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OPERATIONS-FOCUSED VENOUS THROMBOSIS STRATEGIC ROADMAP

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1. EXECUTIVE SUMMARY

In this document, the HRE-HS team highlights various approaches to address key knowledge gaps in our understanding of venous thrombosis (VT) that were identified by the Space Medicine Team (SMT). While many of these gaps can be addressed by fundamental science to expand our knowledge, the occurrence of an atypical, internal jugular VT in a crew member during spaceflight means that our priority is proposing research avenues that provide an opportunity for exploration-focused science and are in line with ESA's commitment to advancing space technology and research to support human presence beyond low Earth orbit (LEO). Since Life Science bridges exploration-enabled and exploration-focused science, it is important to prioritise such research avenues to ensure crew health and develop relevant countermeasures, while simultaneously having a beneficial application on Earth. Since this is a core focus of Explore2040's strategy, focusing on such research efforts aims to promote sustainable human exploration. Hence, future research studies should keep the possible design of the Artemis mission(s) towards Gateway in mind (but not exclusively) and reflect, as closely as possible, the duration of mission segments and countermeasures that will be available in those segments.

Therefore, this document prioritises the VT roadmap objectives based on their potential application in ESA's upcoming crewed missions and highlights whether these objectives should be investigated in the short-term (at the next available opportunity), medium-term (for consideration in relevant ESA roadmaps e.g. HRE-HS/Tech-MMG), or long-term (beneficial to have if the opportunity arises or based on further evidence/activities). These objectives were ordered based on priority, opportunity, and maturity of the objectives. Addressing these objectives will not only inform ESA operations but will also benefit international partner agencies.

2. ACRONYMS AND ABBREVIATIONS

Acronym	Description
µg	microgravity
ConTa	contingency taskforce
CRP	C-reactive protein

Acronym	Description
DI	dry immersion
DVT	deep vein thrombosis
GBF	ground-based facility
HDTBR	head-down tilt bed rest
ICP	intracranial pressure
IJV	internal jugular vein
ISS	International Space Station
LBNP	lower body negative pressure
LEO	low Earth orbit
MR DTI	magnetic resonance direct thrombus imaging
PD	pharmacodynamic
PFC	parabolic flight campaign
PK	pharmacokinetic
PoC	point-of-care
SANS	space associated neuro-ocular syndrome
SMT	Space Medicine Team
TIM	Technical Interchange Meeting
US	ultrasound
VFI	vector flow imaging
VM	Valsalva manoeuvre
VT	venous thrombosis

3. TERMINOLOGY

While this document discusses thrombotic pathology involving the venous system, the precise origin remains uncertain; therefore, the term 'VT' has been used throughout the document. However, it should be noted that deep vein thrombosis (DVT) typically describes this occurrence in deep veins of the lower extremity. Hence, although DVT may be the most clinically correct term to describe this occurrence if it originated from the lower extremities, 'VT' has been used as the most operationally correct term. Furthermore, the use of the word 'uncommon' in the document's title reinforces that VT in the upper extremity is usually rare, so the context of this document is specifically related to space and alterations that occur within zero-gravity.

4. INTRODUCTION

In 2019, an incidental finding of a potentially occlusive thrombus within the left internal jugular vein (IJV) was reported in an astronaut two months into their mission (Auñón-Chancellor *et al.,* 2020). Despite successful management of the case (Auñón-Chancellor *et al.,* 2020), its occurrence in an uncommon location (Marshall-Goebel *et al.,* 2019) and the high percentage of crew that demonstrate stagnant or retrograde flow within the left IJV in subsequent surveillance (Pavela *et al.,* 2022) highlights a clear need to better understand VT risk factors, and develop better prevention, diagnostic, and treatment approaches appropriate for spaceflight.

VT is a major concern for astronauts during spaceflight since cephalad fluid shifts typical in microgravity (*μg*) may promote abnormal stasis or flow and may contribute to the promotion of a prothrombotic state. If undetected, VT can propagate to the cerebral sinus and ultimately lead to fatal events such as cerebral stroke or lung embolism, threatening both the crew member's life and the overall mission. The pathophysiology of VT is underpinned by three interlinked domains: stasis, hypercoagulability, and vascular endothelial injury described by Virchow's triad (Bagot and Arya, 2008) (Figure 1). Each domain can significantly elevate the risk of thrombus formation and have been hypothesised to contribute to thrombosis in spaceflight (Kim *et al.,* 2021; Harris *et al.,* 2022; Harris *et al.,* 2023; White and Wenthe, 2023; Elahi *et al.,* 2024). Although classical markers of hypercoagulability and endothelial injury may not be consistently altered in microgravity (Laurie *et al*, n.d.), one research study revealed stasis or retrograde flow in the jugular veins by flight day 50 in 55% of crew that underwent ultrasound (US) assessment (Marshall-Goebel *et al.,* 2019; Auñón-Chancellor *et al.,* 2020). However, none of these crew members

developed symptomatic VT inflight (Marshall-Goebel *et al.,* 2019; Auñón-Chancellor *et al.,* 2020). Additionally, in an inflight Surveillance Program, six of 11 astronauts were found to have mild-moderate echogenicity in the left IJV, while none exceeded mild echogenicity in the right IJV (Pavela *et al.,* 2022). On Earth, stasis alone is considered to represent a low VT risk (Malone and Agutter *et al*., 2009) and it is unclear whether the other two domains of Virchow's triad, hypercoagulability and endothelial injury, are also implicated in spaceflight. It is unknown what combination of Virchow's triad resulted in the clinical presentation of VT inflight – and whether these patterns, or elements of them are present asymptomatically in other crew members.

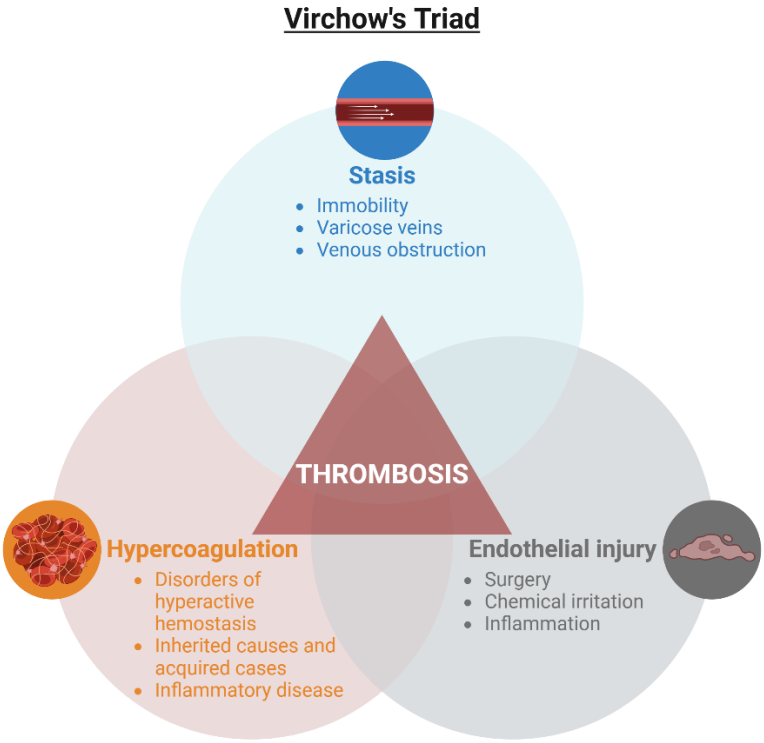

Figure 1. Illustration of Virchow's triad describing the three key inter-linking domains that contribute to VT: stasis, hypercoagulability, and endothelial injury.

