Hurdles for the Delivery of Clinical Trials: Insights From the REMAP-CAP Trial in Europe

A data-driven analysis of ethical, administrative, regulatory, and logistical (EARL) delays

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netherlands centre for one health

ZonMw

Transparency declaration

- No conflict of interests

"Is the Clinical Trials Enterprise Broken? And How Can It Be Fixed?"

Bibbins-Domingo et al. Introducing the JAMA Summit. April 2024


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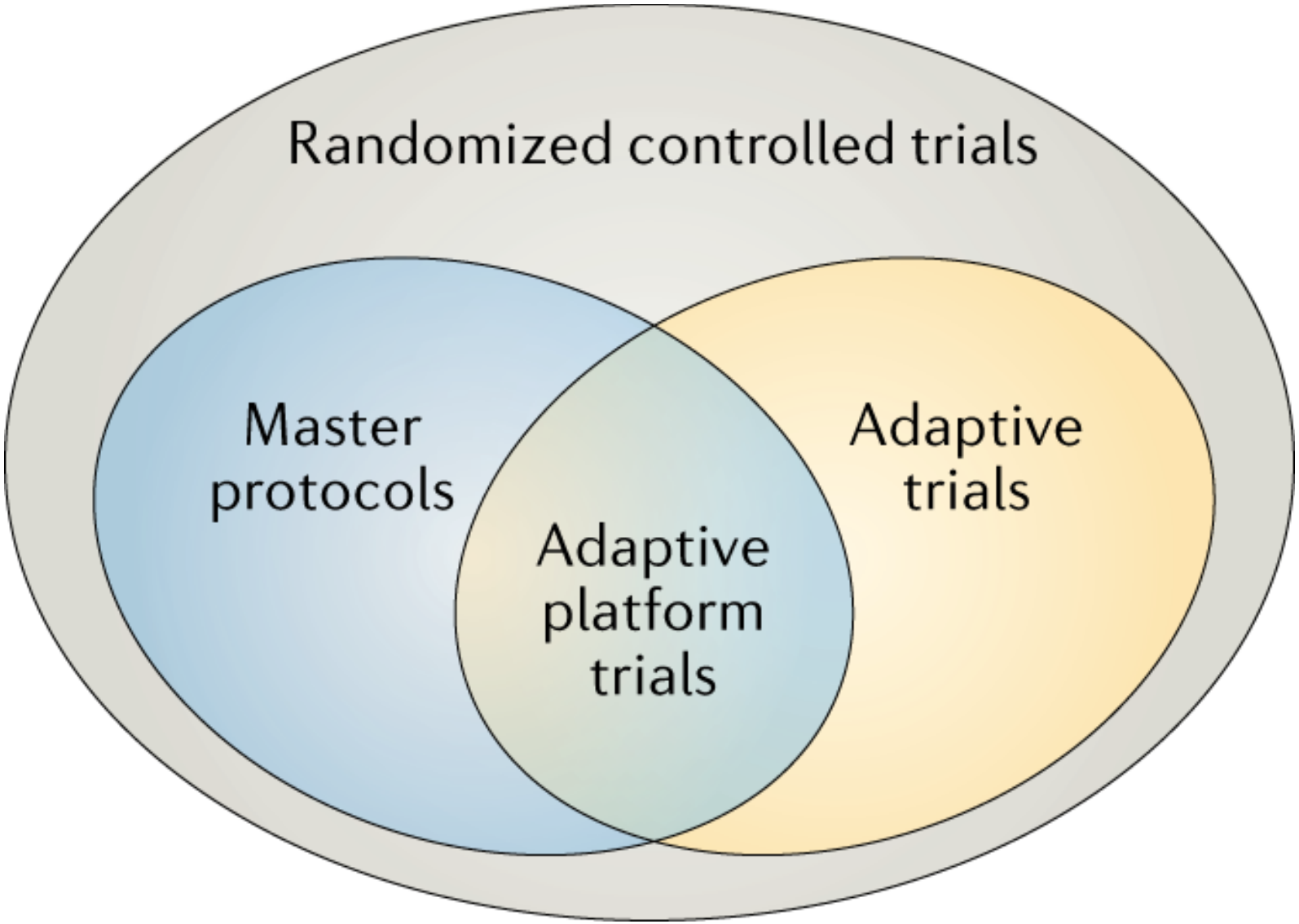
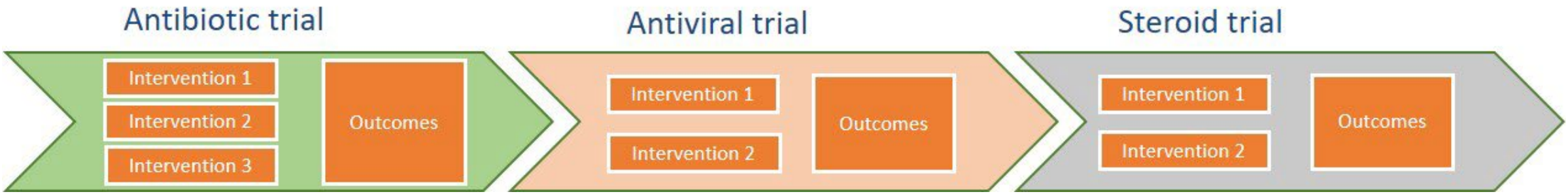
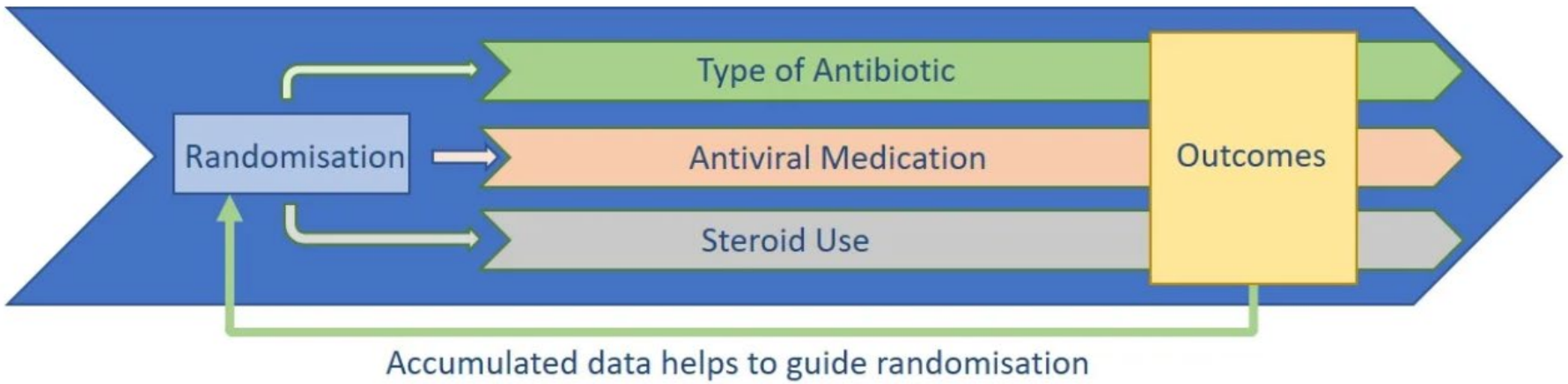


