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Fetal alcohol spectrum disorder and attention deficit hyperactivity disorder stimulant trial in children: an N-of-1 pilot trial to compare stimulant to placebo (FASST): protocol

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ABSTRACT

Introduction Fetal alcohol spectrum disorder (FASD) is a neurodevelopmental disorder caused by alcohol exposure during pregnancy. FASD is associated with neurodevelopmental deviations, and 50%–94% of children with FASD meet the Diagnostic and Statistical Manual of Mental Disorders-fifth edition diagnostic criteria for attention deficit hyperactivity disorder (ADHD). There is a paucity of evidence around medication efficacy for ADHD symptoms in children with FASD. This series of N-of-1 trials aims to provide pilot data on the feasibility of conducting N-of-1 trials in children with FASD and ADHD.

Methods and analysis A pilot N-of-1 randomised trial design with 20 cycles of stimulant and placebo (four cycles of 2-week duration) for each child will be conducted (n=20) in Melbourne, Australia.

Feasibility and tolerability will be assessed using recruitment and retention rates, protocol adherence, adverse events and parent ratings of side effects. Each child's treatment effect will be determined by analysing teacher ADHD ratings across stimulant and placebo conditions (Wilcoxon rank). N-of-1 data will be aggregated to provide an estimate of the cohort treatment effect as well as individual-level treatment effects. We will assess the sample size and number of cycles required for a future trial. Potential mediating factors will be explored to identify variables that might be associated with treatment response variability.

Ethics and dissemination The study was approved by the Hospital and Health Service Human Research Ethics Committee (HREC/74678/MonH-2021-269029), Monash (protocol V6, 25 June 2023).

Individual outcome data will be summarised and provided to participating carers and practitioners to enhance care. Group-level findings will be presented at a local workshop to engage stakeholders. Findings will be presented at national and international conferences and published in peer-reviewed journals. All results will be reported so that they can be used to inform prior information for future trials.

Trial registration number NCT04968522.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The trial will assess the feasibility of the N-of-1 methodology by testing currently prescribed stimulants relative to placebo, with results allowing for evidence-informed shared clinical decision-making regarding stimulant prescription.
⇒ This individualised N-of-1 design will enable the investigation of interindividual variability in a heterogeneous population such as fetal alcohol spectrum disorder.
⇒ The study aims to include hard-to-reach regional participants and children in out-of-home care.
⇒ The 8-week N-of-1 trial requires significant time and effort to collect daily ratings, as well as a willingness to cease existing medication in the placebo phase, which might result in selection bias for selecting families.
⇒ Exclusion of medication-naive participants, children unable to swallow capsules and children who have ceased stimulants might result in selection bias but will mirror clinical care, increasing implementation readiness.

INTRODUCTION

Fetal alcohol spectrum disorder (FASD) is a diagnostic term for children who fulfil diagnostic criteria[1] and display a range of neurodevelopmental problems with confirmed alcohol exposure in utero. The prevalence of FASD is estimated to be 0.8% globally.[2] Prenatal alcohol exposure (PAE) causes early *brain injury* through teratogenic effects on the human fetus.[3] Effects of PAE can be identified immediately after birth, in infancy or later through childhood, due to the injury impacting skills, such as higher-level thinking and behavioural control that are expected as a child gets older. Impairments associated with FASD are long term;

however, they can be reduced with early identification and intervention.[4]

Attention problems are a hallmark feature of PAE. Between 50% and 94% of children with FASD meet the diagnostic criteria for attention deficit hyperactivity disorder (ADHD).[5 6] ADHD symptoms provide a target for intervention and a path to ameliorating secondary impairments. Methylphenidate and dexamphetamine are first-line pharmacotherapies for ADHD in children[7]; however, further research is needed to assess this intervention for ADHD in children with FASD. First, children with FASD plus ADHD have shown a preferential response to dexamphetamine over methylphenidate in a retrospective study.[8 9] Second, evidence for ADHD medication efficacy in FASD is limited to two prior randomised control trials of stimulants with small sample sizes (n=12 and n=4, respectively).[10 11] Authors of a recent systematic review concluded that current evidence is insufficient.[12] Third, children with ADHD and FASD demonstrate distinct attention profiles; children with FASD demonstrate greater difficulties in encoding and shifting relative to children with ADHD alone.[13] Encoding and shifting are reported to be vulnerable to heavier doses of PAE.[14] These differences suggest that ADHD may have a different clinical profile than FASD and, therefore, require targeted interventional studies.