Therefore, while surveillance of blood flow in the jugular veins during spaceflight will increase, and many international partners have agreed to participate in this Surveillance Program, research is required to understand the inter-related pathophysiology of stasis, hypercoagulability, and vascular endothelial health. Investigating these domains in spaceflight will improve our ability to identify VT risk factors, diagnostic approaches, management strategies, and prevention methods.

To address the potential significant crew health concerns of the uncommon jugular VT presents in spaceflight, a contingency taskforce (ConTa) was established, consisting of members of ESA's SMT with the support of HRE-HS. ConTa held a Technical Interchange Meeting (TIM) with medical operation representatives from ESA, NASA, CSA, and JAXA, and were joined by invited experts in clinical terrestrial medicine, and selected researchers from across Europe in December 2024. Various key knowledge gaps and how these may be specifically addressed via the co-ordinated use of ESA's ground-based facilities (GBFs) and potentially on the International Space Station (ISS) in the short-term were identified and discussed in the TIM research splinter. These knowledge gaps are outlined and prioritised in this document.

5. HOW GROUND BASED FACILITIES COULD BE UTILISED TO STUDY VENOUS THROMBOSIS AND VIRCHOW'S TRIAD

In the short-term, the TIM members proposed implementing multilateral research utilising GBFs such as parabolic flight campaigns (PFCs) and head-down tilt bed rest (HDTBR), as these platforms were identified as potentially effective analogues to study VT. Other GBFs, such as dry immersion (DI), Drop Tower, and Concordia, were not deemed a high priority for this purpose.

Although VT events have not been recorded in GBFs simulating *μg* to date, PFC is a useful model to assess acute stasis, while 'strict' -6° HDTBR can be used to assess chronic space associated neuro-ocular syndrome (SANS) symptomology (Figure 2). Hence, the purpose of utilising such GBFs is not to induce VT occurrences, but rather to investigate other aspects of Virchow's triad or other mechanisms that may overlap with VT (such as the development of SANS), as well as to assess candidate countermeasures.

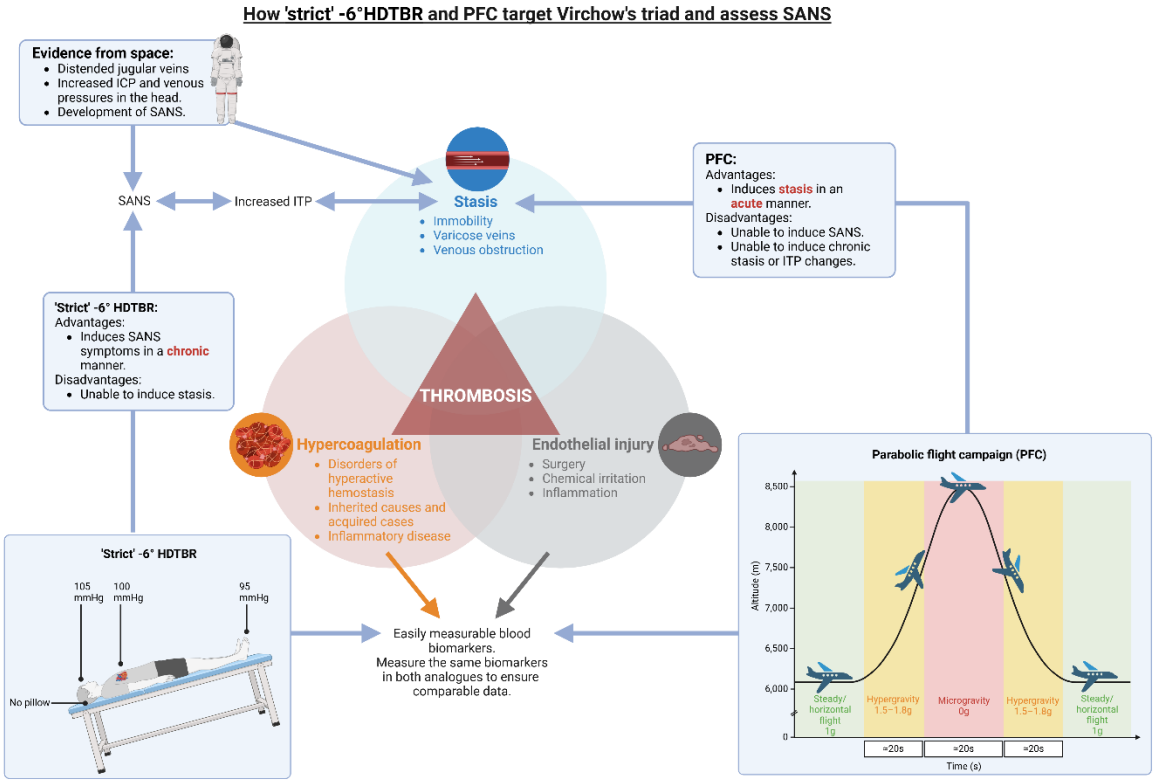

Figure 2. How PFC and 'strict' -6º HDTBR target Virchow's triad, making them effective analogues to investigate VT. Currently, PFC is the only known GBF to deploy stagnant and retrograde flow in the left IJV.

5.1. Parabolic Flight Campaigns

PFCs can induce acute changes in central venous (Foldager *et al.,* 1996) and ocular pressures (Mader *et al*., 1993), along with choroidal blood flow (Ansari *et al*., 2002). Reversible stagnant flow in the left IJV was recently reported in one out of 14 participants taking part in *μg* PFCs (Marshall-Goebel *et al.,* 2024). Additionally, increased left and right IJV cross-sectional- areas (Lee *et al.,* 2020; Marshall-Goebel *et al*., 2024), along with increased IJV pressure (Martin *et al.,* 2016) occur. Although parabolic flight is transient in nature and stasis is reversed by standing or sitting in hyper- or normo-gravity, it is unknown what effect parabolic flight has on other domains of the triad. Since net fluid shift and stasis can occur within the vessels during PFC, this could be a potential acute analogue for investigating stasis and consequent alterations in coagulation or endothelial pathways in line with Virchow's triad (Figure 2).

