Experience & Challenges
EU-SolidAct & MOSAIC

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Lessons-learned workshop on Clinical Trials in emergencies
EMA, Amsterdam 9th June 2023

Introduction to the trials

European Research and Preparedness Network for Pandemics and Emerging Infectious Diseases

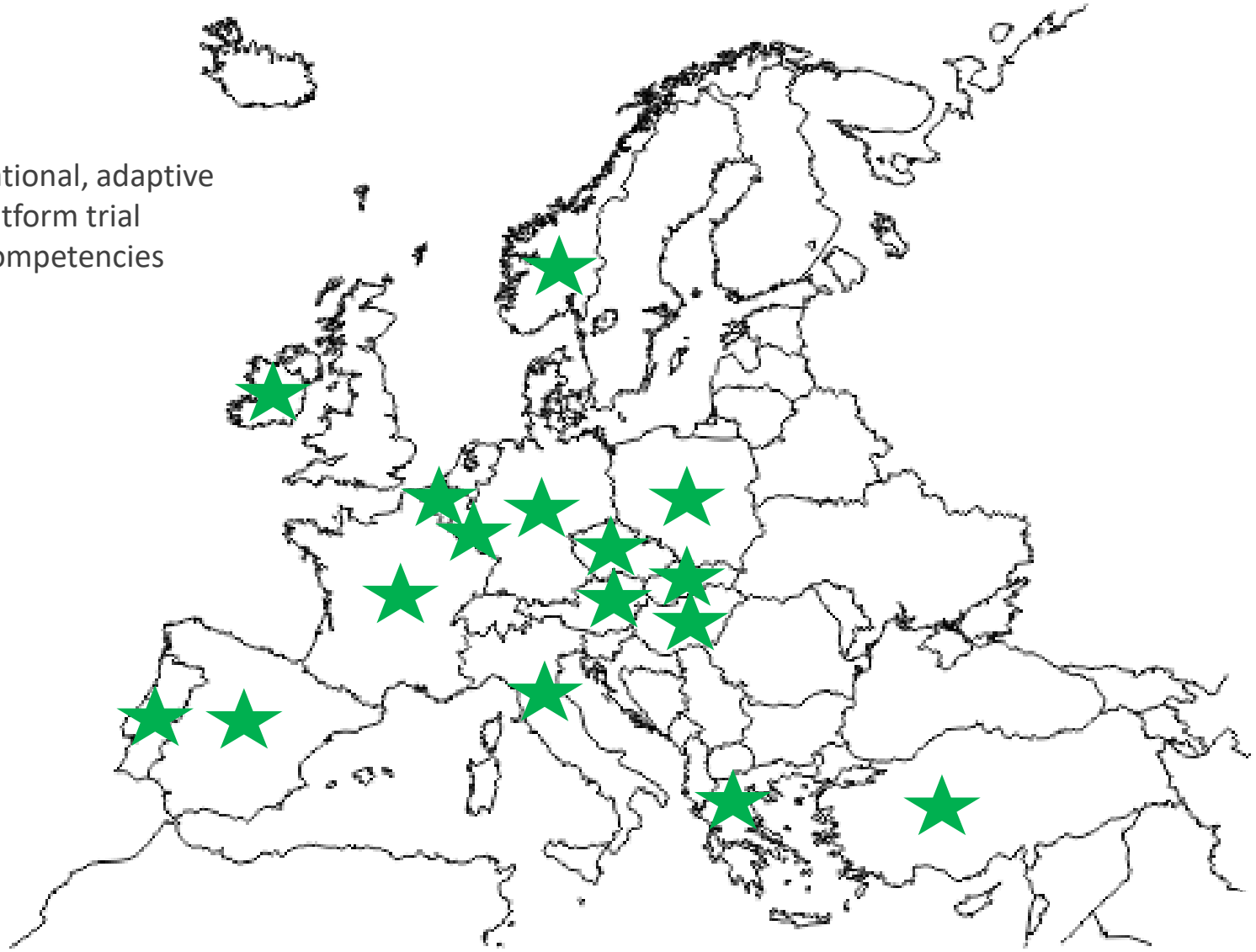
Start date 01/07/2020 – End date 30/06/2025

The overall objective of this proposal is to build a multinational, adaptive European COVID-19 and emerging infectious diseases platform trial network, based on existing initiatives, experiences and competencies

Sites opened in:

France
Norway
Belgium
Luxembourg
Austria
Portugal
Slovakia
Czech Republic
Italy

Poland
Hungary
Ireland
Spain
Greece
Turkey
Germany



EU-SolidAct: creating a platform trial for future pandemics (COVID-19)

- Pragmatic enough to enable patient inclusion across Europe
- Granular enough to enable EMA approval of tested drugs
- Modular data capture to enable fexibility related to epidemic waves and available resources

Part of EU-RESPONSE
EU SOLIDACT

Trials

Bari-SolidAct

- Phase 3
- Population:
  - Hospitalised with severe COVID-19
- Intervention/control:
  - Baricitinib (JAK inhibitor) vs placebo
- Primary endpoint:
  - 60 days mortality

AXL-SolidAct

- Phase 2b
- Population:
  - Hospitalised with moderate pulmonary COVID-19
- Intervention/control:
  - Bemcentinib (AXL inhibitor) vs placebo
- Primary endpoint:
  - WHO progression scale score at day 8

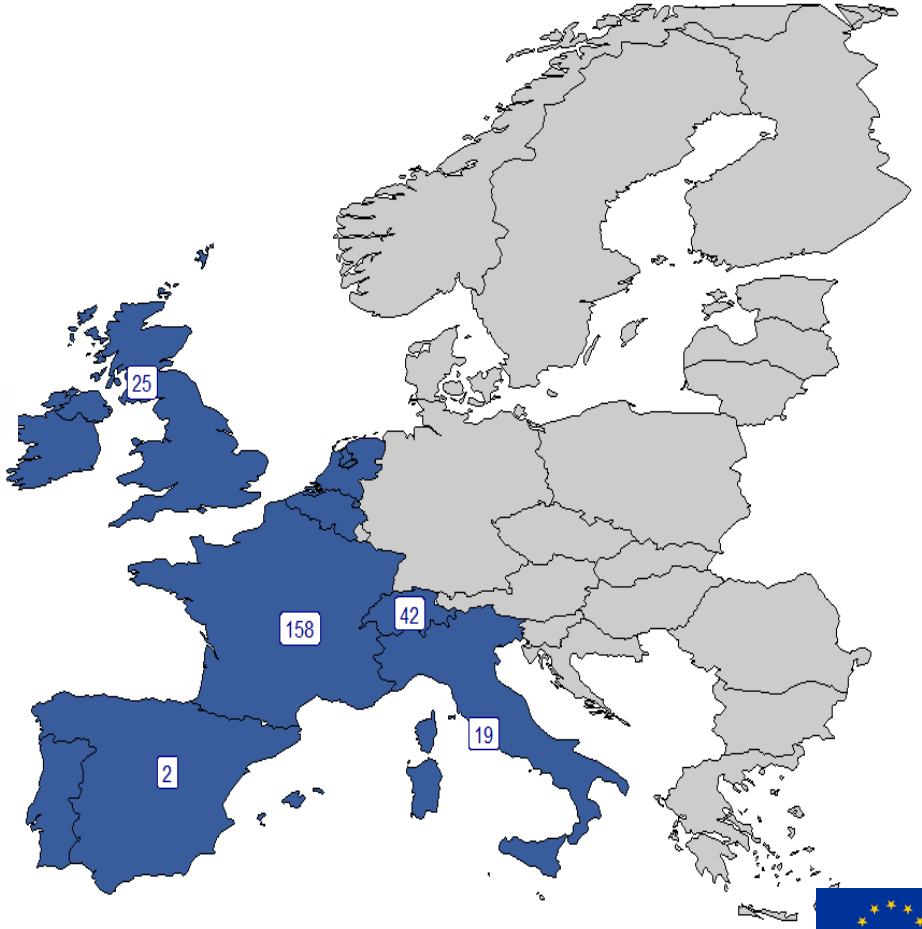
MOSAIC – A multi-centre, multi-country cohort study

- 10 participating countries: Belgium, France, Italy, Ireland, Netherland, Portugal, Spain, Switzerland, United Kingdom (where 20,000 confirmed cases occur, more than 75% of the European cases) and Singapore

Overall coordinating centre and sponsor: University of Oxford

Coordinating centers for:

- **EU/EEA**: ANRS Maladies Infectieuses Emergentes
- **Switzerland**: HUG (Hôpitaux Universitaires de Genève)
- **Singapore**: Tan Tock Seng Hospital



To-date **246 participants enrolled** in France, Switzerland, UK, Italy and Spain of which **231 confirmed** cases and **31 treated with tecovirimat**