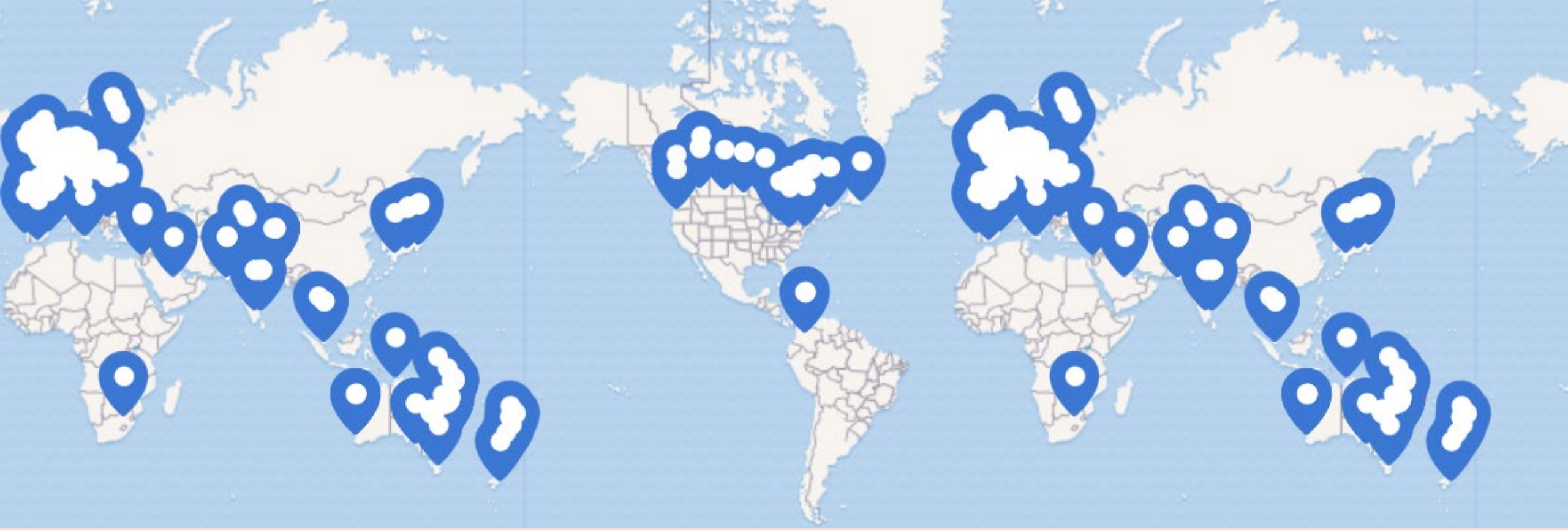
Adaptive Platform Trials Coalition. Nat Rev Drug Discov. 2019