Rationale for trial

N-of-1 trials provide an opportunity to provide a rigorous assessment of medicine efficacy and can help inform individualised treatment approaches. Highly controlled, randomised individual trials may be on par with a randomised controlled trial, which has traditionally been considered the gold standard to determine treatment efficacy.[15] N-of-1 trials have been successfully conducted to establish ADHD medication efficacy[16 17] but are yet to be used in the FASD population. Group treatment trials may fail to identify individual treatment response differences in this heterogeneous population. Additionally, stimulants show substantial interindividual variability in response, such that the dose must be titrated in the individual, incorporating clinical response.[18 19] Furthermore, existing studies in the FASD population have found significant within-subject variability ($F=4.02$, $df=4$ and $p<0.01$) potentially obscuring group treatment effects.[10] Data from our group identified that approximately 25% of children with FASD and ADHD are prescribed either stimulants or non-stimulants for ADHD symptoms, and 18% are prescribed multiple stimulants or stimulants and non-stimulants for ADHD symptoms.[20] Together, this points to a critical need to conduct high-quality research to inform individual treatment choices for ADHD in FASD, which is offered by N-of-1 methodologies.

Aim and objectives

The aim of the Fetal Alcohol Spectrum Stimulant N-of-1 Trial (FASST) is to conduct a series of N-of-1 trials for ADHD medication in children with ADHD and FASD to assess:

1. Feasibility and acceptability of N-of-1 trial methods and the FASST study design.
2. Preliminary effectiveness data to inform sample size, frequency and duration of intervention or placebo cycles for future studies.

Preliminary effectiveness data for each patient individually (N-of-1 trial data):

- Assessing the effectiveness of stimulants for each participant individually (N-of-1 trial data) by comparing symptoms of attention, hyperactivity and impulsivity as reported by teachers (primary outcome) between stimulant medication and placebo conditions.
- Evaluating the efficacy of stimulant medication (relative to placebo) on ADHD behaviours as reported by parents.
- Evaluating differences in functional impairment between stimulant medication and placebo conditions.
- Evaluating differences in parent-rated behaviours of concern between stimulant medication and placebo conditions.
- Comparing participant attention performance on stimulant medication relative to placebo.
- Recording adverse event (AEs) during the stimulant medication and placebo phases.
- Recording post-trial stimulant prescribing decisions made by the participant's carer and prescribing paediatrician after receiving N-of-1 trial data.

Group-level secondary objective:

- Exploring pooled N-of-1 data for estimates of the cohort treatment effect and individual-level treatment effects and exploring potential mediating factors.

METHODS AND ANALYSIS

Study design and duration

The clinical trial protocol conforms with the SPENT statement (online supplemental material 1; SPENT checklist).

This pilot study will trial the N-of-1 methodology in the FASD and ADHD populations. It consists of a series of N-of-1 trials of currently prescribed, encapsulated stimulants relative to placebo. Each N-of-1 trial is a randomised, placebo-matched, researcher-blinded and participant-blinded multiple cross-over trial in a single participant. Each 8-week N-of-1 trial will consist of four cycles of 2 weeks duration within which the intervention will be randomised to either active medication (A) or placebo (P) or PA, in which A is a stimulant and P is a matched placebo. Each stimulant or placebo period consists of 5 weekdays (Monday–Friday (M–F)) during school terms to enable teachers to report ADHD symptoms. Weekend schedules will accommodate drug pharmacokinetics. Methylphenidate has an elimination half-life of 2–3 hours in children,[18] thus would be cleared from the body after 10–15 hours. For dexamphetamine, children exhibit a shorter half-life than adults (typically 7 hours, cf 10–12 hours).[19] The drug would thus be cleared from the body between 35 hours and 2.5 days (the latter in

