REMAP-CAP

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NIHR | National Institute for Health Research

REMAP-CAP

SITE INITIATION VISIT

UK - PAEDIATRICS

VERSION 5.1

16 DEC 2024

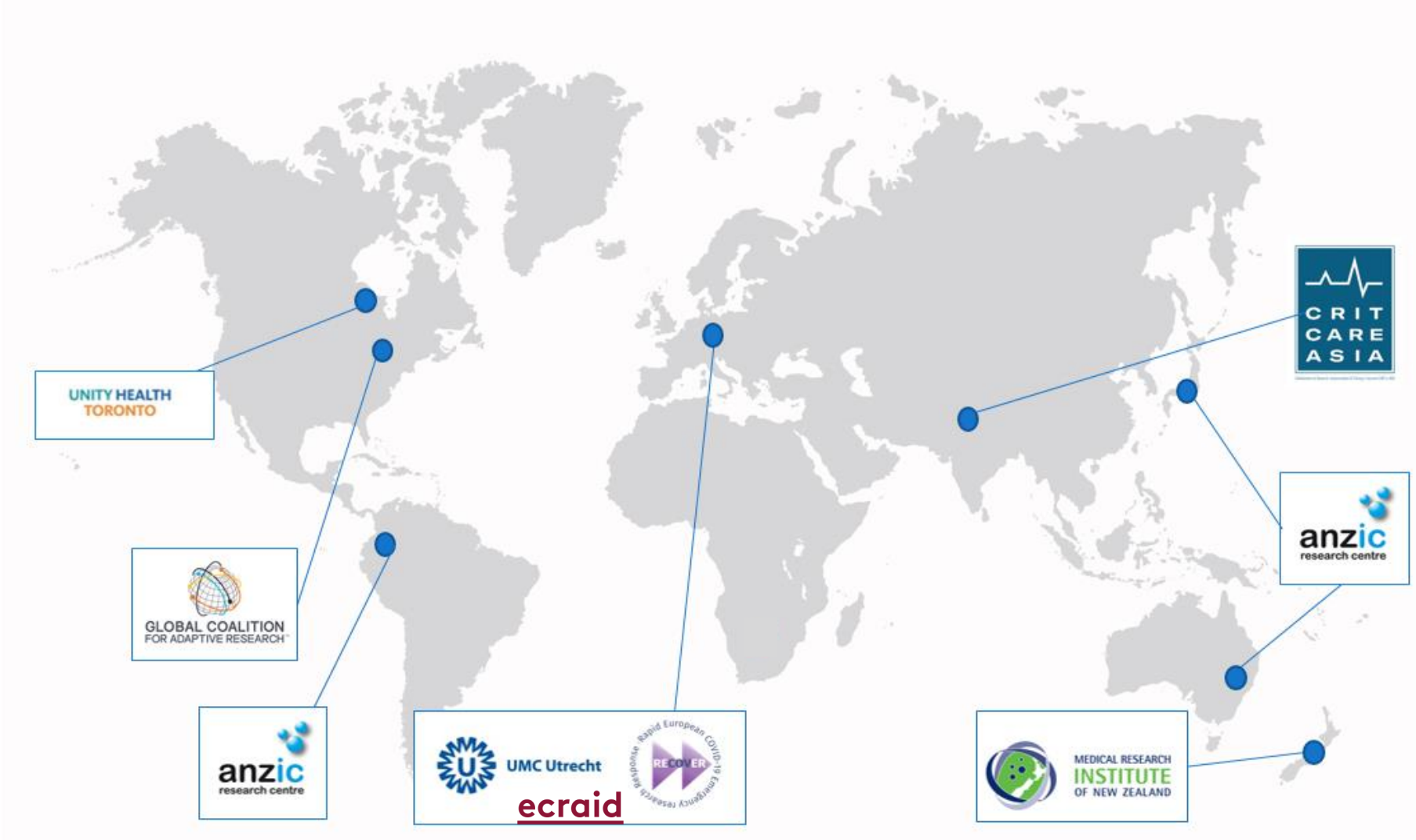
AGENDA

REMAP-CAP

- Meet the team
- Trial design
- Protocol
- Safety
- Study procedures
- ICH-GCP & GDPR
- Practical information

REMAP-CAP MEET THE TEAM

SPONSORS AROUND THE GLOBE



TEAM INTRODUCTION: SPONSOR

Lead Investigator EU: Lennie Derde

Co-lead Investigator EU: Marc Bonten

Co-Investigator EU: Helen Leavis, Marjolein Hensgens

Medical Monitor EU: Lennie Derde, Marjolein Hensgens, Anthony Gordon

Country PM: Lina Malkova

Country CTA: Sonal Patil

REMAP-CAP
Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia

UMC Utrecht

TEAM INTRODUCTION: COUNTRY

Country lead PI: Prof Anthony Gordon

UK Management: Imperial College London

UK CTU: ICNARC

UK Management & Monitoring Team: Janis Best-Lane, Aisha Anjum, Lucy Stronach, Beren Barklam, Lindsay Jack, Elizabeth Fagbodun, Tina Reetun, and Walton Charles

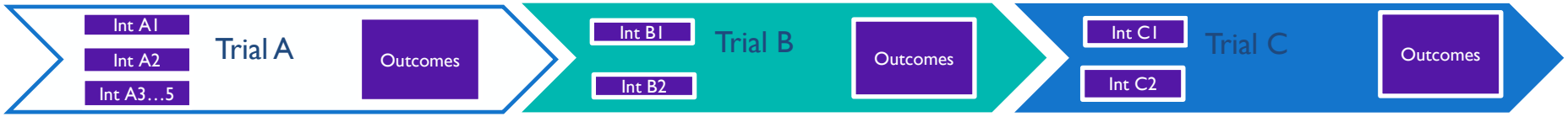
REMAP-CAP
Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia

REMAP-CAP TRIAL DESIGN

TRIAL DESIGN: ADAPTIVE PLATFORM TRIAL (APT)

