FUNDED BY

NIHR | National Institute for Health Research

REMAP-CAP

SITE INITIATION VISIT

UK - PAEDS

VERSION 5.2

01 JUNE 2025

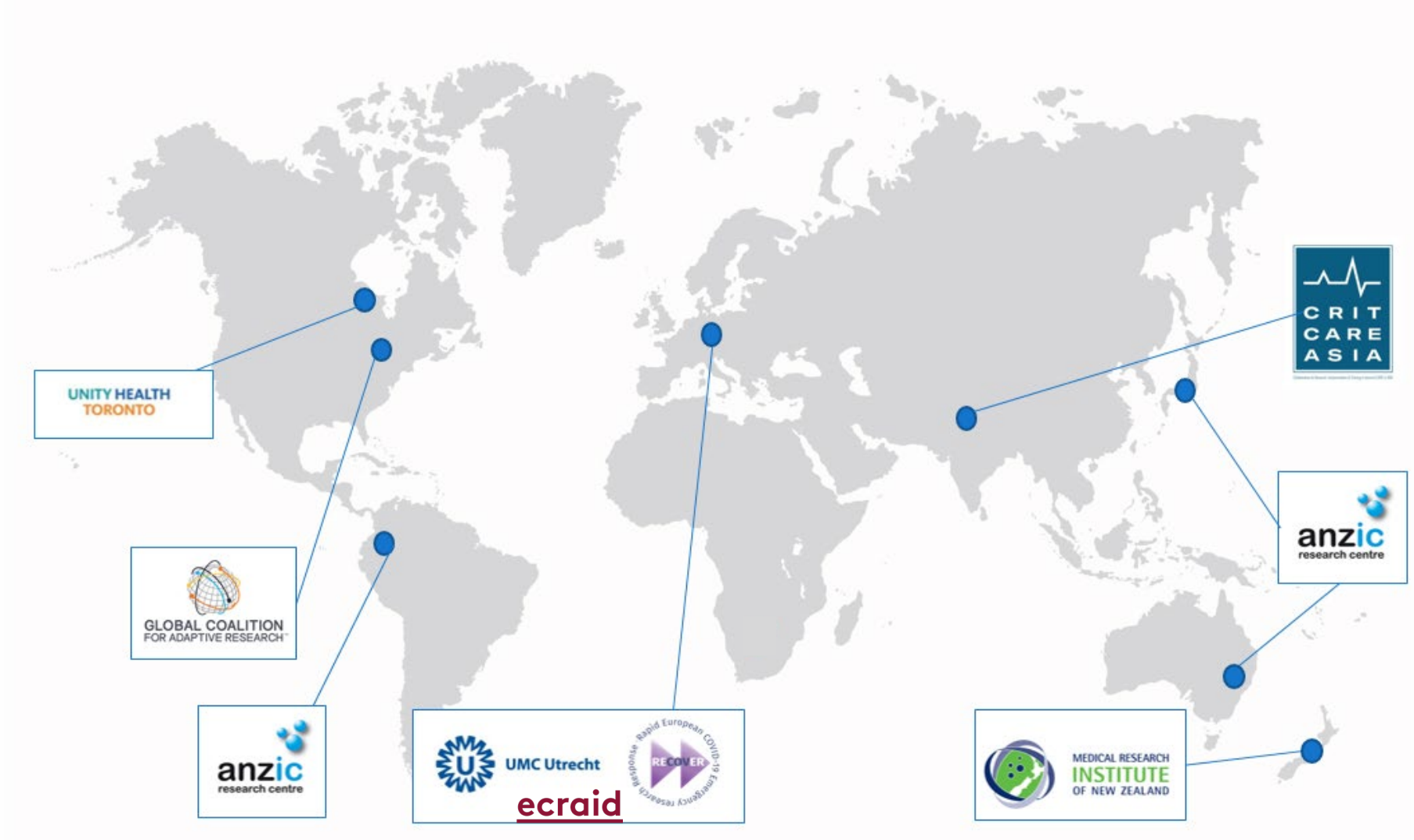
AGENDA

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, Lindsay Jack, Tina Reetun, Jodi Meyerowitz and Walton Charles

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

REMAP-CAP TRIAL DESIGN

TRIAL DESIGN: HOW TO IMPROVE?

Pre-planned

Pre-approved

Practiced

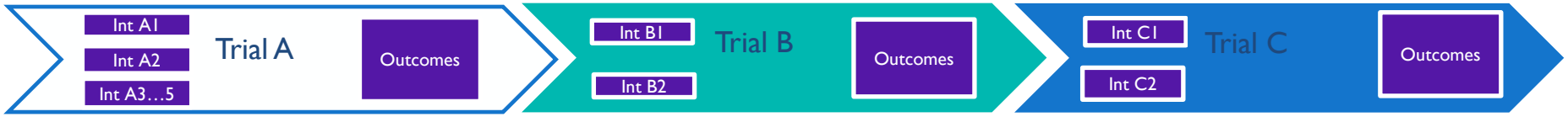
REMAP-CAP

Randomised, Embedded, Multi-factorial, Adaptive, Platform

TRIAL DESIGN: ADAPTIVE PLATFORM TRIAL (APT)

