ACTIVATE

Full Title

ACTIVATE**: A** randomised **C**ontrolled evaluation of **T**humos: a cognitive-behavioural **I**nter**V**ention for medic**A**l s**T**ud**E**nts

Short title

ACTIVATE: A randomised controlled trial of a cognitive behavioural intervention (THUMOS)

RESEARCH PROTOCOL
(Version 2.3) 15th January 2026

REC Reference: 2024-21589-38791
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Authorised by: Dr Judith Johnson

Protocol amendments

Document ID	Description of changes from previous version	Effective Date
Protocol V 1.0	First Protocol submitted for review by university UREC committee	20.12.2024 UREC favourable ethical opinion received. UREC Ref: 2024-21589-38791
Protocol V 2.0	1) Update the flow chart to include ReQoL and sickness absence 2) Add in these two measures as measures for T1/2/3/4 questionnaires 3) Inclusion of new edited process evaluation questionnaires 4) Question about service use is added. 5) Added detail about following people up for the adverse events item in T2.	20.03.2025 Amendment approved by university ethics committee UREC Amendment Ref: 2025-21589-40219
Protocol V 2.1	Minor amendment submitted: 1) Updated AE questionnaire Item to include more detail about potential examples of adverse events	13.05.2025 Amendment approved by university ethics committee UREC Amendment Ref: 2025-21589-41297
Protocol V 2.2	Minor amendment submitted: 1) Updated recruitment text and materials to include more details about exclusion/inclusion criteria (e.g. example year of study) and additional details about the intervention arm of the study (e.g. number of workshops).	21.10.2025 Amendment approved by university ethics committee UREC Amendment Ref: 2025-21589-44079
Protocol V 2.3	Minor amendments submitted: 1) Increase recruitment by the number of participants who withdraw following randomisation but by no more than 10% overall. 2) A tightening of the screening process through contacting participants who have not provided a university email address during completion of consent	11.12.2025 Amendment approved by university ethics committee UREC Amendment Ref: 2025-21589-44883

	and baseline measures, by contacting them and requesting a university email address at T2 and T3. The addition of a screening question as part of the baseline measure to collect university emails for newly consenting participants in T1.

ACTIVATE: A randomised **C**ontrolled evaluation of **T**humos: a cognitive-behavioural **I**nter**V**ention for medic**A**l s**T**ud**E**nts

Acronym: **ACTIVATE**

This document describes a randomised controlled trial,and provides information about procedures for entering participants. Amendments may be necessary; these will be circulated to all interested parties.

Abstract

Background
Medical students experience high rates of burnout and mental health distress, with approximately half reporting burnout, one-third experiencing depression, and one-tenth having suicidal thoughts. These issues are exacerbated during clinical placements and contribute to workforce attrition after qualification. Existing interventions are largely generic and show limited effectiveness. Thumos, a cognitive-behavioural therapy-based intervention specifically tailored for healthcare professionals and medical students, addresses the stressful situations intrinsic to medical training and practice. This randomised controlled trial will evaluate whether Thumos improves psychological resilience, confidence in dealing with stressful situations, burnout, and depression in medical students compared with services as usual (SAU).

Methods/design:
Two hundred and twenty UK medical students in a year that contains a clinical placement of a week or longer will be recruited nationally from UK medical schools. Participants will be randomised 1:1 to receive either Thumos (two online group workshops and one individual video/phone call) or SAU. Assessments will occur at baseline, post-intervention, 4-month, and 9-month follow-up. The primary outcome is psychological resilience measured by the Brief Resilience Scale at 4-month follow-up. A mixed-methods process evaluation will assess acceptability and feasibility.

Discussion:
To our knowledge, this is the first randomised controlled trial of an intervention specifically designed to prepare medical students for stressful clinical events. If effective, Thumos could potentially be adapted for medical students in other countries.

Contents

Abbreviations

Definition of terms

AE	Adverse Event
CBT	Cognitive-Behavioural Therapy
CI	Chief Investigator
CRF	Case Report Form
DMEC	Data Monitoring and Ethics Committee
GCP	Good Clinical Practice
ISRCTN	International Standard Randomised Controlled Trials Number
MPS	Medical Protection Society
MRC	Medical Research Council
PCF	Participant Consent Form
PIS	Participant Information Sheet
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAU	Services As Usual
SOP	Standard Operating Procedure
TMG	Trial Management Group
TSC	Trial Steering Committee

1. General information

1.1 Investigator details

Chief Investigator:
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1.2 Sponsor Details

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1.3 Role of the Funder

The Medical Protection Society (MPS) Foundation

The funder has reviewed the research protocol but will have no role in data collection, analysis, data interpretation, report writing or in the decision to submit the report for publication.

1.4 Protocol amendments

NONE

Trial Summary

Study title	ACTIVATE: A randomised Controlled evaluation of Thumos: a cognitive-behavioural InterVention for medicAl sTudEnts
Sponsor	The University of Manchester
Funder	The MPS Foundation
ISRCTN	ISRCTN12744098 https://doi.org/10.1186/ISRCTN12744098
Project start date	01/12/2024
Project end date	31/03/2027
Aims and objectives	To establish whether medical students receiving Thumos, a cognitive behavioural intervention, will have improved psychological resilience at 4 month follow up in comparison to medical students receiving services as usual (SAU). Secondary objectives are: 1. To determine whether Thumos is superior to SAU at 9-month follow-up in increasing psychological resilience. 2. To determine whether Thumos is superior to SAU at 4-month and 9-month follow-ups in the endpoints of confidence, burnout, depression, mental health and self-reported sickness absence.
Trial design	Randomised controlled parallel groups intervention trial
Setting	Online
Participants	UK medical students in years involving clinical placements of a week or longer nationally. We will recruit from these groups for the main trial until the recruitment target is reached.
Intervention & control groups	UK medical students in clinical placement years will be randomised 1:1 to receive either (Intervention group) Thumos (a CBT intervention of two online group workshops and one individual video/phone call) or (Control group) Services As Usual (SAU).
Primary outcome(s)	To determine whether Thumos is superior to SAU at a 4-month follow-up in increasing psychological resilience.

Secondary outcome(s)	To determine whether Thumos is superior to SAU at a 9-month follow-up in increasing psychological resilience. To determine whether Thumos is superior to SAU at 4-month and 9-month follow-ups in the endpoints of confidence, burnout, depression, mental health and self-reported sickness absence.
Duration of recruitment period and first enrolment date	Recruitment period to run from 1/06/2025 to 31/03/2026. Date of first enrollment is 16/06/2025.
Duration of follow-up	Nine months from enrollment.
Target sample size	220
Definition of end of trial	The end of trial is defined as the collection of data from the last recruited participants' follow-up questionnaire (9-month follow up).

2. Introduction

2.1 Background

Healthcare systems internationally are experiencing a workforce crisis, with a current global shortage of six million physicians [1]. While poor workforce planning has contributed to this problem, high turnover has been identified as the main contributing factor [2]. Inadequate staffing is linked with negative patient outcomes including extended hospital stays and mortality [3]. It also creates a vicious cycle, whereby existing staff become overworked and burnt-out, a syndrome characterised by exhaustion and disengagement [4]. Higher burnout then increases the risk of sickness absence and turnover, further exacerbating staffing shortages [5, 6] and directly leading to the delivery of poorer patient care [7].

In a review of 170 studies in doctors, higher burnout was associated with twice the risk of patient safety incidents and a two-fold reduction in patient satisfaction [7]. Within this vicious cycle, provider burnout and poor wellbeing must be recognised as an active component, serving to drive the workforce crisis. Equally, addressing this component by better supporting healthcare professionals could help to break this cycle, leading to reduced sickness absence, better retention and better patient care [8].

Most burnout research has focused on qualified professional groups, but there is a growing recognition that it could be beneficial to intervene during training, prior to professional registration, due to high rates of mental health distress in these cohorts [9]. Studies in medical students indicate half report burnout, one in three report depression and one in ten experience suicidal thoughts [10-12]. Furthermore, the immediate post-qualification years have been recognised as a high-risk time for physicians leaving the profession [13]. Poor mental health and burnout are linked with higher attrition [14], so improving their mental wellbeing could be one way to enhance retention and reduce physician shortages.

Multiple risk factors unique to medical training have been implicated in these mental health difficulties, notably demanding academic requirements and perfectionism-related cognitive patterns [15, 16] and exposure to stressful clinical events on placement [17]. Indeed, rates of burnout in medical students increase significantly during the years involving clinical placements [18]. However, there has been a lack of interventions tailored for medical students and none which prepare medical students for stressful workplace events [19]. Previous evaluations of mental health support for medical students have predominantly examined non-tailored approaches such as mindfulness-based programmes, relaxation techniques, and yoga. [19]. Evidence for

these interventions is weak and mixed, and they have been criticised for lacking relevance [20]. A recent meta analysis of resilience interventions for medical students indicated that these interventions are moderately effective at reducing stress and mildly affective at increasing resilience within medical students [21]. The implication that these interventions may have more favourable impacts on stress suggests that further research is required to examine the specific factors that influence resilience. There is an urgent need for effective, preventative interventions which help students cope with the specific occupational stressors they will encounter during their placements, training, and beyond.

The current trial will evaluate Thumos, an intervention that employs cognitive-behavioural therapy (CBT) techniques to prepare healthcare professionals and students to manage stressful work or training events. This approach has been investigated, tested and developed in several studies previously [9, 22-24]. The approach used in Thumos differs from many previously evaluated psychological interventions for medical students in three ways. Firstly, it has been designed with healthcare professionals in mind, based upon a combination of 1) research into the effects of patient safety incidents and other work stressors, 2) resilience theory, and 3) CBT techniques. Secondly, Thumos integrates complementary therapeutic formats: group sessions that facilitate peer connection, alongside an individual consultation that provides personalised support. Thirdly, Thumos addresses the stressful situations that are intrinsic to healthcare work, providing support for those unavoidable events that cannot be improved through organisational interventions.

Characteristics of Thumos may make it particularly well suited for medical students. For example, the preventive framing of the intervention may help address barriers related to help-seeking stigma, which research has identified as a significant obstacle to engagement with mental health support among medical students [11, 25, 26]. It also uses case studies and materials which are tailored towards the stressful experiences medical students may face on placements. This approach increases the sense of relevance of the intervention for participants which may increase engagement [9]. Furthermore, it directly addresses unhelpful perfectionist thinking styles that have been associated with psychological distress in this population [16].

There have been three uncontrolled evaluations of of versions of Reboot, a CBT-based intervention for medical professionals which indicate positive findings. The first was in a group of 66 multi-disciplinary healthcare professionals and students; results indicated it was associated with improvements in participants' confidence, coping

knowledge and psychological resilience [22, 27]. The second was in 80 Critical Care Nurses (CCNs) [23, 28]. Participation was associated with increased confidence and resilience and reduced depression and burnout. Nurses also reported a lower intention to leave clinical practice following the intervention [23]. The third evaluation was in 115 medical students [9]. Findings indicated the intervention was feasible and potentially effective in this group, with participants reporting significant increases in resilience and confidence in coping with adverse events, and significant decreases in burnout and depression [9]. Qualitative findings from these evaluations indicate that participants appreciate the intervention's tailored format and opportunity for peer support alongside professional input. They describe increased self-awareness and reported the acquisition of psychological skills which they could apply to cope with work stressors [22, 23, 27].

2.2 Rationale for current study

Feedback from these evaluations was used to make improvements to, and to further tailor, the intervention towards medical students, including new exercises, reduction of didactic information and changing the phone call discussion. There is now a need to test the intervention, Thumos, and to ascertain whether observed improvements in outcome indicators can be attributed to the intervention. This study addresses this gap, through a definitive randomised controlled trial (RCT). The comparator intervention is Services as Usual (SAU); this comparison will establish whether and what benefits Thumos may offer above what is currently available. The final follow-up time point is 9 months and create the possibility of conducting a subsequent 5-year follow-up study, should initial results be positive.

3. Aims and objectives

The main purpose of the trial is to establish whether Thumos increases resilience and improves mental health in medical students. The primary objective is to determine whether Thumos is superior to the control condition (services as usual; SAU) at 4 month follow-up in increasing psychological resilience in medical students. Secondary objectives are:

1. To determine whether Thumos is superior to SAU at 9-month follow-up in increasing psychological resilience.
2. To determine whether Thumos is superior to SAU at 4-month and 9-month follow-ups in the endpoints of confidence, burnout, depression, mental health and self-reported sickness absence.

3. To assess acceptability and how Thumos is delivered in practice through a process evaluation with users, medical educators and providers

4. Trial Design

This study is a randomised controlled parallel groups intervention trial, conducted across multiple medical schools in the United Kingdom (UK). All UK medical schools will be invited to participate (see Appendix 1.0). Participants will be self-selecting and screened for eligibility based on the criteria that they are a) UK medical student and b) in a year of study that contains a placement of one week or longer. The trial will compare Thumos to a control condition of services as usual (SAU), where medical students in either condition can continue to access available mental health support as they usually would. Data collection will occur at four timepoints, Time 1 (T1), pre-intervention (baseline); Time 2 (T2), post-intervention (following completion of Thumos/6 weeks after baseline for control group); Time 3 (T3), 4 months following baseline and Time 4 (T4), 9 month following baseline. All elements will be conducted online, with questionnaires administered via Qualtrics and interviews/intervention sessions via online video platform. Informed consent will also be taken online, with participants asked to read the information sheet and provide informed consent prior to responding to any data collection items (see Appendix 2.0). A process evaluation will be conducted which will include medical student participants, medical educators from medical schools of participating students and the Thumos therapists.

We will request permission to contact participants for further follow-up data at 2 and 5-years. If T4 indicates Thumos is effective, we can seek funding and a new ethics approval to conduct a subsequent study of long-term outcomes.

4.1 Blinding

Randomisation to the two groups will be undertaken following completion of baseline assessments using the web-based Sealed Envelope software. Randomisation will be in the ratio 1:1 to the two groups. The randomisation system will ensure blinding of the statistician. The CBT therapists, researchers and participants will be unblind.

4.2 Unblinding

There is no procedure for unblinding participants and CBT therapists as they are already unblinded. However, in the event that a Data Monitoring and Ethics committee (DMEC) is required for the study, the DMEC will be established and will be able to request unblinded data and recommend study termination to the Trial Steering Committee (TSC) on the grounds of safety or futility should any SAEs occur that are deemed related to the trial.

5. Selection of participants

The selection of participants for the randomised controlled trial and the process evaluation is described below in Figure 1.