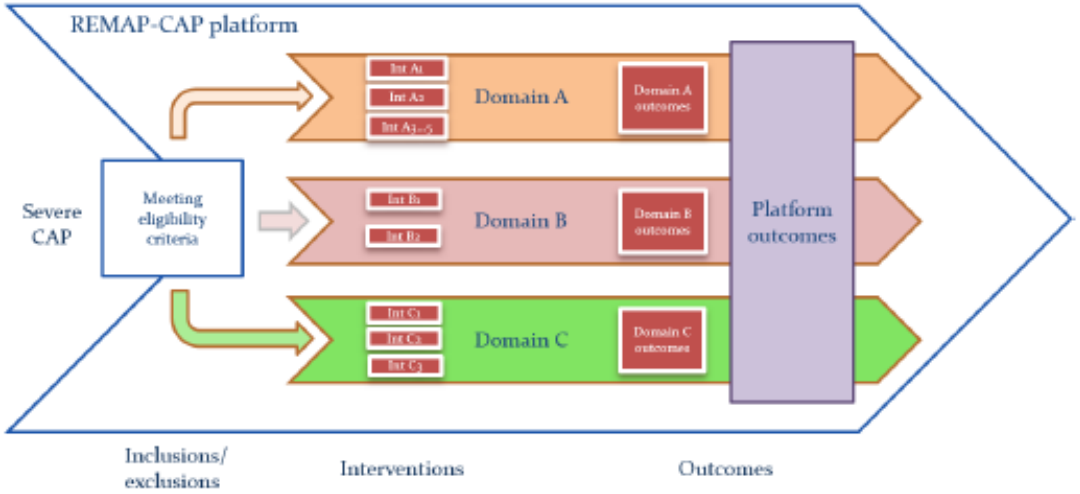
Traditional RCTs

- Serial testing of single hypotheses
- Set randomization ratio

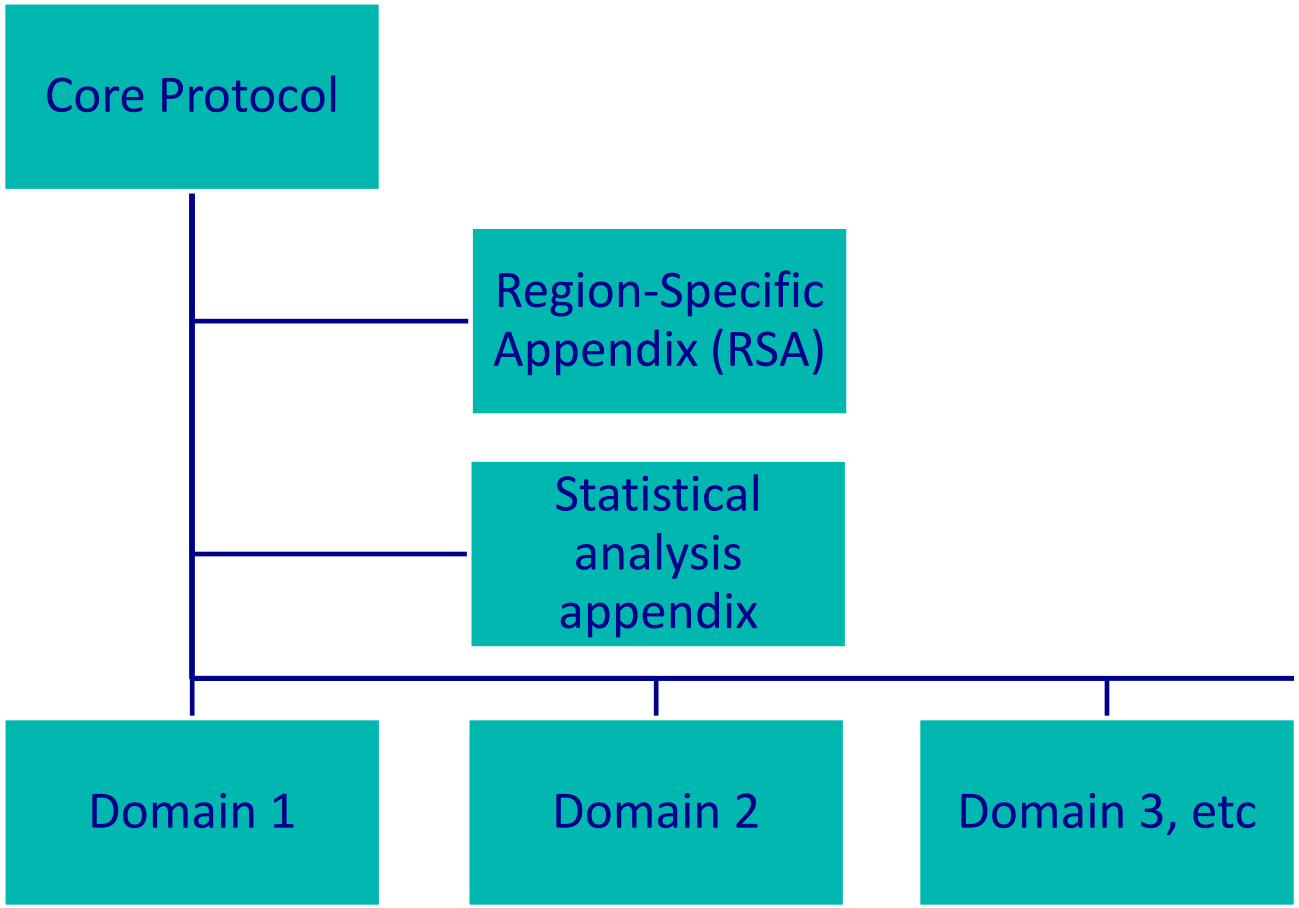


APT – REMAP-CAP

- Parallel testing of multiple hypotheses
- Adaptive
  - Interventions added or removed over time
  - Response Adaptive Randomization (RAR)



