CEVAC | CENTRUM VOOR VACCINOLOGIE

Workshop 2: Impact of the EU-CTR

"Perspective from a clinical investigator"

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Immunity for Health: Vaccines & Immunotherapy

The impact of EU-CTR:

An emergency signal from 2 large academic vaccine trial centers in Belgium

Final report – dd. 22 May 2024*

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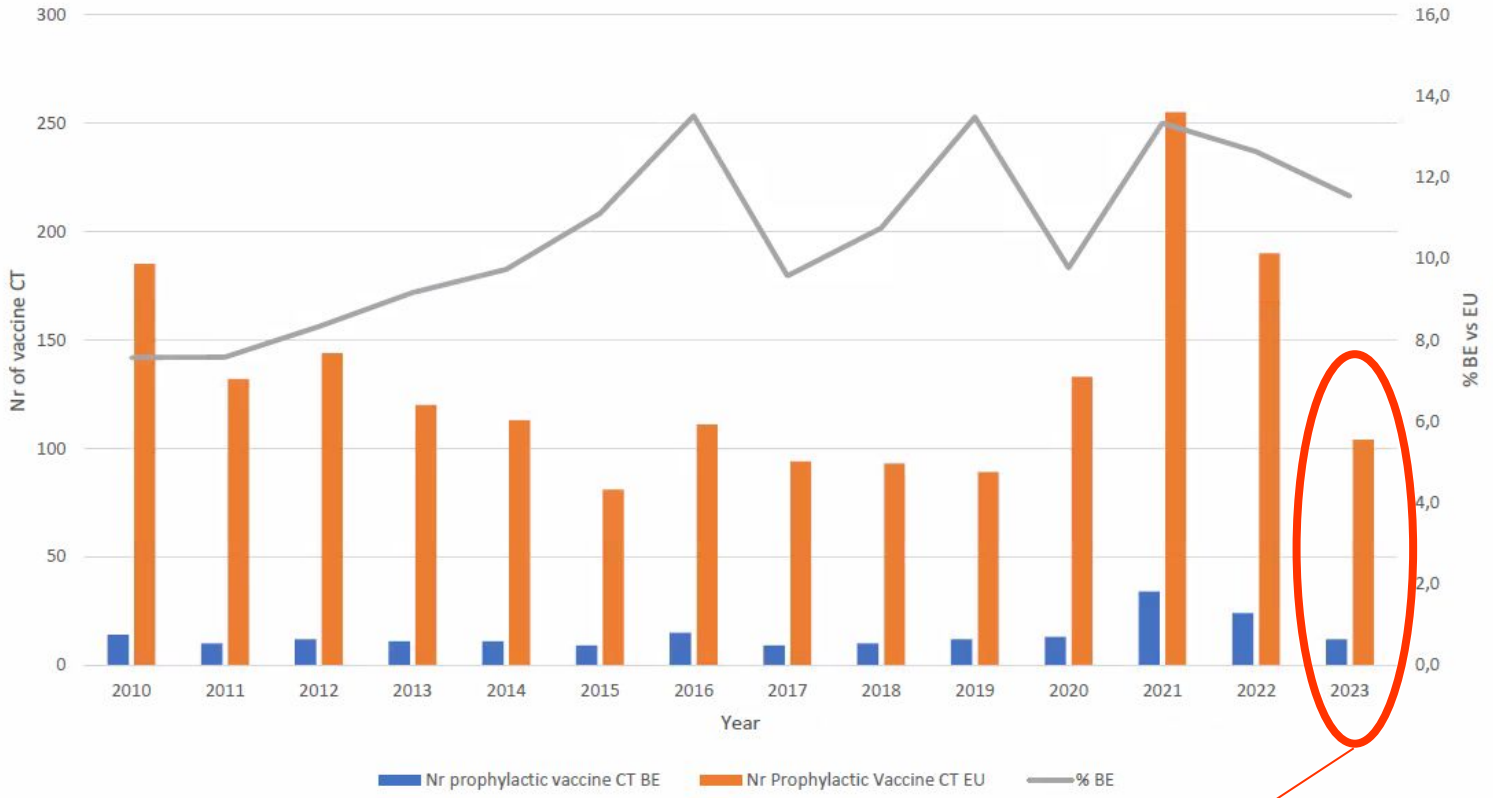
* corrections made on 05JUN2024

Number of prophylactic vaccine clinical trials in Belgium vs Europe (2010 – 2023)

