REMAP-CAP

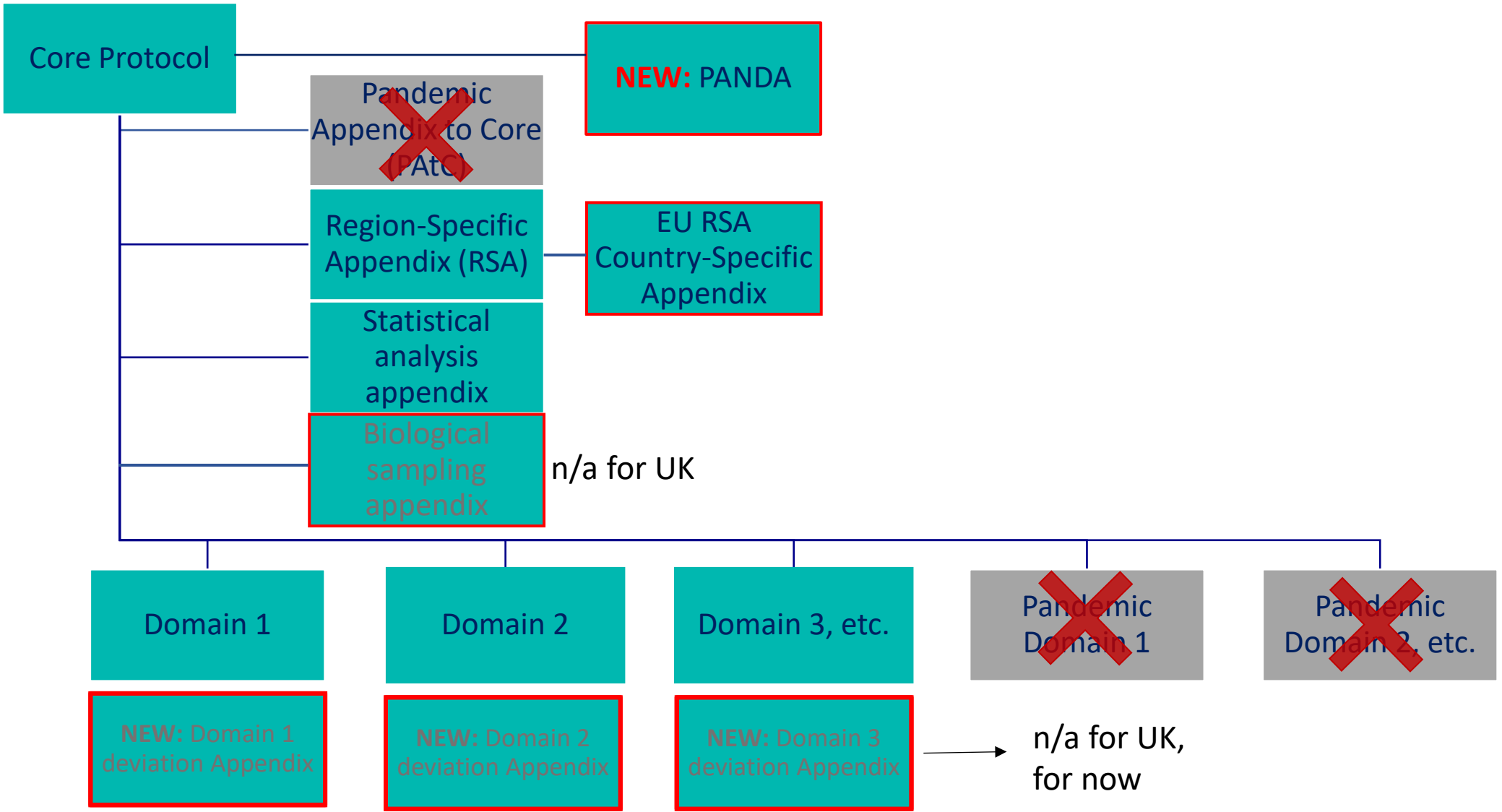
Transition to Core Protocol V4.0 UK

VERSION 4.1

05 MAR 2026

(WITH AUDIO)

Structure of the Protocol



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Core Protocol V4.0

Main Changes

1. Broader platform definition
2. Revised eligibility criteria
3. Revised primary outcomes and endpoints
4. Removal of Pandemic Appendix
5. Introduction of Patient, Pathogen and Disease Appendix (PANDA)
6. Clarification for transferred patients
7. Addition of PedsQL for paediatrics
8. Addition of a ‘Recovering’ state
9. Revised/updated statistical information

1. Broader Platform Definition

- Any reference to '(severe) community-acquired pneumonia (CAP)' / 'severe pneumonia' → **Respiratory tract infections**
- Any reference to '(admitted to) ICU' → **(admitted to) hospital/hospitalized**
- Removal of references to adults
- Example: aim (synopsis)
  - V3.1 – old: The primary objective of this REMAP is, for patients with severe CAP who are admitted to an ICU, to identify the effect of a range of interventions to improve outcome as defined by all-cause mortality at 90 days.
  - V4 – new: The primary objective of this **platform trial** is, for patients **hospitalized** with **respiratory tract infection**, to identify the effect of a range of interventions to improve **patient outcomes**.

2. Broader Platform Eligibility Criteria

Any **hospitalised patient with a respiratory tract infection** is potentially eligible for the Platform.

Simplified Inclusion criteria:

1. Aged ≥ 28 days* (*CGA for paeds)
2. Hospitalised
3. Have an acute respiratory tract infection
    - Includes patients hospitalised with a primary reason other than respiratory tract infection
    - Includes hospital-acquired infections

(Removal of the requirement for the patient to have community-acquired pneumonia)

Exclusion criteria:

- **Removal of '14 days has elapsed since hospital admission'**
- Other minor wording changes

Eligibility criteria for the study are still applied at multiple levels:

- All Platform inclusion criteria met and no exclusion criteria
- Domain-specific eligibility criteria met
- Patient eligible for at least two interventions within a domain

3. Revised Primary Endpoint

Primary endpoint: **Survival and Recovery Trajectory - a trajectory of illness and recovery to 28 days.**

- All cause mortality at Day 90 post-randomisation
- Among Day-90 survivors, daily respiratory support level as defined by five-category ordinal scale:
    1. Hospitalized on extracorporeal life support (ECLS) or invasive mechanical ventilation (IMV)
    2. Hospitalized on non-invasive ventilation or high-flow oxygen*
    3. Hospitalized on low-intensity oxygen
    4. Hospitalized, no oxygen
    5. Discharged from index hospitalisation

    - High-flow oxygen defined as a fractional inspired oxygen concentration of 0.4 or higher and with flow rate of at least 30 liters per minute (or at least 2 liters per minute per kilogram of bodyweight in children less than 15 kilograms).

Does not change data collection required by sites at follow-up

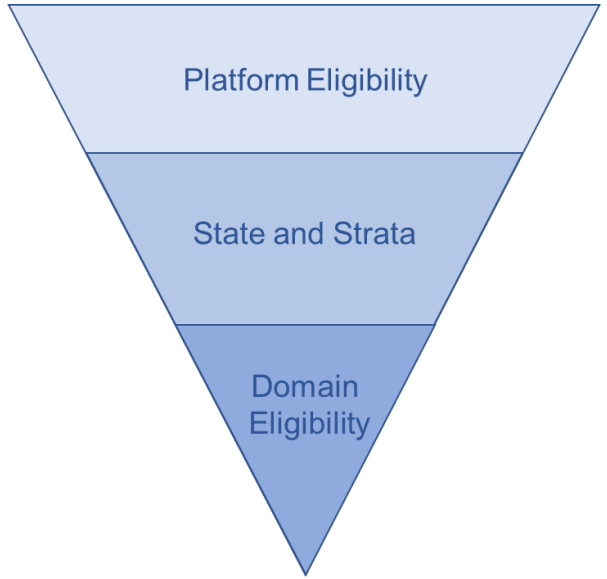
4. Removal of Pandemic Appendix to Core

Closure of pandemic strata.

Participants will no longer be classified as Pandemic Infection Suspected or Proven (“PISOP”) or Pandemic Infection Neither Suspected Nor Proven (“PINSNP”)

5. Patient, Pathogen and Disease Appendix (PANDA)

- Describes how specific patient, pathogen, disease, illness severity and additional clinical features are defined and categorized
- Does not include information about interventions
- PANDA may be amended in the context of a future pandemic, but it is intended that any amendments to the PANDA will be infrequent



Platform: Patients hospitalized with respiratory tract infection

Characteristics to constrain eligibility or stratify analysis (set for each Domain)

Patient and setting
(fixed)

Age
≥ 18 yrs
≥ 12 yrs ≤ 18 yrs
≥ 28 days ≤ 12 yrs

Immunosuppression
Present
Absent

Regional income level
High
Upper middle
Lower middle
Low

Infection
(fixed)

Acquisition
Community
Hospital
Ventilator

Pathogen(s)
Influenza
SARS-CoV-2
MERS-CoV
RSV
Other resp virus
Bacteria
Novel pandemic
(incl. co-infection)

Disease, severity stage & clinical features
(dynamic = 'states', category fixed at randomization)