TRIAL DESIGN: MODULAR PROTOCOL STRUCTURE



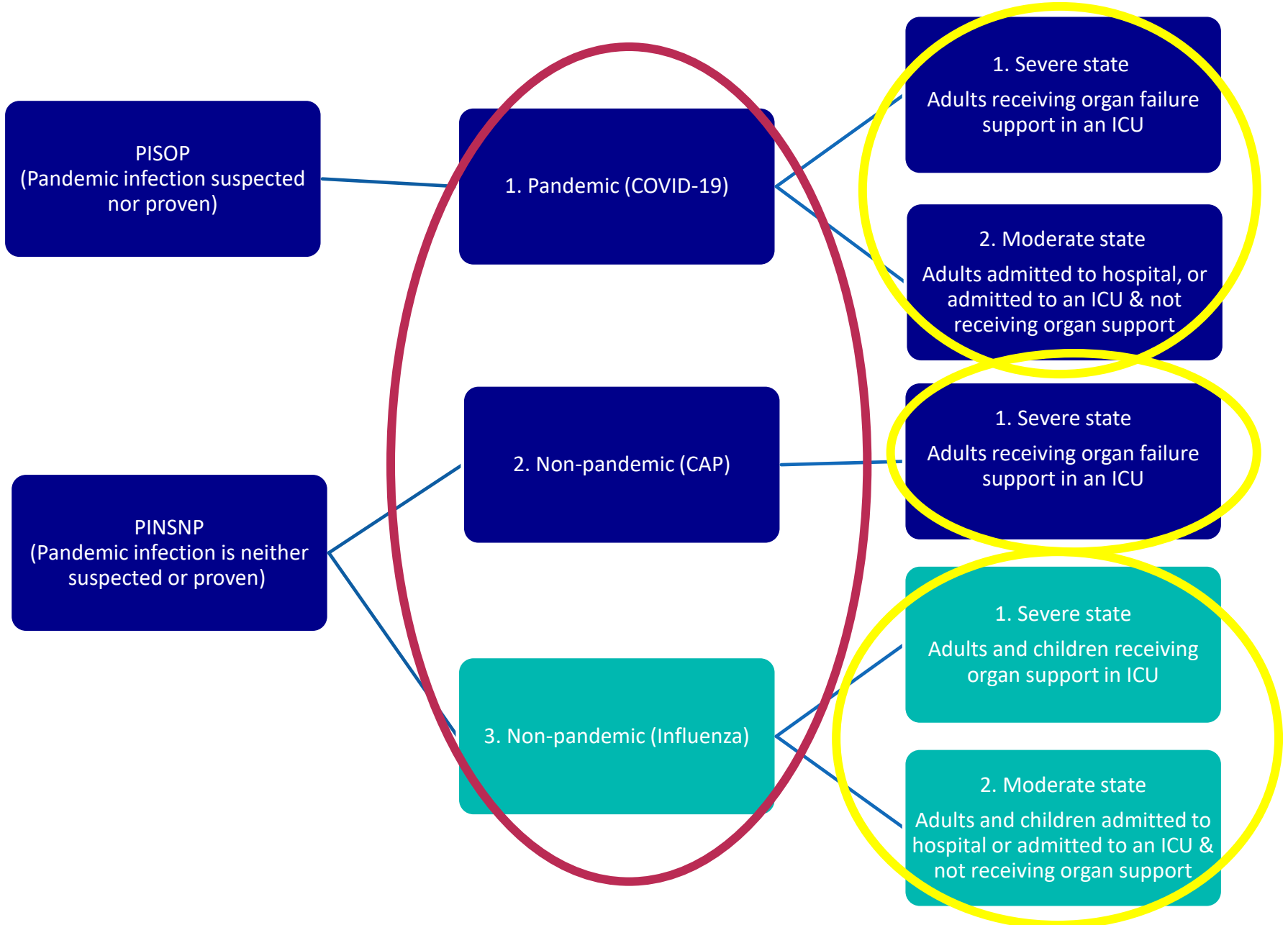
Non-pandemic situation

REMAP-CAP PROTOCOL
CORE PROTOCOL AND PANDEMIC APPENDIX TO CORE

PATIENT POPULATION

The trial is divided into
3 strata
1. Pandemic
2. Non-pandemic CAP
3. Non-pandemic FLU

2 states
1. Severe
2. Moderate



PATIENT POPULATION

	Non-pandemic subjects (CAP)	Non-pandemic subjects (FLU)		Pandemic subjects (COVID-19)	
Strata	PINSNP (Pandemic infection is neither suspected nor proven)	PINSNP (Pandemic infection is neither suspected nor proven)		PISOP (Pandemic infection is suspected or proven)	
Patients	Adults	Adults and Children		Adults	
	Admitted to Hospital for CAP	Admitted to Hospital for Influenza		Admitted to hospital for acute illness (suspected to be) caused by pandemic infection	
	←	within 14 days of hospital admission		→	
States	<u>Severe</u> receiving organ failure support in an ICU	<u>Moderate</u> Ward patient, **OR** admitted to an ICU but not receiving organ failure support	<u>Severe</u> receiving organ failure support in an ICU	<u>Moderate</u> Ward patient, **OR** admitted to an ICU but not receiving organ failure support	<u>Severe</u> receiving organ failure support in an ICU

ELIGIBILITY CRITERIA – CORE PROTOCOL V3.1

Inclusion Criteria

1. Adult or paediatric patient (28 days or older) hospitalised with an acute illness due to a lower respiratory tract infection

ELIGIBILITY CRITERIA – CORE PROTOCOL V3.1

Exclusion Criteria

1. More than 14 days has elapsed since admission to hospital
2. If receiving organ failure support in an ICU, more than 48 hours has elapsed since admission to ICU
3. Expected to be discharged from this hospital admission within the next 24 hours
4. Death is deemed to be imminent and inevitable during the next 24 hours AND one or more of the patient, substitute decision maker or attending physician are not committed to full active treatment.
5. Previous participation in this REMAP within the last 90 days

ENDPOINTS

Endpoints will be merged
in the next Protocol

	Non-pandemic subjects	Pandemic subjects
Primary	Day 90 mortality	Day 21 mortality and organ support free days
Secondary	Day 180 mortality / Quality of Life Questionnaires	Day 90 mortality and Day 180 mortality / Quality of Life Questionnaires
Remember	Endpoints require timely entry in the eCRF	Response Adaptive Randomization!

REMAP-CAP DOMAIN SPECIFIC APPENDICES (DSA)

Refer to DSAs for:

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

Domain summary slides are part of this SIV training

In addition **review DSA and DSA training slides**

Reach out to the Project Team with any **questions**

****All treatments should commence immediately after randomisation****

NON-PANDEMIC FLU STRATA
- INFLUENZA ANTIVIRAL DOMAIN
-CORTICOSTEROID DOMAIN

BACKGROUND - INFLUENZA

Seasonal influenza estimated ~ 300,000 to 650,000 deaths worldwide annually

Currently, recommended antiviral agents for influenza (**oseltamivir**) have **not been studied** in placebo controlled randomised trials to demonstrate survival benefit in hospitalized patients with influenza

Widely used in clinical practice

Baloxavir is a newly approved antiviral with evidence of benefit in outpatients on time-to-symptom resolution, but no evidence of benefit in inpatients

Whether it has value by itself, or in combination with oseltamivir, in inpatients is an open question

INFLUENZA ANTIVIRAL DOMAIN

VERSION 2.1, 14FEB23

Domain	Strata	State	Patients	Intervention	Administered
Influenza Antiviral (A)	**Non-pandemic and pandemic FLU (ie co-infections are eligible)**	**Severe & moderate**	**Adults & Children**	I1 - No antiviral for influenza	-
				I2 - 5 days of Oseltamivir	5 days / discharge
				I3 - 10 days of Oseltamivir	10 days / discharge
				I4 - Baloxavir	Days 1 and 4 / discharge
				I5 - 5 days Oseltamivir and Baloxavir days 1 and 4	5 days OT and day 1 and 4 Balox / discharge
				I6 - 10 days Oseltamivir and Baloxavir days 1 and 4	10 days OT and day 1 and 4 Balox / discharge