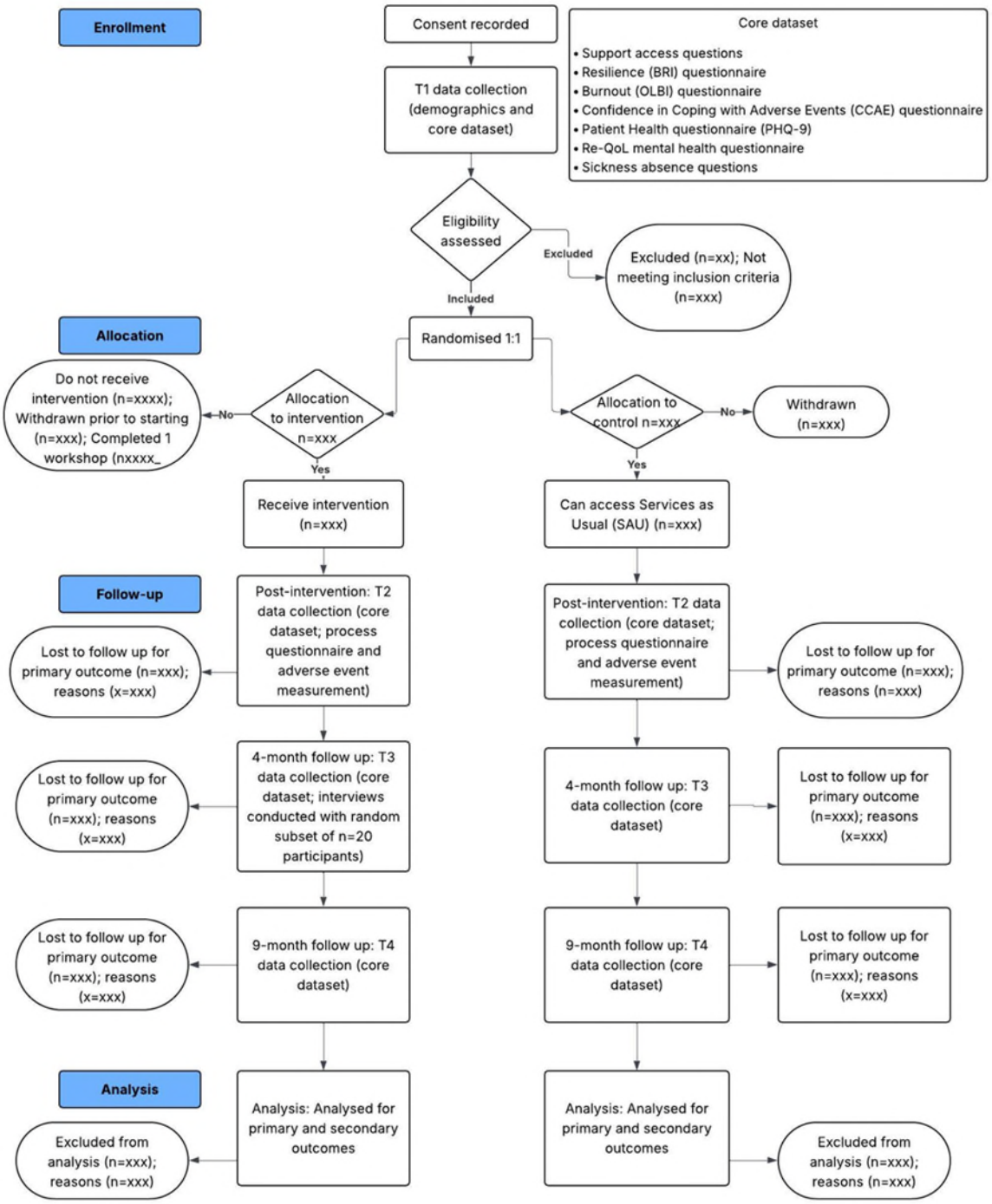

Fig 1: Flow diagram of participants through the trial

Study population for randomised controlled trial

5.1 Inclusion criteria

UK medical students in years involving clinical placements of a week or longer nationally. We will recruit from these groups to the main trial until recruitment numbers are saturated.

5.2 Exclusion criteria

We will not exclude anyone who meets the inclusion criteria. However, we will stop recruiting once we have reached our maximum number of participants to recruit (n=220) and exclude all prospective participants at this time.

Study population for process evaluation

5.3 Inclusion criteria

Participating medical students: We will recruit medical students in the main trial to also take part in the process evaluation. Both control and intervention arm students will be invited to complete process questionnaires; only intervention arm medical students will be invited to take part in qualitative interviews.

UK medical educators: We will recruit medical educators in schools with participating students within the intervention arm to qualitative interviews as part of the process evaluation.

The cognitive behavioural therapists/clinical psychologists delivering the intervention will be invited to qualitative interviews as part of the process evaluation.

5.4 Exclusion criteria

We will not exclude anyone who meets the inclusion criteria. However, for qualitative interviews, we will stop recruiting once we have reached data saturation, defined as ‘information redundancy’ where no new information or value is generated from the data.

5.5 Participant identification

Medical student participants will be recruited via the Medical Protection Society (emails to medical student members), the Medical Schools Council (email cascade to

UK medical schools), direct email communications to heads of UK medical school and via posts on social media (LinkedIn, BlueSky, Twitter, Instagram).

For the process evaluation, medical educators in schools with participating students who were allocated to the intervention arm will be contacted via emails sent to heads of medical schools with participating students. Trial therapists will be contacted directly via email.

5.6 Informed consent process

Informed consent will be taken online via Qualtrics, with participants asked to read the information sheet and provide informed consent prior to responding to any data collection items.

6. Trial treatment

6.1 Participants randomised to THUMOS

Thumos is delivered over a 4-week period and consists of three core components: two online group workshops and one individual coaching call. The group workshops are conducted with around 6-8 participants and last two hours each. During these workshops, participants engage in both individual exercises and group-based activities. These are followed by a one-hour individual phone call, which allows for personalisation of the workshop content to each participant's specific needs. All sessions are delivered remotely via video platform or phone. The intervention is delivered by qualified Clinical Psychologists or Cognitive Behavioural Therapists who have received specific training in the Thumos intervention protocol manual.

Intervention condition participants can continue to access mental health services that are usually available via medical schools, universities or to the public throughout the period that they are participating in the study.

6.2 Participants randomised to Control Group

Control condition participants will not receive an alternative intervention. However, they can continue to access mental health services that are usually available via medical schools, universities or to the public throughout the period that they are participating. Services available to medical students will vary depending upon what their university and medical school provides as standard, but all will be able to access NHS primary care services.

7. Randomisation and enrollment

Participants will be randomised using simple 1:1 allocation via the Sealed Envelope platform, which generates the allocation sequence and maintains allocation concealment to ensure investigators remain blinded to treatment assignment. With 220 participants undergoing individual-level randomisation, simple randomisation is expected to achieve adequate balance between treatment arms without the need for blocking or stratification. Any post-randomisation covariate imbalances will be addressed through standard statistical adjustment methods during analysis. As all quantitative outcomes are self-reported rather than researcher-rated, researcher blinding is not a relevant consideration.

8. Outcomes

Outcome Measures

A core online questionnaire set including measures of resilience (Brief Resilience Scale [29]), burnout (Oldenburg Burnout Inventory; OLBI [4]) confidence in coping with adverse events (CCAE [9]) depression (Patient Health Questionnaire, PHQ-9 [30]), mental health (Recovery of Quality of Life-Utility Index, ReQoL-UI)[31]) sickness absence and support access will be completed at T1, T2, T3 and T4. In addition, at T2 a process questionnaire will be added to this dataset.

Table 1:

Table 1. Outcome measures

Outcome	Time	Variable definition	Measure
BRS (primary)	T3/T4	BRS mean score	Adjusted mean difference/Cohen's *d*
CCAE	T3/T4	CCAE mean score	As above
OLBI	T3/T4	OLBI total and subscales	As above
PHQ-9	T3/T4	PHQ-9 total score	As above
ReQoL-UI	T3/T4	Utility score	As above
ReQoL-UI QALYs	BL-T4	QALYs area under the curve	Adjusted mean difference
Sickness absence	T3/T4	Days lost in past 4 weeks	Adjusted rate ratios with 95% CI

BRS: Brief Resilience Scale; CCAE: Confidence in Coping with Adverse Events; OLBI: Oldenburg Burnout Inventory; PHQ-9: Patient Health Questionnaire-9 item depression scale; ReQoL-UI: Recovering Quality of Life – Utility Index; QALYs: Quality-adjusted life years; BL: Baseline; T1, T2, T3, T4: Time points 1, 2, 3, and 4 (T = time)

Table 2:

Table 2. Outcome scoring					
Outcome	**Items**	**Measure**	**Construct(s) & direction**	**Time points**	**Derived variable/scoring**
BRS (Primary)	6	Brief Resilience Scale	Resilience; higher = better	T3 [12–24 wks]	Mean of 6 items (with required reverse scoring)
BRS	6	Brief Resilience Scale	Resilience; higher = better	T4 [30–44 wks]	Mean score
CCAE	3	Confidence in Coping with Adverse Events questionnaire	Confidence coping with adverse events; higher = better	T3, T4 [12–24, 30–44]	Mean of 3 items
OLBI (total & subscales)	16	Oldenburg Burnout Inventory	Burnout (exhaustion, disengagement); higher = worse	T3, T4 [12–24, 30–44]	Subscale means and total mean (with required reverse scoring)
PHQ-9	9	Patient Health Questionnaire-9	Depressive symptoms; higher = worse	T3, T4 [12–24, 30–44]	Sum of 9 items (0–27)
ReQoL-UI (utility)	10	Recovery of Quality of Life – Utility Index (ReQoL-UI)	Quality of life utility; higher = better	T3, T4 [12–24, 30–44]	Utility index via ReQoL-UI algorithm
ReQoL-UI QALYs	10	Recovery of Quality of Life – Utility Index (ReQoL-UI)	Quality adjusted life years; higher = better	Baseline–T4	Area under utility time curve
Sickness absence	2	Sickness absence items	Days lost last 4 weeks; higher = worse	T3, T4 [12–24, 30–44]	Count of days lost in past 4 weeks

8.1 Primary outcome

To determine whether Thumos is superior to SAU at a 4-month follow-up in increasing psychological resilience.

Brief Resilience Scale (BRS): The 6-item BRS measures perceptions of personal resilience, including ‘I tend to bounce back quickly after hard times’. This questionnaire has good internal reliability (α=.80-.91), concurrent validity with other resilience questionnaires [28], and detects learning changes [9].

8.2 Secondary outcomes

To determine whether Thumos is superior to SAU at 4-month and 9-month follow-ups in the endpoints of confidence, burnout, depression, mental health and self-reported sickness absence.

Oldenburg Burnout Inventory (OLBI). The scale comprises 16 items and two subscales (exhaustion and disengagement). It has been used widely and found to have good internal reliability (α=.88) [4].

Confidence in coping with Adverse Events (CCAE) questionnaire: This 3-item questionnaire assesses how confident participants are in coping with adverse events, e.g., 'If I was involved in an adverse event for which I thought I held some responsibility I know the things I would do to help manage my stress levels'. Previous studies suggest this scale has good internal reliability (α=0.85) [24] and detects learning changes [9].

Patient-Health Questionnaire-9 (PHQ-9). This 9-item questionnaire is widely used to measure depression and has been validated in various groups, including medical students [32]. It has good internal consistency (α=.83) and captures fluctuations [33].

Recovery of Quality of Life-Utility Index (ReQoL-UI) [31]. Mental health will be measured with the 10-item ReQoL-UI. This validated, reliable questionnaire measures mental health across areas of quality of life. It applies to the full spectrum of mental health conditions and provides Quality of Life Adjusted Years (QALY) estimates.

Self-reported sickness absence. Two items will be used to measure sickness absence, the first which asks about total days lost within the past 4 weeks; the second of which asks how many working or studying days specifically were lost within this timeframe.

Support access. Four items will be used to assess whether participants are accessing any form of psychological wellbeing service, which type of support they are accessing, when they began accessing this, and when they anticipate, they will stop accessing this.

We are adjusting for age, medical school and gender.

8.3 Process evaluation outcomes

To assess acceptability and how Thumos is delivered in practice through a process evaluation with users, medical educators and providers.

We drew upon UK Medical Research Council (MRC) guidance for process evaluations of complex interventions [34] to design a mixed-methods approach to the process evaluation.

Psychological therapist logs: Weekly logs will assess therapists' experiences of intervention delivery, including perceived benefits, mechanisms and challenges.

Process questionnaires: Process questionnaires at T2 (post-intervention) will explore participants' reasons for participating, and their perceptions and experiences [35]. Participants in the intervention arm will be asked about their affective attitudes to the intervention, general acceptability, perceived effectiveness, ethicality, intervention coherence and mechanisms, self-efficacy, burdens, opportunity costs, and barriers and facilitators. Participants in the control arm will be asked about their reasons for participating, and their perceptions and experiences of the study.

Field notes: Researchers' field notes will track any changes in the delivery of the intervention; enabling recording of protocol changes.

Participant interviews: At T3, a randomly selected subset of participants from the intervention arm will be invited to 30-minute semi-structured interviews (n=20) to generate information regarding intervention delivery, feasibility and acceptance, and barriers and facilitators to participation.

Medical educator interviews: Once all experimental participants have completed T2 data collection, medical educators (n=15) at schools where students have participated in the study will be interviewed to explore 1) their perceptions of the research process, and 2) perceived benefits or drawbacks of Thumos at an organisational level, 3) ways Thumos could be implemented at scale for medical students.

Therapist interviews: Once all experimental participants have completed T2 data collection, all trial therapists will be invited to 30-minute semi-structured interviews exploring their experiences of delivering the intervention.

9. Assessments and procedures

Primary and secondary outcomes will be collected via online questionnaires using Qualtrics software. Participants will be contacted at four timepoints (including base-line) via email with a link to complete the questionnaire.

9.1 Study assessments schedule

Table of measures used in questionnaire assessments.

Table 3:

	Baseline	T2 (post intervention or equivalent time)	T3 (4 month follow up)	T4 (9 month follow up)
Enrolment				
Informed consent form	X	-	-	-
Primary out-come				
Brief Resilience Scale (BRS)	X	X	X	X
Secondary out-comes				
Oldenburg Burn-out Inventory (OLBI	X	X	X	X
Confidence in coping with Ad-verse Events (CCAE) question-naire	X	X	X	X
Patient-Health Questionnaire-9 (PHQ-9)	X	X	X	X
Recovery of Qual-ity of Life-Utility Index (ReQoL-UI)	X	X	X	X
Self-reported sick-ness absence	X	X	X	X
Support access	X	X	X	X

Process evaluation				
Process questionnaires	-	X	-	-

9.2 Procedures for treatment fidelity

Researchers will observe a minimum of 20% of workshop cycles and observe recordings of 10% of video/phone calls, using documented fidelity assessment criteria. These will consider how the intervention is conducted and assess fidelity. All medical student participants and Clinical Psychologists/CBT therapists delivering the intervention will be asked to provide their consent for this at baseline.

