.010 and not significant (bootstrap p-value 0.361). The more modest decline in country-trial participation than in presence is consistent with the remaining trials using more member states. I conclude that the CTR did not increase EU participation and may have reduced it by up to one fifth of its pre-period level.

Reallocation across member states

If slow national authorisation had deterred sponsors, equalising timelines should have shifted participation toward previously slow member states. Panel B of Table 3 finds no such shift. A one standard deviation slower pre-CTR authorisation is associated with a −0.0038 change in post-CTR participation (standard error 0.0068, wild cluster bootstrap p-value 0.594). The estimate stays close to zero with a dose-specific trend, from 2019 onward, without Germany and among trials with an EU site. The delay measure is precise, with a split-half reliability of 0.95, so attenuation from measurement error is small. The design could detect an effect of 1.9 percentage points per standard deviation, about 11 per cent of mean participation, with 80 per cent power. Prediction 3 is therefore rejected for effects of this size. Before the CTR, the choice of member states appears to have been driven by patient pools and investigator networks rather than by national authorisation speed.

Heterogeneity

Table 4 and Fig. 3 show where the effects are concentrated. The decline in presence is largest in phase 1 trials (17.5 points), followed by phase 2 (12.7 points) and phase 3 (7.7

points). This gradient matches prediction 1. Early-phase trials use few countries, so the fixed cost of entering Europe weighs most heavily relative to any gain from coordinated multi-country assessment, and they are the most sensitive to timelines and to the disclosure of protocols. The decline is larger in oncology (14.7 points) than outside it (9.2 points) and somewhat larger for the 25 largest sponsors (13.5 points) than for others (9.1 points).

The breadth increase is confined to sponsors outside the 25 largest firms (15.3 per cent), to phase 2 trials (9.4 per cent) and to non-oncology trials (11.1 per cent). The largest sponsors, which already ran national submissions through dedicated regulatory teams and contract research organisations, show no change (−2.0 per cent). This pattern fits the marginal-cost channel of prediction 2, since a single dossier should matter most for sponsors without such capacity. The selection problem documented above applies with at least equal force to these subsamples, however, so the breadth splits should be read as descriptive.

Table 4 Heterogeneity of the CTR effect

Subsample	EU presence	Log EU member states	Trials
Phase 1	−0.175*** (0.029)	0.024 (0.046)	2,333
Phase 2	−0.127*** (0.017)	0.094*** (0.028)	5,305
Phase 3	−0.077*** (0.013)	0.027 (0.021)	5,317
Top-25 sponsors	−0.135*** (0.013)	−0.020 (0.020)	6,110
Other sponsors	−0.091*** (0.016)	0.153*** (0.025)	6,845
Oncology	−0.147*** (0.016)	−0.059** (0.024)	4,811
Non-oncology	−0.092*** (0.013)	0.111*** (0.021)	8,144

Notes Each cell reports the EU × Post coefficient from the baseline trial × region specification in Table 2 Panel A estimated on the indicated subsample. Trial counts refer to the presence regressions. Standard errors clustered by trial in parentheses. * p<0.10, ** p<0.05, *** p<0.01.

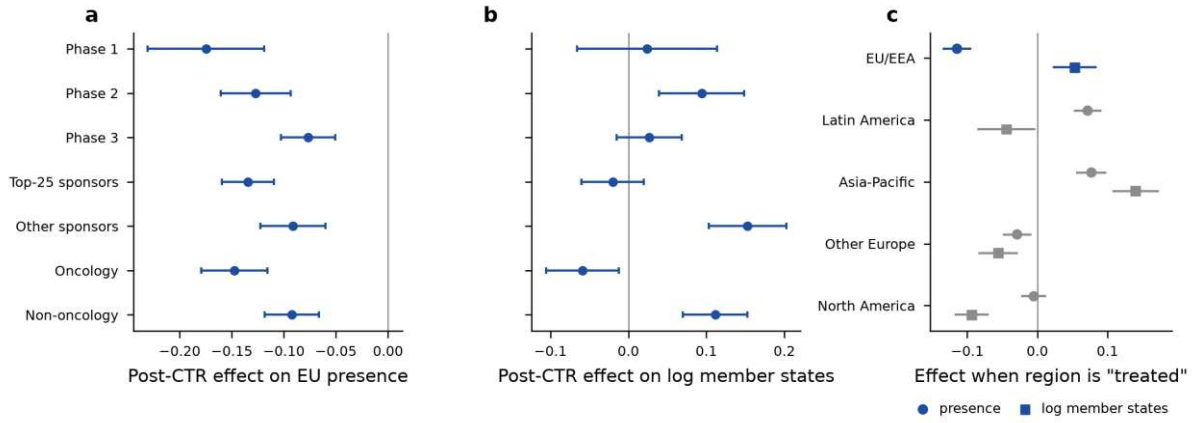


Fig. 3 Heterogeneity and placebo regions. Panels a and b show EU × Post coefficients for EU presence and log member states by phase, sponsor size and therapeutic area, with 95 per cent confidence intervals. Panel c reassigns treatment to each region in turn and plots the resulting Post coefficients for presence (circles) and log member states (squares). The EU/EEA is highlighted