Disease entity
URTI →
LRTI →
Pneumonia →

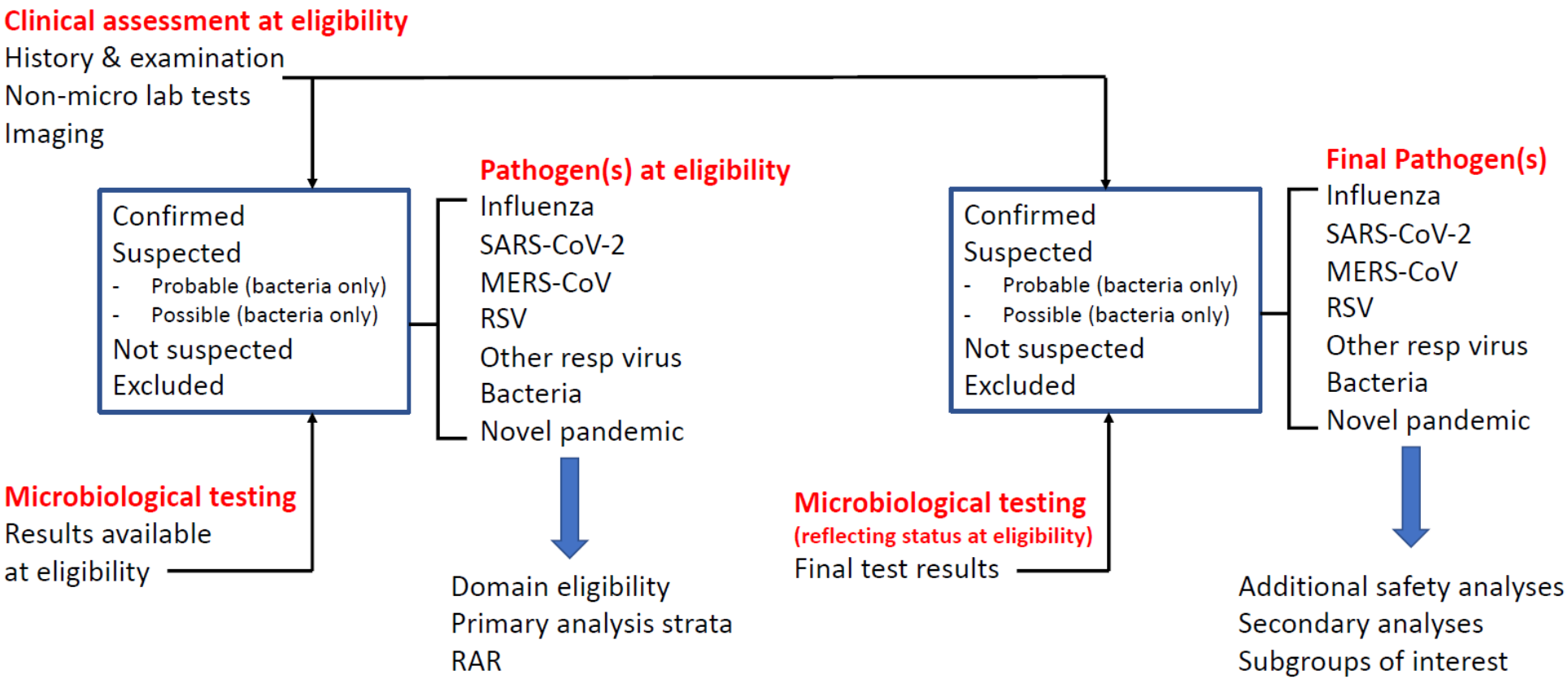
Illness severity
Moderate → Severe → Recovering →

ARDS
Absent → Present → Resolved →

Hypoxia
Not on IMV → IMV P/F ≥200 — P/F <200 — P/F ≥200 →

Shock
Absent → Present → Resolved →

Pathogen status



6. Clarification for Transferred Patients

Core Protocol V4 clarifies protocol adherence for participants who are **transferred between locations**.

If a participant is transferred from a participating location to:

- a non-participating hospital
- a non-participating clinical area within a participating hospital
- a participating hospital/clinical area that is not participating in the domain/intervention to which the participant has been allocated

Continuation or discontinuation of allocated interventions becomes a **clinical decision**, rather than an intervention administered under trial protocols.

7. PedsQL at Day 180 Follow-up for Paediatrics

Paediatric quality of life questionnaire, by age group:

- **<2 yrs** = none/not applicable
- **2-4 yrs** - completed by parent
- **5-7 yrs** - completed by parent or child
- **8-12 yrs** - completed by parent or child
- **13-18 yrs -** completed by parent or child
  (REMAP-CAP defines a paediatric up until 17yrs but they may turn 18 during follow up period)

4 x Qs on physical, emotional, social and daycare/nursery/school functioning.

8. Recovering State

Core Protocol V4 adds the **Recovering State**

The Recovering State is defined as:

- Hospitalised patients who, in the opinion of the treating clinician, are **clearly recovering** from their acute respiratory tract infection AND are **unlikely to require or receive a significant escalation in level of organ failure support** for the remainder of their hospital admission

Currently **no domains are available for patients in the Recovering State**, meaning that they cannot be randomised into the Platform

- Future domains may permit enrolment of patients in the Recovering State

9. Statistics

- Merge of two statistical models (interpandemic and pandemic), & possibly Ventilation Domain
- New trigger terminology added
  - Possible treatment effects : superiority, **efficacy,** inferiority, equivalence, **noninferiority, futility, and harm**
  - Core protocol sets default thresholds for statistical triggers
- Adaptive analyses will occur frequently, approximately proportional to the rate of recruitment
- Response Adaptive Randomization: proportions are determined by analysis of the available data informing the primary outcome measure in participants **after at least 28-days of follow-up**
  - For domains with only two available interventions, default is that RAR will not be applied
  - Allocation proportions capped at 60% for two-intervention domains, unless otherwise specified

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Domain Specific Appendices

Refer to DSAs for:

- Domain specific **eligibility criteria**
- Domain **rationale**
- **Concomitant care**
- Potential **domain-specific adverse events**
- Domain-specific **endpoints**
- Domain-specific **protocol deviations**
- **Other** domain specific information

General Domain Updates

- The broadening of Platform-level eligibility criteria mean that domain-level eligibility criteria wording has been updated to ensure continuity and correct domain constraints:
    - Removal of pandemic/non-pandemic strata in all DSAs.
    - Addition of age strata in relevant DSAs (flu domains).
    - Consistency in mention of the moderate state in steroid and antiviral DSAs.
- Although it may look like there are a lot of changes, **in practice the patients who are eligible for these domains will be the same as were eligible under previous versions**.
- In most cases there are **no changes to interventions** or their delivery.

Domain	Moderate State	Severe State	Paediatric (≥28 days)	Adolescent (≥12 years)	Adult (≥18 years)
Antibiotic Domain	✗	✓	✗	✗	✓
Macrolide Duration Domain	✗	✓	✗	✗	✓
Corticosteroid Domain	✓	✓	✓	✓	✓
Influenza Antiviral Domain	✓	✓	✓	✓	✓
Immunoglobulin Domain	✓	✓	✗	✓ (≥16 years)	✓
Mechanical Ventilation Domain	✗	✓ - n/a UK	✗	✗	✓ - n/a UK
Endothelial Domain	✗	✓- n/a UK	✗	✗	✓ - n/a UK
Influenza Immune Modulation Domain	✗	✓	✓ (≥2 years)	✓	✓

Domain Eligibility Changes

Steroid eligibility

- CAP is removed from platform incl. criteria, but added to steroid domain incl. criteria for severely ill patients
- Patients must have a lower resp. tract infection (platform is open to lower and upper)
- Confirmed SARS-CoV-2 infection is an exclusion
- Hospital-acquired respiratory tract infection is an exclusion except for flu

Antiviral eligibility – no changes

Immune modulation eligibility

Removed from platform exclusion and added to domain exclusion:

- More than 48 hours has elapsed since commencement of sustained organ failure support

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eCRF for Core Protocol V4.0

eCRF Changes

The REMAP-CAP case report form (CRF) has undergone a thorough review and substantial update. These changes are intended to:

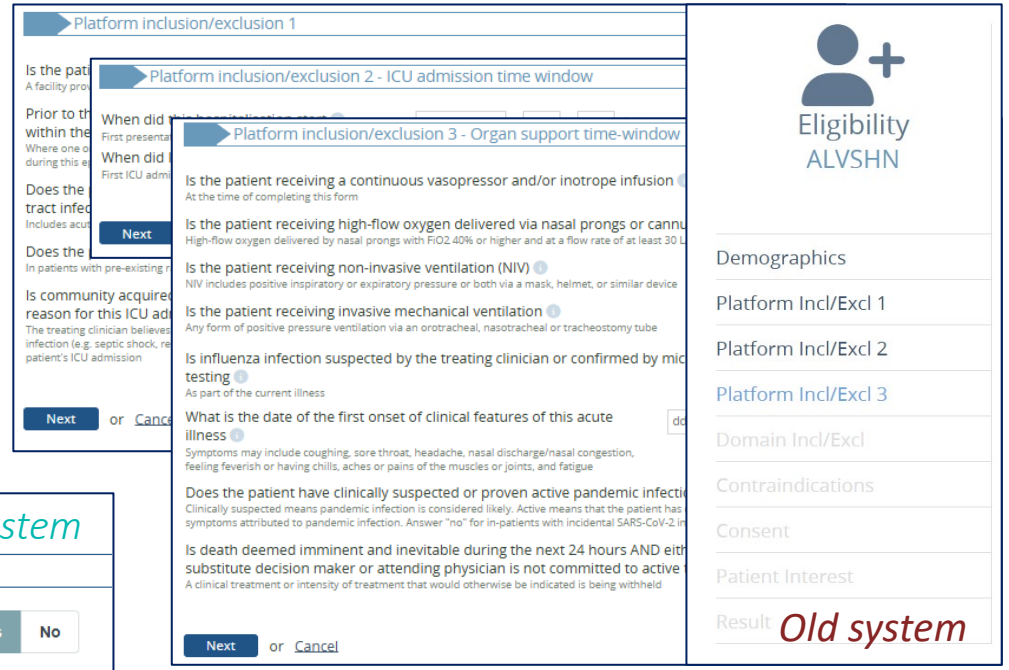
- Reflect changes to Core Protocol V4
- Reduce burden of data collection by removing unnecessary fields / finding more efficient ways of capturing necessary data; and
- Future-proof for any future public health emergencies