9.3 Procedure for assessing safety

The researchers will take all appropriate steps during the conduct of the trial for ensuring participant safety, in both arms of the trial. Concerns over safety of THUMOS or involvement in ACTIVATE identified through Adverse Events (AEs) and Serious Adverse Events (SAEs), as described in the follow-up questionnaires would, in the first instance, lead to protocol amendments, but could lead to study termination at any time, please refer to section 13.3 for our stopping guidelines. Our experience with this population and type of intervention suggests that THUMOS (intervention) proving unacceptable or too distressing to participants is a low risk. However, should this outcome occur, it would provide empirical evidence to inform future research.

9.4 Participant withdrawals

If a participant is found to be ineligible for the trial after consenting and providing baseline (T1) questionnaire responses, this will be communicated to them by email (including the reasons for their ineligibility) and the reason recorded.

Participants may withdraw their consent for the study at any time, without providing a reason for this. If a participant in either study arm tells us that they would like to withdraw following consent or randomisation, we will ask for their reasons why and record this. Although the participant is not required to give a reason for discontinuing their study participation, a reasonable effort will be made to establish this reason while fully respecting the participants' rights.

If a participant in the intervention arm tells us that they would like to withdraw once they have completed Workshop 2, we will seek clarity on whether they would like to withdraw from both the intervention and the questionnaires, or whether they would like to withdraw from the intervention but continue to complete follow-up questionnaires. We will let them know that as Workshop 1 and Workshop 2 constitute minimum criteria for engagement, they can continue to respond to questionnaire follow-ups if they choose.

Should a participant withdraw from the study, unless they request that it is withdrawn, we will still use any previous data collected from that participant up to the point of withdrawal for the purposes of analysis. However, we will make no further attempt to contact them or collect data from them.

9.5 Lost to contact

Participants in the intervention arm may be considered lost to contact if they do not respond to requests to complete the intervention (e.g. they have completed one workshop). To enhance adherence to the intervention, participants in the intervention arm will be contacted by email, text message and phone call if they do not book onto or attend the workshops or individual phone call. Minimum adherence to the intervention will be defined as completion of both workshops. All randomised participants will be invited to complete the T2, T3 and T4 questionnaires irrespective of their level of adherence, unless they withdraw consent for further contact. The minimum adherence definition will be used for descriptive summaries of engagement and for prespecified per protocol and complier average causal effect (CACE) analyses, but not to determine who is followed up. If during follow up an intervention participant cannot be reached after successive attempted contacts to complete the questionnaire they will be considered lost to contact. Control arm participants will be defined as lost to contact in the follow up stage if after successive contact attempts they do not respond or complete the requested follow up questionnaire. If a participant is lost to contact, this will be recorded in the trial master file. Please refer to the statistical analysis plan for a comprehensive discussion of analytical implication of lost to contact participants.

10. Safety Reporting

10.1 Definitions

Term	Definition

Adverse Event (AE)	Any untoward medical occurrence in a study participant.
Unexpected AE/SAE	An adverse event or serious adverse event which has not been pre-specificed as expected.
Serious Adverse Event (SAE)	An AE which is serious, defined as any untoward medical occurrence or effect that : • Leads to death • Poses a threat to life* • Necessitates hospital admission or prolongation of existing hospitalisation and emergency care** • Cause lasting or significant impairment/disability or incapacity***
Related AE/SAE	An AE or SAE which is related to a research procedure
Notable Event	An event of particular interest that does not necessarily meet the criteria for seriousness but requires expedited reporting as per the protocol.

*The term life-threatening in the definition of a serious event refers to an event in which the participant is at risk of death at the time of the event; it does not refer to an event that hypothetically might cause death if it were more severe.

**Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, that has not worsened or for an elective procedure do not constitute an SAE.

***Other important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event/experience when, based upon appropriate medical judgement, they may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

In this study, an adverse event (AE) will be considered any untoward medical occurrence occurring in an ACTIVATE participant whether or not related to the research procedures or intervention. An adverse reaction (AR) will be defined as an untoward and unintended response in a participant that is potentially connected to any aspect of ACTIVATE. All study participants that have completed baseline measures will be followed up for adverse events unless they explicitly state they wish to withdraw from

the study and receive no further contact. Adverse events will be recorded and reviewed by the CI and summary reports provided to the TSC for review of any possible patterns.

Foreseeable adverse events: as a significant proportion of medical students experience mental health problems such as depression, certain expected lower-level AEs will be reported to the TSC only at planned meetings, such as experiences of low mood, anxiety, or lower risk self-harming behaviours (e.g., superficial scratching) that do not need professional medical care. However, SAEs that could potentially occur—though less frequently—include mental health problems requiring hospitalisation or severe self-harm incidents (requiring medical treatment) and suicide. All adverse events will be recorded and shared with the CI. Potentially serious and unexpected adverse events will be reviewed by the CI who makes an assessment as to whether the event is defined as serious in consultation with definitions in the protocol. Advice and consultancy will be sought from the Chair of the TSC.

AEs will be monitored and recorded at T2 via the inclusion of a survey question, "Have you had any serious negative life experiences since you started the study? These might be social (e.g., problems with friends, family, peers, etc), personal (e.g., problems with a partner, housing, finances etc), psychological (e.g., occurrence or increase in symptoms of depression or anxiety, etc), medical (e.g., health-related ailments, self-harm or injury etc) or relate to other issues. If so, please describe what this was or these were. (Yes [please describe/open text box]; No)." We will also monitor them via items on the process questionnaires relating to moral and ethical concerns about the study, affective attitude towards the study (like/dislike) and experience of the study (degree of comfort experienced). Where participants report significant moral or ethical concerns, strongly disliking the study or feeling very uncomfortable, they will be contacted for more information. All participants who 1) agree with the AE statement and provide information which indicates or may indicate an AE in line with our definition, or 2) provide these responses on the process questionnaire will be contacted for further information and to determine whether the incident can be classed as an AE, AR, SAE or SAR.

If participants indicate during any other part of the study (e.g., during the workshops, the one-to-one call, interviews, or by contacting the study team) that an AE or SAE has occurred, they will similarly be contacted by the study team and asked to provide

more information. The information sheet provided to participants includes contact details for individuals they should reach out to if they believe they have experienced any harm from participating in the study or if they want to file a formal complaint regarding how the study was conducted.

An SAE occurring to a research participant will be reported to the Chair of the Ethics Committee where in the opinion of the Chair of TSC that the event was: i) related, that is resulted from the administration of any of the research procedures and ii) unexpected – that is, the type of event is not listed in the protocol as an expected occurrence. The CI and the trial management team will review all SAEs, whether or not they are judged to be attributable to the trial or interventions. Based on this information, and in consultation with the Chair of the TSC, they will determine whether the participant should be withdrawn, and/or the trial should be suspended, stopped or continued. All AEs, ARs, SAEs and SARs will be fully documented and included in both the final trial report and published journal article.

11. Statistics

A detailed statistical analysis plan (SAP) approved by the independent Statistician can be seen in appendix 3.0. All analysis will be conducted in R (R Foundation for Statistical Computing, Vienna, Austria).

11.1 Sample size

In the study of Reboot in medical students [9], the within-group standardised mean change in Brief Resilience Scale (BRS) scores from baseline to 4-month follow up was large (Cohen's d ≈ 0.90). Mean BRS increased from the "low" resilience band (1–2.99; T1 mean 2.74, SD 0.73) into the "normal" range (3–4.3; T4 mean 3.16, SD 0.72) on the 1–5 scale.

For the present trial, we powered the primary between-group comparison more conservatively for a standardised mean difference at 4-month follow up (T3) of d = 0.50, with 80% power at a two-sided α = 0.05. On the 1–5 BRS scale, *d* = 0.50 corresponds to a shift of roughly 9–11% of the possible range and would be expected to move a meaningful proportion of students from the low resilience band (BRS < 3) into the normal range. Effects of this magnitude are similar to those observed between clinically relevant groups in studies of Reboot with clinicians and are therefore considered potentially clinically important at the group level.

Power was estimated in R using the powerlmm package, under the planned mixed model for repeated measures. The primary contrast was the adjusted mean difference in BRS at T3 between the intervention (Thumos) and services as usual arms (Thumos minus control). Simulations assumed:

- Up to three post-baseline BRS observations per participant (T2, T3, T4); where more than one completion occurred within a time window, the response closest to the nominal time point was retained, preserving the repeated-measures structure;
- A within-participant intra-class correlation coefficient (ICC) of 0.30–0.50, representing a moderate correlation between repeated BRS scores on the same student, consistent with published test–retest data indicating that BRS is reasonably stable over time (doi:10.1080/10705500802222972);
- Variance ratio scenarios across time points using powerlmm defaults, specifying plausible ratios of between-participant to within-participant variance and allowing for heteroscedasticity over time and between arms (see powerlmm reference manual: http://cran.nexr.com/web/packages/powerlmm/powerlmm.pdf);
- Differential attrition of 40% in the control arm and 30% in the intervention arm up to T4, with monotone missingness. These rates were chosen to be conservative, based on studies of Reboot and meta-analytic data from occupational and mental health intervention trials that report similar or lower attrition (e.g. doi: 10.5271/sjweh.4173).

11.2 Statistical Analysis

Recruitment, retention, adherence and participant characteristics will be summarised using appropriate descriptive statistics. Minimum adherence to the intervention is defined as completion of two workshops. Adverse events/serious adverse events will be summarised descriptively by arm, with risk differences and 95% confidence intervals and narrative summaries by event type and seriousness.

The primary outcome (T3 BRS) will be analysed using linear mixed models for repeated measures (MMRM) with random intercepts for participant and fixed effects for treatment group, time, group by time interaction, baseline BRS and baseline covariates (age, gender, medical school). Adjustment for baseline BRS and covariates im-

proves the power and plausibility of the analysis (e.g. make missing at random assumptions more credible by conditioning on variables related to outcome *and* dropout). Although the primary estimand is the adjusted mean difference in BRS at T3, we model T2/T4 BRS because BRS is measured repeatedly and the mixed model accounts for within participant correlation; it allows all post baseline data to contribute to estimation of the T3 contrast, improving precision relative to single time point models; and it gives valid inference when outcome data are missing at random given observed covariates and outcomes from studies of Reboot, which is realistic for the longitudinal design.

Continuous outcomes will be analysed on their original scales and results reported as adjusted mean differences with 95% confidence intervals, *p* values and standardised effect sizes (Cohen's *d*). A two-sided of $\alpha = 0.05$ is considered significant. Model assumptions will be explored and robust standard errors and/or alternative covariance structures will be considered as necessary.

Secondary count outcomes (sickness absence) will be modelled with Poisson models and binary outcomes (support access indicators) with mixed effects logistic regression, including random intercepts for participant and the same fixed effect structure as primary analyses. We will report incidence rate ratios and odds ratios with 95% confidence intervals and *p* values. Secondary analyses will be interpreted as supportive rather than confirmatory; to describe multiplicity we will report false discovery rate adjusted *q* values for secondary outcomes at T3-T4.

Patterns of data missingness will be described and explored using logistic regression models for missingness indicators. Sensitivity analyses will include multiple imputation under MAR, pattern mixture "worse than MAR" scenarios using fixed negative offsets to imputed BRS values, and a last post baseline carried forward analysis.

Adherence and subgroup effects will be explored in prespecified additional analyses, including per protocol analyses and complier average causal effect (CACE) estimation using randomisation as an instrument for full receipt of the intervention.

Interviews conducted as part of the process evaluation will be transcribed verbatim and analysed using Reflexive Thematic Analysis (RTA). Field notes and logs will also be analysed using RTA. RTA is a theoretically flexible approach for identifying, ana-

lysing and reporting patterns in qualitative data and is useful for obtaining detailed insights [36]. Internal reliability of qualitative data will be strengthened through the adoption of qualitative credibility strategies such as respondent validation of transcripts, peer debriefing and negative case analysis. Qualitative data will then be combined with quantitative data from the process questionnaires using a narrative discussion where the quantitative survey scores are presented alongside the themes produced by RTA [37]. In particular, we will follow the approach of Guetterman and Mitchel [38] who included a separate section following initial presentation of the quantitative (frequency) and qualitative (thematic) findings, labelled, ‘mixed-methods integration’. The purpose of this section will be to bring quantitative results together with relevant qualitative insights, to generate a nuanced and full picture of the dataset. This narrative discussion will be facilitated by the use of a side-by-side joint data display; a table where complementary and divergent qualitative and quantitative findings are included in columns to support the generation of complex insights [39].

12. Trial supervision

The trial has been carefully designed to ensure compliance with GCP and scientific integrity. The implementation of the trial through its design and development is managed by the CI and the co-applicants, in consultation with expert researchers and other expert collaborators from within and outside of the CI's institution.

A trial manager will manage the day to day running of the trial, reporting to the CI. A trial management group (TMG), a trial steering committee (TSC) will be established to oversee specific aspects of the trial as described in detail in the next section/s. A Data Monitoring and Ethics Committee (DMEC) will be formed if deemed necessary by the TSC, with the purpose of reviewing unblinded data. The DMEC will be formed separately and independently to the TSC.

13.1 Trial Steering Committee

The Trial Steering Committee (TSC) will provide guidance and supervision for the trial on behalf of the project's sponsor and funder and to ensure that it is conducted to the rigorous standards set out in the University of Manchester's Code of Good Research Conduct and policies and guidelines. The specific role the TSC will provide is a regular review of the trial's progress including recruitment figures, data completeness, adherence to protocol treatment and follow-up, and safety data. The TSC will

ensure the rights, safety and well-being of the participants are given the most important considerations and should prevail over the interests of science and society. It will ensure that all appropriate ethical approvals have been obtained and adhered to and approve any proposals for substantial protocol amendments. It will comprise seven independent members: a chairperson, one clinician, a statistician, a registered psychologist, and two experts by experience (medical students).

13.2 Data Monitoring and Ethics Committee

As a relatively small trial of N =220 participants of a preparatory intervention for medical students, ACTIVATE does not require a separate Data Monitoring and Ethics Committee (DMEC). A DMEC will be formed if deemed necessary by the TSC, with the purpose of reviewing unblinded data. The DMEC will be formed separately and independently to the TSC.

13.3 Stopping Guidelines

The trial will be paused in the event of two SAEs which are probably related to the study procedures. Information regarding these events will be collected by the CI and research team and passed on to the TSC Chair for consultation. If the TSC Chair deems the SAEs are related to the study procedures, the Chair of the Ethics Committee will be informed and consulted. The advice of the TSC and the Chair of the Ethics Committee will be sought and acted upon. The trial may be permanently discontinued at this point, or continued after review and with recommendations from the TSC and the Chair of the Ethics Committee addressed. The trial may be permanently discontinued in the event of three SAEs which are considered to be probably related to the trial procedures. The TSC Chair who will advise on whether to continue or discontinue the study, will make a recommendation to the sponsor.

All adverse events will be reported to the TSC who will review them. If the rate of AEs is >30% higher in one arm, the TSC may pause the trial to review further and consider whether the study is causing harmful effects. If after this review it is decided that the study is causing harmful events, it may be permanently discontinued.