Triple difference and European comparators

Panel A of Table 5 reports the triple difference. With region × start-year fixed effects, EU presence fell by 14.3 percentage points more for phase 1 than for phase 3 trials after the CTR became mandatory. The estimate is similar without the region × year fixed effects (13.2 points), with trial-level China-site fixed effects (16.1 points), when China-site trials are excluded (14.2 points) and when standard errors are clustered by region × start year. Pooling phases 1 and 2 against phase 3 gives 9.6 points. The event study in Fig. 4a shows no differential pre-trend. The 2013–2018 coefficients are between −0.017 and 0.061 and jointly insignificant ($p = 0.903$). The phase 1 gap widens gradually from 2020 and is largest for the 2025 cohort (−0.193). Because the region × year fixed effects absorb any shock common to all phases, this result cannot be explained by the pharmaceutical package, the pandemic or a secular decline of Europe, unless

those shocks affected early-phase trials disproportionately. There is no corresponding differential for smaller sponsors (−0.010), so the entry cost appears to bind by trial type rather than by sponsor size.

Panel B compares the EU/EEA with the United Kingdom and Switzerland. The results are consistent with the main estimates but should be read as supporting evidence, given the UK reforms. EU presence fell by 6.3 points relative to these two countries, by 10.2 points net of an EU-specific trend and by 3.5 points against Switzerland alone. Fig. 4b shows that the EU's position relative to the United Kingdom and Switzerland had stabilised in 2019–2022, after an earlier period in which UK and Swiss presence was falling, and dropped from the 2023 cohort onward. The phase 1 triple difference against these two countries is −0.053 but imprecise, because few phase 1 trials include either country.

Table 5 Triple difference by phase and European comparators

Panel A Phase 1 relative to phase 3, EU/EEA relative to other regions

Specification	Coefficient	Observations
Phase 1 vs phase 3, region × year fixed effects	−0.143*** (0.030)	38,250
Phase 1 vs phase 3, without region × year fixed effects	−0.132*** (0.030)	38,250
Phase 1 and 2 vs phase 3, region × year fixed effects	−0.096*** (0.019)	64,775
Phase 1 vs phase 3, region × China-site fixed effects	−0.161*** (0.029)	38,250
Phase 1 vs phase 3, excluding trials with a China site	−0.142*** (0.034)	30,560
Phase 1 vs phase 3, clustered by region × start year	−0.143*** (0.041)	38,250
Other vs top-25 sponsors, region × year fixed effects	−0.010 (0.019)	64,775
Joint test of 2013–2018 event-study coefficients (χ^2, 6 df)	2.17 (p = 0.903)	

Panel B EU/EEA relative to the United Kingdom and Switzerland

Specification	Coefficient	Observations
Baseline	−0.063*** (0.012)	25,910
EU-specific linear trend	−0.102*** (0.019)	25,910
Region × China-site fixed effects	−0.059*** (0.012)	25,910
Starts 2019 onward	−0.078*** (0.014)	16,398
Switzerland only as comparator	−0.035*** (0.011)	25,910
Phase 1 vs phase 3 triple difference, region × year fixed effects	−0.053 (0.033)	15,300
Joint test of 2013–2018 event-study coefficients (χ^2, 6 df)	12.46 (p = 0.053)	

Notes Panel A estimates the EU × Post × phase 1 interaction in the trial × region panel restricted to phase 1 and phase 3 trials (or phases 1–3 where indicated), with trial, region × phase, region × sponsor China-exposure and region × start-year fixed effects unless stated otherwise. The sponsor row replaces phase 1 with an indicator for sponsors outside the top 25. Panel B compares EU/EEA presence with presence in the United Kingdom or Switzerland, with trial, region × phase and region × sponsor China-exposure fixed effects. Standard errors clustered by trial, or by region × start year where indicated, in parentheses. * p<0.10, ** p<0.05, *** p<0.01.