ELIGIBILITY CRITERIA – INFLUENZA ANTIVIRAL DOMAIN

Inclusion Criteria

1. Adult or paediatric patient (28 days or older, CGA)
2. Influenza infection is confirmed by microbiological testing

ELIGIBILITY CRITERIA – INFLUENZA ANTIVIRAL DOMAIN

Exclusion Criteria

1. Moderate state: More than 96 hours since hospital admission
2. Severe state: More than 48 hours since ICU admission
3. Already received 2 doses of oseltamivir (or any other neuraminidase inhibitor) or 1 dose of baloxavir – other neuraminidase may include zanamivir and peramivir
4. Known hypersensitivity to agents
5. Pregnancy (baloxavir interventions only)
6. Clinician does not feel best interests in participating

INFLUENZA ANTIVIRAL INTERVENTIONS (ADULTS & CHILDREN)

• No antiviral agents active against influenza -	Do not prescribe any antiviral active against influenza, including oseltamivir until the end of study day 28 or hospital discharge, whichever occurs first

Oseltamivir

• **5-days of oseltamivir***	Prescribe a 5-day course of oseltamivir commencing immediately after randomization – (10 doses with BD administration)
• 10-days of oseltamivir	Prescribe a 10-day course of oseltamivir commencing immediately after randomization – (20 doses with BD administration)

Can use hospital stock of Oseltamivir. Dosing for adults & children in as per local guidelines.
Standard adult dose is of Oseltamivir is 75 mg enterally BD - Dosing for children is 6 mg/kg/day, divided into two doses up to children of 40kg.
See protocol for dose adjustment for renal dysfunction
Cease all treatment after the treatment course (5 days / 10 days) or after hospital discharge, whichever occurs first.
***5-days of oseltamivir -** For continuity across regions, important for all sites to participate in this intervention

INFLUENZA ANTIVIRAL INTERVENTIONS

Baloxavir (adults & children)

• Baloxavir on days 1 and 4	Given on days 1 and 4 , can give an added dose on day 7 if the treating clinician feels it is clinically indicated
• Combination Baloxavir + 5 days oseltamivir	Baloxavir given on days 1 and 4 and oseltamivir given for 5 days (10 doses oseltamivir with BD administration)
• Combination Baloxavir + 10 days oseltamivir	Baloxavir given on days 1 and 4 and oseltamivir given for 10 days (20 doses oseltamivir with BD administration)

Baloxavir is supplied by Roche (via study team), can use hospital stock too if available.
Baloxavir dose: <40kg = 2mg/kg (max dose of 40mg), 40-80kg = 40mg, >80kg = 80mg
No adjustment for renal/hepatic impairment

SWAB COLLECTION (ANTIVIRAL DOMAIN ONLY)

- After site activation nasal swab kits/safe boxes will be provided to site.
- Please collect nasal swabs from ALL positive influenza patients on the following days:-
  - Day 1 (soon after randomisation)
  - Day 3 (+/- 24 hrs or asap if D3 not possible)
  - Day 7 (+/- 24 hrs or asap if D7 not possible)

- Please post patients' Day 1 and Day 3 samples together in one safe box. Do not wait for Day 7 sample to be taken as samples are not viable after 5 days. Day 7 sample to be sent separately.
- Please enter sample collection on the eCRF

SWAB COLLECTION (ANTIVIRAL DOMAIN ONLY)

Notes:

- Subsequent sample(s) should be taken even if a sample is missed.
- Please do not use hospital swabs as these are not the correct type that we require for the study
- Sites may use a sample tracker if they wish Influenza Antiviral Swab Tracker V1.0 30.01.2024 – Remapcap-UK

Xmas/Easter

Do not send swab samples as central labs are closed – keep refrigerated until labs are open.

If you have no refrigeration space, miss the samples, it will not be PD

BACKGROUND - CORTICOSTEROIDS

- Several RCTs and meta-analyses have suggested benefit of treatment with corticosteroids, however existing evidence is not definitive, and corticosteroids have a range of potentially adverse effects

- Potential benefit appears to be more likely for patients who are severely ill

- Uncertainty about the use of corticosteroids in:
  - Patients with CAP due to influenza
  - Patients with septic shock vs those without septic shock
  - Patients with ARDS vs no ARDS.

CORTICOSTEROID DOMAIN

VERSION 5.0, 09NOV22

Adults

Domain	Strata	State	Intervention	Administered
Corticosteroid (C)	Non-pandemic CAP & FLU	Severe	C1 - No corticosteroid C3 - Shock-dependent hydrocortisone C4 – Fixed-course dexamethasone	- During septic shock 10 days
	Non-pandemic CAP & FLU	Moderate	C1 - No corticosteroid C4 – Fixed-course dexamethasone	 10 days

Children

Domain	Strata	State	Intervention	Administered
Corticosteroid (C)	Non-pandemic CAP & FLU	Severe	C1 - No corticosteroid C4 – Fixed-course dexamethasone	- 10 days
	Non-pandemic CAP & FLU	Moderate	C1 - No corticosteroid C4 – Fixed-course dexamethasone	- 10 days

ELIGIBILITY CRITERIA – CORTICOSTEROID DOMAIN

Inclusion Criteria

1. Adult or paediatric patient (28 days or older, CGA)
2. If in the Moderate State, receiving some form of supplemental oxygen
    - Simple facemask, low- or high-flow oxygen, or non-invasive ventilation

ELIGIBILITY CRITERIA – CORTICOSTEROID DOMAIN

Exclusion Criteria

1. Intention to prescribe systemic corticosteroids for a reason that is unrelated to the current episode of CAP/FLU (or direct complications of CAP)
2. More than 24h have elapsed since ICU admission (if in the Severe State)
3. Known hypersensitivity to any corticosteroid
4. The treating clinician believes that participation in this domain is not in the best interests of the patient

Note: If in the Moderate State, platform exclusion applies - More than 14 days have elapsed while admitted to hospital

CORTICOSTEROID INTERVENTIONS

- No Corticosteroids - Adults & Children

  Do not prescribe any systemic corticosteroid, including hydrocortisone or dexamethasone until the end of study day 28 or hospital discharge, whichever occurs first. *Administration of systemic corticosteroids for the treatment of new illnesses that develop in the course of a patient's ICU stay (i.e., not resulting from CAP/FLU or its direct complications) is permitted*

- Shock-dependent hydrocortisone - Adults Only

  Commence hydrocortisone IV 50 mg 6 hourly when patient is in septic shock*, cease once clinician believes septic shock is resolved, *note that septic shock is always considered to be resolved when vasopressors have not been administered via infusion in the preceding 24 h*