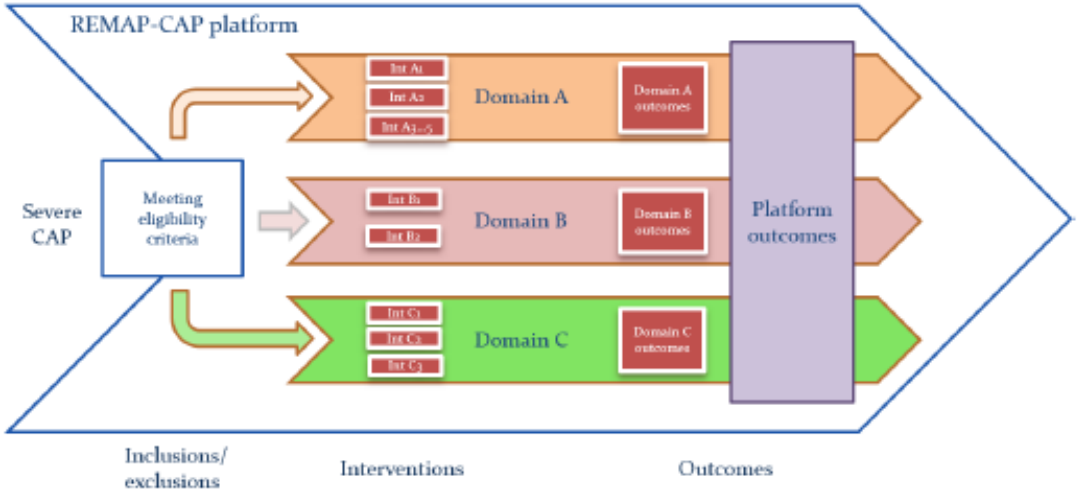
Traditional RCTs

- Serial testing of single hypotheses
- Set randomization ratio

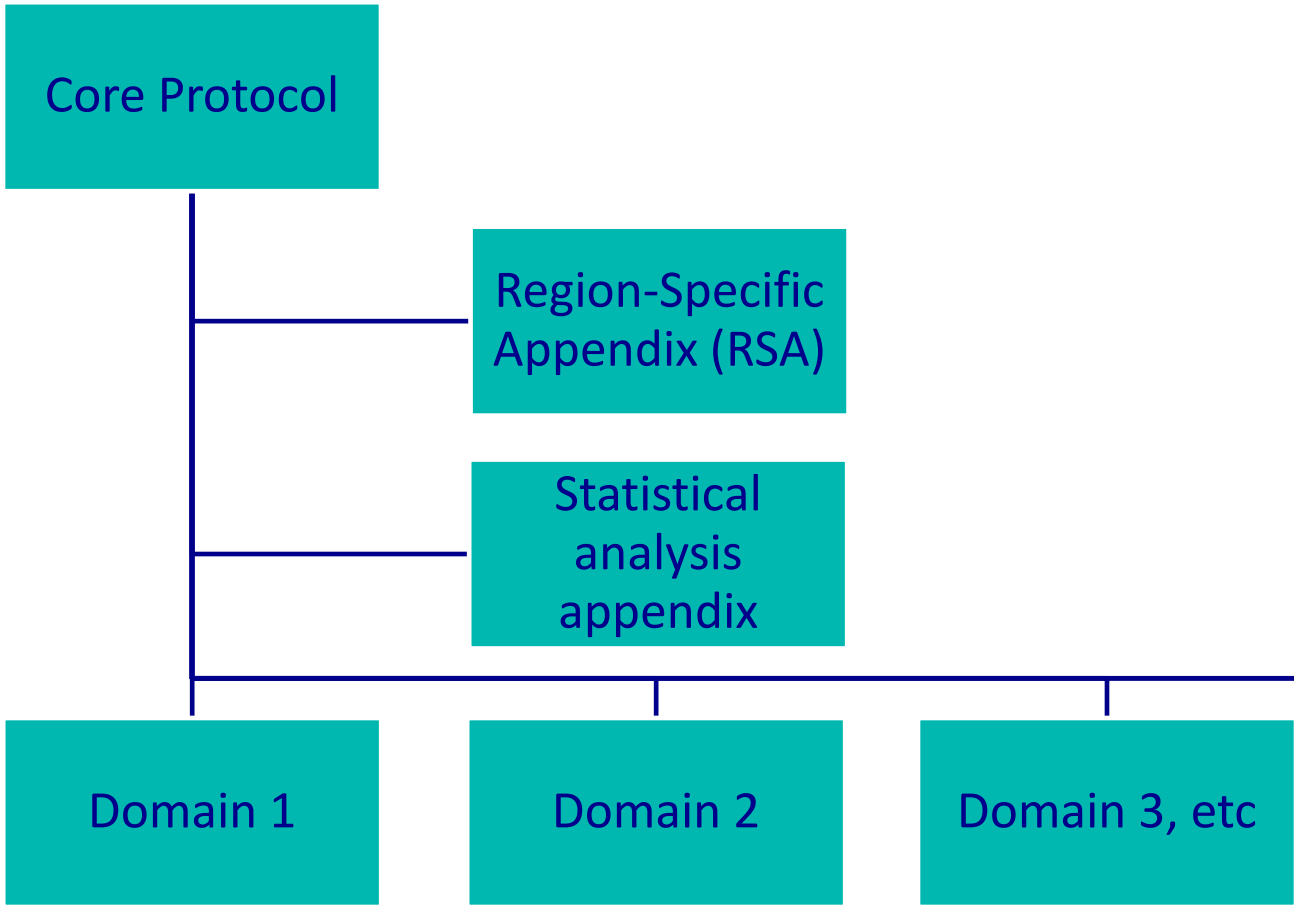


APT – REMAP-CAP

- 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

REMAP-CAP PROTOCOL
CORE PROTOCOL AND
PANDEMIC APPENDIX TO CORE

PATIENT POPULATION

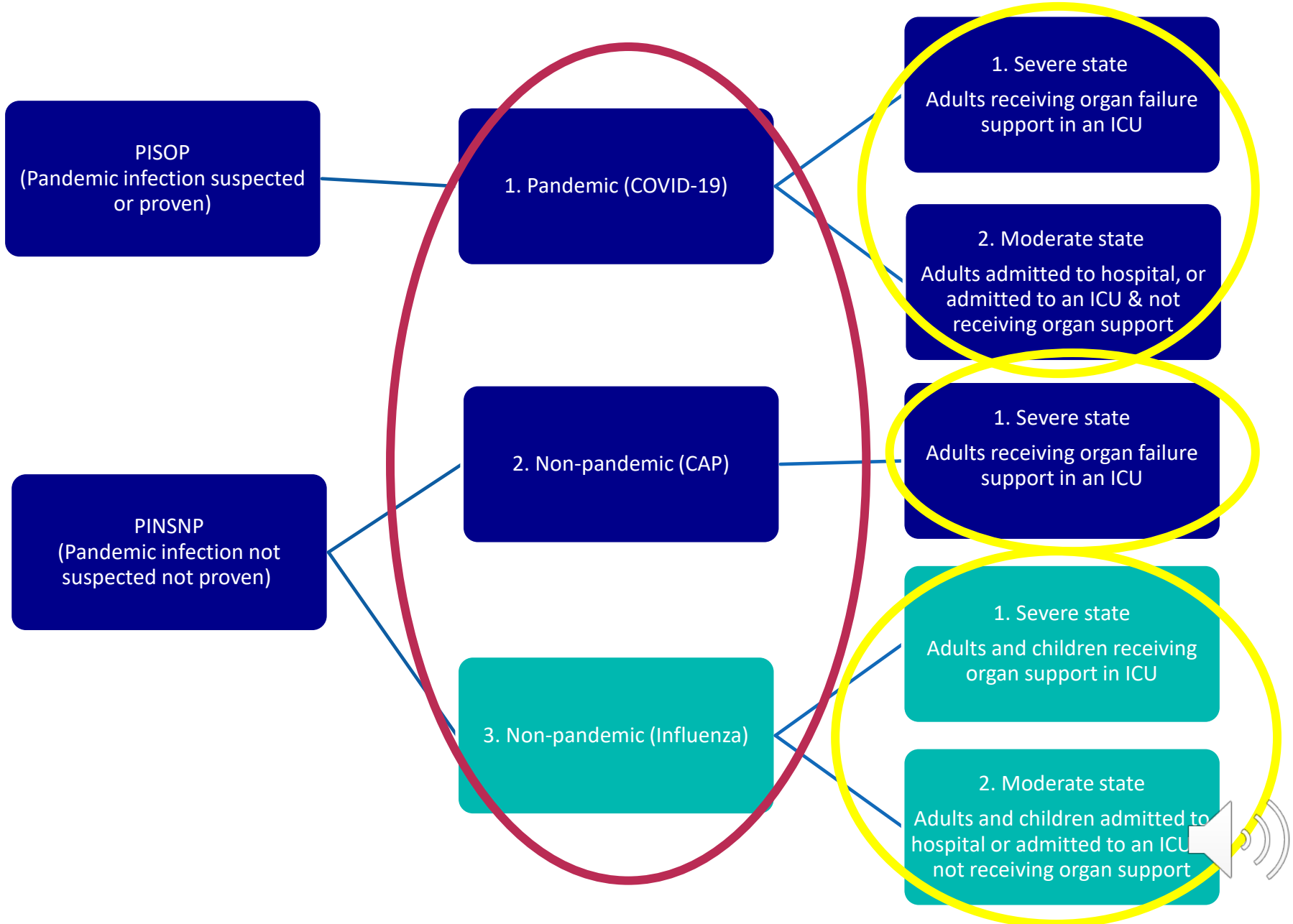
The trial is divided into

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	Severe receiving organ failure support in an ICU	Moderate Ward patient, **OR** admitted to an ICU but not receiving organ failure support	Severe receiving organ failure support in an ICU	Moderate Ward patient, **OR** admitted to an ICU but not receiving organ failure support	Severe 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

REMAP-CAP PROTOCOL
DOMAIN SPECIFIC APPENDICES

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
- IMMUNE MODULATION

INFLUENZA STRATA

	ADULTS		CHILDREN	
	Moderate (Ward, ICU no Organ Support)	**Severe** (ICU Organ Support)	**Moderate** (Ward, ICU no Organ Support)	**Severe** (ICU Organ Support)
Influenza Antivirals				
Oseltamivir	✓	✓	✓	✓
Baloxavir	✓	✓	✓	✓
Hydrocortisone	X	✓	X	X
Dexamethasone	✓	✓	✓	✓
Immune Modulators				
Tocilizumab	X	✓	X	✓
Baricitinib	X	✓	X	✓

BACKGROUND - INFLUENZA

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

Currently, recommended antiviral agents for influenza **(i.e. 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.

Immune modulators **(baricitinib/tocilizumab)** were shown to improve survival in hospitalised covid patients, covid and flu share some inflammatory features and provide a rationale for evaluating these drugs for flu.

BACKGROUND CONT.

