Altering Dynamics of Autonomic Processing Therapy (ADAPT) Trial: A novel, targeted treatment for reducing anxiety in joint hypermobility

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Abstract:

**Background:** Hypermobility is a poorly-recognised and understood musculoskeletal disorder thought to affect around 20% of the population. Hypermobility is associated with reduced physiological and psychological functioning, quality of life, and is a known risk factor for the development of an anxiety disorder. To date no evidence-based, targeted treatment for anxiety in the context of hypermobility exists. The present intervention (ADAPT) is a novel therapy combining cognitive approaches from clinical health psychology targeting the catastrophisation of internal sensations, with bio-behavioural training improving autonomic trait prediction error.

**Method:** Eighty individuals with diagnosed hypermobility will be recruited and the efficacy of ADAPT to treat anxiety will be compared to an Emotion-Focused Supportive Therapy (EFST) comparator therapy in a randomised, controlled trial. The primary treatment target will be post therapy score on the Beck Anxiety Inventory and secondary outcomes will also be considered in relation to anxiety, depression, alexithymia, social and work adjustment, panic symptoms and dissociation. Due to COVID restrictions, the intervention will be moved to online delivery and qualitative assessment of treatment tolerance to online therapy will also be assessed.

**Discussion:** Online delivery of an intervention targeting anxiety would improve the quality of life for those experiencing anxiety disorder, and help the £11.7 billion that anxiety disorders cost the UK economy annually.

Keywords: Hypermobility, Anxiety, CBT, Interoception, RCT
Introduction

Hypermobility is a poorly-recognized and understood musculoskeletal disorder (1), affecting approx. 20% of the population (2). Hypermobile individuals are more likely to experience severe chronic widespread pain, have co-morbid rheumatic conditions (60%) (3) and dysautonomia (4). Generally, musculoskeletal disorders are associated with impairments in physical, psychological functioning and health-related quality of life (5) and work functioning (6). Therefore, the burden on quality of life can be substantial in those with hypermobility (7).

Symptomatic hypermobility is more prevalent, but less well-recognised and treated than inflammatory and other arthritides (1), accounting for up to 45% of general rheumatology outpatients referrals (estimated 900,000 attendances in 2014-2015 in England (NHS Digital, Hospital Outpatient Activity)) (8). A quarter of patients attending rheumatology clinics experience anxiety, higher than rates in other medical clinics (9). In-line with this, hypermobility is a risk factor for development (10) and presence of anxiety/panic (OR 4.39, OR 6.72) (11). This association has long been recognised (10-12). The health economic impact of hypermobility and anxiety is unknown but direct cost of anxiety disorders alone in the UK is £11.7 billion (13). As such, given the associated impairments people with musculoskeletal disorders experience, it is likely experiencing hypermobility and anxiety comorbidly may cost the UK a significant amount of money if adequate treatments are not found and many people with hypermobility may continually struggle with anxiety.
Treatment recommended for generalised anxiety disorder and panic disorder in adults is generally based on the principles of cognitive behavioural therapy (CBT) due to its associated effectiveness (National Institute for Health and Care Excellence). First, people should be educated about these disorders and offered self-help materials and/or psychoeducational groups. Where these do not lead to improvement, formal psychological therapies should be offered: CBT or applied relaxation for generalised anxiety disorder and CBT for panic disorder (NICE, 2019). Suggestions have been made that CBT may help people with hypermobility develop effective coping strategies, which can be linked to managing chronic pain, and work on cognitive distortions. One pilot study used a multidisciplinary rehabilitation program combining physical and cognitive-behavioral therapy for people with EDS/JHS and found significant changes in perceived performance of daily activities and self-perceived pain but impact on anxiety was not considered.