MOSAIC – Design

Objectives

- To describe clinical and virological outcomes in patients with mpox virus (MPXV) disease treated or not treated with tecovirimat (or other antiviral drugs)
- To describe safety outcomes in patients with MPXV disease treated with tecovirimat (or other antiviral drugs)

Participants

All patients, with:

- Laboratory confirmation pending, but who are being managed as a presumptive case
- Laboratory confirmed mpox virus disease prospectively or retrospectively

Procedures

- Collects clinical data and research samples [D0, D14] follow-up: D28, D60 and D180

Planned Sample Size

Up to 1400 patients

Type of study

Observational (UK, CH) and LICT (EU/EEA)

CTIS - Experiences

SolidAct Timelines - Experiences

Bari-SolidAct

- VHP: 158 days to approval
  - Min 83 days max 253 days
- Transition:
  - 48 days (IQR 43 to 51)

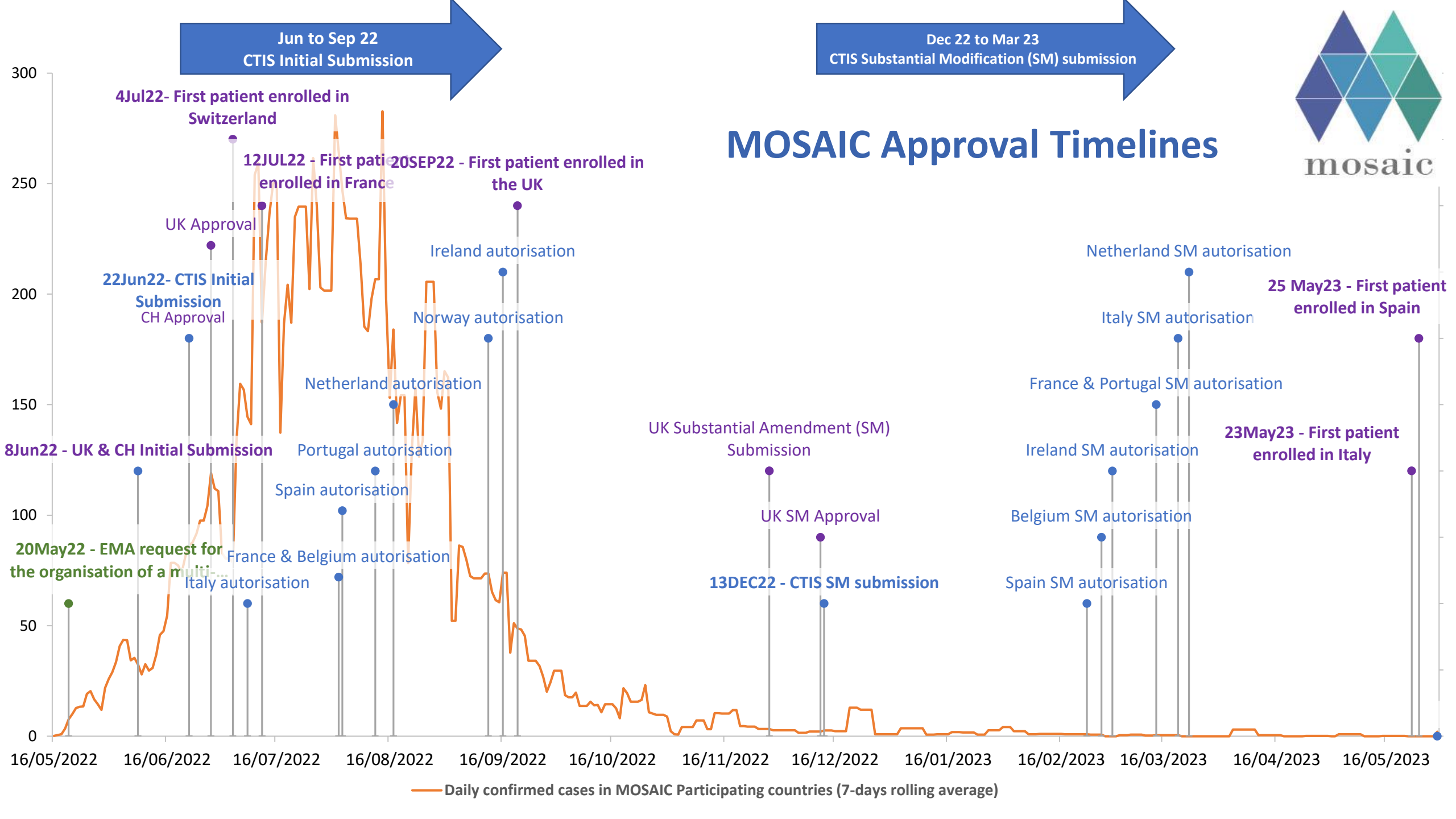
For comparison;