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 or without ARDS

CORTICOSTEROID DOMAIN

VERSION 5.0, 09NOV22

Adults

Strata	State	Intervention	Frequency	Dose
Non-pandemic CAP & FLU	Severe or Moderate	C1 - No corticosteroid*	-	-
		C3 - Shock-dependent hydrocortisone**	6 hourly during shock	50mg
		C4 – Fixed-course dexamethasone***	Daily for 10 days	6mg

Children

Strata	State	Intervention	Frequency	Dose
Non-pandemic CAP & FLU	Severe or Moderate	C1 - No corticosteroid	-	-
		C4 – Fixed-course dexamethasone**	10 days	0.15 mg/kg to a max dose of 6mg/day

** Administration of systemic corticosteroids for the treatment of new illnesses that develop in the course of a patient's ICU stay is permitted*

***See protocol for septic shock definition. Septic shock is always considered to be resolved when vasopressors have not been administered via infusion in the preceding 24 h.*

**** If patient develops septic shock, a switch from dexamethasone to hydrocortisone is permitted*

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

On eCRF, one of the eligibility Qs defines HIGH FLOW OXYGEN as >30 L/min and an FiO2>= 0.4
If receiving above this - answer YES. If receiving below this - answer NO

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

INFLUENZA ANTIVIRAL DOMAIN

VERSION 2.1, 14FEB23

Adults and children

Domain	Strata	State	Intervention	Frequency	Dose
Influenza Antiviral (A)	**Non-pandemic and pandemic FLU (ie co-infections are eligible)**	**Severe & moderate**	I1 - No antiviral	-	-
			I2 - 5 days of Oseltamivir	Twice a day, for 5 days (10 doses)	**Adults:** 75mg **Children:** 6mg/kg/day, divided into two doses
			I3 - 10 days of Oseltamivir	Twice a day, for 10 days (20 doses)	**Adults:** 75mg **Children:** 6mg/kg/day, divided into two doses up to 40kg weight
			I4 - Baloxavir	Once daily on Days 1 and 4	Weight <40kg = 2mg/kg Weight 40-80kg = 40mg Weight >80kg = 80mg
			I5 - 5 days Oseltamivir and Baloxavir days 1 and 4	Osel: twice a day for 5 days Balox: once daily, Days 1 + 4	See above
			I6 - 10 days Oseltamivir and Baloxavir days 1 and 4	Osel: twice a day for 10 days Balox: once daily, Days 1 + 4	See above

Oseltamivir: *Dose adjustment for renal dysfunction as per local guidelines or DSA*
Baloxavir: *No adjustment for renal/hepatic dysfunction or ECMO*

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

IMMUNE MODULATION DOMAIN

VERSION 1, 29SEP23

Adults and children

Strata	State	Intervention	Frequency	Dose
Non-pandemic CAP & FLU	Severe	N1 - No immune modulation	-	-
		N2 - Tocilizumab	Single dose	≥30kg weight = 8mg/kg <30kg weight = 12mg/kg
		N3 - Baricitinib	Daily for 10 days	*By age and GFR:* 2-9 yrs old 0-2mg based on eGFR ≥ 9 yrs+ old 0-4mg based on eGFR

ELIGIBILITY CRITERIA – IMMUNE MODULATION DOMAIN

Inclusion Criteria

1. Adult or paediatric patient (2 years or older)
2. Influenza virus infection has been confirmed by microbiological testing
3. In the opinion of the treating clinician, the primary contributor to the patient's Severe Illness State is a respiratory tract infection

ELIGIBILITY CRITERIA – IMMUNE MODULATION DOMAIN

Exclusion Criteria

1. SARS-CoV-2 infection has been confirmed by microbiological testing
2. Known condition or treatment resulting in ongoing immune suppression including neutropenia prior to this hospitalization
3. A neutrophil count $<1.0 \times 10^9$ / L
4. Confirmed or strongly-suspected active mycobacterial infection or invasive fungal infection
5. Patient has already received any dose of one or more of any form of tocilizumab or another IL-6 receptor antagonist (e.g. sarilumab), baricitinib or another JAK inhibitor (e.g. tofacitinib, ruxolitinib or upadacitinib) during this hospitalization or is on long-term therapy with any of these agents prior to this hospital admission.
6. The treating clinician believes that participation in the domain would not be in the best interests of the patient
7. Known hypersensitivity to an agent specified as an intervention in this domain will exclude a patient from receiving that agent
8. Known or suspected pregnancy (baricitinib + tocilizumab)

ELIGIBILITY CRITERIA – IMMUNE MODULATION DOMAIN

Exclusion Criteria

9. An alanine aminotransferase or an aspartate aminotransferase that is more than five times the upper limit of normal will result in exclusion from receiving tocilizumab
10. A platelet count < 50 x 109 / L will result in exclusion from receiving tocilizumab
11. For adults and children ≥ 9 years of age, a baseline eGFR <15 mL/min/1.73m2 and/or receipt of renal replacement therapy (including long-term renal replacement therapy) at baseline will result in exclusion from receiving baricitinib

SWAB COLLECTION (ANTIVIRAL & IMMUNE MOD DOMAINS 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 CONTINUED

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 classed as a Protocol Deviation

REMAP-CAP SAFETY

SAFETY - DEFINITIONS

Event	Definition
Adverse Event (AE)	Any untoward medical occurrence in a subject to whom a medicinal product is administered
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**
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

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**
AE's	**NO**
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 site staff becoming aware of event

Investigator assesses: **relatedness to study/intervention** (possibly, probably, definitely)

expectedness as per intervention RSI i.e. SmPC, IB

severity as per clinical description, mild/moderate/severe

seriousness as per last slide

Use **SAE form in the eCRF**	**Back-up** paper 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**

All reports to be signed off in the eCRF

Medical Monitor reviews all reported safety events

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

SUSARs will be reported to Ethics/MHRA/Sponsor by the Trial Management team.

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.	**<u>ALWAYS</u> 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 - **PAEDS** - FLOWCHART

Is parent/guardian competent to consent prior to screening procedures?