Table 1 Schedule of assessments for N-of-1 trial

	Pretrial		Postallocation								Post-Trial
Cycle			**Cycle 1**		**Cycle 2**		**Cycle 3**		**Cycle 4**		
Time point	**Baseline**	**Allocated**	**Week 1 (M–F)**	**Week 2 (M–F)**	**Week 3 (M–F)**	**Week 4 (M–F)**	**Week 5 (M–F)**	**Week 6 (M-F)**	**Week 7 (M-F)**	**Week 8 (M-F)**	
Intervention example sequences (sequence 1)			P	A	A	P	P	A	P	A	
Sequences 2–16			A	P	A	P	P	A	A	P	
Outcome	FASD diagnostic assessment, baseline demographics		Daily: **T**, P, WFIRS, TPA Weekly: SE	Daily: **T**, P, WFIRS, TPA Weekly: SE	Daily: **T**, P, WFIRS, TPA Weekly: SE	Daily: **T**, P, WFIRS, TPA Weekly: SE	Daily: **T**, P, WFIRS, TPA Weekly: SE	Daily: **T**, P, WFIRS, TPA Weekly: SE	Daily: **T**, P, WFIRS, TPA Weekly: SE	Daily: **T**, P, WFIRS, TPA Weekly: SE	Treatment decision

FASD diagnostic assessment: as per the Australian guide to the diagnosis of FASD (1). Bold letter indicates the main N-of-1 outcome, daily (M–F).
Note: this sequence listed is an example of one of the many possible sequences in the trial (randomly allocated).
FASD, fetal alcohol spectrum disorder; M–F, Monday–Friday; P, parent-rated Conners 3 early childhood; T, teacher-rated Conners 3 early childhood; TPA, top problems assessment; WFIRS, Weiss Functional Rating Scale.

teenagers and adults). Therefore, on weekends, children will commence usual medication for either 2 or 0 days (methylphenidate and dexamphetamine regimes, respectively) and either 0 or 2 days of washout (methylphenidate and dexamphetamine regimes, respectively).

The active drug and placebo will be encapsulated using the same opaque capsule product so that participants cannot distinguish the two visually. Where the active medication amount is small for the capsule, there will be additional Starcke 1500 (maize starch and pregelatinised maize starch) added to fill the capsule so that the active drug and capsule also weigh approximately the same. Participants will continue non-stimulant medication as usual and record particulars in the medication diary. The design of the trial is presented in table 1.

At trial completion, individual trial findings will be provided to the participant's family and paediatrician. At 3 months after receiving the trial results letter, paediatricians will be surveyed to examine the impact of trial findings on clinical decision-making. Individualised efficacy data could be used to explore whether further dose optimisation or trials of a different stimulant drug option would be worthwhile.

Outcome measures

Primary outcomes

The acceptability and feasibility of this individual trial design will be informed by several outcomes. Trial feasibility will include recording the number of people eligible for the study, recruitment rates, refusal rates, retention rates for recruited participants and response rates for study outcomes across teacher and parent ratings. Management and resource findings (data issues, resource requirements and budget) will be described. Adherence to the study drug and regime will be assessed via inspection of participant medication diaries and completion of outcome measures. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and calculated once for each participant. We will describe AEs across the trial and report relevant key information (eg, start date, stop date, severity, relationship, expectedness, outcome and duration). AEs leading to premature discontinuation from the trial intervention and serious treatment-emergent AEs will be detailed.

Secondary outcomes

The first secondary outcome is the severity of ADHD behaviours measured using the teacher version of the Conners 3 Short Form (S) (for children aged 6–18 years) and the Conners early childhood (EC) (for children aged 2–6 years).[21] Teacher ratings were chosen as the main individual outcome as they have been shown to more accurately predict FASD diagnosis than parent ratings.[22] Additionally, teachers observe the child over the course of the day so they are able to observe the rapid onset–offset action of stimulants. The Conners 3 (S) includes 41 items, which are a subset of the full-length form, including the content scales. The hyperactivity and inattentive subscales and the inattention/hyperactivity subscale will provide the data points for Conners inattention/hyperactivity 3 (S) and Conners EC, respectively. T scores are generated for age and gender and will be used as the primary outcome of interest. A higher T score is indicative of a greater expression of symptoms. A T score above 60 is considered clinically elevated. This measure has good reliability and validity for assessing ADHD symptoms in children. Test–retest values for the Conners (S) scales indicate excellent reliability, internal consistency (Cronbach's alpha=0.89) and reasonable temporal stability (ranging from 0.70 to 0.83

mean adjusted test–retest correlation).[21] The individual outcome measures and how they correspond to the study design are outlined in table 1.

Other secondary outcomes

Parent ratings of individual child-ADHD behaviours will be assessed using the hyperactivity and inattentive subscales and the inattention and hyperactivity subscales on the Conners 3 (S) and Conners EC, respectively, of the Conners 3 (S) and Conners EC, parent report (43 items).