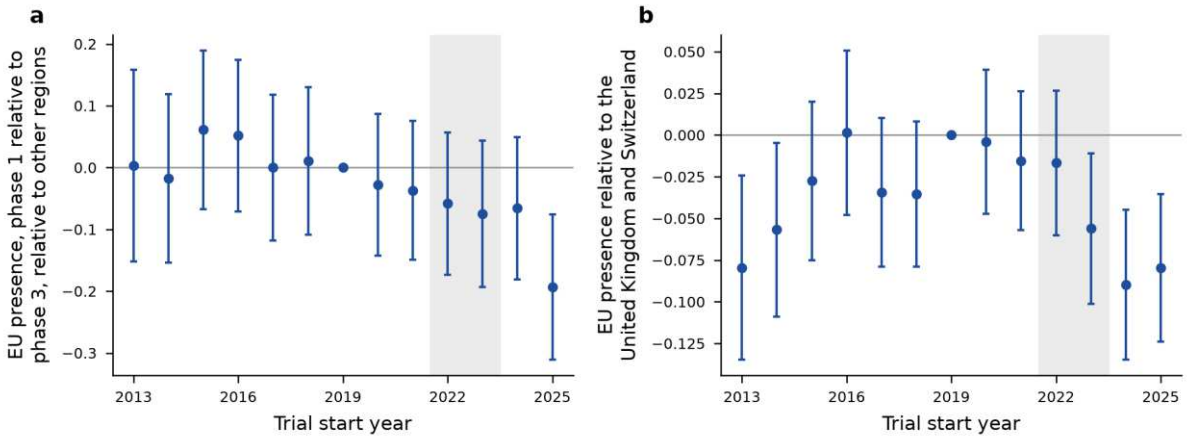


Fig. 4 Triple difference and European comparators. Panel a plots coefficients on EU × phase 1 × start year relative to 2019 from the triple-difference specification with region × start-year fixed effects. Panel b plots coefficients on EU × start year relative to 2019 in a comparison of EU/EEA presence with presence in the United Kingdom or Switzerland. Bars are 95 per cent confidence

intervals with standard errors clustered by trial. The shaded band marks the 2022–2023 transition cohorts

Alternative explanations

Several alternative explanations are inconsistent with the presence result. The pandemic cannot explain it, because the estimate is larger when the 2020–2021 cohorts are excluded and because presence fell further after the pandemic cohorts had passed. China's growth is addressed by controlling for sponsors' predetermined China exposure, by trial-level China-site fixed effects and by excluding China-linked trials, and the estimate is similar in all three cases. The war in Ukraine is addressed by excluding Russia, Ukraine and Belarus from the comparison regions. The United Kingdom is classified outside the EU/EEA throughout, because it never applied the CTR, and the country-level results are robust to dropping it. The General Data Protection Regulation, which has been linked to a shift of early-phase trials away from countries with strict data protection (Yom-Tov and Ofran 2022) and to lower technology investment in Europe (Jia et al. 2021), took effect in 2018, and the 2018 presence coefficient is small (−0.006). Registry updating is another concern, because site lists of recent trials may still be incomplete. If European sites were added later than others, this would bias recent presence downward. Yet presence is as low for the 2024 cohort as for the 2025 cohort, and the estimate is −0.104 when the post window is limited to trials that had at least two years to complete their site lists.

The most important remaining confounder is the uncertainty created by the 2023 pharmaceutical package, which proposed to modulate regulatory data protection (European Commission 2023a, 2023b). This shock coincides with the CTR deadline and could also reduce Europe's attractiveness for trials. The triple difference addresses it directly. Region × year fixed effects

absorb any effect of the package that is common to all phases, and the package should weigh least on phase 1 trials, which are run years before marketing authorisation. The phase 1 differential of 14.3 points therefore points to the CTR. The triple difference cannot rule out an EU-specific shock that affected only early-phase trials, and the level effect on all phases combines the CTR with any such common shocks.

Discussion

The CTR achieved its procedural objective. It replaced a fragmented system with a single procedure and nearly eliminated cross-country differences in authorisation times. Its median of 118 days from submission to decision matches the figure reported by the EU's own monitoring (European Medicines Agency 2026). It did not achieve its economic objective of making Europe more attractive for trials. After the CTR became mandatory, fewer multinational industry trials included Europe, especially in early phases, and EU country-trial participation did not rise. The early-phase decline survives a triple difference that absorbs EU-wide shocks, which is the most direct evidence that the regime change itself mattered. The pattern is consistent with a higher fixed cost of entering Europe, for which I propose three candidate sources, namely the learning cost of CTIS, a harmonised timeline slower than the fastest national systems, and disclosure obligations. My design cannot separate them.

The results bear on the Biotech Act negotiations in three ways, each of which should be read as consistent with the evidence rather than as a tested policy effect. First, the margin that moved is entry into Europe, and it moved most for early-phase trials, where Europe's position is weakest (EFPIA et al. 2024; De Paola et al. 2025). Shortening the common timeline, as the Biotech Act proposes, addresses one candidate source of the entry cost. Reforms of CTIS usability and of

disclosure rules address the others. Second, the supplementary protection certificate extension conditioned on trials in more than two member states rewards breadth. My evidence on breadth is mixed, and the increase I observe is confined to smaller sponsors, so the incentive may mostly benefit large sponsors whose breadth did not change. Third, equalising national timelines did not shift trials toward previously slow member states. Building research capacity in those countries requires investment in sites, investigators and patient recruitment, not only faster authorisation.