To date, no targeted treatments of anxiety exist for people with hypermobility. The brain-body mechanisms underlying this association have been explored in previous research and characterise these by aberrant autonomic control and central representation (i.e. autonomic trait prediction error). These mechanisms are grounded in theoretical models and offer a novel target for a pioneering interventional trial (proof of concept), providing deeper insight into psychophysiological mechanisms of anxiety and its alleviation in hypermobility, helping fill a substantial knowledge and service gap. Data will be used to support future funding bids, with associated impact on patient choice of treatment.
Choice of comparators

Given the evidence described for treating anxiety with cognitive behavioural principles, ADAPT (Altering Dynamics of Autonomic Processing Therapy) will combine cognitive approaches from clinical health psychology with bio-behavioural training (i.e. interoceptive training based on the work in (20). This work will target catastrophisation of internal sensations (22) and train participants to more accurately perceive their own heartbeats to reduce autonomic trait prediction error (i.e. to increase correspondence between measured changes in heart rate and subjective judgement of these changes) respectively. This active intervention will be compared to a control therapy which replicates therapist contact but is not focussed on interoception or cognitive behavioural approaches, i.e. emotion focussed supportive therapy (EFST). Past evidence suggests that EFST can lead to improvements in anxiety (23).

Objectives

The primary objective of this study is to assess the efficacy of ADAPT. We hypothesise that participating in ADAPT will lead to significantly reduced anxiety, and more substantive improvement compared to EFST. We also hypothesise that autonomic trait prediction error will be significantly reduced in ADAPT but remain unaffected in EFST.
Method

**Trial design**

The design is a single-blind, randomised controlled trial comparing two non-drug therapies for anxiety in hypermobility (ADAPT vs. EFST). We have used SPIRIT reporting guidelines (24) throughout this paper.

**Participants**

Participants will be recruited from the United Kingdom via online advertising and will be 18 years old or over, have lived experience of both joint hypermobility (score ≥/> 2 on the hypermobility self-report questionnaire OR a hypermobility related diagnosis (Joint Hypermobility Syndrome (JHS), Hypermobility Spectrum Disorder (HSD), Ehlers Danlos Syndrome (EDS)), and anxiety (score >16 on the Beck Anxiety Inventory). They will be free of other major psychiatric disorder except comorbid depression. Full inclusion and exclusion criteria are available in Table 1. Stable dose of medication (two months without change) and not currently receiving another form of talking therapy are inclusion criteria adopted to increase the validity of possible findings related to the non-drug therapies used.

[Insert table 1 here]

Interested participants will be initially contacted by the research team and sent a participant information sheet (PIS). If happy to proceed, a phone screening will take place to establish if the participant has met the inclusion criteria and then referred to a research psychologist to obtain informed consent and conduct the full study assessment measures (see Table 2 for full list of measures). Those who do not meet the criteria will be informed sensitively and referred on to other services where
clinically appropriate. The GP details will be noted during assessment and informed about participation for those eligible.

**Table 2: Outcome measures**

| Level of outcome | Outcome measures |
|------------------|------------------|
| Primary outcome  | Anxiety levels (BAI) |
| Secondary outcomes | Autonomic trait prediction error (measured from z score of objective signs of orthostatic intolerance – subjective symptoms of orthostatic intolerance) |
|                   | Interoception measures |
|                   | Presence/absence of psychiatric disorder as evidenced by M.I.N.I |
|                   | Psychiatric symptomatology as evidenced by scores on |
|                   | 1. Beck Depression Inventory |
|                   | 2. GAD-7 |
|                   | 3. PHQ-9 |
|                   | 4. Work and Social Adjustment Scale |
|                   | 5. Anxiety Sensitivity Index |
|                   | 6. Agoraphobic Cognitions Questionnaire |
|                   | 7. Safety Behaviours Questionnaire |
|                   | 8. Toronto Alexithymia Scale-20 |
|                   | 9. Dissociative Experiences Scale |
|                   | 10. Panic Disorder Severity Scale |
|                   | Feasibility measures of RCT (e.g., practicability, tolerability, willingness to be randomised) |

**Interventions**

Both intervention arms will be delivered by trained Clinical Psychologists. Patients in both treatment groups will receive 8 sessions lasting up to 90 minutes in duration (12 hours total). These sessions were completed weekly where possible.

**Emotion-focused Supportive Therapy (EFST).**

EFST is a manualised, non-directive therapy focusing on the emotional experience of the participant and the link emotions may have to events in their life. The intervention
focuses on building a safe therapeutic relationship, summarising, labelling and exploring emotions in sessions. As a non-directive therapy, participants can freely choose what is to be covered in each session. To control for the confound of homework in the ADAPT intervention arm, participants will also complete weekly homework diaries listing emotional responses to events in the week to be potentially discussed in the subsequent session. As a comparator therapy, the intervention does not include cognitive appraisals, or direct participants to the symbiotic relationship between thoughts and behaviours. EFST will not involve any interoception training.