Eligibility Form Changes

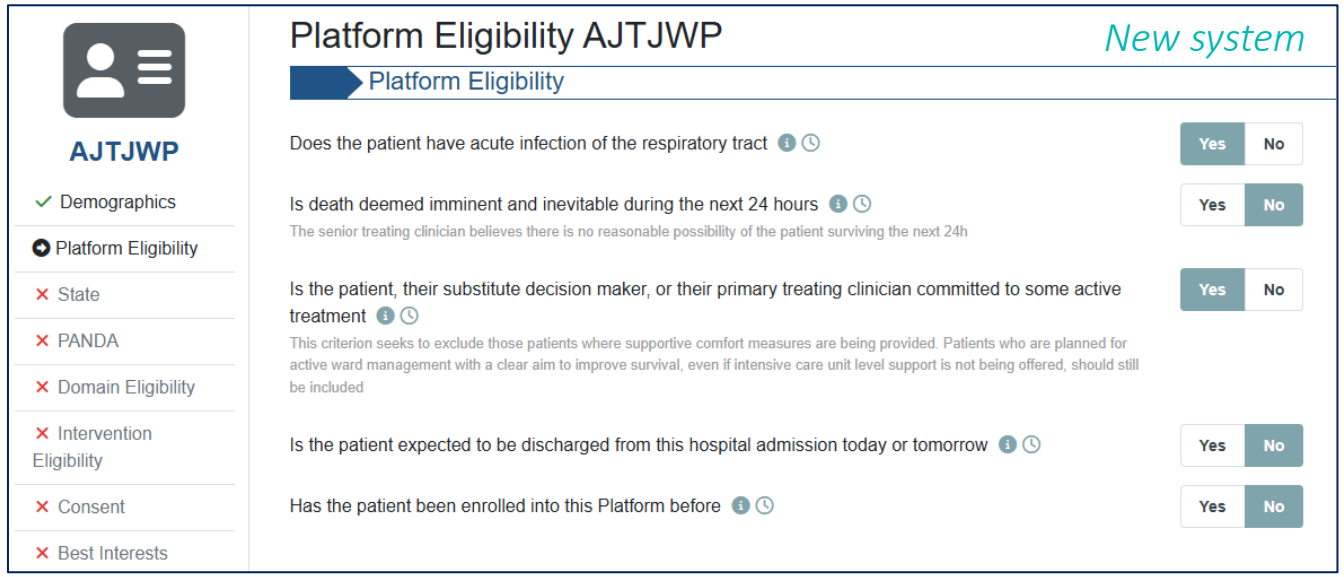
The eligibility assessment was updated to:

- Reflect the reduced Platform eligibility criteria
- Reflect modifications to domain-specific eligibility criteria
- Manage the complexity of simultaneously assessing eligibility for multiple domains and interventions

Used to be ±20 platform eligibility questions on 3 pages

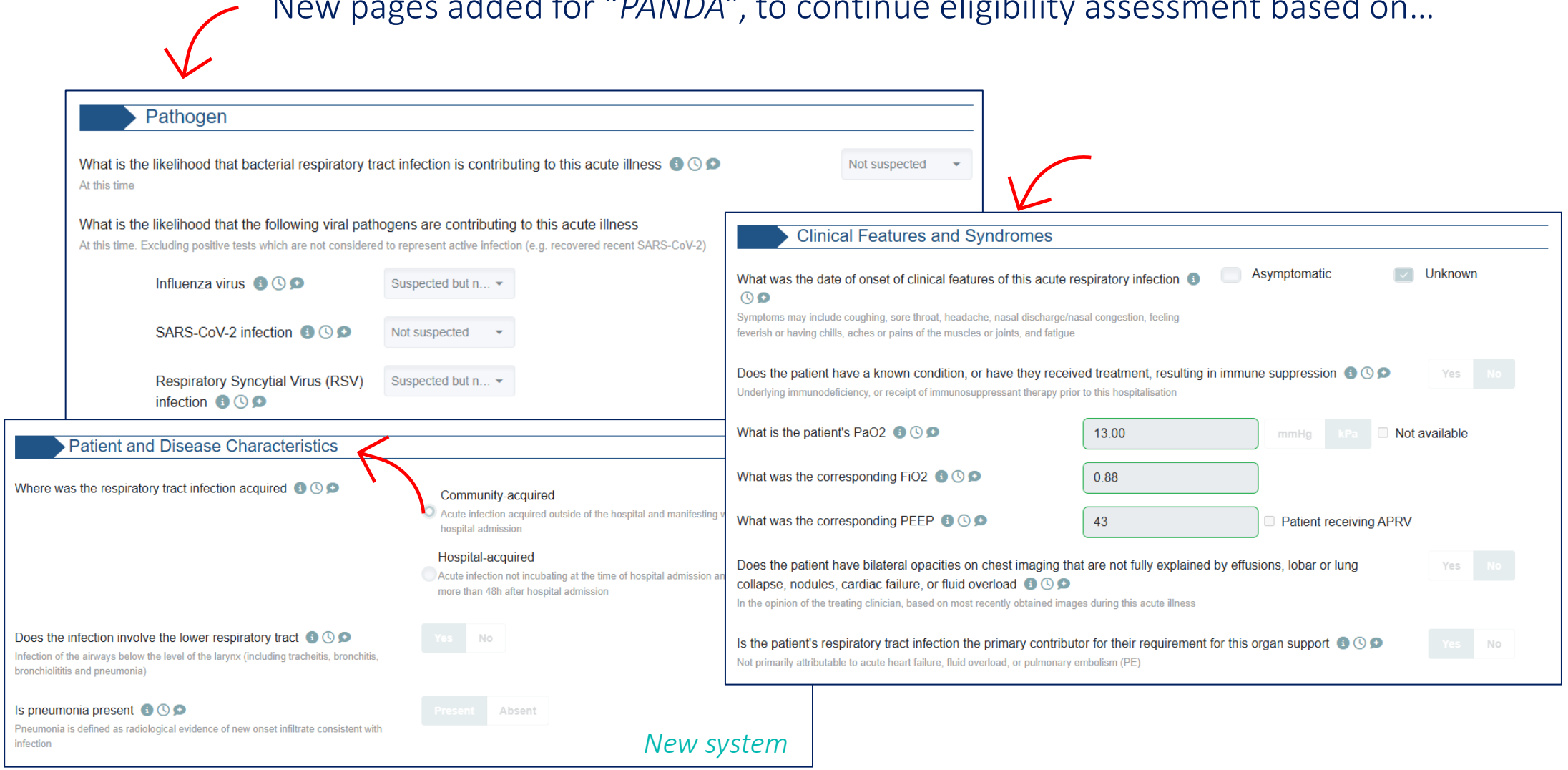


5 platform eligibility questions on 1 page

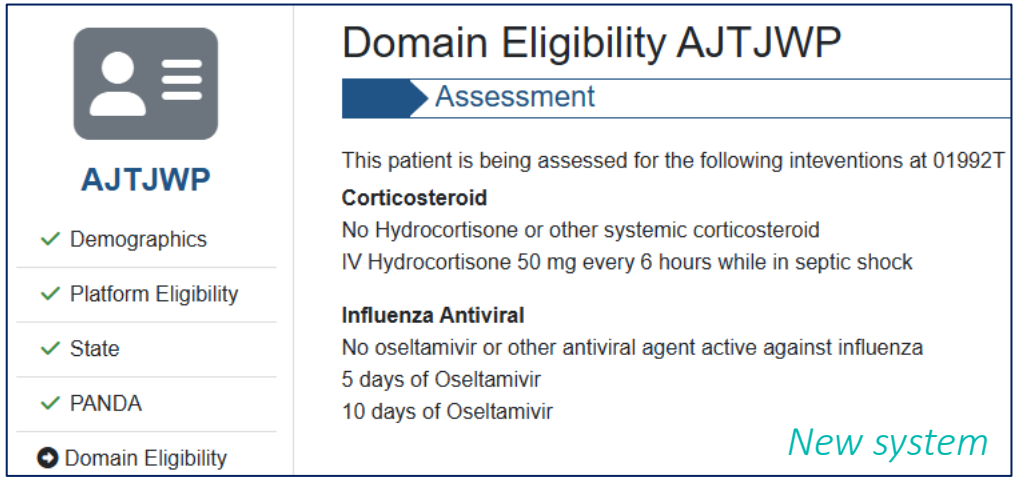


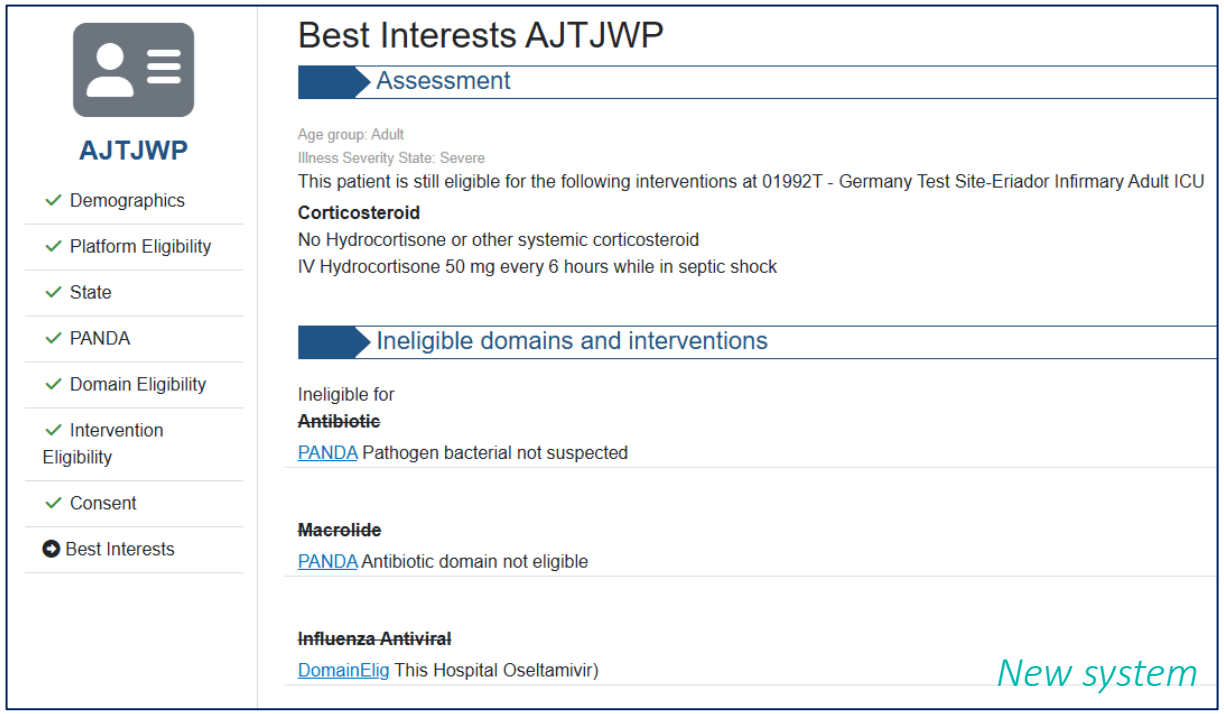
Fewer questions necessary to assess **Platform** eligibility