No

Professional Legal Representative present?

No

Is treatment urgent and study enrolment beneficial for the patient?

Written consent possible from parent/guardian?

No

Verbal consent (in person)
Remote verbal (telephone
With impartial witness**)**

Follow up with written consent if/when possible

Yes

Prospective consent

Yes

Deferred consent

Parent/guardian consent must be obtained once capacitated

Yes

Delayed consent

Consent must be obtained from ProLR as soon as possible, ideally within 24hrs

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 FORMS – 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 - SITE PROCEDURES

Clear process needed for:

- Procedures for obtaining informed consent in an emergency setting
- Procedures for documentation of method /type of consent i.e. completion of consent statement
- Procedures and documentation of checking validity of Professional Legal Representatives, signing CFs on behalf of patients
- Procedures for where CFs are collected/placed out of hours when research nurses or access to study files are not available, to avoid loss of forms

REMAP-CAP Work Instruction: Informed Consent V2.0, dated 25th Jul 2024

REMAP-CAP WI Consent Appendix III V1.0, dated 18th Jul 2024

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.

INFORMED CONSENT - RETROSPECTIVE

If ProLR consent has been taken:

- Attempts MUST be made to obtain consent from the Patient/Parent/Guardian as soon as available ideally before hospital discharge
- If not, attempts MUST be made to obtain consent after discharge:
  - In person if they have a follow up appointment
  - Via telephone, followed by written consent by post/email

Please try to obtain telephone (remote) consent prior to postal written consent in case this is not returned or received (even if they have agreed they will send it back)

INFORMED CONSENT – ENDING PARTICIPATION

Discontinuation of study treatment	Withdrawal of consent
Refers to discontinuation or withdrawal of patient participation in study treatment only. **Patient/PerLR will be asked if they consent to ongoing follow up and data collection..**	Refers to withdrawal of consent to participate in <u>all</u> aspects of the trial.
- Document reason (if provided) in source. - 'Consent event' eCRF needs to be completed. - Continue follow up/data collection in the eCRF as usual if consent for this continues.	- Document reason (if provided) in source. - 'Consent event' eCRF needs to be completed. - Treatment stopped, **unless this may cause harm to the patient (to be determined by treating clinician)** - Follow-up and data collection are stopped. - The patient record will be **locked** in the eCRF.

INFORMED CONSENT – ECRF ENTRY

eCRF informed consent instructions → **WI Informed Consent: Section 6 / Appendix III + eCRF Completion Guidelines**

All consent discussions relating to participation in REMAP-CAP must be entered into the eCRF, including those with no decision / outcome.

A separate entry must be made for EACH consent event.
For example:

- Professional LR consent
- PerLR consent (verbal)
- Patient consent (written)
- Withdrawal of consent

Agreement for domain participation must be selected when entering consent.

INFORMED CONSENT FORM – LOCALISATION

Please do not localise PIS/CFs at sites yourselves - the process for REMAP-CAP is for the Trial Management team to do this.

This is because there are adaptable parts of the PIS/CF depending on which domains and interventions sites are taking part in and the adapting/localising process has caused some issues in the past (wrong versions being used, adaptations made incorrectly etc. resulting in invalid consents and deviations)

In response to this we now localise/adapt the PIS/CFs and provide locked PDF versions to sites, with site version tracking.

INFORMED CONSENT FORM – COMMON MISTAKES

Incorrect or missing study details (site name/number, investigator name, pt ID)

Boxes ticked rather than initialled or blank boxes

Missing signatures or dates/times, incorrect dates

Incomplete names i.e. 'J. Kim' or nicknames

Failure to use the latest approved version of the PIS/consent documents

Original Consent Forms not filed in the ISF

Consent process not documented in medical records

INFORMED CONSENT FORM – CORRECTIONS

Incorrect or missing study details (site name/number, investigator name, pt ID)
Staff to add info retrospectively and initial/date these changes

Boxes ticked rather than initialled or blank boxes
Re-consent if possible and document attempts (or pt can amend and initial/date if just concerning 1 box)

Missing signatures or dates/times
Re-consent if possible and document attempts. Please note missing signatures (even if all boxes are ticked/initialled) means consent is not valid

Incomplete names i.e. 'J. Kim' or nicknames i.e. Terry
Ask patient or staff to amend retrospectively and initial/date this change

Failure to use the latest approved version of the PIS/consent documents
Re-consent if possible and document attempts

Original Consent Forms not filed in the ISF
Locate and file original in ISF, put copy in medical records

Consent process not documented in medical records
Record retrospectively as soon as possible or if too late, complete a file note to explain why not documented

CONSENT WI APPENDIX III (2 PAGES)

Study	Category	Finding summary	Finding detail	Site Action	PD / NO PD
REMAP-CAP	Process	No consent obtained	No informed consent obtained to confirm subject/LAR has agreed to study participation. - subject alive	Obtain subject/LAR consent as soon as possible. After D180: Add no patient consent expected to eCRF	PD
REMAP-CAP	Process	No consent obtained	No informed consent obtained to confirm subject/LAR has agreed to study participation. - subject deceased	In countries with no approved delayed consent process: Obtain personal LAR consent to use subject data as soon as possible. In countries with approved delayed consent process: if required by local law in country, obtain personal LAR consent to use subject data as soon as possible Add no patient consent expected to eCRF	PD
REMAP-CAP	Process	No patient consent obtained	No patient consent after LAR consent even though subject has the capacity/became capacitated to provide consent – during hospitalisation	Obtain patient consent.	PD
REMAP-CAP	Process	No patient consent obtained	No patient consent after LAR consent even though subject has the capacity/became capacitated to provide consent – after hospital discharge prior day 180	Obtain patient consent (remotely). For subjects that remain incapacitated at hospital discharge sites are expected to check at least at day 90 and day 180 if the subject has regained capacity to provide consent, if still alive. Document the reason why no consent was	Possibly