[Insert table 3 here]

**Altering Dynamics of Autonomic Processing Therapy (ADAPT).**

With expert collaborators, cognitive approaches from health psychology (targeting catastrophisation of internal sensations ((22, 25, 26)) will be combined with bio-behavioural training to reduce *autonomic trait prediction error* (i.e. to increase correspondence between measured changes in heart rate and subjective judgement of these changes). Cognitive Behavioural principles will be used to address anxiety through structured sessions, problem identification, formulation and behavioural experiments. Sessions will focus on addressing beliefs and appraisals around anxiety and safety seeking behaviours, imagery rescripting, and homework tasks to be completed between sessions adapted from (Clark, Salkovskis et al. 1999). Participants will be allocated to one of four protocols detailed below (Table 3). Each week therapists will review homework tasks with participants to assess progress and intervention adherence. Interoception training will be conducted in five of the therapy sessions. Interoception training will be completed via a MATLAB platform on a laptop and will require participants to wear a pulse oximeter (NONIN), which will enable their
heartbeats to be recorded. Interoception training will involve two tasks; heartbeat tracking and heartbeat discrimination. In heartbeat tracking participants will be asked to count their heartbeats across a period of time across 6 trials (range 10-50 seconds). Participants will start using ‘Set B’ with trials in duration between 10 and 25 seconds. If the participants get 4 trials correct (within 3 beats of the actual answer) they change sets to ‘Set A’ with trials 25-50 seconds in duration. If participants get 4 trials 5 bests or more out on Set A, they reduce the next training back to Set B. In heartbeat discrimination, participants will be played their real heartbeat (10 beats) however the task randomly introduces a delay of 300ms in some of the trials. Participants will have to decide if the heartbeat they hear is in or out of sync with their actual heartbeat. Participants will complete 20 trials of the heartbeat discrimination task. After each trial, participants will be asked to make a confidence judgment on their response on a VAS ranging from 0 (not at all confident) to 100 (extremely confident). Participants will be informed after each trial the actual number of heartbeats in the trial, or whether the tone was in or out of sync with their actual heartbeat. They will then exercise for 2 minutes to raise their heart rate, and repeat both heartbeat tracking and heartbeat discrimination tasks.

**Outcome**

The primary outcome measure is the Beck Anxiety Inventory and secondary outcomes are the presence or absence of psychiatric disorder on the Mini International Neuropsychiatric Interview, the GAD-7, PHQ-9, work and social adjustment scale, Anxiety Sensitivity Index, Agoraphobic Cognitions Questionnaire, Safety Behaviours Questionnaire, Toronto Alexithymia Scale-20, Dissociative Experiences Scale, Panic Disorder Severity Scale (see Table 2). All psychological interview assessments will be
completed by trained Clinical Psychologists and research assessments by a trained Research Assistant. Qualitative interviews post-therapy will also be completed to assess treatment tolerance, and tolerance to therapy.

Sample size

A sample size of 80 is required. Based on previous experimental data (mean anxiety levels in hypermobile subjects (Beck Anxiety Inventory) 24.5 (sd 9.36)), this sample size is powered (90% power, 0.05 α) to detect a clinically meaning difference on BAI of 7.5 points (34 participants per group). To obtain good quality data to inform planning of a future definitive trial, a sample size of 35 per group is recommended, based on estimating the standard deviation of the primary outcome with good precision (20). Studies conducted by the applicant indicate an attrition rate of approx. 14% thus sample size of 40 per group will take this into account. In the event that a participant withdraws from the study, no further follow-up measures will be obtained.

Recruitment

Participants will primarily be identified through ethically approved advert. These adverts will be displayed at clinical sites and distributed via electronic and paper messaging boards/newsletters to potential participants, e.g. research small ads at University of Sussex and Facebook/Twitter accounts/newsletters of relevant patient/research organisations (e.g. via BSMS and partner universities, by funder (MQ: Transforming Mental Health), and by patient organisations (e.g. Hypermobility Syndromes Association, Ehlers Danlos UK). Where possible such electronic advertisement will use geo-targeting to the Sussex and wider South East area.
Potential participants will also be identified using the Sussex Partnership NHS Foundation Trust Research Network.