New pages added for "*PANDA*", to continue eligibility assessment based on…



Clearer output for users regarding which domains a participant is being assessed for on the "*Domain Eligibility*" page…





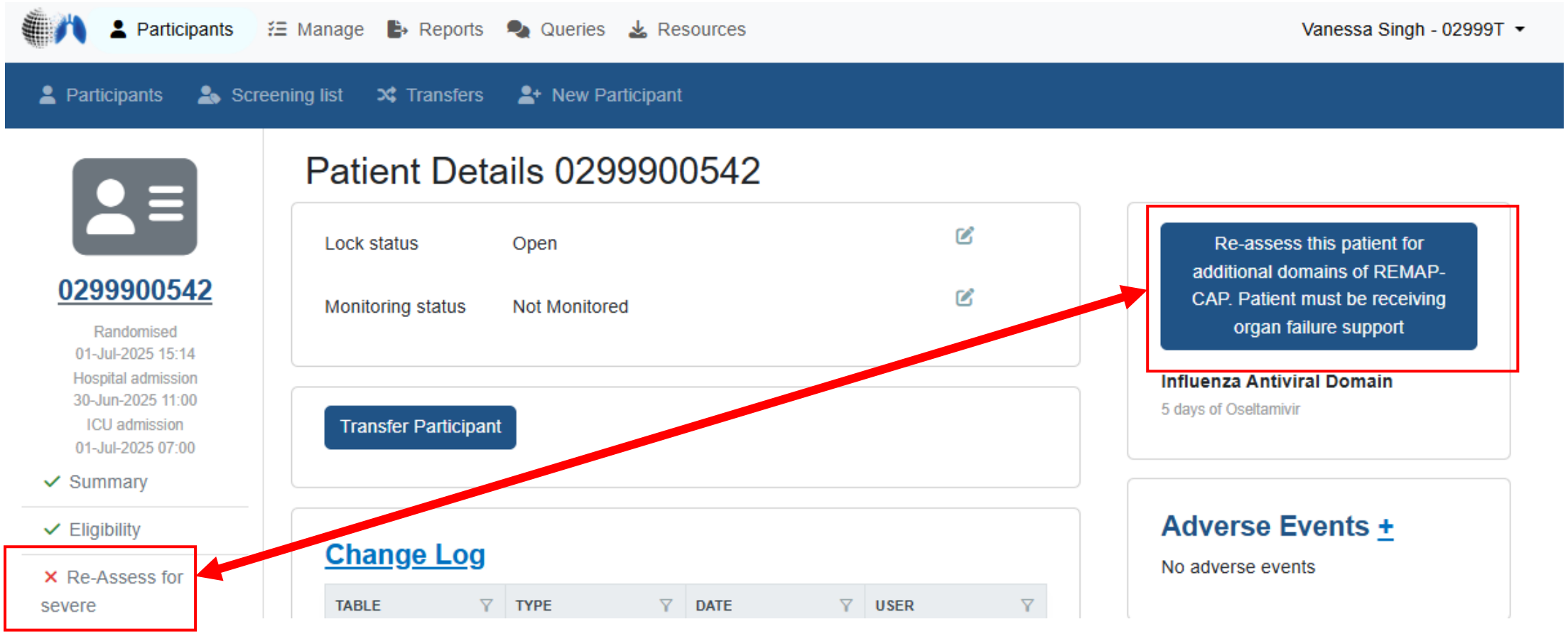
… and why participants are ineligible for certain domains on the "*Best Interests*" page.

Re-assessment of Eligibility

Patients who have been randomised in the Moderate State may be eligible to be randomised again to additional domains if they progress to the Severe State.

However, patients cannot be randomised in the Moderate State AFTER the Severe State.

To reassess a participant's eligibility for domains in the Severe State, navigate to the **patient summary page.**


Participants
Manage
Reports
Queries
Resources
Vanessa Singh - 02999T
Participants
Screening list
Transfers
New Participant
Patient Details 0299900542
0299900542
Randomised
01-Jul-2025 15:14
Hospital admission
30-Jun-2025 11:00
ICU admission
01-Jul-2025 07:00
Summary
Eligibility
Re-Assess for severe
Lock status
Open
Monitoring status
Not Monitored
Transfer Participant
Change Log
TABLE
TYPE
DATE
USER
Re-assess this patient for additional domains of REMAP-CAP. Patient must be receiving organ failure support
Influenza Antiviral Domain
5 days of Oseltamivir
Adverse Events +
No adverse events

Consent Form Changes

- Qs re patient capacity and PerLR/ProLR made clearer to avoid accidental randomisations
- For paediatrics, ‘proxy’ consent should be selected if the parent is providing consent

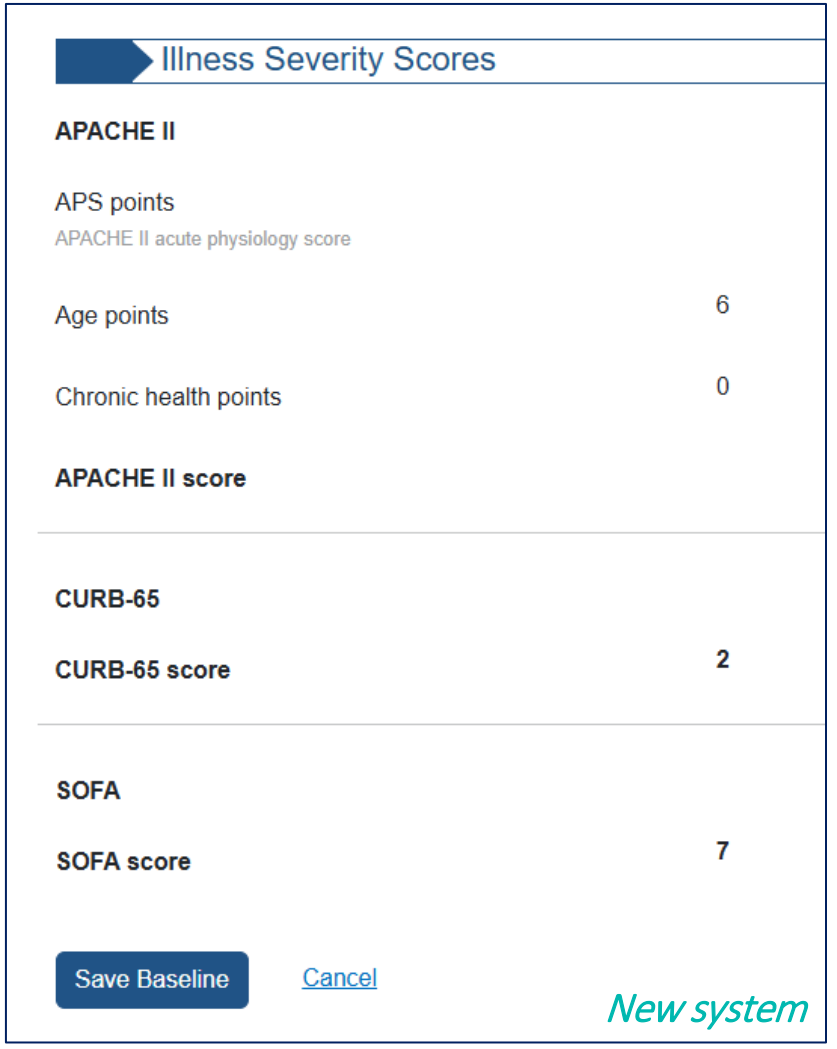
Can indicate why written consent wasn’t obtained from child participant i.e. did not have capacity (if too young/can’t fully understand) or enter your own free text if preferred under ‘another reason’ option

- ‘Best interest’ statement added for emergency enrolment of patients without any consent in place i.e. Patient has no capacity, PerLR/ProLR is not available, and timeframe is running out.

Reminder: ALL consent discussions mentioned in source notes must be entered on eCRF even if there is no outcome/no decision made!