The trial may also be discontinued if recruitment rates fall below 50% of the monthly target for 4 consecutive months. Recruitment rates will be monitored by the CI and research team and reported to the TSC. Should recruitment fall below this threshold, the CI will seek the advice of the TSC regarding whether to discontinue the study.

If the study is prematurely discontinued, active participants will be informed. In consultation with the TSC Chair, next steps will be agreed upon. It is most likely that data

collection would continue but that participants would no longer receive the intervention.

13.4 Trial Management Group

A trial management group (TMG) will meet regularly; its membership will include the investigators, collaborators and PPI medical students. The TMG will be chaired by the CI and is responsible for the day to day running of the trial, ensuring good communication between the members of the research team, overseeing recruitment progress, intervention completion, adverse events and reviewing overall trial progress against milestones. It will oversee the preparation of reports to the TSC (and DMEC if required).

14. Data handling and record keeping

Participant contact details, demographic information and quantitative data will be collected via the University of Manchester access to the Qualtrics platform. Qualitative data will be collected via the University of Manchester access to the Microsoft Teams platform, using the recording and transcription functions. Qualitative interviews will be conducted by the University of Manchester-employed researcher. At the end of the study, all quantitative data will be downloaded from Qualtrics and deleted from their system. Qualitative videos will be downloaded from Teams following each interview, and uploaded to secure University of Manchester systems. They will then be deleted from Teams. Once the anonymised transcript for each video has been completed, the video will be deleted from the University of Manchester system, and no copy of the video will exist.

All data will be electronic, there will be no hard copies. Electronic identifiable data will be stored on secure, password protected University drives, in encrypted files. Data will be pseudonymised; a code will be used to match personal identifiable data and research data, which only the University of Manchester team has access to. Personal data will not be shared outside of the University of Manchester research team. Personal identifiable data will be stored for up to 5 years following recruitment of the final participant. This is to enable potential follow-up studies to be conducted, dependent on further grant funding being awarded to conduct these studies. However, the personal information stored will only be used to contact participants to invite them to future studies, not as part of the research data set in and of itself.

15. Data access and quality assurance

All data will be kept secure at all times and maintained in accordance with the requirements of the Data Protection Act, and archived according to clinical trial GCP regulations. Personal data will be stored in encrypted, password protected formats. Identifiable personal data will be stored separately to other study data to help maintain confidentiality. Only the University of Manchester research team members will have access to the data. No personal or identifiable data will be transferred. Only anonymised datasets will be shared with collaborators outside of the University of Manchester during the project, for the purposes of analysis.

The full dataset will be retained for up to 5 years in first instance, to enable possible follow-up studies to be conducted, should additional funding be gained. It will then be deleted, and only anonymised datasets will be retained and uploaded to the University of Manchester data archive/repository. Consent forms will also be retained during this time and destroyed at the end of this time.

The anonymised datasets (the anonymised quantitative dataset and the anonymised qualitative transcripts) will be uploaded after the project has finished to the University of Manchester archive/data repository. Participants are asked to give permission on the consent form for the anonymised dataset to be uploaded to a repository. Providing this permission is necessary to take part in the study. To avoid any issues with data sharing, only anonymised data will be uploaded to a repository. The anonymised datasets created during the present study will be available in a public repository, hosted at the University of Manchester research - (https://figshare.manchester.ac.uk/).

Relevant parties (e.g., ethics committee, TSC) will be notified of any modifications to the protocols or data management plan in a timely manner.

16. Publication

The trial protocol will shortly be submitted for publication. Planned main publication in high-impact peer-reviewed journal with paper analysing the primary outcomes of the effectiveness of Thumos in increasing psychological resilience compared to SAU at 4-month follow-up. This paper will also report on the secondary outcomes of the effectiveness of Thumos compared to SAU at post-intervention, 4- and 9-month follow-ups in the endpoints of confidence, burnout, depression, mental health and self-reported sickness absence.

17. Finance

This trial is funded by The MPS Foundation. The Funder reviewed and approved the content of the protocol, but does not have a role in data collection, management, analysis, or interpretation; nor in the writing of the final report or decision to submit the report. The views expressed in this publication are those of the authors and not necessarily those of the MPS Foundation.

18. Ethics approval & regulatory compliance

The project was approved on 20/12/2024, by the University of Manchester Research Ethics Committee 1 (2nd Floor, Christie Building, The University of Manchester, Oxford Road, Manchester, M139PL, United Kingdom; +44 (0)161 306 6000; urec1@manchester.ac.uk), ref: 2024-21589-38791, prior to study commencement.

19. Medical Student Involvement

At least four medical students will be involved; at least two will join the TSC to provide independent oversight to study management, and at least two will join the trial management committee to provide feedback on study materials and delivery.

22. Indemnity / Compensation / Insurance

The University of Manchester has in place research study insurance against liabilities for which it may be legally liable and this cover includes any such liabilities arising out of this study.

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Appendices

Appendix 1.0

1.0. List of eligible UK medical schools

University of Southampton School of Medicine
Hull York Medical School (HYMS)
University of Leicester Medical School
Brighton and Sussex Medical School
University College London Medical School (UCL)
King's College London GKT School of Medical Education (KCL)
City St George's, University of London
University of Birmingham School of Medical Sciences
University of Dundee School of Medicine
University of Liverpool School of Medicine
University of Sheffield medical school
University of Manchester medical school
Anglia Ruskin University School of Medicine
Aston University Medical School
Brunel University Medical School
Cardiff University School of Medicine
Edge Hill University Medical School
Imperial College London Faculty of Medicine
Keele University School of Medicine
Kent and Medway Medical School
Lancaster University Medical School
London School of Hygiene and Tropical Medicine (LSHTM)
Newcastle University School of Medical Education
North Wales Medical School, Bangor University
Norwich Medical School, University of East Anglia
Pears Cumbria School of Medicine
Peninsula Medical School Plymouth University
Queen Mary, University of London School of Medicine
Queen's University Belfast School of Medicine
St Mary's University, Twickenham School of Medicine
University of Cambridge, School of Clinical Medicine
University of Oxford, Medical Sciences
University of Edinburgh, Medical School
University of Glasgow, School of Medicine
University of Bristol, Medical School
University of Buckingham Medical School
University of Lancashire School of Medicine
Swansea University Medical School
Three Counties Medical School, University of Worcester
Ulster University, School of Medicine
University of Aberdeen School of Medicine
University of Chester Medical School
University of Exeter Medical School
University of Greater Manchester, Medical School
University of Leeds School of Medicine
University of Lincoln Medical School
University of Nottingham School of Medicine

University of St Andrews School of Medicine
University of Sunderland School of Medicine
University of Surrey School of Medicine
University of Warwick Medical School

Appendix 2.0

2.0 Participant Information Sheet and Consent Form

V3 11-03-2025 – medical students

A randomised controlled trial evaluating whether a CBT-based group and one-to-one supportive intervention can improve burnout and mental health in medical students

Participant Information Sheet (PIS) for medical students

You are being invited to take part in a research study evaluating an intervention in medical students. Before you decide whether to take part, it is important for you to understand why the research is being conducted and what it will involve. Please take time to read the following information carefully before deciding whether to take part, and discuss it with others if you wish. Please ask if there is anything that is not clear or if you would like more information. Thank you for taking the time to read this.

About the research

Who will conduct the research?

Dr Judith Johnson and Lucy Pointon who are based in the Division of Nursing, Midwifery and Social Work at The University of Manchester. A researcher from the University of Sheffield is also participating.

What is the purpose of the research?

The study aims to evaluate a supportive programme (Thumos) designed to prepare medical students for stressful events faced at work.

Am I suitable to take part?

We'd love to hear from you if you are a medical student in a year involving clinical placements. This is usually year 4 or year 5 for most medical schools, but can vary.

Will the outcomes of the research be published?

We will publish our findings in peer-reviewed journal articles. We might also promote the findings via social media.

Who has reviewed the research project?

The project has been reviewed by The University of Manchester Research Ethics Committee.

Who is funding the research project?

The Medical Protection Society Foundation.

What would I be asked to do if I took part?

If you decide to take part in the research study, you will be asked to complete a consent form and some baseline questionnaires, which will ask for demographic details (e.g., age, gender) and your thoughts and perceptions relating to your mental health and psychological wellbeing. They will take about 20m altogether. You will then be randomised to either receive the Thumos intervention, or to the control group, where you will not receive the intervention. Half of participants will be randomly allocated to receive the intervention; the other half will not be allocated to receive the intervention. This decision is completely random and is not affected by any of your responses to the questionnaires. In either group, you can continue to access your usual wellbeing or mental health support services as usual.

If you are randomly allocated to receive the intervention, we will ask you to:

- Engage in the Thumos programme, combining 2 small group online workshops and a personalised coaching call. The workshops will each last up to 2 hours and the coaching call will last up to an hour (5 hours total).
- Complete further online questionnaires after Thumos has finished, first on completion of the coaching call, then 4 months after starting the study and finally 9 months after starting the study. This will take around 20m at each time.
- Over the course of the study, some workshops will be observed by a researcher who will join the call, and we will request permission to video record some of the coaching calls. This is so that we can observe the therapist and identify how closely they are following the intervention plan. Any recordings will be destroyed once they have been watched by the research team and scored for how closely they are following the intervention plan.
- We will also ask your permission to retain your contact details, so we could contact you again in 2 and 5 years' time, to ask you to complete further questionnaires.
- A subgroup of participants will be asked to answer additional questions as part of a qualitative interview at around 4 months after the first questionnaire, discussing your experiences of Thumos. These will last up to 30 minutes. These interviews will be conducted on Teams and video recorded.

If you are randomly allocated not to receive the intervention, we will ask you to:

- Complete further online questionnaires 4-6 weeks after the first questionnaire, again 4 months after starting the study and then finally 9 months after starting the study. This will take around 20m at each time.
- We will also ask your permission to retain your contact details, so we could contact you again in 2 and 5 years' time, to ask you to complete further questionnaires.

Will I be compensated for taking part?

You will not be compensated for completing the first set of questionnaires. However, for each of the remaining three follow-up questionnaires, you will receive a £10 shopping voucher. For participants who take part in the qualitative interviews, you will receive a further £10 shopping voucher.

What happens if I do not want to take part or if I change my mind?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and will be asked to provide your name and tick a box to confirm consent on Qualtrics survey software online. If you decide to take part you are still free to withdraw at any time without giving a reason and without detriment to yourself. However, it will not be possible to remove your data from the project once it has been anonymised as we will not be able to identify your specific data. This does not affect your data protection rights. If you decide not to take part you do not need to do anything further.

For participants who are invited to take part in the qualitative interviews, these will be conducted on Teams and will be video recorded. We need this recording to be able to analyse the data, so we need to do this for you to take part in the interview. If should be comfortable with the recording process at all times and are free to stop recording at any time, should you feel uncomfortable.

Data Protection and Confidentiality

What information will you collect about me?

In order to participate in this research project we will need to collect information that could identify you, called “personal identifiable information”. Specifically we will need to collect:

- Your name
- Contact details and address (for posting the paper workbook to you)
- Gender
- Ethnicity
- Age
- Region
- Your year of medical school
- Whether you are in a year involving clinical placements
- Whether you have begun or completed one or more clinical placements
- Which medical school you attend
- For participants who take part in the qualitative interviews, these will be conducted on Teams. We will ask permission to video record the discussion.

Under what legal basis are you collecting this information?

We are collecting and storing this personal identifiable information in accordance with UK data protection law which protect your rights. These state that we must have a legal basis (specific reason) for collecting your data. For this study, the specific reason is that it is “a public interest task” and “a process necessary for research purposes”.

What are my rights in relation to the information you will collect about me?

You have a number of rights under data protection law regarding your personal information. For example you can request a copy of the information we hold about you, including video recordings.
If you would like to know more about your different rights or the way we use your personal information to ensure we follow the law, please consult our Privacy Notice for Research.

Will my participation in the study be confidential and my personal identifiable information be protected?

In accordance with data protection law, The University of Manchester is the Data Controller for this project. This means that we are responsible for making sure your personal information is kept secure, confidential and used only in the way you have been told it will be used. All researchers are trained with this in mind, and your data will be looked after in the following way:

- For the questionnaire data, we have taken measures to ensure confidentiality, such as providing participants with an assigned ID number only known to the research team (known as pseudonymised).
- We will ask your permission to retain your data for up to 5 years after the end of the study. This is to enable us to contact you again in 2 and 5 years to conduct further follow up studies, should we gain additional funding for this. If you decline to provide permission, your identifiable data will be deleted at the end of the study, which will be 2 months after the final participant has provided their follow-up data. You can indicate your choice on the consent form. If you provide consent for this, your details will be safely stored on UoM servers in a digital folder only accessible to the study team and used only for the purposes described above.
- Data will be held on secure University of Manchester OneDrive servers. Only completely anonymised data will be shared with any other organisations (e.g., anonymous quantitative data files; anonymised transcripts, where all identifying details have been changed). This data will be shared for the purposes of statistical analysis.
- Identifiable and anonymised data will be stored for up to 5 years on University of Manchester secure OneDrive servers.
- At the end of the project we will deposit a fully anonymised dataset [e.g. including de-identified interview transcripts] in an open data repository where it will be permanently stored. We will use the University of Manchester Library. Researchers at other institutions and others can access the anonymised data directly from the repository and use it for further research or to check our analysis and results.
- For participants who take part in online qualitative interviews, the recordings will be used to create transcripts. This will be done initially by the Teams transcription software and then will be checked and corrected by a study team researcher.
    - Personal identifiable information will be removed in the final transcript
    - The recordings will be destroyed following transcription
    - Your participation in the qualitative interview will be recorded in Teams and your personal data will be processed by Microsoft. This may mean that your personal data is transferred to a country outside of the European Economic Area, some of which have not yet been determined by the United Kingdom to have an adequate level of data protection. Appropriate legal mechanisms

to ensure these transfers are compliant with the Data Protection Act 2018 and the UK General Data Protection Regulation are in place. The recordings will be removed from the above third party platform and stored on University of Manchester managed file storage as soon as possible following the completion of data collection.

The study team at The University of Manchester will have access to your personal information and they will anonymise it as soon as possible. Your name and any other identifying information will be removed and replaced with a random ID number. The research team will have access to the key that links this ID number to your personal information. Your consent form will be retained for 5 years on secure University of Manchester OneDrive servers for audit purposes.

So that we can provide the shopping/Amazon voucher as a thank you for your time, your full name and email address will be shared with our Finance department who will send the voucher to you. Your full name and email address will be securely retained by Finance for a period of up to 7 years for audit purposes only and then destroyed. It will not be used for them for any other purpose.