All further contact with potential participants will be via phone, email and post as described below and per potential participant preference.

Interested participants responding to the advert will then contact the research team (email/phone) and be sent (email/post) an appropriate for phase Participant Information Sheet (PIS) inviting them to contact the research team (email/phone) for further information. A trained member of the research team will then conduct a basic telephone screening to check if potential participants meet inclusion criteria for the study. If participants are deemed eligible to take part in the study they will be invited to take part in the Study Assessment by a study Clinical Psychologist. Informed consent will be collected prior to undergoing assessment by a trained Research Assistant or a member of the research team.

Those who do not meet criteria will be informed sensitively by the research team and an explanation given. They will be signposted to relevant support organisations as appropriate and reassured that their routine clinical care will not be affected in any way.

**Treatment Allocation and Blinding**

Participants will be allocated to either ADAPT or EFST through the online randomisation service Sealed Envelope (https://www.sealedenvelope.com/). The randomisation protocol utilises minimisation with a random element (80% probability
of being allocated to the arm which minimises imbalance) and participants will be additionally stratified by gender and anxiety score (BAI ≤ 25 vs. > 25). The allocation sequence will not visible to the psychologists delivering the therapy. Allocation concealment will occur until the participant has been determined eligible for the intervention and Sealed Envelope reveals to the psychologists which treatment participants have been allocated. Therefore, randomisation will be conducted without any influence of the study team. Due to the nature of the intervention, the psychologists will not be blind to treatment group. Whilst they will not reveal to the participant whether the therapy is ADAPT or EFST, due to the nature of the interventions participants it is possible they will not be completely blinded to allocation. A Research Assistant will be blinded to condition when assessing treatment outcome and questionnaires will be completed without involvement from researchers.

**Data Collection**

The principal investigator will train the clinical research coordinators, research psychologists and research assistant in data collection, entering, coding and checking as appropriate. Outcome data will generally be collected data will be anonymised using participant ID. Weekly process data will be also collected and psychologists will access these prior to the therapy sessions starting. Data be accessible by the study team using a secure login. Interoception data will be collected securely and accessed by members of the study team. Objective signs of orthostatic intolerance will be assessed by the trained Research Assistant using a finometer (SMART MEDICAL). Where source data is collected on paper, including the hypermobility (at baseline) and MINI assessments (at baseline and end of treatment), an exact copy of the anonymised data will be manually input into the trial database by a named member of
the study team. The research assistant will code all data except treatment allocation group which will be entered by the principal investigator.

Participants will be reimbursed £20 and £25 at the start and end of therapy respectively for completion of trial assessments and to aid retention.

 Dropout or choosing to withdraw from the study will be recorded including reasons where given. Participants are free to withdraw at any point during the study and can request their previously collected data not to be used. Withdrawal or declining to participate will not affect their NHS care in any way, participants are informed of this in the participant information sheet. Participants may be withdrawn from the intervention if their clinical presentation changes in relation to exclusion criteria (e.g. being started on beta-blocker medication) or if their clinical condition requires urgent other treatment (e.g. if the participant develops a psychotic disorder). Withdrawn participants will not be replaced.

**Data management**

The study team will treat participant information with confidentiality at all times; data will be anonymised on held records and password-protected databases, participant ID numbers will be assigned, and data handling and storage will be fully compliant with the General Data Protection Regulation and the Data Protection Act. Therefore, personal information will be kept separate from the trial data. All members of the research team and any other individuals from collaborating Trusts or Universities involved in collecting, inputting, processing, using and sharing data will have had Information Governance Training. Data management will be a standard item on the agenda for both research team and steering group meetings. Behavioural data will be
collected on password protected computers and stored in link-anonymised data files. All data will be backed up to a central storage facility automatically, related to the University of Sussex. Paper files will be kept in locked cabinets.

For statistical analysis, the anonymised data will be downloaded onto password-protected computers. This will be accessible by the trial statistician and principal investigator.