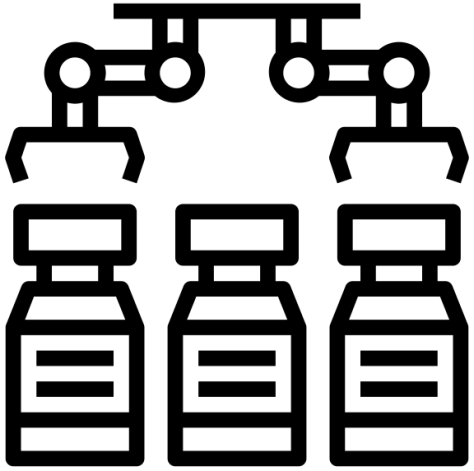


Note: UK data until 2020

Real decline (due to EU-CTR) vs return to “pre-COVID normal?”

Is there a real decline in clinical (vaccine) trial activity in Belgium since implementation of EU-CTR?

We expected a boost in activity….



Created by Studio 365
from Noun Project

Rich vaccine development pipeline

Created by kholifah
from Noun Project

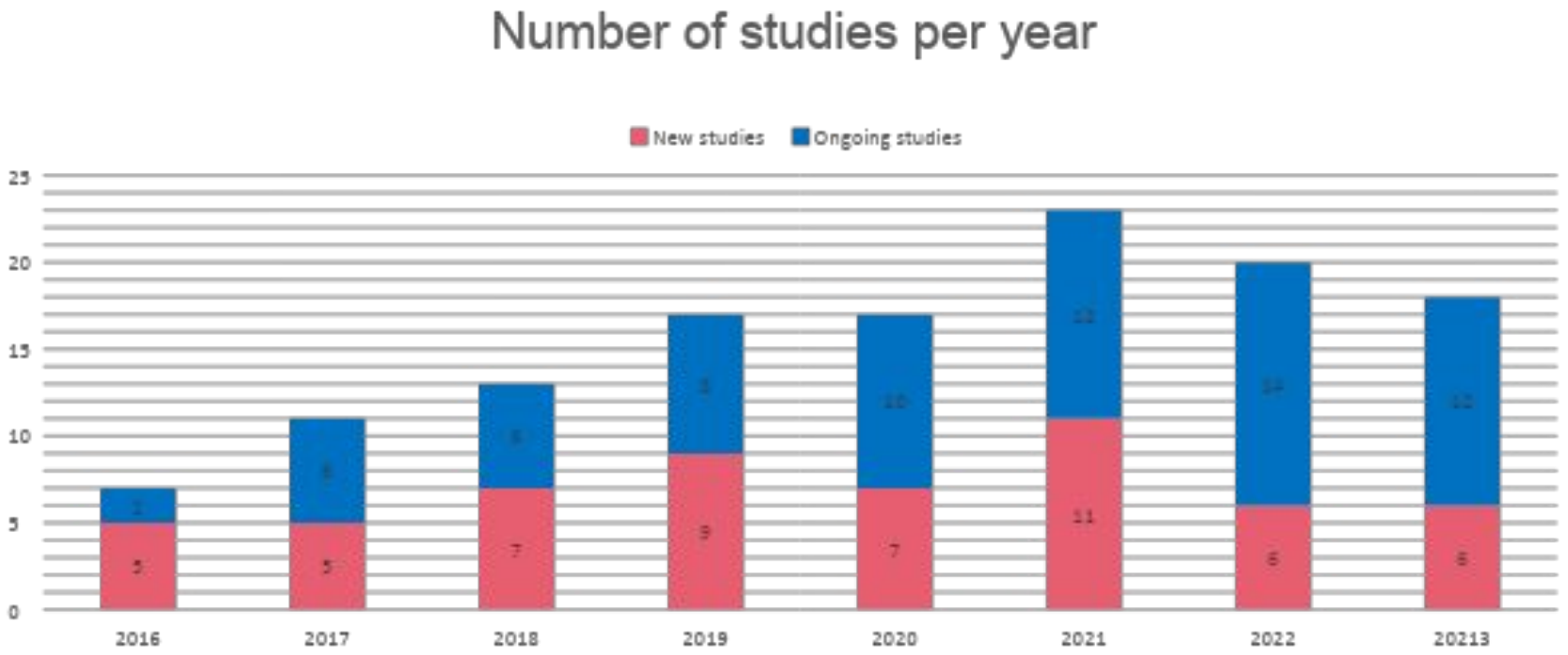
Many feasibility questionnaires

Created by popcornarts
from Noun Project

Positive feedback on performance (quality, budget, enrolment, …)