Traditional design: sequential trials



Multifactorial platform trial





REMAP-CAP Global

Randomised **E**mbedded **M**ultifactorial **A**daptive **P**latform trial for **C**ommunity-**A**cquired **P**neumonia

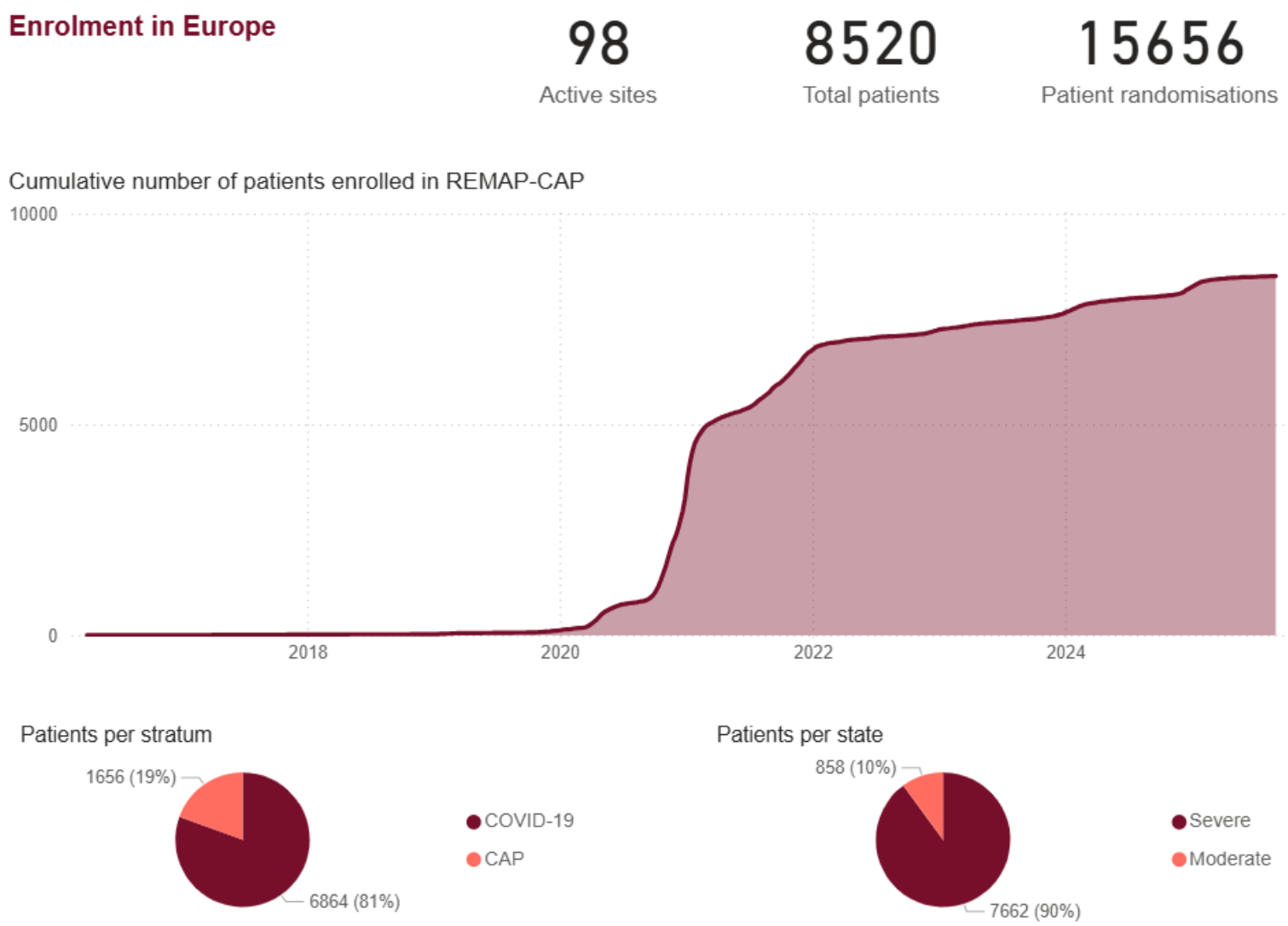
www.remapcap.org

REMAP-CAP Europe

Randomised **E**mbedded **M**ultifactorial **A**daptive **P**latform trial for **C**ommunity-**A**cquired **P**neumonia