Furthermore, PFC enables the investigation of IJV flow physiology under partial gravities. This is an important research question as living in lunar or Martian gravity could still be associated with disturbed venous flow of neck veins.

5.2. ‘Strict’ Head-Down Tilt Bed Rest

-6° HDTBR is the primary analogue of chronic *µg* exposure on Earth, but recent data from NASA suggests that the -6° HDTBR model does not induce venous stasis within the IJVs (unpublished data). However, no efforts have been made so far to optimise the HDTBR model for VT research, and therefore the full potential of this model has not been deployed yet. Although HDTBR does not induce stasis, ‘strict’ -6º HDTBR (precluding the use of pillows, any lifting of the head and torso, and raising elbows for support) has been demonstrated to induce SANS symptomology in a significant proportion of participants (Taibbi *et al.,* 2016; Laurie *et al.,* 2017; Laurie *et al*., 2019; Laurie *et al*., 2020; Clément *et al*., 2022). While the key risk factors and pathophysiology of SANS remain unknown (Ong *et al.,* 2021), there may be shared mechanisms contributing to both VT and SANS pathologies. For example, cephalad fluid shift and central venous congestion may underpin chronically elevated intracranial pressure (ICP) and contribute to the typical symptoms of SANS (Galdamez *et al.,* 2025). Since elevated ICP potentially promotes stasis in the cranial venous vasculature as well as dysfunctional glymphatic drainage, and central venous congestion stimulates the production of inflammatory markers (Galdamez *et al.,* 2025), key domains of Virchow's triad may be upregulated, possibly increasing the risk of VT in the upper body vascular tree (Figure 3). As such, 'strict’ -6º HDTBR appears to induce upper body fluid shifts and vascular flows in a manner more akin to chronic *µg* exposure than ‘historic’ HDTBR. Therefore, although HDTBR has not yet been demonstrated to specifically induce IJV stasis or indeed lead to VT, a ‘strict’ -6º HDTBR analogue offers an opportunity to validly investigate the effect of chronic changes upon systemic coagulability and endothelial status, as well as further investigate SANS – which is considered a key human health risk by NASA's Human Research Program (NASA, n.d.). While a 'strict’ -6º HDTBR study duration should be 60 days, available data from 30-day HBTBR studies suggests that 30 days may be sufficient, but this warrants further consideration.

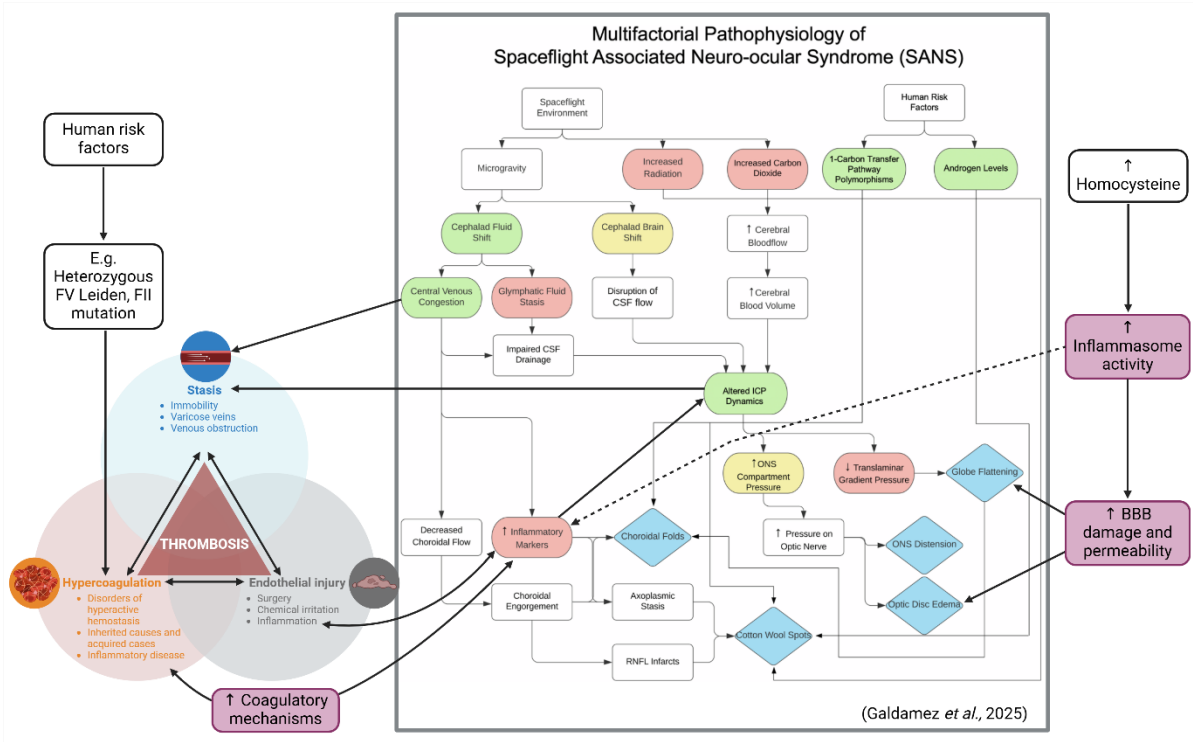

Figure 3. Illustration of how SANS mechanisms may inter-link with coagulatory mechanisms, demonstrating how 'strict' -6º HDTBR is a potential GBF to investigate VT. Direct coagulatory influences are highlighted in purple and influence Virchow's triad. Cephalad fluid shifts contribute to elevated ICP, and this in turn can potentially promote stasis – a key component of Virchow's triad – potentially influencing downstream coagulation pathways and endothelial integrity. Furthermore, central venous congestion stimulates the production of inflammatory markers. Since systemic inflammation has a bidirectional relationship with both coagulation and endothelial injury, it further amplifies Virchow's triad, thereby increasing the risk of VT. Adapted from Galdamez *et al.,* 2025.

6. HOW THE INTERNATIONAL SPACE STATION COULD BE UTILISED TO STUDY VENOUS THROMBOSIS AND VIRCHOW'S TRIAD

Short duration missions (up to two weeks on the ISS, e.g. Axiom, or ~72-hour orbital flights, e.g. Polaris dawn) provide a clear understanding of how early-adaptation and cephalad congestion overlap can be differentiated. They are also useful to evaluate candidate diagnostic devices and identify venous flow abnormalities. Additionally, implementing some aspects of the new VT guidelines (such as surveillance to L+7 to inform pharmaceutical prophylaxis with apixaban) in these short missions offers a useful opportunity to assess pharmaceutical kinetics of oral antithrombotics.