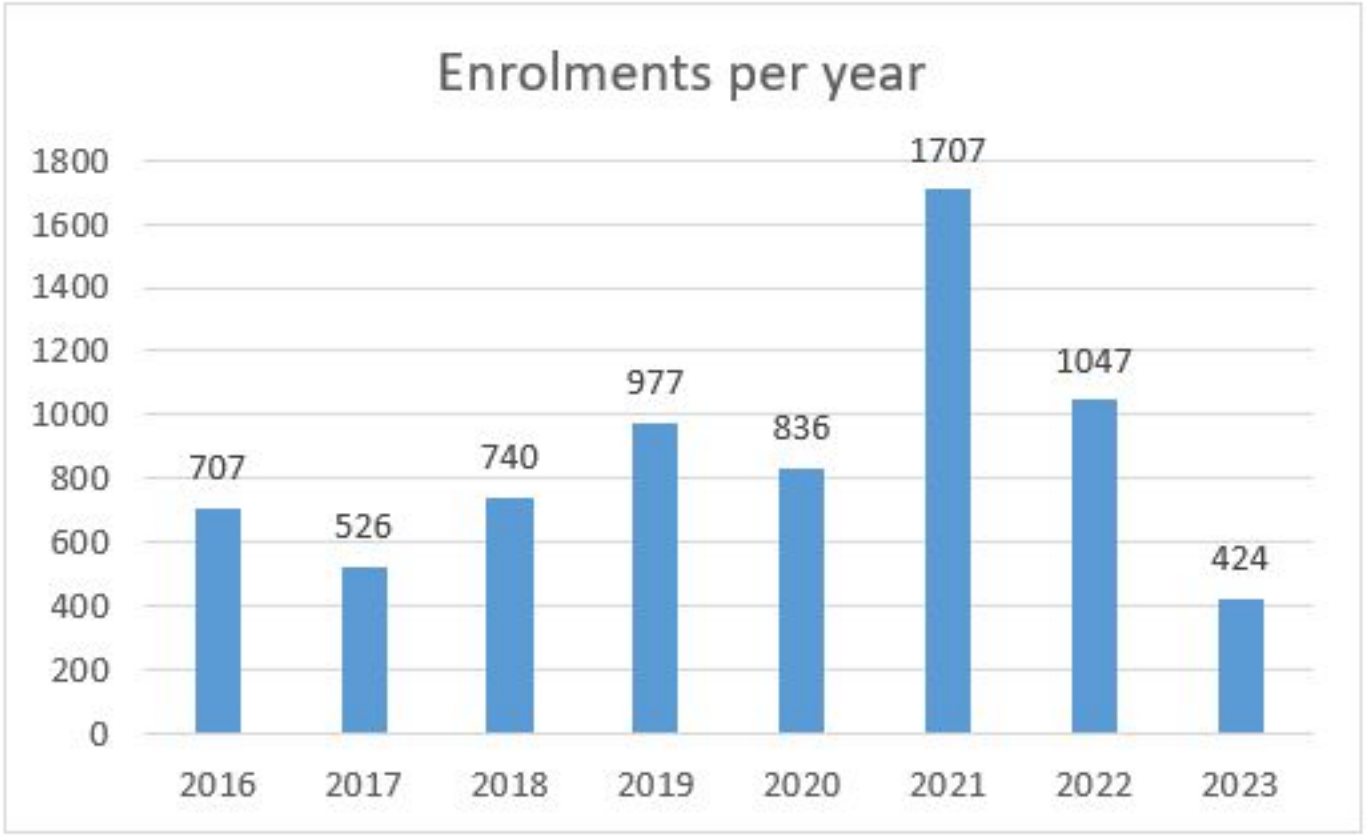
Is there a real decline in clinical (vaccine) trial activity in Belgium since implementation of EU-CTR?

The CEVAC experience: # studies initiated/ongoing from 2016 to 2023



Is there a real decline in clinical (vaccine) trial activity in Belgium since implementation of EU-CTR?

The CEVAC experience: # newly enrolled participants from 2016 to 2023



Not only the number of CTAs signed is an important KPI to monitor, but also the number of enrolled subjects/site/study.

Is there a real decline in clinical (vaccine) trial activity in Belgium since implementation of EU-CTR?