The functional impact of ADHD symptoms will be measured using the Weiss Functional Impairment Rating Scale-Parent Report Form (WFIRS-P).[23] The instrument uses a Likert scale from 0 (never or not at all) to 3 (very often or very much). Higher ratings indicate worse functioning, and ratings over 2 are considered clinically impaired. Two of the six domains most salient to the study—family and school—will be captured in this trial. Family and school domain total scores will be used for the purposes of this analysis.

Parent's perception of participant challenges in relation to ADHD will be measured using the parent top problems assessment (TPA) ratings. The TPA is a brief, idiographic instrument to monitor concerns that are important from the perspective of the caregiver. The caregiver form has evidence of test–retest reliability, convergent and discriminant validity, and sensitivity to change during treatment.[24] The caregivers' three 'top problems' are identified at the initial interview prior to randomisation and are then repeatedly assessed via a brief, progress-monitoring rating scale. The severity of each problem is rated from 0 (not a problem) to 4 (a very big problem). Higher scores indicate greater difficulty.

The child's attention skills will be assessed using the Cambridge Neuropsychological Test Automated Battery (CANTAB)—attention and executive function tasks.[25] The spatial working memory (SWM) task requires the retention of visuospatial information. Stockings of Cambridge (SOC) measures executive function, strategy and errors. Between-search errors on the SWM task and SOC will be the outcome measures of interest.

We will monitor side effects using the Barkley Side Effects Rating Scale (17 symptoms; 0=absent; severity rated from 1 to 9). The total is calculated by summing all the items. Higher ratings indicate more adverse side effects. The most common side effects reported for methylphenidate and dexamphetamine on this measure in Australian samples are decreased appetite, sleep difficulties, not being happy and overly meticulous behaviour (mild or moderate severity).[26]

Post-trial treatment decisions will be measured using a survey capturing (1) changes in prescribed treatments for ADHD after the N-of-1 trial, (2) agreement between treatment decisions and the direction of the trial result, (3) implementation of non-pharmacological treatment plans and (4) satisfaction with N-of-1 trial.

Child baseline data

Child demographic (age and sex) data will be extracted from hospital medical records. Family background data will be coded from medical records: ethnic group, mother and child, family structure (custody) and socioeconomic status (postcode). Child ADHD subtypes (ADHD inattentive type, ADHD hyperactive-impulsive type and ADHD combined type) will be classified according to the Diagnostic and Statistical Manual of Mental Disorders (DMS)-related symptom count cut-offs as reported on the Conners 3 at baseline.

As per the Australian guide to the diagnosis of FASD,[1] baseline demographics (child age and sex), comorbidities (developmental diagnoses, including ADHD, autism spectrum disorder and learning difficulty) and neurodevelopmental functioning will be obtained through the Victorian fetal alcohol service (VicFAS) research database and/or medical record with consent. Neurodevelopmental impairment across the 10 domains assessed for the purposes of FASD diagnostic assessments will be categorised according to the level of impairment (none, mild, moderate and severe as per the FASD guide).[1] Children's overall level of neurodevelopmental impairment will be calculated by tallying the total number of domains assessed as significantly impaired (less than the third percentile on a standardised measure) against Australian FASD diagnostic criteria (0–10), including brain structure and neurology, motor skills, cognition, language, academic achievement, memory, attention, executive function, affect regulation and adaptive behaviour or social communication.

Study setting

Study medication will be couriered to the participants' homes and administered at the participants' homes or schools, as per the child's usual regime. All daily clinical measures will be completed online, via a web link, on paper or by phone, as nominated by the respondent. Child-attention measures will be completed at the participant's home or school via telehealth and online remote administration (according to the teacher's and parent's preference). Daily treatment compliance records will be administered in the home and school (if applicable) settings. Unused study medication will be returned to the trial pharmacy for secure destruction.

Study population

Participants will be children (aged 4–18 years) with both FASD and ADHD seen by the VicFAS team at Monash Children's Hospital, Melbourne, since September 2019 (recruited from February 2022) until recruitment close (8 weeks prior to recruitment close at the end of term 3, 2023 (September 2023, n=20). They are currently prescribed stimulant medication for ADHD symptoms with a confirmed diagnosis of FASD and ADHD. The age range specified is required due to the referral criteria of VicFAS. Inclusion and exclusion criteria are described in table 2.