However, longer-duration space-based studies aboard the ISS in LEO can be utilised and are needed to answer questions that require a chronic duration (for example six months).

7. VENOUS THROMBOSIS ROADMAP OBJECTIVES

The VT roadmap objectives are categorised as short-term (at the next available opportunity) (**red**), medium-term (for consideration in relevant ESA roadmaps e.g., HRE-HS/Tech-MMG) (**orange**), or long-term (beneficial to have if the opportunity arises or based on further evidence/activities) (**green**) within the domains: 1. Pathophysiology (risk), 2. Diagnosis, 3. Treatment/Management, and 4. Countermeasures/Prevention. These objectives were ordered based on priority, opportunity, and maturity of the objectives. The terminology 'determine' has been used for describing knowledge gaps, while 'evaluate' has been used for device or approach testing. Recommendation of platform(s) and/or approach(es) are made with the focus upon evidence relevant to informing and optimising Medical Operations, although significant fundamental knowledge with significant terrestrial benefits may be acquired. Information in the fourth column highlighted in italics indicates activities where the roadmap objective may be potentially addressed. While these objectives are listed in a condensed manner, further explanation/justification for each objective can be found in the Appendices.

7.1. Pathophysiology (risk)

The aim is to establish a comprehensive risk predictor model by assessing risk factors pre-flight. Such risk factors are not to be identified to exclude astronauts at the screening process, but to inform generalised evidence-based VT management.

Should a crew member possess specific (to be defined) risk factors, individualised surveillance and preventative approaches to promote safe flight could be adopted. Therefore, closing several key pathophysiological knowledge gaps is required. In particular, understanding the effect of spaceflight upon each element of Virchow's triad (and how they may interact) in addition to the potential role of anti-thrombotic pathways is required.

ID#	Roadmap Objective	Operational Implication	Recommended Platform(s) and/or Approach(es)
VT_PATHOPHYS_01	Determine whether upper body venous anatomical variation modulates venous flow or stasis and therefore may influence the likelihood of VT development.	An association would inform generalised and individual VT risk assessment.	Since 'strict' -6° HDTBR is unable to mimic stasis observed inflight, PFC or inflight should be adopted as jugular venous stasis has been reported. *Status report: Potentially addressed in a VT-dedicated PFC and ThromboShift HDTBR.*
VT_PATHOPHYS_02	Determine whether SANS (induced as a result of cephalad fluid shift) modulates pro- and anti-thrombotic pathways or other associated biomarkers of Virchow's triad.	An association would inform generalised and individual VT risk assessment, in addition to potentially contributing to surveillance and risk mitigation.	'Strict' 30-day -6° HDTBR could be utilised as it has been proven to be a successful model in inducing SANS symptomology. Additionally, extending marker measurements into re-ambulation helps assess if returning to normal triggers early regulatory changes and may generate insight into pro- and anti-thrombotic pathways that are modulated by DI and HDTBR. *Status report: Addressed in the ThromboShift HDTBR.*
VT_PATHOPHYS_03	Evaluate the sensitivity and clinical utility of vector flow imaging (VFI), a novel imaging technique, in detecting	Confirmation of validity and establishment of clinical utility would facilitate development	PFC as jugular flow stasis is reported.

	modulation of venous flow, effects of venous anatomy, and identification of the presence and evolution of VT.	and implementation of inflight VT diagnosis and enhance surveillance.	*Status report: Potential to be partly addressed in a VT-dedicated PFC.*
VT_PATHOPHYS_04	Determine whether cephalad fluid shifts modulate upper body lymphatic composition and flow, and whether this is associated with modulation of pro- and anti-thrombotic pathways or other biomarkers of Virchow's triad.	An association would inform generalised and individual VT risk assessment, in addition to potentially contributing to surveillance.	'Strict' 30-day -6° HDTBR has been reported to induce SANS symptoms that are associated with sustained cephalad fluid shifts. Lymphatic flow is potentially measurable via ultrafast US (Vullings *et al.,* 2023). Additionally, extending marker measurements into re-ambulation helps assess if returning to normal triggers early regulatory changes and may generate insight into pro- and anti-thrombotic pathways that are modulated by DI and HDTBR.
VT_PATHOPHYS_05	Determine whether bi-lateral jugular flow and biomarkers of Virchow's triad and/or systemic inflammation are significantly modulated in *μg*, and is there an effect of exposure duration?	An association would inform generalised and individual VT risk assessment, in addition to potentially contributing to surveillance.	Since a long-duration study is required to induce chronic changes, ISS/true extended *μg* exposure is deemed the only suitable platform. Additionally, extending marker measurements into re-ambulation helps assess if returning to normal triggers early regulatory changes and may generate insight into pro- and anti-thrombotic pathways that are modulated by DI and HDTBR.

			Status report: Can potentially address whether bi-lateral jugular flow links to these biomarkers in ThromboShift HDTBR.
VT_PATHOPHYS_06	Determine the use of endothelial/microvascular function tests and an analytical system(s) pre-flight that can identify individuals at an elevated risk of inflight VT.	Inform generalised and individual VT risk assessment.	Any platform where thrombotic pathways are known to be modulated.
VT_PATHOPHYS_07	Determine the effect of sex hormones upon pro- and anti-thrombotic pathways or other Virchow's triad markers.	An association would inform generalised and individual VT risk assessment.	Any platform where thrombotic pathways are known to be modulated.
VT_PATHOPHYS_08	Determine the effect of chronic mild dehydration upon pro- and anti-thrombotic pathways.	An association would inform generalised and individual VT risk assessment and contribute to risk mitigation.	'Strict' -6° HDTBR could be utilised as it is a more chronic platform and allows convenient monitoring of fluid intake and output. Alternatively, ISS/true extended *μg* exposure could be utilised. Additionally, extending marker measurements into re-ambulation helps assess if returning to normal triggers early regulatory changes and may generate insight into pro- and anti-thrombotic pathways that are modulated by DI and HDTBR.
VT_PATHOPHYS_09	Determine platelet and concomitant (innate) immune cell interaction in *μg*/spaceflight and whether this is associated with modulation of pro- and	An association would inform generalised and individual VT risk assessment, in addition to	In vivo spaceflight sampling or in vitro e.g. clinostat, sounding rockets.

	anti-thrombotic pathways or other biomarkers of Virchow's triad.	potentially contributing to surveillance and risk mitigation.	
VT_PATHOPHYS_10	Determine the effect of chronic exposure to space radiation upon endothelial function, clot formation, and pro- and anti-coagulation pathways.	An association would inform generalised and individual VT risk assessment, in addition to potentially contributing to surveillance and risk mitigation.	In vitro e.g. vessel/cell on chip within IBER.
VT_PATHOPHYS_11	Determine the effect of increasing (body/core/brain) temperatures on pro- and anti-thrombotic pathways or other biomarkers of Virchow's triad and jugular flow.	An association would inform generalised and individual VT risk assessment, in addition to potentially contributing to surveillance and risk mitigation.	In vivo sampling or in vitro e.g. clinostat, sounding rockets.