The CEVAC experience: feedback from sponsors

"Unfortunately we have to inform you that the strategical decision was taken not to start the trial in Belgium/EU because of the slow EU-CTR approval timelines"

Once selected as a country and as a site with an enrolment target of e.g. 120 participants:

"We are sorry to inform you that we have only managed to protect an enrolment target of 35 subjects for your site because of the slow start-up process in Europe"

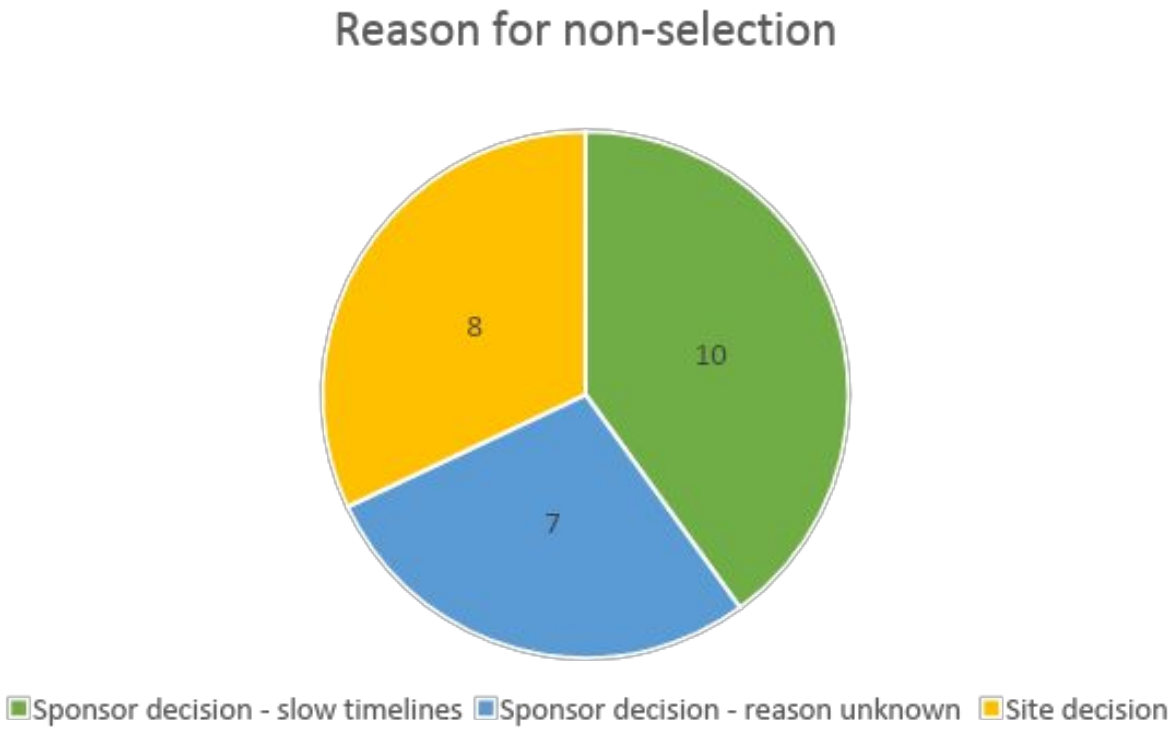
"We are sorry to inform you that the start-up activities at your site will be halted immediately as the enrolment target has been reached following rapid enrolment in other regions of the world (USA). We wish to thank you and your team for all the efforts"

 This has almost become the standard (for multinational studies)

Is there a real decline in clinical (vaccine) trial activity in Belgium since implementation of EU-CTR?

The CEVAC and CEV experience:

Analysis of 25 studies for which both sites were not selected to participate in 2023