If, during the study, you disclose information about patient safety hazards or risks you are facing on placement, we will advise you that you have a responsibility to raise these issues via your clinical supervisor and we will support you to do this. If you refuse to raise issues of concern via the normal routes, and it is likely that disclosure will prevent harm to others in future, we may need to contact the relevant NHS trust directly and communicate the risks/concerns directly to the trust's local patient safety team on your behalf. We will maintain confidentiality wherever possible but break confidentiality and disclose your identity if necessary.

If, during the study, you disclose that you have experienced a serious negative event while participating in the study, we will contact you to request more information about the event, to try and understand if it is related to the study procedures.

Please also note that individuals from The University of Manchester or regulatory authorities may need to look at the data collected for this study to make sure the project is being carried out as planned. This may involve looking at identifiable data. All individuals involved in auditing and monitoring the study will have a strict duty of confidentiality to you as a research participant.

What if I have a complaint?

Contact details for complaints

If you have a complaint that you wish to direct to members of the research team, please contact: **DR JUDITH JOHNSON, JUDITH.JOHNSON@MANCHESTER.AC.UK.**

If you wish to make a formal complaint to someone independent of the research team or if you are not satisfied with the response you have gained from the researchers in the first instance, then please contact:

The Research Ethics Manager, Research Office, Christie Building, The University of Manchester, Oxford Road, Manchester, M13 9PL, by emailing: research.complaints@manchester.ac.uk or by telephoning 0161 306 8089.

If you wish to contact us about your data protection rights, please email dataprotection@manchester.ac.uk or write to The Information Governance Office, Christie Building, The University of Manchester, Oxford Road, M13 9PL at the University and we will guide you through the process of exercising your rights.

You also have a right to complain to the Information Commissioner's Office about complaints relating to your personal identifiable information Tel 0303 123 1113

Contact Details

If you have any queries about the study or if you are interested in taking part, then please contact the researchers:

Lucy Pointon: lucy.pointon@manchester.ac.uk or ThumosTrial@manchester.ac.uk
Dr Judith Johnson: Judith.johnson@manchester.ac.uk

V3 11-03-2025 – medical students

A randomised controlled trial evaluating whether a CBT-based group and one-to-one supportive intervention can improve burnout and mental health in medical students

Consent Form for medical students

If you are happy to participate please tick each box and then enter your name below.

	Activities	Tick to indicate agreement
1	I confirm that I have read the attached information sheet (**Version 3, Date 11-03-2025**) for the above study and have had the opportunity to consider the information and ask questions and had these answered satisfactorily.	
2	I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving a reason and without detriment to myself. I understand that it will not be possible to remove my data from the project once it has been anonymised and forms part of the data set. I agree to take part on this basis.	
3	If I am invited to a qualitative interview and choose to take part in this, I agree to the **interviews** being **video recorded**	
4	I agree that any data collected may be included in anonymous form in **publications/conference presentations.**	
5	I agree that any research publications can include direct quotes of my responses in **anonymous** format.	
6	I understand that a fully anonymised dataset will be deposited in an open data repository at the end of the project.	
7	I understand that data collected during the study may be looked at by individuals from The University of Manchester or regulatory authorities, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my data.	
8	I understand that my full name and email address will be passed to the University's Finance team for the sole purpose of sending me the **shopping/Amazon voucher.**	
9	I understand that there may be instances where during the course of the research information is revealed which means the researchers will be obliged to break confidentiality and this has been explained in more detail in the information sheet.	

10	I understand that if I disclose evidence of patient safety risks in my clinical placement, I will be encouraged to report these to the relevant authorities. If I choose not to and it is likely that disclosure will prevent harm to others in future, I understand that the research team may need to raise these risks with the relevant NHS Trust, and that they will make every effort to maintain my confidentiality, but may need to disclose this and will do so if necessary.	
11	I understand that some workshops may be observed by a researcher and that my therapist may request permission to video record our coaching call. I understand that this is for the purpose of understanding how closely the therapist is following the intervention protocol, and provide my permission for these observations/recordings.	
12	I understand that if I disclose that a serious negative event has occurred to be during the course of the study, the research team will contact me to request more information about this.	
13	I agree to take part in this study.	

The following activities are optional, you may participate in the research without agreeing to the following:

14	I give permission for my contact details to be retained for up to 5 years to enable potential follow up studies to be conducted, regarding the intervention. I agree that the researchers may contact me in future about these projects, but do not give permission to be contacted about any other research projects.	
15	I agree that the researchers may retain my contact details in order to provide me with a summary of the findings for this study.	

Data Protection

The personal information we collect and use to conduct this research will be processed in accordance with UK data protection law as explained in the Participant Information Sheet and the Privacy Notice for Research Participants.

By providing my full name and email address below, I declare that I have provided accurate identity details.

_____ _____

Name of Participant Email address Date

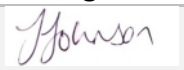
This consent form will be retained on the Qualtrics platform. You can request a copy by contacting the research team (Dr Judith Johnson, Judith.johnson@manchester.ac.uk; Lucy Pointon, lucy.pointon@manchester.ac.uk)

Appendix 3.0

ACTIVATE Statistical Analysis Plan (SAP)

Administrative Information

Item	Description
Version | date	0.**6** | **16**/13/25
Project title	A randomised controlled evaluation of Thumos: a cognitive-behavioural intervention for medical students
Acronym	ACTIVATE
SAP author	Dr Luke Budworth
ISRCTN	12744098
REC reference	2024-21589-38791
Funded by	The MPS Foundation
Grant reference	
Chief Investigator	Dr Judith Johnson
Sponsor	University of Manchester

Approvals	Name	Signature	Date
Chief Investigator	Dr Judith Johnson		15-12-2025
Trial Statistician	Dr Luke Budworth		16-12-202
Trial Co-Investigator	Dr Christopher Taylor		
TSC Independent Statistician	Prof Mona Kanaan		22-12-2025

This document details the presentation and analysis strategy for the primary papers reporting results from the ACTIVATE Trial. It is intended that the main trial results paper will follow the strategy set out in this Statistical Analysis Plan document; subsequent papers which could be of a more exploratory nature will not be bound by this analysis plan but will be expected to follow the broad principles laid down for the primary paper(s).

The principles are not intended to curtail exploratory analysis or to prohibit sensible statistical and reporting practices but they are intended to establish the strategy that will be followed as closely as possible in analysing and reporting the trial.

This SAP has been prepared in accordance with the Sheffield Clinical Trials Research Unit (CTRU) Standard Operating Procedures (SOP) “The Statistical Analysis Plan” Ref ST001 (02-Jul-2025). It follows the Guidelines for the Content of Statistical Analysis Plans in Clinical Trials (Gamble et al, 2017) (see Section 13 for a completed checklist).

Background & aims

Background

Medical students experience high rates of burnout and psychological distress, which worsen during clinical placements and contribute to workforce attrition. Thumos is a cognitive-behavioural intervention designed to help medical students manage stressful clinical events. For a comprehensive review of the rationale and evidence base, see Section 2.1 of the main ACTIVATE trial protocol.

Aims

The main purpose of the trial is to establish whether Thumos increases resilience and improves mental health in medical students. The primary objective is to determine whether Thumos is superior to the control condition (services as usual; SAU) at 4 month follow-up in increasing psychological resilience in medical students. Secondary objectives are:

- To determine whether Thumos is superior to SAU at 9-month follow-up in increasing psychological resilience.
- To determine whether Thumos is superior to SAU at 4-month and 9-month follow-ups in the endpoints of confidence, burnout, depression, mental health and self-reported sickness absence.
- To assess acceptability and how Thumos is delivered in practice through a process evaluation with users, medical educators and providers.

Synopsis

Background & aims

This Statistical Analysis Plan should be read in conjunction with the ACTIVATE trial protocol (Version 8, 25th November 2025). The full scientific background and rationale for the trial are provided in Section 2.1 of the main protocol and are not repeated here to avoid duplication. In brief, the ACTIVATE trial evaluates Thumos, a CBT-based intervention targeting psychological resilience in medical students during clinical placement years.

Design

- Two-arm, parallel group superiority RCT with individual randomisation 1:1 to Thumos or service as usual (SAU) control arm
- Data at baseline (T1), post-intervention or 6 weeks for controls (T2), 4 months (T3, primary), 9 months (T4)
- All questionnaires are completed online via Qualtrics

Eligibility criteria

UK medical students in years involving clinical placements (e.g. Y4/Y5) nationally. We will stop recruiting once we have reached our sample size target and exclude all additional participants.

Sample size

Target = 220 randomised (110 per arm).

Primary outcome

Brief Resilience Scale (BRS) at T3.

Secondary outcomes (quantitative only)

BRS at T4, plus:

- Confidence in coping with adverse events (CCAE)
- Oldenburg Burnout Inventory (OLBI)
- Patient Health Questionnaire-9 (PHQ-9)
- Recovery of Quality of Life Utility Index (ReQo-UI)
- Self-reported sickness absence (novel measure)
- Support access (novel measure)

At T3 and T4.

Primary analysis

Mixed effects model accounting for repeated measures with covariate adjustment, estimating adjusted mean difference at T3.

Interim analyses

None planned

Multiplicity

- Primary endpoint tested two-sided at 5%
- Secondary endpoints reported with 95% CIs and *q*-values for transparency

Statistical software

R (v4.5.1) with Stata (v19) used for cross checking where useful (all code version controlled).

Objectives & Hypotheses

Primary objective

Determine whether Thumos increases resilience at 4 months versus SAU.

Secondary objectives

- Examine effects at T3 and T4 on confidence, burnout, depression, mental health utility and QALYs, sickness absence, and support access
- Assess acceptability and delivery via mixed methods process evaluation (not outlined in this document)

Main hypothesis

Thumos provides a 'moderately' higher mean BRS at T3 versus SAU controls. A difference of 0.35–0.45 BRS points corresponds to a Cohen's *d* of ~0.5 given baseline SD ~0.7. Where *d* (aka. standardised mean difference, SMD) of 0.2 is considered small, 0.5 moderate, and 0.8 large by convention.

On the 1–5 BRS scale this equates to roughly 9–11% of the possible range and would be expected to shift a non-trivial proportion of students out of the low resilience band (BRS < 3) into the normal range.

Estimand(s)

Section in alignment, where relevant, with the estimands framework:

Kahan B C, Hindley J, Edwards M, Cro S, Morris T P. (2024). The estimands framework: a primer on the ICH E9(R1) addendum. BMJ. doi:10.1136/bmj-2023-076316.

Primary estimand

'Policy' effect of offering Thumos on resilience at 4 months

- **Treatment**

Assignment to Thumos versus assignment to services as usual.

- **Population**

All randomised UK medical students in clinical placement years who meet inclusion criteria.

- **Variable**

BRS mean score at T3, around 4 months post-baseline. The BRS outcome at each time point will be calculated as the mean of the six BRS items (range 1–5). The primary treatment effect is the adjusted between-group difference in mean BRS at T3; we do not average scores across repeated measurements, but use the mixed model to account for the correlation between time points

- **Summary measure**

Covariate adjusted (i.e. to boost statistical power) mean difference in BRS at T3, Thumos minus control, with 95% confidence interval and *p*-value. Report Cohen's *d* with 95% confidence interval.

- **Intercurrent events and strategies**
    - Non-adherence to Thumos components
        - Strategy: treatment policy, or in other words: analyse as allocated
    - Use of external psychological support
        - Strategy: treatment policy, record at each time point and explore as a variable using adjustment in sensitivity analyses
    - Missing T3 outcome
        - Strategy: estimated under *missing at random* (MAR) given observed data, with planned sensitivity analyses that relax MAR.

Secondary estimands

Same treatment, population and intercurrent event strategies as the primary estimand. Variables and summaries differ by outcome (Table 1).

Table 1. Outcome measures

Outcome	Time	Variable definition	Measure
BRS	T3/T4	BRS mean score	Adjusted mean difference/Cohen's *d*
CCAE	T3/T4	CCAE mean score	As above
OLBI	T3/T4	OLBI total and subscales	As above
PHQ-9	T3/T4	PHQ-9 total score	As above
ReQoL-UI	T3/T4	Utility score	As above
ReQoL-UI QALYs	BL-T4	QALYs area under the curve	Adjusted mean difference
Sickness absence	T3/T4	Days lost in past 4 weeks	Adjusted rate ratios with 95% CI

BRS: Brief Resilience Scale; CCAE: Confidence in Coping with Adverse Events; OLBI: Oldenburg Burnout Inventory; PHQ-9: Patient Health Questionnaire-9 item depression scale; ReQoL-UI: Recovering Quality of Life –

Utility Index; QALYs: Quality-adjusted life years; BL: Baseline; T1, T2, T3, T4: Time points 1, 2, 3, and 4 (T = time)

Supplementary estimand

Effect among likely *full* (i.e. adhering to the above) *participants* at 4 months

Defined as students who would, if offered Thumos, attend both workshops and complete the one-to-one call within the protocol window with at least 75% attendance per session, and without major protocol deviations, at 4 months.

- **Target**

Complier average causal effect (CACE) for BRS at T3 among students who would complete both workshops and the one-to-one call within the protocol window if offered Thumos.

- **Strategy**

Principal-stratum estimand estimated via instrumental variables with randomisation as the instrument. Report alongside the primary effect.

Assessment windows

- T2 target 6 weeks after baseline (window 4-10 weeks)
- T3 target 16 weeks (12-24 weeks)
- T4 target 36 weeks (30-44 weeks)

If multiple responses fall within a window, the response closest to the nominal time will be used.

Sensitivity analyses

These will not change the targets above. Instead, probe robustness to assumptions (expanded on in sections below):

- For key missing outcome data: multiple imputation including outcomes at all times, baseline covariates and support access, similarly pattern mixture models with negative delta adjustments for non responders at T3/T4
- Checks for therapist or cohort clustering in the intervention arm

Sample Size Estimation

Power was simulated in *powerlmm* (R package) assuming:

- Standardised between group difference at T3 d = 0.50 (with 20% false negative rate, i.e. 80% power)
- As above, on the 1–5 BRS scale d = 0.50 equates to roughly 9–11% of the possible range and would be expected to shift a non-trivial proportion

of students out of the low resilience band (BRS < 3) into the normal range. Effects of this size are comparable to those seen between clinically relevant groups in studies of Reboot with clinicians and validation studies and are therefore considered potentially clinically important at the group level.