7.2. Diagnosis

The aim is to improve diagnostic tools, biomarker-monitoring systems, and point-of-care (PoC) devices to provide real-time health management in spaceflight. Testing potential diagnostic devices and improvement of the current diagnostic techniques will play a critical role in ensuring astronaut health and mission success. Currently there is no means of measuring coagulation activity in spaceflight to date, nor have alternative devices been identified that could be useful during spaceflight to assess coagulation function. If the existing surveillance protocol is changed, it would be essential to note whether an increased number of asymptomatic VT cases are recorded.

ID#	Roadmap Objective	Operational Implication	Recommended Platform(s)/Approach(es)
VT_DIAGNOSIS_01	Evaluate the performance of commercial thrombosis PoC devices in *μg* and establish normative (and potentially threshold) values inflight.	Confirmation of validity and establishment of normative values would facilitate development and implementation of inflight VT diagnosis and promote valid surveillance.	PFC for evaluation of performance in *μg* and inflight assessment for normative (threshold values). *Status report: Partially addressed in September 2025 PFC.*
VT_DIAGNOSIS_02	Evaluate the sensitivity and clinical utility of novel imaging techniques in confirming clot presence and identifying newly forming clots.	Confirmation of validity and establishment of clinical utility would facilitate development and implementation of inflight VT diagnosis and promote valid surveillance.	PFC as jugular flow stasis is reported. Candidate techniques include VFI, ultrafast US, and magnetic resonance direct thrombus imaging (MR DTI). *Status report: Potentially partly being addressed in a VT-dedicated PFC.*

7.3. Treatment/Management

To provide optimal mission compatible VT treatment/management strategies, determination of factors that may affect drug delivery and/or an individual's response to terrestrial standard healthcare in space are required. As antithrombotic apixaban treatment was effective in space and is also recommended as prophylaxis in the current ESA VT Guidelines, optimisation of its prescription should be prioritised.

ID#	Roadmap Objective	Operational Implication	Recommended Platform(s)/Approach(es)
VT_TMT_01	Determine the bioavailability of anticoagulation treatment in *μg*.	Establishment of characteristics that may affect bioavailability and/or efficacy of anticoagulation treatment will facilitate optimisation of VT treatment/management strategies.	Peak and trough (metrics of bioavailability) apixaban concentrations should be investigated as appropriate including upon thrombosis progression. Observational data should be collected from crew in true extended *μg* exposure that have been prescribed prophylactic medication inflight.
. VT_TMT_02	Determine the pharmacokinetic (PK), pharmacodynamic (PD), and any other characteristics that may affect bioavailability and/or efficacy of anticoagulation treatment in a relevant inflight model (e.g. animal).	Establishment of characteristics that may affect bioavailability and/or efficacy of anticoagulation treatment will facilitate optimisation of VT treatment/management strategies.	Should be assessed in a relevant inflight model (e.g. animal).

7.4. Countermeasures/Prevention

Determination of evidence-based valid, proportionate, and mission-compatible VT countermeasures or preventative approaches are required which may have significant terrestrial benefits.

ID#	Roadmap Objective	Operational Implication	Recommended Platform(s)/Approach(es)
VT_CM_01	Determine whether lower body negative pressure (LBNP) and/or venous thigh cuffs should be utilised as countermeasures for VT and determine the risks and/or benefits of the methodologies upon thrombotic pathways, biomarkers of Virchow's triad, and/or the location and evolution of VT.	Establishment of the effect of these methodologies will facilitate their appropriate adoption/optimisation as a VT countermeasure strategy.	Since a chronic model is required to assess the effectiveness of the countermeasures, 'strict' -6° HDTBR could be utilised. Alternatively, these methodologies can be tested on the ISS or in true extended *μg* exposure. Additionally, extending marker measurements into re-ambulation helps assess if returning to normal triggers early regulatory changes and may generate insight into pro- and anti-thrombotic pathways that are modulated by DI and HDTBR.
VT_CM_02	Determine whether use of the ISS Treadmill 2 and harness should be considered a potential inflight VT risk factor.	Establishment of the effect of the ISS Treadmill 2 and harness upon jugular vein flow and/or evidence of thoracic outlet syndrome may facilitate VT prevention.	Perform jugular vein or thoracic outlet syndrome surveillance US either on the ISS or a simulate harness during PFC and/or vertical treadmill. *Status report: Potentially partly being addressed in a VT-dedicated PFC. Ongoing on the ISS now as part of inflight surveillance.*
VT_CM_03	Determine the risks and/or benefits of repeated Valsalva manoeuvre (VM) performance during resistance training upon thrombotic pathways, biomarkers of Virchow's triad, and/or the location and evolution of VT.	Establishment of the effect of repeated VM performance during resistance training will facilitate appropriate adoption/optimisation of resistance exercise.	Long-duration 'strict' -6° HDTBR and or *μg* exposure. Additionally, extending marker measurements into re-ambulation helps assess if returning to normal triggers early regulatory changes and may generate insight into pro- and anti-

			thrombotic pathways that are modulated by DI and HDTBR.
VT_CM_04	Determine the risks and/or benefits of current and planned exercise (particularly if associated with repetitive application of pressure on upper body veins) upon thrombotic pathways, biomarkers of Virchow's triad, and/or the location and evolution of VT.	Establishment of the effect of current and planned exercise will facilitate appropriate adoption/optimisation of exercise countermeasures.	Since a chronic model is required to assess the effectiveness of the countermeasure, 'strict' -6° HDTBR could be utilised. Alternatively, this can be tested on the ISS or in true extended *μg* exposure. Additionally, extending marker measurements into re-ambulation helps assess if returning to normal triggers early regulatory changes and may generate insight into pro- and anti-thrombotic pathways that are modulated by DI and HDTBR.
VT_CM_05	Determine whether simple mission-compatible neck flow countermeasures modulate thrombotic pathways, biomarkers of Virchow's triad, and/or the location and evolution of VT.	Establishment of the effect of mission-compatible neck flow countermeasures will facilitate determination of appropriate adoption/optimisation as a VT countermeasure.	Long-duration *μg* exposure with mission-compatible neck flow countermeasures e.g., neck suction.
VT_CM_06	Determine whether artificial gravity (e.g. centrifugation) could mitigate VT risk via modulation of thrombotic pathways, biomarkers of Virchow's triad, and/or the location and evolution of VT.	Establishment of the effect of artificial gravity will facilitate determination of appropriate adoption/optimisation as a multi-system including VT countermeasure.	'Strict' -6° HDTBR if shown to modulate VT biomarkers or alternatively, in long-duration μg exposure. Additionally, extending marker measurements into re-ambulation helps assess if returning to normal triggers early regulatory changes and may generate insight into pro- and anti-thrombotic pathways that are modulated by DI and HDTBR.