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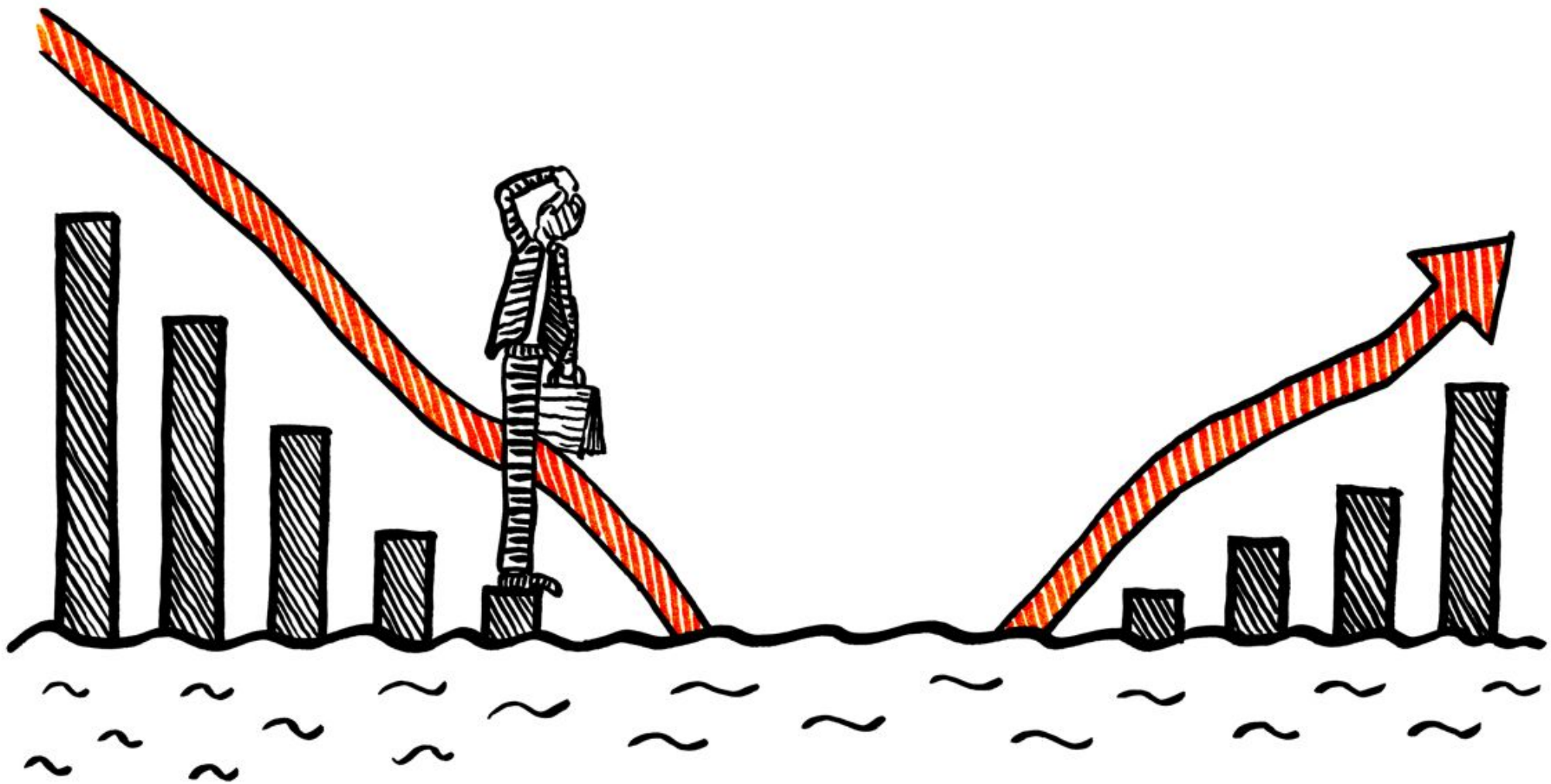
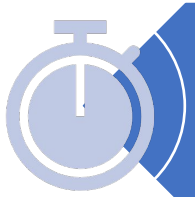


How can we minimize the negative impact of EU-CTR and reverse the trend?



Timelines

Flexibility in CTIS

Requests for information (RFI's)