www.remapcap.eu

www.ecraid.eu/study/remap-cap



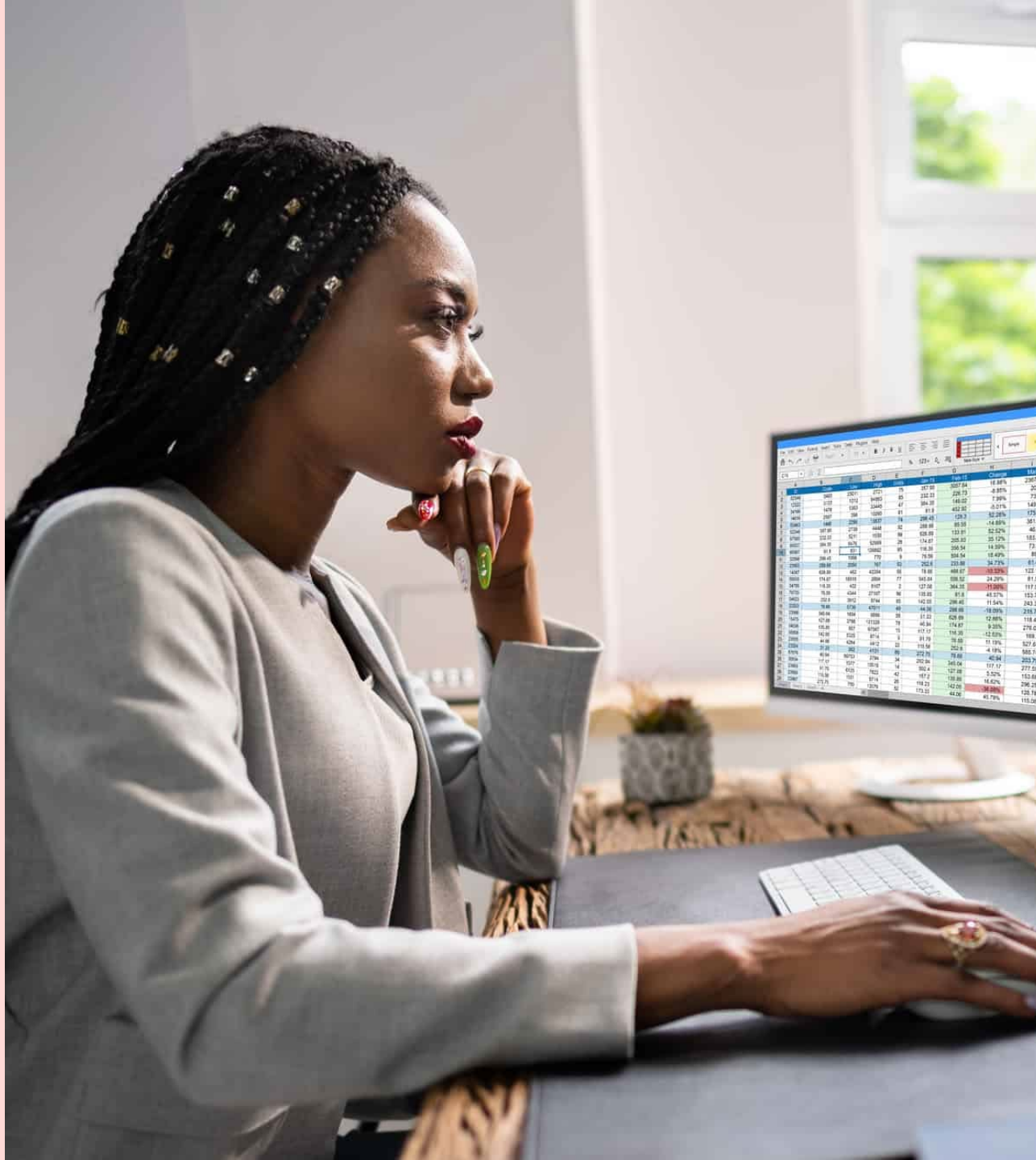
ecraid

Findings thus far

Conclusion	Result	Publications
Corticosteroids	Benefit	JAMA 2020;324(13):1317-1329
Lopinavir/ritonavir Hydroxychloroquine	Likely harm Harm	ICM 2021 Aug;47(8):867-886
Tocilizumab Sarilumab Anakinra Interferon beta-1a	Benefit Benefit Futile Operationally futile	NEJM 2021;384(16):1491-1502
Heparin – moderate	Benefit	NEJM 2021;385(9):790-802
Heparin – severe	Futile	NEJM 2021;385(9):777-789
Convalescent plasma	Futile	JAMA 2021;326(17):1690-1702
Aspirin	Futile	JAMA 2022;327(13):1247–1259
ACEi and ARB	Likely harm	JAMA 2023;329(14):1183–1196
Long term outcomes	Consistent	JAMA 2023;329(1):39-51
continued TAC - severe	Likely harm	ICM 2023 May 31
Vitamin C	Likely harm	JAMA 2023;330(18):1745-1759