The findings also connect to the broader literature on regulation and the diffusion of pharmaceutical innovation. Price regulation and reference pricing delay launches in lower-price markets (Kyle 2007; Danzon et al. 2005; Maini and Pammolli 2023; Berndt and Cockburn 2014), and health technology assessment shapes launch sequences and prices in Europe (Büssgen and Stargardt 2023; Righetti 2026). My results show that the regulation of evidence generation also affects where innovation is developed, and that this location effect operates at the level of the region rather than the country. Because market size shapes innovation incentives (Acemoglu and Linn 2004; Dubois et al. 2015) and faster review shortens time to market (Downing et al. 2012), losing early-phase trials may have long-run effects on where new medicines are first developed and launched. The representation of European patients in trials also matters for the external validity of evidence used in European reimbursement decisions (Alsan et al. 2024).

The study has limitations. ClinicalTrials.gov covers industry multinational trials well, but its coverage of academic trials in Europe is incomplete, so my results apply to commercial development. Site lists record whether a country participates, not how many patients it enrols. The post-CTR period covers two and a half years of trial starts, so longer-run adjustments, including learning by sponsors and regulators, are not yet observable. The Directive-era delay measure comes from a systematic sample of the EU Clinical Trials Register and starts from

protocol entry rather than submission, so I interpret only its dispersion. With only five regions, conventional inference on region-level contrasts should be complemented by the placebo assignments and the triple difference I report. Finally, the EU-specific pre-trend means that the magnitude of the presence effect depends on how that trend is modelled. I therefore report a range of 3.9–11.5 percentage points for the baseline specifications, and the conclusion that the CTR did not reverse Europe's decline holds throughout.

Conclusion

Harmonising clinical trial authorisation in the EU removed cross-country differences in authorisation speed but did not make Europe more attractive for trials. After the CTR became mandatory, fewer multinational industry trials included any European site, particularly in early phases, and EU country-trial participation did not rise. Pre-CTR differences in national authorisation speed did not drive the allocation of trials across member states. Reforms that aim to restore Europe's attractiveness for clinical research should therefore focus on the speed and cost of entering Europe, especially for early-phase trials, rather than on further harmonisation alone.

Declarations

Funding The author received no specific funding for this work.

Conflict of interest The author declares no conflict of interest.

Data availability All data are publicly available from ClinicalTrials.gov, the EU Clinical Trials Register and the Clinical Trials Information System. The replication package, containing extraction and estimation code and the processed analysis files, is available from the author on request and will be deposited in a public repository upon publication.

Ethics approval Not applicable. The study uses publicly available trial-level registry data and involves no human participants or personal data.

Declaration of generative AI use During the preparation of this work, the author used Claude (Anthropic) to assist with statistical programming and language editing to improve readability. After using this tool, the author reviewed and edited the content as needed and takes full responsibility for the publication's content.

References

Acemoglu, D., and J. Linn. 2004. Market Size in Innovation: Theory and Evidence from the Pharmaceutical Industry. The Quarterly Journal of Economics 119 (3): 1049–1090. https://doi.org/10.1162/0033553041502144.

Alsan, M., M. Durvasula, H. Gupta, J. Schwartzstein, and H. Williams. 2024. Representation and Extrapolation: Evidence from Clinical Trials. The Quarterly Journal of Economics 139 (1): 575–635. https://doi.org/10.1093/qje/qjad036.

Berndt, E. R., and I. M. Cockburn. 2014. The Hidden Cost Of Low Prices: Limited Access To New Drugs In India. Health Affairs 33 (9): 1567–1575. https://doi.org/10.1377/hlthaff.2013.1307.

Borusyak, K., X. Jaravel, and J. Spiess. 2024. Revisiting Event-Study Designs: Robust and Efficient Estimation. Review of Economic Studies 91 (6): 3253–3285. https://doi.org/10.1093/restud/rdae007.

Budish, E., B. N. Roin, and H. Williams. 2015. Do Firms Underinvest in Long-Term Research? Evidence from Cancer Clinical Trials. American Economic Review 105 (7): 2044–2085. https://doi.org/10.1257/aer.20131176.

Büssgen, M., and T. Stargardt. 2023. Does health technology assessment compromise access to pharmaceuticals? The European Journal of Health Economics 24 (3): 437–451. https://doi.org/10.1007/s10198-022-01484-4.