**Statistical Methods**

Intention-to-treat analysis will be used and include all participants randomised (i.e. including those who drop out). The primary outcome will be the BAI which will be compared from baseline assessment to end of therapy. A linear mixed model will be used to test treatment effects, including group comparisons on mean scores of primary and secondary symptom outcome measures. The main effects of condition and time (i.e. repeated measurements) and their interactions will be examined. Effect sizes of any effects found will be calculated. A range of possible covariates will be investigated included baseline anxiety score, depression score, number of hypermobile features. Missing data will be explored and reported.

In accordance with the Oxford Clinical Trials Research Unit and the Medicines for Human Use Clinical Trials Regulations (2004), a Data Monitoring Committee has not been arranged because intervention occurs over a short period, the protocol will not be modified irrespective of data collected during the intervention and there are minimal risks to participants. No interim analyses are planned.
The independent Trial Steering Committee will help monitor safety (including adverse events), assess adherence to the study protocol, the statistical analysis plan, and oversee progress with data collection. Members include the trial statistician, the PI, the trial Consultant Clinical Psychologist, and independent expert and a patient representative. Data will be regularly audited by the principal investigator to check for possible errors and completeness. If participants or others have concerns regarding the trial conduct they are advised to contact Patient Advice and Liaison Service at Sussex Partnership NHS Foundation Trust. This is independent from investigator and sponsor.

**Patient and Public Involvement**

A Lived Experience Advisory Panel (LEAP) was formed via Sussex Partnership NHS Trust to engage patients and public in design of study, design of materials for ethical approval, and strategies for recruitment and dissemination.

**Adverse events and ethical issues**

Adverse events or effects will be monitored throughout the study. It is possible that a participant may evidence risk during the assessment or intervention, such as in relation to reported or likely significant to themselves or others. If so, risk will be assessed by the psychologists, discussed with the principal investigator and a supportive plan agreed. This could include informing the participant’s GP, informing appropriate authorities and/or signposting the participant for support where needed. If a serious adverse event occurs, if deemed potentially ‘related’ and/or ‘unexpected’ in relation to the administration of the research procedures, this will be reported to the
research ethics committee and sponsor in line with ethical approval. The sponsor (University of Sussex) has appropriate insurance in place.

The research tests that are conducted are not for diagnostic purposes and the examination should not be considered an alternative to a proper medical consultation. However, sometimes the joint examination, related assessments (heart rate and blood pressure), questionnaires or brain scans may suggest a clinically significant issue. If this is the case or the participant needs further tests, the GP will be contacted in the first instance. The GP will then contact the participant if further tests are required. If the participant has any concerns about this, they are invited to contact a member of research team. At the end of therapy, the psychologist will make an assessment of whether a further clinical intervention is required and if so refer to the relevant NHS team for assessment and ongoing management.

To ensure effective dissemination, the results will be published in appropriately selected peer-reviewed journals. Summaries of the findings will be published on the Brighton and Sussex Medical School website and links provided to publications. This will aid the dissemination of the research and data, both to other researchers and interested parties. Summaries will also be sent to participants who consented to receive this. Once the data collection and analysis are completed, fully anonymized data will be made freely available via an open repository such as Open Science Framework.

**Changes to method due to COVID-19:**
The study assessments will be moved from being completed at the Brighton & Sussex Medical School campus to online assessment (Qualtrics) due to COVID-19 quarantine restrictions. The interoception training will no longer be delivered via MATLAB on computers at Brighton & Sussex Medical School and rather has been developed as an app (Heartrater, CELL SOFTWARE). This app will be installed on a tablet device (Samsung Galaxy Tab A) which will be posted to participants adhering to government safety guidance. Participants will also receive a pulse oximeter (NONIN), which they will wear whilst it is connected to the tablet device via USB connection, to enable their heartbeats to be recorded. Participants will complete both therapies and interoception training in their own homes in a private space on a PC, laptop or smartphone with internet capabilities. Therapy resources will be shared via Zoom videoconferencing software using the secure university account and videocalls will be password protected. All tablet devices will be locked down using Miradore software to ensure participants can’t install interfering software and the study team can format the tablets remotely if needed. The Heartrater app data will only be accessible to the study team and will require a password to access the online data generated. No personally identifiable information will be stored with the data collected online. Heart rate measurements will not be collected via a finometer, and instead will be observed over videoconference using a pulse oximeter sent to participant with tablet.