- Fixed dose dexamethasone - Adults & Children

  Prescribe dexamethasone (IV or enteral), adults 6mg / children 0.15 mg/kg (max 6mg) daily, cease after 10 days or hospital discharge, whichever occurs first.
  See protocol for pregnancy requirements. *If patient develops septic shock, a switch from dexamethasone to hydrocortisone is permitted.*

Can use hospital stock of hydrocortisone and dexamethasone

***See protocol for septic shock definition**

REMAP-CAP SAFETY

SAFETY - DEFINITIONS

Event	Definition	Causal relation Necessary
Adverse Event (AE)	Any untoward medical occurrence in a subject to whom a medicinal product is administered	NO
Serious Adverse Event (SAE)	Any untoward medical occurrence that at any dose requires • **inpatient hospitalisation or prolongation of existing hospitalisation**, results in • **persistent or significant disability or incapacity**, results in • **a congenital anomaly or birth defect,** • is **life-threatening**, or results in • **death**	NO
Domain specific SAE's	Safety events defined in the Domain Specific Appendices	YES
Suspected Unexpected Serious Adverse Reactions (SUSAR)	'Unexpected serious adverse reaction' means a serious adverse reaction, the nature, severity or outcome of which is not consistent with the reference safety information	YES

SAFETY - REPORTING

Event type	Reporting required per protocol
SAE's related to a study intervention or study participation (including SUSARs)	**YES** (from randomization to hospital discharge)
SAEs not related to study intervention or study participation	**NO** (unless needed per country requirements)
AE's	**NO** (unless needed per country requirements)
Domain-specific SAE's	**YES** (refer to DSA for details)
Domain-specific secondary endpoints	**YES** - report as SAE and endpoint for SAE's related to study intervention or study participation **NO** - for SAE's not related to a study intervention or study participation, unless needed per country requirements – report endpoints via eCRF discharge page

SAFETY - REPORTING

Report safety event within 24 hours of becoming aware of event

Investigator assesses **relatedness,**

expectedness,

severity,

seriousness

	SAE types
	Not related
	Unlikely to be related
Expected to be reported	Possibly related
	Probably related
	Definitely related

Use an **SAE form in the eCRF**	**Back-up** SAE form available in ISF E-mail to: eu.remapcap@umcutrecht.nl ukremap-cap@icnarc.org	**Document relevant information** in the patient file Follow up with patient until SAE is resolved

SAFETY - REPORTING

SAE report types:

- **Initial SAE report**
- **Follow-up SAE report**
- **Final SAE report** → **Print and file in ISF**

Medical Monitor reviews all reported safety events

The monitor will follow up on any requests from the Medical Monitor.

The **Data Safety Monitoring Board** monitors overall safety for REMAP-CAP.

REMAP-CAP INFORMED CONSENT

INFORMED CONSENT - DEFINITION

'a process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form' (ICH-GCP)

INFORMED CONSENT PROCESS - WHO

Consent types	Definition	Involved	Use	
Parent / guardian	Consent obtained from parent/ guardian	Subject Parent/guardian	When parent/guardian has capacity	**ALWAYS IN ACCORDANCE WITH APPROVED PROCESSES PER LOCAL LAW AND REGULATION**
ProLR consent	Consent obtained from a person other than the parent/ guardian	ProLR: Clinician **independent** of the study for child	When parent/guardian does not have capacity or is not available to consent and ProLR is present.	
Witnessed consent	Consent obtained in the presence of an impartial witness	Subject Parent / guardian Impartial witness: Visitor or **independent** nurse	Required when parent/guardian/ cannot write and verbal consent is taken instead of written consent or When remote consent is obtained (via telephone)	

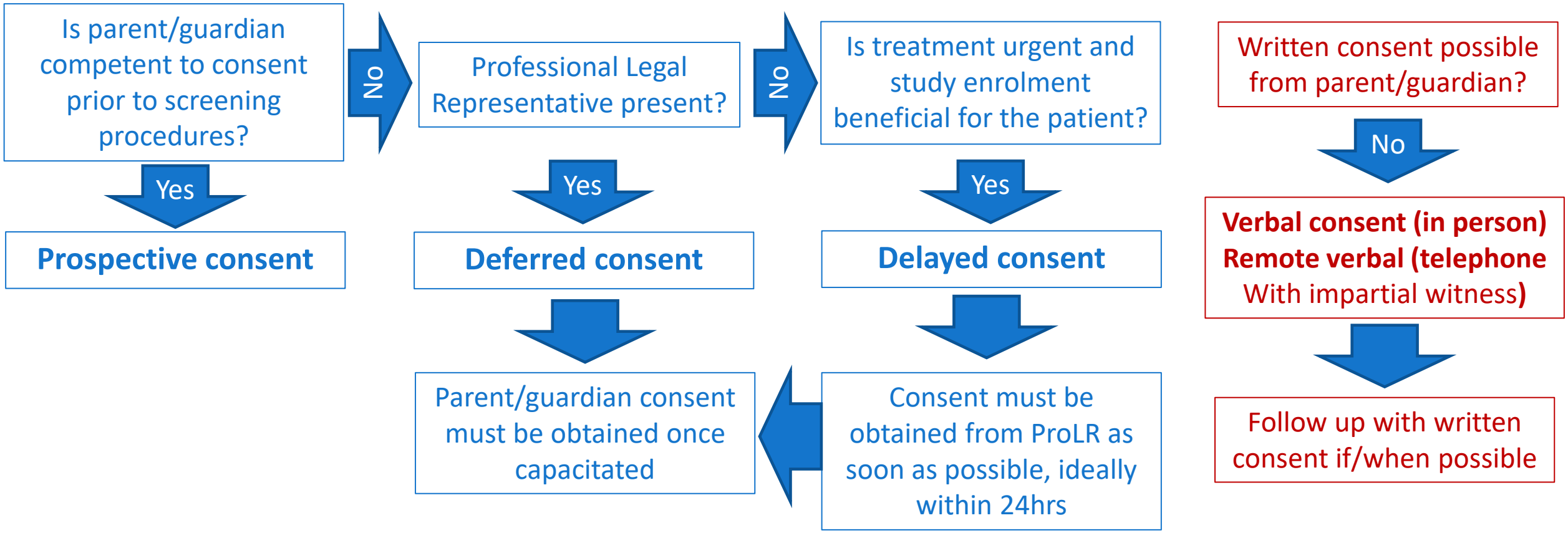
INFORMED CONSENT PROCESS - WHEN

Consent types	Time point	Involved	Use	
Prospective consent	Consent obtained prior to start of screening activities	Parent/guardian (witness, if verbal/remote)	When parent/guardian has capacity.	**ALWAYS IN ACCORDANCE WITH APPROVED PROCESSES PER LOCAL LAW AND REGULATION**
Deferred consent	Consent obtained prior to screening activities	ProLR	When parent/guardian doesn't have capacity or not available and ProLR is present.	
Delayed consent	Consent obtained after patient is enrolled in study	Parent/guardian or ProLR (witness, if verbal/remote)	In emergency setting when parent/ guardian doesn't have capacity or is not available and ProLR also not available. Consent must be attempted/obtained as soon as possible from parent/guardian or ProLR (ideally within 24 hrs).	
Retrospective consent	Consent obtained after patient is enrolled in study	Parent/guardian (witness, if verbal/remote)	Where only ProLR consent was obtained. Obtained when parent/guardian is available and capacity is regained.	