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9. APPENDICES

Appendix 1: Pathophysiology (risk)

VT_PATHOPHYS_01

Determine whether upper body venous anatomical variation modulates venous flow or stasis and therefore may influence the likelihood of VT development.

Anatomical variations between individuals (assessed via MRI) may contribute to changes in flow dynamics, an increased risk of stasis in the upper thorax and head (such as in the IJV), and/or elevated systemic inflammation and coagulation markers. Understanding this is crucial to determine whether they render individuals more susceptible to adverse coagulatory or inflammatory events. Additionally, this objective may offer novel screening areas.

Several candidate anatomical risks have been proposed including left-to-right cranial drainage asymmetries in the cerebral sinuses and the “retrosternal distance” between the sternum and aortic arch. The left-to-right cerebral drainage asymmetry is common in the general population and may be a contributing factor to the frequency of flow abnormalities observed in the right and left IJV’s during PFC. Additionally, in clinical studies of patients undergoing contrast venogram, the retrosternal distance correlates with the level of reflux of contrast in the right IJV during contrast injection into the left arm (Tseng *et al*., 2007; Jeon *et al*., 2020).

VT_PATHOPHYS_02

Determine whether SANS (induced as a result of cephalad fluid shift) modulates pro- and anti-thrombotic pathways or other associated biomarkers of Virchow’s triad.

SANS was first reported in 2011 following long-duration spaceflight (Mader *et al.,* 2011), with symptoms evident in approximately 70% of crew members, although there is significant intra-individual variability (Lee *et al*., 2020). Given the potential non-reversible risk to ocular (and potentially cerebral) health, SANS is of significant concern for space medicine operations and is considered a key human health risk by NASA's Human Research Program (NASA, n.d.). The key risks factors and pathophysiology of SANS remain unknown (Ong *et al.,* 2021); however, cephalad fluid shift and central venous congestion may underpin chronically elevated ICP and contribute to the typical symptoms of SANS. However, understanding why some crew express symptoms, and others do not may be critical, as it suggests that individual risk factors, and/or operational factors that differ between crew such as exercise performance or diet may play a role (Ong *et al.,* 2021).

Should an association between VT markers and SANS be established, it may even suggest that elements of current (or future) SANS monitoring are also incorporated into VT monitoring. 'Strict' -6° HDTBR could be utilised and include SANS-related outcome measures. Outcome measures of SANS previously incorporated into 'strict' -6° HDTBR studies (e.g., the 30-day Vision Impairment and Intracranial Pressure and Psychological Envihab Research (VaPER) study (Clément *et al*., 2022) and the SANS-CM study investigating LBNP applied for six hours per day (Clément *et al.,* 2024)), such as changes in ocular anatomy (e.g. optic disk oedema, total retina thickness) should be implemented in addition to those which are performed inflight. Ideally, the study duration would be 60 days. However, based on available data from 'strict' -6° HDTBR, 30-day campaigns may be sufficient, but this warrants careful consideration. Additionally, it is anticipated that large sample sizes of control (i.e., no countermeasure) participants would be necessary.

Moreover, this same model ('strict' -6° HDTBR without a countermeasure) will help us 'predict' the response of an individual to bed rest without any countermeasure to understand and define the individual variability to bed rest.

VT_PATHOPHYS_03

Evaluate the sensitivity and clinical utility of vector flow imaging (VFI), a novel imaging technique, in detecting modulation of venous flow, effects of venous anatomy, and identification of the presence and evolution of VT.

Current assessment of flow dynamics involves the direction and magnitude of the Doppler signal observed between the left and right jugular veins, as well as differences like crew members in the supine or seated position on Earth. However, given recent inflight and PFC data, this grading system may warrant further refinement. A comparison between the current grading system using conventional US with newer imaging techniques, such as VFI, may enable improved characterisation of the current known flows (suppressed, stagnant, and retrograde) and help us understand how different venous flow increases or decreases the risk of clot formation. Part of the rationale for this objective's high priority is the need for large amounts of data to characterise flow patterns observed with VFI against traditional Doppler velocity traces.

VT_PATHOPHYS_04

Determine whether cephalad fluid shifts modulate upper body lymphatic composition and flow, and whether this is associated with modulation of pro- and anti-thrombotic pathways or other biomarkers of Virchow's triad.

The lymphatic system regulates interstitial fluid balance, which also has an impact on blood viscosity and clotting. Therefore, changes in lymph composition can affect

coagulation factors (Zhang *et al.,* 2021). Additionally, since stasis or retrograde flow in the blood has been observed in 54.5% of the assessed astronauts approximately 50 days into a mission (Marshall-Goebel *et al.,* 2019; Auñón-Chancellor *et al.,* 2020), it could potentially slow lymphatic drainage and cause stasis in the lymphatic system. This could further contribute to clot formation by concentrating clotting factors in certain areas and potentially cause localised lymphatic thrombosis (Lippi *et al.,* 2012). Additionally, venous stasis appears to correlate with VT (Ashrani *et al.,* 2009), so this should be thoroughly investigated. Furthermore, the entry localisation of the thoracic duct into the venous system varies among individuals (Nomura *et al*., 2019), raising the question of whether there are anatomical causes for susceptibility to flow aberrations among astronauts. MRI visualisation of the entry location could increase and help identify a potential area for prevention or increased surveillance strategies in astronauts at risk (Sun *et al.,* 2023). Moreover, the lymphatic system also transports immune cells and inflammatory mediators. Since inflammation and coagulation have a bi-directional link (Levi *et al.,* 2004), this could theoretically contribute to an increased clotting risk.

VT_PATHOPHYS_05

Determine whether biomarkers of Virchow's triad and/or systemic inflammation are significantly modulated in µg, and is there an effect of exposure duration?