Simvastatin	Likely small benefit	NEJM 2023;389:2341-2354
Fixed dose hydrocortisone	Futile (possible harm)	ICM 2025; 51:665–680

→ Which does not mean there were no challenges (!)

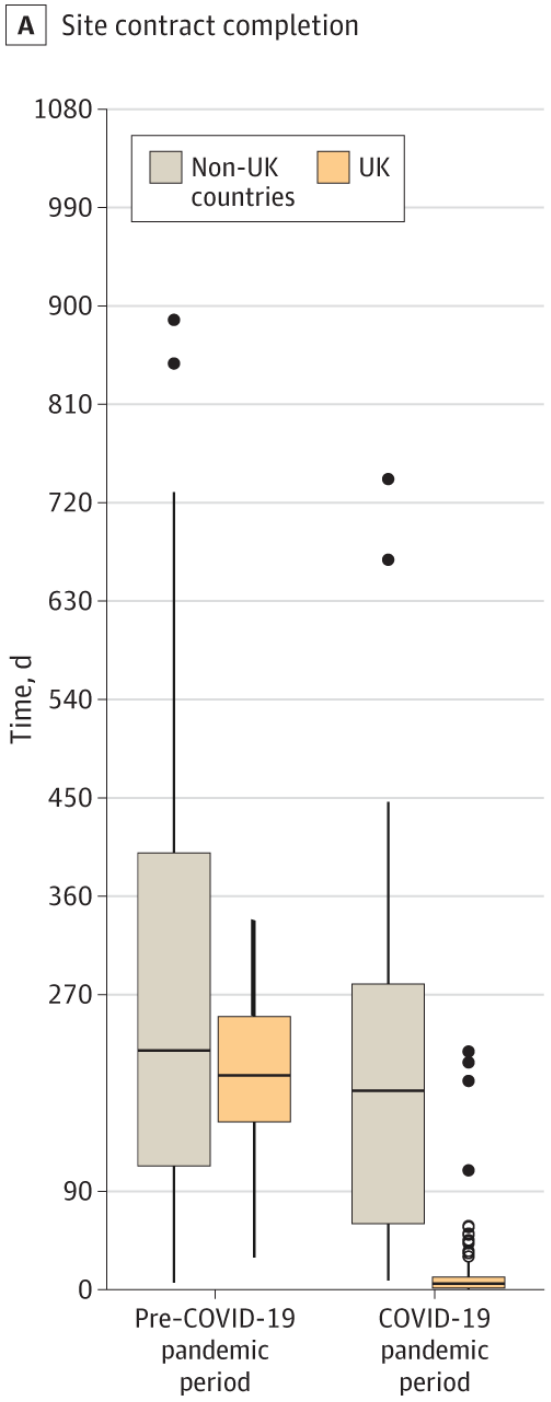
If we want innovation to reach patients faster, we need to treat hurdles in clinical trial delivery as a scientific problem; and solve it with the same rigor



Before sites can enroll, contracts must be signed

N = 257 study sites with fully signed first contract

UK had much larger reduction in site contract completion times than non-UK countries



	Prepandemic period median (IQR)	COVID-19 Pandemic period median (IQR)	Difference (95% CI)
Non-UK countries	224 days(119 to 412)	183 days (62 to 91)	-18% (-43% to 52%)
UK	196 days (154-250)	5 days (1 to 11)	-97% (95% to 98%)