Nor-Solidarity (1st wave of COVID)

- 3 days to approval

AXL-SolidAct

- New application:
  - 80 days to approval
  - IQR 79 to 84
- MS not adhering to agreed timelines (CT-Cure) or not part of CT-Cure


Jun to Sep 22
CTIS Initial Submission
Dec 22 to Mar 23
CTIS Substantial Modification (SM) submission
MOSAIC Approval Timelines
mosaic
4Jul22- First patient enrolled in Switzerland
12JUL22 - First patient enrolled in France
20SEP22 - First patient enrolled in the UK
UK Approval
Ireland autorisation
22Jun22- CTIS Initial Submission
CH Approval
Norway autorisation
Netherland autorisation
8Jun22 - UK & CH Initial Submission
Portugal autorisation
Spain autorisation
20May22 - EMA request for the organisation of a multi-...
France & Belgium autorisation
Italy autorisation
UK Substantial Amendment (SM) Submission
UK SM Approval
13DEC22 - CTIS SM submission
Netherland SM autorisation
Italy SM autorisation
25 May23 - First patient enrolled in Spain
France & Portugal SM autorisation
23May23 - First patient enrolled in Italy
Ireland SM autorisation
Belgium SM autorisation
Spain SM autorisation
300
250
200
150
100
50
0
16/05/2022
16/06/2022
16/07/2022
16/08/2022
16/09/2022
16/10/2022
16/11/2022
16/12/2022
16/01/2023
16/02/2023
16/03/2023
16/04/2023
16/05/2023
Daily confirmed cases in MOSAIC Participating countries (7-days rolling average)

Lengthy time to approval

CTIS Initial submission

Part 1 →
Time from submission to approval = 13 days

Part 2 →
Median time from submission to approval = 46.5 days (IQR 41 to 62)

Contracts with country coordinating centre

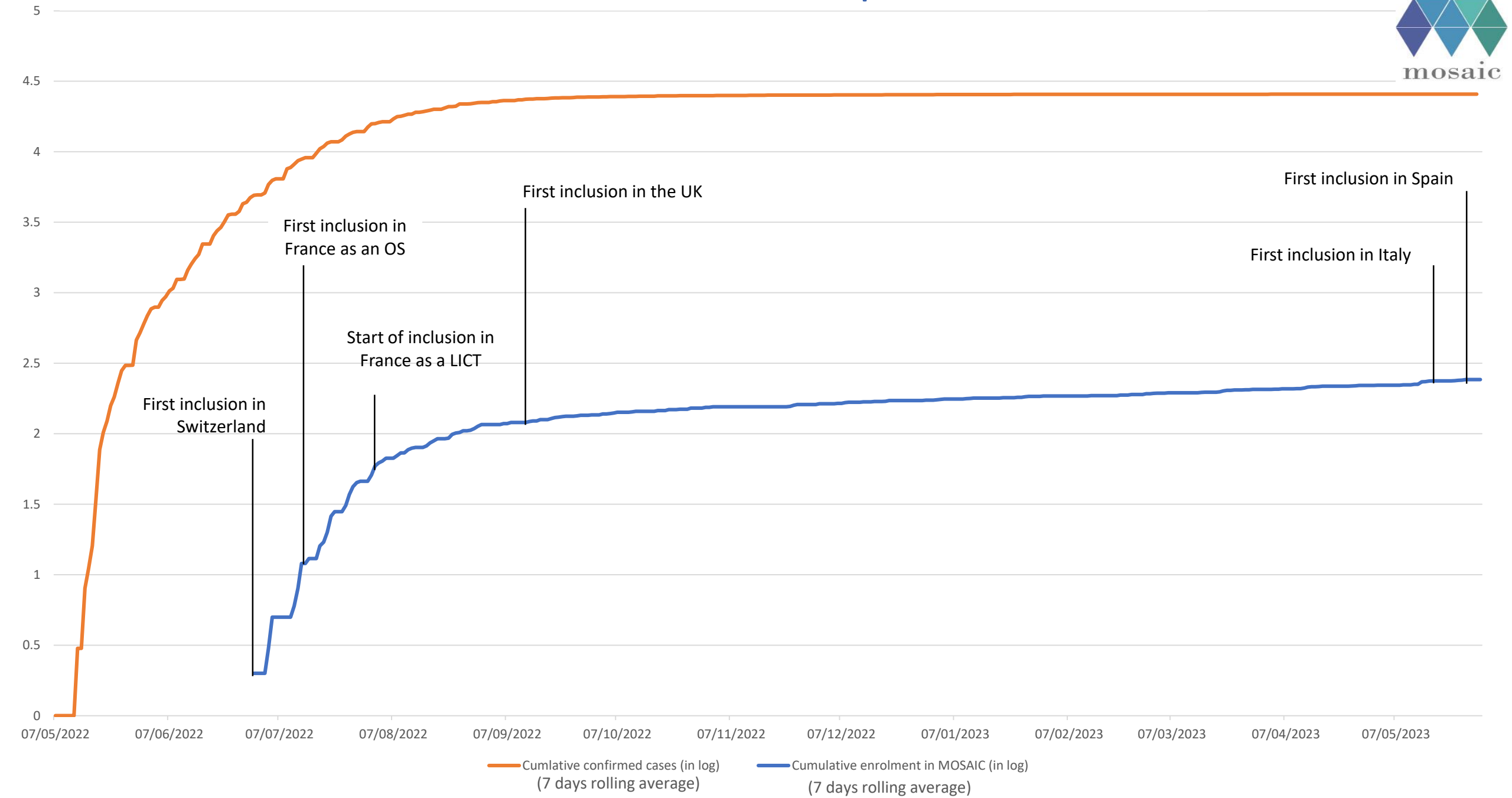
5 out 7 contracts signed →
Median time from CTIS authorisation to signature = 89.5 days (IQR 69 to 137)