Assessing whether biomarkers related to thrombosis, inflammation, and/or vascular alterations are altered in- and immediately post-flight would help us create a database of standard measures and identify potential candidate biomarkers for ongoing adverse mechanisms in chronic *µg* exposure. It is important to track and monitor how these biomarker concentrations may change over time during analogue trials and inflight missions. Such biomarkers include:

- Coagulation biomarkers such as D-dimer (may be able to serve as a confirmation tool for US scans and monitoring after detecting stasis and risk factors) and standard coagulation tests (activated partial thromboplastin time (aPTT); prothrombin time (PT); fibrinogen; protein C; protein S; FII; FVII; FVIII).
- Systemic inflammatory molecules such as C-reactive protein (CRP).
- Thrombin generation markers and endothelial activation markers, including prothrombin fragments 1+2, plasma thrombin-antithrombin complexes (TAT), Tissue-Plasminogen Activator (tPA), and Tissue factor (TF).

VT_PATHOPHYS_06

Determine the use of endothelial/microvascular function tests and an analytical system(s) pre-flight that can identify individuals at an elevated risk of inflight VT.

Since endothelial function and coagulation are linked through Virchow's triad (Bagot and Arya, 2008), it is possible that markers of endothelial injury or activation may represent an underlying hypercoagulable state, or those who are at risk of adverse coagulable events.

VT_PATHOPHYS_07

Determine the effect of sex hormones upon pro- and anti-thrombotic pathways or other Virchow's triad markers.

Assessing the potential prothrombotic effects of sex hormones during space travel is essential for determining an individual's risk of clotting. Reproductive risks in women, such as increased oestrogen and testosterone, play a key role in regulating coagulation. However, men appear to have a higher baseline risk of thrombosis (Roach *et al.,* 2014). Hence, understanding these sex differences can help guide personalised prevention strategies and improve medical protocols for long-duration missions where immediate treatment options are limited.

VT_PATHOPHYS_08

Determine the effect of chronic mild dehydration upon pro- and anti-thrombotic pathways.

Since changes in hydration levels affect blood viscosity, it could also potentially influence clot formation. Although some studies have mentioned that chronic mild dehydration (a body water loss of around 1–2%) (Riebl and Davy, 2013) could promote decreased coagulation (Hoen et al., 2023), the exact correlation between dehydration and coagulation needs to be determined. For example, a study could monitor fluid intake, urine density, and haematocrit.

VT_PATHOPHYS_09

Determine platelet and concomitant (innate) immune cell interaction in µg/spaceflight and whether this is associated with modulation of pro- and anti-thrombotic pathways or other biomarkers of Virchow's triad.

Since platelets are essential in the clotting process, impaired platelet function or platelet hyperactivation may be indicative of a hypercoagulable state (Sang *et al*., 2021). Furthermore, platelet-leukocyte interaction plays a critical role for deep vein thrombosis (Stark & Massberg, 2021). Platelet function testing could be performed, as well as assessing markers of platelet hyperactivation and platelet-leukocyte interaction. Moreover, platelets and immune cell interactions play an essential role, and gravity and flow effects shall be addressed.

VT_PATHOPHYS_10

Determine the effect of chronic exposure to space radiation upon endothelial function, clot formation, and pro- and anti-coagulation pathways.

Radiation has been shown to induce adverse coagulopathies in animal models (Krigsfeld *et al.,* 2014), and space radiation may induce direct vascular injury during spaceflight (Malkani *et al.,* 2020). Therefore, the exact effect of space radiation on vascular injury, coagulation, inflammation, and immune dysregulation should be investigated further.

VT_PATHOPHYS_11

Determine the effect of increasing (body/core/brain) temperatures on pro- and anti-thrombotic pathways or other biomarkers of Virchow's triad and jugular flow.

Cephalad fluid shift and changes in heat convection in space increase the brain temperature (especially during exercise) and can lead to additive effects that are not yet fully understood. All enzymatic and cellular properties and performances are also a function of the temperature at the site of action. The sum phenotype of these temperature-dependent effects is yet to be investigated but the intermittent heat peaks during exercise may exceed protective properties along the principle of preconditioning to the tissue and may help preventing or mitigating the pathology (Stahn *et al.,* 2017).

Appendix 2: Diagnosis

VT_DIAGNOSIS_01

Evaluate the performance of commercial thrombosis PoC devices in µg and establish normative (and potentially threshold) values inflight.

Compression US is currently the clinical gold standard to diagnose VT. Anything that can complement this current diagnostic method (e.g., if US imaging alone is unclear, or a clot is in a location that cannot be visualised) should be prioritised. Hence, establishing the validity and utility of PoC devices would prove useful. However, whether these devices work in *µg* needs to be assessed and baseline values must be established. Examples of PoC devices measuring CRP and D-dimer include:

- Cobas H 232 PoC System (Roche, Germany)
- LumiraDx Platform High Sensitivity Microfluidic Device (Roche, Germany)
- Quidel Triage MeterPro 1 meter (Fisher Scientific, USA)

Other devices worth investigating:

- PowerBlade: This is an automated microfluidic platform developed by the National Research Council (NRC) in Canada. It works utilising centrifugal and pneumatic forces to process a minute volume of sample for analysis of immune capabilities and coagulation factors, for example. This tool seems to be suitable for functional properties rather than single biomarkers that are likely targeted by commercial-off-the-shelf (COTS) devices as mentioned above. Aggregometric testing of thrombocyte function.
- Roche Multiplate analyser.

Viscoelastic tests that are cartridge-based, user-friendly, and capable of assessing the entire clotting cascade:

- Thromboelastography (TEG)
- Thromboelastometry (TEM)
- Sonoclot

VT_DIAGNOSIS_02

Evaluate the sensitivity and clinical utility of novel imaging techniques in confirming clot presence and identifying newly forming clots.

In situations where US images are unclear, the implementation of novel imaging techniques may support the diagnosis of VT. In the future, these techniques could potentially help us estimate the age and evolution of a thrombus, and how it responds with treatment.

Techniques that could be tested:

- VFI: VFI has high-resolution imaging capabilities, providing multidimensional visualisation of blood flow in both axial and lateral directions (Goddi *et al*., 2017).
- Ultrafast US: Plane-wave technology (Villemain *et al.,* 2020) can provide blood flow visualisation with high temporal resolution (Tanter and Fink, 2014), but it additionally can visualise lymphatic vessels and flow (Vullings *et al*., 2023).
- MR DTI: Direct thrombosis imaging pre- and post-flight (Tan *et al.,* 2014; van Dam *et al.,* 2020). MR DTI allows to determine the age of thrombotic findings and to investigate thrombosis propagation.

However, it will take time to establish whether these devices can be utilised as a diagnostic or pathophysiology tool.

Appendix 3: Treatment/Management

VT_TMT_01

Determine the bioavailability of anticoagulation treatment in µg.

Medication is administered in spaceflight under the assumption that it acts identically as on Earth. However, physiological changes may occur during spaceflight to change pharmacokinetic (PK) and pharmacodynamic (PD) properties. Therefore, the risk of anticoagulant medication in space and optimal reversal strategies for anticoagulants during spaceflight must be determined, specifically the role of direct oral anticoagulants (DOACs) and their reversal agents.