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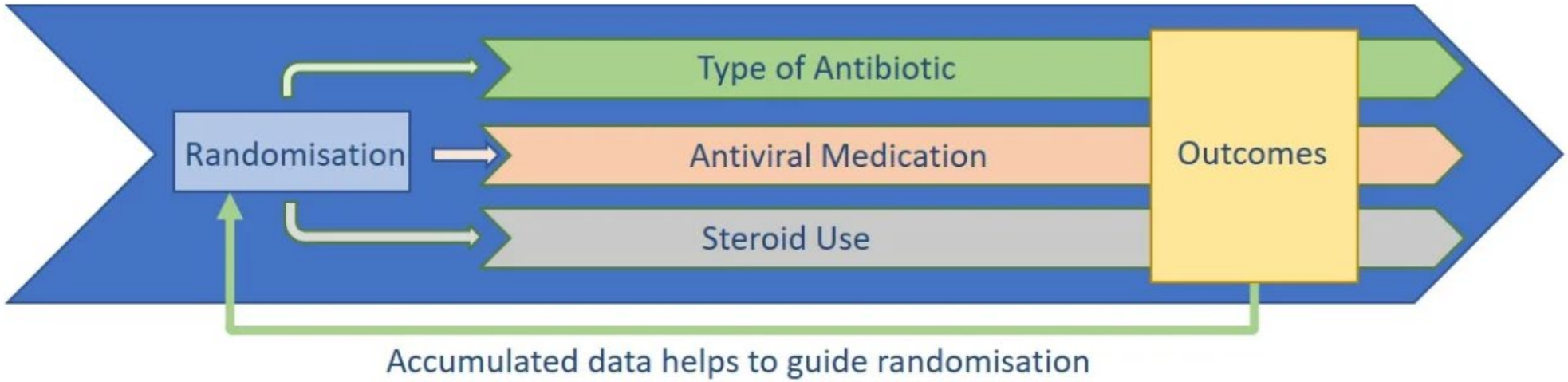
Analysis of time to protocol approval; making use of APT design

