NHS
Blood and Transplant

REMAP-CAP Updated Immunoglobulin Domain

Combined Training Slides

REMAP-CAP

Caring Expert Quality

Context

- REMAP-CAP is a multicentre, international trial assessing treatments for COVID-19 in intensive care
- Reached 10,000th participant milestone on the 30th November 2021

- The original immunoglobulin domain of REMAP-CAP ran in the UK between April 2020 and January 2021:
  - It concluded that there was no evidence of benefit in administering convalescent plasma to all patients in ITU
  - However, there was some benefit in sub-groups, such as **immunocompromised** patients
    - 89.8% posterior probability of superiority
  - Further analysis was recommended

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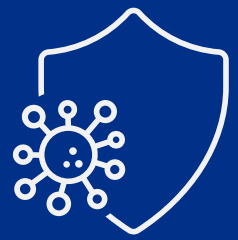
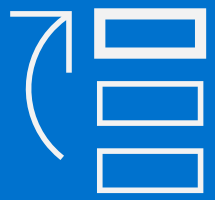
Key Changes



Only immunocompromised patients can be randomised to this domain

Limited treatment options for this group of patients
They don't respond as well to vaccination



High titre vaccinated convalescent plasma only

Plasma collected from donors who were both naturally infected AND vaccinated

Ordering on a named patient basis through OBOS

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- **New product codes**
- Must order new units rather than using those in stock

Eligibility (1)

- Patients are eligible for this domain if:
  - SARS-CoV-2 infection is confirmed by microbiological testing
  - Patient has an underlying immunodeficiency or has received recent immunosuppressant therapy, corresponding to the APACHE II definitions (Knaus et al., 1985), extended to take into account equivalent forms of immunosuppressant therapy that post-date the APACHE II definitions.

Immunosuppressed population	Estimated number in England November 2020
Receiving immunosuppressive therapy e.g. rituximab	114,000
Blood cancers	188,000
Other solid cancers receiving chemotherapy	56,000
Lung cancer receiving radical radiotherapy	3,000
Long-term steroids	1,367
Stem cell transplants (within 6 months)	2,000
Stem cell transplants + immunosuppression	681
Solid organ transplants	56,000
Total	Approx 500,000

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Eligibility (2)

Patients will be excluded from this domain if they have any of the following:

- Do not meet REMAP-CAP platform criteria
- **Patient has already received treatment with any non-trial prescribed polyclonal antibody therapy (hyperimmune immunoglobulin, or convalescent plasma) intended to be active against COVID-19 during this acute illness.**
- The treating clinician believes that participation in the domain would not be in the best interests of the patient
- Known hypersensitivity/allergy to an agent specified as an intervention in this domain will exclude a patient from receiving that agent
- Known previous history of transfusion-related acute lung injury will exclude a patient from receiving high titre plasma
- Known objection to receiving plasma products will exclude a patient from receiving any plasma components

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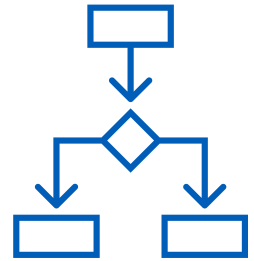
Randomisation



- Randomisation performed on REMAP-CAP platform by research team
- Includes COVID-19 Immunoglobulin domain randomisation
- Patient allocated with unique trial ID (10 digits, in the form R_ _ _ _ _ _ _ _ _ _)

- If a patient is randomised to the intervention arm – the research team will notify transfusion laboratory that the patient has been randomised, and vaccinated convalescent plasma should be ordered ASAP.
- The research team will provide transfusion laboratory with unique patient trial ID number

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Sampling

- Samples are to be taken from all patients in this domain
- A blood sample will be taken at baseline (Day 1) to check for antibody levels
  - Please ensure this takes place before ordering VCP if the patient is randomised to receive it

- Respiratory (swab) samples will be taken at baseline and every subsequent week that the patient is in hospital (Day 1, Day 8, Day 15 etc.) or until they test negative (2 consecutive negatives)
  - Variant detection and sequencing

- No samples should be transferred to the Research Laboratory until an appropriate form of written consent is in place (e.g. professional legal representative)
- There is a separate lab SOP to follow
- Packaging kits (with pre-paid postage) will be provided

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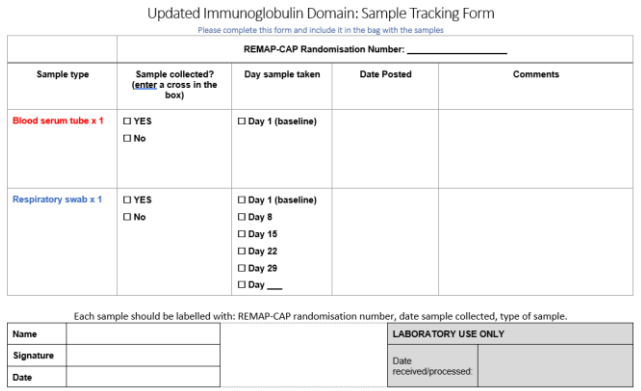
Sample Tracking and Transport