Cockburn, I. M., J. O. Lanjouw, and M. Schankerman. 2016. Patents and the Global Diffusion of New Drugs. American Economic Review 106 (1): 136–164. https://doi.org/10.1257/aer.20141482.

Danzon, P. M., Y. R. Wang, and L. Wang. 2005. The impact of price regulation on the launch delay of new drugs—evidence from twenty-five major markets in the 1990s. Health Economics 14 (3): 269–292. https://doi.org/10.1002/hec.931.

De Paola, E., L. Del Bono, D. A. Dri, R. Maione, S. Petraglia, F. Galliccia, and G. Gori. 2025. Tracking a decade of phase I clinical trials in Italy: trends and insights from national and european registries amid regulatory change. Frontiers in Pharmacology 16: 1661186. https://doi.org/10.3389/fphar.2025.1661186.

Dhingra, A., G. Fiorentini, A. Fouda, and N. Moy. 2026. Tough versus soft regulations to promote generic medications in Italy. The European Journal of Health Economics 27 (2): 453–477. https://doi.org/10.1007/s10198-025-01826-y.

DiMasi, J. A., H. G. Grabowski, and R. W. Hansen. 2016. Innovation in the pharmaceutical industry: New estimates of R&D costs. Journal of Health Economics 47: 20–33. https://doi.org/10.1016/j.jhealeco.2016.01.012.

Downing, N. S., J. A. Aminawung, N. D. Shah, J. B. Braunstein, H. M. Krumholz, and J. S. Ross. 2012. Regulatory Review of Novel Therapeutics — Comparison of Three Regulatory Agencies. New England Journal of Medicine 366 (24): 2284–2293. https://doi.org/10.1056/NEJMsa1200223.

Draghi, M. 2024. The future of European competitiveness. Brussels: European Commission.

Dubois, P., O. de Mouzon, F. Scott-Morton, and P. Seabright. 2015. Market size and pharmaceutical innovation. The RAND Journal of Economics 46 (4): 844–871. https://doi.org/10.1111/1756-2171.12113.

EFPIA, Vaccines Europe, and IQVIA. 2024. Assessing the clinical trial ecosystem in Europe. Final report, August 2024. Brussels: European Federation of Pharmaceutical Industries and Associations.

European Commission. 2023a. Proposal for a Directive of the European Parliament and of the Council on the Union code relating to medicinal products for human use. COM(2023) 192 final. Brussels, 26 April 2023.

European Commission. 2023b. Proposal for a Regulation of the European Parliament and of the Council laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing rules governing the European Medicines Agency. COM(2023) 193 final. Brussels, 26 April 2023.

European Commission. 2025. Proposal for a Regulation of the European Parliament and of the Council on establishing a framework of measures for strengthening Union's biotechnology and biomanufacturing sectors particularly in the area of health (European Biotech Act). COM(2025) 1022 final, 2025/0406 (COD). Strasbourg, 16 December 2025.

European Medicines Agency. 2025. EU clinical trials during the 3-year CTR transition period. Amsterdam: Accelerating Clinical Trials in the EU (ACT EU).

European Medicines Agency. 2026. Monitoring the European clinical trials environment, January–March 2026. Amsterdam: Accelerating Clinical Trials in the EU (ACT EU).

European Parliament and Council of the European Union. 2001. Directive 2001/20/EC of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. Official Journal of the European Communities L 121: 34–44.

European Parliament and Council of the European Union. 2014. Regulation (EU) No 536/2014 of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC. Official Journal of the European Union L 158: 1–76.

Fabbro, E., U. Lamichhane, R. Sudbrak, L. Ogilvie, A. Vitiello, A. Zovi, and M. Sabbatucci. 2025. Investment gaps in antimicrobial resistance research & development: trends in Europe, 2017–2021. The European Journal of Health Economics 26 (9): 1597–1611. https://doi.org/10.1007/s10198-025-01796-1.

Getz, K. A., and R. A. Campo. 2017. Trends in clinical trial design complexity. Nature Reviews Drug Discovery 16 (5): 307–307. https://doi.org/10.1038/nrd.2017.65.

Glickman, S. W., J. G. McHutchison, E. D. Peterson, C. B. Cairns, R. A. Harrington, R. M. Califf, and K. A. Schulman. 2009. Ethical and Scientific Implications of the Globalization of Clinical Research. New England Journal of Medicine 360 (8): 816–823. https://doi.org/10.1056/NEJMsb0803929.

667 Hartmann, M. 2012. Impact assessment of the European Clinical Trials Directive: a longitudinal,
668 prospective, observational study analyzing patterns and trends in clinical drug trial
669 applications submitted since 2001 to regulatory agencies in six EU countries. Trials 13 (1):
670 53. https://doi.org/10.1186/1745-6215-13-53.

