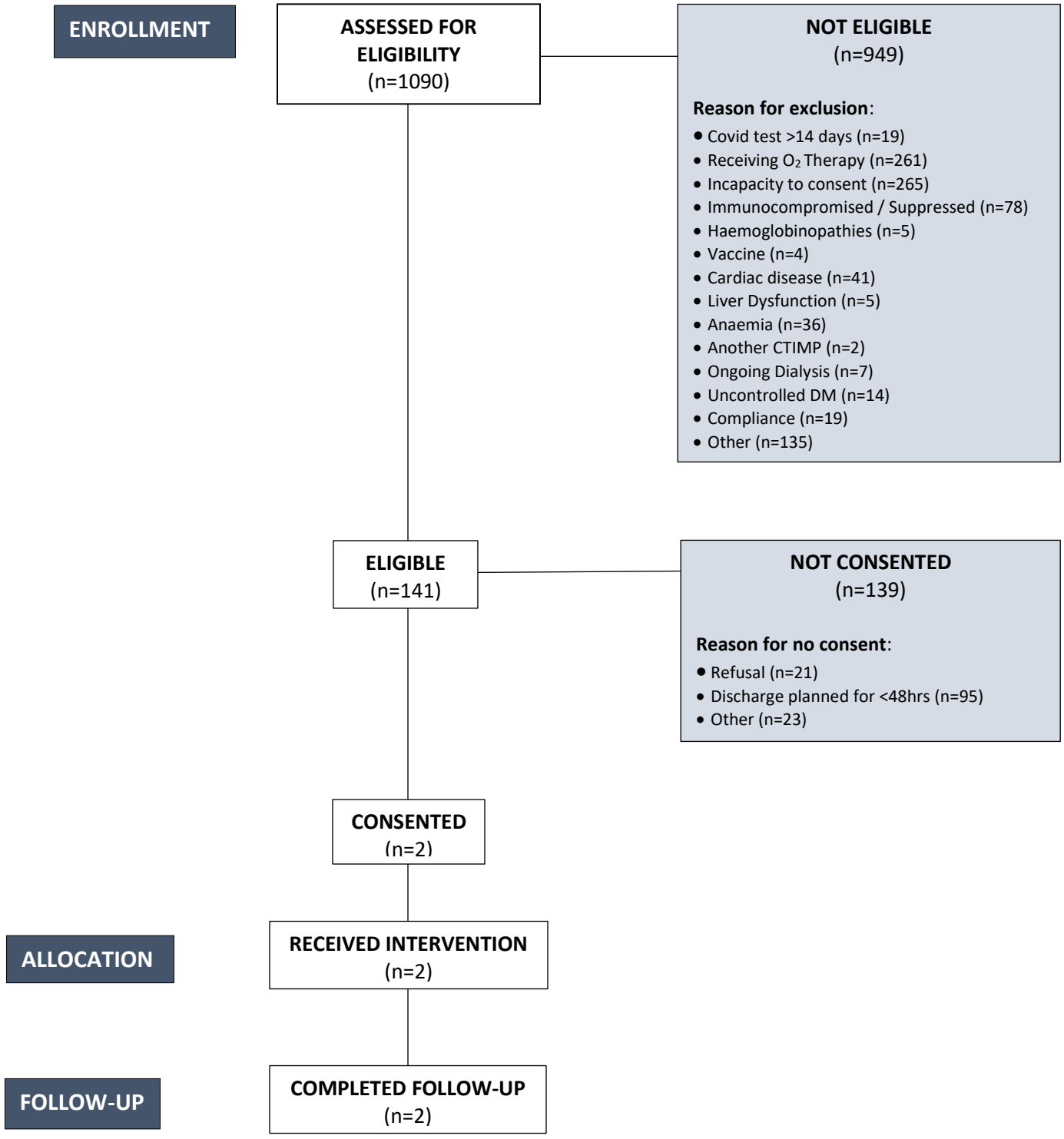
1. PARTICIPANT FLOW



2. BASELINE CHARACTERISTICS

As the trial only recruited 2 participants to Appendix 3, baseline characteristics have been provided for each participant rather than as a range.