Table 2 Inclusion and exclusion criteria

Inclusion	Exclusion criteria
► Paediatric patient of VicFAS (aged 4–18 years at the time of randomisation). ► Meet the diagnostic criteria for FASD or 'at risk' of FASD according to the Australian guide to the diagnosis of FASD. ► Have confirmed prenatal alcohol exposure. ► Meet the diagnostic criteria for ADHD (DSM-IV criteria). ► Be currently prescribed (for at least 1 month prior to trial start) a stimulant medication for the treatment of ADHD symptoms. ► Provide signed consent from the legal guardian. ► Signed consent to be approached for future research (VicFAS database).	► Inability to read or speak sufficient English for either the child or parent or guardian to complete assessment tasks. ► Currently prescribed a medication for treatment of ADHD symptoms other than stimulants.* ► Allergy or sensitivity to Starcke 1500 (maize starch and pregelatinised maize starch).* ► Inability to swallow capsules.* ► Intracranial symptoms or pathology, such as epilepsy, hydrocephalus, diagnosed traumatic. brain injury or progressive intracranial tumours that may impact cognitive and behavioural function (children with asymptomatic or static lesions will be eligible).* ► An abnormal ECG result at the time of screening was deemed clinically significant by the participant's paediatrician.* ► The presence of a significant comorbid psychiatric or psychological disorder (excluding ADHD, oppositional defiant disorder, conduct disorder, pervasive development disorder or autism spectrum disorder), including depressive disorder, anxiety disorder, psychotic disorder, suicidality, Tic disorder, anorexia or bulimia nervosa, predominates their profile and makes them clinically unsuitable to participate.* ► Treatment with any other investigational drug within 8 weeks prior to randomisation.* ► Is known to be pregnant.* ► Is deemed by their primary paediatrician to be medically unsafe for trial participation for any reason.* ► Parents or guardians are not consenting for researchers to contact the participant's paediatrician or school. ► The child's school is unwilling to participate in outcome assessments.

Criteria with an asterisk will be discussed with the participants' ongoing paediatrician to ensure suitability for the study.
ADHD, attention deficit hyperactivity disorder; DMS-IV, Diagnostic and Statistical Manual of Mental Disorders, fourth edition; FASD, fetal alcohol spectrum disorder; VicFAS, Victorian fetal alcohol service.

Sample size

The multiple N-of-1 trials will comprise a convenience sample (n=20).

N-of-1 data

Estimation of the needed number of cross-overs (ie, 'sample size' in N-of-1 studies) was based on having at least 80% power (β=0.20) to detect a 5.9-point reduction in Conners 3 ratings at the individual level (defined as an important difference from prior studies)[27] and following sample size calculations of N-of-1 trials as suggested by others.[28] We set significance testing at the α=0.05 level. Using our clinically important difference of 5.9 (variance of 42.05) with 36 observations per participant (18 placebos and 18 active medications), we achieve >80% power (one-sided hypothesis test). To accommodate dropouts and/or missing data (completely at random), we increased the trial to 40 observations per patient (20 placebos and 20 active medications).

Handling of missing data

The occurrence of missing data will be reported. These occurrences will be explored to assess whether there are any patterns in the missingness. If concerns arise about such patterns, the potential impact of missing data will be explored via single value imputation, implementing a best-worst-case and worst-best-case sensitivity analysis. Within the Bayesian analyses, standard Bayesian imputation will be implemented such that the uncertainty in the missing data will be accounted for when evaluating the treatment effect.

Randomisation, treatment allocation and blinding

All eligible, consented participants will be randomised to a trial arm sequence combination. Each sequence combination denotes the active and placebo treatment combinations (ie, A/P in a randomised order) within four cycles. This yields 16 unique sequence combinations, which are assigned to each participant based on their study ID at enrolment. The sequence combinations are allocated to participants such that each block of 16 participants will be assigned all possible sequence combinations (in a randomised order). For subsequent participants, additional sequences would be randomly generated in the same way as the first 16. The site trial pharmacy will assign the active drug or placebo condition to the sequence (A or P), and this allocation will be only held by the site pharmacies and not accessible to investigators. Those who are eligible but decline will be noted to assess trial uptake for feasibility.

The random allocation is blinded to the clinician, parent, teacher and participant. At the end of the trial, the order of medications will be unmasked and compared with the teacher's (then parent's) observations of the child's behaviour.