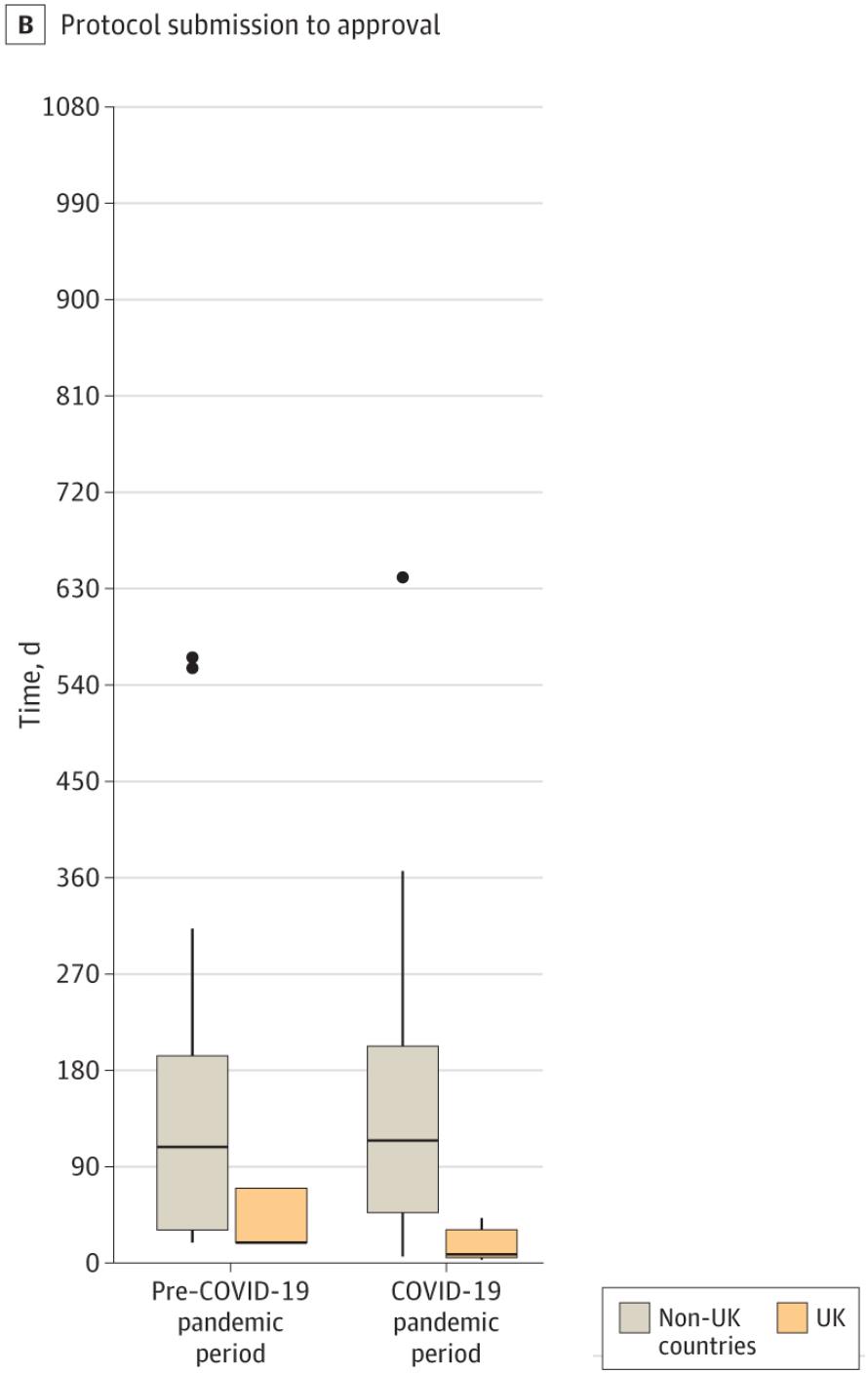


Time to protocol approval

- Primary submission of the trial occurred in 19 countries

- 44 interventions in 16 domains → n=232 approved protocol submissions for analysis

	Number of submissions	Median (range)	Median difference (95% CI)
Pre-COVID-19 pandemic period			
UK	7	19 days (19 to 70)	90 days (38 to 142)
Non-UK countries	64	109 days (19 to 567)	
COVID-19 pandemic period			
UK	17	8 days (3 to 42)	107 days (76 to 123)
Non-UK	144	115 days (6 to 642)	



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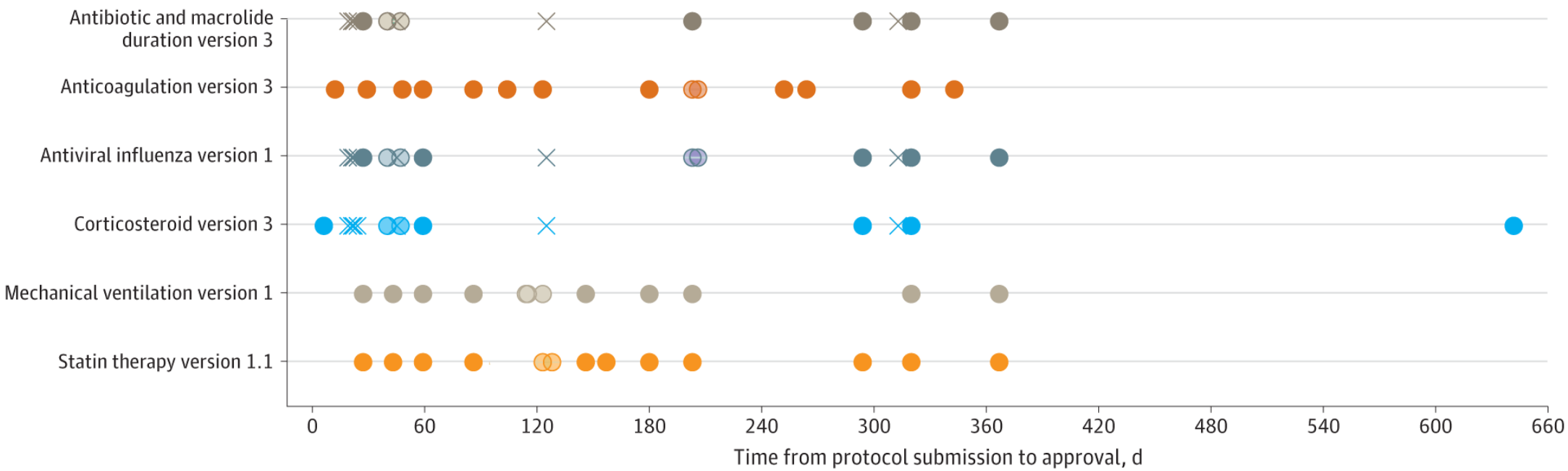
Variability in time to approval of identical protocols across countries