INFORMED CONSENT PROCESS - HOW

Consent types	Applied when	Involved	Documentation	
Written consent	Parent/guardian or ProLR, can write	Parent/guardian ProLR	Documented on a paper Informed Consent Form (ICF) – written version.	**ALWAYS IN ACCORDANCE WITH APPROVED PROCESSES PER LOCAL LAW AND REGULATION**
Verbal consent	Parent/guardian cannot read or write	Parent/guardian Impartial witness	Documented on a paper Informed Consent Form (ICF) – written version with witness section completed.	
Remote / Telephone consent	Parent/guardian and site staff are not in the same location or cannot be present in person promptly or When patient is d/c from hospital promptly and retrospective parent/ guardian consent is required	Parent/guardian Impartial witness	Documented on a paper Informed Consent Form (ICF) – telephone version with witness section completed. Also obtain written consent from parent/guardian if possible.	
Video consent	Parent/guardian have requested information in a different format	Parent/guardian	Documented on a paper Informed Consent Form (ICF) – video version. Provide copy of full PIS too.	

INFORMED CONSENT PROCESS - **ADULTS** - FLOWCHART



INFORMED CONSENT PROCESS – PAEDIATRICS

The following consent forms are available:-

- **Young Child and Guardian**
  To be used where children are <10 years old

- **Children and Guardian 10-15**
  For children 10-15yrs old

- **Child 16-17**
  For children between 16-17 yrs old

Waiting to be approved as part of Am42:

- Telephone consent form
- Video consent form
- Summary IS/CF

INFORMED CONSENT PROCESS - DOCUMENTATION

Documentation must include information regarding:

- **Who informed the parent/guardian/ProLR** about the study **and when** was this interview held.
- **Method for obtaining informed consent** (including alternative methods during a pandemic).
- For parent/guardian consent: **Confirmation status was adequate to decide on study participation.**
- For ProLR consent: **Verification of status** i.e. independent of study

Additional preferred items:

- Parent/guardian/ProLR were **able to ask questions** from a study investigator
- Parent/guardian/ProLR was **given enough time** to consider study participation
- **Which version** of the ICF was signed
- Parent/guardian/ProLR were **given a copy** of the PIS/ICF

It should be clear from the documentation site adhered to site and REMAP-CAP approved procedures for obtaining Informed Consent.

REMAP-CAP STUDY PROCEDURES

SCREENING

Site specific eligibility checklist to be printed/downloaded from eCRF (Spinnaker)
Complete screening and enrolment log
Eligible patients entered in eCRF and go through the **digital eligibility assessment**
Subject randomized, or if screen failure → moved to Registry list

What is your **screening method**?

SUBJECT RECRUITMENT

Important to have a clear recruitment strategy

Who is involved in subject recruitment?
Who is responsible for subject recruitment?
What is your **target recruitment frequency**?
Any expected **challenges**?
How is REMAP-CAP **shared with non-study staff**?
Can we provide **support**?

What is your **recruitment strategy?**

RANDOMISED SUBJECTS

- Treat patients according to protocol & randomization result
- Study participation must be visible in patient (electronic) file
- If applicable: order study drugs
- Complete eCRF pages (can be weekly)
  - Enter endpoint data on time (notification is sent)

If subject withdrawn from treatment	**If subject withdraws consent**
Document reason in source	Consent event eCRF needs to be completed ➡ The patient will be locked in the eCRF

PROTOCOL DEVIATIONS - DEFINITIONS

	PD category	Minor	Major
1	Violation of one or more of the eligibility criteria	Violation of 1 of the eligibility criteria, not affecting subject safety.	Violation of > 1 of the eligibility criteria, or 1 deviation that affects subject safety.
2	Incorrect study treatment/drug dosing	≥2 doses of Oseltamivir missed ≥1 doses of Baloxavir missed	> 2 dose errors
3	Use of protocol prohibited concomitant care	-	Always major
4	SAE	Late reporting / incorrect or incomplete reporting	Unreported SAE
5	ICF	Incorrect version or completion ICF / ICF process	Missing ICF
6	Missing study data or (primary) endpoint	Missing data (no endpoint)	Missing endpoint data
7	Other deviation/violation	At the discretion of the monitor; when in doubt consider the deviation major.	
8	Domain specific protocol deviations	Refer to the Domain specific appendices for definitions of domain specific protocol deviations.	

PROTOCOL DEVIATIONS - REPORTING

Protocol deviations (PD) must be:

- Reported to the monitor
- Entered in the eCRF (per eCRF completion guideline)
- Signed off by the PI

Domain-specific deviations:

- Randomized but ineligible
- Allocated IMP not administered per protocol
- Received prohibited empiric IMP

In the eCRF

- Platform eligibility deviations
- Domain-specific deviations

For any other deviation use:

- Platform eligibility deviations => 'OTHER'

PDs are listed in the follow-up letter
File in ISF

INVESTIGATIONAL MEDICINAL PRODUCT (IMP)

Supply via:

- Hospital stock
- Pharmaceutical company

Ordering/procurement:

- Hospital stock: Via regular procedure of hospital pharmacy.
- External supply (pharmaceutical company): Via drug order request form.

IMP

Storage conditions per:

- SmPC (section 6.3 and 6.4) (only for registered medication)
- Pharmacy Guide

Labelling:

IMP

Preparation & administration per:

- Domain Specific Appendix
- Administration guide
- Pharmacy guide

Drug accountability at Pharmacy level:

- For marketed IMPs, Pharmacy inventory logs should be made available to the sponsor upon request for
  - IMP that is part of hospital stock, managed by hospital Pharmacy (routine records)
  - IMP provided by Sponsor/external, managed by Clinical Trials Pharmacy

- For unmarketed IMPs: This will always be managed by Clinical Trials Pharmacy and study specific inventory log templates will be provided

IMP

Drug accountability at ICU/Ward level

Marketed IMP: Dispensing accountability only, returns not required/accounted for

REMAP-CAP Study drug Accountability Log

EudraCT number	2015-002340-14	Site Name	
PI Name		Site Number	

Complete this part when collecting IMP from Pharmacy: *Complete this part when using the study drug on ICU:*

Date (dd/mm/yy)	Batch No.	Study Drug name	Study drug serial number	Expiry date (dd/mm/yy)	Collected from Pharmacy by (Initials)	Date used (dd/mm/yy)	Administered as per Protocol (Y/N)	Patient study ID	Monitor Review (initial & date)

Original to be kept in Investigator Site File.