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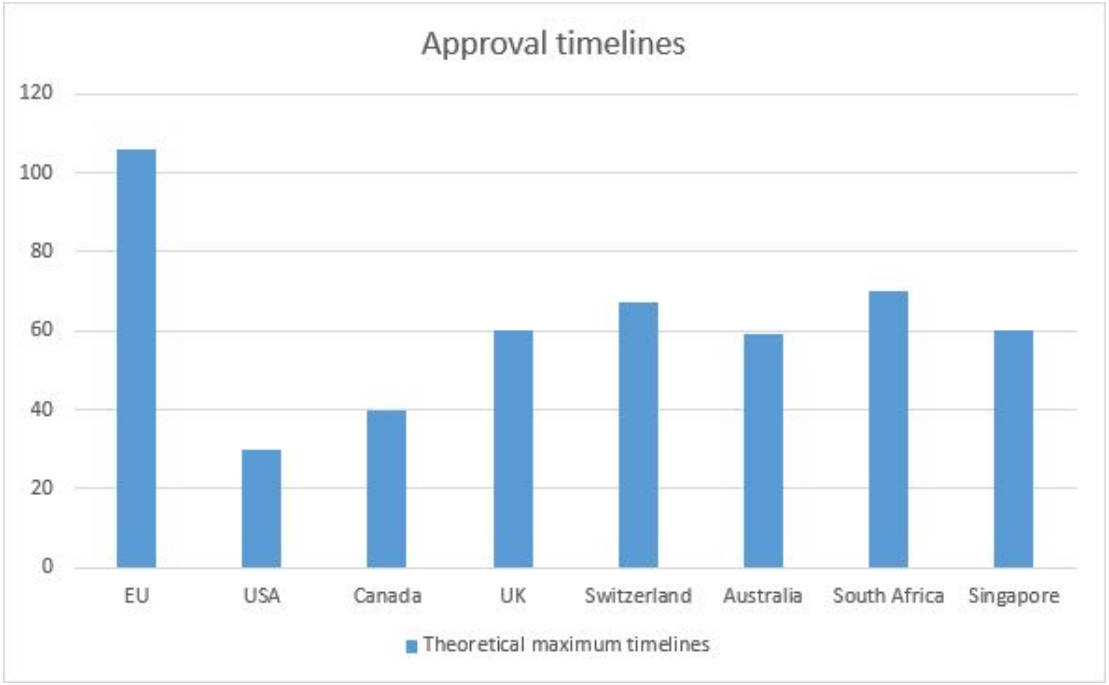
Timelines

- The streamlined process across EU countries is certainly a step forward
- Key concern is the length of the review process
- Pre-CTR Belgium was part of the ‘premier league’
- Comparison of EU-region with non-EU individual countries
- No obligation to start up studies in EU ⟷ USA
- Shortening timelines is not feasible in the short term



EU (region)	Non EU individual countries
Approval system	Some have a notification system
Long timelines, but defined and more or less predictable	Shorter timelines, but some with ‘pausing system’
Many stakeholders from different countries, a lot of coordination to take a decision	Decisions can be made at country-level

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Expedited timelines

- Currently expedited review for **mononational phase 1 trials** (66 days)
  - To be expanded to mononational phase 2 trials?
  - *FAHMP will evaluate the feasibility after the end of the transition period from CTD to CTR*

- **Trend of conducting multinational studies in a single EU country** (RMS=MSC) to expedite review and start-up. Large MS in particular take advantage of this (recruitment capacity, access to larger market, …) competition between MS cannot be avoided

RMS: reporting member state
MSC: member state concerned

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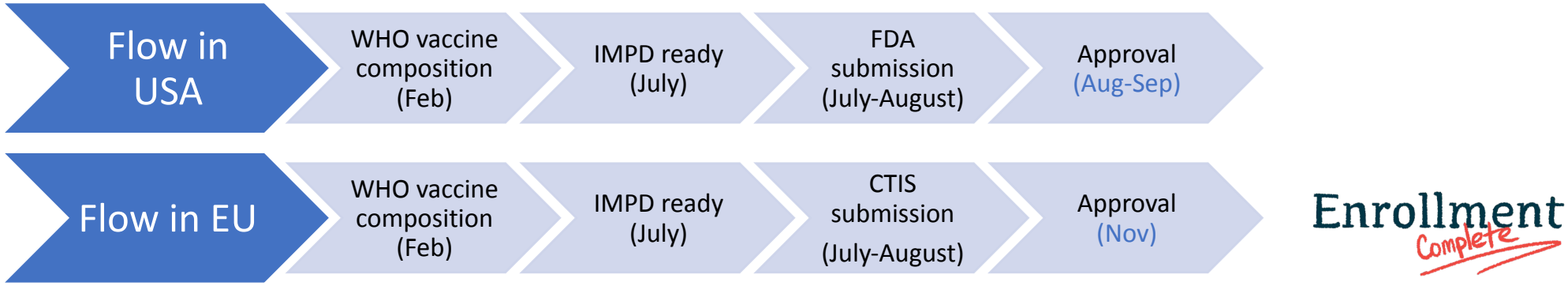
Flexibility in CTIS (1/2)

- Currently, deviations from the established CTIS workflow are not easily accommodated
- Need to adapt to specific trial needs
- Case 1: Phase 3 multinational influenza vaccine trials: seasonal and competitive recruitment



- Solutions?
  - 2-step submission: allow the IMPD to be submitted in a second phase, along with the RFI
  - Expedited timelines: certain MS are willing to accommodate this (e.g. DE, ES, BE)

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Flexibility in CTIS (2/2)

- Case 2: RSV vaccine trial with duration of 3 years
  - Initial protocol: 3 groups:
    - 1 vaccination (season 1) vs annual vaccination (S1, S2, S3) vs placebo
  - Post-season 2: no added value of annual revaccination
  - Pre-season 3:
    - substantial amendment submitted to omit annual vaccination S3 □ 106 days review timelines
    - No timely approval of the substantial amendment □ numerous participants received dose 3
  - Solution?
    - If continuing the study under the current protocol version leads to ethically unacceptable situations, there should be an expedited workflow.