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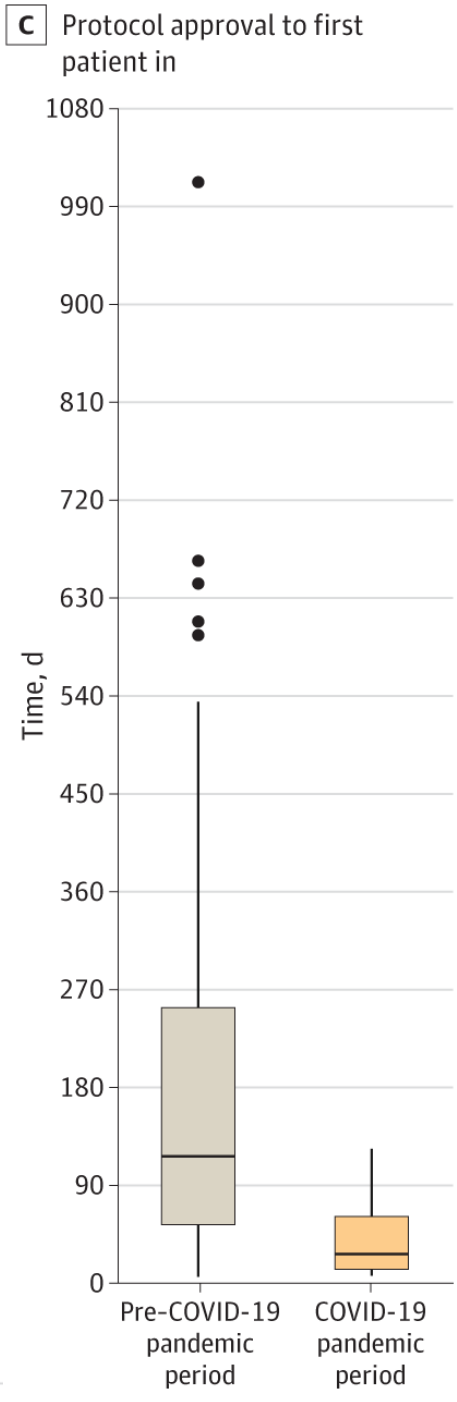
Time between approval and first patient in (FPI) during COVID-19 pandemic

Overall median 89 days (range 5 to 1014)

Non-UK countries median 116 days (range 5 to 1014)
UK median 26 days (range 6 to 123)

On average, first patient randomization was **3 months faster** in the UK compared with non-UK countries (median difference 90 days 95% CI 42 to 142 days)



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Secondary label text:
REMAP-CAP trial. EudraCT: 2015-002340-14.
Sponsor: University Medical Center Utrecht.
PO BOX 85500, 3504 GA Utrecht, The Netherlands.
eu.remapcap@umcutrecht.nl
+31 (0) 6 277 444 77
Acetylsalicylic acid 80 mg.
1 package with 30 dispersible tablets.
Directions for use: for oral use, see Study Administration Guide.
Batch No.:_____.
Investigator:_____.
Site:_____.
Trial Subject ID:_____.
For clinical trial use only.
Store < 25 °C.
Store contents in outer package.
Expiry date:_____.
Keep out of reach of children.

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Recent important step forward

- As of January 2022: major change in legislation for clinical trials with medicinal products in EU since **Clinical Trial Regulation No 536/2014**
  - Centralized regulatory submission across countries via a single portal (CTIS)

→ Aim: more harmonized landscape across EU countries

→ Challenging: new site and new PI = substantial modification

Conclusions

EARL processes are a substantial bottleneck in trial initiation, slowing down patient access to new therapies. We identified:

1. Slow negotiations on study site contracts
2. Large variability between countries in time to approval of identical protocols (*nb., under previous EU legislation*)
3. Slow start of patient enrollment in non-UK countries despite urgent pandemic situation

- United Kingdom should serve as a positive example:
  - fast-track, simplified, non-adaptable contracts
  - Relatively fast time to approval
  - Shorter time to FPI

Lessons we have learned & recommendations

1. ✅ Ensure trial applications are complete and clear
2. ✅ Ensure alignment with each country's requirements during applications
3. 🌐 Collaborate closely with experienced national researchers
4. 💡 Highlight where innovative designs differ from traditional trial features
5. 📚 Be aware of specific EARL challenges in APTs
    - E.g. Operational and modular protocol complexity, regulatory acceptance and understanding, variability in domains, interventions, and participant information across sites, unusual legal aspects such as no fixed sample size, perpetual design
6. ⚖️ Don't underestimate legal and contracting processes; invest time early
7. 🤝 **Share your lessons learned so others can benefit**

A thought on Embedded randomized clinical trials

If trials are only embedded in clinical care but not in the institutional machinery that supports research, they'll still be slowed down

We could think of embedded trials as having two layers: embedding in *care delivery* and embedding in *system delivery*

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ICNARC
Paul Mouncey
Prof. dr. David Harrison

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Learn → Improve

We must study our timelines and delays before we can make trials faster and better.

Thank you for your attention

For more information on this work:
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doi:10.1001/jamanetworkopen.2025.18503