REMAP-CAP Study drug Accountability Log V1.0, 04.06.2020 Page 1 of 1

Unmarketed IMP: Dispensing + returns logged, individual patient accountability logs

Subject Drug Accountability Form

Use 1 form per drug per subject

Site code (ABC-XYZ): ABC	PI name: Lennie Derde	Subject number (Spiral): 0199900001
Drug (compound): DMX-200	Drug (trade name): Repagermanium	Drug form & strength: 120 mg per capsule (30 capsules per bottle)

NB: complete one line for each IMP dose administration

Line #	Date dispensed	Amount & Units[1] dispensed; Route	Lot / Batch Number	Expiry date	Dispensed by (initials + date[2])	Amount & Units[1] remaining / returned[3]	Accountability completed by (initials + date[2])[3]	CRA review (initials + date)[3]
1	1 Apr 2020	120 mg = 1 capsule	X12345	02 Sept 2024	HP 1 Apr 2020	29 capsules	HP 1 Apr 2020	
2	2 Apr 2020	120 mg = 1 capsule	X12345	02 Sept 2024	HG 2 Apr 2020	28 capsules	HG 2 Apr 2020	
3	2 Apr 2020	120 mg = 1 capsule	X12345	02 Sept 2024	RW 2 Apr 2020	27 capsules	RW 2 Apr 2020	
4	3 Apr 2020	120 mg = 1 capsule	X12345	02 Sept 2024	HP 3 Apr 2020	26 capsules	HP 3 Apr 2020	
5	3 Apr 2020	120 mg = 1 capsule	X12345	03 Sept 2024	SS 3 Apr 2020	25 capsules	AD 3 Apr 2020	

[1] Example: 20 tablets, 3 ml, etc.
[2] Enter date of completion and signed initials. Staff member must be listed on the Authorization Form.
[3] Only applicable for IMPs without marketing authorization

IMP

Temperature control:

- For marketed IMPs: Temperature monitoring/excursions to be managed as per local processes. Any concerns submitted/discussed with Sponsor. Records to be made available to Sponsor upon request.
- For unmarketed IMPs: Temperature monitoring and study specific excursion forms to be maintained. Study templates will be provided.

Return and destruction:

- Hospital stock: Via routine local procedures
- Sponsor/external stock: Sponsor must be contacted. Study templates will be provided, but local destruction forms can be used.

Local pharmacies are responsible for monitoring expiration dates of IMPs throughout the study.

INVESTIGATOR SITE FILE

A (digital) Investigator Site File (ISF) is provided

Site responsibility to keep the ISF up-to-date

ISF tasks:

- File received ISF **document updates and correspondence**
- Add **documents of team members**
- Add **updates of certificates**
- Keep **logs up-to-date**
- Use **document referral notes** to document where to find specific documents (if not filed in standard location of ISF)

INVESTIGATOR SITE FILE: INDEX

1. Contact Information Study
2. Regulatory and Ethical documents
3. Financial Contracts / Signed Agreements
4. Study Protocol
5. Research Subject Information
6. WMO Subject Insurance
7. Site Personnel
8. Monitoring / Audit / Inspection documents
9. Working Procedures
10. Product Information / Pharmacy
11. Laboratory
12. Safety (including **SAE forms**)
13. Case Report Form (CRF)
14. File Notes
15. Documents of attended meetings
16. Lab Labels, request forms, shipment forms
17. Correspondence
18. Other

REMAP-CAP ICH-GCP & GDPR

ICH-GCP: INVESTIGATOR RESPONSIBILITIES

The investigator is **responsible for supervising** any individual or party to whom the investigator delegates **trial-related duties and functions** conducted at the trial site.	The investigator has **overall responsibility** for all aspects of the trial conducted at site.	The investigator must ensure the trial is conducted in accordance with: **ICH-GCP and applicable regulatory requirements.**

ICH-GCP: SOURCE DATA

The investigator/institution should maintain **adequate source documents and trial records**.

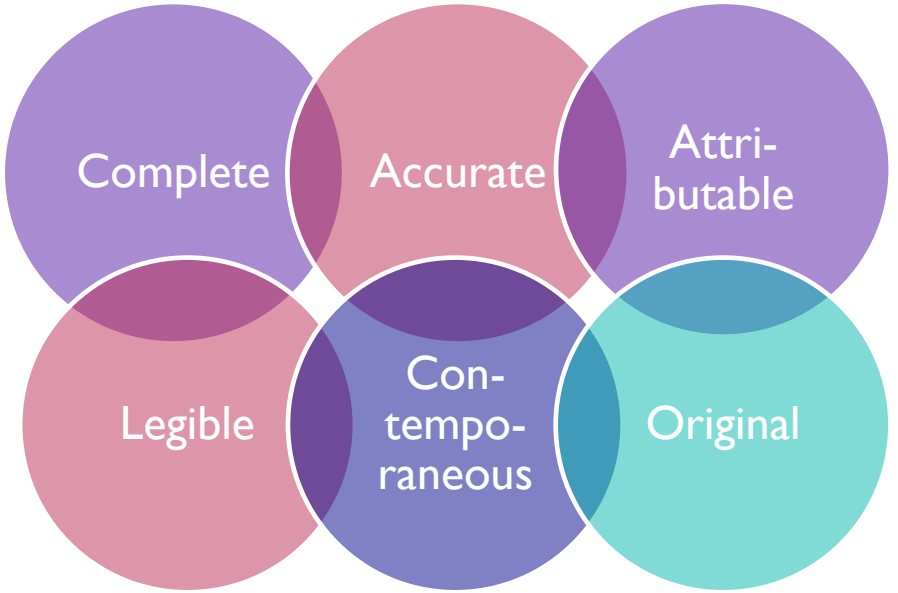
Source data should be: **attributable, legible, contemporaneous, original, accurate, and complete**.