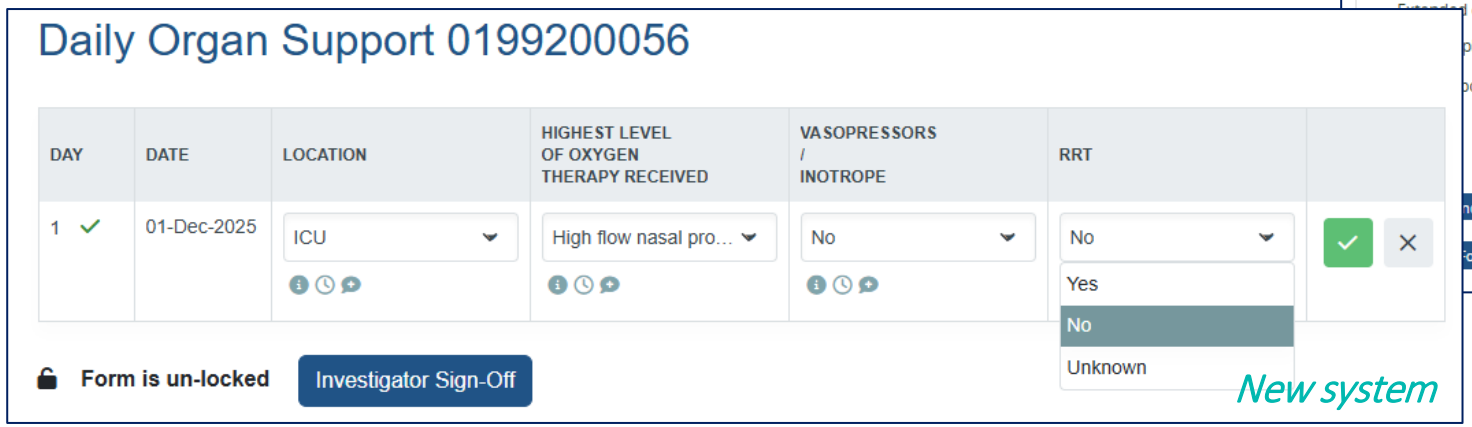
Baseline Form Changes

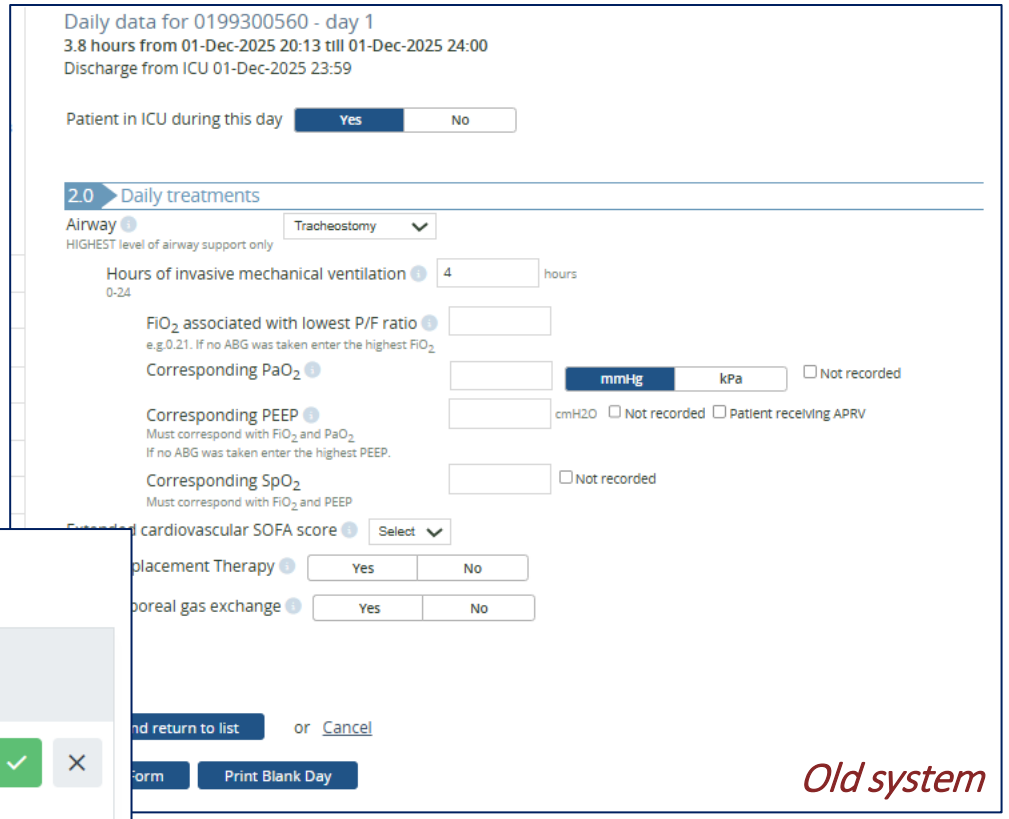
- Some questions in the Baseline Form have been made domain-specific.
- Some questions in the Baseline Form have been removed.
- Illness Severity Scores are now calculated automatically by the database for ICU patients, based on data entered in the Baseline Form.



Daily Data Form Changes

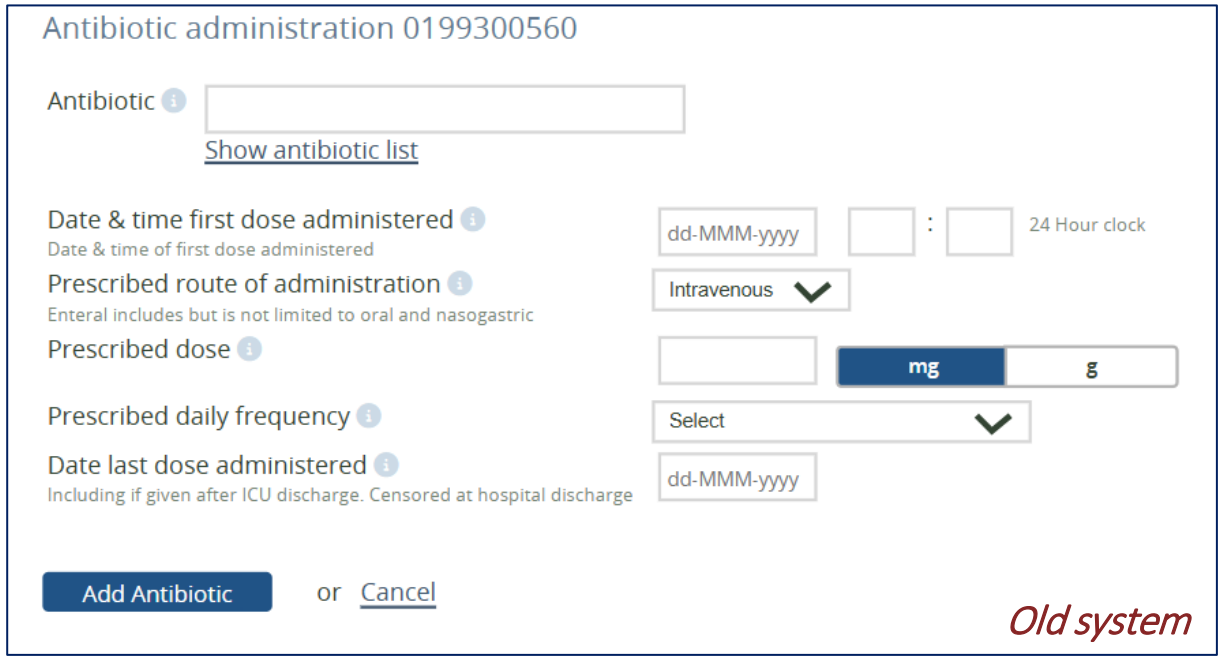
- Focus on organ support.
- Study days are now defined by **calendar days** instead of ICU chart days.
- **Yes/No** questions about organ support received on each study day



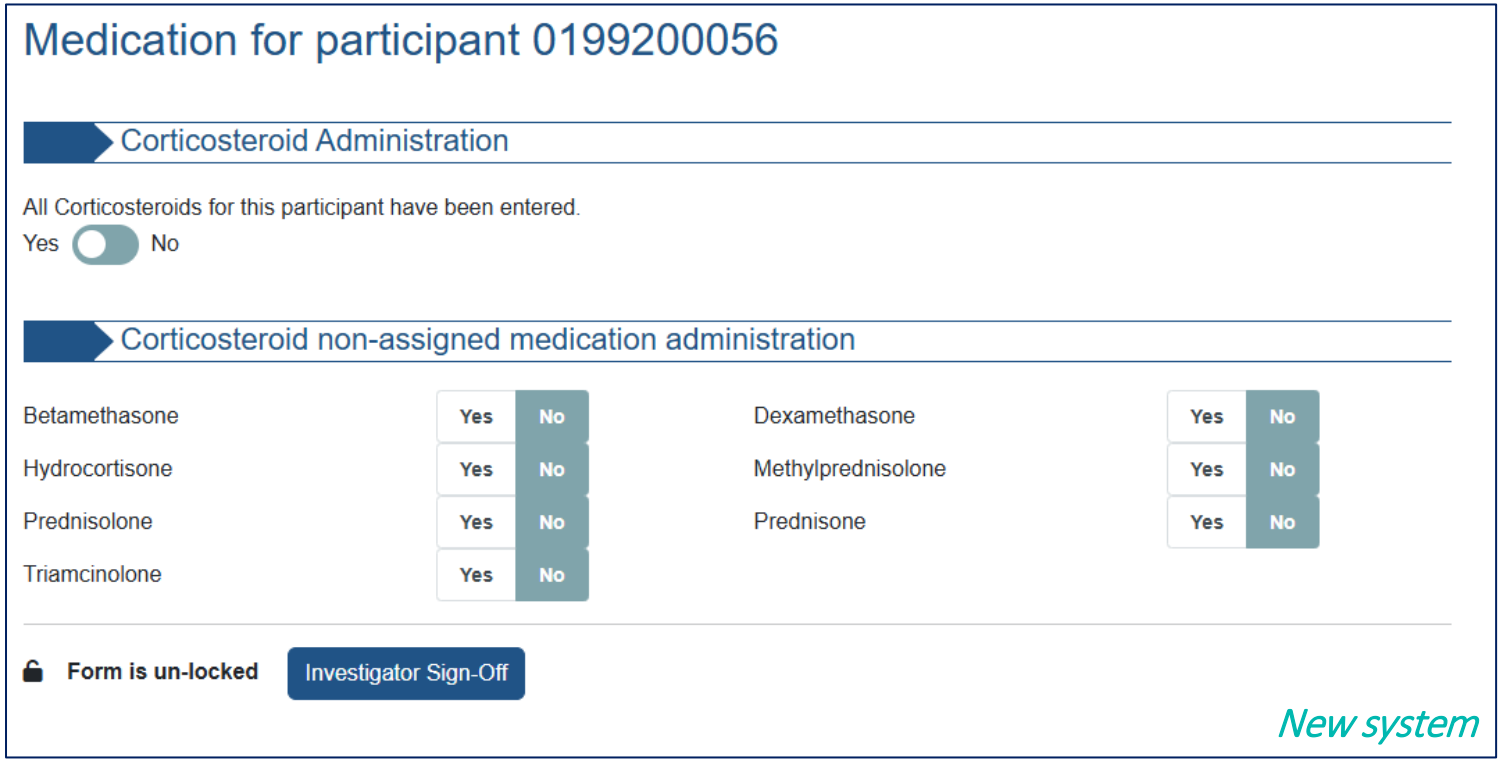


Medication Form Changes

- Focus on daily administration of allocated intervention, instead of details of each prescribed course.