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Requests for information (RFI's)

- Belgium is among the **top 3** EU countries with the highest number of RFIs (on part 2)*
- Data from 1 sponsor*: 6-fold higher number of RFIs on **ICF** in BE vs NL
- The number of RFI's is closely monitored by sponsors, and if too many, this sometimes is an additional reason to stop the study in that country (or in the EU)

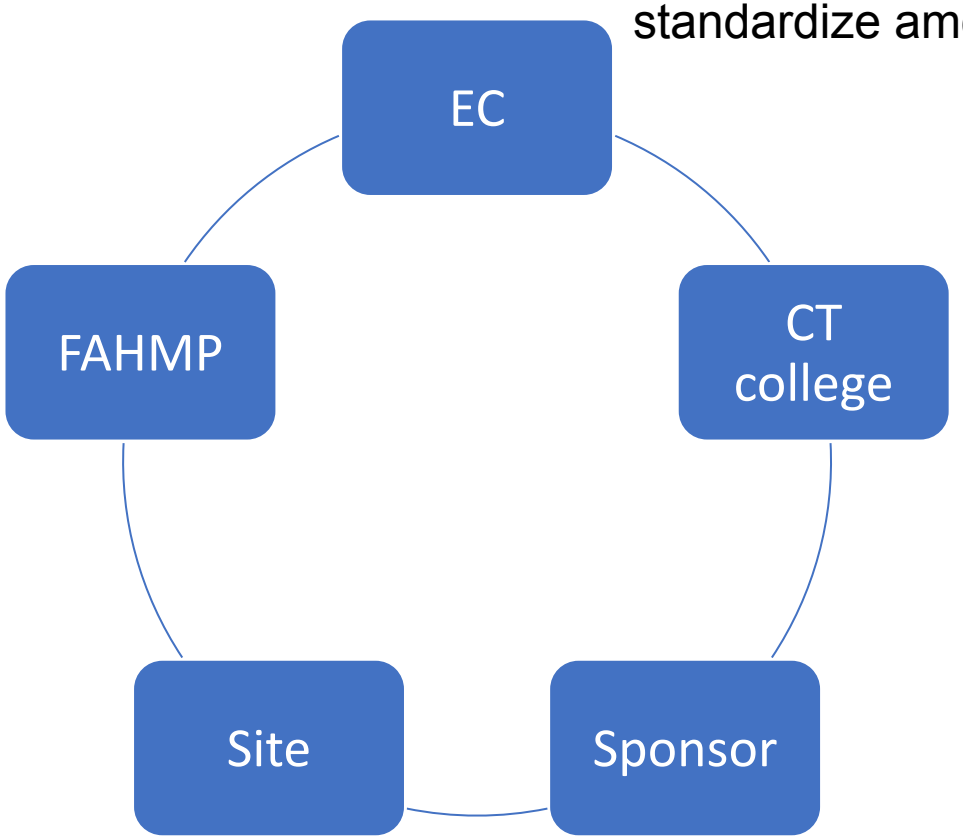
- **Key issues:**
  - Unpredictability of RFIs: each EC has its own sensitivities and focus
  - Lack of anticipation: because EC allocation is anonymous, we cannot take into account these EC-specific sensitivies, leading to avoidable RFIs
  - Lack of time: documents are submitted under high time pressure, often no time for review by the site
  - Experience: some ECs have less experience with reviewing clinical vaccine trials

*Personal communication Prof. Dieter Deforce, UGent – member SAWP EMA

Reduce the number of RFIs: suggestions for improvement

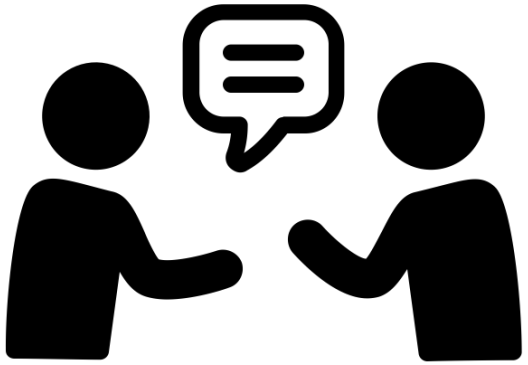
Increase awareness among members, standardize among ECs (BAREC)