671 Hearn, J., and R. Sullivan. 2007. The impact of the 'Clinical Trials' directive on the cost and
672 conduct of non-commercial cancer trials in the UK. European Journal of Cancer 43 (1): 8–
673 13. https://doi.org/10.1016/j.ejca.2006.09.016.

674 Jia, J., G. Z. Jin, and L. Wagman. 2021. The Short-Run Effects of the General Data Protection
675 Regulation on Technology Venture Investment. Marketing Science 40 (4): 661–684.
676 https://doi.org/10.1287/mksc.2020.1271.

677 Kyle, M. K. 2007. Pharmaceutical Price Controls and Entry Strategies. Review of Economics and
678 Statistics 89 (1): 88–99. https://doi.org/10.1162/rest.89.1.88.

679 Lakdawalla, D. N. 2018. Economics of the Pharmaceutical Industry. Journal of Economic
680 Literature 56 (2): 397–449. https://doi.org/10.1257/jel.20161327.

681 Li, N., H.-Y. Huang, D.-W. Wu, Z.-M. Yang, J. Wang, J.-S. Wang, S.-H. Wang, H. Fang, Y. Yu,
682 Y. Bai, Z. Yan, Y. Cao, M. Jiang, Y.-F. Liu, K.-Y. Li, B.-H. Xu, Y. Sun, and J. He. 2019.
683 Changes in clinical trials of cancer drugs in mainland China over the decade 2009–18: a
684 systematic review. The Lancet Oncology 20 (11): e619–e626.
685 https://doi.org/10.1016/S1470-2045(19)30491-7.

686 Maini, L., and F. Pammolli. 2023. Reference Pricing as a Deterrent to Entry: Evidence from the
687 European Pharmaceutical Market. American Economic Journal: Microeconomics 15 (2):
688 345–383. https://doi.org/10.1257/mic.20210053.

Martin, L., M. Hutchens, C. Hawkins, and A. Radnov. 2017. How much do clinical trials cost? Nature Reviews Drug Discovery 16 (6): 381–382. https://doi.org/10.1038/nrd.2017.70.

Moore, T. J., H. Zhang, G. Anderson, and G. C. Alexander. 2018. Estimated Costs of Pivotal Trials for Novel Therapeutic Agents Approved by the US Food and Drug Administration, 2015-2016. JAMA Internal Medicine 178 (11): 1451–1457. https://doi.org/10.1001/jamainternmed.2018.3931.

Muniz, R. L., V. S. Pinto, F. de Assis Acúrcio, A. A. Guerra, and J. Alvares-Teodoro. 2026. Pricing of innovative medicines and advanced therapies worldwide: an scoping review. The European Journal of Health Economics. https://doi.org/10.1007/s10198-026-01962-z.

Panhuysen, J., E. Goetjes, M. Shaikh, and K. E. Blankart. 2026. The consequences of medicine shortages on healthcare utilization and care fragmentation. The European Journal of Health Economics. https://doi.org/10.1007/s10198-026-01953-0.

Patrick-Brown, T. D. J. H., J. Bourner, S. Kali, M. Trøseid, Y. Yazdanpanah, P. Olliaro, and I. C. Olsen. 2024. Experiences and challenges with the new European Clinical Trials Regulation. Trials 25 (1): 3. https://doi.org/10.1186/s13063-023-07869-x.

Rambachan, A., and J. Roth. 2023. A More Credible Approach to Parallel Trends. Review of Economic Studies 90 (5): 2555–2591. https://doi.org/10.1093/restud/rdad018.

Righetti, G. 2026. The Impact of Health Technology Assessment on Pharmaceutical Prices: Evidence from Germany. The European Journal of Health Economics. https://doi.org/10.1007/s10198-026-01924-5.

Roth, J., P. H. Sant'Anna, A. Bilinski, and J. Poe. 2023. What's trending in difference-in-differences? A synthesis of the recent econometrics literature. Journal of Econometrics 235 (2): 2218–2244. https://doi.org/10.1016/j.jeconom.2023.03.008.

Sertkaya, A., H.-H. Wong, A. Jessup, and T. Beleche. 2016. Key cost drivers of pharmaceutical clinical trials in the United States. Clinical Trials 13 (2): 117–126. https://doi.org/10.1177/1740774515625964.

Thiers, F. A., A. J. Sinskey, and E. R. Berndt. 2008. Trends in the globalization of clinical trials. Nature Reviews Drug Discovery 7 (1): 13–14. https://doi.org/10.1038/nrd2441.

Wouters, O. J., M. McKee, and J. Luyten. 2020. Estimated Research and Development Investment Needed to Bring a New Medicine to Market, 2009-2018. JAMA 323 (9): 844–853. https://doi.org/10.1001/jama.2020.1166.