CONSENT CHECK LOG

REMAP-CAP Consent Check Log

Protocol Number	2015-002340-14	**Site Name**	
PI Name		**Site Number**	

Patient no.	Date Patient Randomised	Date of Consent	Type of Consent *(Patient/ PerLR/ProLR/ Retro)*	For ProLR consent only, confirm ProLR is not on the delegation log	Version/ Date of Consent Form	Person taking Consent[1] (Role and Name)	Is this Person[1] on Delegation Log? *(Y/N)*	Consented for Day 180 Questionnaire Follow-up by ICNARC Team	Consent Log Completed by and Date	Comments

Original to be signed, dated and filed in TMF and a scanned copy sent to ukremap-cap@icnarc.org .

INFORMED CONSENT - MONITORING

Consent (form) monitoring:

- Was the correct version / type used
- Are all fields completed on the form and in a GCP complaint way
- Was consent provided for all randomized domains (if relevant)
- Was form dated and signed by delegated and trained staff member
- Are all pages of form filed (not only signature page)
- PATIENT consent: Was form signed and dated by patient? If not, was there confirmation in source/on form that subject was (in)capacitated?
- LAR consent: Does LAR relation to patient meet country regulatory requirements?
- For professional LAR consent: Was the professional LAR independent from the trial? (i.e. did not perform trial-related tasks including eligibility assessment, and is not on the delegation log)
- For professional LAR consent: Was it appropriate to defer to professional LAR?
- For NO CONSENT: documented attempts to reach the subject or personal LAR.
- For No Patient/personal LAR consent: reason for no consent is documented in source and eCRF.
- For verbal consent: Did impartial witness, if applicable, sign the form? Was the reason for verbal consent documented in source?

Imperial College London

[Insert hospital/ trust logo here]

PROTECT HF

Full Title of Project: Physiological versus Right ventricular pacing Outcome Trial Evaluated for bradycardia Treatment (PROTECT-HF)

Chief Investigator: Dr Daniel Keene
Study Protocol Number: 22HH7931
IRAS ID: 312355

Participant Study ID Number:	
Site Number/Name:	[illegible]
Name of Principle Investigator:	Dr S. Smith

Participant Consent Form

Please initial each box if you agree with the following:

1. I confirm that I have read and understand the participant information sheet version 3.0 dated 29/02/24 for (Physiological versus Right ventricular pacing Outcome Trial Evaluated for bradycardia Treatment (PROTECT-HF)) and have had the opportunity to ask questions which have been answered fully.	SS
2. I understand that my participation is voluntary, and I am free to withdraw at any time, without giving any reason and without my legal rights nor treatment / healthcare being affected. If I withdraw, I understand that the data collected whilst I was on the study will be retained and used by the research team who are obliged to keep my identity confidential.	SS
3. I understand that sections of any of my medical notes may be looked at by responsible individuals from Imperial College London, from NHS Trust or from regulatory authorities where it is relevant to my taking part in this research. I understand that if I have Medtronic CareLink, the coordinating study team will access my Cardiac Compass data (CCD) to obtain my remote pacemaker follow-up data (I understand that my personally identifiable data will not be shared with Medtronic).	SS

1 copy for participant; 1 copy for Investigator Site File; 1 copy for participant notes
To ensure confidence in the process and minimise risk of loss, all consent forms must be printed, presented and stored in double sided format

4. I agree to my data (which includes my identifiable data [name, email address and contact telephone numbers]), and that of my nominated other if applicable, being entered onto a secure database, held at Imperial College London, in accordance with the Data Protection Act 2018.	SS
5. I understand that if I am eligible for the study, a member of the coordinating research team from Imperial College London will have access to my identifiable data (and my nominated other if applicable) to allow contact (via telephone and email) for follow up purposes as specified in the Participant Information Sheet.	SS
6. I agree to my GP being informed about my participation in this research study and any incidental findings to be conveyed to them.	SS
7. I understand that data collected from me is a gift donated to Imperial College and that I will not personally benefit financially if this research leads to an invention and/or the successful development of a new test, medication treatment, product or service.	SS
8. I give consent for identifiable data to be stored and shared securely with NHS Digital. This data will include my NHS number, date of birth, postcode and gender. This secure sharing of data with NHS Digital will be used to link information regarding hospital admissions, emergency care and civil registration.	SS
9. I give consent for information collected about me to be used to support other research or in the development of a new test, medication, medical device or treatment by an academic institution or commercial company in the future, including those outside of the United Kingdom (which Imperial has ensured will keep this information secure).	SS
10. I agree to the central study team to contact me via email/phone for follow up purposes as specified in the Patient Information Sheet.	SS
11. Should I lose capacity during the study, and only if this occurs after my pacemaker implantation, I understand that my health status related data will still be collected by the coordinating research team at Imperial College London from my medical notes by contacting my local clinical and research teams and from NHS Digital. This will include data from my pacemaker device checks and any hospital visits or admissions. Attempts would not be made to contact me or my nominated other directly after this time. I will no longer be asked to complete study related questionnaires. If I lose capacity prior to my pacemaker device implant, I will be withdrawn from the study and receive the standard of care treatment.	SS
12. I consent to take part in the PROTECT-HF study.	