Interventions and dosing schedule

Children will take their currently prescribed stimulant dose and schedule based on their script at enrolment in the trial, as determined and titrated by their primary paediatrician. The medication will be orally administered.

Trial procedure

Appropriately trained research psychologists will carry out the screening for inclusion and exclusion criteria and enrol participants in the trial. The trial outcomes will be administered by an appropriately trained psychologist in the format and location determined by the parent's preference.

Safety evaluation

AEs and serious AEs (SAEs) are defined according to the National Health and Medical Research Council (2016).[29] AEs will be monitored throughout the N-of-1 trial. All SAEs' serious adverse reactions (SARs) occurring during the trial will be reported to the site human research ethics committee (HREC). Routine AE monitoring will be completed by the principal investigator and will be reported separately to the hospital HREC and trial pharmacy. Unblinding will occur if there is reason to believe an SAE or suspected unexpected SAR (SUSAR) was due to the study medication and if the participant cannot be treated without knowing which treatment they were receiving. Unblinding and the reason for unblinding will be recorded. All AEs, SAEs and SUSARs will be followed up until they are considered to have abated or stabilised. Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB), comprised of three independent clinicians and one biostatistician. The trial developmental paediatrician (KH) will provide consultation to enable rapid professional opinion regarding safety and clinical management options. The principal investigator and mentors, KW and PJA, along with KH, are the study management group. This group will provide oversight, be responsible for the day-to-day management of the trial and respond to any audits by the local HREC.

Removal from the trial

Participants may discontinue trial treatment for the following reasons: (1) the participant or legal guardian requests to discontinue, (2) the investigator's decision to discontinue a participant, (3) the participant is pregnant, (4) experiences serious or intolerable AEs, (5) develops, during the course of the trial, symptoms or conditions listed in the exclusion criteria and (6) requires early discontinuation for any other reason (to be noted in the participant file). The investigator may also withdraw all trial participants from the trial treatment if the trial is terminated. The date and reason for discontinuation of the trial intervention will be recorded.

Premature termination of the study

The trial will be terminated prematurely if SAEs occur that are considered in all likelihood to be attributable to the trial procedures or medication. This decision will be made by the DSMB.

Analysis

Study sample

We will describe the resulting sample in terms of key demographics (age and sex), medication particulars and diagnostic outcomes.

Primary analysis of group data

The feasibility and tolerability of the N-of-1 will be explored by using rates of trial uptake, continuation and compliance (medication diaries) and by inspecting numbers and types of AEs. AEs will be coded using MedDRA and calculated once per participant. We will describe the number of AEs across the trial and report relevant key information (eg, start date, stop date, severity, relationship, expectedness, outcome and duration). AEs leading to premature discontinuation of the trial intervention and serious treatment-emergent AEs will be reported.

Secondary outcome (N-of-1 data)

We will explore the individual N-of-1 data visually by plotting each outcome over time to provide an indication of the difference between treatments for each participant.

The individual efficacy endpoint was defined a priori as the change in scores between placebo and active drug on the teacher's Conners 3 Inattentive and Hyperactive Index T scores (or inattention/hyperactivity for the Conners EC). We will test for a significant difference between the two phases using a Wilcoxon rank-sum test. We will use intention-to-treat analysis. Clinically important differences will also be reported in terms of whether the mean and median difference is greater than 5.9 and whether this is significant.[27]

Wilcoxon rank-sum test analysis will be run separately and repeated for all N-of-1 data for secondary outcomes to compare individual data on stimulant medication relative to placebo for the following: Conners 3/EC parent hyperactivity and inattention ratings (T scores), WFIRS total score (family and school domains), total problem ratings, weekly child cognitive data (CANTAB) and side effect ratings. Bayesian analyses on the N-of-1 series will also be considered, allowing for the probability of a clinically significant difference between medication and placebo conditions to be estimated. For these analyses, weakly informative prior information (calibrated by prior predictive checks) will be used such that the conclusions are essentially data-driven.