Yao, L., and M. Liu. 2025. Strategic behavior and entry deterrence by branded drug firms: the case of authorized generic drugs. The European Journal of Health Economics 26 (4): 561–575. https://doi.org/10.1007/s10198-024-01721-y.

Yom-Tov, E., and Y. Ofran. 2022. Clinical trials are moving to countries with fewer data protections. medRxiv. https://doi.org/10.1101/2022.07.09.22277461.

Appendix

Table A1 Variable definitions

Variable	Definition	Source
EU presence	Indicator that the trial lists at least one site in an EU/EEA country	ClinicalTrials.gov
Log EU member states	Log number of distinct countries of a region in which the trial lists sites, for regions with at least one site	ClinicalTrials.gov
EU country inclusion	Indicator that a given country hosts at least one site of the trial	ClinicalTrials.gov
Post	Trial start from July 2023 onward	ClinicalTrials.gov
Transition	Trial start between January 2022 and June 2023	ClinicalTrials.gov
China site	Indicator that the trial lists at least one site in mainland China	ClinicalTrials.gov
Sponsor China exposure	Lead sponsor's share of 2013–2019 industry trials with a site in China, grouped as zero, up to 10 per cent, above 10 per cent, or no trials before 2020	ClinicalTrials.gov
Top-25 sponsor	Lead sponsor among the 25 industry sponsors with most trials starting in 2013–2019	ClinicalTrials.gov
Oncology	Condition text contains cancer, carcinoma, tumour, lymphoma, leukaemia, myeloma, melanoma, sarcoma, glioma, neoplasm, malignant, NSCLC, metastatic, myelodysplastic, blastoma or mesothelioma	ClinicalTrials.gov
CTR authorisation	CTIS number without an earlier EudraCT number among secondary identifiers	ClinicalTrials.gov
Pre-CTR delay deviation	Country mean of within-trial deviations of log days from protocol entry to the later of competent authority and ethics decisions, 2016–2021	EU Clinical Trials Register
CTR delay deviation	Country mean of within-trial deviations of log days from submission to first national decision	CTIS

Table A2 National authorisation times by member state

Country	Directive era deviation (log)	Directive median days	Directive decisions	CTR era deviation (log)	CTR median days	CTR decisions
Iceland	−0.564	29	5	0.440	268	4
Cyprus	−0.499	21	1	−0.005	128	5
Estonia	−0.474	42	75	0.069	119	87
Greece	−0.429	49	163	0.034	118	598
Slovenia	−0.379	50	37	0.090	122	44
Spain	−0.276	62	613	−0.036	117	2359

Country	Directive era deviation (log)	Directive median days	Directive decisions	CTR era deviation (log)	CTR median days	CTR decisions
Poland	−0.209	59	578	0.013	120	1610
Italy	−0.189	77	100	−0.020	117	1835
Romania	−0.185	29	6	0.054	123	555
Finland	−0.163	56	154	0.062	117	229
Hungary	−0.160	57	477	0.007	119	789
Lithuania	−0.146	54	102	0.053	118	138
Latvia	−0.109	68	114	0.034	118	117
Slovakia	−0.065	62	191	0.025	117	305
Austria	−0.056	66	262	0.020	122	519
Bulgaria	−0.015	70	336	0.010	120	597
France	0.009	75	391	−0.012	118	1846
Belgium	0.010	74	483	−0.017	117	1064
Denmark	0.035	70	277	−0.008	115	585
Czechia	0.040	77	417	0.013	118	881
Sweden	0.068	71	211	0.002	118	424
Norway	0.217	106	63	0.064	118	224
Netherlands	0.227	98	365	0.011	118	931
Ireland	0.261	91	67	0.073	121	218
Portugal	0.262	107	147	0.050	118	449
Germany	0.373	114	843	−0.029	117	1936
Croatia	—	—	—	0.052	122	172
Luxembourg	—	—	—	0.008	119	1

Notes Deviations are country means of within-trial deviations of log decision time. Medians are in days. Directive-era statistics use protocols entered in 2016–2021 in the sampled EU Clinical Trials Register records. CTR-era statistics use multinational pharmaceutical-company trials initially authorised in CTIS. Cyprus, Iceland and Romania have fewer than 30 Directive-era decisions and are excluded from the reallocation analysis.