**Discussion**

This is the first study to test a targeted intervention for people with hypermobility and anxiety. The study will investigate whether ADAPT or EFST are effective in reducing anxiety. The treatments will particularly be compared in relation to anxiety symptoms,
but also in terms of autonomic trait prediction error, interoceptive ability, psychiatric disorder, well-being and quality of life measures. While we expect both treatments will be beneficial, the results will help determine their relative effectiveness across the aforementioned outcomes. The trial will also investigate treatment tolerance for remote therapy which has been found to be effective in previous studies in anxiety and depression ((27)). An online format has the potential to increase access, and reduce the costs of providing evidence-based intervention to those in need.

**Declarations**

**Trial status**

Ongoing, recruitment began August 2020

**Acknowledgements**

The authors would like to acknowledge the assistance of Professor Sarah Garfinkel, Dr Lisa Quadt and Georgia Savage

**Authors' contributions**

JAE designed the study, led the proposal and protocol development. NG, JLLC, GD, HB and JD contributed to the protocol development. JC and GD were the trial therapists and contributed to adapting the protocol due to COVID-19. All authors read and approved the final manuscript. All authors meet criteria for authorship according to ICMJE

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Funding

This study underwent external peer-review and JAE was competitively awarded an MQ Versus Arthritis Fellowship (MQ17/19) to conduct this randomised clinical trial. Additional funding has been provided by Sussex Partnership NHS Foundation Trust. Neither the funders or study sponsor have had any role in the study design, management or analysis or interpretation of data, the writing of the report, or decision to submit for publication.

Availability of data and material

Anonymised datasets and associated material will be available on reasonable request to the corresponding author.

Ethics approval and consent to participate

Ethical approval of the research protocol was gained from London – Bloomsbury Research Ethics Committee on 4 January 2019 (reference: 18/LO/1920, IRAS project ID: 248326). This is protocol version 4, where changes have been approved by the sponsor, ethics committee and health research authority. Written, informed consent to participate will be obtained from all participants.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.
## Table 2: Inclusion and exclusion criteria