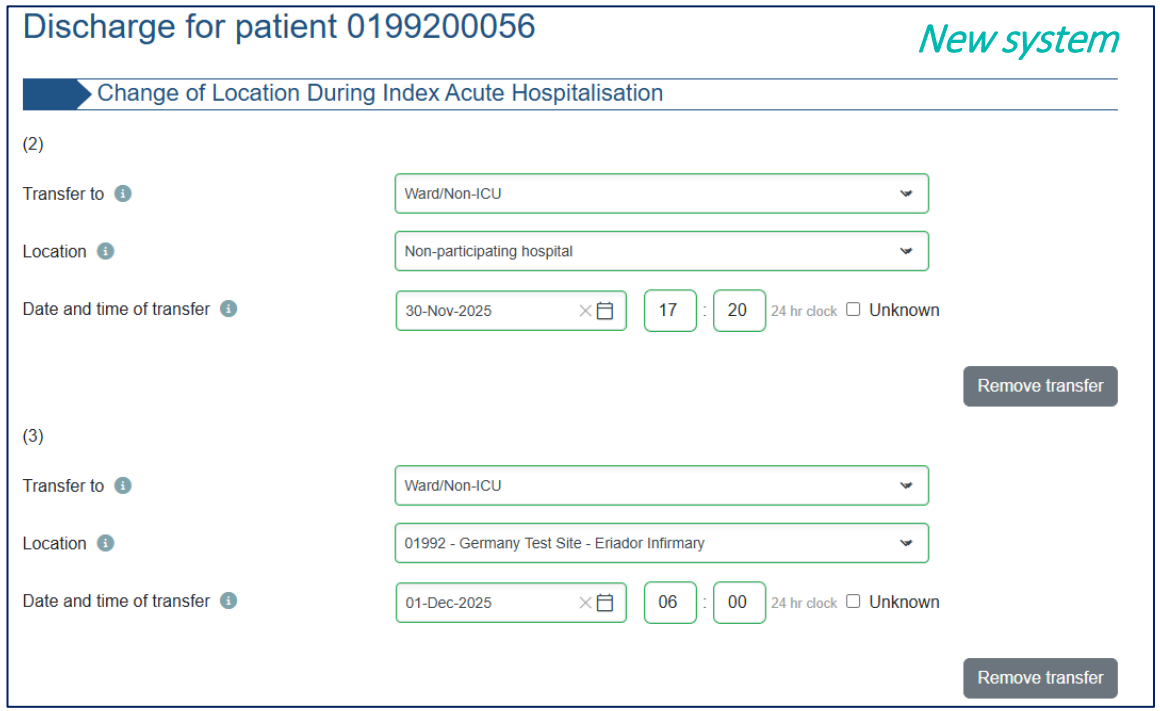


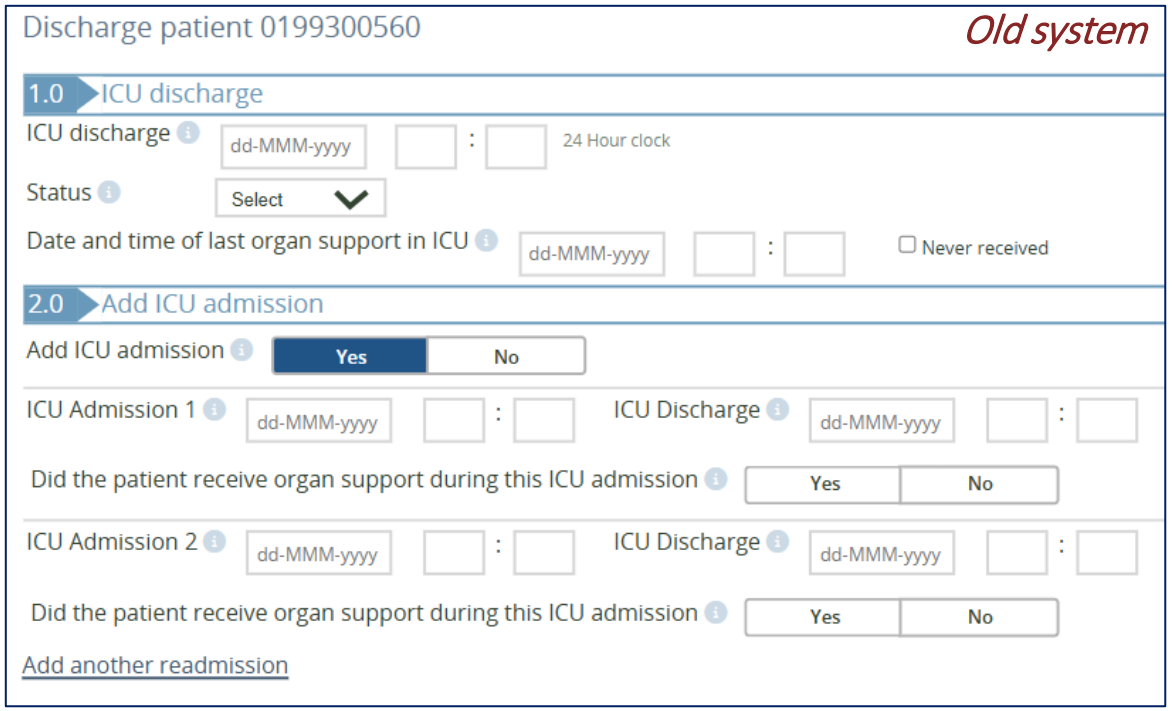
- Non-study medications of interest will be collected in a simplified **“Yes / No”** format.
- Data collection will be domain-specific.



Discharge Form Changes

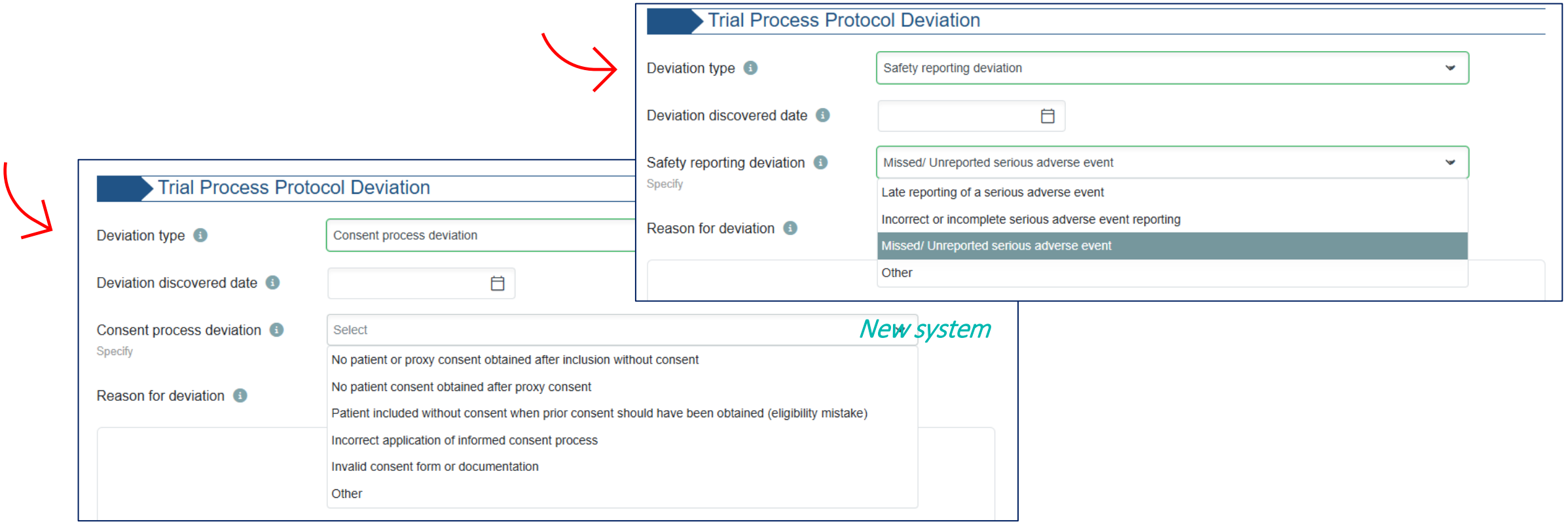
- Modified to more clearly capture participant movement during the acute hospital admission, including between hospitals in case of transfers.
- Cause of death will be collected for paediatric participants who die in hospital.





Protocol Deviation Form Changes

- The Protocol Deviation Form now allows entries that relate to trial processes, including safety reporting and consent processes.