Changes to source data should be:

- **Traceable** (with date and signed initials),
- **Not obscure** the original entry,
- and be **explained if necessary**

Direct entry of data is permissible for some data

The source must be clear from the **source data location log**



GDPR

General Data Protection Regulation			
Applicable in the **European Union**	Requirements for processing *(collecting, using and retaining)* **personal data and the rights of data subjects**	Subjects give explicit **permission** to use data on the **informed consent form**	**Refer to** https://gdpr-info.eu/

At site:

- Documents and data safely stored
- Study data collected in eCRF
- No patient identifiers in eCRF
- Only subject number

Study data processing:

- eCRF server in Australia
- Data transfer and processing according to GDPR

REMAP-CAP PRACTICAL INFORMATION

SITE ACTIVATION

Required documents

- Study / site / PI approval by CA, CEC and LEC
- Fully signed Clinical Trial Agreement
- Site specific ICF form
- Subject insurance
- Normal values or ranges
- CV / GCP certificate
- Site confirmation of IMP receipt (if centrally supplied)
- (Digital) ISF at site

Forms to be completed by site:

- Protocol Acceptance Form
- Domain choice pages
- Delegation Log
- Spiral database form
- Source Document Location Log
- Retention of records statement
- Self-training log: training of Domains
- SIV training attendance Log
- Monitor visit log for SIV

Complete

Site activation!

Green Light Letter and Site-specific ICF is sent

eCRF account is activated

Enrolment can start!

INTERIM MONITORING AND FURTHER SITE CONTACT

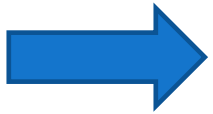
First monitor visit	Next monitor visit	Monitor contact
after 3 subjects enrolled or within 6 months of first patient inclusion	every 6 months, every year or every 2 years (depending on site performance)	Regular contact moments with monitor to discuss study & recruitment status

- **Invoice payment** – start-up fee and patient-fees (as per contract)
- **Audits/Inspections** – please notify the Sponsor immediately when announced

ELECTRONIC SOURCE DATA AND MONITORING

Requirements for electronic patient records:

- Access rights regulated
- Security systems in place
- Laboratory values etc. can be evaluated electronically (checked for clinical significance)
- Audit trail
- Read only monitor account



Certified copies can be used if read only access (or audit trail) is not possible

Or **'over the shoulder access'** with site staff member

PLATFORM CONCLUSIONS & PUBLICATIONS

Platform conclusions can lead to Domain (intervention) changes

- Sites will be notified about platform conclusion

Platform Conclusion relevant to public health:

- Presentation and/or publication
- Site staff is listed as collaborators

Sites **may not publish** or present interim or definite results

CLOSE-OUT

In theory, REMAP-CAP will run indefinitely

Limiting factors

- Funding
- Poor site performance
- Site request to stop recruitment
- All scientific questions have been answered

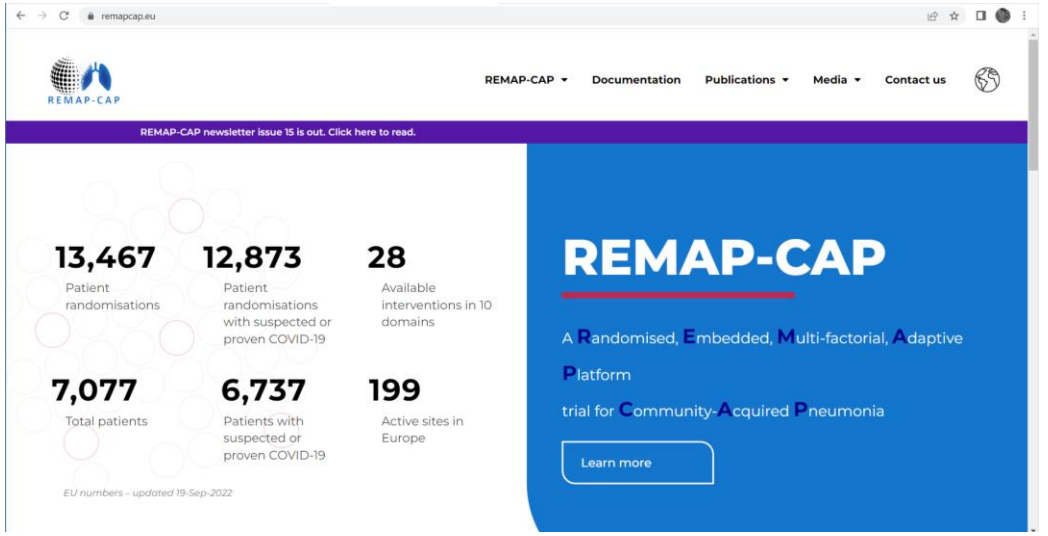
Close-Out visit by CRA/Sponsor

Study records must be retained for **25 Years**

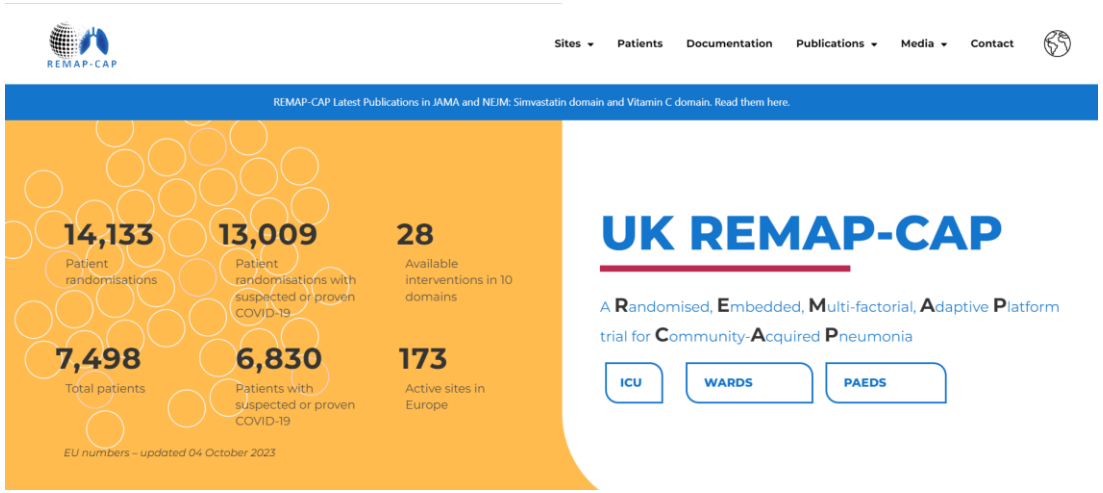
STAY UP TO DATE

REMAP-CAP communication channels

- www.remapcap.org / www.remapcap.eu
- Recruitment updates
- Newsletters
- Podcast, We4U (recordings), Instagram, LinkedIn, Twitter



- UK website: https://remapcap.co.uk/



CLOSING MESSAGE

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REMAP-CAP

THANK YOU

#REMAPCAPFAMILY