- All samples will be posted to COVID Oxford BioArchive [COBA] (using packaging supplied).
- Complete Sample Tracking Form (**away from clinical area**), and include in the box
- Affix the Royal Mail label and the sticker to the outside of the bag, then post the same day if possible
- If it's Friday/a weekend please store the samples in the fridge until they can be sent
- Email ctu@nhsbt.nhs.uk after posting and add to the log (Local Sample Tracking Log)



Updated Immunoglobulin Domain: Sample Tracking Form

Please complete this form and include it in the bag with the samples

REMAP-CAP Randomisation Number: _____

Sample type	Sample collected? (enter a cross in the box)	Day sample taken	Date Posted	Comments
Blood serum tube x 1	☐ YES ☐ No	☐ Day 1 (baseline)		
Respiratory swab x 1	☐ YES ☐ No	☐ Day 1 (baseline) ☐ Day 8 ☐ Day 15 ☐ Day 22 ☐ Day 29 ☐ Day ___		

Each sample should be labelled with: REMAP-CAP randomisation number, date sample collected, type of sample.

Name			LABORATORY USE ONLY
Signature			Date received/processed:
Date			

REMAP-CAP Trial Sample

0									

Blood: Day 1
Respiratory: Day 1 / Day 8 / Day 15 / Day 22 / Day ___
Date collected: d d / m m / y y y y

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Immunoglobulin Domain
(immunosuppressed patients)

This is a:
☐ blood sample
☐ respiratory sample

Receiving lab: if this is a respiratory sample, please store in the fridge as soon as possible

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Ordering Vaccinated Convalescent Plasma

- **Please destroy any old stocks of convalescent plasma locally**
- Transfusion labs will order on a named patient basis – no local stock
- You can order 1 or 2 units via OBOS (1 at a time may be easiest if you have wastage/storage concerns at your site, NB. both units should be transfused within 48 hours)
- Enter 10-digit REMAP-CAP randomisation (R) number in order Line Notes for traceability
- Scotland, NI and Wales will complete a plasma log like last year
- Units will be issued in yellow ‘for trial use only’ bags

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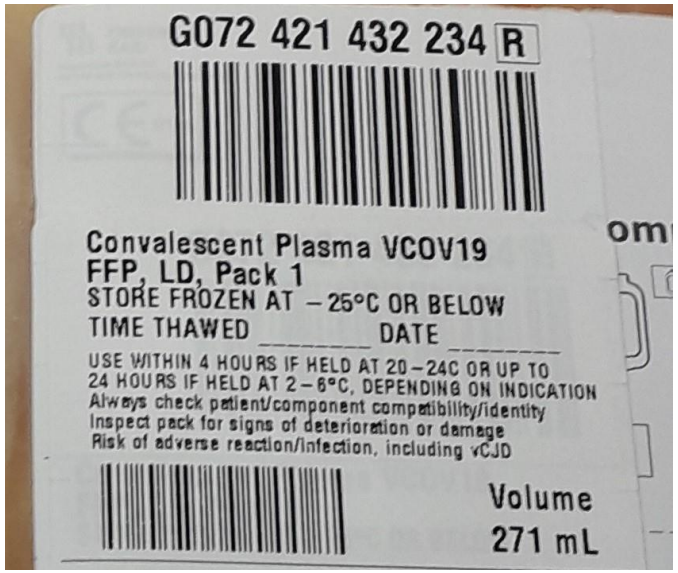
New Product Codes

Component description	NHSBT Pulse Code	Start Code	Barcode No.	Stop Code	Shelf life (days)	Codabar Barcode
Vaccinated convalescent plasma COVID-19. FFP. Pack 1	CHP5	a0	29601	3b	1095	
Vaccinated convalescent plasma COVID-19. FFP. Pack 2	CHP6	a0	29602	3b	1095	



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Issuing

- 1 unit of ABO compatible vaccinated Convalescent Plasma thawed as per normal transfusion laboratory procedures (ABO matched if possible) (use standard compatibility practice).
- Issue vaccinated Convalescent Plasma via LIMS or other standard systems
- Each unit must be prescribed, requested and issued as separate events.
- Laboratory staff must record the patient's trial number in the Convalescent Plasma Log/download via LIMS system. Provide to CTU@nhsbt.nhs.uk weekly.