CTIS Substantial Modification submission

Part 1 →
Time from submission to approval = 42 days

Part 2 →
Median time from submission to approval = 74 days (IQR 62 to 76)

Evolution of MOSAIC Enrolment and confirmed cases in Europe



Shared experiences

Document amount – CTR Experiences

- **High number documents required at initial submission** (particularly if the trial is multi-country):
  - AXL-Solidact = 535 documents (for 10 countries)
  - MOSAIC = 329 documents (for 8 countries)

- Document burden is increased by **the need to upload different versions of a same document**

- The document burden is also complicated by **requirements of each country:**
  - Inconsistency between country documents requirements,
  - Different legal requirements between countries.

- **Are all documents in all their different formats critical to the approval of the trial?**

Modifications – CTR Experiences

Clinical trials set up during an outbreak require a **flexible framework** that can be adapted to an evolving understanding about a disease for which there is poor pre-existing knowledge

- **Modifications take a substantial amount of time** which risks trials adapting according to need
- **Multiple modifications cannot be submitted in parallel**
- **Cost of process** – financial and human resources – prohibitive for academic Sponsors

CTIS technical– Experiences

- **Time consuming amount of training** needs to be done before access to CTIS is granted
- Guidance documents are **burdensome and not user friendly**
- **Inconsistency** between public and sponsor information
- Deadlines for responses to RFIs vary widely
- There is no **notification system** in place to alert users to new RFIs or approvals
- Bugs and errors

Legal - Experiences

- Sponsor – Site agreements
  - Great variability (sometimes within one country)
  - Translation issues
  - Template issues
    - Sponsor's template vs site/region/country template
  - Local requirements
  - Lengthy negotiations

Opportunities, challenges and solutions

1- Regulatory /Ethics consistency across all MS

Challenge	Solution
Varying documentation required between MS	• **Define a single essential document list** that all MS must accept • **Define a reduced essential document list** for research on health emergencies at the submission stage; remaining dossier to be submitted later
Varying MS adherence to expedited timelines	• Enable tacit approval for expedited timelines
Varying legal requirements between MS	• **Develop** a **user-friendly guidance** document describing important variations between MS laws e.g. assent and consent for children

2 - Centralised functional process

Challenge	Solution
Approvals are delayed due to minor administrative or formatting problems in submitted documents	• Approvals to be issued on the basis of document **content** • Endorse electronic signatures
Absence of notifications (e.g. of new RFIs or approvals) from CTIS to users	**Implement a notification system** to alert users via email about new RFIs and approvals
Unreliable system	Fix bugs and errors, restore confidence