- Within-participant intra-class coefficient (ICC) of 30-50% across time
    - The ICC here is the proportion of total variance in BRS that is attributable to stable between student differences, rather than occasion specific fluctuation. In other words, it reflects the correlation between repeated BRS measurements on the same student across T2, T3 and T4. Values in the region of 0.30–0.50 correspond to a moderate correlation between time points and are consistent with published test–retest data (doi:10.1080/10705500802222972) showing that BRS is reasonably stable over time.
    - Each participant can contribute up to three post baseline BRS observations, at T2, T3 and T4. If multiple questionnaire completions fall within a given time window, the response closest to the nominal time is used for that *time point*. This rule does not change the longitudinal structure of the data, which still consist of repeated measures over time, and is therefore compatible with assuming a within participant ICC in the power simulations.
- Variance ratio scenarios across time points per powerlmm defaults
- Attrition: 40% control, 30% intervention up to T4 (with monotone missingness, i.e. in line with typical dropout patterns in trials over time).
    - These were considered conservative estimates and were partly based on studies of Reboot, partly on past meta-analyses (see: doi: 10.5271/sjweh.4173).
- α = 0.05 two-sided for the primary objective comparison

Power was evaluated for the primary contrast, defined as the adjusted mean difference in BRS at T3 between the Thumos and services as usual arms (Thumos minus control) from the planned mixed model for repeated measures. Simulations indicated 200 participants gives around 80% power for the T3 contrast in the planned primary analysis model. The final sample size target was inflated by 10% to 220 to allow for any additional attrition or guard against misspecification of our estimated parameters in this power analysis.

Randomisation, Concealment & Blinding
Randomisation & concealment

Simple 1:1 individual randomisation via Sealed Envelope. The platform generates and holds the allocation sequence. Allocation is revealed only after consent and baseline completion within Sealed Envelope; the sequence is not accessible to the trial team.

Blinding

Outcomes are self-reported. The data analyst will conduct the analysis with masked arm labels (A/B); labels remain masked until final unblinding, which occurs only after: SAP sign-off, code is written/complete and independently reviewed, and analysis dataset locked.

Analysis Populations & Protocol Deviations

Analysis sets

- **Full analysis set (FAS aka. ITT: intention to treat, primary analysis)**

All randomised participants, analysed as allocated, regardless of intervention receipt or post-randomisation events. Participants with no post-baseline outcomes appear in flow and baseline tables but will not contribute to outcome models. This set underpins the treatment-policy estimands (as outlined above).

- **Per protocol set (PP, sensitivity analysis)**

FAS excluding major protocol deviations (see below) and excluding Thumos participants who do not meet the compliance definition (see below). Requires a valid T3 BRS within the T3 window.

- **CACE (supplementary estimand)**

Binary indicator of ‘full receipt’ used in the instrumental variables (IV) analysis (see below). All randomised participants will remain in the IV analysis.

Compliance definition (relevant to PP/CACE only)

For descriptive reporting only, we may present a stricter completion metric that includes the one-to-one call, but PP and CACE will use the minimum adherence definition below to avoid ambiguity:

- **Thumos arm**

Attended both group workshops within 6 weeks of randomisation, with at least 75% attendance of each session. The one-to-one call is not required for minimum adherence.

- **Control arm**

No receipt of any Thumos component. Accessing usual external psychological support is allowed in both arms and is not a deviation (as this is not specified within the trial protocol).

Protocol deviations

All deviations will be logged prospectively and classified before unblinding.

- **Minor**

Unlikely to affect the primary outcome or its interpretation, for example small lateness to sessions, questionnaire completed within the window but not on the target day. Minor deviations remain in all analysis sets.

- **Major**

May affect the primary outcome. These include:

- Invalid consent or ineligibility
- Allocation error/breach of concealment
- Any receipt of Thumos intervention in the SAU/control arm
- No valid T3 BRS within the prespecified T3 window
- Data integrity issues such as very unusual or impossible values recorded, or identified falsification

Major deviations remain in the FAS but will be excluded from PP. Non-completion of Thumos is not a deviation for the FAS, but it excludes participants from the PP sample and defines non-receipt for the CACE indicator.

Timing rules

Assessment windows are defined as follows: T2 = 4–10 weeks, T3 = 12–24 weeks, and T4 = 30–44 weeks post-baseline.

Where multiple responses fall within a window, the response closest to the nominal time point will be used.

Any assessments obtained outside these windows will be documented, with the number and timing reported in the main paper. If the proportion of out-of-window assessments is substantial, a sensitivity analysis will be undertaken to assess the impact on results.

Outcomes

Overview (Table 2)

Table 2. Outcome scoring

Outcome	Items	Measure	Construct(s) & direction	Time points	Derived variable/scoring

BRS (Primary)	6	Brief Resilience Scale	Resilience; higher = better	T3 [12–24 wks]	Mean of 6 items (with required reverse scoring)
BRS	6	Brief Resilience Scale	Resilience; higher = better	T4 [30–44 wks]	Mean score
CCAE	3	Confidence in Coping with Adverse Events questionnaire	Confidence coping with adverse events; higher = better	T3, T4 [12–24, 30–44]	Mean of 3 items
OLBI (total & subscales)	16	Oldenburg Burnout Inventory	Burnout (exhaustion, disengagement); higher = worse	T3, T4 [12–24, 30–44]	Subscale means and total mean (with required reverse scoring)
PHQ-9	9	Patient Health Questionnaire-9	Depressive symptoms; higher = worse	T3, T4 [12–24, 30–44]	Sum of 9 items (0–27)
ReQoL-UI (utility)	10	Recovery of Quality of Life – Utility Index (ReQoL-UI)	Quality of life utility; higher = better	T3, T4 [12–24, 30–44]	Utility index via ReQoL-UI algorithm
ReQoL-UI QALYs	10	Recovery of Quality of Life – Utility Index (ReQoL-UI)	Quality adjusted life years; higher = better	Baseline–T4	Area under utility time curve
Sickness absence	2	Sickness absence items	Days lost last 4 weeks; higher = worse	T3, T4 [12–24, 30–44]	Count of days lost in past 4 weeks

(All measures are collected at T1 and T2 in addition to T3/T4; T3 and T4 are the pre-specified endpoints for efficacy analyses)

Common across outcomes

- **Mode of questionnaire completion**

All questionnaires will be administered online (Qualtrics). Support access detail (type/start/anticipated end) will be collected (as per the protocol) and may be used in pre-specified sensitivity analyses

- **Scale reliability (rationale)**

Multi-item scales are only useful if their items reliability measure their intended construct (e.g. ‘reslience’). Because some measures (e.g. CCAE) are relatively new or have limited UK validation data in medical students, we will report internal consistency (e.g. Crobach’s alpha – detailed below) estimates at each time point to confirm the scales perform in this population. Poor reliability would reduce observed treatment effects and potentially complicate interpretation of the results. Documenting reliability therefore will support the validity of our conclusions around efficacy.

- **Scoring & item missingness**

In the Qualtrics survey, most key items are set as required for completion. This means that within any given measure we will not normally find individual missing items. Missingness is expected to occur mainly through break offs (e.g. participants exiting mid questionnaire), in which case completed measures up to that point will be scored and any incomplete measure will be handled using the rules below.

Guidance for PHQ (NHS digitial guidance) and ReQoL-UI measures (DOI: 10.1192/bjp.2017.10) provide explicit rules on how to handle within measure missing data (Table 3).

Where manuals are absent, we apply a simple rule that is widely used for patient reported outcome and quality of life scales (Table 3). Specifically, a scale or subscale score is calculated if only a small proportion of items are missing and missing items are replaced by the person-specific mean of the completed items on that scale. Large quality of life programmes, such as the EORTC QLQ series (guidance), allow imputation of missing items provided at least half of the items in a scale are present, using the mean of completed items to replace missing values.

Simulation work on multi-item questionnaires suggests that, when item-level missingness is low (for example no more than about 10–20% of items in a scale), simple approaches such as person-mean substitution can yield small imputation errors relative to measurement error and produce very similar estimates to more complex methods, whereas performance deteriorates as missingness increases (DOI: 10.1023/A:1004782230065; DOI: 10.1177/0011000012445176; DOI: 10.1097/DBP.0000000000001061).

On this basis we adopted a conservative threshold of 10–15% allowable missingness per scale or subscale to retain as much information as possible from

otherwise complete questionnaires while limiting risk of bias from imputation, and avoids letting a small number of imputed items determine the overall scale score.

Where mean substitution is used in Table 3 this refers to person-mean substitution within the relevant scale or subscale, that is, replacing a missing item with the mean of the other completed items from that scale for that participant at that time point. For BRS, CCAE, OLBI, PHQ-9 and ReQoL-UI, any within-scale missing items that fall below the thresholds will be handled by this single item-level imputation method.

When missingness exceeds the thresholds in Table 3, the scale score at that time point will be set to missing and handled at the analysis stage using the planned mixed models and multiple imputation under a missing-at-random assumption, as described in the missing data section.

Table 3. Outcome missing item data approach

Measure	Items	Rule for scoring with missing data	Mean imputation allowed?	Threshold (max % missing)
BRS	6	Compute mean if ≥5 items present; if 1 item missing, impute with person mean; otherwise missing	Yes, 1 item	~16.7%
CCAE	3	All 3 items required; no imputation	No	0%
OLBI	16 (two 8-item subscales)	Subscale mean if ≥7/8 items present; if 1 missing, impute with subscale mean; if either subscale fails, total = missing	Yes, 1 per subscale	~12.5%
PHQ-9	9	If 1 missing, impute with person mean; round final score to nearest integer; if ≥2 missing, set to missing	Yes, 1 item	~11%
ReQoL-UI (utility)	10	Score if ≤1 missing among first 10 items using person-mean substitution; otherwise missing	Yes, 1 item	10%
Sickness absence	2 single items	Stand-alone items; no imputation applicable	No	N/A

Statistical Reporting

See Section 15 for example R code snippets.

Primary inference & analysis scale

For the primary analysis, the BRS at T3 will be analysed with a two-sided significance level of α = 0.05. Although our central hypothesis is that Thumos is beneficial, effects could plausibly occur in either direction; regardless, our emphasis is on estimation rather than dichotomous/binary significance. All continuous outcomes will be analysed on their original scales to retain clinical interpretability (e.g. points on the BRS).

Model diagnostics/robustness

Model assumptions will be examined using residual and influence diagnostics. If there is clear evidence of severe non-normality or heteroskedasticity, we will repeat the analysis with *clubSandwich* (R package) robust standard errors as a sensitivity (clustered by participant for repeated measures). In all cases, the target estimand remains the adjusted mean difference on the original scale.

Reporting, baseline imbalance & multiplicity

For each endpoint we will report point estimates with 95% confidence intervals and exact *p*-values (to three decimals rounded up, e.g. $p < .001$ for a value of $p = .0009$, or $p = .054$ for $p = .0544$).

Baseline comparability will be described, not tested (randomisation *could* lead to imbalance – which is simply the random nature of randomisation). We will present absolute standardised differences for baseline variables by arm; values that seem unusually large will be flagged as potentially meaningful chance imbalances that may inform covariate-adjusted or sensitivity analyses without changing the estimand.

We will not apply a formal correction for doing multiple/many tests when drawing our main conclusions. Secondary and exploratory findings will be treated as supportive rather than definitive. To be transparent about the risk of chance positives (Type 1 error), we will also report *q*-values for the secondary outcomes. These are multiple comparison adjusted *p*-values (using the via the *qvalue* R package). We will calculate them separately for each time point: all secondary outcomes at T3 as one set (family) and all at T4 as another; this will give us a sense of the risk of Type 1 error given the large number of tests.

Scale reliability

As is standard in psychological research, to provide some confirmation of the internal reliability of our multi-item scales, we will report internal consistency for each scale at every time point. Cronbach's α and McDonald's ω will be estimated with 95% bootstrap CIs (1000 resamples), pooled across arms per time point and by arm at baseline. Thresholds of 0.70 will be considered ac-

ceptable, 0.80 good, and 0.90 excellent. For the 3-item CCAE we will also report the mean inter-item correlation, with 0.20-0.50 indicating adequate coherence.

Missing data

See Section 15 for example R code snippets.

Primary analyses will use all available data in a linear mixed model for repeated measures. Each participant can contribute up to three post baseline BRS observations at T2, T3 and T4. The primary estimand is the adjusted between group difference in mean BRS at T3, but the model will include BRS at T2, T3 and T4 with a random intercept for participant to account for the within student correlation over time.

Scoring follows the rules set out above (Outcomes section). If a scale cannot be scored at a given time point it will be set to missing for that outcome and time. Primary mixed model analyses will assume that outcome data are missing at random (MAR) given observed outcomes and covariates included in the model. We will describe the pattern and predictors of missingness to assess the plausibility of this assumption by:

- summarising response rates by arm and time;
- tabulating stated reasons for non completion where available; and
- comparing key baseline characteristics and earlier outcome values (for example BRS at T1 and T2) between participants who do and do not provide BRS at T3 and T4, including logistic regression models with missingness indicators as outcomes and baseline variables and earlier outcomes as predictors.

These checks cannot prove MAR, but they will highlight strong associations between non response and poorer prior outcomes, which would make MAR less plausible. As sensitivity analyses, we will perform:

- Multiple imputation (MI) of missing outcome values under MAR, using models that include outcomes at all time points, randomised group, and key baseline covariates (for example baseline BRS, age, gender, medical school, and baseline values of secondary outcomes where relevant). Imputation will be carried out separately by randomised arm and will respect the type of each outcome (for example appropriate models for continuous, binary or count data). The MI analysis will mirror the primary model and combine estimates across imputations using Rubin’s rules.
- Pattern mixture “worse than MAR” scenarios were we apply fixed negative offsets (‘delta adjustments’) of 0.10, 0.20 and 0.30 BRS points to

imputed BRS values for participants who are missing at T3 or T4. These deltas represent increasingly pessimistic departures from MAR, with 0.10–0.30 BRS points corresponding to roughly 0.15–0.45 standard deviations given the expected BRS SD of about 0.7–0.9. This places the sensitivity range in the small to moderate effect size region and is consistent with recommendations to explore clinically plausible departures rather than extreme scenarios.

- A last post baseline carried forward (LPCF) analysis, where the most recent observed post baseline value is carried forward to replace a missing endpoint (T3 carried forward to T4 if T4 is missing, T2 carried forward to T3 or T4 if T3/T4 are missing; if no post baseline value exists, baseline is carried forward). This represents a conservative missing not at random scenario where outcomes are assumed not to improve after dropout.

Results will be considered robust if the direction and magnitude of the primary T3 BRS effect are broadly consistent across the primary mixed model analysis and these sensitivity analyses.

If the sensitivity analyses find materially different conclusions (for example, the primary analysis suggests significant benefit but one or more sensitivity analyses do not, or vice versa), we will present all results transparently and interpret the primary finding with appropriate caution. In such cases, we will examine which assumptions are most plausible given the observed missingness patterns and baseline predictors of dropout, and will discuss the range of pausbile treatment effects rather than relying on a single estimate.

Primary Analysis

See Section 15 for example R code snippets.

- **Model & outcome**

The primary outcome is BRS at T3, scored as the mean of the six BRS items (range 1–5) at the T3 assessment window (12–24 weeks). Each participant can contribute up to three post-baseline BRS measurements at T2, T3 and T4.

The primary analysis will use a linear mixed model for repeated measures (MMRM) with BRS at T2, T3 and T4 as the repeated outcome and baseline BRS (T1) included as a covariate. The primary contrast is the adjusted between-group difference in mean BRS at T3 (Thumos minus services as usual) estimated from this model.