Pooled N-of-1 trial outcome data

An aggregated analysis of the pooled N-of-1 trial data will be undertaken for the child ADHD ratings (teacher

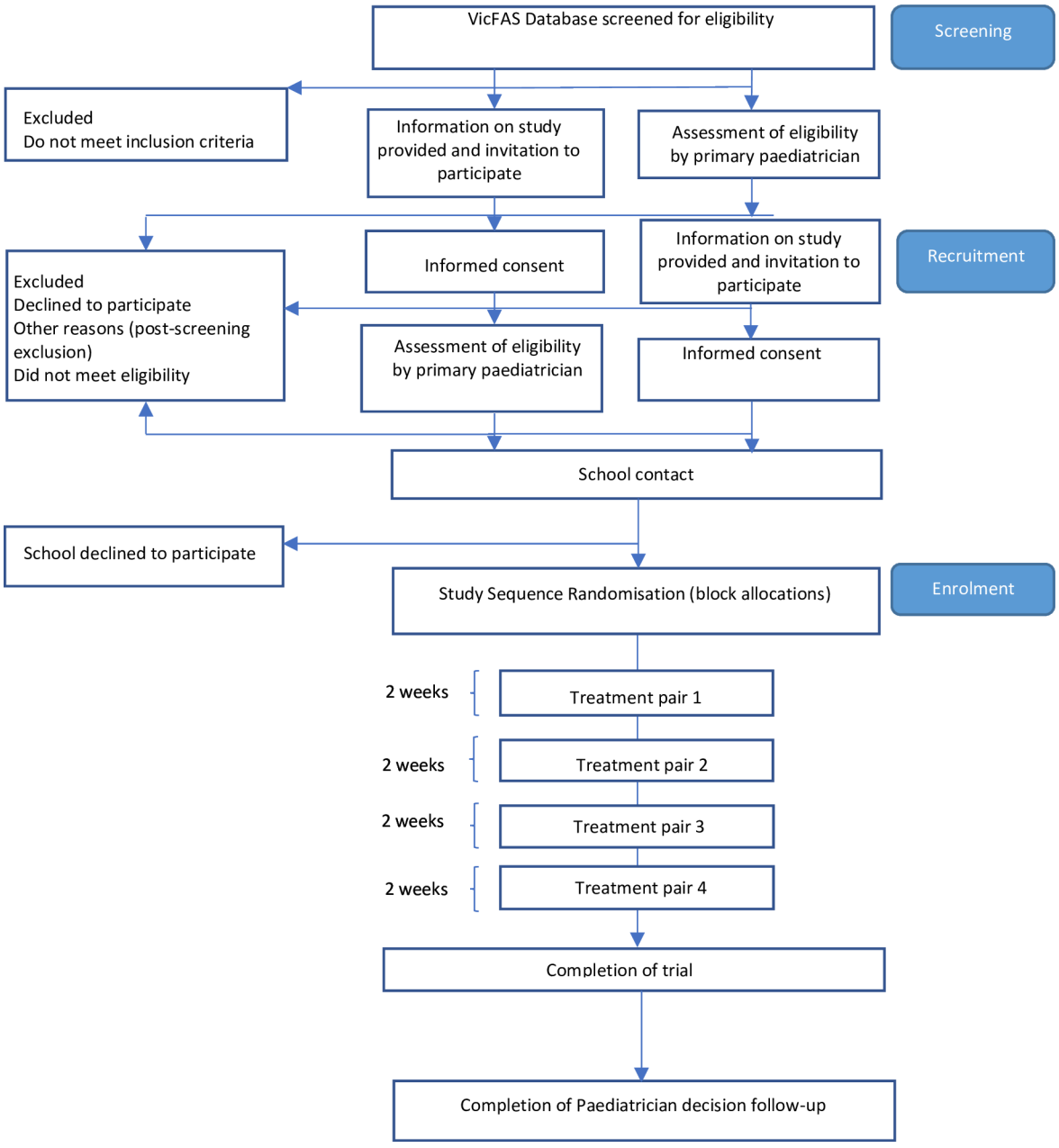

Figure 1 Participant flow.

report). This will entail fitting a hierarchical model that accounts for the between-individual and within-individual variability in the trial data. This analysis will provide an estimate of the population or cohort treatment effect as well as individual-level treatment effects. This group-level aggregated analysis will inform a future larger trial in terms of the degree of difference observed between stimulant and placebo conditions in this population. Potential mediating factors such as child cognition, neurodevelopmental impairment and sociodemographic factors will be explored to identify variables that might be associated with the variability of the response between individuals. The existing trial is not sufficiently powered to examine stimulant-to-stimulant differences between methylphenidate and dexamphetamine due to the small overall sample size and anticipated number in each medication group. Importantly, studies comparing different formulations of the same drug revealed no significant differences in terms of symptom control,[30] suggesting it is feasible to pool data for the current study purposes while providing pilot data to inform future larger trials, including data from different stimulant medication types.