VARIABLE	
Age	65/78
Gender	1F/1M
Ethnicity	White British (n=2)
Smoking Status	Ex-smoker (n=2)
BMI	21/25.4
Reason for admission	Fall resulting in compression fracture Fall resulting in head injury but no LOC
SARS CoV2 DETAILS	
Number of days from positive test to intervention	3/9
SARS CoV2 SYMPTOMS	
Fever	n=1
Cough	n=2
Wheeze	n=0
Dyspnoea	n=2
Loss of taste/smell	n=0
Sore throat	n=2
Headache	n=0
Diarrhea	n=1
Nausea/vomiting	n=2
Malaise/fatigue	n=2
Myalgia (muscle pain)	n=1
Arthralgia (joint pain)	n=2
Other	n=0

Past Medical History

	Dose Administered		Total	
	Dose Group 1			
	N	%	N	%
Total	2	100	2	100
Chronic cardiac disease (not hypertension)				
No	2	100	2	100
Hypertension				
No	1	50	1	50
Yes	1	50	1	50
Chronic pulmonary disease				
No	2	100	2	100
Asthma				
No	2	100	2	100
Chronic kidney disease				
No	2	100	2	100
Chronic liver disease				
No	2	100	2	100
Chronic neurological disorder				
No	2	100	2	100
Diabetes				
No	2	100	2	100
Malignancy				
No	2	100	2	100
Immunocompromised				
No	2	100	2	100
Other				
Yes	2	100	2	100

Where other co-morbidity has been indicated, the following table shows the description:

	Dose Administered		Total	
	Dose Group 1			
	N	%	N	%
If yes, please detail				
Osteoarthritis- awaiting hip operations. Inguinoscrotal hernia repair. Allergies - allergic to contrast. Benign prostatic hypertrophy. Urinary frequency	1	50	1	50
hypothyroidism, osteoporosis	1	50	1	50

Baseline Physical Assessment

Baseline Abnormalities – All categories

	Dose Administered		Total	
	Dose Group 1			
	N	%	N	%
Total	2	100	2	100
General appearance				
Abnormal	2	100	2	100
Heart				
Normal	2	100	2	100
Respiratory				
Normal	2	100	2	100
Abdomen				
Normal	1	50	1	50
Abnormal	1	50	1	50
Neurological				
Abnormal	2	100	2	100
Other				
No	2	100	2	100

Baseline Abnormalities - General

	Dose Administered		Total	
	Dose Group 1			
	N	%	N	%
Total	2	100	2	100
If abnormal, please detail				
Bilateral pitting oedema to knee	1	50	1	50
Venous eczema of legs	1	50	1	50

Baseline Abnormalities - Abdominal

	Dose Administered		Total	
	Dose Group 1			
	N	%	N	%
Total with abdominal abnormality	1	100	1	100
If abnormal, please detail				
bruising to lower abdomen	1	100	1	100

Baseline Abnormalities - Neurological

	Dose Administered		Total	
	Dose Group 1			
	N	%	N	%
Total with neurological abnormality	2	100	2	100
If abnormal, please detail				
Generalised weakness	1	50	1	50
Left Lateral Gaze palsy	1	50	1	50

3. OUTCOME DATA

The primary outcome for Appendix 3 of the Define CTIMP was safety, and this was assessed a number of ways (see table below).

Objectives	Endpoints
Primary	
To evaluate the safety of SARS-CoV-2 VSTs as add-on therapy to SoC in patients with COVID-19.	Safety will be assessed using: • Haematological and biochemical safety laboratory investigations • Directed cardio-respiratory physical examination • Vital signs (blood pressure / heart rate / respiratory rate, temperature) • Adverse events **No daily electrocardiogram (ECG) readings required for this appendix (only required at screening)*

Summary safety detail can be found in the tables below. However, as only 2 participants were recruited, no conclusions can be made using these results, and the research team have made no attempt to do so.

Clinically significant blood results (haematology and biochemistry safety)

Dose Administered	Description of clinically significant blood result	Event Name
Dose Group 1	Abnormal LFT's noted -clinical team made aware	Day 7
Dose Group 1	Lymphocyte count, neutrophil count, and white cell count deemed to be clinically significant by Sub-Investigator. AE recorded.	Day 21

Directed cardio-respiratory physical exam day 1 to 7 (post infusion) - Respiratory

Record ID	Event Name	Respiratory Examination
A3-001	Day 1	Normal
A3-001	Day 2	Normal
A3-001	Day 3	Normal
A3-001	Day 4	Normal
A3-001	Day 5	Normal
A3-001	Day 6	Normal
A3-001	Day 7	Abnormal
A3-002	Day 1	Normal
A3-002	Day 2	Normal
A3-002	Day 3	Abnormal
A3-002	Day 4	Abnormal
A3-002	Day 5	Abnormal
A3-002	Day 6	Abnormal
A3-002	Day 7	Abnormal

Abnormal entries were the result of crepitations being heard during the daily cardio-respiratory assessment.