Suggestions for anticoagulant medications such as apixaban:

- Measure the peak and trough levels of apixaban in crew members undertaking prophylactic or full treatment doses (ESA-HRE-HM-MOP-MAN-0001 guidelines) in *µg*. The sample represents the lowest levels of drug bioavailability and will help determine if the dosing regimen for both treatment and prophylaxis is appropriate. Additionally, peak levels likely relate to bleeding risk.
- Another aspect to consider is how long the drug remains in the system (and therefore, what is the bleeding risk after stopping treatment) when treatment stops before extravehicular activity (EVA) or undock and landing. Are the current guidelines sufficient to lower this risk of severe bleeds with mild trauma?

Other suggested methods to monitor PK may include:

- Absorption rates: In saliva or blood by conventional methods as well as by means of innovative devices such as the PowerBlade.
- Identification of patterns of volatile compounds reflecting drug metabolism by breath gas analysis.
- Identifications of soluble biomarkers as products of drug metabolism.
- EEG in the case of sleep-promoting drugs.
- New micro and nanotechnologies such as microneedle biosensors.

Suggested methods to monitor PD:

- Inclusion of physiological parameters such as blood pressure or electrocardiogram.

Traditional non-invasive metrics can also be collected using wearables including US, blood pressure monitors, and smartwatches.

VT_TMT_02

Determine the pharmacokinetic, pharmacodynamic, and any other characteristics that may affect bioavailability and/or efficacy of anticoagulation treatment in a relevant inflight model (e.g. animal).

Determining the PK and PD characteristics of anticoagulant medication would require a relevant inflight model (e.g. animal) to act as a chronic model and induce physiological adaptations. Such physiological adaptations might influence absorption, distribution, metabolism, and excretion of drugs, thereby affecting their PK and/or PD. Additionally, changes in fluid shifts may alter drug PK. Induced hypovolemic situations with concomitant deviations in plasma proteins and endothelial cell functions may have an impact on distributions of medicines and drug-receptor interactions and potentially affect clinical response to medication. Likewise, loss of muscle and bone mass is also suspected to impact the distribution of drugs.

Ideally, a pharmacovigilance system should be implemented to gain deep insights into PK/PD and exposome-induced alterations. In addition, the integration of biobanks and innovative technologies like artificial intelligence, including machine learning, may further enhance PK modelling leading to personalised treatments.

Appendix 4: Countermeasures/Prevention

VT_CM_01

Determine whether lower body negative pressure (LBNP) and/or venous thigh cuffs should be utilised as countermeasures for VT and determine the risks and/or benefits of the methodologies upon thrombotic pathways, biomarkers of Virchow's triad, and/or the location and evolution of VT.

Countermeasures such as LBNP have been shown to modulate SANS symptoms in 'strict' -6º HDTBR (Marshall-Goebel *et al*., 2021; Hönemann *et al*., 2024) and on the ISS (Arbeille *et al.,* 2021; Greenwald *et al*., 2021). This suggests LBNP may be a candidate operational countermeasure for SANS, in addition to promoting post-flight orthostatic tolerance. Similarly, venous thigh cuffs have the ability to alleviate symptoms associated with cephalad fluid shift early in space (Arbeille *et al.,* 1999; Fomina *et al.,* 2004), while their use in GBFs has shown to reduce hypovolemia but not prevent orthostatic intolerance (Custaud *et al.,* 2000; Millet *et al.,* 2000; Pavy-Le Traon *et al.,* 2001). Although appropriate durations and doses of these methodologies may be able to reduce SANS symptomology and potentially modulate VT risk factors (if there is an overlap in mechanisms of SANS and VT), induction of rapid fluid shifts may itself be provocative for VT and thus should be evaluated (Limper *et al.,* 2021).

VT_CM_02

Determine whether use of the ISS Treadmill 2 and harness should be considered a potential inflight VT risk factor.

LBNP could be adapted to replicate the loading of the shoulders, such as that induced by the T2 treadmill harness. US of the IJV during T2 sessions to assess the potential difference between terrestrial and space environments could be performed. This study should include the replacement of one surveillance session to include harness use. Additionally, this could be linked to the pre-flight MRI assessments of crew for factors that impede venous drainage of the head, such as the presence of cerebral venous anatomical asymmetry, or the effect of external compression on vascular flow. In this regard, such an investigation could share common outcome measures during parabolic flight, to acutely explore these effects on vascular flow in microgravity.

VT_CM_03

Determine the risks and/or benefits of repeated Valsalva manoeuvre (VM) performance during resistance training upon thrombotic pathways, biomarkers of Virchow's triad, and/or the location and evolution of VT.

VM during resistance exercise has been shown to increase the stability of the spine owing to augmented intra-abdominal pressure (Nachemson, Andersson, & Schultz, 1986; Cresswell, Blake, & Thorstensson, 1994). However, VM has also been associated with an increased systolic blood pressure, meaning it is unsuitable for individuals with a history of heart and cardiovascular disease (Williams *et al.,* 2007). Hence, evaluating VM during resistance training is necessary.

VT_CM_04

Determine the risks and/or benefits of current and planned exercise (particularly if associated with repetitive application of pressure on upper body veins) upon thrombotic pathways, biomarkers of Virchow's triad, and/or the location and evolution of VT.

Certain exercises may promote vascular health and increase the risk of thrombosis at the same time. Activities that involve prolonged or repeated compression of veins (e.g., treadmill with T2 harness) could lead to endothelial stress, inflammation, or even clot formation, particularly in environments like space where fluid shifts and altered haemodynamics influence blood flow. Understanding these effects will help in designing safe exercise protocols and new harness equipment in upcoming missions.

VT_CM_05

Determine whether simple mission-compatible neck flow countermeasures modulate thrombotic pathways, biomarkers of Virchow's triad, and/or the location and evolution of VT.

Since space missions have limited budgets and cargo capacity, if such low-cost, low-mass interventions are effective in preventing VT in space, they could reduce the need for expensive and time-consuming countermeasures and risk-carrying pharmaceutical treatments.

VT_CM_06

Determine whether artificial gravity (e.g. centrifugation) could mitigate VT risk via modulation of thrombotic pathways, biomarkers of Virchow's triad, and/or the location and evolution of VT.

Understanding the potential benefits of artificial gravity, such as centrifugation, could inform future spacecraft design or medical countermeasures for long-duration missions. However, in practical terms, installing a centrifuge inflight is not currently feasible. Therefore, while studying its effects may provide valuable insights into thrombosis prevention, it is of lower priority compared to developing more immediately applicable countermeasures for spaceflight.