3 - Centralised review process

Challenge	Solution
Part II review is not centralised	In health emergencies, there is **one centralised review process for Part II** for initial submissions and modifications including ethics review
No way of the Sponsor to communicate with Part II reviewers when queries arise e.g. to clarify RFI requirements	When the Part II review is assigned to an ethics committee, their **contact details** should be visible within the CTIS record
Designed for trials outside health emergencies	**Created expedited review pathway f**or trials in health emergencies

4- Centralised modification process

Challenge	Solution
CTIS can only process sequential modifications meaning urgent or important changes cannot be made	• Create a flexible modification process that allows multiple modifications to be submitted in parallel • Enhance ability for non-substantial modifications • Conditional approvals -> allow non-substantial amendments

5 - Clear agreements to protect the participants

Challenge	Solutions
Lengthy negotiations with sites	• Develop **standardised EU-endorsed templates**, translated • Enable networks of clinical sites with **pre-agreed contract** templates

WRAP UP

To reduce the impact of future epidemics: ambitious objectives needed

- "To make diagnostics, therapeutics, and vaccines available within 100 days"
- To enrol the first patient in clinical trials within 14 days after declaration

- Harmonised & central regulatory and ethical approval procedures
- Flexible framework (can be adapted to an evolving understanding about a disease for which there is poor pre-existing knowledge)
- Standardised EU-endorsed contract templates

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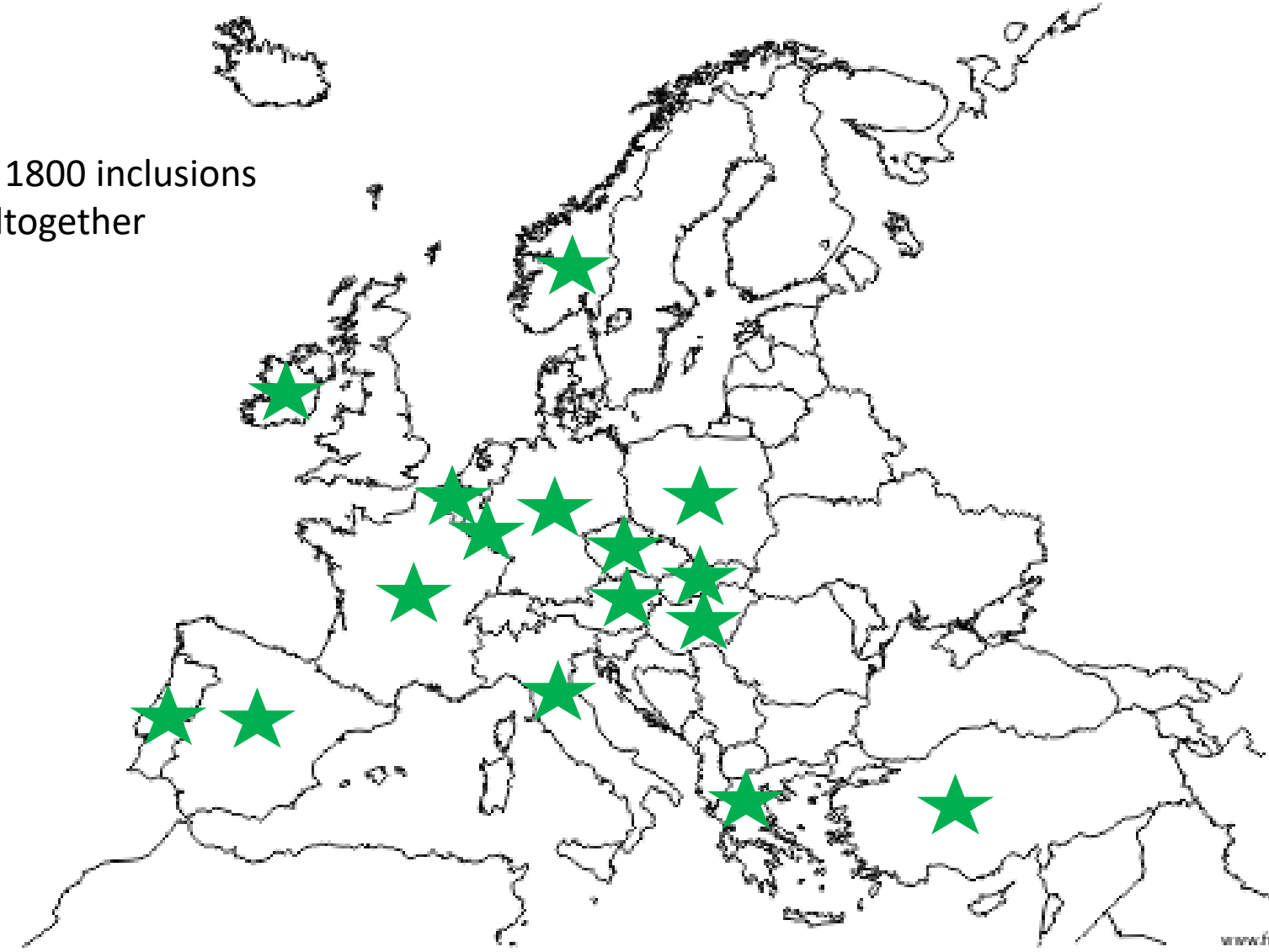
- Elise Pesonel - *ISARIC (International Severe Acute Respiratory and emerging Infection Consortium), Pandemic Sciences Institute, University of Oxford, UK*