No cardiovascular abnormalities were reported post infusion Day 1-7.

4. ADVERSE EVENTS

No infusion reactions were reported during the trial.

Table below details the adverse event reported during the trial, with summary details below.

Event Number	Adverse Event	SAE	Severity	Causality	Expectedness	Outcome (at end of trial)
1	HYPOTENSION	NO	Moderate	Possibly related	Unexpected	Resolved
2	TACHYCARDIA	NO	Mild	Unrelated	N/A	Resolved
3	HYPOXIA	NO	Mild	Unrelated	N/A	Resolved
4	INTERMITTENT OVERNIGHT CONFUSION	NO	Mild	Unrelated	N/A	Resolved
5	PRODUCTIVE COUGH	NO	Mild	Unrelated	N/A	Resolved
6	OXYGEN SATURATION REDUCED	NO	Mild	Unrelated	N/A	Resolved
7	ABNORMAL LIVER FUNCTION TESTS	NO	Mild	Unrelated	N/A	Resolved
8	URINARY TRACT INFECTION	NO	Mild	Unrelated	N/A	Resolved
9	HOSPITAL ACQUIRED CHEST INFECTION REQUIRING ANTIBIOTICS	NO	Mild	Unrelated	N/A	Resolved
10	RAISED TROPONIN	NO	Mild	Unrelated	N/A	Ongoing
11	LOW MOOD	NO	Mild	Unrelated	N/A	Ongoing
13	LOW POTASSIUM (=3.1mmol/L)	NO	Mild	Unrelated	N/A	Resolved
14	INFECTION OF UNKNOWN SOURCE - POSITIVE BLOOD CULTURES	NO	Moderate	Unrelated	N/A	Resolved
15	LOW WHITE CELL COUNT	NO	Mild	Unrelated	N/A	Resolved
16	HOSPITAL ACQUIRED PNEUMONIA	NO	Mild	Unrelated	N/A	Resolved
17	HYPOKALAEMIA	NO	Mild	Unrelated	N/A	Resolved
18	DEHYDRATION	NO	Mild	Unrelated	N/A	Resolved
19	VOMITING	NO	Mild	Unrelated	N/A	Resolved
20	SKIN IRRITATION (BACK)	NO	Mild	Unrelated	N/A	Resolved
21	BILATERAL LOWER LEG OEDEMA	NO	Mild	Unrelated	N/A	Ongoing
22	PRURITIS (BACK)	NO	Mild	Unrelated	N/A	Ongoing
23	HYPOTENSION	NO	Mild	Unrelated	N/A	Resolved
24	LOW ALBUMIN	NO	Mild	Unrelated	N/A	Ongoing

Summary of adverse event data

24 events reported for 2 participants.
No event was assessed as meeting criteria for SAE
2 of the 24 had severity assessed as moderate, all others were assessed as mild
Only 1 event was assessed as being possibly related to the intervention, and was unexpected.
4 of the 24 events were ongoing at the end of the trial.

5. APPENDIX 1 – FINAL FUNDER REPORT

CHIEF SCIENTIST OFFICE

CODE: TCS/21/43

RESEARCH PROJECT BRIEFING

First in human clinical trial of a T cell therapy for COVID-19

AIMS

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is the virus that causes COVID-19. In this study, a cell therapy, SARS-Cov-2 Virus Specific T cells (SARS-Cov-2 VST), was developed using donor immune cells collected from people who had recovered from COVID-19. The aim of the project was to undertake a phase Ib/IIa First in Human (FIH) clinical trial to establish the safety and feasibility of SARS-Cov-2 VST for the treatment of COVID-19 in hospitalised patients.

KEY FINDINGS

- 1090 patients were screened in total. Due to a policy change in the mandatory testing of SARS-CoV-2, there was a significant drop in the identification of SARS-CoV-2 positive cases.
- Two patients of our target of eleven patients were recruited to the phase Ib/IIa FIH clinical trial and were administered SARS-Cov-2 VST, with no reported adverse events.
- The clinical trial could not be completed due to insufficient patient recruitment.