D90 & D180 Follow Up

- Survival status will continue to be collected at D90 and D180
- Questionnaires will continue to be collected at D180:

Adults D180	Paediatrics D180
EQ-5D-5L	EQ-5D-Y
WHODAS	PedsQL SF15 - **New**

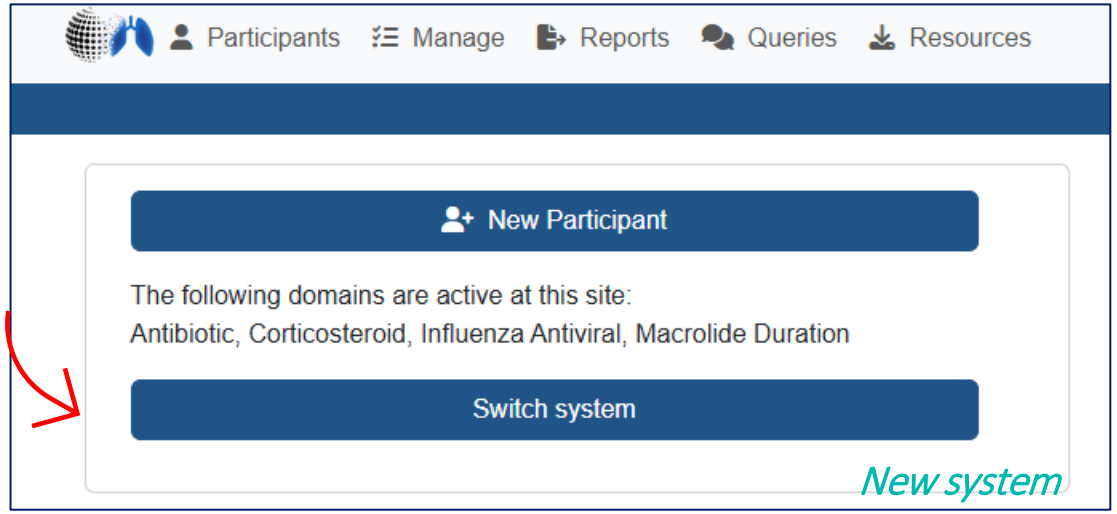
New Form: Pregnancy Outcome

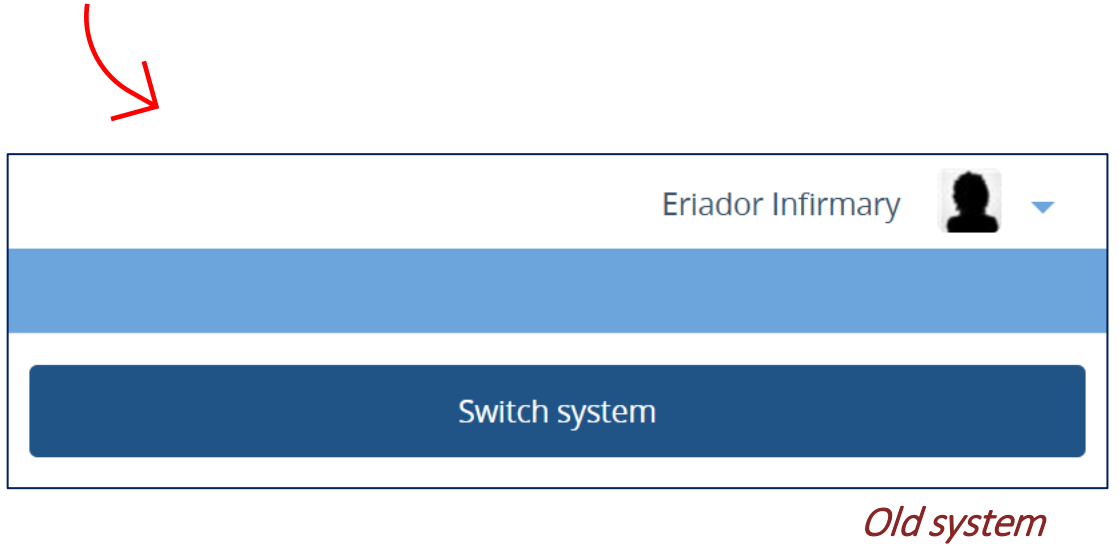
- Pregnancy status at hospital discharge if part of Immune Modulation domain
- If no longer pregnant at hospital discharge, complete from medical records
- If pregnant at hospital discharge, follow up at d180 unless info is available earlier from medical records
- If still pregnant at d180, complete additional follow up approx. 6 weeks after delivery due date

Qs include neonatal outcome, date, birth weight, sex, NICU admission info, neonatal status 1 month post birth, anomalies at delivery.

Old vs. New Database

- Once your site is activated for Core Protocol V4.0, your eCRF accounts will be linked to the new database system.
- You can access the entered eCRF data under **both** database systems by selecting the **“Switch System”** button on your landing page.

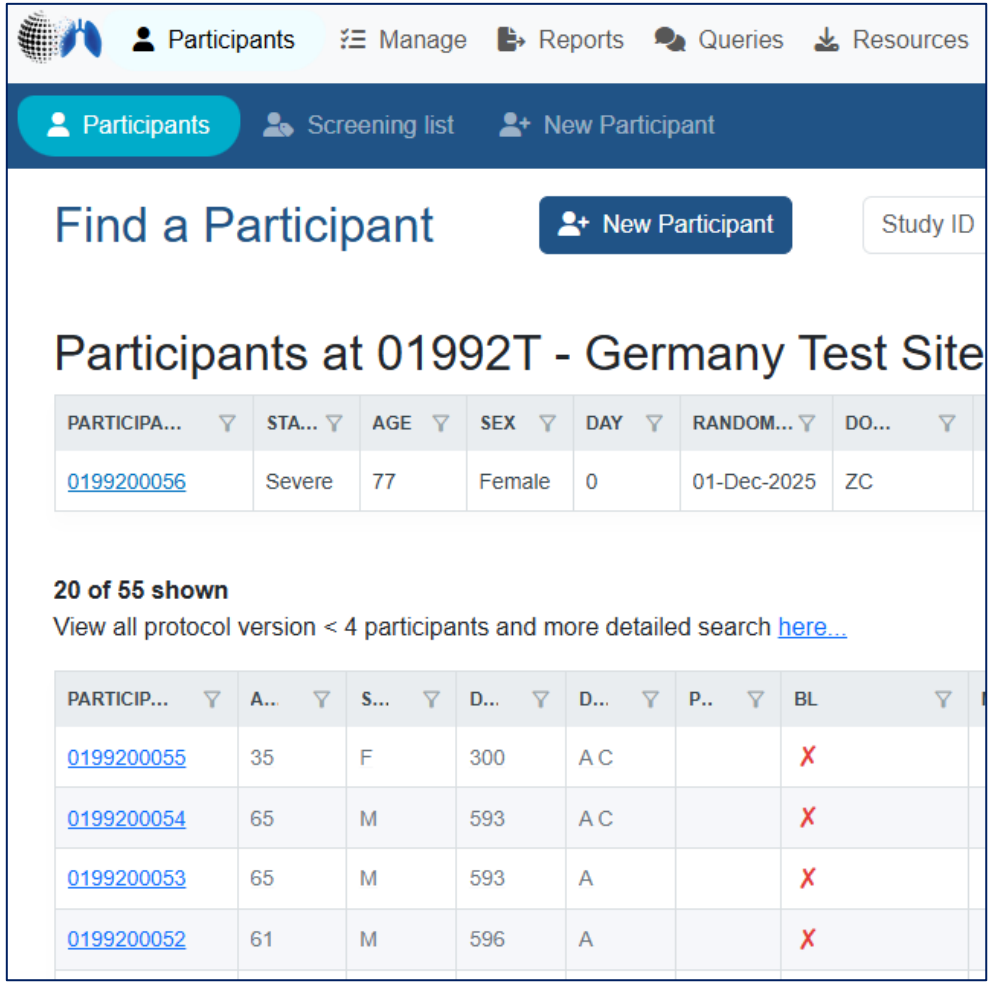




Only **new patients** recruited under Core Protocol V4.0 are saved in the **new database** system.

Previously enrolled participants under Core Protocol V3.1 remain in the old database system.

No reconsent is needed for patients recruited under Core V3.1 (no changes in protocol).

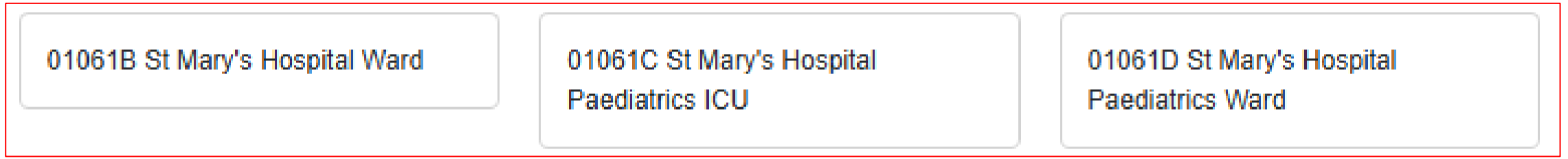


New system

Email Notifications

Updated format for randomisation email notifications:

- **Site code** in email body will include a letter denoting site type (adult ICU/ward or paed ICU/ward) i.e. A, B, C, D or T for test site



- **2-character domain codes** will replace the previous single letter domain code
- **Illness Severity State** (“moderate” or ”severe”) will replace previous text of “Pandemic infection not suspected or confirmed” and ‘Pandemic infection suspected or confirmed”

Hi Vanessa Singh,

Vanessa Singh has enrolled new participant 0299900558 at 02999T - AU Test Site 99

Randomised into:
XA Tropical Antibiotic
ZC Corticosteroid
ZI Influenza Antiviral (Reveal pending)
ZM Macrolide Duration (Reveal pending)
ZN Influenza Immune Modulation (Reveal pending)

State: Severe

Participants enrolled by 02999T - AU Test Site 99: 14
Trial participants: 0

Go to the REMAP-CAP online platform.

from,
Spinnaker Software for the REMAP-CAP Study
Please do not reply to this email as I'm just a piece of software and I won't understand your email.

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IMP Procedures

IMP Procedures

Baloxavir & Tocilizumab are provided by Roche from clinical trial stock and is supplied with clinical trial labelling.

All other IMP are from hospital stock.

For IMP from external suppliers (Roche):

- Training on ordering, temperature and storage monitoring, drug accountability and destruction is provided prior to activation of domains. Study templates also provided.

For IMP from hospital stock: Site's routine procedures to be followed for drug accountability, temperature monitoring and destruction

- As long as information is clearly captured and accountability can be monitored from drug charts/medical notes

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Safety

Safety Reporting

Safety event definitions were updated in the protocol.