1 copy for participant; 1 copy for Investigator Site File; 1 copy for participant notes
To ensure confidence in the process and minimise risk of loss, all consent forms must be printed, presented and stored in double sided format

The following is an optional aspect of the trial, please initial the appropriate box:

	Yes	No
1. I give consent to being contacted about the possibility to take part in other research studies.	✓	
2. I agree for study related questionnaires to be sent to me via electronic means.		✓

SANDRA SMITH	S	01 SEP 2024
Name of participant	Signature	Date & Time
J. Kim		01 OCT 2024 11:30
Name of person taking consent	Signature	Date & Time

REMAP-CAP STUDY PROCEDURES

SCREENING

Site specific eligibility checklist to be printed/downloaded from eCRF (Spinnaker)
Complete screening and enrolment log on paper/spreadsheet
Confirm eligibility (inclusion criteria) with a doctor/practitioner and document in source notes
Enter eligible patient in eCRF and go through the full **digital eligibility assessment**
Subject randomized, or if screen failure → moved to Registry list

What is your **screening method**?

If consent intends on being collected but not yet obtained, do not enter 'No' for consent, rather SAVE the eCRF and complete the rest later. Selecting No for consent does not prevent randomisation – it assumes 'delayed consent' process is being followed and will randomise!

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

  DO NOT intend to override treatment based on result

- Study participation must be visible in patient (electronic) file
- If applicable: order study drugs

- Complete eCRF pages and any queries (can be weekly i.e. reasonable timeframe)
- Enter endpoint data on time (notification is sent to sites)

PROTOCOL DEVIATIONS - DEFINITIONS

	PD category	Minor - examples	Major - examples
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	≥ 1 dose of Baloxavir missed or ≥ 2 doses Oseltamivir 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

In the eCRF

- Platform eligibility deviations
- Domain-specific deviations

For any other deviation use:

- Platform eligibility deviations => ‘OTHER’

INVESTIGATIONAL MEDICINAL PRODUCT (IMP)

Supply via:

- Hospital stock (Oseltamivir, Hydrocortisone, Dexamethasone, Baricitinib)
- Pharmaceutical company (Baloxavir, Tocilizumab)

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

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.

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

INVESTIGATOR SITE FILE

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

Site responsibility to keep the ISF up-to-date

ISF tasks:

- File received **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**.

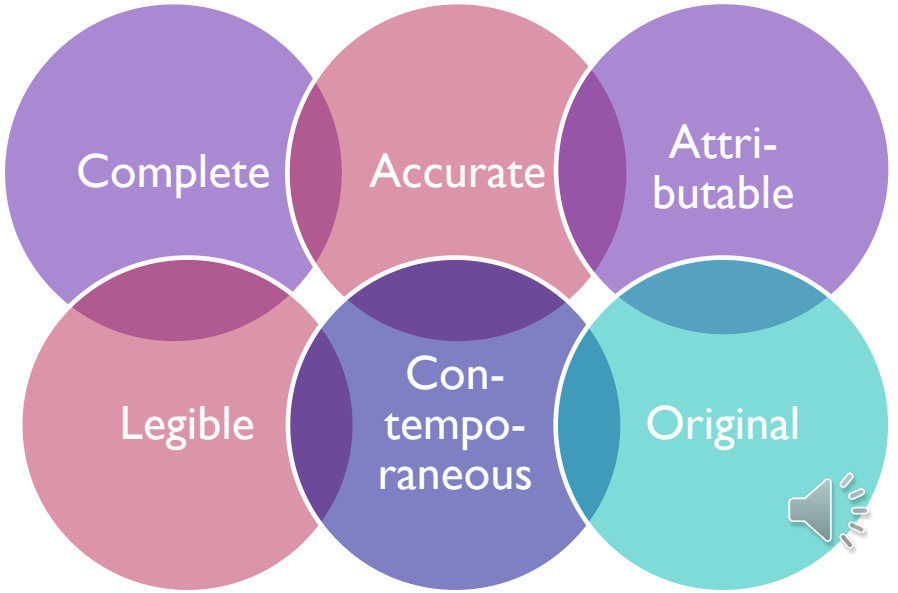
Source data should be: **attributable, legible, contemporaneous, original, accurate, and complete**.

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:

- Site R&D approval
- Signed Clinical Trial Agreement / funding agreement
- Site localised and locked PIS/CFs
- Lab accreditation and normal ranges
- Staff CVs / GCP certificates for minimum PI, RN + Pharm
- (Digital) ISF followed by paper ISF via post
- Pharmacy prescription setup, if required
- Access to MACRO, if a CAP site
- Site creation on study database
- Nasal swab kits
- New site/domain checklist signed by TM

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 logs: training of protocol and domains (separate to SIV)
- SIV attendance Log + Site Visit Log
- Dummy randomisation on eCRF test site

Complete

Site activation!