WHAT DID THE STUDY INVOLVE?

This study was part of the DEFINE trial platform, designed to evaluate new or repurposed treatments for COVID-19.

The study involved:

- A dose escalation phase Ib/IIa clinical trial to assess the safety and feasibility of treatment with SARS-Cov-2 VST and to examine a range of clinical and immunological responses to the infused cells.

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www.cso.scot.nhs.uk @CSO_Scotland

- Patient eligibility criteria included: patients over 16, SARS-CoV-2 positive, must have oxygen levels of 92% or higher prior to infusion, no vaccinations up to 3 weeks prior to infusion and must not be pregnant or breastfeeding.
- Patients provided blood samples prior to infusion to establish viral load, human leukocyte antigens (HLA) type to ensure the donor and patient have closely matched immune system markers, and to identify baseline values for clinical parameters (physical, electrolyte, haematological and liver function).
- Seven SARS-Cov-2 VST batches were available for clinical use.
- Patients were administered a single infusion of HLA-matched SARS-Cov-2 VST. The clinical trial design included 3 cohorts to test dose escalation, with the first 3 participants receiving the lowest dose (group 1, $1.5x10^6$ cells total), the next 3 participants receiving the middle dose (group 2, $1.5x10^7$ cells total), and the last five participants receiving the highest dose (group 3, $1.5x10^8$ cells total).
- Following completion of the infusion, patients were sampled after 2-3 hours, then subsequently at 24h and 48h (patients remained in hospital for a minimum of 48 hours), with full patient monitoring run for 6-weeks post infusion.
- The patient information sheet was reviewed by a patient representative, and their suggestions were included in the final document. Feedback from participants from earlier arms of the trial was taken into consideration when developing the protocol, and sampling requirements and frequency were amended to reduce the burden on patients.

WHAT WERE THE RESULTS AND WHAT DO THEY MEAN?

Two of eleven patients were recruited to the clinical trial and administered SARS-Cov-2 VST, with no reported adverse events. Early in the study (September 2022), a policy change from the Scottish government resulted in the cessation of routine SARS-CoV-2 testing in NHS Lothian, with only symptomatic patients being tested for SARS-CoV-2. This resulted in a significant drop in SARS-CoV-2-positive cases being identified within the hospital and impacted the number of patients that could be screened for recruitment to the trial. The trial strategy had been to approach patients in the hospital setting who had coincidentally tested positive for SARS-CoV-2 but were otherwise well regarding COVID-19. Due to removal of asymptomatic COVID-19 testing, many patients identified did not meet the inclusion/exclusion criteria for the trial. Several mitigations were put in place, including opening a second site, establishing a mechanism to help identify SARS-CoV-2 positive patients and changing the eligibility criteria to include patients maintaining saturations at ≥92% on a minimum of 28% supplemental oxygen therapy. Despite the mitigations, we were unable to reach our recruitment target and fully demonstrate product safety.

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RESEARCH PROJECT BRIEFING

WHAT IMPACT COULD THE FINDINGS HAVE?

The manufacturing process developed for SARS-CoV-2 VST is applicable in principle to adaptation to SARS-CoV-2 variants and to a wide range of other viral infections including other coronaviruses and influenza which have caused previous pandemics. Development of new treatment options would particularly benefit those patients who are immunocompromised and are at risk of persistent infection or more serious disease.

HOW WILL THE OUTCOMES BE DISSEMINATED?

Details of the study can be found on the ISRCTN registry (ISRCTN14212905) and the EU Clinical Trials Register (EudraCT 2020-002230-32).

CONCLUSION

The clinical trial could not be completed because we were unable to reach our recruitment target. The initial strategy of this study was to validate SARS-CoV-2 VST safety in a generally healthy patient group. Despite rapid development and manufacturing of the SARS-CoV-2 VST, during the study a policy change resulting in the cessation of routine SARS-Cov-2 testing led to a significant drop in the identification of SARS-CoV-2 positive cases. This raises an important challenge in designing trials for treatments of emerging viruses.

RESEARCH TEAM & CONTACT

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Additional Information

The study ended on the 30th April 25 and received £280,403 of funding from the Chief Scientist Office.