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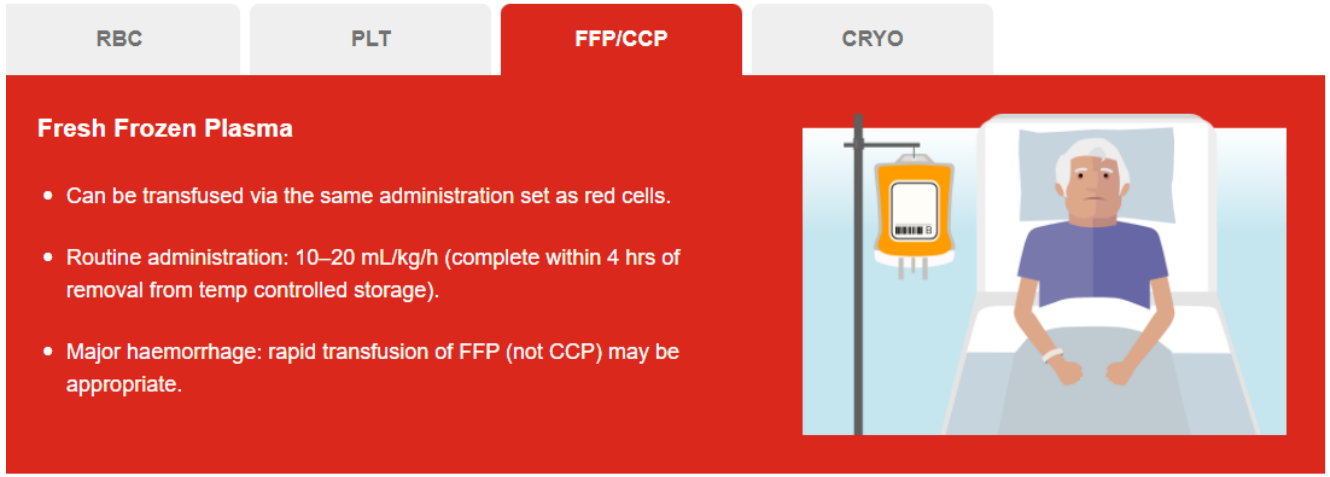
Administration of VCP (1)

Patients assigned to receive plasma will receive:

- two adult units of ABO compatible vaccinated convalescent plasma (total volume 550ml ± 150ml)
- within 48 hours of randomisation if there have been no reactions

The units will ideally come from different donors, if stock allows.

The Blood Assist app can be used to do a quick compatibility check at the bedside.



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Administration (2)

- All administration bedside transfusion safety checks must be undertaken.
- Perform TACO checklist prior to each unit transfused: https://www.shotuk.org/wp-content/uploads/myimages/TACO-Checklist.jpg
- Staff administering need to be compliant with local standards for transfusion
- Donation number (G no), volume transfused, and start and finish date and time of transfusion should be documented on the eCRF and patient's medical notes by the research team. Infusion rate as per standard practice.

- Patients can receive other blood components, as required.
- Both units should be given within 48 hours of randomisation if there are no reactions
    - Provided the patient has not had any serious adverse reactions, the research team will request a second unit from the transfusion laboratory.
    - Ensure timely communications to laboratory staff to facilitate this.
    - If the second unit is not required then it should be stored on site

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Transfusion Related Adverse Reactions and Adverse Events

- All transfusion-related serious adverse events / reactions are reportable to SHOT/MHRA.
- Other reportable events include:
  - wrong component transfused (includes patients given standard FFP instead of vaccinated convalescent plasma and vice versa)
  - trial plasma issued/transfused to a non-trial patient

- Staff managing the patient must inform blood bank/transfusion practitioner of any serious reaction and/or error immediately.
- Definitions document available here: https://www.shotuk.org/wp-content/uploads/myimages/SHOT-Definitions-active-January-2022.pdf

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Transfusion Related Adverse Reactions and Adverse Events (2)

- Reports to SHOT/MHRA via the SABRE portal within 48 hours by transfusion teams.
  - Must include trial name and patient's trial number on the SHOT reporting system in addition to the other details of the reaction.
- Transfusion-related SAE/SARs should also be reported in the REMAP-CAP eCRF by the research team
- In case of any serious reaction, appropriate measures should be taken including:
  - Stopping the transfusion
  - Investigations and treatments initiated

SHOT
Serious Hazards of Transfusion

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Domain Specific Outcomes

- All-cause mortality at 28 days, censored at hospital discharge
- Confirmed deep venous thrombosis
- Confirmed pulmonary embolism
- Confirmed ischaemic stroke
- Confirmed acute myocardial infarction
- Other confirmed thrombotic events
- Serious Adverse Events (SAEs) as defined in core REMAP-CAP documents and qualified in this domain
- Serious Adverse Reactions (SARs)

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Co-enrolment with RECOVERY

Ward-based immunocompromised patients who have been randomised into RECOVERY can be randomised into this domain of REMAP-CAP **≥48 hours later** if they have deteriorated clinically (or as soon as they are admitted to ICU).

Patients in this domain of REMAP-CAP can be co-enrolled with all of the RECOVERY domains

However, participants in RECOVERY receiving Paxlovid are not eligible for REMAP-CAP simvastatin comparison; conversely REMAP-CAP participants allocated simvastatin should not be included in RECOVERY Paxlovid comparison.

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RECOVERY
Randomised Evaluation of COVID-19 Therapy

NHS
Blood and Transplant

Thank you!

Any questions?

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