| Inclusion criteria | Exclusion criteria |
|--------------------|--------------------|
| **Age** | Adults aged 18 years or over | Participants under the age of 18 |
| **Capacity** | All participants must be able to give informed consent | Unable to give informed consent |
| **Joint hypermobility** | Diagnosis of hEDS/HSD/JHS OR Score of 2 or more on 5-point questionnaire to detect Joint Hypermobility | No Diagnosis of hEDS/HSD/JHS AND Score of 1 or less on 5 point questionnaire to detect Joint Hypermobility |
| **Anxiety** | Self-reported lived experience of anxiety disorder AND A score of 16 or more on Beck Anxiety Inventory endorsing moderate anxiety level AND Anxiety should be the primary psychiatric problem | No Self-reported lived experience of anxiety disorder OR A score of 15 or less on Beck Anxiety Inventory OR Anxiety is not the primary psychiatric problem |
| **Other psychiatric disorder** | No presence of major psychiatric disorder, except co-morbid depression | Presence of major psychiatric disorder (other than co-morbid depression) e.g. Bipolar Affective Disorder, Schizophrenia or Psychosis OR Personality Disorder (e.g. Emotionally Unstable Personality Disorder) OR Diagnosed Neurodevelopmental disorder such as Attention Deficit Hyperactivity Disorder or Autism Spectrum Condition OR Neurological disorder |
| **Medication use** | All participants should be on a stable dose of medication for 3 months OR Medication free AND Willing to consider omitting medication that directly affects heart rate (e.g. beta blockers) during the trial | Not on a stable dose of medication (or medication free) for 3 months |
| **Language** | All participants must have a reasonable level of both written and spoken English as therapies and assessments will be conducted in English | Poor level of both written and spoken English |
| **MRI safety** | All participants must be MRI safe (i.e. no non-removable metal work in body) and be able | MRI incompatibility (i.e. non-removable metal work in body) OR be unable to lie flat comfortably for one hour |
| Sessi on | GAD | Panic Disorder | Social Anxiety | Anxiety NOS |
|---------|-----|----------------|----------------|------------|
| One     | Problem identification, goals, formulation, psychoeducational, worry history outcome. | Problem identification, goals, formulation, Safety Seeking Behaviours (SSB), psychoeducational, panic diary. | Problem identification, goals, formulation, psychoeducational, socialise to video recording, focus of attention work, anxiety trigger diary. | Problem identification, goals, formulation, psychoeducational, problem-specific homework diary. |
|         | Interoception training | Interoception training | Interoception training | Interoception training |
| Two     | Evidence for beliefs, thought suppression, worry postponement. Worry free zones | Panic diary in formulation, SSB, downward arrow for threat beliefs, selective attention training | Review between session work, identify safety behaviours and avoidance, observer vs field perspective, attention training. | Review homework, socializing to model, belief identification, Theory A/Theory B. |
|         | Interoception training | Interoception training | Interoception training | Interoception training |
| Three   | Diaphragmatic breathing, challenge beliefs, positive behaviour scheduling. | Review formulation, BE relating to feared symptoms, symptom-induction, review BE and beliefs, Theory A/Theory B. | Manipulation of self-focused attention, plan and do BE (video/audio). | Review beliefs and SSB, threat versus coping, plan BE. |
|         | Interoception training | Interoception training | Interoception training | Interoception training |
| Four    | Progressive muscle relaxation, attention training, setting, behavioural experiment (BE). | BE, review beliefs, verbal reattribution, Theory A/Theory B. | BE feedback review, prediction versus outcome, explore feared consequences, BE planning. | BE, unhelpful thinking styles psychoeducational / survey work. |
|         | Interoception training | Interoception training | Interoception training | Interoception training |
| Five    | Introduction of the worry tree, | BE, review beliefs. | Review BE and beliefs, survey work. | Review BE, review goals and formulation. |
|   | Imagery re- scripting. | Interoception training | Interoception training | Interoception training |
|---|------------------------|------------------------|------------------------|------------------------|
| Six | o Continue BE, surveys and imagery work continued. | o BE, review beliefs and imagery. | o Widening the bandwidth experiments, review BE. | o Review BE, review goals and formulation, survey/unhelpful thinking styles work. |
| Seven | o Continue BE and exploration of beliefs in relation to cognitive formulation. | o BE, reappraise beliefs, imagery re-scripting. | o Review BE, imagery re-scripting, function of worry and rumination, BE. | o Review BE, imagery re-scripting. |
| Eight | o Interoception training | o Interoception training | o Interoception training | o Interoception training |
|   | o Conclusion of therapy, review goals, relapse prevention. | o Conclusion of therapy, review goals, relapse prevention. | o Conclusion of therapy, review goals, relapse prevention. | Conclusion of therapy, review goals, relapse prevention. |

Note. GAD = generalised anxiety disorder, BE = behavioural experiment, NOS = not otherwise specified, SSB = safety seeking behaviours
Appendices

Appendix 1 – Informed consent form

CONSENT FORM: ASSESSMENT (TRIAL)

Title of Project: ADAPT: A novel treatment for reducing anxiety in hypermobility (Trial Phase)

Name of Researchers: Dr Jessica Eccles, Dr Nick Grey, others TBA

1. I confirm that I have read the information sheet for ADAPT: A novel treatment for reducing anxiety in hypermobility (Trial Phase) dated 08/01/2019 (version 4) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.

3. I understand that my participation in the assessment is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

4. I understand that relevant sections of my data collected during the study, may be looked at by individuals from BSMS, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.

5. I understand that relevant sections of my data collected during the study, may be looked at by individuals from BSMS, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.

6. I understand that the assessment may find that I am not eligible for the ADAPT trial and that I may be referred for treatment to an appropriate service.

7. I understand that the information collected about me will be used to support other research in the future, and may be shared anonymously with other researchers.

8. I agree to any necessary exchange of information about me between my GP and the research team, including clinically significant findings.

9. I agree to the assessment being audio-recorded for research quality assurance purposes. I understand that these files will be kept securely and not linked to any personal data.

10. I agree to take part in the above assessment.
| Name of Participant | Date   | Signature |
|---------------------|--------|-----------|
| Name of Researcher  | Date   | Signature |

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