BACK UP Slides

Country	Discovery: sites opened	EU-SolidAct: sites opened
France	35	15
Belgium	5	3
Luxembourg	1	1
Austria	1	2
Portugal	2	3
Slovakia	1	1
Czech Republic	1	1
Poland	-	-
Hungary	-	1
Ireland	1	4
Spain	-	2
Norway	3	10
Greece	1	-
Turkey	-	-
Germany	-	1
Italy		13
Total	51 sites	57 sites

> 1800 inclusions altogether



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Document amount - Experiences

High number documents submitted at initial submission (particularly if the trial is multi-country)

- AXL-Solidact = 535 documents (for 10 countries)
- MOSAIC = 329 documents (for 8 countries)

Document burden is increased by **the need to upload different versions of a same document :**

- Redacted and non-redacted formats
- In case of modifications: tracked change, clean, redacted and non-redacted
- There is currently no way to track and maintain general oversight of all documents submitted in their various formats

The document burden is also complicated by **requirements of each country:**

- Inconsistency between country documents requirements, *e.g. Ireland does not approve initial submissions without a DPIA; Luxembourg requires a copy of the CRF; Greece requires copies of signed agreements between sites and Sponsor etc)*
- Different legal requirements between countries, *e.g. format of consent documents for children varies between countries requiring upload of multiple versions of the same PIS/consent documents with different age brackets etc.*

Are all documents in all their different formats critical to the approval of the trial?

- Is the content of all PI CVs and site suitability assessments reviewed in the Part II review?
- Does the absence of a redacted site suitability form jeopardise the scientific value or conduct of a trial?

Modifications - Experiences

- Clinical trials set up during an outbreak require a **flexible framework** that can be adapted to an evolving understanding about a disease for which there is poor pre-existing knowledge

- **Modifications take a substantial amount of time** which risks trials adapting according to need
  - CTIS and its associated administrative processes determine the reactivity of a trial to implement necessary changes
  - This means trials continue with known deficiencies for months unable to make improvements

- Multiple modifications cannot be submitted in parallel
  - The need for changes to essential documentation can be identified while the lengthy review process for initial submissions and modifications is ongoing
  - Sponsors are therefore blocked from making important changes by the review process
  - Importantly, new countries cannot be added existing reviews have completed – detrimental to recruitment and need for rapid data collection during outbreaks

- Fees are also highly variable and prohibitively high for academic Sponsors
  - High fees for submissions risks exclusion of academic study teams who typically have smaller budgets than industry

CTIS technical– Experiences

- **Time consuming amount of training** needs to be done before access to CTIS is granted
  - For a Sponsor: 14 online training sessions + time in sandbox environment
  - This limits the reactivity of trial teams responding to health emergencies – particularly for small teams with limited resources