Green Light email is sent

eCRF account is activated

IMP can be ordered

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 (printed and signed/dated by study staff) 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

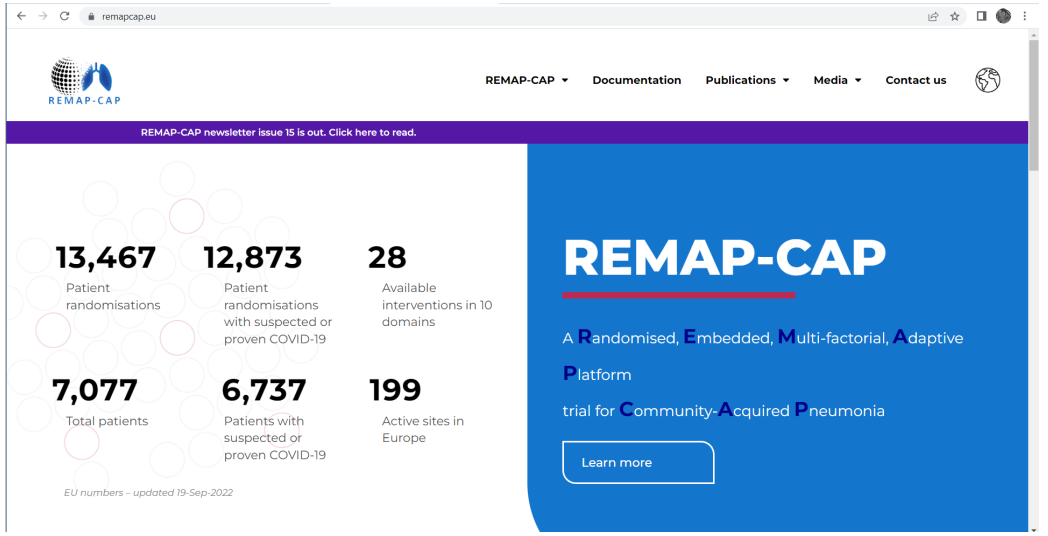
Close-Out visit by CRA/Sponsor

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

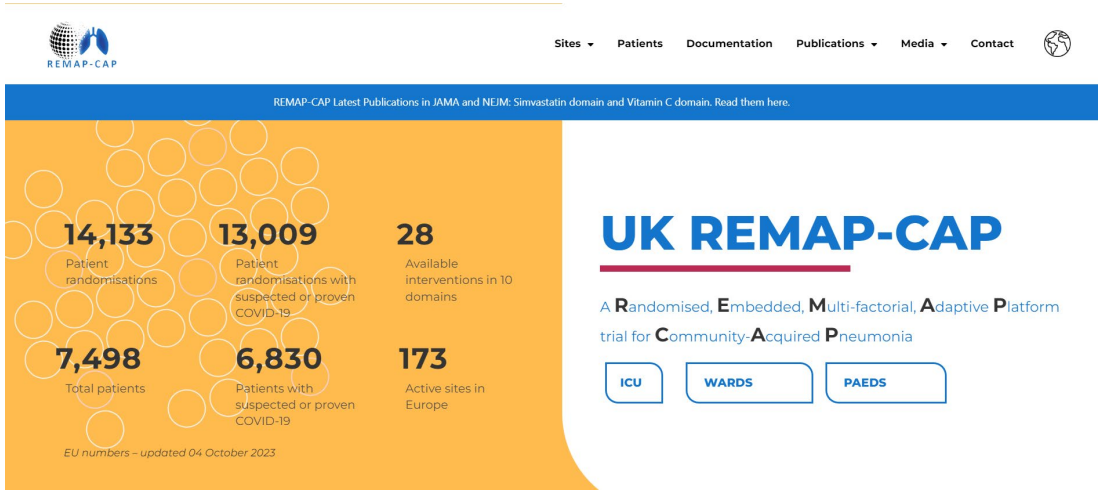
STAY UP TO DATE

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

UK Trial Management Contacts:

ukremap-cap@icnarc.org

Aisha Anjum **07956 800722**

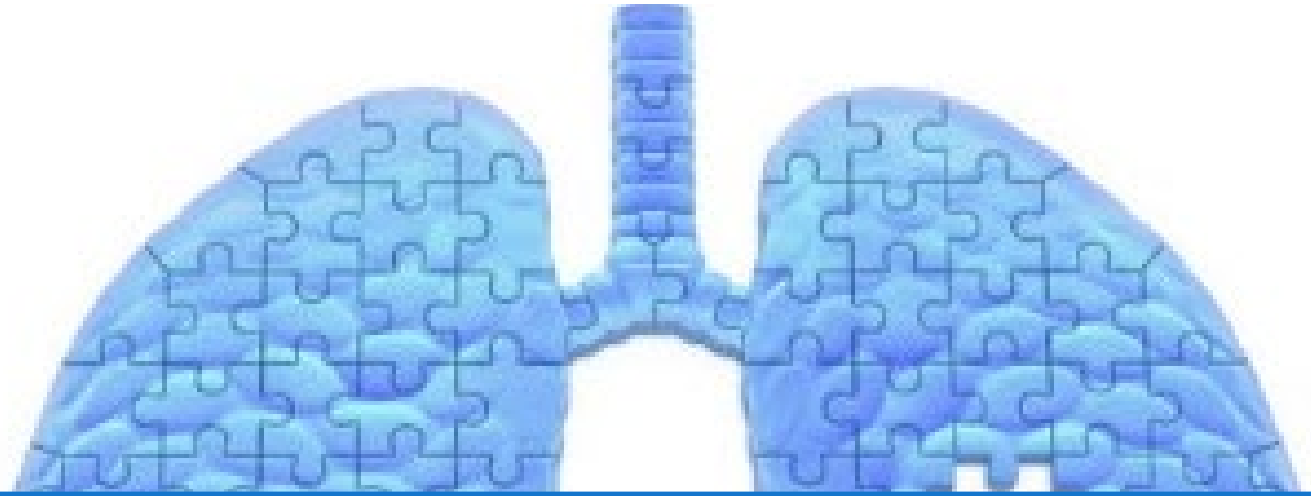
Janis Best-Lane **07714 051680**

Lucy Stronach **07714 051401**

For urgent situations outside UK office hours

+31 (0) 6 277 444 77

Eu.remapcap@umcutrecht.nl



REMAP-CAP

THANK YOU

#REMAPCAPFAMILY