Table A3 Member states per multinational commercial trial in European registries

Registry	Year	Commercial trials	Share multinational	Member states per multinational trial
EUCTR (Directive)	2016	705	0.467	5.06
EUCTR (Directive)	2017	671	0.474	5.31
EUCTR (Directive)	2018	656	0.450	5.12
EUCTR (Directive)	2019	659	0.387	5.17
EUCTR (Directive)	2020	690	0.358	5.02
EUCTR (Directive)	2021	601	0.331	4.34
CTIS (CTR)	2023	1,467	0.579	6.17

Registry	Year	Commercial trials	Share multinational	Member states per multinational trial
CTIS (CTR)	2024	1,745	0.500	6.27
CTIS (CTR)	2025	1,224	0.618	6.02

Notes EU Clinical Trials Register rows use commercial-sponsor trials by year of first protocol entry in the sampled records. CTIS rows use trials with a pharmaceutical company sponsor that were not transitioned from the Directive, by year of the CTIS number.

Table A4 Placebo assignment of treatment to each region

Region treated	Presence	Log member states
EU/EEA	−0.115*** (0.010)	0.053*** (0.016)
Latin America	0.072*** (0.010)	−0.044** (0.021)
Asia-Pacific	0.077*** (0.011)	0.140*** (0.017)
Other Europe	−0.029*** (0.010)	−0.056*** (0.015)
North America	−0.005 (0.009)	−0.094*** (0.013)

Notes Each row reassigns the Post and Transition indicators to the named region and re-estimates the trial × region specifications of Table 2 Panel A. Standard errors clustered by trial in parentheses. * p<0.10, ** p<0.05, *** p<0.01.

Table A5 Event-study coefficients

Start year	EU presence	Log EU member states	EU country inclusion
2013	−0.003 (0.023)	0.046 (0.040)	0.007 (0.017)
2014	0.017 (0.021)	0.029 (0.035)	0.011 (0.012)
2015	0.032 (0.020)	0.024 (0.032)	0.012 (0.012)
2016	0.047 (0.020)	−0.008 (0.034)	0.013 (0.008)
2017	0.021 (0.018)	−0.009 (0.031)	0.003 (0.008)
2018	−0.006 (0.018)	−0.059 (0.030)	−0.009 (0.006)
2020	−0.054 (0.019)	−0.041 (0.030)	−0.018 (0.009)
2021	−0.071 (0.018)	−0.015 (0.028)	−0.019 (0.006)
2022	−0.043 (0.018)	−0.008 (0.030)	−0.021 (0.007)
2023	−0.083 (0.019)	−0.061 (0.031)	−0.037 (0.009)
2024	−0.123 (0.019)	0.090 (0.031)	−0.034 (0.015)
2025	−0.133 (0.019)	0.033 (0.030)	−0.032 (0.014)
2019	reference	reference	reference

Notes Coefficients on EU × start year relative to 2019 from the specifications in Table 2. Standard errors in parentheses are clustered by trial for the first two columns and by country for the third.

Table A6 Additional robustness checks

Check	EU presence	Log EU member states
Joint Wald test of 2013–2018 event-study coefficients (χ^2, 6 df)	10.72 (p = 0.097)	11.58 (p = 0.072)
Dropping Asia-Pacific	−0.102*** (0.010)	0.094*** (0.016)
EU/EEA versus Asia-Pacific only	−0.153*** (0.014)	−0.135*** (0.024)
Dropping Latin America	−0.103*** (0.010)	0.047*** (0.016)
EU/EEA versus Latin America only	−0.149*** (0.013)	0.035 (0.029)
Dropping other Europe	−0.130*** (0.011)	0.039** (0.017)
EU/EEA versus other Europe only	−0.069*** (0.012)	0.061*** (0.020)
Dropping North America	−0.124*** (0.011)	0.003 (0.017)
EU/EEA versus North America only	−0.088*** (0.012)	0.111*** (0.019)
Trimming bound (baseline presence loss)	—	−0.102*** (0.015)
Trimming bound (trend-adjusted presence loss)	—	0.006 (0.016)
Randomisation-inference p-value across five regions	0.20	0.40
Relative-magnitude breakdown value, reference 2019	0.66	—
Relative-magnitude breakdown value, reference 2022	0.80	—

Notes Coefficients on EU × Post from the baseline trial × region specifications of Table 2 Panel A unless stated otherwise. Dropping a region removes it from the comparison group, and the pairwise rows compare the EU/EEA with one region only. Trimming bounds drop from the pre-period the EU trials with the fewest member states, in proportion to the baseline (14.6 per cent) or trend-adjusted (5.0 per cent) presence loss. The randomisation-inference p-value is the rank of the EU/EEA estimate among the five placebo assignments in Appendix Table A4. The relative-magnitude breakdown value is the ratio of post-period year-to-year deviations from parallel trends to the largest 2013–2019 year-to-year change at which the average 2024–2025 presence

754 effect stops being significant (Rambachan and Roth 2023). Standard errors clustered by trial in
755 parentheses. * $p<0.10$, ** $p<0.05$, *** $p<0.01$.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementaryfile.docx