Reminder: Only protocol defined SAEs need to be reported

- 1. SAEs deemed to be possibly, probably or definitely related to study treatment / participation.
- 2. Pre-specified SAEs listed in the DSAs

Reminder: It is expected that site investigators make an initial (documented) assessment on event severity, relatedness and expectedness:

- An SAE is considered 'expected' if the nature and severity of the event is consistent with the current approved version of the reference safety information (SmPCs).
- Expectedness should be assessed "from the perspective of previously observed, not on the basis of what might be anticipated from the pharmacological properties of a medicinal product" (ICH E2A, 1994).

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Informed Consent

Informed Consent

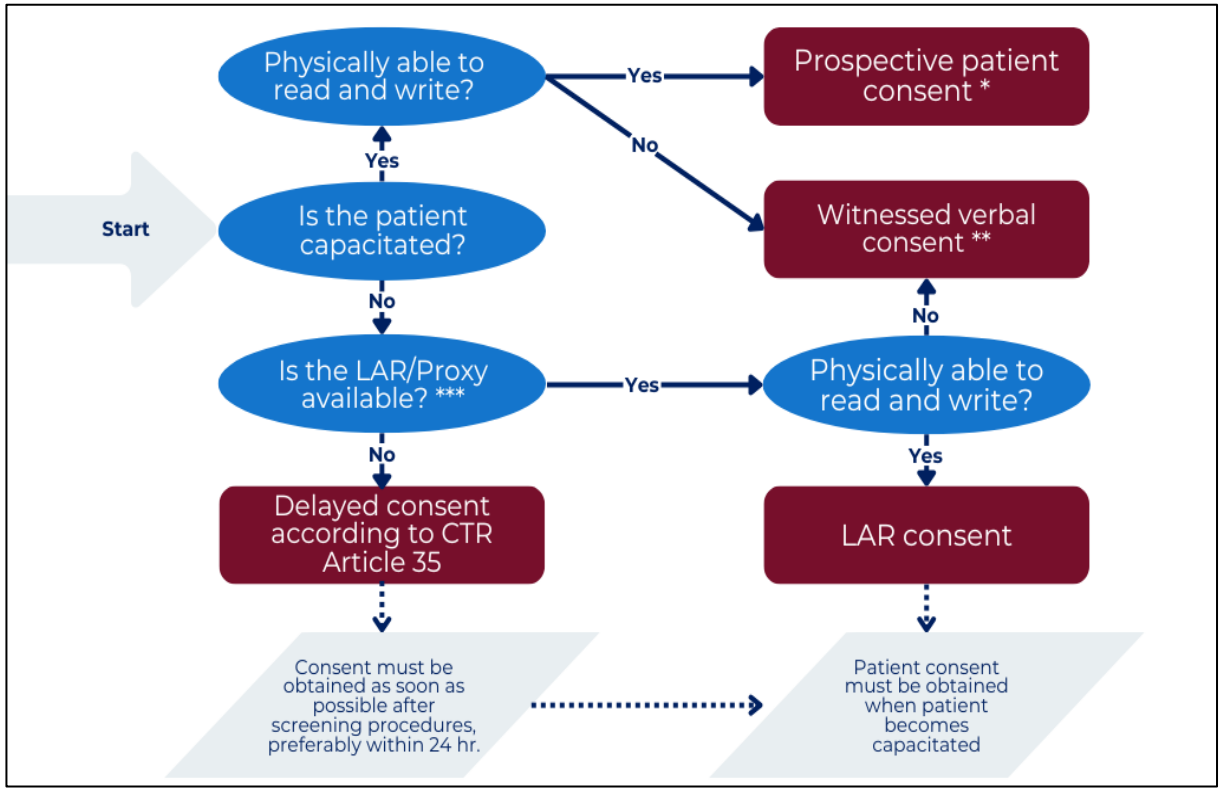
- Obtaining Informed Consent in an emergency setting is now described in the **EU RSA V4** for all countries and aligned with CTR requirements.
- **EU RSA: UK Country Annex** lists approved consent types and procedures, as described in refresher training session.

*** Prospective patient consent** is the default consent type.

**** In case of verbal/telephone consent,** the witness should be impartial (not involved in the trial). Alternative methods for consent include watching a video, or summary IS.

***** Order of Legal Representative priority:**

1. Legal rep appointed by court (adults/children) or parent (children)
2. Personal Legal Rep (adults)
3. Professional Leg Rep (adult/children)



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ICH-GCP

ICH-GCP E6 R3

Effective date for Revision 3 was 23rd July 2025 in the EU.

Mandatory in the UK as of 28th April 2026.

Please file your (updated) GCP certificates in the ISF and share with Trial Management team for TMF filing, **by end of April 2026!**

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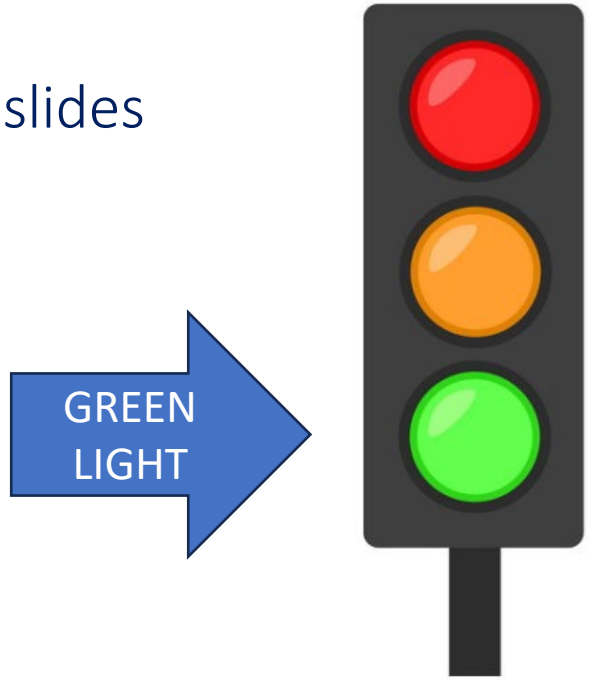
Practical Information

What's Next?

Expected from sites:

- Attend Core Protocol V4 Transition training / self-train via slides
- Provide (self-) training logs for:
  - Core protocol v4 transition training
  - Protocol v4 and associated documents
  - Updated DSAs

- Complete Protocol Signature Page and Choice Pages
- Complete Spiral Database Form
- All the above to be filed in ISF



Provided to sites by us:

- Self-training logs with all mandatory documents/slide decks listed for self-training
- Updated eCRF guides and associated eCRF documents
- Protocol documents and PIS/CFs (already sent as part of Am43 and on the study website under **Protocol v4 training module**)

Site staff should be trained on Core V4 and provide all documents before conducting any Core V4 trial-related tasks!!!

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AoB

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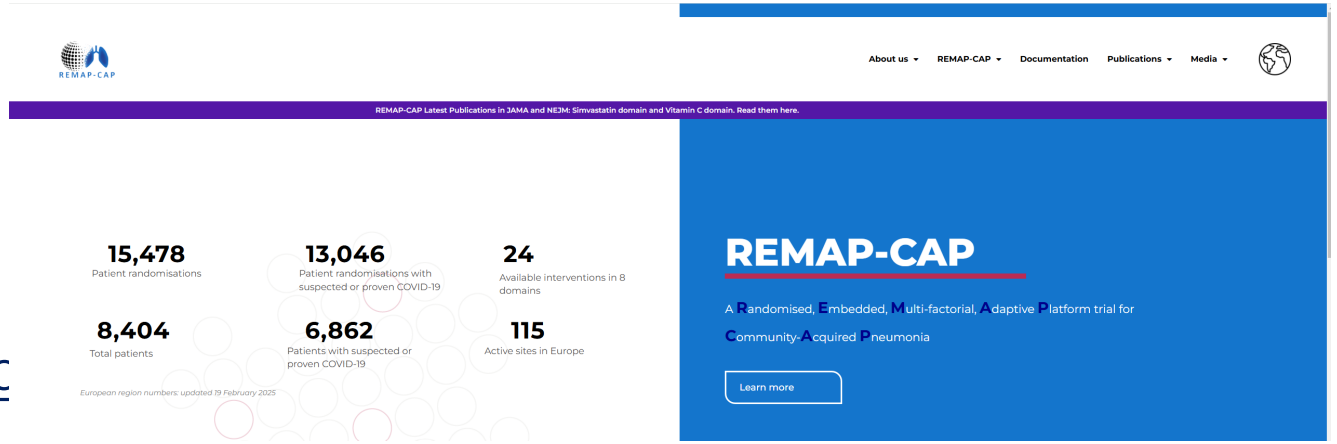

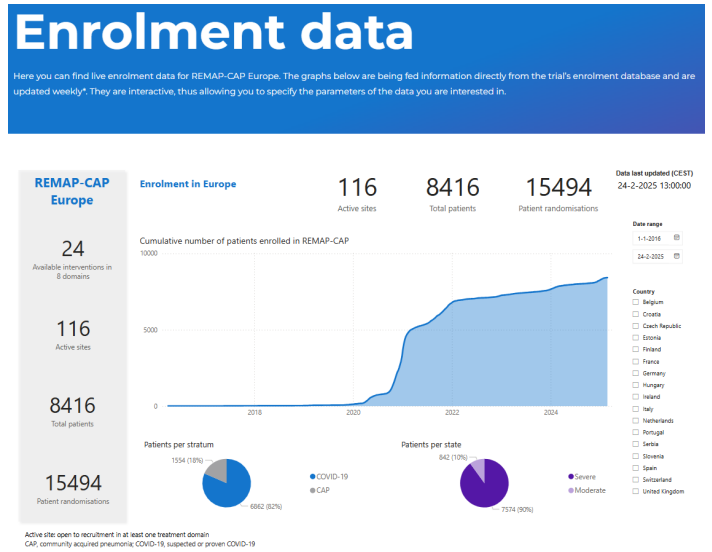

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Lindsay Jack - Trial Monitor

Tina Reetun - Trial Monitor

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THANK YOU!