Exploratory analysis

We use descriptive statistics to report the post-trial paediatrician decision after receiving N-of-1 trial data.

Ethics and dissemination

Ethics

This clinical trial will be conducted in compliance with all stipulations of this protocol, the conditions of the ethics committee approval, the NHMRC National Statement

on Ethical Conduct in Human Research (2007 and all updates) and the Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2), dated 9 November 2016. The trial has undergone review and approval from the site HREC (Monash HREC, HREC Reference Number: HREC/74678/RES-21-0000-248A). Protocol amendments will be updated via Clinical Trials.gov.

Recruitment

Two pathways to recruitment will be pursued, aligned with the participants' clinical pathways. Pathway 1 includes participants seen for direct assessment by VicFAS (August 2019–September 2023) and whose parents or guardians previously consented to the VicFAS database (HREC RES-19-0000-706A), as well as consent for contact for future research. The VicFAS database was established as a prospective study by AC as principal investigator in 2019 and captures core data on children seen for FASD diagnostic assessment from August 2019 onwards, against the Australian guide to the diagnosis of FASD.[1] Parents or guardians will be approached directly to provide written consent for participation. Pathway 2 includes participants assessed through secondary consultation by the VicFAS team. The participant's primary paediatrician will be approached to screen the participant's eligibility and obtain the participant's contact details prior to contacting the participant's guardian to request written consent. The inclusion criteria must be met by all the participants.

To encourage participant retention, teachers and parents nominate their preferred response format at their preferred time each day. Should families need to attend the hospital, they will be reimbursed for parking or travel expenses.

Compensation

The trial participant's parents and teachers will receive a $50 voucher for reimbursement of their time.

Participant flow

Participant flow through the trial is outlined in figure 1.

Data storage and retention

Participant confidentiality is strictly held in trust by the principal investigator, participating investigators, research staff and their agents. Participant data and samples will be identified through the use of a unique participant trial number assigned to the trial participant ('reidentifiable'). Electronic deidentified data will be securely stored in Monash University's Research Electronic Data Capture (REDCap) database system and in files stored in Monash University network file servers, which are backed up nightly and electronic files will be stored in locations accessible only by appropriate designated members of the research team. Data will be stored for at least 15 years after the completion of the study or until the youngest participant has turned 25 years.

Patient and public involvement

A participant representative was consulted in the design of the protocol, measures, timing and methods of assessment. Key areas of input and subsequent protocol revision included planning a washout day on Sunday rather than Monday for long-acting formulations, minimising school disruption, reducing questionnaire length to reduce overall carer burden and revisions to increase useability of the online platform (RedCAP). Participants and their primary paediatrician will receive a letter detailing individual participants' responses to the stimulants compared with placebo to facilitate a decision on further treatment.

Dissemination of findings

Research findings will be published in journal articles and conference proceedings, in which all data will be deidentified to protect the privacy of participants and ensure confidentiality is maintained. Collated results of the trial and its outcomes will be provided to parents or guardians and paediatricians in a final newsletter.

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Contributors AC is the principal investigator and was responsible for study design and oversight, the first draft of the manuscript and ongoing input and oversight of all versions to submission. JN provided consultation on the protocol regarding N-of-1 methodology and reviewed and contributed to the protocol. JMM is a consultant statistician with N-of-1 trial analysis experience and provided consultation around N-of-1 trial design and statistical methods, protocol input and manuscript revisions. KH is a developmental paediatrician at Monash Children's Hospital, Head of the VicFAS and Adj. Clinical Associate Professor at Monash University, Department of Paediatrics. KH has over 20 years' experience working with children with FASD. She provided consultation on the implementation of the trial integrated with clinical service delivery, clinical advice regarding medications and participant adverse effects, and revision and input to the protocol. PJA is currently the Head of the Neurodevelopment Programme, Turner Institute for Brain and Mental Health, School of Psychological Sciences, Monash University. PJA provided insight into trial assessment methods and research methods, reviewed and revised the protocol. KW is a developmental paediatrician, public health physician and clinical epidemiologist with 25 years' experience working in neurodevelopmental paediatrics and community child health. She provided research mentorship oversight for the project and reviewed and revised the protocol.

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