T4 occurs after T3, but including BRS at T2 and T4 in the model does not change the definition of the primary outcome. The MMRM jointly models the mean trajectory over time and the within-participant correlation structure; it does not “use future data to predict past outcomes” in a causal sense. It allows all available post-baseline BRS data to contribute to estimation and gives an efficient and unbiased estimate of the T3 treatment contrast under the missing-at-random assumptions described in the missing data section.

- **Specification**

Fixed effects will include:

- treatment group (Thumos vs services as usual)
- categorical time (T2, T3, T4)
- treatment-by-time interaction
- baseline BRS (T1)
- baseline covariates: age, gender, and medical school

Baseline BRS is expected to be strongly predictive of BRS at T3 and later, so adjusting for it will increase the precision (power) of the treatment effect estimate. Age, gender and medical school are pre-randomisation characteristics that may also be associated with BRS and with missingness. Including them also improves precision and supports a more plausible missing-at-random mechanism by conditioning on key baseline predictors. Randomisation already protects against confounding, so not adjusting for these covariates would not bias the treatment effect, but it would generally mean less precise estimates and give weaker control for systematic differences in follow-up and response.

The model will include a random intercept for participant to account for clustering of repeated BRS scores within students. The within-subject covariance for the residuals at T2–T4 will be specified as unstructured in the primary analysis, allowing each time-specific variance and each covariance to be estimated freely. If this model fails to converge, we will use a more parsimonious structure, such as first-order autoregressive [AR(1)], in which correlations between two measurements on the same participant decline geometrically with the time lag between them (for example, corr[T2,T3] > corr[T2,T4]).

Degrees of freedom for tests and confidence intervals for fixed effects will be obtained using the Satterthwaite approximation.

- **Diagnostics & reporting**

Model assumptions will be checked using:

- residual plots (fitted values vs residuals) and Q–Q plots for normality

- assessment of influential observations and fit indices (for example AIC/BIC)
- inspection of estimated covariance parameters (including whether simpler structures such as AR(1) provide an adequate fit)

If serious departures from assumptions are detected, we will report their impact through pre-specified sensitivity analyses (for example, models with robust standard errors or alternative covariance structures).

We will report:

- adjusted marginal means for BRS at T3 in each arm
- the adjusted mean difference at T3 (Thumos minus control) with 95% confidence interval and p-value
- a standardised effect size (Cohen's d) with 95% confidence interval, calculated using the model-based marginal SD for BRS at T3

Cohen's *d* is reported to provide a scale-free measure of the treatment effect that is comparable across studies and outcomes, and to link directly to the effect size used in the sample size calculation (target $d \approx 0.5$) and to the interpretation of clinical importance described in the estimands and sample size sections. The primary inference, however, is based on the adjusted mean difference and its confidence interval on the original BRS scale.

Additional Analyses

See Section 15 for example R code snippets.

Secondary outcomes efficacy analysis

All continuous secondary outcomes will be analysed using the same repeated measures framework as the primary analysis. Each participant can contribute outcome values at T2, T3 and T4 (with baseline included as a covariate), and the primary focus for each outcome will be the adjusted between group difference at T3, with T4 estimates reported descriptively and inferentially as secondary, specifically:

For CCAE, OLBI total and subscales, PHQ-9 and ReQoL-UI utility scores, we will fit linear mixed models for repeated measures with:

- fixed effects for treatment group, categorical time (T2, T3, T4), treatment-by-time interaction, baseline value of the outcome, and baseline covariates (age, gender, medical school);
- a random intercept for participant;
- unstructured within-participant covariance (with AR(1) as a fallback if required).

- For each outcome we will report adjusted marginal means by arm at T3 and T4, adjusted mean differences with 95% CIs and p values, and standardised mean differences (Cohen's d) with 95% CIs.

For the two sickness absence items (count of days lost from work or study in the past 4 weeks), we will treat T2, T3 and T4 as repeated measures and fit generalised linear mixed models with a log link:

- Poisson mixed models will be used initially; if over dispersion is evident we will use negative binomial mixed models.
- Fixed effects will include treatment group, time, treatment-by-time interaction, and baseline covariates as above, with a random intercept for participant.
- We will present adjusted incidence rate ratios (IRRs) comparing Thumos to services as usual at T3 and T4 with 95% CIs.

For the four support access indicators (any vs none), measured at T2–T4, we will use mixed effects logistic regression with:

- fixed effects for treatment group, time, treatment-by-time, baseline covariates;
- participant random intercept.
- We will report odds ratios for Thumos vs services as usual at T3 and T4 with 95% CIs.

Quality adjusted life years (QALYs) will be derived from ReQoL-UI utility scores measured at baseline, T2, T3 and T4. For each participant we will:

- obtain utility values at each time point from the ReQoL-UI algorithm;
- linearly interpolate between observed utilities over time;
- compute the area under the utility–time curve from baseline to T4 and divide by the relevant time horizon (in years), giving QALYs accrued over baseline to T4. This follows standard practice for trial based QALY estimation using area under the curve with linear interpolation (DOI: 10.1002/hec.944).

We will then analyse QALYs using linear regression, with QALYs from baseline to T4 as the dependent variable and:

- treatment group as the main predictor;
- baseline ReQoL-UI utility and the same baseline covariates as the primary analysis (age, gender, medical school) as adjustment variables.
- We will report the adjusted mean difference in QALYs (Thumos minus services as usual) with 95% CI.

Clustering

Randomisation is at the individual level, but Thumos is delivered in therapist led groups. The primary models do not include therapist effects. As a sensitivity analysis we will refit the primary BRS model and key secondary outcome models with an additional random intercept for therapist in the Thumos arm (and, where feasible, fixed effects for medical school), to assess robustness of the treatment effect estimates to potential clustering by therapist.

Adherence (PP + CACE only)

- **Per protocol (PP)**

We will repeat the primary analysis in the per protocol set, defined in line with the estimand section (for example excluding major protocol deviations and participants in the Thumos arm who do not complete both workshops and the one to one session within the protocol window, and requiring a valid T3 BRS).

- **Complier average causal effect (CACE)**

We will estimate CACE (see: doi: 10.1080/01621459.1996.10476902; doi: 10.1191/0962280205sm403oa; doi: 10.1093/biostatistics/kxx029) for BRS at T3 using two-stage least squares with randomisation as the instrument for a binary *full receipt* indicator (completed both workshops + one-to-one within window).

- Stage 1: model the probability of full receipt as a function of randomised group and baseline covariates (baseline BRS, age, gender, medical school).
- Stage 2: regress BRS at T3 on the predicted probability of full receipt from Stage 1 and the same baseline covariates; the coefficient of the predicted receipt term estimates the local average treatment effect among compliers.

We will report the local average treatment effect (point estimate and 95% CI), the first stage F statistic as a measure of instrument strength, and the estimated complier proportion. The key instrumental variable assumptions (independence of allocation and potential outcomes, exclusion restriction, monotonicity) will be stated and considered in interpreting the CACE estimate.

Safety

We will summarise adverse events (AEs) and serious adverse events (SAEs) descriptively by randomised arm, reporting:

- the number and proportion of participants with at least one AE and at least one SAE in each arm;
- risk differences with 95% CIs;
- narrative summaries by event category and seriousness.

SAP Reporting Checklist

In accordance with:

Gamble C, Krishan A, Stocken D, Lewis S, Juszczak E, Doré C, Williamson PR, Altman DG, Montgomery A, Lim P, Berlin J, Senn S, Day S, Barbachano Y, Loder E. Guidelines for the Content of Statistical Analysis Plans in Clinical Trials. JAMA. 2017;318(23):2337-2343.

Section/Item	Index	Checklist description as written	How addressed
Section 1: administrative information			
Trial and trial registration	1a	Descriptive title that matches the protocol, with SAP either as a forerunner or subtitle, and trial acronym (if applicable)	A randomised controlled evaluation of Thumos: a cognitive-behavioural intervention for medical students Acronym: ACTIVATE
	1b	Trial registration number	ISRCTN: 12744098 REC reference: 2024-21589-38791
SAP version	2	SAP version number with dates	Version 0.6, dated 16/12/2025
Protocol version	3	Reference to version of protocol being used	Protocol version 5, dated 5th June 2025
SAP revisions	4a	SAP revision history	See version history section below
	4b	Justification for each SAP revision	See version history section below
	4c	Timing of SAP revisions in relation to interim analyses, etc.	N/A (no interims planned)
Roles and responsibility	5	Names, affiliations, and roles of SAP contributors	SAP author: Dr Luke Budworth TSC independent statistician: Prof Mona Kanaan Chief Investigator: Dr Judith Johnson

			Trials Co-Investigator: Dr Chris Taylor Sponsor: University of Manchester Funder: MPS Foundation
Signatures	6a	Person writing the SAP	Dr Luke Budworth
	6b	Senior statistician responsible	Prof Mona Kanaan
	6c	Chief investigator/clinical lead	Dr Judith Johnson
Section 2: introduction			
Background and rationale	7	Synopsis of trial background and rationale including a brief description of research question and brief justification for undertaking the trial	Evaluate whether Thumos improves resilience and related outcomes in UK medical students in clinical years (see trial protocol for full detailed rationale)
Objectives	8	Description of specific objectives or hypotheses	Primary: effect on resilience (BRS) at 4 months (T3). Secondary: effects on e.g. coping, burnout, depression, sickness absence (and others) at T3 and T4. Main hypothesis: adjusted mean difference at T3 corresponding to Cohen's *d* around 0.5
Section 3: study methods			
Trial design	9	Brief description of trial design including type of trial (e.g., parallel group, multi-arm, crossover, factorial) and allocation ratio and may include brief description of interventions	Two-arm, parallel-group superiority RCT; 1:1 individual randomisation to Thumos vs service as usual. Data at T1 baseline, T2 around 6 weeks, T3 4 months (primary), T4 9 months. All questionnaires online via Qualtrics

Randomisation	10	Randomization details, e.g., whether any minimization or stratification occurred (including stratifying factors used or the location of that information if it is not held within the SAP)	Simple 1:1 via Sealed Envelope. Allocation sequence generated and held by platform. Revealed post-consent and post-baseline only
Sample size	11	Full sample size calculation or reference to sample size calculation in protocol (instead of replication in SAP)	Target = 220 (110 per arm). Power simulated in *powerlmm*
Framework	12	Superiority, equivalence, or noninferiority hypothesis testing framework, including which comparisons will be presented on this basis	Superiority
Statistical interim analysis and stopping guidance	13a	Information on interim analyses specifying what interim analyses will be carried out and listing of time points	No interim analyses planned
	13b	Any planned adjustment of the significance level due to interim analysis	N/A
	13c	Details of guidelines for stopping the trial early	N/A
Timing of final analysis	14	Timing of final analysis, e.g., all outcomes analysed	Final analysis after follow-up completion and data lock. Analyst unblinds only after SAP

		collectively or timing stratified by planned length of follow-up	sign-off, code complete and reviewed and dataset locked
Timing of outcome assessments	15	Time points at which the outcomes are measured including visit “windows”	T2 4-10 weeks; T3 12-24 weeks; T4 30-44 weeks
Confidence intervals and p values	16	Level of statistical significance	Primary inference: two-sided α of .05 for BRS at T3, though estimates will have 95% CI and we aim to emphasise estimation over dichotomous significance
	17	Description and rationale for any adjustment for multiplicity and, if so, detailing how the type 1 error is to be controlled	No formal multiplicity adjustment. For transparency we will provide 95% CIs and Benjamini–Hochberg *q* values for secondary endpoints
	18	Confidence intervals to be reported	We will report 95% CIs for *all* estimates
Adherence and protocol deviations	19a	Definition of adherence to the intervention and how this is assessed including extent of exposure	Minimum adherence definition for the analysis: Thumos participants attend both workshops and complete one-to-one within 6 weeks of randomisation with at least 75 percent attendance per session. Control arm: no Thumos component
	19b	Description of how adherence to the intervention will be presented	Presentation: PP analysis excludes non-adherent Thumos participants and major deviations. CACE estimated via instrumental variables with randomisation as instrument
	19c	Definition of protocol deviations for the trial	Deviations defined as minor vs major. Major: invalid consent or ineligibility, allocation error or concealment breach, any Thumos in control, no valid T3 BRS in window, data integrity issues

	19d	Description of which protocol deviations will be summarized	Deviations logged and summarised by type/arm before unblinding
Analysis populations	20	Definition of analysis populations, e.g., intention to treat, per protocol, complete case, safety	Full analysis sample (FAS/ITT): all randomised, analysed as allocated. PP: FAS excluding major deviations and non-compliers, requires valid T3 BRS. CACE: all randomised with binary *full receipt* instrumented by allocation
Screening data	21	Reporting of screening data (if collected) to describe representativeness of trial sample	See protocol: screening data plan is documented in the protocol, not the SAP
Eligibility	22	Summary of eligibility criteria	UK medical students in clinical placement years meeting inclusion criteria (see protocol)
Recruitment	23	Information to be included in the CONSORT flow diagram	Screened if applicable, randomised, received intervention, follow-up at T2–T4, analysed, with reasons for non-participation and loss (see protocol for shell)
Withdrawal or follow-up	24a	Level of withdrawal, e.g., from intervention and/or from follow-up	We will summarise withdrawal from intervention and from follow-up by arm and time
	24b	Timing of withdrawal/lost to follow-up data	T2, T3, T4 windows
	24c	Reasons and details of how withdrawal/lost to follow-up data will be presented	We will list and summarise descriptively in CONSORT and missing data summary
Baseline patient characteristics	25a	List of baseline characteristics to be summarized	Age, gender, year of study, medical school, baseline outcomes (BRS, OLBI, PHQ-9, ReQoL-UI, CCAE), and any other variables pre-specified in the protocol