Facilitate direct communication (reactive, also proactive)



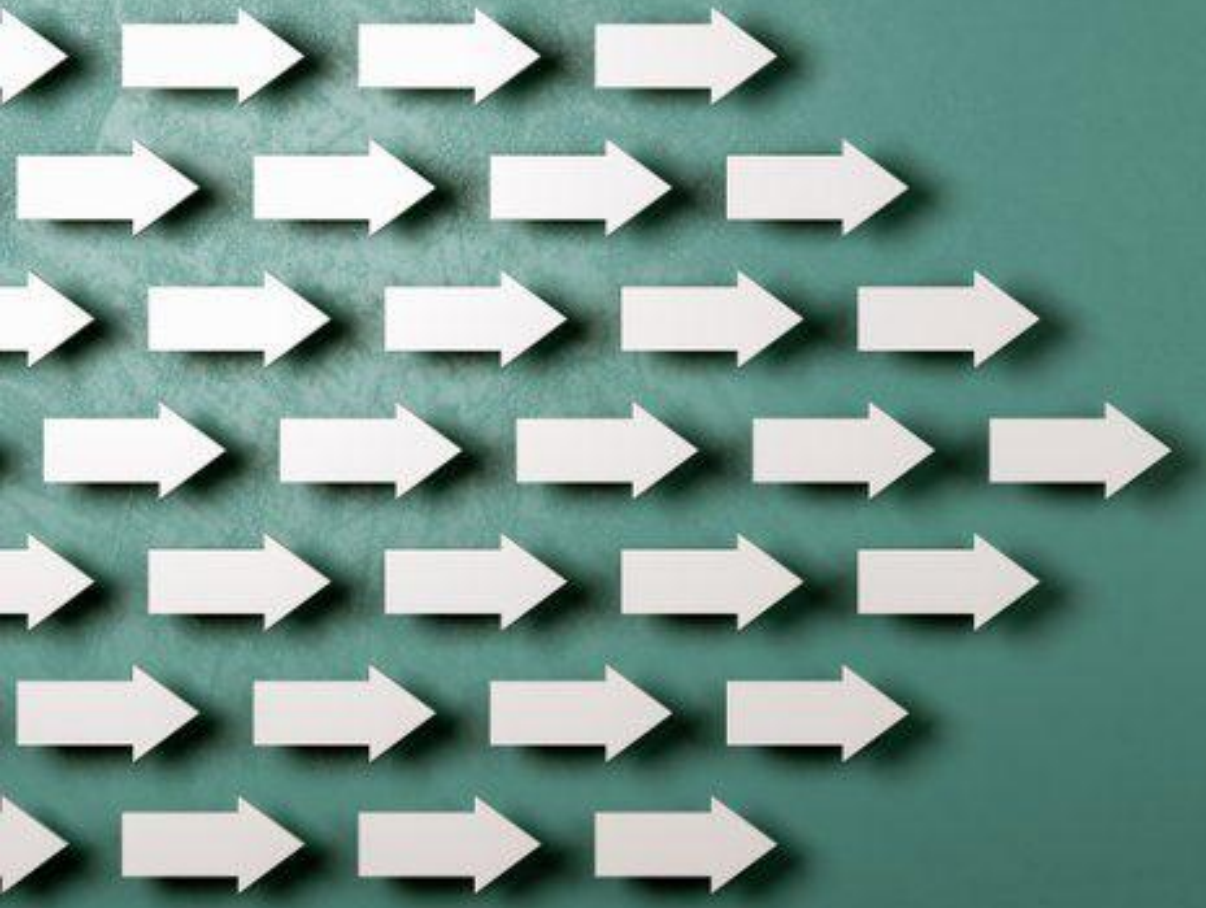
Consolidation of RFIs
Encourage/facilitate direct communication (reactive, also proactive)

COLLABORATION & DIRECT COMMUNICATION



Allow read-only access to CTIS, prepare clear documents, time for review of ICF

Follow best practices for CTIS submission



Conclusion

The full impact of EU-CTR can only be assessed with time

If Belgium wants to maintain its attractiveness for clinical research, we have to improve the process according to what is possible within the current framework, e.g.

- At the EU level: expedited review timelines for seasonal studies
- At the BE level: further optimization of the process, direct communication between FAHMP/CT college/EC and PI/sponsors

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