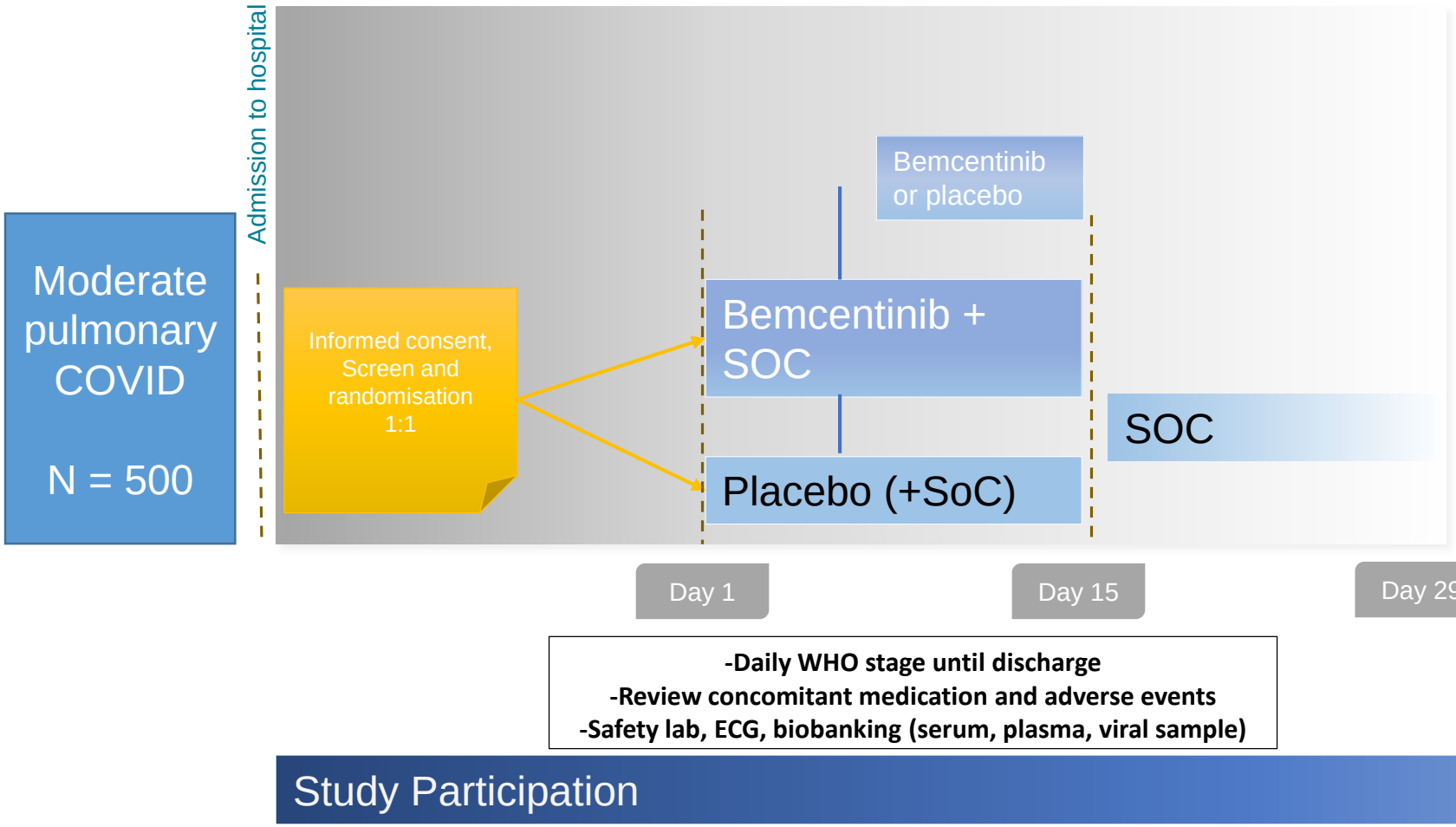
- Guidance documents are **burdensome and not user friendly**
  - Finding information to resolve even simple queries is challenging due to the large number of long guidance documents
  - Queries sent to the helpdesk often not answered directly and instead the user is directed to guidance documents of 50+ pages

- **Inconsistency** between public and sponsor information
  - E.g. For Axl-Solidact the wrong version of protocol exists on the public page

- Deadlines for responses to RFIs vary widely
  - E.g. in MOSAIC deadlines for responses have varied from 2 to 14 days and don't appear to be related to the burden of work involved in the response

- There is no **notification system** in place to alert users to new RFIs or approvals
  - Sponsor needs to log-in to CTIS and check the platform everyday for important events

Phase 2b trial of bemcentinib in moderate COVID-19 disease



- *Primary end point:*
  - WHO score on ordinal scale at Day 8
- *Core secondary end point:*
  - Occurrence of disease progression to severe/critical disease or death within 14 days
- *Secondary end points:*
  - Disease state at day 15 and day 29
  - Survival at day 28, day 60
  - SaO2/FiO2 ratio at day 8
  - Time to sustained recovery
  - Time to first hospital discharge
  - Viral clearance
  - Inflammatory markers
  - PROM at 90 days
  - Safety

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