25b		Details of how baseline characteristics will be descriptively summarized	Continuous = mean/SD or median/IQR if skewed; categorical = n/%. Absolute standardised differences between arms. We will not *test* for baseline imbalance but assess magnitude of differences of the above
Section 6: analysis			
Outcome definitions	26a	Specification of outcomes and timings. If applicable include the order of importance of primary or key secondary end points (e.g., order in which they will be tested)	Primary outcome: BRS at T3. Secondary: BRS at T4; CCAE at T3 and T4; OLBI total and subscales at T3 and T4; PHQ-9 at T3 and T4; ReQoL-UI utilities at T3 and T4; QALYs baseline to T4; sickness absence counts at T3 and T4; support access any vs none at T3 and T4
	26b	Specific measurement and units (e.g., glucose control, hbA1c [mmol/mol or %])	BRS mean score; CCAE mean score; OLBI subscale and total means; PHQ-9 total; ReQoL-UI utility index; QALYs from utilities; sickness absence days in past 4 weeks (2 separate related items, to be analysed separately); support access binary indicators (four, to be analysed separsately)
	26c	Any calculation or transformation used to derive the outcome (e.g., change from baseline, QoL score, Time to event, logarithm, etc.)	Scores will be generated as per each measure's guidelines. If not specified, we will only compute the scale when more than 79% items are present using mean across items after reverse scoring; otherwise = missing for that time point. ReQoL-UI utilities via algorithm; QALYs by area under utility time curve with linear interpolation
Analysis methods	27a	What analysis method will be used and how the treatment effects will be presented	Primary: mixed models for repeated measures (REML) on T2–T4 with T1 as covariate. Estimate adjusted Thumos vs SAU difference at T3 with 95% CI and *p* value; report Cohen's *d*. Continuous secondary endpoints mirror this. For other secondary outcome/endpoint types:

			counts = Poisson/negative binomial with adjusted incidence rate ratios, binary = mixed effects logistic regression with adjusted odds ratios, QALYs = linear regression adjusting for baseline ReQoL-UI and the same covariates as the primary analysis
	27b	Any adjustment for covariates	Baseline outcome, age, gender, medical school if recorded
	27c	Methods used for assumptions to be checked for statistical methods	We will examine model residuals, QQ plots, influence statistics, information criteria. If clear non-normality or heteroskedasticity, we will repeat with cluster robust SEs via *clubSandwich* as sensitivity analyses
	27d	Details of alternative methods to be used if distributional assumptions do not hold, e.g., normality, proportional hazards, etc.	Alternatives if assumptions fail in mixed modelling include using AR(1) as a fallback if unstructured covariance leads to non-convergence; Poisson to negative binomial if over-dispersion (for count secondary outcome); and we will examine robust SEs as above if basic model diagnostics fail
	27e	Any planned sensitivity analyses for each outcome where applicable	Sensitivity analyses: multiple imputation using outcomes at all times and key baseline covariates; pattern-mixture worse than MAR deltas 0.10, 0.20, 0.30; PP analysis; therapist clustering sensitivity; CACE instrumental variables analysis
	27f	Any planned subgroup analyses for each outcome including how subgroups are defined	None prespecified for efficacy. Therapist and medical school effects only in clustering sensitivity (as above)
Missing data	28	Reporting and assumptions/statistical methods to handle missing data (e.g., multiple imputation)	Primary analyses use all available data which is valid if missing at random (MAR) given observed outcomes and covariates. We will summarise response rates by arm and time; describe reasons where known;

			compare key baseline characteristics between completers and non-completers descriptively. Sensitivity: multiple imputation and pattern mixture deltas as above.
Additional analyses	29	Details of any additional statistical analyses required, e.g., complier-average causal effect10 analysis	We will estimate CACE via two stage least squares with randomisation as instrument for a binary full receipt indicator. We will report local average treatment effect, 95% CI, first stage *F* statistic, and the estimated complier proportion. To assess clustering sensitivity we will add a therapist random intercept in Thumos arm and medical school fixed effects, or treat both as fixed if random effects unstable
Harms	30	Sufficient detail on summarizing safety data, e.g., information on severity, expectedness, and causality; details of how adverse events are coded or categorized; how adverse event data will be analysed, i.e., grade 3/4 only, incidence case analysis, intervention emergent analysis	Harms and safety reporting are specified in the protocol
Statistical software	31	Details of statistical packages to be used to carry out analyses	Primary analyses in R. Stata used for cross checking where useful. All code version controlled
References	32a	References to be provided for non-standard statistical methods	All methods standard in trials (packages commonly used and available on CRAN)
	32b	Reference to Data Management Plan	N/A

	32c	Reference to the Trial Master File and Statistical Master File	N/A
	32d	Reference to other standard operating procedures or documents to be adhered to	N/A

Example R code snippets

	R code snippet

Libraries	`## libraries`
	
	`core   <- c("dplyr","tidyr","lme4","lmerTest","mice")`
	`extras <- c("em-`
	`means","broom","broom.mixed","gtsummary","readr",`
	`"lubridate","jani-`
	`tor","ggplot2","qvalue","psych",`
	`"clubSandwich","influence.ME","car","AER","pan")`
	
	`pkgs <- c(core, extras)`
	`to_install <- setdiff(pkgs, rownames(installed.packages()))`
	`if (length(to_install)) install.packages(to_install)`
	
	`invisible(lapply(core,   require, character.only = TRUE))`
	`invisible(lapply(extras, require, character.only = TRUE))`

Timepoints data prep	`# assuming df$timepoint is weeks since baseline (numeric)`
	
	`dat <- df %>%`
	`  mutate(`
	`    weeks = as.numeric(timepoint),`
	`    time_f = case_when(`
	`      weeks >=  4 & weeks <= 10 ~ "T2",`
	`      weeks >= 12 & weeks <= 24 ~ "T3",`
	`      weeks >= 30 & weeks <= 44 ~ "T4",`
	`      TRUE ~ NA_character_`
	`    ) |> factor(levels = c("T2","T3","T4")),`
	`    therapist_f = factor(therapist),`
	`    treat       = factor(treat),`
	`    miss_T3     = as.integer(time_f == "T3" & is.na(out-`
	`come)),`
	`    miss_T4     = as.integer(time_f == "T4" & is.na(out-`
	`come))`
	`  ) %>%`
	`  filter(!is.na(time_f)) %>%`
	`  select(pid, outcome, treat, weeks, time_f, baseline, ther-`
	`apist_f, miss_T3, miss_T4)`

Mixed model examples	`# continuous outcome`
	
	`fit_cont <- lmer(outcome ~ treat * time_f + baseline + ther-`
	`apist_f + (1 | pid), data = dat, REML = TRUE)`
	
	`# binary outcome`
	
	`fit_bin  <- glmer(outcome ~ treat * time_f + baseline +`
	`therapist_f + (1 | pid), data = dat, family = binomial())`
	
	`# counts`

	`fit_pois <- glmer(outcome ~ treat * time_f + baseline + therapist_f + (1 | pid), data = dat, family = poisson(link = "log"))`

Missing data (MI + pattern mixture) example	`meth <- make.method(dat)`
	`pred <- make.predictorMatrix(dat)`
	`pred[, "pid"] <- -2 # cluster id`
	`pred[, c("miss_T3","miss_T4")] <- 0`
	`meth[] <- ""`
	`meth["outcome"] <- "2l.pan"`
	
	`imp_mar <- mice(dat, m = 50, method = meth, predictorMatrix = pred, print = FALSE)`
	
	`# primary model, pooled with T3 as reference`
	`fit_mar <- with(imp_mar, {`
	`  time_f <- stats::relevel(time_f, ref = "T3")`
	`  lmer(outcome ~ treat * time_f + baseline + therapist_f + (1 | pid))`
	`})`
	`summary(pool(fit_mar), conf.int = TRUE, conf.level = 0.95)`
	
	`# delta: apply to imputed values at T3/T4 only`
	`apply_delta <- function(imp, delta = -0.20) {`
	`  L <- complete(imp, action = "long", include = TRUE)`
	`  is_imp <- L$.imp > 0`
	`  t3 <- is_imp & L$time_f == "T3" & L$miss_T3 == 1`
	`  t4 <- is_imp & L$time_f == "T4" & L$miss_T4 == 1`
	`  L$outcome[t3] <- L$outcome[t3] + delta`
	`  L$outcome[t4] <- L$outcome[t4] + delta`
	`  as.mids(L)`
	`}`
	
	`# example delta = -0.20 refit with T3 as reference`
	`imp_d20 <- apply_delta(imp_mar, delta = -0.20)`
	`fit_d20 <- with(imp_d20, {`
	`  time_f <- stats::relevel(time_f, ref = "T3")`
	`  lmer(outcome ~ treat * time_f + baseline + therapist_f + (1 | pid))`
	`})`
	`summary(pool(fit_d20), conf.int = TRUE, conf.level = 0.95)`

Multiplicity adjustment in *qvalue* package	`# BH method`
	`p_bh <- p.adjust(p, method = "BH")`
	
	`# Storey q values`
	`qobj <- qvalue::qvalue(p)`
	`q <- qobj$qvalues`

QALYs calculation example	`# df_util must have: pid, date, utility (from reqol-ui index)`
	
	`qaly <- df_util %>%`
	`  arrange(pid, date) %>%`
	`  group_by(pid) %>%`
	`  mutate(`
	`  dt_years = as.numeric(difftime(date, dplyr::lag(date), units = "days")) / 365.25,`
	`  area = ((utility + dplyr::lag(utility)) / 2) * dt_years`
	`  ) %>%`
	`  summarise(qaly = sum(area, na.rm = TRUE), .groups = "drop")`

Complier adjusted causal effect analysis	`## CACE at T3 using IV, with multiply imputed dataset`
	
	`.fit_iv_once <- function(dat) {`
	`  D <- data.frame(`
	`  Y = dat$outcome,`
	`  Z = dat$treat, # instrument: randomised allocation`
	`  D = dat$full_receipt, # endogenous: full receipt indicator`
	`  B = dat$baseline,`
	`  Th = dat$therapist_f,`
	`  T = dat$time_f`

	)
	D <- subset(D, T == "T3")
	# ivreg: Y ~ D + covars | Z + covars
	AER::ivreg(Y ~ D + B + Th | Z + B + Th, data = D)
	}
	
	# fit across imputations and pool
	
	fits_iv <- with(imp_mar, .fit_iv_once(data.frame(pid, out-
	come, treat, full_receipt, baseline, therapist_f, time_f)))
	sum_iv <- summary(pool(fits_iv), conf.int = TRUE,
	conf.level = 0.95)
	sum_iv # coefficient on D
	
	# 1st stage F statistic (instrument strength from the first
	imputation
	
	D1 <- complete(imp_mar, 1)
	D1 <- subset(D1, time_f == "T3")
	m1 <- lm(full_receipt ~ treat + baseline + therapist_f,
	data = D1)
	m0 <- lm(full_receipt ~ baseline + therapist_f, data
	= D1)
	fs <- anova(m0, m1) # partial F for treat given covari-
	ates
	fs # look at the F value in the sec-
	ond row
	
	# estimated complier proportion (receipt rate in treated at
	T3)
	
	comp_rate <- with(imp_mar, {
	d <- data.frame(treat, time_f, full_receipt)
	mean(d$full_receipt[d$time_f == "T3" & as.integer(d$treat)
	== 2], na.rm = TRUE)
	})
	mean(unlist(comp_rate$analyses))

Scale reliability analysis examples	# e.g. assuming items <- df %>% select(item1, item2, item3, item4, item5) # Cronbach's alpha with 95% CI via bootstrap (1000 itera- tions) alpha_boot <- psych::alpha(items, n.iter = 1000) alpha_boot$total$raw_alpha alpha_boot$boot.ci # McDonald's omega with 95% CI via bootstrap omega_boot <- psych::omega(items, nfactors = 1, n.iter = 1000, plot = FALSE) omega_boot$omega.tot omega_boot$omega_h omega_boot$boot.ci
Model diagnostics examples	# Residual diagnostics for mixed model fit <- lmer(outcome ~ treat * time_f + baseline + thera- pist_f + (1 | pid), data = dat, REML = TRUE) # Visual diagnostics par(mfrow = c(2,2)) plot(fit) # residuals vs fitted

	qqnorm(residuals(fit)); qqline(residuals(fit)) # Q-Q plot hist(residuals(fit), breaks = 30) # histogram plot(fitted(fit), sqrt(abs(residuals(fit)))) # scale-location # tests shapiro.test(residuals(fit)) # normality car::leveneTest(residuals(fit) ~ dat$treat * dat$time_f) # homoscedasticity # Influence diagnostics infl <- influence(fit, obs = TRUE) dfbetas_vals <- dfbetas(infl) cooks_d <- cooks.distance(infl) # influential observations threshold <- 4 / nobs(fit) influential_obs <- which(cooks_d > threshold) length(influential_obs)

Robust standard error model example	# CR2 variance estimator
	
	robust_vcov <- vcovCR(fit, cluster = dat$pid, type = "CR2")
	robust_test <- coef_test(fit, vcov = robust_vcov)
	
	# Compare original vs robust Ses
	
	comparison <- data.frame(
	  parameter = rownames(summary(fit)$coefficients),
	  orig_se = summary(fit)$coefficients[, "Std. Error"],
	  robust_se = robust_test$SE,
	  orig_p = summary(fit)$coefficients[, "Pr(>|t|)"],
	  robust_p = robust_test$p_Satt
	)
	comparison$se_ratio <- comparison$robust_se / comparison$orig_se
	print(comparison)
	
	# Robust confidence intervals for treatment effects
	
	conf_int_robust <- conf_int(fit, vcov = robust_vcov, level = 0.95)
	conf_int_robust[grep("treat", rownames(conf_int_robust)),]

Version history

Version	Date	Key changes
0.1	27/08/2025	
0.2	28/08/2025	Added completed checklist
0.3	03/09/2025	Modified in line with Christopher Taylor's comments (draft with comments kept) Modified to be more in line with previous published examples e.g. SleepWell and iMAPS-2 SAPs

		Included more background, specified more detail how to handle missingness in items on measures, clarified things such as missing data approaches, multiplicity adjustment, added code snippets, and added this version history section
0.4	25/09/2025	Modified after further feedback from Chritopher, Judith Johnson, and Lucy Pointon: • The handling of 'intercurrent 'events is narrower, with academic interruptions dropped, and external support is now only explored in sensitivity analyses rather than adjusted directly. • Support access, previously a listed secondary outcome, is no longer specified as such. • The PP/CACE compliance definition is relaxed so that only both workshops (≥75% attendance within 6 weeks) are required, whereas the one-to-one call is optional. • Missing-item rules are slightly stricter, reverting OLBI back to ≥7 of 8 items per subscale (max 1 imputation) rather than the older ≥6 with up to 2 imputations. • The primary model covariates are trimmed (dropping "year of study") and clustering sensitivity is simpler (therapist intercept only, without medical school effects). • Section wording is also more extensive, with greater emphasis on SOPs and guidelines.
0.5	15/11/2025	Modified after feedback from our independent statistician. Mainly clarifications, including:

		- Converting standardised effect sizes to real units to further justify sample size analysis - Added much more detail to sample size section - Clarified the use of multilevel models - Labelled tables and provided definitions - Added more clarity and corrections around handling missing item data for outcome measures - Rewritten the missing data section for clarity - Added more detail to analyses sections - Added more citations throughout to justify some of our decisions
0.6	16/12/2025	Addressed the following final comments from Mona, the trial independent statistician, namely: *“The motivation for the reliability analyses need to be captured earlier on before these are introduced in the statistical analyses.* *Under Missing data there are three strategies that are going to be explored, as Luke rightly points out the "Results will be considered robust if the direction and magnitude of the primary T3 BRS effect are broadly consistent across the primary mixed model analysis and these sensitivity analyses." My question is what happens if the methods were not broadly consistent.”*

Background references

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